Oncol Res Treat
43(suppl 1) VII–265 (2020)

43 | S1 | 20

print
ISSN 2296–5270

online
e-ISSN 2296–5262

www.karger.com/ort

e-ISBN 978-3-318-06686-9

Oncology Research and Treatment

Band 43,
Supplement 1,
Februar 2020
online only

34. Deutscher Krebskongress

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Berlin, 19.–22. Februar 2020

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Disclosure Statement

The Editor declares that he has no conflict of interest.

Impressum

ISSN Print Edition: 2296–5270
ISSN Online Edition: 2296–5262

Journal Homepage: www.karger.com/ort
Bibliographic Indices: This journal is regularly listed in bibliographic services, including PubMed/MEDLINE, Web of Science, Google Scholar, Scopus, Embase.

Publication Data: *Oncology Research and Treatment* is published 10 times a year. Volume 43, each 10 issues, appears in 2020.

Subscription Orders:
Orders can be placed at agencies, bookstores, or directly with the Publisher.

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Supplement 1/2020
e-ISBN 978-3-318-06686-9

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DOI: 10.1159/000487109

Basic Research

Best-of-Abstracts-Vorträge

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The Oncogenic MDm4 Protein acts as a Supporter of DNA-Replication

Kai Wohlberedt[1]; *Ina Klusmann*[1]; *Polina Derevyanko*[1]; *Valentina Manzini*[1]; *Celeste Giansanti*[1]; *Josephine Choo*[1]; *Anna Magerhans*[1]; *Christine Eischen*[2]; *Aart Jochemsen*[3]; *Matthias Dobbelstein*[1]

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Purpose: The Mdm4 (alias Mdmx) oncoprotein heterodimerizes with Mdm2 and together they antagonize the tumor suppressor p53. p53-independent activities of the two Mdm proteins are emerging, and we have reported the ability of Mdm2 to modify chromatin [1] and to support DNA replication by suppressing the formation of DNA/RNA hybrids (R-loops) [2]. We asked whether Mdm4 can also contribute to an unperturbed DNA replication fork progression.
Methods: Quantification of the speed and processivity of single DNA replication forks in tumor-derived as well as non-transformed cell lines was assessed by DNA fiber assays upon removal of Mdm4. Immunoblots and immunofluorescence microscopy allowed us to determine indicators of replicative stress. Cell proliferation assays and cytometry following EdU incorporation were used to investigate cell survival and overall DNA synthesis.
Results: The loss of Mdm4 in p53-deficient cells strongly impaired DNA replication fork progression. Co-depletion of Mdm4 and Mdm2 compromised DNA replication even further, arguing that they act through partially distinct mechanisms. Further analysis revealed that the RING domain of Mdm4 was necessary to ensure DNA replication fork progression. By inducing the formation of DNA/RNA hybrids, Mdm4 depletion significantly increased replication stress. Due to elevated firing of replication origins, loss of Mdm4 only marginally affected cell proliferation but sensitized p53-/- cells to the nucleoside analogue gemcitabine.
Conclusions: Mdm4 supports DNA replication by preventing the accumulation of DNA/RNA hybrids independent of p53. These findings suggest a new route of chemosensitization with low toxicity using Mdm4 inhibitors and further support Mdm4 as a therapeutic target in cancer.

References:

1. Wienken et al., Molecular Cell 2016
2. Klusmann et al., PNAS 2018

Disclosure Statement: The authors declare no conflict of interest.

Poster

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Differences in Mitochondria between Normal and Cancer Cells as Molecular Cancer Target

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Purpose: Cancer prevention therapies with an induction of apoptosis in cancer cells with least adverse effects on normal cells is a particularly desirable strategy in cancer research.
Methods: Fluorescence, transmission and scanning electron microscopy, Immunohistochemistry, RT-PCR, Western Blot analysis.
Results: We demonstrated that a matched pair of isogenetic normal and transformed counterpart cells (WI38/WI38VA) showed a selective induction of the mitochondrial-mediated apoptotic pathway only in tumor but not in normal cells in response to resveratrol analogs, black tea-derived theaflavins, and oxidative stress. Tumor cells bearing a bubble-like mitochondrial network showed intrinsic apoptosis in response to various inducers. In contrast, normal counterpart cells or tumor cells which were resistant to apoptosis were composed of a web-like mitochondrial reticulum.
Conclusions: In summary, our results indicate a correlation between mitochondrial morphology and the capacity for induction of apoptosis. Knowledge about mitochondrial morphology or cellular components impacting mitochondria (e.g. microtubule) thus offer a unique molecular site against which selective natural-derived bioactives and/or physico-chemical inducers might be targeted.

Relevant References:

1. Gosslau, A., Pabbaraja, S., Knapp, S., and Chen, K.Y. (2008) Trans- and cis-stilbene polyphenol derivatives induced rapid perinuclear mitochondrial clustering and p53-independent apoptosis in cancer cells but not normal cells. *Eur. J. Pharmacol.*, 587, 25-34
2. Gosslau, A., and Chen, K.Y. (2004) Nutraceuticals, apoptosis, and disease prevention. *Nutrition* 20, 95-102 (Review)

Disclosure Statement:
Relevant financial relationships:
Professor, Dept. of Science (Biology), City University of New York, BMCC
Relevant non-financial relationships:
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Mechanisms of Mitigating Aneuploidy-Induced Telomere Replication Stress by Telomerase

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Purpose: Aneuploidy represents a hallmark feature of carcinogenesis in humans but mutations in the canonical ploidy-control genes are rare as these mutations impair cell fitness. Recent data indicate that aneuploidy can inhibit or instigate tumorigenesis dependent on the genetic background. These observations imply that aneuploidy can be induced by non-canonical ploidy-control mechanisms and tumor cells activate mechanisms to allow survival of aneuploid cells. We have recently identified non-canonical ploidy-control genes and could show that telomerase represents an aneuploidy survival mechanism. We aim to elucidate the pathways of canonical and non-canonical aneuploidy induction and the mechanisms how telomerase suppresses aneuploidy-induced cell senescence.
Methods: Knockdown or knockout of MAD2 (canonical ploidy-control gene) or ORP3 (non-canonical ploidy control gene) is achieved in telomerase positive and telomerase negative human fibroblasts by shRNAs or the CRISPR-Cas9 technology. The replication stress is evaluated by immunofluorescence staining of p-RPA2, an established marker for replication stress. We further use proteome analyses to answer the question whether telomerase itself is sufficient to suppress aneuploidy-induced replication stress or whether it requires cooperation partners for this process.
Results: The knockdown and knockout of ORP3 induces aneuploidy in both, telomerase negative and positive cells. As reported previously, aneuploidy induction resulted in increased replication stress and impairment of cell proliferation in telomerase negative primary human fibroblasts (BJ) while ectopic expression of telomerase in these cells (BJ-hTERT) suppresses aneuploidy-induced replication stress. Initial results indicate the involvement of helicases mitigating aneuploidy-induced replication stress and to allow continuous proliferation of aneuploid cells.
Conclusions: The data indicate that telomerase requires cooperation partners, such as helicases, to suppress to suppress aneuploidy-induced replication stress.

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Identification of Microvesicle-Specific Proteins and their Implications in Vesicle Biogenesis

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Purpose: Extracellular vesicles are increasingly recognized as important mediators of intercellular communication and biomarkers in cancer. They are divided into two main populations, the small exosomes (Exo, diameter <150 nm) that derive from multivesicular endosomes, and larger microvesicles (MV, diameter 100-1000 nm) that bud off directly from the cell membrane. While key regulators of Exo secretion have been recently identified, the biogenesis of MV is barely understood. Therefore, the aim of this study was to identify novel MV proteins that might play a role in MV biogenesis.
Methods: We isolated MV and Exo from SK-BR-3 breast cancer cells and used SILAC (stable isotope labeling by/with amino acids in cell culture) followed by mass spectrometry to compare their proteome. MV-specific proteins were validated by Western Blot and analyzed for their effect on MV biogenesis.
Results: Comparison of the MV and Exo proteome revealed 171 proteins to be significantly differentially expressed, among them many proteins associated with cytoskeletal organization that were exclusively present on MV. We validated the expression of these proteins on MV and Exo from several breast cancer as well as normal cell lines and showed that Rgap1, Prc1 and Kif4a were indeed expressed specifically on MV from all cells. Knockdown of these proteins by siRNA in SK-BR-3 cells and subsequent analysis of their secreted vesicles by Western Blot and Nanoparticle Tracking Analysis suggested that the three proteins were indeed involved in MV biogenesis. Interestingly, all three proteins are associated with microtubules and play an important role in cytokinesis. Therefore, our ongoing research focuses on analyzing the intracellular expression and co-localization of the identified markers with other known MV-specific proteins as well as studying the influence of microtubule inhibitors on MV biogenesis.
Conclusions: Taken together, our results identified 3 novel regulators of MV biogenesis and suggest that microtubules are involved in this process.

Disclosure Statement: The authors have nothing to disclose.

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The Non-Canonical WNT Ligand-Receptor Pair WNT11/ ROR2 Mediates Breast Cancer Invasion through RHOA/ROCK Signaling

Kerstin Menck[1,2]; *Saskia Heinrichs*[1,2]; *Maren Sitte*[3]; *Tim Beissbarth*[3]; *Helen Noeding*[4]; *Andreas Janshoff*[4]; *Claudia Binder*[2]; *Annalen Bleckmann*[1,2]

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Purpose: Breast cancer (BC) is the second most common tumor entity worldwide. Tumor progression leads to the formation of metastases for which there is still no curative therapy. Several studies have suggested that BC metastasis involves activation of the Wnt pathway. In this study we aimed to identify novel pathways members involved in BC progression.
Methods: Gene expression data from BC patients were analyzed for the expression of Wnt proteins associated with metastasis. Candidate proteins were modulated for their expression in cell lines and their role in tumor progression was analyzed by functional assays and molecular characterization.
Results: Using a targeted analysis of gene expression data from BC primary tumors and metastases, we found that especially the β-catenin independent, non-canonical Wnt signaling pathway is active in metastases and associated with poor survival. In particular the non-canonical Wnt receptor Ror2 was found to be highly expressed in BC brain metastases and was associated with worse metastasis-free survival. To understand the molecular basis for these observations, we overexpressed Ror2 in human BC cell lines which led to an increase in tumor invasion that was dependent on increased RhoA and Rock expression. Ror2-overexpressing cells showed defects in cell morphology and cell-cell contacts in microscopic assays as well as Electric Cell-Substrate Impedance Sensing (ECIS) measurements. In order to identify the ligand responsible for these changes, cells were characterized by RNA-Seq and real-time PCR which revealed an upregulation of the non-canonical Wnt11 ligand. Co-immunoprecipitation confirmed that Wnt11 acted as a novel ligand for Ror2. Wnt11 activated Rock signaling and its knockdown reversed the pro-invasive phenotype and changes in Ror2-overexpressing cells. High Wnt11 levels in primary BC patient samples were associated with poor metastasis-free survival.
Conclusions: Our study has revealed Wnt11/Ror2 as a novel target driving tumor invasion and progression in BC.

Disclosure Statement: The authors have nothing to disclose.

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CXCR4-LASP1 Interaction – Differences between Breast Cancer and CML

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Purpose: CXCR4 has been reported to play an important role in cell survival, proliferation, migration, as well as metastasis of tumors. Activation by SDF-1 activates PI3K/AKT signaling. In breast cancer (BC), overexpression of CXCR4 is involved in directing metastasis of CXCR4 positive tumor cells to organs producing SDF-1. In CML, CXCR4 is down-regulated by BCRABL causing defective adhesion of CML cells to bone marrow stroma.
Recently, the cytoskeletal and adaptor protein LASP1 was described as a novel CXCR4 binding partner and a promoter of the PI3K/AKT pathway. We sought to investigate the LASP1-CXCR4 axis in solid and hematopoietic malignancy and propose a model in which both signaling pathways are interconnected.
Methods: MDAMB-231 BC and K562 CML cells were used to investigate the phosphorylation-dependent differences in binding of LASP1 to CXCR4 by immunoblotting, pull-down experiments and immunofluorescence staining. Cells with knockdown of CXCR4/LASP1 as well as CXCR4-CFP/Venus-LASP overexpressing HEK293 cells were employed for probing CXCR4-LASP1 signaling.
Results: In BC cells, overexpressed LASP1 shows S146 phosphorylation and nuclear translocation whereas in advanced CML, the protein is down-regulated and Y171 hyperphosphorylation is observed.
Binding of LASP1 to CXCR4 only occurs after S146 phosphorylation. The phosphorylation is transient: Upon CXCR4 stimulation, dephosphorylation of LASP1 at the PKA-site (S146) and concomitant phosphorylation at Y171 by TKs occurs. Opposite effects are observed in CXCR4 deficient CML cells treated with TKI to block BCR-ABL.
Conclusions: In BC cells, binding of pLASP1-S146 stabilizes the C-tail of the CXCR4 and hinders the phosphorylation at multiple PKC serine phosphorylation sites important for receptor internalization. In contrast, increased LASP1-Y171 phosphorylation by BCR-ABL renders the protein less affine to the CXCR4 C-terminus, and facilitates serine and tyrosine phosphorylation, resulting in down-regulation of CXCR4 and causing defective adhesion of CML cells to bone marrow stroma.

Disclosure Statement: EB and JF have received grants from the German Cancer Aid (Project numbers: 70112717 and 70112142).

The authors declare no conflicts of interests.

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IL-17A+ CD4+ T Cell Heterogeneity in Colorectal Cancer

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Purpose: Recently, cancer therapy has been overturned by the discovery of immunotherapies targeting co-inhibitory receptors (CIR) as PD-1. However, in CRC, immunotherapies did not meet the expectations, as only a minority benefit. We hypothesize that two key factors can contribute to the poor efficacy in CRC: (I) the functional heterogeneity of the targeted cells and (II) the local microenvironment.
Methods: Human T cell analysis by FACS, RNAseq, TCRseq and CITE-seq. Functional tests in murine CRC models with different microbiota. In vitro T cell differentiation by co culture with 3-dimensional primary tumor structure.
Results: We show accumulation of different subsets of IL-17A+ CD4 T cells in CRC. One subset is characterized by the co-expression of FoxP3, the key regulator of anti-inflammatory T-cells, and of IL-17A, a pro tumorigenic cytokine. In line, our murine data suggest strong tumor fostering activity of IL17A+ FoxP3+ CD4 T cells. Importantly, these cells express several CIR. Therefore, they react to immunotherapy, but in an undesirable, tumor supporting manner. In addition, tumor progress is modified by different microbiota. Interaction of CD4 T cells and the microbiome is of pivotal importance in directing immune response 1. Interestingly, there is evidence that the microbiota composition impacts the success or failure of immunotherapy 2. If the microbiota modulates IL-17A+ FoxP3+ CD4 T cell abundance and their CIR pattern needs to be clarified. This might determine the efficacy of immunotherapy.
Conclusions: IL17A+ FoxP3+ CD4 T cells are promoting tumor growth and express several CIR. If these CIR correlates with a special composition of the colonic microbiome needs to be elucidated. Characterizing this pro tumorigenic cell population, we seek to determine the best immunotherapy regimen for CRC patients.

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2. Gopalakrishnan, V., et al., Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients. Science, 2018.

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Characterization of Tumor Cell-Derived Extracellular Vesicles in Liquid Biopsies

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Purpose: Extracellular vesicles (EVs) are released by eukaryotic cells including tumor cells[1]. Due to their small size (< 1 µm), they can be detected in all body fluids. In order to be used as diagnostic markers in liquid biopsies, EV subpopulations (e.g. exosomes, ectosomes, apoptotic bodies) need to be detected and characterized. Here, we share our experiences and give suggestions for technical improvements.
Methods: We used the human pancreatic cancer cell line COLO357 as a source for EVs. EV subpopulations were separated by sequential centrifugation based on size and mass. Membranes of intact EVs were labeled with CFSE and analyzed using a high-resolution flow cytometer as well as nanoparticle tracking analysis (NTA). According to previous publications, and in accordance with our observations, cells, cellular debris and apoptotic bodies were pelleted using (2x) 2.500 x *g* (low speed). Then, an EV sub-fraction was selectively enriched (ectosomes) by 10.000 x *g* (high speed). Nevertheless, a sheer separation of ectosomes and exosomes was not possible due to overlapping sizes.
Results: Subsequently, we optimized staining conditions and adapted settings for flow cytometry analysis. While 1 µM CFSE was sufficient for membrane labeling of cells, we now recommend a 40-fold higher concentration for EVs; of note: unlabeled high-speed EVs were indistinguishable from background noise. Short incubation times and stable temperature conditions were of major importance for yielding intact vesicles. Most important, threshold adjustment of fluorescence channel affected the resolution of CFSE-labeled EVs and thus, significantly influenced EV quantification.
Conclusions: Liquid biopsies embody the future of precision medicine in oncology. Protocol optimization and standardization for sample collection, processing and analysis have to be defined precisely for accurate and comparable results.

Reference:

1. Yáñez-Mó et al., J Extracell Vesicles 2015

Disclosure Statement: The Authors declare no conflict of interest.

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Novel Nanowell-Based Workflow for Single Circulating Tumor Cell Isolation with Cellcelector™

Liwen Yang[1]; Mahdi Rivandi[1]; André Franken[1]; Constantin Nelep[2]; Jens Eberhardt[2]; Dieter Niederacher[1]; Tanja Fehm[1]; Hans Neubauer[1]

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Purpose: The CellCelector™ system enables the isolation of single circulating tumor cells (CTCs) for comprehensive genomic analysis. However, although different technologies are used to pre-enrich CTCs, high numbers of contaminating white blood cells (WBCs) are still impeding single cell isolation.
In addition, deposition control of isolated CTCs is currently not possible due to separation of deposition and aspiration areas of CellCelector, which causes extra costs when empty tubes will be processed e.g. by whole genome amplification.
We aimed to implement technical solutions to both issues in order to optimize and speed-up single cell micromanipulation.
Methods: SKBR3 cells were loaded onto PDMS nano-well chips of different geometries. We tested the size of nano-wells with cavities ranging from 15µm to 30µm in diameter and determined a) the cell seeding rate (% of cells captured in nano-wells); b) the cell picking success rate; c) the cell purity rate (i.e. isolation of the target cell without co-aspiration of cells in neighbouring well); and d) on chips staining recover rate. Deposition was verified by microscopic inspection with flat bottom tubes. Validation experiments were done with the patient's CellSearch sample.
Results: Best cell seeding rates were observed with 30µm nano-wells, with 15µm nano-wells many cells were not captured. The experiments using 30µm wells of different geometries are in progress. On-chip staining resulted in a recovery rate of 80%-90%. Deposition control worked to 100% with 4titudes flat bottom tubes. A new adapter for CellCelector was designed and produced to execute this workflow on the microscope stage thereby also increasing the speed of micromanipulation by approx. 50% to 60%.
Conclusions: We have improved single CTCs isolation with the CellCelector by implementing nano-well chips for cell separation and flat bottom tubes to control cell deposition. Apart from the reduced processing time this will also reduce the costs caused by unsuccessful cell deposition.

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Low Dose Irradiation Stimulates Spherogenesis via Alterations in Cytokine Secretion

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Purpose: Ionizing radiation is a known risk factor for the development of meningiomas. However, the underlying mechanism is largely unknown. It is discussed whether radiation triggers mutations or (immuno-)modulatory processes, that might lead to the dedifferentiation of somatic cells and ultimately to the development of tumor stem cells. The aim of this study was to investigate the influence of ionizing radiation on immunomodulatory processes in meningioma cells (PMCs) and non-pathological dura mater cells (DMCs) in vitro.
Methods: Three PMC and three DMC cultures were cultivated under standard conditions. The confluent monolayers were exposed to a single dose of photon irradiation (1, 2, 4, 8, 12, 16, 20 Gy). 24h and 7, 14, 21 and 28 days after treatment, cells were passed and analyzed. Analyses were performed in respect to morphology (cell shape, generation times, etc.), molecular biology and immunological aspects .
Results: In the high-dose radiation group (>= 8Gy) morphological analyses showed clear signs of necrosis in all cell types. Under certain conditions all cell types showed a tendency to detach from the subsurface, and low-dose irradiated cells (<= 4Gy) tended to form spheroids. Compared to DMS, in PMCs this effect was seen later (7d vs. 21d). In addition, 28d after irradiation, DMCs were more sensitive to radiation than PMCs. It was found that the equivalent experimental group to the IC50 values determined for each culture was also the group with the highest IL6 secretions after 28d. Further correlations were found between the time of the maximum IL6 secretions and the occurrence of spheroids in the PMCs. The IL8 secretion also showed a relation between the replacement of the cells at spherogenesis by decreasing concentrations.
Conclusions: Based on the presented data, a correlation between the secretion of IL6+IL8 and the formation of stem cell specific spheroids might be hypothesized. Thus, it seems possible that a radiation-induced cytokine secretion may trigger a stem cell-like phenotype formation.

Disclosure Statement: The authors report no conflicts of interest.

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Defined Glucose Levels Stimulate Metabolic Reprogramming and Tumor Augmenting Processes in Human Meningioma Cells

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Purpose: In contrast to normal mammalian cells, cancer cells use glycolysis to generate energy due to their increased metabolism. This effect has an important role in carcinogenesis and tumor progression. The extent to which this also applies to meningiomas has not yet been investigated. The aim of this study is to investigate the influence of different glucose levels during glycolysis on tumor-promoting processes in human meningiomas.
Methods: The meningioma cell line Ben Men-1 was cultured 24h in a glucose-free medium. Afterwards, the metabolic activity was measured by MTT assay and the proliferation rate by BrdU ELISA under 14 different glucose concentrations (0 to 100 mM). A peak fitting analysis was used to determine the concentrations for maximum effect in both assays. Subsequently, 5 concentrations were determined that promote maximum, minimum and optimal activities. The cells were seeded at a density of 6x 10^5 cells/25cm^2 and further cultured under the previously defined conditions. Doubling times, morphological changes and marker expression were determined by immunocytochemistry.
Results: A maximum of metabolic activity was seen at glucose concentrations of 17.2 mM and 66.7 mM, and maximum proliferation rates at concentrations of 18.5 mM, 35.6 mM and 57.3 mM. Based on these facts, meningioma cells were then cultured and analyzed with glucose concentrations of 0, 15, 40, 65 and 100 mM. It was found that long-term cultivation (>p4) under 15-65 mM glucose was possible. Cells fed with 65 mM glucose showed the fastest doubling times. The IHC characterization showed surprisingly decreasing vimentin and EMA signals in the 65 mM group in contrast to the other investigation groups. In addition, we found increased values for pmTOR and GLUT3.
Conclusions: Our results show that meningioma cells also respond to an increase in environmental glucose levels with an increased tumor progression. In particular, the increased expression of GLUT3 and p-mTOR suggests a possible metabolic re**programming** in this context.

Disclosure Statement: The authors report no conflicts of interest.

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Irradiation as a Trigger for Cellular Reprogramming of Human Meningioma Cells

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Purpose: In previous studies it could be shown that irradiation is a decisive risk factor for the development of meningiomas. The underlying mechanism is still largely unknown. A promising hypothesis is based on the existence of tumor stem cells expressing embryonic NANOG1 as well as tumor-specific NANOGP8 at different levels. The aim of this study was to investigate the effects of ionizing radiation on the induction of pluripotent stem cells from primary WHO°I meningioma cells (PMC) in vitro.
Methods: Three PMC cultures were incubated under standard conditions and subsequently exposed to single dose photon irradiation (1, 2, 4, 8, 12, 16, 20 Gy). After 24h the cells were first passed and cultivated for 9 more passages or 84d. At the end of the experiment the expression of NANOG (immunocytochemistry) as well as the secretion of the cytokines IL-6 and IL-8 were analysed. The difference between NANOG1 and NANOGP8 mRNA expression was determined.
Results: Especially in the low-dose radiation range (1-4 Gy), PMCs showed a change in morphological properties towards cell clusters and spheroid cells, which is a well-known property of stem cells. Additionally, after low-dose irradiation, PMCs showed a clear tendency towards faster growth. Immunocytochemistry showed weak NANOG expression in tumor cells. qPCR showed a significantly higher expression of the *NANOG1* gene variant in the 1 Gy (p=0.038), 2 Gy (p=0.045) and 4 Gy (p=0.005) radiation group compared to untreated cells. Analysis of *NANOGP8* showed no significant differences. Additionally, the treated cells showed an altered, partially stronger secretion of the cytokines IL6 and IL8.
Conclusions: Irradiation affects the proliferation of meningioma cells in different ways and can induce the formation of spheroids in low-dose irradiated cultures. In addition, photon exposure leads to a significantly higher expression of embryonic and stem cell associated NANOG1. Therefore, ionizing radiation seems to be a potential factor in cell re**programming** and thus in tumor development.

Disclosure Statement: The authors report no conflicts of interest.

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Hepatocyte-Specific Deletion of Mtor Accelerates Colorectal Liver Metastasis

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Purpose: The mTOR protein is of central importance for the regulation of cell proliferation, metabolism and autophagy. Activation of the mTOR pathway is frequently found in cancer, resulting in the notion that targeting mTOR represents a useful approach for cancer therapy. Of note, mTOR inhibitors have thus far failed to demonstrate significant antiproliferative efficacy in the majority of cancer types. It is therefore of pivotal importance to better understand the functional significance of mTOR inhibition for the pathogenesis of cancer. We sought to characterize the cell type-specific role of mTOR for the pathogenesis of colorectal liver metastases.
Methods: We established a liver epithelial cell (LEC)-specific knock-out (KO) of mTOR via the Cre/loxP-system (termed $mTOR^{LEC}$ mice) and characterized the growth of colorectal liver metastases (CRLM) in $mTOR^{LEC}$ mice compared to wildtype (WT) controls.
Results: Unexpectedly, tumor nodules in the CRLM model were significantly larger in $mTOR^{LEC}$ mice compared to controls. We hypothesized that the KO of mTOR in LECs resulted in the formation of a pro-tumorigenic microenvironment in the liver. To further analyze this, we determined the expression of pro-inflammatory factors in WT versus KO livers. While the expression of COX-2, HIF-1α, TNF-α and IL-6 was not affected, IL-1β gene expression was found to be significantly higher in the livers of $mTOR^{LEC}$ mice. Furthermore, $mTOR^{LEC}$ mice displayed periportal leukocyte accumulation that was absent in livers from WT mice. The functional relevance of this finding for the accelerated metastasis formation in $mTOR^{LEC}$ mice is currently being evaluated by us.
Conclusions: We show an unexpected acceleration of liver metastases upon functional deletion of mTOR specifically in liver epithelial cells. Our results add a further layer of complexity to the biology of mTOR and suggest that cell and tissue type-specific factors need to be considered in order to comprehend the role of mTOR for tumor biology.

Disclosure Statement: none

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PGRMC1 Alters de Novo Lipid Biosynthesis Resulting in Enhanced Oncogenic Signaling

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Purpose: Progesterone Receptor Membrane Component-1 (PGRMC1) is upregulated in breast cancers and is associated with a worse survival in breast cancer patients. In the present study we describe a potential mechanism by which PGRMC1 potentially contributes to breast cancer progression through deregulation of cholesterol and lipid homeostasis, leading to enhanced oncogenic signaling.
Methods: PGRMC1 interaction partners were identified by co-immunoprecipitation followed by mass spectrometry and validated using proximity ligation assay (PLA) in various breast cancer cell lines. To study how elevated PGRMC1 expression contributes to cholesterol homeostasis, we determined levels of cholesterol and estradiol in PGRMC1 overexpressing breast cancer cells and investigated sensitivity to statin treatment. Additionally, we determined the activity of estrogen receptor (ERα) at conditions of PGRMC1 overexpression and downregulation.
Results: PGRMC1 overexpression resulted in increased proliferation rates in cell culture and in significantly increased tumor volume in xenograft models. PGRMC1 was further found to interact with proteins involved in cholesterol and lipid synthesis. Overexpression of PGRMC1 resulted in increased cholesterol- and estradiol levels, indicating a contribution of PGRMC1 to cholesterol homeostasis. Interestingly, PGRMC1 overexpressing cells established a higher sensitivity to statin treatment, indicating an increased dependence on cholesterol biosynthesis pathway in these cells. Finally, a positive correlation between PGRMC1 and ERα expression levels and -activation was identified, suggesting the activation of ERα signaling by cholesterol metabolites.
Conclusions: PGRMC1 is potentially involved in cholesterol homeostasis by modulation of enzymes of the respective biosynthesis pathway resulting in elevated levels of cholesterol and its metabolites. Subsequent activation of oncogenic signaling cascades could contribute to breast cancer progression. Therefore PGRMC1 represents a potential target for anti-cancer therapy.

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Serum- Cytokine Profile after Extended Liver Resection

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Purpose: An extended partial hepatectomy (ePHx) is often the only curative option for patients suffering from primary or secondary liver tumors. The substantial loss of liver parenchyma may lead to organ dysfunction respectively liver failure. The molecular ways, which are accompanied by liver failure, are not known in detail yet. For this reason this study should show the change of cytokine profiles after liver resection.
Methods: In this study 100 cytokines in the serum of patients, undergoing an ePHx (>70%) in cause of liver tumor, were determine. The cytokines were quantified 24h before and after liver resection with the Proteome ProfilerTMHuman Cytokine Array Kit (R&D systems).
Results: 14 out of 100 defined cytokines shows a significantly higher level 24h after liver resection compared to preoperative status. MIF (Macrophage migration inhibitory factor) and ST2 (Interleukin 1 receptor-like 1; Receptor for interleukin-33) shows more than doubling in the level of intensity. Also Lipocalin-2, MMP9 (Matrix metallopeptidase 9), PDGFAA (Platelet-derived growth factor alpha polypeptide) and TFF3 (Trefoil factor 3) were influenced by the extended liver resection. The significantly influenced cytokines were analyzed by the STRING database, resulting in a calculation of the affected KEGG pathways. This calculation clearly shows an effect of the liver resection on the TNF signaling pathway (pathway ID: 04668) (p=0.00542) and the immune system process (pathway ID: 0002376) (p=9.52e-6).
Conclusions: Due to liver resection, a number of different immunological processes will be influenced. Based on this study the TNF signaling pathway seems to be one of the main important processes in liver regeneration in our mind. Identifying such pathways and detecting there influence in liver regeneration forms the foundation of developing new molecular targets which will open up new therapeutic approaches supporting the post-operative liver regeneration.

Disclosure Statement: nothing to declare

Breast Cancer

Vorträge

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Impact of Chemotherapy-Induced Ovarian Failure (CIOF) on Disease-Free Survival (DFS) and Overall Survival (OS) in Young Women with Early Breast Cancer (EBC)

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Purpose: Previous data has shown that chemotherapy (CT)-induced amenorrhea was associated with a better DFS and OS in premenopausal patients (pts) with EBC, regardless of the hormone receptor status.
Methods: 740 pts aged ≤45yrs treated with anthracycline/taxane (A/T)-based CT for EBC from 4 German neo-/adjuvant trials were examined. Centrally assessed estradiol (E2) and follicle-stimulating hormone (FSH) in blood samples were collected at baseline and 4 wks after the last chemotherapy administration. CIOF was defined as E2 <52.2 ng/L and FSH >12.4IU/L after CT for pts with premenopausal hormone levels at baseline (n=696). We present 4-year DFS and OS overall and in subgroups by hormone receptor status and age.
Results: Median follow-up was 49.6 [48.8-50.3] months. Overall DFS: in all pts without CIOF vs CIOF 65.2% vs 84.0%, p<0.001 (hazard ratio [HR] 2.06, 95%CI 1.36-3.12); in HR+ pts (n=395) 61.8% vs 87.5%, <0.001 (HR 2.69, 95%CI 1.57-4.60); in HR- pts (n=301) 71.6% vs 79.6%, p=0.266 (HR 1.47, 95%CI 0.74-2.89); in pts <30 yrs (n=60) 68.3% vs 92.6%, p=0.026 (HR 4.87, 95%CI 1.05-22.63); in pts 30-34 yrs (n=99) 59.9% vs 80.1%, p=0.108 (HR 1.99, 95%CI 0.85-4.68); in pts 35-39 (n=200) yrs 63.5% vs 81.9%, p=0.116 (HR 1.85, 95%CI 0.85-4.04); in pts ≥40 yrs (n=337) 69.3% vs 85.2%, p=0.565 (HR 1.41, 95%CI 0.44-4.51). OS in pts without CIOF vs CIOF was 89.5% vs 92.7%, p=0.272 (HR 1.46, 95%CI 0.74-2.90); within subgroups a trend towards a better OS was seen only in HR+ pts: 88.4% vs 95.9%, p=0.035 (HR 0.49, 95%CI 1.04-5.99).
Discussion: Our results support that pts with CIOF after CT for EBC had a better DFS compared to pts without CIOF, in particular if very young. Moreover, we show that in HR+ BC, CIOF was associated with a significant improvement of DFS and OS.
Conclusions: Pts with CIOF after A/T-based CT for EBC show a better DFS, especially if <30 yrs or HR+. This DFS improvement translates in an OS advantage in the latter group.

Reference:
1. Swain et al. NEJM 2010

Disclosure Statement: The study was supported by Walter Schulz Stiftung.

AS reported grants from Celgene, Roche, AbbVie, Molecular Partner; personal fees from Roche, AstraZeneca, Celgene, Pfizer, Novartis, MSD, Tesaro, Lilly. VM reported personal fees from Amgen, AstraZeneca, Diichi-Sankyo, Eisai, Pfizer Novartis, Roche, Celgene, Teva, Janssen-Cilag, Genomic Health, Hexal, Pierre Fabre, MSD, Lilly, Tesaro, Nektar and grants from Novartis, Roche, Seattle Genetics. PAF reported grants from Novartis, Biontech, Cepheid and personal fees from Novartis, Roche, Pfizer, Celgene, Daiichi-Sankyo, Teva, Astra Zeneca, Merck Sharp & Dohme, Myelo Therapeutics, Macrogenics, Eisai, Puma. MvM reported personal fees from AstraZeneca, Novartis, Amgen.

The other co-authors had nothing to disclose.

Poster

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Gibt es einen Zusammenhang zwischen Silikonimplantaten und dem Anaplastisch-Großzelligem Lymphom?

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Purpose: Über 80% der Brustrekonstruktionen werden weltweit mit Implantaten durchgeführt. Die Sicherheit dieser Medizinprodukte und vor allem der Zusammenhang der Bildung eines sehr seltenen Tumors des lymphatischen Systems, das Breast Implant Associated Anaplastic Large Cell Lymphoma (BIA-ALCL) sowie die Entstehung eines unklaren Symptomenkomplexes, dem Autoimmune/Inflammatory Syndrome Induced by Adjuvants (ASIA) werden diskutiert.

Die Inzidenz des BIA-ALCL wird in der Literatur sehr unterschiedlich angegeben. Dies liegt an uneinheitlich verwendeten Klassifikationssystemen, unstrukturierten Datensammlung, möglichen Doppelmeldungen in die Register, unsicheren klinischen und pathologischen Angaben und fehlenden Daten zur Anzahl implantierter Implantate als Denominator. In Deutschland sind bisher zwölf Fälle gemeldet.

Methods: Anhand der im Tumorzentrum Regensburg erhobenen Daten über 17 Jahren errechneten wir die Inzidenz des CD-30 positiven und ALK negativen Lymphoms.

Results: Von 170.293 erfassten Tumoren bei einer Population von 2.1 Millionen waren zwölf Fälle CD30 positiv und ALK negativ. In keinem Fall war der Tumor mit einem Burstimplantat assoziiert.

Conclusions: Anhand von Hochrechnungen können wir eine Inzidenz des BIA-ALCL von 4 auf 1.000.000 Implantat Jahre angeben. Infolge handelt es sich bei dem BIA-ALCL um eine äußerst seltene Komplikation von Silikonimplantaten.

Disclosure Statement: keine

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Neratinib + Capecitabine Versus Lapatinib + Capecitabine in Patients with HER2+ Metastatic Breast Cancer Previously Treated with ≥ 2 HER2-Directed Regimens: The Multinational, Randomized, Phase III Trial Nala

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Purpose: NALA (NCT01808573) is a multinational, randomized, open-label, phase III trial of neratinib (an irreversible pan-HER tyrosine kinase inhibitor [TKI]) + capecitabine (N+C) vs lapatinib (a reversible dual TKI) + C (L+C) in patients with stage IV HER2+ metastatic breast cancer (MBC) who had received ≥ 2 prior HER2-directed regimens for MBC.

Methods: Patients were randomized 1:1 to N (240 mg qd po) + C (750 mg/m2 bid po) or L (1250 mg qd po) + C (1000 mg/m2 bid po). Patients on N had mandatory diarrhea prophylaxis. Co-primary endpoints were centrally assessed progression-free survival (PFS) and overall survival (OS). Secondary endpoints were objective response rate (ORR); duration of response (DoR); clinical benefit rate (CBR); time to intervention for symptomatic metastatic central nervous system (CNS) disease; safety.

Results: 621 patients were randomized (307 to N+C; 314 to L+C). PFS was improved with N+C vs L+C (HR = 0.76; 95% CI 0.63–0.93; p = 0.006); 6-month PFS rates were 47.2% vs 37.8% for N+C vs L+C, respectively. OS rates at 12 months were 72.5% vs 66.7% (HR = 0.88; 95% CI 0.72–1.07; p = 0.2086). ORR in patients with measurable disease was 32.8% with N+C vs 26.7% with L+C (p = 0.1201) with longer DoR for N+C (HR = 0.50; 95% CI 0.33–0.74; p = 0.0004). CBR for N+C was 44.5% vs 35.6% for L+C (p = 0.0328). Time to intervention for symptomatic CNS disease was delayed with N+C vs L+C (overall cumulative incidence 22.8% vs 29.2%; p = 0.043). Treatment-emergent adverse events (TEAEs) were similar between arms. G3 diarrhea was more frequent with N+C (24.4% vs 12.5% for L+C) but with similar median duration (4 d). TEAE-related discontinuation rates were lower for N (10.9%) than for L (14.5%).

Conclusions: N+C significantly improved PFS with a trend towards improved OS vs L+C. N+C resulted in a reduced incidence of interventions for CNS progression compared to L+C. No new safety signals were observed.

The study was published at the ASCO Annual Meeting 2019.

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Germline Mutation Status and Therapy Response in High-Risk Early-Stage Breast Cancer: a Secondary Analysis of the Geparocto Randomized Clinical Trial (NCT02125344)

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Purpose: GeparOcto compared the efficacy of two neoadjuvant treatment regimen in high-risk early breast cancer (BC): Sequential intense dose-dense epirubicin, paclitaxel, and cyclophosphamide (iddEPC) and weekly paclitaxel plus non-pegylated liposomal doxorubicin (PM), plus carboplatin (PMCb) in triple-negative BC (TNBC). There was no difference in pathological complete response (pCR) rates (Schneeweiss et al. Eur J Cancer. 2019;106:181-192).

Methods: Germline mutation analysis of *BRCA1/2* and 16 further BC predisposition genes using blood-derived DNA from 914 female patients (pts) enrolled (393 pts with TNBC, 156 pts with HER2-/HR+ BC; and 365 pts with HER2+ BC). pCR rates (ypT0/is ypN0 definition) were stratified

according to the germline (g) mutation status overall, by treatment arm, and tumor subtype.
Results: 96 of the 914 pts (10.5%) carried g*BRCA1/2* mutations and achieved higher pCR rates than pts without g*BRCA1/2* mutations (60.4% vs 46.7%, OR:1.74, P=.012). The *gBRCA1/2* mutation prevalence was 17.6% in TNBC, 14.1% in HER2-/HR+ BC, and only 1.4% in HER2+ BC. Irrespective of the treatment arm, pts with TNBC and g*BRCA1/2* mutations showed higher pCR rates compared with TNBC pts without *gBRCA1/2* mutations (69.6% vs 46.0%, OR:2.69, P=.001). A positive g*BRCA1/2* mutation status predicts therapy response in both, the PMCb arm (74.3% vs 47.0%, OR:3.26, P=.005) and the iddEPC arm (64.7% vs 45.0%, OR:2.24, P=.040); differences between treatment arms did not reach levels of significance (P=.389). In the subgroup of pts with HER2-/HR+ BC, a positive g*BRCA1/2* mutation status predicts significantly higher pCR rates (31.8% vs 11.9%, OR:3.44, P=.020).
Conclusions: Effective chemotherapy for g*BRCA1/2*-mutated TNBC is commonly suggested platinum-based. With a pCR rate of 64.7%, we demonstrate that iddEPC appears to be similar effective in these pts. Of interest is the significantly higher pCR rate in HER2-/HR+ g*BRCA1/2* carriers compared to non-carriers. The question arises whether all pts with high-risk luminal BC should be offered g*BRCA1/2* testing prior to treatment start.

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Factors Influencing the Time to Surgery after Neoadjuvant Chemotherapy in Breast Cancer Patients

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Purpose: It is suspected, that delayed surgery after neoadjuvant chemotherapy leads to a worse outcome in breast cancer patients. We therefore determined time interval between the end of neoadjuvant chemotherapy (NACT) and surgery, as well as possible influencing factors.
Methods: All patients receiving NACT due to newly diagnosed breast cancer from 2015 to 2017 at Department of Gynecology, Saarland University Medical School, were included. The time interval between end of NACT and surgery was defined as primary endpoint. Possible delaying factors were investigated: Age, study participation, outpatient and inpatient presentations, implants/expander, MRI preoperatively, discontinuation of chemotherapy, genetic mutations.
Results: Data of 139 patients was analyzed. The average age was 53 years (+/- 13). The time interval between end of NACT and surgery was 28 days (±9). Clinical presentations on outpatient and inpatient basis showed a statistically significant prolonging effect on the time between NACT and surgery (p=0.002; p<0.001). Also, discontinuation of NACT led to a prolonged time to surgery (p=0.005). In contrast, a proven genetic mutation shortened the time to surgery (p<0.001).
Conclusions: Every outpatient presentation prolonged the time to surgery by an average of two days, inpatient presentations prolonged the time to surgery by an average of seven days. Discontinuation of NACT delayed surgery by an average of six days. Patients with proven genetic mutation had surgery seven days earlier. Patients age, participation in clinical studies, oncoplastic surgery and preoperative MRI scans did not delay therapy onset.

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The Potential of Claims Data for Long-Term Follow-Up of Breast Cancer Patients in Germany

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Purpose: Population-based data on long-term treatment patterns and clinical outcomes in cancer patients are important but hardly available from German cancer registries. Exemplified by breast cancer (BC) patients, we aimed to explore the potential of German claims data for providing long-term follow-up information on cancer patients.
Methods: We used the German Pharmacoepidemiological Research Database (GePaRD) containing claims data from four statutory health insurances with information on ~25 million persons. Based on previously developed algorithms using ICD-10 codes, we identified patients newly diagnosed with BC in 2008 and classified them into three groups: no affected lymph nodes/metastasis (noNM), affected lymph nodes only (onlyN) or distant metastasis (M) at diagnosis. The cohort was followed up until end of 2016 or death. We characterized the groups regarding initial and subsequent therapies (surgery, medical therapy and radiotherapy), metastases and deaths occurring during follow-up.
Results: After exclusion of patients switching health insurance during follow-up (9% of the initial cohort) we included 11,717 BC patients diagnosed in 2008 (noNM: 82%, onlyN: 12%, M: 7%) with a mean age of 63 years (median follow-up: 8.4 years). During the observation period, 11% of the cohort received no breast surgery (group M: 21%), 28% received more than one surgery (second surgery in first year: 81%; later: 19%) and 29% had a mastectomy (in first year: 91%, only later: 9%). Of the total cohort, 8% received neoadjuvant therapy, 7% ever received monoclonal antibodies, 52% never received chemotherapy (group noNM: 92%) and 28% never received radiotherapy. Overall, 25% of the cohort died (group M: 22%).
Conclusions: Claims data provide valuable information on the long-term course and treatment of cancer patients, avoiding substantial loss-to-follow-up and incomplete reporting of therapies. Combining claims data with cancer registry data containing detailed tumor information may create synergies that should be explored.

Disclosure Statement: None.

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HER4 Expression in Estrogen Receptor-Positive Breast Cancer is Associated with Decreased Sensitivity to Tamoxifen Treatment and Reduced Overall Survival of Postmenopausal Women

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Purpose: The sensitivity of estrogen receptor positive breast cancers to tamoxifen treatment varies considerably and the molecular mechanisms affecting the response rates are manifold. The human epidermal growth factor receptor related receptor HER2 is known to trigger intracellular signaling cascades that modulate the activity of coregulators of the estrogen receptor which in turn reduces the cell sensitivity to tamoxifen treatment. However, the impact of HER2 related receptor tyrosine kinases HER1,

HER3, and in particular HER4 on an endocrine treatment efficiency is largely unknown.
Methods: Here we retrospectively evaluated the importance of HER4 expression on the outcome of tamoxifen and aromatase inhibitor treated estrogen receptor positive breast cancer patients (n = 258) – either pre- or postmenopausal. In addition, we experimentally analyzed the efficiency of tamoxifen treatment as a function of HER4 coexpression *in-vitro*.
Results: We found a significantly improved survival of tamoxifen treated postmenopausal breast cancer patients in the absence of HER4 compared to those with pronounced HER4 expression. In accordance with this finding the sensitivity to tamoxifen treatment of estrogen and HER4 receptor positive ZR-75-1 breast cancer cells can be significantly enhanced by HER4 knockdown.
Conclusions: We suggest an HER4 / estrogen receptor interaction that impedes tamoxifen binding to the estrogen receptor and reduces treatment efficiency. Whether the sensitivity to tamoxifen treatment can be enhanced by an anti-HER4 targeting needs to be prospectively evaluated.

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[…] **Brockhoff G**. HER4 expression in estrogen receptor-positive breast cancer is associated with decreased sensitivity to tamoxifen treatment and reduced overall survival of postmenopausal women. Breast Cancer Res. 2018 Nov 20;20(1):139.

Disclosure Statement: The authors declare no conflicts of interest.

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Capivasertib (AZD5363) Plus Fulvestrant Versus Placebo Plus Fulvestrant After Relapse or Progression on an Aromatase Inhibitor in Metastatic ER-Positive Breast Cancer (Faktion): a Randomized, Double-Blind, Placebo-Controlled, Phase II Trial

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Purpose: The PI3K/AKT signaling pathway is frequently activated in patients (pts) with estrogen receptor (ER) positive breast cancer (ER+BC) and has been implicated in endocrine therapy resistance. Capivasertib (Capi) is a highly-selective, oral, small molecule AKT inhibitor. The FAKTION trial investigated the addition of Capi to fulvestrant (Ful) for postmenopausal women with ER+ and HER2- BC after relapse or disease progression on an aromatase inhibitor (AI).
Methods: FAKTION is an investigator-led, double-blind, placebo-controlled, randomised phase II trial. Patients were recruited from 21 UK sites and randomly assigned (1:1) to Ful 500mg (day 1 and 15 of cycle 1 and day 1 only of subsequent 28 day cycles) with either Capi 400mg bd or placebo (4 days on/3 days off starting C1D15) until disease progression, unacceptable toxicity or withdrawal of consent. Allocation was balanced by minimisation according to PIK3CA mutation and PTEN expression status, measurable/non-measurable disease, and primary/secondary endocrine resistance. The primary endpoint was PFS. The trial had 90% power to detect a hazard ratio of 0.65 at the one-sided 20% significance level. Secondary endpoints included OS, ORR and clinical benefit rates, safety and the effect of PI3K/AKT pathway activation on PFS.
Results: Between Mar 2015 and Mar 2018, 140 pts were randomised to Ful + Capi (n = 69) or Ful + placebo (n = 71). In the ITT analysis, after 112 events, mPFS was 10.3 months (m) for Capi compared to 4.8m for placebo (HR 0.57; 95% CI: 0.39 to 0.84; one-sided p = 0.0017; two-sided 0.0035). Fifty-two deaths were reported. Median OS was 26.0m for Capi compared to 20.0m for placebo, with a survival difference starting to emerge after 12m (HR = 0.59; 95% CI: 0.34 to 1.05; two-sided p = 0.071).
Conclusions: The trial met its primary endpoint. Addition of Capi to Ful for patients with endocrine resistant advanced breast cancer resulted in significantly longer PFS and an improvement in OS. Results warrant further investigation of Capi for the treatment of ER positive breast cancer.

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Identification of a Novel Gene Disrupting Germline Mutation Derived from L1PA7 Transposition Into The BRCA2 Coding Sequence: Further Improvement of the Trurisk® Gene Panel Analysis

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Purpose: Although the sensitivity of molecular genetic diagnostics has been improved by next generation sequencing (NGS) applications, no causal mutations can be identified in many high-risk breast and ovarian cancer (BC/OC) families. One possible reason is the existence of yet unknown genetic risk factors; another explanation is the limitation of NGS analyses e.g. the identification of large insertions (Qian et al. Cancer Genet. 2017). By re-analyzing NGS data, we focused on identifying gene disruptions by large insertions of mobile genetic elements.
Methods: An in-house approach was employed to scan BWA (Burrows-Wheeler Aligner)-MEM (maximal exact matches) algorithm-produced read mappings of 4,218 BC/OC index patients for accumulations of break points in split-read alignments (Li 2013. arXiv:1303.3997). We performed long-range polymerase chain reaction (PCR) by using primers flanking the predicted insertion breakpoint c.3258_3259 in *BRCA2*, subsequent Sanger sequencing of gel-extracted PCR products, and sequence analysis of the insertion using RepeatMasker.
Results: We were able to identify a novel insertion c.3258_3259insL1 in *BRCA2* which is predicted to cause a frameshift and premature protein truncation p.(Ile1086Metfs*54) resulting in the loss of 2,280 amino acids. Therefore, loss of BRCA2 function is very likely and the variant can be classified as pathogenic (IARC class 5). The insertion derives from the transposition of ~400 bp of the 3´-end of human retrotransposon LINE-1 (L1Hs), also known as L1PA7, into the *BRCA2* coding sequence.
Conclusions: Re-analyzing NGS data from 4,218 BC/OC index cases, we identified the novel *BRCA2*-disrupting insertion c.3258_3259insL1 in a female patient with bilateral BC (age at first diagnosis 30 and 36 years). Although only identified once, this study underlines the need for continuous improvement of bioinformatic NGS data analysis. Detection of unusual pathogenic variants further improves the sensitivity of routine diagnostics in order to provide the best possible counselling and risk calculation to those seeking advice.

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Clinical Significance of PIK3CA and ESR1 Mutations in CTDNA and FFPE Samples from The Monarch2 Study of Abemaciclib Plus Fulvestrant

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Purpose: We assessed clinical significance of *PIK3CA* and *ESR1* mutations from patients treated with abemaciclib (A)+fulvestrant (F) and placebo (P)+F.
Methods: Baseline plasma samples (n=334) and FFPE tumor samples (n=434) from 669 MONARCH2 patients were analyzed. Extracted DNA

was analyzed by droplet digital PCR for 4 hotspot mutations of *PIK3CA* (E542K; E545K; H1047L; H1047R) and *ESR1* (D538G; Y537C; Y537N; Y537S). Samples failing DNA QC or with mutation status undetermined were excluded from analysis.
Results: *PIK3CA* mutations were detected in 40.3% of plasma and 39.9% of FFPE samples. H1047R was the most frequent mutation. Concordance of *PIK3CA* mutations in ctDNA and FFPE samples was 62.8%. *ESR1* mutations were detected in 64.4% of plasma and 4.4% of FFPE samples. D538G was the most frequent mutation. Concordance of *ESR1* mutations in ctDNA and FFPE samples was 37.1%; this is explained in part by the biopsy site (primary vs metastatic). Co-mutations in *PIK3CA* and *ESR1* were observed in 36.1% plasma and 1.5% FFPE samples. In *PIK3CA* wild-type (WT) median PFS was 20 mo for A+F and 12.7 mo for P+F (HR: 0.68; 95%CI: 0.42, 1.09); *PIK3CA* mutant (M): median PFS=15 mo for A+F and 5.7 mo for P+F (HR: 0.46; 95%CI: 0.27, 0.78); *ESR1* WT: median PFS=16.3 mo for A+F and 11.6 mo for P+F (HR: 0.69; 95%CI: 0.41, 1.18); *ESR1* M: median PFS=21.9 mo for A+F and 10.3 mo for P+F (HR: 0.49; 95%CI: 0.33, 0.73).
Conclusions: *PIK3CA* and *ESR1* mutations in ctDNA correlated with response to A. Addition of A to F improved PFS regardless of *PIK3CA*/*ESR1* status; however, magnitude of benefit was numerically greater when *PIK3CA*/*ESR1* mutations were present.

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A Phase 2 Study of Abemaciclib in Patients (PTS) with Brain Metastases (BM) Secondary to HR+, HER2- Metastatic Breast Cancer (MBC)

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Purpose: Clinical data demonstrate that abemaciclib penetrates blood-brain with comparable concentrations in tissues and plasma.
Methods: JPBO is a Simon 2-stage trial evaluating abemaciclib in 6 pt cohorts with BM secondary to HR+ MBC, non-small cell lung cancer, or melanoma. We report on HR+, HER2- MBC pts. Eligible pts had ≥1 new or not previously irradiated measurable BM ≥10mm or a progressive previously irradiated BM. Endocrine therapy (ET) was permitted to be continued provided that extracranial disease was stable ≥3 months and BM progression occurred on the ET. Abemaciclib was orally administered 200mg BID. Primary endpoint was objective intracranial response rate (OIRR; [complete response (CR)+partial response (PR)]) based on Neuro-Oncology BM response assessment criteria. Secondary endpoints were intracranial clinical benefit rate, progression-free survival (PFS), and safety.
Results: 58 pts were enrolled; 52 were evaluable. Pts had median of 4 prior systemic therapies, 75% had prior chemotherapy (0-6, median 2), 71% had prior ET (0-4, median 1) in the metastatic setting. 50% pts had prior whole-brain radiotherapy (RT), 39% stereotactic radiosurgery and 8% surgical BM resection. Median time from RT to study enrollment was 9.4 months. Out of 52 evaluable pts, 3 had a confirmed intracranial response (6% OIRR); 38% had a decrease in the sum of intracranial target lesions. Intracranial clinical benefit rate (CR+PR+stable disease persisting for ≥6 months) was 25%. Median PFS was 4.4 months (95%CI 2.6-5.5). Safety and tolerability were similar to previous reports for abemaciclib.
Conclusions: Abemaciclib demonstrated intracranial clinical benefit in the study pts. Further evaluations are ongoing to identify MBC pts with BM who might benefit most from abemaciclib.

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Breast Units – a Comparison of the Landscape in Germany and the United Kingdom

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Purpose: Survival rates of Breast Cancer patients still differ in European countries. Studies like the EUROCARE-5 study show a lower 5-year-survival-rate in Eastern Europe and the United Kingdom (UK)/Ireland compared to the European average and Germany. [1] Here we select key performance indicators (KPIs) with presumable impact on survival of Breast Cancer patients and compare certification/inspection systems in Germany and the UK. We focus on the systems of OnkoZert (Germany), the Care Quality Commission (CQC, England) and the European Society of Mastology (EUSOMA). Utilization of certification systems like OnkoZert and EUSOMA is voluntary, whereas the CQC keeps the care providers under obligatory surveillance.
Methods: KPI selection resulted from literature analysis and an expert survey. Experts were defined as people involved in Breast Cancer patient care (i.e. physicians, nurses and people working in quality management or certifying bodies). 78 experts were asked to fill in a short questionnaire. The rate of return was 68%.
Results: Selected KPIs assumed to have a positive impact on the survival rate of Breast Cancer patients were for example an early stage diagnosis, a short interval between diagnosis and start of therapy, early access to new therapies and a multidisciplinary collaboration of the treatment team. Many of the selected KPIs were integrated into the requirements of the analyzed certification/inspection systems. However, the level of detail and frequency of inspection differed markedly.
Conclusions: Harmonization of certification systems on a European level seems to be reasonable. More than 90% of the responding experts are convinced that certification of Breast Units has a positive impact on care and survival of Breast Cancer patients.

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Disclosure Statement: No disclosures.

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Routine Care Reality of Patients with Metastatic Anti-Human Epidermal Growth Factor Receptor 2 (HER2) Positive Breast Cancer Who Received Treatment in Oncology Group Practices in Germany Between 2012 and 2017

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Purpose: Many treatment options have become available since the discovery of an overexpression of HER2 in approximately 15–25% of all breast cancer patients. Real world data concerning treatment sequences and outcome from unselected patients who receive routine care are not known.
Methods: Retrospective analysis of all patients with metastatic HER2 positive breast cancer who were treated between 01/2012 and 12/2017 in five community-based oncology group practices in Germany. Data were

extracted from patient files into a database and analyzed statistically using SPSS.
Results: 146 female patients with a median age of 59.5 years (24–91) were analyzed. 35% were in stage IV at diagnosis, 75% were hormone receptor positive. Localizations of metastases were distributed as follows: 55% visceral, 17% bone, 5% CNS, 8% lymph nodes and 9% others. 1st line Anti HER2 therapy consisted of trastuzumab+pertuzumab in 54%, trastuzumab in 36%, lapatinib in 5% and trastuzumab emtansine in 4%. 2nd line treatment was trastuzumab+pertuzumab in 63%, trastuzumab in 23%, trastuzumab emtansine in 7%, lapatinib in 4% and trastuzumab+lapatinib in 2%. 3rd line therapy consisted of trastuzumab emtansine in 43%, trastuzumab in 28%, trastuzumab+pertuzumab in 23% and lapatinib in 8%. Median overall survival (OS) was 54 months (1.1-69.4). OS was significantly correlated with hormone receptor status. Patients with triple positive tumors had a median OS of 56 months (3.8-69.4) compared to 33 months (1.1-62.1) in HER2 only positive patients (p=.004). OS dependent strongly but not statistically significant on the number of metastasis localizations. Median OS of patients with 1 localization was 54.0 months (1.1-69.4) compared to 40.8 months (2.1-56.4+) in patients with two or more localizations.
Conclusions: OS improvements of patients with metastatic HER2 positive breast cancer are strongly restricted to hormone receptor positive tumors most likely due to improved targeted therapies directed against HER2 and the estrogen receptor.

Disclosure Statement: All authors report no conflicts of interest

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First Results of the Detect IVA Study –Everolimus Treatment in Patients with HER2-Negative, Hormone-Receptor Positive Metastatic Breast (MBC) Cancer and Circulating Tumor Cells (CTC)

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Purpose: The DETECT-IVa trial is a single-arm, open-label phase II study for postmenopausal patients with HER2-negative, hormone-receptor positive MBC and HER2-negative CTCs. One of the main aims is to evaluate the suitability of CTCs to provide both prognostic and predictive information.
Methods: The DETECT IVa trial started in February 2014 and comprises two subsequent patient cohorts – the first cohort received endocrine therapy combined with the mTOR inhibitor everolimus, while the second cohort of this ongoing trial receives endocrine therapy combined with the CDK 4/6 inhibitor ribociclib. We performed an unplanned interim analysis (data cutoff July 2019) to obtain preliminary, first results with regard to patient characteristics, presence of CTCs 3 to 12 weeks after study initiation and overall survival (OS) for the first (everolimus) cohort comprising 90 patients.
Results: Median age of the 90 patients of the everolimus cohort was 63 years (range 40 – 88 years). Median number of CTCs detected at baseline was 5.5 (range 1 – 400 CTCs). At the time of data cutoff, end of study treatment was documented for 71 patients. 7 out of 8 patients that received everolimus for the full study treatment period (12 months) had no CTCs after 3 to 12 weeks (no CTC data for one patient). 63 patients had to terminate everolimus treatment prematurely because of death (6.3%), progress (58.7%), patients wish (11.1%), non-hematological toxicity (20.6%) or treatment delays (3.2%). 23 (51.1%) out of 45 patients with premature termination of everolimus treatment and available CTC data showed presence of CTCs after 3 to 12 weeks. Median OS for 56 patients with data available was 18.9 months (95% confidence interval 11.8 – 26.0 months), and presence of CTCs after 3 to 12 weeks was significantly associated with poor OS (log rank test, p = 0.046).
Conclusions: Preliminary first results of the DETECT-IVa trial indicate that everolimus is still a valuable option for postmenopausal patients with HER2-negative, hormone-receptor positive MBC. CTC detection provides prognostic information also in this clinical context.

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A Real-World Evidence Study of CDK4/6 Inhibitor Treatment Patterns and Outcomes in Metastatic Breast Cancer by Gbrcamutation Status

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Purpose: Limited data exist on the real-world treatment patterns and effectiveness of cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors in the germline *BRCA* (g*BRCA*) mutated breast cancer population.
Methods: Adults with human epidermal growth factor receptor 2 negative (HER2-), hormone receptor positive (HR+) metastatic breast cancer (mBC) treated with a CDK4/6 inhibitor from 01Jan2013–31Jan2018 were retrospectively selected from the Flatiron Health Oncology electronic medical record database. Patients with known gBRCA status were classified as having gBRCA mutated (gBRCAm) or wild type (gBRCAwt) disease. Time to first subsequent therapy or death (TFST) and overall survival (OS) were calculated from start of the earliest line of therapy with a CDK4/6 inhibitor. Kaplan-Meier (KM) medians were estimated, and TFST and OS compared between gBRCA groups with Cox models stratified by line of therapy and adjusting for demographic and clinical characteristics that modified hazard ratios (HRs) for gBRCA status by > 10%.
Results: Of 2968 HER2- HR+ patients with mBC receiving a CDK4/6 inhibitor, gBRCA status was known for 859 (28.9%). Patients with gBRCAm and gBRCAwt received letrozole plus palbociclib (42.4 and 39.8%, respectively), fulvestrant plus palbociclib (32.9 and 30.7%), or other CDK4/6 regimens (24.7 and 29.5%) across all lines. The gBRCAm group had a non-significant, shorter TFST than gBRCAwt (stratified HR 1.24; 95% CI 0.96–1.59). OS was significantly shorter in gBRCAm than gBRCAwt patients (stratified HR 1.50; 95% CI 1.06–2.14).
Conclusions: The results of this real-world study suggest that treatment outcomes with CDK4/6 inhibitors may be poorer in patients with gBRCAm compared with gBRCAwt disease. These findings indicate a higher unmet need among patients with gBRCAm, potentially requiring alternative treatment options.

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Routine Care of Advanced Breast Cancer: The Prospective, National Research Platform Opal for Patients with Advanced Breast Cancer in Germany

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Purpose: The Tumor Registry Breast Cancer (TMK) has prospectively documented treatment and outcome of patients (pts) with breast cancer (BC) by oncologists in Germany since 2007. OPAL continues this successful work focusing on changes in treatment reality of advanced BC (ABC), patient-reported outcomes (PROs) and representation of all specialists (medical and gynecologic oncologists) treating ABC in Germany.
Methods: OPAL like the TMK is a prospective, observational, open, multicentre clinical registry. In addition to the 4500 pts from the TMK, at least 2000 pts will be recruited in OPAL, stratified into 3 cohorts: 1000 pts with hormone receptor positive, HER2-negative, 500 pts with HER2-positive and 500 pts with triple-negative ABC. In total, up to 200 sites (comprehensive cancer centres, clinics and office-based gynecologic and medical oncologists) will be participating. All pts are recruited at start of their first palliative systemic treatment to avoid overestimation of outcome data. OPAL collects detailed information on all (sequential) treatments, patient and tumor characteristics, physician-reported factors influencing treatment decision, biomarker testing and additional treatments. Follow-Up is until death or up to 5 years. Associated projects are a decentralized biobank and the collection of PROs in clinical routine (every 3 months for 3.5 years).
Results: By August 2019, a total of 5319 pts had been recruited, 677 since the start of OPAL in December 2017. 2348 pts with ABC recruited by 130 sites are now available for analyses of the combined TMK/OPAL database. First results from the interim analysis 2019 will be presented.
Conclusions: OPAL will show how the choice of treatment changes over time, which sequential treatments are applied and what the effectiveness and PROs are in a "real world" setting. It will reveal the impact of new treatments in pts in routine care and allow to identify areas for improvement of care.

Disclosure Statement: None of the authors declare conflicts of interests regarding the topic of this abstract.

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Skeletal-Related Events in Patients with Breast Cancer and Bone Metastases: Frequency, Predictors and Mortality in a Real-World Setting

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Purpose: Breast cancer is the most common cancer among women in Germany with more than 70,000 new cases per year. In contrast the mortality rate is much lower (20%). A large proportion of patients with advanced disease are affected by bone metastases, or BM, (80%) and skeletal-related events (SREs) resulting from BM. Moreover, observational studies of patients with prostate cancer and BM have shown an association between an increase of SREs and poorer survival. This study aims to investigate this association in breast cancer patients with BM in a real-world setting.
Methods: Data were obtained for analysis from the health claims InGef database and limited to female breast cancer patients with newly diagnosed BM between 2012 and 2015. Event rates (ER) for distinct SREs were calculated per 5 person-years (PY). In addition, using a time dependent multivariate cox regression, we first quantified the association between SREs and all-cause death and second, through an exploratory analysis, we evaluated the relation between use of bone-targeted agents (BTAs) and SREs.
Results: The study population comprised of 2,522 female breast cancer patients with a mean age of 65,8 years (SD +/- 13,0). ER per 5 PY varied in frequency starting from radiation to the bone (ER=1.72), surgery to the bone (ER=0.53) and pathologic fractures (ER=0.47) to spinal cord compression (ER=0.07). Significant associations ($p<0,05$) for a higher risk of all-cause death were identified for the SREs pathologic fractures (HR=2.41, 95% CI: 2.06-2.81) and radiation to the bone (HR=1.55, 95% CI: 1.39-1.74). Finally, an exploratory analysis revealed that patients treated with BTAs experienced a 42% reduction in the risk of developing SREs (HR=0.58, 95% CI: 0.47-0.71).
Conclusions: Our study shows that pathologic fractures and radiation to the bone are common SREs in advanced breast cancer patients, both leading to a higher risk of earlier death in this population. Treatment with BTAs reduce the risk of developing SREs and therefore may lead to longer survival in these patients.

Conflicts of Interest:

This study was sponsored by Amgen GmbH which provided funding to WIG2 GmbH for the execution of the study and medical writing support. InGef – Institute for Applied Health Research Berlin GmbH acted as subcontractor and received funding from WIG2 GmbH for the execution of the study and medical writing support.
Ingo Diel has received consulting fees for participation in advisory boards and has given several presentations at speakers' bureaus for Amgen.
Eugen Dornstauder is an Amgen employee and holds Amgen stock.
Robert Bartsch is an Amgen employee and holds Amgen stock.
Michael Kellner is an Amgen employee and holds Amgen stock.
Lennart Hickstein is an employee of InGef – Institute for Applied Health Research Berlin GmbH and received funding from WIG2 GmbH for the execution of the study and medical writing support
Josephine Jacob is an employee of InGef – Institute for Applied Health Research Berlin GmbH and received funding from WIG2 GmbH for the execution of the study and medical writing support.
David Hohmann was an Amgen employee during conduction of the analysis.

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Male and Female Breast Cancer: a Comparison of a 15-Year Population-Based Cohort

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Purpose: The aim was to compare prognostic factors, treatment, and outcome of male and female breast cancer patients.
Methods: A total of 467 men and 58,484 women diagnosed with breast cancer between 2002 and 2016 in the catchment area of the Munich Cancer Registry (MCR) were included in this analysis. A descriptive analysis of prognostic factors and treatment, a comparison of outcome using the Kaplan-Meier method, cumulative incidence (CI) in consideration of competing risks and multivariate Cox regression analysis were conducted.
Results: At the time of diagnosis affected men were about 5 years older than women (mean age 68 vs. 63 years). The proportion of T3/4- tumors (16% vs.11%), positive lymph nodes (45% vs. 36%), and primary metastases (9% vs. 7%) was higher in men. Biologically, 99% of male tumors were endocrine sensitive (vs. 87%) and 6% were HER2/neu positive (vs. 15%). Men underwent more mastectomies (90% vs. 27%) and less radiotherapy (44% vs. 71%). Frequencies of axillary surgery, chemotherapy, and endocrine therapy were not statistically different.
The time to local recurrence (TTL) was also similar in both groups. The CI in time to metastasis (TTM) was higher in men (12% vs. 8% after 5 years), however this difference was not statistically significant. Respective multivariate cox-regression analysis also showed no significant gender differences.
Survival improved slightly between 2002-2008 and 2009-2016, but only in female patients. Survival was lower in men than in women, and this difference was greater for overall survival (OS) than for relative survival (RS) (10-year-OS: 56% vs. 70%; 10-year-RS: 78% vs. 81%). After adjusting for prognostic factors, the univariate hazard ratio declined from 1.8 (95%-CI 1.5-2.1) to 1.3 (1.1-1.5).
Conclusions: Probably, delayed diagnosis of breast cancer in male patients lead to a more advanced tumor stage. After adjusting for prognostic factors, TTM was similar, whereas a statistically significant difference in OS remained. Whether this finding is attributable to differences in health/lifestyle/other factors remains to be seen.

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When Breast Cancer Wants to Spread, Suppress CYR61/CCN1

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Purpose: Matricellular proteins modulate tumor micro environment and are recognized to contribute to tumor cell invasion and dissemination. CYR61, member of the CCN family of matricellular proteins, is upregulated in mesenchymal transformed and invasive breast cancer cells and correlates with poor prognosis of breast cancer patients. Yet the signaling whereby cancer cells gain invasive properties with regards to the epithelial-mesenchymal transition (EMT) needs further research.
Methods: Mesenchymal transformed breast cancer cell lines were generated using prolonged mammosphere cultivation. Microarray analysis, quantitative PCR and immune/histochemical approches were used to analyze gene expression alterations upon CYR61 expression regulation in 4 highly invasive breast cancer cell lines. Transient gene silencing was conducted using RNA interference. Proliferation was assessed using AlamarBlue Assay. To examine the prognostic value of CYR61 and S100A4 expression in 239 patient samples immune-histochemical analysis were performed.
Results: We investigated the use of CYR61 as a therapeutic target and prognostic marker for invasive breast cancer and metastasis. Our data indicates that CYR61 regulates metastasis-associated protein S100A4. Suppression of CYR61 reduces the expression of S100A4 through changes in ERK1/2 activation. Treatment with extracellular CYR61 increased tumor cell invasion of non-invasive breast cancer cells. Immune-histochemical analysis of 239 patient tissue samples revealed that higher CYR61 and S100A4 expression correlates with invasive breast cancer and metastasis.
Conclusions: Our data suggest that CYR61 regulates cancer cell invasion in highly invasive and aggressive breast cancer cells by altering S100A4 expression. These findings identify mechanism by which CYR61 suppresses cell invasion and suggest it to be a potential therapeutic target and prognostic marker for invasive breast cancer and metastasis.

Disclosure Statement: The authors declare no disclosures.

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Palbociclib Plus Fulvestrant as First-Line Therapy for Patients with Locally Advanced, Inoperable or Metastatic HR+/HER2- Breast Cancer in Germany: Interim Results of the Inge-B Phase 2 Study

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Purpose: In the PALOMA-3 trial, palbociclib plus fulvestrant demonstrated a clinically meaningful improvement in overall survival compared with fulvestrant plus placebo in patients (pts) with hormone receptor-positive (HR+), HER2-negative (HER2-) metastatic breast cancer who had relapsed or progressed on prior endocrine therapy (Turner NC et al., NEJM 2018). Detailed analyses for first-line (1L) and later- line (2L+) therapy are still limited.
Methods: The prospective, multicenter phase 2 INGE-B trial was designed to generate efficacy and safety data on the combination of palbociclib with aromatase inhibitors or fulvestrant (1L, 2L+). This pre-planned interim analysis was conducted to evaluate data on pts receiving palbociclib plus fulvestrant as 1L or 2L+ therapy. The primary objective was the clinical benefit rate (CBR) in pts with measurable disease according to RECIST

v1.1. Key secondary endpoints included the overall response rate (ORR), the CBR for all pts, and safety. Data were analyzed with descriptive statistics.
Results: At the cut-off date of the interim analysis (Dec 17, 2018), 124 pts have been recruited to receive palbociclib plus fulvestrant (1L: 57 pts; 2L+: 67 pts). Of those, 54 pts treated in 1L were evaluable. Median age was 69.5 years, 96.3% of pts had an ECOG performance score of 0 or 1. 31.5% (n=17) of pts had non-measurable bone-only disease. The CBR was 58% (n=21) for the 36 pts with measurable disease (RECIST v1.1) and 65% (n=35) for all pts (investigator assessment). Grade 3/4 adverse events experienced by at least 10% of pts were neutropenia (n=17, 31.5%) and leukopenia (n=8, 14.9%).
Conclusions: This INGE-B interim analysis showed for the first time a remarkable clinical benefit for palbociclib plus fulvestrant as first-line therapy for pts with HR+/HER2- advanced breast cancer. No new safety signals emerged.

Reference:
1. Welt A et al., Annals of Oncology (2019) 30 (suppl_3)

Disclosure Statement: AW, Advisory Boards: AstraZeneca, Novartis, Roche, Eisai, Pfizer, Amgen, Lilly; Fees: COCS GmbH, iOMEDICO AG, Interplan AG; Funding of scientific programs: Novartis. DL, Member of Advisory Board with Amgen, Novartis, Eli Lilly, Pfizer, Celgene and Astra Zeneca; Corporate-sponsored research by Novartis. MW, Advisory board or board of directors: Amgen, Bristol-Myers Squibb, Celgene, GILEAD, HEXAL, Janssen, Lilly, medac, NOVARTIS, Roche, SANOFI; Corporate-sponsored research with AMGEN, Astellas, Astra Zeneca, Celgene, GILEAD, HEXAL, Janssen, Lilly, NOVARTIS, Roche. NM, Employment or Leadership Position: iOMEDICO, Stockholder Ownership: iOMEDICO, Financing of Scientific Research: Pfizer

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Palbociclib Plus Fulvestrant as Second- or Later-Line Therapy for Patients with Locally Advanced, Inoperable or Metastatic HR+/HER2- Breast Cancer in Germany: Interim Results of the Inge-B Phase 2 Study

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Purpose: In the PALOMA-3 trial, palbociclib plus fulvestrant demonstrated a clinically meaningful improvement in overall survival compared with fulvestrant plus placebo in patients (pts) with hormone receptor-positive (HR+), HER2-negative (HER2-) metastatic breast cancer who had relapsed or progressed on prior endocrine therapy (Turner NC et al., NEJM 2018). Detailed analyses for first-line (1L) and second- or later- line (2L+) therapy are still limited.
Methods: The prospective, multicenter phase 2 INGE-B trial was designed to generate efficacy and safety data on the combination of palbociclib with aromatase inhibitors or fulvestrant (1L, 2L+). This pre-planned interim analysis was conducted to evaluate data on pts receiving palbociclib plus fulvestrant as 1L or 2L+ therapy. The primary endpoint was the clinical benefit rate (CBR) in pts with measurable disease according to RECIST v1.1. Key secondary endpoints included the overall response rate (ORR), the CBR for all pts, and safety. Data were analyzed with descriptive statistics.
Results: At the cut-off date of the interim analysis (Dec 17, 2018), 124 pts have been recruited to receive palbociclib plus fulvestrant (1L: 57 pts; 2L+: 67 pts). 57 of 67 pts treated in 2L+ were evaluable. Median age was 68.0 years, 91.2% (n=52) of pts had an ECOG performance score of 0 or 1. 28.1% (n=16) of pts had non-measurable bone-only disease. The CBR was 35% (n=14) for the 40 pts with measurable disease (RECIST v1.1) and 51% (n=29) for all pts (investigator assessment). Grade 3/4 adverse events experienced by at least 10% of pts were neutropenia (n=21, 36.8%) and leukopenia (n=7, 12.3%).
Conclusions: This INGE-B interim analysis showed a remarkable clinical benefit for palbociclib plus fulvestrant as second- or later-line therapy for pts with HR+/HER2- advanced breast cancer. No new safety signals were detected.

Reference:
1. Lüftner D et al., ESMO 2019, #1423

Disclosure Statement: DL, Advisory board or board of directors: Amgen, Eli Lilly, Celgene, Novartis, Pfizer, Teva, Tesaro, Loreal, MSD, Astra Zeneca; Corporate-sponsored research with Amgen, Novartis; MW, Advisory board or board of directors: Amgen, Bristol-Myers Squibb, Celgene, GILEAD, HEXAL, Janssen, Lilly, medac, NOVARTIS, Roche, SANOFI; Corporate-sponsored research with AMGEN, Astellas, Astra Zeneca, Celgene, GILEAD, HEXAL, Janssen, Lilly, NOVARTIS, Roche, SANOFI; AW, Advisory board or board of directors: Roche, Novartis, AstraZeneca, Lilly, Eisai, Pfizer, Amgen; Corporate-sponsored research: Novartis (scientific grant);NM, Employment or Leadership Position: iOMEDICO, Stockholder Ownership: iOMEDICO, Financing of Scientific Research: Pfizer

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Long-Term Adjuvant Therapies for Breast Cancer are Over-Treatments

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Purpose: Breast cancer guidelines recommend adjuvant endocrine therapies (EAT) for 10 years because randomized trials with tamoxifen improved survival by 2.8% after 15 years. However, there is no convincing reason for a long duration of treatment.
Methods: These findings are based on known facts and studies on incidence, growth and diagnosis of primary breast cancer (PT) and its metastases (MET). Many studies have shown the effect of neoadjuvant and adjuvant therapies on manifest and occult PTs and their METs. When these therapies are shortened, prolonged, delayed or interrupted inconsistencies between effects, duration of treatment and treatment windows arise.
Results: The survival benefit of EATs is real, but EATs are not evidence-based. Extensions after 1, 2 or 5 years have no effect on survival for 5 years each, although 49%, 42% or 28% of all METs occur at these intervals. If therapies are delayed by months or years, the effects are comparable to those of primary treatment without delay, but all METs expected without therapy appear in the delay phase. The 2.8% effect is achieved by "chemoprevention", the neoadjuvant treatment of ipsilateral and contralateral occult second malignancies, which eradicate 50% and with them about 25% of their expected METs. The effect size is determined by the higher risk of secondary breast cancers. But for the duration of the prevention of 5 years, there are no convincing explanations. Due to the slow growth of the PTs and the large treatment window, in which newly emerging up to almost detectable PTs are rapidly eradicated, these EATs can be interrupted without disadvantage and the therapy can be significantly de-escalated.
Conclusions: From known facts can be deduced: Intermittent therapies can reduce long-term therapies by 70-80% with equal effect. Less side effects with a higher quality of life and better survival rates through higher compliance would be a therapy innovation for almost one million breast cancer patients in Germany alone. The challenge for optimal duration is: how short is short enough.

Disclosure Statement: No conflict of interest.

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Circulating Non-Coding RNA – Biomarker Potential in Neoadjuvant Chemotherapy of Triple Negative Breast Cancer?

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Purpose: Early response to neoadjuvant chemotherapy (NACT) is highly associated with beneficial outcome in breast cancer (BC) patients especially in triple negative (TNBC) and Her2 enriched molecular subtypes. Non-coding RNAs (ncRNAs) such as microRNAs (miR) are involved in carcinogenesis and cell proliferative processes where they can act either as tumor suppressors or as oncogenes. Liquid biopsy-based ncRNA biomarkers might represent valuable innovative tools in the prediction of NACT response of TNBC patients improving patients' outcome.
Methods: One triple positive (BT-474) and three triple negative (BT-20, HS-578T, MDA-MB-231) breast cancer cell lines were treated with cytostatic drugs (carboplatin, epirubicin, gemcitabine and paclitaxel). Intra- and extracellular evaluation of 12 microRNAs, 1 piRNA and 1 tRNA expression profiles were performed by extracellular vesicular RNA-isolation and subsequent qRT-PCR. Relative quantification was performed according to Busk et al. 2014. Eight TNBC patients as well as ten healthy women provided serum and urine specimen. ncRNA expression level comparison was performed applying two-sample t-test. Preliminary, samples of TNBC patients were compared at two time points.
Results: Distinct ncRNA expression alterations in (TN)BC cell lines in both the intra- and extracellular compartment were observed after chemotherapeutic treatment. Serum and urine-based ncRNA expression identified as applicable tool to discriminate TNBC vs. controls. Time point comparison of TNBC urine samples revealed a general ncRNA rise. Serum data identified diversely, implying a potential correlation with an NACT-driven clinical complete response.
Conclusions: This study provides new insights into the involvement of a BC-related ncRNA panel in the response of TNBC to NACT both in vitro and in vivo. On the one hand, distinct ncRNA expression profiles could help to improve TNBC diagnosis. On the other hand, monitoring of serum or urine ncRNA levels mightt contribute to TNBC therapy response management with the goal of improving patients` outcome.

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Monarch 2: Interim Overall Survival of Abemaciclib Plus Fulvestrant in Patients with HR+, HER2-Advanced Breast Cancer

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Purpose: In MONARCH 2, abemaciclib+fulvestrant significantly improved progression-free survival (PFS) vs placebo+fulvestrant (median: 16.4 vs 9.3 months, HR: 0.553) with a tolerable safety profile.
Methods: MONARCH 2 was a global, randomized, double-blind phase3 trial of abemaciclib+fulvestrant (N=446) or placebo+fulvestrant (N=223) in women with advanced endocrine therapy (ET)-resistant hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC). ET resistance was defined as progression on (neo)adjuvant ET, or ≤12 months from end of adjuvant ET, or on first-line ET for metastatic BC. Patients with measurable disease (per RECIST v1.1) or nonmeasurable bone-only disease and any menopausal status were included (pre- or perimenopausal women also received a gonadotropin-releasing hormone agonist). Prior chemotherapy was permitted only in (neo)adjuvant setting. 669 patients were randomized 2:1, stratified based on nature of disease (visceral, bone-only, or other metastases) and resistance to prior ET (primary vs secondary). Abemaciclib or placebo 150mg was dosed Q12H, and fulvestrant 500mg was administered per label. The primary objective was investigator-assessed PFS. OS is an important secondary endpoint. The family-wise type I error is controlled at 0.025 (1-sided), with a gate-keeping strategy between PFS and OS. For OS, an α-spending function will be used to account for interim and final analyses. OS will be compared using a 1-sided stratified log rank test.
Results: The preplanned interim OS analysis at approximately 331 events will be conducted and presented at the meeting.
Conclusions: Following the preplanned interim OS analysis, the associated conclusions will be presented at the meeting.

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Monarcher: A Randomized Phase 2 Study of Abemaciclib Plus Trastuzumab with or without Fulvestrant Versus Trastuzumab Plus Standard-of-Care Chemotherapy in Women with HR+, HER2+ Advanced Breast Cancer

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Purpose: Abemaciclib showed efficacy and tolerability in patients (pts) with HR+, HER2- advanced breast cancer (ABC). In preclinical models, inhibition of CDK4 by abemaciclib enhanced the activity of HER2-directed agents and re-sensitized resistant tumors to HER2 blockade, suggesting a crosstalk between HER2 signaling and the cyclin D1/CDK4 signaling pathways in HER2+ BC.We report the effect of abemaciclib in pts with HR+, HER2+ ABC.
Methods: monarcHER is a Phase 2 study comparing the efficacy of abemaciclib (150mg PO Q12H on Days 1-21 of a 21-day cycle)+trastuzumab (IV infusion on Day 1 of 21-day cycle) with fulvestrant (F; 500mg IM on Cycle 1 D1 and D15 and Cycle 2 D8, then Q4W; Arm A) or without F (Arm B) vs trastuzumab+standard-of-care chemotherapy (per label on 21-day cycle; Arm C) in pts with HR+, HER2+ ABC. Eligible pts were postmenopausal women with ≥2 HER2-directed therapies for advanced disease and received prior T-DM1 and taxane in any disease setting, had ECOG PS ≤1, and LVEF ≥50%. 237 pts were randomized 1:1:1 and stratified based on the number of prior systemic regimens (excluding single-agent ET) for ABC (2 to 3 vs 3+) and nature of the disease (measurable vs nonmeasurable). Primary objective was to compare the PFS of Arm A and B to Arm C. Secondary objectives included OS, response evaluation, safety, efficacy, and pharmacokinetics. The primary analysis was planned at ~165 PFS events, providing 80% statistical power to detect superiority of Arm A over Arm C, assuming a HR of .667 at 1-sided α=.1.
Results: The monarcHER study was conducted in 14 countries. The last patient entered treatment on February 28, 2018. The data from the primary analysis for efficacy and safety will be available mid-May 2019.
Conclusions: The conclusion for PFS, objective response rate (complete response [CR]+partial response [PR]), disease control rate (CR+PR+stable disease [SD]), clinical benefit rate (CR+PR+SD ≥6 months) and safety data will be presented at the meeting.

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Secretome Analysis Reveals Driver for Bone-Directed Breast Cancer Invasion

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Purpose: The tumour metastatic cascade is highly regulated by the micro environmental changes. Drugs are needed to modify the breast micro environment, where tumour cells gain the ability to disseminate. Here we suggest potential drivers of initial dissemination of tumour cells with regards to bone-directed metastasis. While an increased CTGF expression in human breast cancer correlates with poor patient outcome and drug resistance (1), a major questions has remained: Will targeting CTGF help to prevent breast cancer cell dissemination into the surrounding tissue? And which underlying molecular mechanisms are involved in breast cancer directed bone metastasis?
Methods: Here, we apply secretome analysis, proteome analysis and microarray data to elucidate drivers of epithelial-mesenchymal transition and cell invasion. Gene ontolgy enrichment analysis led us to the prominent regulated pathways. To examine in vitro invasive properties we assessed 2D invasion in a modified boyden chamber, 3D spheroid invasion, cell-ECM adhesion and ECM degradation.
Results: CTGF is highly upregulated when MCF-7 non-invasive breast cancer cells are co-cultured with osteosarcoma cells and gain invasive properties. Suppression of CTGF reduced invasion and expression of EMT-related genes. GnRH agonist Triptorelin reduces CTGF expression in a RhoA -dependent manner.
Conclusions: Our data indicate a mechanism by which extracellular CTGF drives cell dissemination by regulating cell adhesion, ECM degradation and regulation of EMT inducing factor TGFBI. Moreover it was assessed that CTGF expression is regulated by RhoA activity. The performed experiments support the value of CTGF as therapeutic target for invasive breast cancer, and GnRH agonist Triptorelin treatment could be of value in clinical applications.

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Disclosure Statement: The authors declare no disclosures.

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Micrometastases in Axillary Lymph Nodes and Outcome of Breast Cancer

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Purpose: The axillary lymph node status is one of the most important prognostic factors in patients with primary breast cancer. Micrometastases (pN1mi) are defined as nodal metastases with deposits from >0.2 ≤ 2mm. Their impact on overall survival (OS) and recurrence-free survival (RFS) of patients with breast cancer remains unclear. There are no recommendations concerning the performance of adjuvant chemotherapy. Thus, the aim of this study was to analyze the effect of micrometastases on the clinical outcome of patients with breast cancer according to their adjuvant chemotherapy status.
Methods: We performed a retrospective registry-based study. 26353 patients were investigated and 14070 were excluded and 12283 were eligible for analysis: 11743 were identified as pN0 and 540 as pN1mi.
Results: Micrometastases in regional lymph nodes were associated with a reduced 10-year rate of OS and RFS among women with early-stage breast cancer, who did not receive systemic adjuvant chemotherapy. The effect however, was not confirmed in the multivariate analysis after adjustment for age, tumor size, grading (etc.). Furthermore, in the group of patients with micrometastases systemic treatment improved neither the OS (hazard ratio (HR) 1.51, 95% confidence interval (CI) 0.80-2.85) (p=0.208) nor the RFS (HR 1.12, 95%CI 0.63-1.97) (p=0.705) as demonstrated by multivariate cox-regression analysis.
Conclusions: Chemotherapy did not improve significantly the outcome of breast cancer patients with nodal micrometastases. In this regard, nodal micrometastases should not be considered in our treatment decision.

Reference:
1. De Bowe et al.: Micrometastases or Isolated Tumor Cells and the Outcome of Breast Cancer. NEJM. August 13, 2009.

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Evidence-Based Decision Support System for Breast Cancer

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Purpose: In order to increase the patients' ability to make their own informed decisions about their breast cancer therapy and to support patient empowerment in general, it is necessary to provide decision-relevant information in an understandable mode. This aim will be targeted by generating computer-based systems which provide the relevant information resulting in guideline-based decisions.
Methods: By using the evidence-based guidelines for the treatment of breast cancer[1,2] a web-based decision support platform for patients and health care professionals is being created. The design and content will be kept up-to-date by involving the target groups in the development.
Results: Two prototypes for an evidence-based decision support platform were created to test if it was possible to translate the medical guidelines to a digital rule-based system, which is able to create relevant suggestions based on the information given by a patient. Those prototypes were evaluated by a patient and a health care professional and will be continuously improved and tested.
Conclusions: The first evaluations proofed that there is a need for patient information systems, especially for diseases with a high risk for complications and a wide field of treatment options. In order to improve the quality of shared decision making and thus increase the patients' compliance with selected treatment choices, these systems could support the patients by increasing this decease-related knowledge. The continuous development and evaluation of evidence-based decision support systems for breast cancer patients and for other malignant or chronic diseases is one of our major goals.

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Disclosure Statement: The author declares that he has no relevant or material financial interests that relate to the research described in this paper

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Panel-Guided Personalized Medicine in Metastatic Breast and Gynecological Cancer, First Experiences at te CCC Munich LMU

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Purpose: Some tumorigenic alterations associated with cancer cell development and progression can be therapeutically addressed by molecularly targeted agents. Comprehensive genomic profiling identifying such actionable alterations aims to offer personalized treatment to cancer patients. Here, we report first experiences of the Comprehensive Cancer Center Munich Molecular Tumor Board (MTB) in breast and gynecologic malignancies. Our aim was to measure the impact of recommendations made by a multidisciplinary tumor board on the overall survival of patients with gynecologic cancers, that progressed under standard treatment.
Methods: 99 patients diagnosed with metastatic breast or gynecologic malignancies underwent molecular diagnostic test (panel). From May 2017 through March 2019, our MTB reviewed the clinical cases carefully considering tumor profile and discovered genetic aberrations and provided further diagnostic and therapy recommendations. All patients were part of a prospective registry (Der informative Patient).
Results: 95 patients with metastatic gynecologic tumors were discussed in the MTB (68% breast cancers, 20% ovarian cancer, 5% cervical cancer, 3% endometrial cancer and 4% others). The genes with the highest mutation rate were PI3KCA, KRAS, FGFR1 and CCND1. Overall, 34 patients (36%) received an alteration-specific targeted therapy recommendation. Recommended therapies included various drugs such as protein-kinase inhibitors (45%), combination therapies (24%) and clinical trials (20%). Therapeutic recommendations were implemented in 9 cases; 4 patients experienced a clinical benefit with a partial response or stabilization lasting over 4 months, including 3 of them receiving off-label treatment.
Conclusions: In the setting of a multidisciplinary molecular tumor board, a small but clinically meaningful group of breast and gynecologic cancer patients derives benefit from comprehensive genomic profiling. Main problems of precision cancer medicine include patients' referral at late stage disease and limited access to targeted agents.

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Recommendation of Trastuzumab Therapy for Patients with Non-Metastatic, HER2/NEU-Positive Breast Cancer: Results from 3,052 Patients Treated in Certified German Breast Cancer Centres

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Purpose: Since 2006 it is possible to treat non-metastatic, Her2/neu-positive breast cancer (BC) patients with Trastuzumab in Germany which is now a highly accepted therapy strategy. Even if the treatment of Her2/neu-positive BC patients with Trastuzumab is part of the quality indicator 9 of the evidence-based German Guideline for Breast Cancer (S3), recent studies highlight that there are some Her2/neu-positive BC patients for whom physicians do not recommend a Trastuzumab therapy (TT). We investigate for which patients a TT is recommended in Breast Cancer Centers (BCC) certified by the German Cancer Society and the German Society for Senology.
Methods: We included Her2/neu-positive, non-metastatic BC patients (≥ pT1c) treated in German BCCs by surgery between 2006 and 2019. For 3,052 patients, data collected for the certification progress including more than 150 attributes specifying clinical and treatment characteristics for each patient were available. A multi-level analysis including these 3,052 patients nested in 17 BCCs was performed.
Results: Recommendation of TT does not differ much between BCCs (ICC null model: 0.14). Our analysis show that physicians in BCCs more often recommend TT to patients who are younger than 69 years and who had another oncological disease before. Patients with a recommendation for any additional therapy (chemo-/endocrine therapy, radiation) to surgery receive more likely a recommendation for TT as well (all $p < 0.05$), if controlled for T- and N-stage, sex and estrogen- and progesterone-receptor status. Furthermore, there is a significant increase in recommendation of TT over the years (frequency of recommendation of TT for patients treated between 2006 and 2011: 43.4% vs. patients treated between 2012 and 2019: 78.7%).

Conclusions: In certified German BCCs, the knowledge and acceptance of guideline-adherent TT is increasing (positive cohort effect). Recommendation of TT for Her2/neu-positive BC patients in BCCs are significantly associated to age and the recommendations for other additional therapies apart from surgery.

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Age-Related Differences in Overall and Metastases-Free Survival after Guideline Concordant Chemotherapy in Patients with Hormone Receptor Positive and Nodal Positive, Early Breast Cancer

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Purpose: The German guideline for breast cancer recommends using chemotherapy (CHT) in patients with hormone receptor positive and nodal positive, invasive breast cancer. The aim of this study was to analyse the effects of CHT in this patient group on overall survival (OS) and distant metastases-free survival (DMFS), especially considering the 70-year threshold.
Methods: 1772 patients from the clinical cancer registry Regensburg (Germany) with hormone receptor positive and nodal positive, invasive breast cancer diagnosed between 2003 and 2013 were analysed in a retrospective cohort study. OS and DMFS were evaluated by means of Kaplan-Meier and multivariable Cox-regression method. Results were further examined according to age at diagnosis.
Results: The comparison of 1544 patients with CHT to 228 patients without CHT showed a significant benefit for CHT regarding 5-years OS (91.3% vs. 76.8%) and 5-years DMFS (86.7% vs. 74.4%, both p<0.001). Likewise, better OS and DMFS were seen in patients ages <70 years using CHT compared to patients without CHT of the same age. Patients ages >=70 years with CHT had a minimal benefit regarding 5-years OS compared to patients without CHT, but no advantage considering DMFS. All results were confirmed in multivariable analyses except for patients being >=70 years of age.
Conclusions: Patients with hormone receptor positive and nodal positive, invasive breast cancer benefit from chemotherapy with regard to a significantly better overall and distant metastases-free survival, although chemotherapy use in patients ages >=70 years results in a smaller benefit considering OS and no benefit considering DMFS.

Disclosure Statement: The authors declare no conflict of interest.

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Abus as an Alternative to Hand Held Ultrasound for Response Control in Neoadjuvant Breast Cancer Treatment

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Purpose: The "Invenia Automated Breast Ultrasound Screening" (ABUS) for automatic ultrasound examination is indicated as an adjunct to mammography for breast cancer screening in asymptomatic women (approved by the FDA), for whom screening mammography findings are normal or benign but have a high density of breast tissue. ABUS provides efficient exam reading and analysis within 3 to 6 minutes on the work station (1).
The aim of this study is to evaluate the use of ABUS in patients who are under neoadjuvant chemotherapy treatment for response control.
Methods: We conducted regular sonographic response check and ABUS examination in 20 women who were under neoadjuvant chemotherapy treatment. The hand-held sonography was performed with GE Voluson S8. The tumor was measured in 3 dimensions. The last sonographic check took place within the last 4 weeks before the end of chemotherapy. We compared the hand held sonographic measurement and the ABUS measurement with the size of the pathologic tumor.
Results: We found that there was no significant difference between tumor measurements with hand held ultrasound or ABUS ultrasound in neoadjuvant response control.
The average difference from hand held sonographic ultrasound size to final pathological tumor size was 9,2 mm. The average difference from ABUS ultrasound size to final pathological tumor size was 8,6 mm (p=0,3). The median difference between ABUS and hand held ultrasound tumor size was 4,8mm.
Conclusions: ABUS seems to be a suitable method to conduct response control in neoadjuvant breast cancer treatment. ABUS offers remarkable time saving for physicians compared to handheld ultrasound and thus should be considered for clinical practice.

Reference:
1. https://www.ge-ultraschall.com/invenia-abus/

Disclosure Statement: n/a.

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WNT Signaling-Mediated Inhibition of Aromatase Expression – A Possible Endocrine Model for Triple Negative Breast Cancers

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Purpose: Local biosynthesis by aromatase in breast adipose fibroblasts (BAFs) is the most important source for estrogens in estrogen-receptor positive breast cancers (BC). Triple-negative BC depend on other growth-promoting signals, e.g. Wnt-signaling. In this study, we investigated the hypothesis that WNT3a expression in triple-negative BC suppresses aromatase expression in BAFs.
Methods: Effects of WNT3a and BC cell-conditioned medium (CM) on BAFs were investigated by cell-proliferation tests, tritium water release and qRT-PCR assays for aromatase activity and gene expression, respectively. Protein expression was analyzed by western blotting. A combination of reporter gene assays, site-directed mutagenesis, protein overexpression and chromatin immunoprecipitation (ChIP) was used for analysis of transcription factor-binding to different binding-sites.
Results: WNT3a and CM of triple-negative breast cancer cells (e.g. MDA-MB231) increased cell growth and suppressed aromatase activity and promoter I.3/II-driven gene-expression up to 90%. Three putative Wnt-responsive elements (WREs) in the aromatase promoter were found. Promoter activity was inhibited by overexpression of full-length T-cell factor (TCF)-4 in 3T3-L1 preadipocytes in reporter gene assays. Full-length lymphoid enhancer-binding factor (LEF)-1 increased activity. However, WNT3a-stimulation resulted in a loss of TCF-4-binding to WRE1 and induced a switch of nuclear LEF-1 isoforms to a truncated variant. Overexpression of truncated LEF-1 inhibited promoter I.3/II-activity. ChIP revealed a WNT3a-induced replacement of TCF-4 by a LEF-1-variant on WRE1 of the aromatase promoter I.3/II in BAFs. Switching of LEF-1 isoforms may involve canonical Wnt-signaling.
Conclusions: The mechanism described here may contribute to the loss of estrogen responsibility in the etiology of triple-negative breast cancers. Strong Wnt-ligand expression by tumors could suppress aromatase expression in surrounding BAFs.

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Impact of Cytotoxic Treatment on PD-L1 Expression in Human Breast Cancer Cell Lines

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Purpose: The oncologic spectrum for the clinical application of checkpoint inhibitors (CI) expands rapidly. Clinical trials with CI in breast cancer (BC) report an overall response rate of up to 19% with durable clinical responses and tolerable safety profiles. Improved understanding of the immunogenicity of BC under simultaneously applied therapies, e.g., cytotoxic treatments, would help to develop more individual therapeutic strategies to further increase response rates.
Methods: We investigated the expression of PD-L1 on different types (triple negative, luminal-type and HER2-positive) of human BC cell lines and evaluated the effect of standard chemotherapeutical agents (epirubicin and paclitaxel) on PD-L1 expression in selected cell lines.
Results: We found greatly varying levels of PD-L1 expression within the investigated BC cell lines. High PD-L1 expression was found in all three TNBC- and two of three HER2-overexpressing cell lines. Luminal like tumors seem to express low PD-L1 levels, without great variations. Epirubicin treatment caused a decrease and paclitaxel treatment an increase in PD-L1 expression in the TNBC MDA-MB-231 cells. In contrast, PD-L1 expression changed to a minor extent in the HER2-overexpressing SK-BR-3 cell line when exposed to cytotoxic treatments.
Conclusions: The degree of PD-L1 expression among breast cancer cell lines varies considerably. Our analyses revealed different cell type specific responses to cytotoxic treatments. Furthermore, diverse chemotherapeutic agents engender dissimilar PD-L1 expression changes within the same cell line, which likely contribute to the varying clinical responses to CI. Further studies are needed to identify the major mechanisms determining the immunogenic alterations of BC under chemotherapy.

Disclosure Statement: no conflict of interest

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Prevalence of Critical Values of the Functional and Mental Status of Breast Cancer Patients Before the Onset of Cancer Therapy

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Purpose: A reduced functional and mental status even before the cancer therapy may indicate a worse prognosis for mortality or lower resilience throughout the different stages of cancer treatment. The objective of this study was to determine the frequency of breast cancer patients demonstrating parameters of functional and mental status below predicted threshold values [1-4].
Methods: Within the 'Return' study [5] 68 patients with first diagnosis of breast cancer (58±11 yr) in UICC stage 0-IV (0=4.4%, IA=60.3%, IIA=22.0%, IIB=8.8, IIIA=1.5%, IIIC=1.5%, IV=1.5%) were examined prior to cancer therapy. Standardised assessment of functional status included a handgrip strength test (HGS), 6-minute-walk-test (6MWT) and BIA for detection of bioimpedance phase angle (pA). The mental status was investigated using the HADS-A and HADS-D.
Results: 21% of patients presented HGS below individual critical cut-off value (27.8±5.6 kg). 16% showed a critical pA (5.3±0.9°). In 63% of patients there was a shorter individual predicted distance in the 6MWT (470±95m). Clinically relevant (HADS-A and D Score >10) anxiety and depression scores were diagnosed in 53% and 39% of patients respectively. 18% of breast cancer patients presented with a severe form of anxiety. 16% were identified with severe symptoms of depression.
Conclusions: The data provides evidence for the occurrence of critical prognostic values of functional and mental status in breast cancer patients before cancer therapy. Potential risk factors suggest the adaptation and individualisation of medical treatment. In order to optimise the treatment, routine assessments are necessary to establish multidisciplinary interventions. Systematically examining the individual case strengthens the overall treatment modalities and can ultimately have a positive impact on the treatment outcomes.

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Disclosure Statement: The authors have nothing to disclose.

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Application of CDK4/6 Inhibitors in Premenopausal Women with Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer: a Real-World Experience

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Purpose: Recently, a CDK4/6 inhibitor (CDK4/6i) combined with hormonal treatment (HTx) is regarded the most effective first-line therapy in premenopausal patients (pts) with hormone receptor-positive (HR+), HER2-negative (HER-) metastatic breast cancer (MBC). This real-world compilation of data on HTx combined with a CDK4/6i sought to more accurately estimate the importance of this treatment in the clinical routine..
Methods: A total of 33 premenopausal pts were included. Pts were treated with a CDK4/6i and HTx consisting of ovarian suppression and an aromatase inhibitor (AI) in 23 and fulvestrant in another 10 pts; 23 pts received palbociclib and 10 pts were given ribociclib for CDK4/6 inhibition. 11 pts had bone only metastases, 7 pts had visceral metastases and 15 pts suffered from mixed metastatic MBC. 15 pts had received prior systemic therapy for MBC, comprising Ctx in 5, HTx in 7, and both in 3 pts..
Results: 16 pts (48.5%) are still on treatment with a CDK4/6i+HTx. In the remainder, therapy was terminated due to disease progression. There were no additional signals observed indicating significant bone marrow, cardiac, liver, or any other serious toxicity. Median treatment duration is recently 69.4 weeks. Only 3 pts (13.0%) out of this series have died so far after 57.1, 109.7, and 140.6 weeks after starting CDK4/6i so that the median overall survival is not yet reached. The 2-year survival proportion is 94.4%, the 3-year survival is 56.0%..
Conclusions: These data show that CDK4/6i+HTx administered to premenopausal pts with HR+, HER2- MBC is safe and effective in the clinical routine in both the first and later line setting and confirm results of the pivotal randomized clinical trials.

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Care Appropriate to the Needs of Breast Cancer Patients with Disability – Results of the CANDY-study

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Purpose: As life expectancy is increasing in both the general population and in people with disabilities, the WHO expects a significant increase in cancer diseases among people with and without disabilities over the next decades. Nevertheless, the needs of people with severe, life-threatening diseases such as cancer and preexisting disabilities are rarely the focus of health services research. In order to contribute to a need-based health care for breast cancer patients with disabilities, the CANDY-study aims to identify barriers and resources, communication difficulties and information needs of breast cancer patients with disabilities.
Methods: Within the framework of a DFG-funded study (German Research Foundation) (**CA**re Appropriate to the **N**eeds of breast cancer patients with **D**isabilit**Y**) we will conduct 30 interviews with breast cancer patients with a severely disabled person's identity card since July 2019. The patients are recruited in the context of a patient survey for the quality assurance of breast centers in North Rhine-Westphalia, conducted by the University of Cologne. The recruitment of breast cancer patients with various disabilities (physical or sensory impairments, mental illness and intellectual disability) is performed by means of purposeful sampling. The interviews are analyzed by content analysis using an inductive and deductive approach.
Results: So far, there have been 31 positive responses from potential participants and the first interviews have been conducted. The qualitative analyses of all interviews will be completed by the time of the 34th German Cancer congress 2020.
Conclusions: Our research aims to clarify the different perspectives regarding breast cancer care of patients with different types of disability. The CANDY-study will contribute to a more patient-centered provision of health care for people with disabilities.

Disclosure Statement: none

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Lung Cancer attributed Mortality among 316,336 Early Stage Breast Cancer Patients Treated by Radiotherapy or Chemotherapy, 2000-2015: Evidence from US Cancer Registry

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Purpose: To compare lung cancer attributed mortality among early breast cancer patients, treated by radio-and/or chemotherapy, relative to the US female general population. Prognostic factors of lung cancer attributed mortality were also examined.
Methods: Breast cancer data, covering 2000 to 2015 calendar period, were extracted from the Surveillance, Epidemiology and End Results-18 (SEER-18) cancer registry database. A comparison of lung cancer attributed mortality between the breast cancer patients and the general population was computed using standardized mortality ratios. Prognostic of factors of lung cancer mortality and the competing causes were identified using flexible parametric modelling.
Results: Compared with the general population, breast cancer patients who were treated by radio-and/or chemotherapy, only radiotherapy, radiochemotherapy and only chemotherapy had 37% (95% CI: 39 - 34%), 34% (95% CI: 37 - 31%), 46% (95% CI: 51 - 40%) and 38% (95% CI: 45 - 31%) lower overall mortality from lung cancer, respectively. Lung cancer mortality was higher for older patients (compared to those <50 years, $HR_{50\text{-}59}$ = 3.29 [95%CI:2.65 – 4.10], $HR_{60\text{-}69}$ = 7.2 [95%CI: 5.80 – 8.86], $HR_{70\text{-}79}$ = 10.46 [95%CI: 8.46 – 12.93], and HR_{80+} = 10.39 [95%CI: 8.13 – 13.28]) and for those with negative receptors for estrogen and progestron hormones (HR=1.37; 95% CI: 1.21 – 1.55). Relative to the married, patients with widowed, divorced, single or other relationships had 69%, 47% and 25% higher hazard of mortality from lung cancer, respectively. In contrast, lung cancer mortality was lower for American Indian/Alaska Native and Aisan/Pacific Islander ethnicities (HR=0.49; 95% CI: 0.39 – 0.62) and for those diagnosed at a recent period ($HR_{2011\text{-}2015\ vs\ 2000\text{-}2005}$= 0.79; 95% CI: 0.65 – 0.76).
Conclusions: We found no evidence of higher lung cancer attributed mortality among the breast cancer patients relative to their background population. The identified factors could be clinically relevant indicators of lung cancer attributed mortality after breast cancer diagnosis.

Disclosure Statement: None

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Breast Cancer Risk in Familial CHEK2 Germline Mutation Carriers is Modified by the Polygenic Risk Score: A Multicenter Study by the German Consortium for Hereditary Breast and Ovarian Cancer

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Purpose: Pathogenic *CHEK2* germline variants associate with a 20-30% lifetime risk for female breast cancer (BC). It is suggested that additional genetic factors, such as BC-associated SNPs identified by GWAS, modify

individual BC risks. For *BRCA1/2* mutation carriers, the combined effects of BC-associated SNPs (polygenic risk score, PRS) have been shown to be informative for individual risk stratification. The question arises whether PRS based risk stratification is applicable for *CHEK2* germline mutation carriers with familial BC.

Methods: Here, we analyzed 904 female *CHEK2* germline mutation carriers (585 c.1100delC and 208 carriers of other protein-truncating variants, 111 individuals with pathogenic missense variants). A total of 667 mutation carriers were affected by BC (546 unilateral BC, 121 bilateral BC), with a mean age at first/secondary diagnosis of 45.9 (23-89)/49.1 (30-79) years, respectively. 237 mutation carriers were not affected by BC (mean age at last follow-up: 43.4 (18-92) years). A cohort-approach including retrospective and prospective events was applied. Multicenter recruitment was through genetic counseling centers in Germany including index patients and relatives over a period of 21 years. Genotyping of 77-and 88 established BC-associated SNPs, respectively, was performed using the Fluidigm® Access Array with subsequent next generation sequencing. A weighted cohort approach with age at first BC diagnosis as outcome was employed to evaluate the association of standardized PRS with BC risk in *CHEK2* mutation carriers.

Results: PRS values computed on the basis of both PRS sets were statistically significant associated with BC risk for *CHEK2* carriers. The age-specific hazard ratio estimates were used to compute absolute cumulative BC risks for mutation carriers by PRS percentiles. *CHEK2* carriers at the 10th percentile of the PRS had a BC risk of approximately 6% compared to ~18% in the 90th percentile by age 60 years.

Conclusions: Combined genotyping of BC-associated SNPs may improve personalized risk prediction for *CHEK2* mutation carriers.

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Chemotherapy (CT)-Induced Anaemia in Patients (PTS) Treated with Dose-Dense Regimen: Results of the Prospectively Randomised Anaemia Substudy from the Neoadjuvant Geparocto Study

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Purpose: This substudy compared the use of parenteral (IV) ferric carboxymaltose (FCM) with physician's choice (PhCh) anaemia therapy in breast cancer (BC) pts.

Methods: In GeparOcto trial pts with primary BC were randomized to receive sequential, intensified, dose-dense epirubicin, paclitaxel, and cyclophosphamide (iddEPC) or weekly paclitaxel/liposomal doxorubicin +/- carboplatin (PM(Cb))[1]. Pts with anaemia grade≥2 (haemoglobin (Hb)<10g/dl), transferrin saturation (TSAT)≤20% and serum ferritin<300ng/ml (amended to <600ng/ml) were randomized to receive weekly FCM or PhCh (no treatment, oral iron, erythropoiesis-stimulating agent, or both) anaemia therapy. Stratification factors were CT arm (iddEPC vs PM(Cb)) and planned PhCh. Primary objective compared the rate of pts achieving Hb≥11g/dl at 6 weeks (wks) of therapy between two arms. Main secondary objectives were median time to achieve Hb≥11g/dl and changes in iron parameters at baseline vs different time points.

Results: Less than anticipated pts had CT-induced anaemia. 125 pts were randomized (62 in FCM, 63 in PhCh). Median age was 46 years (range 26-66); median levels of Hb, serum ferritin and TSAT were 9.6 (7.6-11.8)g/dl, 201 (3.0-551)ng/ml and 14.0% (4.0%-76.0%), respectively. Overall, 40 (32.0%) pts (22 in FCM and 18 in PhCh arm; p=0.447) reached Hb≥11g/dl at 6 wks. Median time to achieve Hb≥11g/dl was 9.0 wks with FCM vs 10.6 wks by PhCh. Median Hb changes vs baseline were comparable in both arms, while median serum ferritin and TSAT changes at earlier time points were increased in FCM compared to PhCh.

Conclusions: This is the first study investigating IV iron treatment for dose-dense CT-induced anaemia in BC. 32% of pts reached Hb≥11g/dl at 6 wks, irrespective of anaemia therapy. FCM treatment increased ferritin and TSAT levels but did not improve anaemia in comparison to PhCh in this setting.

Reference:

1. Schneeweiss et al. Eur J Cancer 2019

Disclosure Statement: The anaemia supportive treatment substudy was financially supported by Vifor Pharma Ltd and the GeparOcto trial by Amgen, Roche and Teva.

HT reported personal fees from Vofor, Roche, Amgen. CH reported personal fees from Roche, Pfizer Novartis, Celgene, Lilly, AstraZeneca outside the submitted work. SL reported grant from Roche during the work and grants from Celgene, Novartis, Pfizer, Roche, Seattle Genetics, Teva, Vifor, PRIME, Daiichi Sankyo outside of the submitted work, and patent EP14153692.0. CD reported stock and other ownership interests from Sividon Diagnostics; honoraria from Teva, Novartis, Pfizer, Amgen; consulting or advisory role from MSD Oncology, Amgen, Daiichi Sankyo and patents for VMScope digital pathology software; patent application EP18209672 - cancer immunotherapy; patent application EP20150702464 - therapy response. JH reported honoraria, consultancy or advisory role from Lilly, Novartis, Roche, Pfizer, Hexal, Astra Zeneca, MSD, Celgene, Abbvie; grants from Novartis, Celgene and travel expenses from Roche, Pfizer, Novartis, Celgene, Lilly. AS reported grants from Celgene, Roche, AbbVie, Molecular Partner, personal fees from Roche, AstraZeneca, Celgene, Pfizer, AstraZeneca, Novartis, MSD, Tesaro, Lilly outside the submitted work. PAF reported grants from Novartis, Biontech, Novartis, Roche, Pfizer, Celgene, Daiichi-Sankyo, Teva, Astra Zeneca, Merck Sharp & Dohme, Myelo Therapeutics, Macrogenics, Eisai, Puma and grants from Cepheid, during the conduct of the study. VM reported personal fees from Amgen, Celgene, Roche, Myelotherapeutics, Astra Zeneca, outside the submitted work. KR reported personal fees from Tesaro, Astra Zeneca, Pfizer outside the submitted work. SS reported grants from Vifor; other from Amgen, Roche, Teva during the conduct of the study; personal fees Amgen, Hexal, Roche, Mundipharma and other from Novartis outside the submitted work. TL reported non-financial support from AstraZeneca, Pfizer, Pharma Mar, Daiichi Sankyo, Roche; personal fees from MSD, Novartis, Teva, Tesaro. The other co-authors had nothing to disclose.

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Analysis of ESR1 Mutations in Single Circulating Tumor Cells from Metastatic Luminal Breast Cancer Patients Upon Estrogen Deprivation Therapy

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Purpose: Mutations in the ligand-binding domain of the *ESR1* gene are frequently observed as a resistance mechanism against estrogen deprivation therapy (EDT) such as aromatase inhibition in breast cancer patients. Detection of such mutations offers the chance to optimize therapy strategies. However, the predictive utility of the primary tumor for an acquired resistance is limited and obtaining serial biopsies of metastatic lesions is

challenging. To underline the application of a liquid biopsy, single circulating tumor cells (CTCs) were analyzed with a next generation sequencing approach for the *ESR1* coding region.
Methods: 132 CTCs from blood samples of 46 metastatic breast cancer patients were analyzed. CTCs were enriched with the CellSearch® system, isolated and genomic DNA was amplified. Furthermore, tumor tissue samples from corresponding primary tumors and/or metastatic lesions from patients with *ESR1* mutations in CTCs were analyzed.
Results: *ESR1* mutations were detected in CTCs from twelve of 46 patients exclusively in the patient group that was treated with EDT. No *ESR1* mutations were found in CTCs from patients who received no or other ET (*p*-value: 0.048). In seven patients mutations were detected in the hotspot regions located in the ligand binding domain. Six novel mutations were detected. *ESR1* mutations were absent in primary tumor tissue samples of patients with mutated CTCs.
Conclusions: Single cell CTC analysis for *ESR1* mutations may be of clinical value to identify patients who might progress under EDT and might therefore benefit from an early switch to an alternative ET or other treatment regime.

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Germline (G)BRCA1/2 Mutations (M) and Hematological Toxicities in Patients (PTS) with Triple Negative Breast Cancer (TNBC) Treated with Neoadjuvant Chemotherapy (NACT)

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Purpose: *BRCA1/2* plays a central role in DNA repair. Pts with *gBRCA1/2*m treated with CT might be at higher risk of acute hematological toxicities (hemtox) due to the lower level of functional *BRCA*1/2 protein. Published results are discordant.
Methods: Pts with early TNBC and known *gBRCA1/2*m treated with anthracycline-taxane based NACT in the GeparQuinto (n=487), GeparSixto (n=291) and GeparOcto (n=393) studies were included. Primary G-CSF prophylaxis was foreseen only under iddETC in GeparOcto. Primary objective: rate of neutropenia grade (G)3-4 after cycle 1 (C1); secondary objectives: rate of other hemtox G3-4, overall rate after C1 and under taxane.
Results: 209/1171 pts (17.8%) had a *gBRCA1/2*m (177 *gBRCA1*m, 33 *gBRCA2*m). Median age was 48yrs [21-78]. The rate of neutropenia G3-4 after C1 in *gBRCA1/2* wildtype (wt) vs *gBRCA1/2*m was 35.7% vs 37.4% (OR 1.08, 95%CI 0.78-1.48, p=0.658; multivariate analysis (MVA) OR 1.26, 95%CI 0.87-1.82, p=0.226). No difference was found in other hemtox. *gBRCA1/2* m status did also not predict for other hemtox G3-4 (OR 0.94, 95%CI 0.64-1.40, p=0.773; MVA OR 0.94, 95%CI 0.62-1.43, p=0.779). No difference was seen according to *gBRCA1* or 2 m. Under taxane, the rate of hemtox G3-4 in *gBRCA1/2* wt vs *gBRCA1/2*m was 43.1% (n=270) vs 59.5% (n=91) (OR 1.94, 95%CI 1.35-2.77, p<0.001; MVA OR 2.91, 95%CI 1.55-5.45, p=0.001); anemia G3-4 2.6% vs 3.3% p=0.584; leucopenia G3-4 32.7vs 47.1% p=0.001; neutropenia G3-4 35.8% vs 49.3% p=0.003; thrombopenia G3-4 1.4% vs 4.6% p=0.024; febrile neutropenia 5.9% vs 4.6% p=0.696.
Discussion: We show that gBRCA1/2m are not associated with a significantly higher risk of severe hemtox. Under taxane, pts with gBRCA1/2m demonstrate a higher rate of hemtox G3-4, especially neutropenia, compared to wt pts.
Conclusions: Pts with *gBRCA1/2m* receiving taxane therapy should be carefully monitored, being at higher risk for severe hemtox.

Disclosure Statement:
V. Möbus: AMGEN, Roche, Celgene, Myelotherapeutics, Astra Zeneca.
A. Schneeweiss: Celgene, Roche, AbbVie, Molecular Partner, Novartis, AstraZeneca, MSD, Tesaro, Pfizer, Lilly.
H. Tesch: Roche, Novartis.
K. Lübbe: Roche, Novartis, Genomic Health, Lilly.
M. Untch: Lilly Int., MSD Merck, Mundipharma, Myriad Genetics, Odonate, Pfizer GmbH, PUMA Biotechnology, Roche Pharma AG, Sanofi Aventis Deutschland GmbH, TEVA Pharmaceuticals Ind Ltd, Novartis, Abbvie, Amgen GmbH, Astra Zeneca, BMS, Celgene GmbH, Daiji Sankyo, Eisai GmbH, Lilly Deutschland.
J. Huober: Novartis, Lilly, Roche, Pfizer, Astra Zeneca, MSD, Celgene. C; A; Lilly, Novartis, Roche, Pfizer, Hexal, Astra Zeneca, MSD, Celgene. C; A; Celgene, Novartis. O; A; Roche, Pfizer, Novartis, Celgene, Daichi.
F.J. Couch: Qiagen, Ambry Genetics. O; A; AstraZeneca, GRAIL.
I. Bauerfeind: CELGENE, Roche.
C. Hanusch: Roche, Novartis, Lilly Pharma, Celgene, Astra Zeneca.
C. Jackisch: Roche, Amgen.
T. Link: Amgen, AstraZeneca, Pfizer, Pharma Mar, Daiichi Sankyo, MSD, Novartis, Teva, Tesaro, Roche.
S. Loibl: Patent EP14153692.0 pending. Roche, AbbVie, Amgen, AstraZeneca, Celgene, Novartis,
Pfizer, Roche, Seattle Genetics, Teva, Vifor, PRIME, Daiichi.
P.A. Fasching: Novartis, Biontech, Roche, Pfizer, Celgene, Daiichi-Sankyo, TEVA, Astra Zeneca, Merck Sharp & Dohme, Myelo Therapeutics, Macrogenics, Eisai, Puma, Cepheid.

The other co-authors had nothing to disclose.

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Impact of Marging Shaving on Re-Excision Rates in Patients with Primary Invasive Carcinoma and Carcinoma in Situ In Breast Conserving Surgery. Data from a Population Based Cohort of Clinical Cancer Registry

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Purpose: Previous studies reported considerably high re-excision rates in breast-conserving surgery (BCS) about 20%. Circumferencial Marging Shaving (CMS) could be a surgical strategy to reduce re-excision rates. This study aimed to investigate the effects of CMS during BCS on reducing residual tumor.
Methods: Totally, 440 patients with primary carcinoma or carcinoma in situ of the breast who underwent BCS in the University Medical Center Regensburg between 2017 and 2019 were analyzed. Patients who had CMS or targeted re-excision (TRE) depending on intraoperative mammography or sonography were compared with patients receiving BCS without removal of further tissue during primary surgery. The impact of these surgical methods on residual tumor (R1) and further necessary intervention

was analyzed by means of multivariable binary logistic regression model adjusting for tumor size, nodal status, histologic al type, tumor biology, neoadjuvant chemotherapy, surgeon, breast side, and patient´s age.
Results: A total of 306 patients had invasive-ductal carcinoma. Of these, 40 patients received CMS, 82 TRE, and 184 no further excision. After comparing these subgroups in a binary regression model there was a tendency for CMS and TRE to have advantage over missing re-excision regarding residual tumor. Furthermore, after adjusting for different variables, especially patients with T1-tumors had a slightly significant benefit from CMS.
Conclusions: Our results indicate a tendency that CMS reduces residual tumor compared to TRE or to no further surgical action, although final results will be presented.

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2. Systematic cavity shaving: Modifications of breast cancer management and long-term local recurrence, a multicentre study. Héquet, D. et al., Europ. Journ. of Surg. Oncol., Vol. 39, Issue 8, 899 - 905

Disclosure Statement: The authors declare no conflict of interest.

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Pro and Contra Conversation: Vitamin D Deficiency and Cancer: Fact or Fiction?

André Robert Rotmann

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Vitamin D deficiency and cancer Fact or fiction?
It is undisputed that vitamin D is one of the central hormones of our body. Likewise, vitamin D is needed to provide minerals like calcium for your metabolism
making it indispensable for bone health.
Numerous studies show that vitamin D deficiency is responsible for an increased risk of developing common diseases such as diabetes, cardiovascular diseases, or even depression.
In addition, a link with the immune system and the development of cancer is postulated.
A current PUBMED search using the terms “vitamin D” and “cancer” resulted in more than 10,000 hits!
The complementary and integrative oncologists are also increasingly concerned with the possible consequences of vitamin D deficiency and, accordingly, with substitution.
2 experts who deal with osteo-oncology will look at this exciting topic with a pro and con discussion.
Prof. Ingo Diel from Mannheim is a proven, nationally and internationally well-known osteo-oncologist and will take the contra position.
Dr. Andre Rotmann from Rodgau, gynaecologist-oncologist and actively involved for years in the integrative and complementary medical treatment of gynaecological tumours will take the pro position.
The discussion should be conducted based on the current status of science and represent exciting and entertaining aspects of this current topic.

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Breaking News from the Field of Complementary Oncology, an Exiting Presentation of New Integrative Therapies in Breast Cancer Patients

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The aims of the integrative and complementary oncology is to minimalize the side effects of the classic oncologic therapy including such as chemotherapy or antiendocrine therapy and above all to enhance life quality of patients
There is a great interest among patients worldwide in complementary oncological approaches.
The prognosis in the metastasing stage is unfortunately still poor
Curcumin is a plant-based substance known for thousands of years that is seen as a promising substance in numerous preclinical studies, studies of carcinoma cell lines and in animal research.
It has been reported to have a synergistic effect with a number of chemotherapeutic substances.
The aim of our randomised, double-blind, placebo-controlled study was to demonstrate the efficacy of curcumin in combination with taxane in the treatment of advanced breast cancer for the first time
“Study of Efficacy of Curcumin in Combination with Chemotherapy in Patients with advanced Breast Cancer: Randomized, Double Blind, Placebo Controlled Clinical Trial.”
150 patients with advanced breast cancer were randomly divided into two groups of 75 each.
Group A were given paclitaxel with an intravenous placebo for a total of 12 weeks
Group B received curcumin 300 mg intravenously + paclitaxel q1w also for 12 weeks
The aim of the study was to demonstrate the potential benefits of curcumin administered intravenously in combination with paclitaxel compared with the placebo and paclitaxel for patients with advanced breast cancer
The primary objectives were the efficacy of the combined treatment with regard to the objective response rate (ORR), progression-free survival (PFS), time-to-tumour progression (TTP), quality of life (QoL) as well as the influence of tumour markers
The secondary objectives were treatment safety and the observation of possible side effects and disease progression
The exact design of the study and the differentiated results were presented and discussed for the first time anywhere in the world at the 2019 German Senology Congress in Berlin. This lecture was awarded high-ranking and will be published soon

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Cancer Management and Outcome of Young Patients (PTS) with Breast Cancer (BC) Diagnosed at 40 Years (YRS) or Younger

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Purpose: To provide data about modern BC treatment and oncological outcome of young women aged ≤40 yrs.
Methods: The BC in pregnancy registry (BCP/GBG29) is a multicenter, observational study that compares the management and outcome of BC in pregnancy with non-pregnant pts ≤40 yrs as control cohort. All pts are treated according to local standards. This analysis reports descriptively baseline characteristics, BC therapy, short-term and long-term outcome

of the young control cohort. Disease-free (DFS) and overall survival (OS) rates were estimated using the Kaplan-Meier method.
Results: 964 non-pregnant women with a median follow-up of 38.7 months (95%CI 35.2-41.3) comprised the analysis set. Median age was 35 yrs (range 19-40). At diagnosis, 90.4% of pts had a stage T1-2 and 67.0% were nodal negative; 42.7% had HR+/HER2- BC, 31.9% HER2+ BC and 25.4% triple-negative BC (TNBC). 3.2% of pts were M1 at primary diagnosis. 90.7% of pts with early BC (EBC) received chemotherapy (CT). 93.4% of pts with endocrine treatment for EBC received tamoxifen; thereof 35.8 % with a GnRH analogue. Regardless of BC subtype, the highest pCR rates (ypT0 ypN0) were achieved in the cohort of pts age 18-29 yrs (HER2+ 47.8%, TNBC 65.2%, HR+/HER2-40.0%). The 3-yr DFS for pts with EBC was 83.1% (95%CI 79.6%-86.0%) and the 3-yr OS 94.3% (95%CI 91.9%-96.0%). The subgroup analysis per BC subtype suggested a trend towards inferior DFS only in the group of pts ≤34 yrs and HR+/HER2−BC (log rank p=0.058). 3.4% of pts got pregnant after BC with a median time from diagnosis to birth/termination of 3 yrs (range 2-7).
Conclusions: In this large cohort of young BC pts the reported treatments reflect the modern oncological management of these pts. The prognostic relevance of young age by itself could not be shown for pts with HER2+ and TNBC. Yet, similar to previously reported results[1] our data suggest a trend towards inferior DFS in the group of pts ≤34 yrs and HR+/HER2− BC.

Reference:
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Disclosure Statement: SL reported grant from Roche during the work and grants from Celgene, Novartis, Pfizer, Roche, Seattle Genetics, Teva, Vifor, PRIME, Daiichi Sankyo outside of the submitted work, and patent EP14153692.0. SS reported consulting fees from Roche, Amgen, Novartis, Hexal. MR reported personal fees and non-financial support from Novartis , personal fees from Roche , non-financial support from Celgene , personal fees from Lilly , personal fees from Astra Zeneca , personal fees and non-financial support from Pfizer, outside the submitted work; MS reported grants and personal fees from Pierre-Fabre, grants, personal fees and non-financial support from Roche, grants, personal fees and non-financial support from Pfizer, grants and personal fees from Novartis, grants and personal fees from Astra-Zeneca, grants and personal fees from Eisai, personal fees from Amgen, personal fees from Celgene, grants, personal fees and non-financial support from Pantarhei, grants and non-financial support from BioNTech, grants from Genentech, outside the submitted work; In addition, MS has a patent EP2469440 (A3) Molecular markers for cancer prognosis pending, a patent WO2009033941 (A1) A method for predicting the response of a tumor in a patient suffering from or at risk of developing recurrent gynecological cancer towards a chemotherapeutic agent pending, and a patent WO2014118333 (A1) Method for predicting the benefit from inclusion a taxane in a chemotherapy regimen in patients with breast cancer pending. FM reported personal fees and non-financial support from AstraZeneca, personal fees from Clovis, personal fees from Tesaro, personal fees and non-financial support from Roche, personal fees and non-financial support from Novartis, personal fees from AMGEN, personal fees and non-financial support from Pfizer, personal fees from Curevac, personal fees from Vaccibody, personal fees from PharmaMar, personal fees from Eisai, personal fees from Celgene, personal fees from GenomicHealth, outside the submitted work; ES reported Travel Sponsoring from Roche and consulting fees from Roche, Novartis, Pfizer, Astra Zeneca. VM reported consulting fees from Amgen, Roche, Tesaro, AstraZeneca and personal fees for advisory board from Amgen, Roche, MyeloTherapeutics.

The other co-authors had nothing to disclose.

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A Randomized, Double-Blind, Phase III Trial of Neoadjuvant Chemotherapy (NACT) with atezolizumab/Placebo in Patients with Triple-Negative Breast Cancer (TNBC) Followed by Adjuvant Continuation of atezolizumab/Placebo (Gepardouze)

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Purpose: TNBC is associated with higher percentages of pathological complete response (pCR) to NACT, and patients (pts) with a pCR have a favorable prognosis. Pts with residual disease have a substantially higher risk of recurrence than pts with other subtypes of breast cancer.[1,2] Therapeutic blockade of PD-L1 binding by atezolizumab has resulted in relevant anti-tumor efficacy.[3,4] The aim of GeparDouze is to determine whether the addition of atezolizumab to NACT and adjuvant therapy improves pCR and event free survival (EFS) in pts with TNBC.
Methods: GeparDouze (NSABP B-59/GBG96) is a phase III, double blind, placebo-controlled trial. 1520 pts will be randomized (1:1) to NACT + atezolizumab 1200mg or placebo IV every 3wks followed by adjuvant atezolizumab 1200mg or placebo IV for 6 months. Stratification factors are Group (NSABP Foundation Inc.; GBG), tumor size (1.1-3.0cm; >3.0cm), epirubicin or doxorubicin/cyclophosphamide schedule (q2w; q3w), nodal status (positive; negative) and PD-L1 Status (positive; negative; indeterminate). Pts with primary cT1c-cT3 TNBC and centrally assessed hormone receptor-status, HER2-status, and PD-L1-status on core biopsy can be enrolled. Co-primary endpoints are pCR (ypT0/Tis ypN0) and EFS. Main secondary endpoints are overall survival, recurrence-free interval, distant disease-free survival, and toxicity.
Results: GeparDouze is an academic collaboration between NSABP and GBG. So far, 357 patients are enrolled. It is expected that approximately 760 pts will be randomized within 34 months by NSABP sites and approximately 760 patients by GBG sites.
Conclusions: GeparDouze will provide further data on efficacy and safety of atezolizumab in pts with TNBC.

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Disclosure Statement: The trial is financially supported by Genentech/Roche. SL reported grant from Roche during the work and grants from Pfizer, Celgene, Amgen, Novartis, AstraZeneca, Abbvie, Lilly, Daiichi Sankyo, Eirgenix outside of the submitted work, and patent pending EP14153692.0. JC reported grants from Genentech. CJ reported personal fees from Roche, Celgene during the conduct of the study. CG reported grants from Genentech/Roche during the conduct of

the study; grants and non-financial support from AstraZeneca, Abbvie, Genentech/Roche; personal fees from Celgene outside the submitted work. SS reported grants from Genentech/Roche during the conduct of the study. NW reported other from Genentech/Roche during the conduct of the study. PR reported grants from Genentech/Roche during the conduct of the study; other from AstraZeneca, Genentech/Roche, Lilly outside the submitted work. CD reported shareholder and cofounder from Sividon Diagnostics; honoraria/consultation from Teva, Novartis, Pfizer, Roche, Amgen, MSD, Daiichi Sankyo, Celgene, AstraZeneca; atent application: EP18209672 – cancer immunotherapy. MU reported fee to the institution from BMS, Lilly, PUMA Biotechnology; fee and non-financial support to the institution from Abbvie, Amgen, AstraZeneca, Celgene, Daiji Sankyo, Eisai GmbH, Janssen Cilag, Johnsen&Johnsen, MSD Merck, Lilly, Mundipharma, Myriad Genetics, Odonate, Pfizer, Riemser, Roche, Sanofi Aventis Deutschland GmbH, Sividon Diagnostics, TEVA Pharmaceuticals Ind Ltd outside the submitted work. AS reported grants from Celgene, Roche, AbbVie, Molecular Partner, personal fees from Roche, AstraZeneca Celgene, Roche, Celgene, Pfizer, Novartis, MSD, Tesaro, Lilly outside the submitted work. The other co-authors had nothing to disclose.

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Predicting the Risk of Locoregional Recurrence after Early Breast Cancer: an External Validation of the Dutch Influence-Nomogram with Clinical Cancer Registry Data from Germany

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Purpose: Regular follow-up after breast cancer treatment aims for early detection of locoregional recurrences (LRR) to improve the patients' outcome. By estimating individual 5-year recurrence-risks based on different patient- tumor- and treatment characteristics, the Dutch INFLUENCE-nomogram can assist health professionals and patients in developing personalized risk-based follow-up pathways. The objective of this study is to externally validate the INFLUENCE-nomogram on non-Dutch patients.
Methods: Data derive from a large clinical cancer registry in southern Germany, covering a population of 1.1 million. 6520 Patients with curative resection of early-stage breast cancer, diagnosed between 2000 and 2012, were included in the analysis. For every included patient, an individual LRR-risk was estimated by the INFLUENCE-nomogram. Its predictive ability was tested by comparing estimated and observed LRR-probabilities using the Hosmer–Lemeshow goodness-of-fit test and C-statistic based on the receiver-operator-characteristic (ROC) curve.
Results: In the German validation-cohort, 2.8% of the patients developed an LRR within 5 years after primary surgery (n = 184). While the INFLUENCE-nomogram generally underestimates the actual LRR-risk of the German patients ($p < 0.001$), its discriminative ability is comparable to the one observed in the original Dutch modeling-cohort (C-statistic German validation-cohort: 0.73, CI 0.69–0.77 vs. C-statistic Dutch modeling-cohort: 0.71, CI 0.69–0.73). Similar results were obtained in most of the subgroup analyses stratified by age, type of surgery and intrinsic biological subtypes.
Conclusions: The presented outcomes underline the generalizability of the recently developed INFLUENCE-nomogram beyond the Dutch population. The model performance of INFLUENCE could be enhanced in future by incorporating additional risk factors for LRR.

Funding: Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – project number 417891978.

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Predicting the Effectiveness of Sensor-Controlled Scalp Cooling to Prevent Chemotherapy-Induced Alopecia in Primary Breast Cancer Patients: It is the Regimen that Matters

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Purpose: Sensor-controlled scalp cooling (SCSC) is now an accepted means to prevent primary breast cancer (PBC) patients (pts) from chemotherapy (Ctx)-induced alopecia (CIA). This retrospective study sought to determine pts who are most likely to benefit from SCSC while being subjected to CIA-inducing neoadjuvant (NACT) or adjuvant chemotherapy (ACT) with anthracyclines (A), taxanes (T), or both.
Methods: 86 pts were included: NACT, 47 (54.6%); ACT, 39 (45.4%); dose-dense (dd) Ctx, 38 (44.2%); non-dd Ctx 48 (55.8%); premenopausal, 48 (55.8%); postmenopausal, 38 (44.2%). Ctx regimens: A→T, 38 (44.2%), T→A, 23 (26.7%), T, 25 (29.1%). CIA was quantified according to the Dean score (DS). Data were analyzed regarding the SCSC completion rate, and quality of hair preservation (success: DS 0-2, failure: DS 3-4). Moreover, the following parameters were investigated in regard to the success of SCSC: menopausal status, NACT vs ACT, dd Ctx vs non-dd Ctx, Ctx regimen.
Results: The success rate was 64.0% with 35 pts (40.7%) experiencing DS 0, and 20 (23.3%) showing DS 1-2. Effectiveness of SCSC did not differ for most analyzed subgroups. The relative risk (RR) to experience CIA was 1.23 (CI: 0.87-1.74) for post- vs premenopausal pts, 1.07 (CI: 0.78-1.46) for ACT vs NACT, 1.28 (CI: 0.91-1.80) for dd Ctx vs non-dd Ctx, and 1.556 (0.98-2.36) for A+T vs T. However, the SCSC success rate for A→T (47.4%) was significantly lower ($p = 0.016$) as compared to T→A (73.9%) or T (80.0%).
Conclusions: SCSC was effective to prevent CIA in pts with PBC. All therapeutic subgroups benefited from SCSC. A+T-based Ctx *per se* is not a contraindication for SCSC. However, the success rate is significantly higher when the taxane precedes the anthracycline.

Disclosure Statement: All authors declare no conflict of interests. t

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The Aesthetic Results for Reconstruction After Oncoplastic Breast Surgery

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Purpose: To create of the new concept of surgical treatment as a component of multi-therapy treatment of patients with breast cancers on postoperative quality of life (Qol).
Methods: We assessed 437 women who underwent breast conserving surgery (BCS) or total mastectomy (TM) with immediate reconstruction in P.A. Gertsen Moscow Research Institute from 2013 to 2018. Of the 437 patients, 290 (66,4%) had BCS,147(33,6%) – skin-sparing mastectomy (SSM). BCS included glandular reshaping (rotation flap, round-block technique, batwing mastopexy, wise pattern-inverted T, vertical pattern). After SSM, 7(4,7%) patients underwent immediate breast reconstruction using a transverse rectum abdominis musculocutaneous (TRAM) flap, 47 (31,9%) - musculotoracodorsal (TDL) flap, 98 (66,7%) - musculolatissimus dorsi flap and it combination with endoprosthesis. A median follow-up period was 58 months. Only 94 (21,5%) patients received adjuvant polychemotherapy, combinations adjuvant polychemotherapy and radiation therapy – 27 (6,1%) or endocrine therapy – 37(8,5%).

Results: During a median follow-up period local recurrent were detected at 30 (6,9%), distant metastasis – 65 (14,9%) patients. Overall disease-free survival in patients with BCS stage I was 96,2%, IIA– 90%, IIB – 86,7%, IIIA – 86,2% (p>0,05). Overall disease-free survival in patients with SSM stage I was 92,9%, IIA– 91,2%, IIB – 84,4%, IIIA – 91,4% (p>0,05). The postoperative cosmetic result after BCS was assessed in 89,3% patients.
Conclusions: Oncoplastic surgery contributes is the better phychological adaptation of patients. Variety of modifications and options of reconstructive surgery causes problem of choice, which should be solved with patient taking into account the clinical data. The extent of surgical intervention does not affect the performance of the 5-year overall and recurrent survival and depends on the distribution process.

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Disclosure Statement: I agree

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Surgical Resection of The Primary Tumor is Associated with Increased Long-Term Survival in Patients with Stage IV Breast Cancer

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Purpose: The problem of the treatment of disseminated breast cancer (DBC) is specially urgent in the present situation, as there is no uniform standard of care for these patients nowadays. Treatment of patients with stage IV breast cancer is palliative, and, in some cases, symptomatic, so the main task is to maximally prolong the life and improve its quality.
Methods: This investigation comparatively analyzed the results of complex treatment with metastatic breast cancer. We analyzed retrospectively treatment experience of 196 patients with generalized breast cancer in the department of oncology and breast reconstructive surgery of P.A. Herzen Moscow Cancer Research Institute from 2000 to 2018 Invasive ductul carcinoma was verified in128 patients (65,3%), invasive lobular carcinoma - 33 (16,8%), complex form - 19 (9,7%). Complex palliative care involving drug and radiation therapies was performed in two patient groups. The first group includes 124 patients who underwent surgical intervention as complex treatment, the second group includes 72 patients with only medical therapy. Standard systemic therapy was given to all patients.
Results: Overall, 3-and 5-year survival in fist group was 43,8 and 21%, in second - 15,1 and 9,3% respectively [p=0,00002 log-rank]. Median survival in patients with surgical treatment composed 32 month, in patients with only systemic therapy - 21. The factors having influencing an influence on the prognosis and the quality of life outcomes for of patients with generalized breast cancer were are also studied: hormone-dependent tumor, Her2/neu hyper-expression, reproductive function status (age, menopause existence).
Conclusions: Removing primary breast tumor in patients with generalized breast cancer improve long-term outcomes. Three- and five-year survival increased by 28,7 and 16,3% respectively, and median survival – for 11 months. These patients may benefit from resection of the breast tumor. One explanation for the effect of this resection is that reducing the tumor load influences metastatic growth.

Disclosure Statement: I agree

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Transcriptional Factor KLF11 (Kruppel Like Factor 11) As Potential Targets and a New Biomarker for the Prognosis of Human Breast Cancer

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Purpose: This study aims to clarify prognostic impact of KLF11 in breast cancer.
Methods:
1. We retrieved four independent investigation from ONCOMINE database and investigate the prognostic significance of KLF11 mRNA level in patients with BC, by using the Kaplan-Meier Plotter online database.
2. We collected and analyzed the expression of KLF11 in 312 BC samples by immunohistochemistry in our patients' cohort and correlated its expression with several parameters and patient outcome.

Results: According to the meta-analysis across four ONCOMINE datasets, we revealed KLF11 was one of the mostly down-regulated genes in BC. Interestingly, also a meta-analysis from Kaplan-Meier Plotter online database demonstrate that patients with KLF11 high expression had significantly shorter relapse free survival and distance metastases free survival time than those with low expression. Moreover, we performed our analysis to a patient cohort of 320 patients by using immunohistochemistry and finally 312 patients KLF11 expression level was obtained successfully. And we found that KLF11 high expression in BC tissue sections is strongly associated with pT classification, ki67 expression level and molecular subtype grouped by Luminal A type and Not Luminal A type. Importantly, patients with KLF11 low expression had significantly improved disease-free survival time than those with high expression, which was consistent with KMP meta-analyses. In subgroups of this whole cohort, significantly highlight the same DFS trends in pT1, pN0, tumor foci ≥2 , G2-G3 patients and patients without axillary lymph node or contrast BC, also in ER positive, PR positive, Her2 negative, Ki67 expression less than 14% and in Luminal A BC patients. Cox proportional hazard regression analysis further identified KLF11 as an independent factor for poor prognosis.
Conclusions: Taken together, these observations first strongly indicated that KLF11 might be a cancer promoter for BC and a new biomarker for the prognosis of human breast cancer.

Disclosure Statement: This study was funded by laboratory resources.

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Experience of One-Stage Prepectoral Reconstruction with Polyurethane-Coated Implants in Breast Cancer

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Purpose: Results of one-stage prepectoral reconstruction with polyurethane-coated implants in breast cancer.
Methods: Since 2017 to 2019 in the Department of Oncology and Reconstructive Breast and Skin Surgery P. Hertzen Moscow Oncology Research Institute performed 207 one-stage prepectoral reconstruction with polyurethane-coated implants in breast cancer.
Results: We analyzed 97 patients, 59 (60,8%) of them received radiation therapy. The follow-up period ranged from 3 months to 2 years. Radiation therapy in terms of combined/complex treatment 1-2 months after surgery was performed in 42 (71,2%) patients, 6-8 months after surgery (after adjuvant therapy) in 18 (30,5%) patients with breast cancer.
In this group the following complications were revealed: in 28 (25,77%) patients seroma (over 30 days), the "red breast syndrome" - 25 (25,77%) persons, the protrusion/extrusion of the prosthesis – 16 (16,5%), the marginal necrosis/necrosis – 5 (5,15%), the infectious complications - 4 (of

4,12%), the rippling – 6 (6,18%). The capsular contracture III-IV degree occurred in 10 patients (16,9 %) with radiation therapy, 8 (13,5%) cases protrusion also during radiation therapy.
Conclusions: The prepectoral breast reconstruction with a polyurethane coating implants can be applied as an alternative submuscular location, because 80% of patients have a good aesthetic result. According to Breast Q the quality of life of breast cancer patients is improving.

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Disclosure Statement: I agree

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Detection of Sentinel Lymph Nodes in Different Molecular Subtype of Breast Cancer

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Purpose: To analyze the frequency of lymph nodes metastasis in different molecular biological types of breast cancer.
Methods: Surgical treatment of 485 women with primary operable (cT1-2N0M0) invasive breast cancer (BC) and clinically negative regional lymph nodes (LN) was performed from 12.2016 to 11.2018 in National Medical Research Radiological Center of the Russian Federation. At the first stage all patients underwent breast conserving surgery or mastectomy; the status of regional LNs was examined using a sentinel lymph node biopsy. The age of women ranged from 22 to 81 years. Based on the recommendations of St. Gallen Consensus (2013) patients were divided into 5 groups depending on the molecular biological type.
Results: Among 485 patients with primary operable breast cancer and clinically negative regional LN, metastasis in sentinel LN were detected in 115 (23.7%) (p<0,005) cases. After dividing patients into groups it was found that metastasis in the SLN were verified in 55 (22%) (p<0,005) cases with luminal type A, in 47 (29.3%) (p<0,005) cases with luminal type B, Her2/neu-negative, in 5 (17.8%) (p<0,005) with luminal type B, Her2/neu - positive, in 5 (17%) (p<0,005) with a triple negative type and in 3 (15.7%) (p<0,005) cases with Her2/neu overexpressing breast cancer.
Conclusions: There were found out that despite the aggressive course and poor prognosis Her2/neu overexpressing and triple negative breast cancer were less associated with metastasis in regional LNs in contrast to other molecular biological types. However there is needed to make more detailed research with a larger amount of material for an objective judgment about the effect of the tumor molecular biology on lymphogenous metastasis.

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Disclosure Statement: No

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Intrapericardial Chemotherapy for The Management of Malignant Pericardial Effusion of a Metastatic Breast Cancer Patient -A Case Report

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Purpose: Malignant pericardial effusion with hemodynamic instability is a life-threatening condition requiring an acute intervention. Breast cancer (BC) is the second most common malignancy with pericardial metastasis. Due to high relapse rates after pericardiocentesis the therapy of choice includes a temporary pericardial drainage and the application of a local pericardial cytotoxic treatment.
Methods: Presentation of a 48-year old patient with the symptoms of capsular fibrosis 2 years after the primary therapy of a triple positive BC (neoadjuvant CTH [TCH], unilateral mastectomy with axillary LND, primary reconstruction with implant, adjuvant chest and axillary irradiation) under ongoing adjuvant HER2-targeted and endocrine therapy with tamoxifen. After surgical resection of the fibrotic tissue a local relapse was confirmed histologically (HR-positive/HER2-negative) without signs of metastasis in CT scan. The endocrine therapy was modified to letrozole and GnRH-analogue. The patient was presented within 3 weeks with orthopnea, low oxygen saturation and tachycardia. In CT scan pleural, pericardial and mediastinal metastases were detected with pleural and pericardial effusion, causing hemodynamic instability.
Results: The insertion of a subxiphoidal pericardial drainage was carried out (cytology: TNBC) under intensive monitoring. 3 liters of pericardial effusion was drained over 3 days along with the local application of mitoxantrone. We began a systemic monotherapy with epirubicin weekly. A nearby complete remission of the pericardial metastasis was observed along with stable disease of all other metastases over 12 weeks of therapy.
Conclusions: Individual therapy decisions are required in case of malignant pericardial effusion. 80% of the cases are clinically stable without any need for an invasive treatment. In case of hemodynamic instability minimal invasive actions should be preferred to thoracic surgery. Due to high relapse rates the local instillation of cytotoxic substances should also be concerned.

Disclosure Statement: no conflict of interest

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KI67 Expression in Primary Male Breast Cancer

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Purpose: Male breast cancer (MBC) is a rare disease. Approximately 1 % of breast carinoma are diagnosed in men. Only few studies with small patient numbers are available. Guidelines for diagnosis and treatment of MBC are derived from female breast cancer. Both diseases share similarities but there are significant differences regarding risk factors and prognosis. In this study we evaluated the clinical significance of proliferation

factor Ki67 for MBC. The aim was to define optimal Ki-67 scoring methods and cut-off values as prognostic marker for MBC.
Methods: Tumor tissue was obtained from 104 patients with primary MBC. Clincopathologicial characteristics including follow-up data were sampled and investigated. Ki67 expression was evaluated in paraffin-embbeded specimen by using standard immunohistochemistry. We applied three methods to analyse Ki67 expression: (1) Ki67 expression as percentage of nuclear Ki67 tumor staining on average (TA), (2) Ki67 expression at the tumor border (TB) and (3) hotspots of Ki67 expression (HS). Statistical analysis was performed using receiver operating characteristics (ROC) to determine specific cut off points for each method. Based on the calculated cut off points, clinicopathological characteristics and overall survival (OS) univariate and multivariate analysis as well as cox regression were performed.
Results: Ki67 staining was successful in all cases. Ki67 expression cut off points were 13.5 % for TA, 17.5 % for TB and 22.5 % for HS. Ki67 expression correlated with tumor size, nodal stage and tumor grading. All cut off points were significantly associated with OS. In multivariate analysis only Ki67 TA and TB were statistically correlated to OS.
Conclusions: Ki67 expression measured by TA and TB are suitable to provide information regading OS in primary MBC. Patients with Ki67 less than 13.5 % (TA) and 17.5 % (TB) showed significant improved OS.-Our restrospective study illustrates Ki67 expression to be a promising prognostic parameter in MBC.

Disclosure Statement: No disclosure

Cancer of Unknown Primary (CUP)

Cancer Prevention

Poster

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Selection Bias in Observational Studies Evaluating Cancer Screening Tests and Examinations

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Purpose: We previously found that i) mammography screening participants and nonparticipants are not comparable in terms of 4-year all-cause mortality, and ii) comorbidity measures determined based on claims data are insufficient to control for this selection bias [1]. We aimed to extend these analyses to cervical, prostate, colorectal, and skin cancer screening.
Methods: Using claims data of the BARMER covering the years from 2007 to 2017, participants and nonparticipants of the Pap smear, digital rectal exam, fecal occult blood test (FOBT)/colonoscopy, and visual whole-body skin examination were identified. For each cancer screening, Cox proportional hazards regression was used to compare all-cause mortality between participants and nonparticipants within ≤ 7 years. We adjusted for sex (if applicable), age (if applicable), residence, and comorbidity.
Results: Claims data of 5,765,852 persons were analyzed. The crude hazard ratios (HRs) for death from any cause for participants vs. nonparticipants of the respective cancer screening were 0.22 (99.9% confidence interval 0.22-0.23) for Pap smear, 0.88 (0.86-0.89) for digital rectal exam, 0.51 (0.45-0.58) for FOBT/colonoscopy, and 0.70 (0.70-0.71) for skin examination. The adjusted HRs were 0.57 (0.56-0.58), 0.69 (0.68-0.70), 0.57 (0.50-0.65), and 0.75 (0.74-0.76), respectively.
Conclusions: Because cancer screening is expected to reduce all-cause mortality by only 1-3% [2], the observed lower mortality among screening participants must be due to selection bias. The extent of this bias differs considerably between cancer screening tests and examinations. Observational studies evaluating the effectiveness of cancer screening need to apply appropriate methods for controlling selection bias. Controlling only for sex, age, residence, and comorbidity appears to be insufficient.

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Disclosure Statement: No conflict of interest.

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Regional Disparities of Cancer Prevention – the Case of Thuringia

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Purpose: It is a medically undisputed fact that physical activity, a healthy nutrition and the minimization of risk factors (e.g. smoking, drinking) form the three most important pillars of cancer prevention. Although these factors are mainly determined by personal factors, there is no doubt that regional infrastructures play an important role in cancer prevention. Such infrastructures include facilities that address the above-mentioned pillars through offering specialized services related to physical activity, healthy eating or individual control of risk factors. Cancer prevention infrastructures vary considerably from one region to another; in particular, significant differences can be expected between urban and rural areas. This paper aims to compare the current state of regional cancer prevention infrastructure on municipal level.
Methods: Methods of empirical social research (expert interviews, semi-standardized surveys)
Results: Drawing on relevant statistics and other sources, we develop an integrated indicator that combines information on the availability of public and non-public prevention infrastructures, e.g. sports facilities, access to regional unprocessed food and drug prevention services.
Conclusions: This indicator can serve as a basis for local actors to control and further develop cancer prevention on a regional level. Although we use the above indicator to characterize the current prevention infrastructures in Thuringia; the approach proposed can be applied to other regions in Germany and/or abroad.

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Green Tea Extract Versus Placebo for the Prevention of Colorectal Adenomas: a Randomized, Controlled Trial - Miracle Trial

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Purpose: Prevention of colorectal adenomas (CA) is likely to prevent colorectal cancer (CRC). Nutri- or chemoprevention of CRC is not yet established. NSAIDs show some benefit but also increase the bleeding risk. Preclinical and small clinical trials suggest that epigallocatechingallate (EGCG), a major polyphenol in green tea, has a good safety profile and antineoplastic effects in the large bowel, but there are no data from large trials. MIRACLE enrolled 1001 patients to examine the effect of a three year intake of ECGC on the recurrence of CA after polypectomy.
Methods: Double-blinded, placebo-controlled trial, 41 German centers, recruitment 12/2011-6/2015. Patients aged 50-80 years who underwent polypectomy within the last 6 months and tolerated EGCG well during a one month run-in were randomized to standardized decaffeinated EGCG (150 mg bid) or placebo for 3 years. Primary endpoint: Incidence of CA at the 3 year follow-up colonoscopy. Secondary endpoints: Occurrence, number, localization, size, histological subtype of CA, frequency of CRC and biomarker. Strata: Study center and low-dose aspirin (≤100 mg/d).
Results: Clinical parameters were well balanced. Primary endpoint was analysed in the modified ITT set (modITT; n=309 patients in EGCG, n=323 in placebo group giving informed consent and undergoing 3 year follow up colonoscopy). n=102 patients in the EGCG and n=103 in the placebo group were excluded due to missing follow up colonoscopy. Incidence of one or more CA after 3 year of placebo or EGCG 150 mg bid was 55.7 % and 51.1%, respectively (one sided adj. P=0.077, adj. RR 0.904) in the modITT. In the PP-set constituting all modITT patients completing the study without major protocol violations the respective figures were 54.3 % in the placebo and 48.3% in the EGCG group (one sided adj. P=0.058, adj. RR 0.883). There were no safety issues and no major differences in AEs between EGCG and placebo during the randomized phase.
Conclusions: 300 mg EGCG per day was well tolerated and showed a trend towards a preventive effect on CA in the large bowel though not statistically significant.

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Reduction of Genital Warts and Precancerous Lesions in HPV Vaccinated Young Women in Bavaria

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Purpose: HPV (Human Papillomavirus) vaccination has been available in Germany since 2006 and was recommended by the Standing Committee on Vaccination (STIKO) in 2007 for girls and in 2018 for boys. The vaccine should be given before the first sexual contact in order to exclude a prior exposure to the infection. The HPV vaccine is considered highly effective and safe. Data from Australia, where vaccination rates are at 80%, show a marked reduction in the rates of genital warts and precancerous lesions of the cervix uteri in vaccinated young women. In Germany, 44.6% of 17-year-old girls were fully vaccinated in 2015, while vaccination rates were lower in Bavaria.
Methods: We assessed data of legally insured girls from the database of the Bavarian Association of Statutory Health Insurance Physicians (KVB). Vaccination coverage trends were evaluated cross-sectionally and longitudinally. Age at vaccination and type of vaccine administered were investigated. Trends regarding diagnosis of genital warts (ICD-10: A63.0) and precancerous lesions of the cervix uteri (ICD-10: N87.1, N87.2 and D06) between vaccinated and unvaccinated young women were also evaluated.
Results: More than 350,000 girls were vaccinated against HPV in Bavaria from 2008 until 2018. The overall vaccination rate was 46.7%. In 2017, 51% of 18-year old girls were vaccinated at least once against HPV. The number of pediatricians delivering vaccination showed a significant increase in comparison to gynecologists and general *practitioners*. The vaccination rates increased significantly over the years, but with strong regional differences within Bavaria. A reduction in genital warts as well as precancerous lesions is already visible in young women who have been vaccinated against HPV.
Conclusions: The first evaluations on the use of HPV vaccine in Bavaria show a promising decline in the diagnosis of genital warts and precancerous lesions in vaccinated young women. However, a clear increase in vaccination rates is necessary.

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Hasco Study Protocol: Pilot Study for Systematic HPV Self-Sampling for Non-Responders to the Cervical Cancer Screening Program

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Purpose: In this pilot study we will evaluate a systematic approach towards human papillomavirus (HPV) self-sampling for non-responders to the German cervical cancer screening program. In 2020, an organized screening program with co-testing (HPV test + cytology) in 3-yearly intervals will be started. In the past, the participation rate was around 70% in a time frame of three years. The non-participators are at higher risk to develop cervical carcinoma. Previous studies have shown an improving number of patients participating when being re-invited. The willingness to participate in self sampling programs is even higher. Based on this information, the **Ha**nnover **S**elf-**Co**llection study was designed to examine the response rate and practicability of a systematic self-sampling approach.
Methods: 20.000 women aged 30 to 65 years living in the city and region of Hannover, Lower Saxony are randomly included. 10.000 women directly receive a self-sampling kit, the other 10.000 a letter of information and option to participate in the study (opt-out vs. opt-in strategy). Stratifications will be made by age (7 cohorts) and area of living (city vs rural). Women tested positive for high-risk HPV (PCR-based HPV assay)

are prompted to get a cytological smear by their gynecologist. Women with normal cytology will be re-checked after 6 months. Suspicious cytology results lead to an immediate colposcopy. Further treatment will be performed according to the German S3-guideline prevention of cervical cancer.
Results: We designed a prospective randomized study to primarily examine: I) the participation rate (opt-out vs. opt-in model), II) the compliance after a positive HPV test, III) the comparison between two self-sampling gadgets, IV) triaging the samples by new DNA-methylation tests.
Conclusions: To get hold of non-responders to cervical cancer screening programs; self-sampling for HPV is a promising option. Aim of this study is to generate an overall recommendation to improve cervical cancer screening in Germany; especially for non-responders. This study is supported by Deutsche Krebshilfe.

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Protecting Young athletes from UV-Radiation – a Program for Sports Schools

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Purpose: The incidence of melanoma and nonmelanoma skin cancer has increased rapidly.[1] Overexposure to ultraviolet radiation is an established risk factor for the development of melanoma. Due to their intensive sun exposure, student-athletes (SAs) performing outdoor sports have an increased risk for developing skin cancer. [2] Using participatory program planning (PPP), the authors developed a UV-protection-program (UPP) that aims at supporting sports schools in establishing UV-protection strategies.
Methods: To ensure feasibility, UPP was developed in 2019, closely cooperating with students (N=30), parents (N=5), teachers (N=8) and trainers (N=7) of Sportgymnasium Neubrandenburg in 3 focus groups as well as following WHO-recommendations for sun-protection at schools.
Results: In using PPP and working with focus groups-results, UPP could be constructed to meet sports schools' needs, for example employing directive sun-protection briefs and including core values stated most frequently by young athletes. UPP now consists of a project kit containing videospots with tailored messages targeting students, trainers, teachers and parents, as well as posters and a manual about sun-protection and details on its successful implementation.
Conclusions: PPP has shown to be an effective and valuable method in developing UPP for sports schools. Feasibility and acceptance of UPP will be evaluated in September 2019 at Sportgymnasium and Sportoberschule Dresden.

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Disclosure Statement: No conflicts of interest.

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Update on HPV-attributable Cancer in Germany 2016

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Purpose: HPV-attributable cancer is a preventable disease. An estimated ~7.600 people in Germany were predicted to be diagnosed with an HPV-attributable cancer[1,2]. The proportion of oropharyngeal (OP) squamous cell carcinoma (SCC) was assumed to be relatively low (16-20%) based on a pooled analysis of European study results. As country specific results on the changing epidemiology of oropharyngeal (OP) squamous cell carcinoma (SCC) in Germany is available[3], our aim was to update previous estimates on the incidence of HPV-attributable cancer for Germany.
Methods: Nationwide cancer incidence on HPV-related SCC for 2016 was calculated based on estimates of cancer incidence rates from the Center for Cancer Registry Data for Germany. Proportions of cancers attributable to HPV-infection (HPV-AF) were calculated according to previously published methods[2], taking new country specific results on HPV-prevalence in OPSCC into account.
Results: Two clinical studies from Germany attribute >50% of most recently diagnosed OPSCC to HPV (years of diagnosis 2013/2015). When taking the country specific prevalence in OPSCC into account, the HPV-AF in OPSCC will be more than twice as high as previously reported. The total number of HPV-attributable cancer in Germany then approaches 10.000 new cases a year.
Conclusions: Previous estimates attributed a significantly lower proportion of OPSCC to HPV than most recent study results from two single medical institutions in Germany suggest. Although the calculation of HPV-related cancer burden remains methodologically challenging, recent evidence indicates that oropharyngeal cancer increasingly contributes to the burden of cancer. The HPV-AF for OPSCC in Germany will best be estimated by direct testing of HPV DNA/p16 overexpression/E6-E7 mRNA expression in continuous representative sentinel sampling of tumor tissue for monitoring the effects of HPV-vaccination in the German population.

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1. DOI: 10.3238/arztebl.2018.0586;
2. DOI 10.1186/s12885-017-3678-6;
3. DOI: 10.1002/cam4.2039

Disclosure Statement: no conflicts of interest

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Results of Intensified Breast Cancer Screening in Women After Treatment for Hodgkin's Lymphoma in Childhood and Adolescence

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Purpose: Treatment of pediatric Hodgkin´s lymphoma (HD) by radio-/chemotherapy lead to more than 90% survivors within at least 20 years. However, patients suffer from long-term sequelae particularly including former radiation fields (e.g. secondary breast cancer/sBC). Since 2012 patients from HD studies (HD-78 to HD-95/Intervall) received the offer to participate in the structured surveillance program for breast cancer (IFP) within the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC).
Methods: We aimed to prospectively evaluate the efficacy of the iFE in female HD patients who had received radiation to the breast at young ages. Within the "GPOH-HD-Spätfolgen" research project 534 women of a cohort study with more than 30 years´ follow up were still alive in 2012. 224 of them participated in the IFP.
Results: Median age at time of HD diagnosis was 16.3 years. By September 2019, 33 sBC had been diagnosed at a median age of 41.7y (range 26-56y). Median Interval from HD to sBC was 23.4y. 22 prevalent (66.7%) and 11 incident (33.3%) cases of sBC were diagnosed. 10 of 11 (90%) incident cases were detected in early stages (pTis/1a-c, pN0) while 8 of 22 (36.4%) prevalent cases were diagnosed in stage pT2 and/or pN+ and one patient was primarily metastasized. The majority of tumors were ductal invasive (85%, n=22 von 26), G1-2 (72%, n=21 von 29) and hormone receptor positive (81%, n=25 von 31).
Conclusions: Women who received radiation to the breast for HD at young ages face a significantly elevated risk for sBC compared to risk-adjusted general population and should be informed about the IFP at the centers of the GC-HBOC. In further studies we will investigate the role of genetic risk factors in the pathogenesis of sBC.

Central Nervous System Tumors

Poster

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Inhibition of the DNA Damage Response in Neuroblastoma Cells Affects Sensitivity to Platinum Compounds

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Neuroblastoma (NB) are one of the most common malignant paediatric brain tumors. Patients treated with aggressive platinum-based chemotherapy often suffer from long-term sequelae. Additionally, developed drug resistance often limits therapeutic efficacy. Here, we target the DNA damage response (DDR) of NB cells differing in their N-myc status in order to modulate their sensitivity to platinum compounds. Additionally, we comparatively investigated the platinum compound response of NB cells and cisplatin (CisPt) selected drug resistant NB variants. The DDR was modulated by pharmacological inhibition of checkpoint kinases (CHK 1/2) and poly(ADP-ribose)-polymerase 1 (PARP 1) with LY2603618 or Olaparib, respectively.
Cell viability was determined by using the Alamar Blue assay. Alterations in cell cycle progression were assayed by flow cytometric analysis. The formation of Pt-(GpG) intrastrand crosslinks was determined via Southwestern blot. The amount of DNA double-strand breaks (DSBs) was quantified by measuring the levels of nuclear γH2AX (S139 phosphorylated H2AX) and 53BP1 foci via immunocytochemistry. Mechanisms of the DDR were analysed by Western blot and the expression of CisPt-related susceptibility factors by quantitative realtime PCR.
N-myc amplified IMR-32 cells revealed an increased sensitivity to platinum compounds as well as to the pharmacological inhibitors in comparison to the N-myc nonamplified SH-SY5Y cells. Upon months-long CisPt selection, CisPt resistant SH-SY5Y^{R} and IMR-32^{R} variants were isolated, which revealed up to 4-fold increased CisPt resistance as compared to their corresponding wild-types. The resistant variants were cross-resistant to carboplatin (CarboPt) as well as to LY2603618 and Olaparib. Pretreatment with subtoxic concentrations of the inhibitors increased the sensitivity to CisPt in both cell lines.
Based on the data, we conclude, that pharmacological modulation of the DDR/DNA repair is useful for targeting CisPt resistant NB cells and, furthermore, to improve their responsiveness to platinum-based chemotherapy.

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Activity of Larotrectinib in TRK Fusion Cancer Patients with Brain Metastases or Primary Central Nervous System Tumors

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Purpose: TRK fusions are oncogenic drivers of a variety of cancers, many of which can involve the central nervous system (CNS). Larotrectinib is a FDA-approved selective TRK inhibitor for the treatment of TRK fusion cancer. While larotrectinib has been shown to cross the blood–brain barrier, its clinical activity in a series of TRK fusion cancers with primary or metastatic intracranial disease has not been described.
Methods: Patients (pts) with non-primary CNS solid tumors with brain metastases, or primary CNS tumors harboring a TRK fusion treated with larotrectinib in two clinical trials (NCT02637687, NCT02576431) were identified. Larotrectinib was administered until disease progression, withdrawal, or unacceptable toxicity. Disease status was investigator-assessed (RANO, RECIST).
Results: 24 pts were identified: 6 non-primary CNS solid tumors (4 lung cancer, 2 thyroid cancer; fusion type: 2 *ETV6-NTRK*3, 2 *SQSTM1-NTRK3*, 1 *EPS15-NTRK1;* 1 *TPR-NTRK1*; age range 25–79 y) and 18 primary CNS tumors (6 glioblastoma, 4 glioma, 3 glioneuronal, 3 NOS, 2 astrocytoma; 13 fusion genes involving *NTRK2*, and 2 each *NTRK1* and *NTRK1;* aged 2–79 y). In 5 pts with non-primary CNS tumors evaluable for response, the best objective response to therapy was PR in 3 (60%, 1 pending confirmation), SD in 1 (20%). Duration of response ranged from 9+ to 13 mo. In the 18 pts with primary CNS tumors, the best overall response to therapy was CR in 2 pts, PR in 3 pts, for an objective response rate of 36%. 9 pts (64%) had SD. Disease control ≥ 24 w was seen in 10 pts (71%). Duration of treatment ranged from 0.03+ – 16.6+ mo.
Conclusions: Larotrectinib is active in pts with TRK fusion cancers with intracranial disease. Confirmed responses and durable disease control were seen in metastatic disease and primary CNS tumors of various histologies. These results further support expanded testing for TRK fusions across all cancers, including primary CNS tumors.

Disclosure Statement:
Serge Leyvraz reports personal fees from Immunocore, and Bayer outside the submitted work.
Alexander Drilon reports HONORARIA/ADVISORY BOARDS: Ignyta/Genentech/Roche, Loxo/Bayer/Lilly, Takeda/Ariad/Millenium, TP Therapeutics, AstraZeneca, Pfizer, Blueprint Medicines, Helsinn, Beigene, BergenBio, Hengrui Therapeutics, Exelixis, Tyra Biosciences, Verastem, MORE Health; ASSOCIATED RESEARCH PAID TO INSTITUTION: Pfizer, Exelixis, GlaxoSmithKlein, Teva, Taiho, PharmaMar; RESEARCH: Foundation Medicine; ROYALTIES: Wolters Kluwer; OTHER: Merck - Food/Beverage, Puma - Food/Beverage, and CME HONORARIA: Medscape, OncLive, PeerVoice, Physicians Education Resources, Targeted Oncology, Research to Practice.
Steven G. DuBois reports Loxo: consultancy and travel expenses, and Roche: travel expenses.
Anna F. Farago reports Research support – Bayer Healthcare, Loxo Oncology, Inc., Genentech, Roche, Bristol-Myers Squibb, AstraZeneca, AbbVie, PharmaMar, Merck, Ignyta, Amgen, Novartis; Consultant – Bayer Healthcare, Loxo Oncology, Inc., Genentech, Roche, Bristol-Myers Squibb, AstraZeneca, AbbVie, PharmaMar, Boehringer Ingelheim, and Honorarium – Dava Oncology, Clinical Care Options, Medical Learning.
Birgit Geoerger none.
Juneko E. Grilley-Olson none.
David S. Hong reports Research/Grant Funding: AbbVie, Adaptimmune, Amgen, Astra-Zeneca, Bayer, BMS, Daiichi-Sankyo, Eisai, Fate Therapeutics, Genentech, Genmab, Ignyta, Infinity, Kite, Kyowa, Lilly, LOXO, Merck, MedImmune, Mirati, MiRNA, Molecular Templates, Mologen, NCI-CTEP, Novartis, Pfizer, Seattle Genetics, Takeda; Travel, Accommodations, Expenses: LOXO, MiRNA, ASCO, AACR, SITC, Genmab; Consulting or Advisory Role: Alpha Insights, Axiom, Adaptimmune, Baxter, Bayer, Genentech, Glg, Group H, Guidepoint Global, Infinity, Janssen, Merrimack, Medscape, Numab, Pfizer, Seattle Genetics, Takeda, Trieza Therapeutics, and Other ownership interests: Molecular Match (Advisor), OncoResponse (founder), Presagia Inc (Advisor).
Davendra Sohal reports Consulting advisory role, Perthera, Ability Pharma; Honoraria, Foundation Medicine, and Research funding, Novartis, Cellgene, OncoMed, Bayer, Genentech, Bristol-Myers Squibb, Agios, Incyte, Loxo.
Cornelis M. van Tilburg reports Bayer: advisor, and Novartis: advisor.
David S. Ziegler nothing to disclose.
Nora C. Ku is an employee of Loxo Oncology Inc.
Michael C. Cox was an employee of Loxo Oncology Inc.
Shivani Nanda is an employee of Bayer.
Barrett H. Childs is an employee of Bayer.
Francois Doz reports BAYER: travel expenses, advisory board, and ROCHE: advisory board.

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Targetable FGFR3 Fusions and Novel FGFR3 Mutations in Glioma

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Purpose: Fibroblast growth factor receptor (FGFR) inhibitors are currently in clinical development. A subset of IDH wildtype glioblastomas contain fusion genes between FGFR3 and transforming acidic coiled-coil protein 3 (TACC3). The resulting increase in FGFR3 expression is considered as a marker to detect FGFR3 fusions in gliomas. The aim of the present study was (i) to investigate alterations in FGFR3 in the Tübingen glioma cohort and (ii) to evaluate the role of FGFR3 immunohistochemistry in addition to targeted NGS gene panel sequencing and RT-PCR.
Methods: FGFR 3 immunohistochemistry (IHC) screening was carried out in 548 glioma samples using tissue microarrays. The results were validated in external cohorts with a total of 326 patients. RT-PCR screening and IHC was performed in 101 consecutive sampled glioblastomas to determine the frequency of FGFR3 –TACC3 fusions. Further targeted NGS panel sequencing was carried out in 74 samples. The effect of a novel specific mutation was further studied by molecular modelling.
Results: The spectrum of molecular alterations that we detected included FGFR3 fusions, FGFR3 amplification and FGFR3 gene mutations. FGFR3 fusions were associated with strong FGFR3 protein expression and distinct histological patterns. Molecular modelling of the novel mutation suggests that this molecular event leads to an activating FGFR3 kinase function. A detailed analysis will be presented.
Conclusions: Gliomas may carry more than one FGFR3 alteration in the same tumor. FGFR3 IHC might be a useful marker to identify FGFR3-TACC3 fusions in IDH-wildtype tumors and could thus be further included in the regular IHC diagnostic algorithm to detect therapeutic targets.

Disclosure Statement: GT served on Advisory Boards of BMS, MSD and AbbVie; received research and/or travel grants from Roche Diagnostics, Novocure and Medac, received speakers` fees from Medac, Novocure.

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Personalized Medicine for Neuro-Oncology Patients: Implementation and Outcome of the Molecular Tumor Board Tuebingen

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Purpose: The Molecular Tumor Board (MTB) at the University Hospital Tuebingen has been established in 2016 to discuss molecular data-driven personalized therapeutic strategies for all tumor patients. The current study aims at retrospectively reviewing the MTB experience so far for neuro-oncology patients with a particular focus on feasibility, work flows for molecular diagnostics, review of frequent molecular patterns and clinical outcome.
Methods: Medical records from MTB neuro-oncology patients from April 2016 – August 2019 were reviewed. The retrospective study was approved by the ethical board. We discussed molecular profiling reports in the MTB, evaluated the evidence for actionability of molecular alterations and recommended molecular data-driven therapeutic strategies.
Results: So far, around 300 neuro-oncology patients with different histological entities (primary and metastatic tumors) were presented in the MTB. Molecular diagnostics included gene panel sequencing, transcriptome analysis and immunohistochemical staining of associated targets in selected cases. Actionable alterations were frequently detected. A precise analysis will be presented. In the subgroup of glioblastoma patients, molecular alterations in the CDKN2A/2B and in the PTEN gene occurred frequently. Immunohistochemical evaluation of associated targets was included with antibodies detecting relevant downstream targets. Genetic changes and protein data in the associated cellular pathways will be correlated. The final analysis of therapeutic strategies and clinical outcome data will be presented.
Conclusions: A personalized medicine program is feasible for neuro-oncology patients, particularly in the absence of further treatment options or matching clinical trials. The MTB ensures an appropriate interdisciplinary discussion of tumor molecular profiles, therapeutic decisions and documentation of outcome.

Disclosure Statement: GT: served on Advisory Boards of BMS, MSD, AbbVie; research and/or travel grants: Roche, Novocure, Medac, speakers` fee: Medac, Novocure.

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Efficacy of Entrectinib in Patients (PTS) with Solid Tumors and Central Nervous System (CNS) Metastases: Integrated Analysis from 3 Clinical Trials

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Purpose: Entrectinib potently inhibits kinases encoded by the *NTRK* and *ROS1* genes. It attains therapeutic levels in the CNS with antitumor activity in intracranial tumor models. We report integrated data (31/05/18 cut-off) from 3 Phase 1/2 entrectinib trials (ALKA-372-001, EudraCT 2012-000148-88; STARTRK-1, NCT02097810; STARTRK-2, NCT02568267) in adults with *ROS1* fusion-positive NSCLC (*ROS1*+) or *NTRK* fusion-positive solid tumors (*NTRK*+), with/without baseline CNS metastases.
Methods: Pts had locally advanced/metastatic *NTRK*+ or *ROS1*+ tumors by nucleic acid-based confirmation. CNS metastases were detected by CT/MRI. Tumor assessments by blinded independent central review (RECIST v1.1): wk 4, then every 8 wks. Primary endpoints: objective response rate (ORR), duration of response (DOR). Secondary endpoints: clinical benefit rate (CBR), PFS, OS, intracranial efficacy and safety.
Results: Most pts had ≥1 prior therapy; 33% had baseline CNS metastases. Outcomes for *ROS1*+ NSCLC (n=53) and *NTRK*+ solid tumors (n=54; 24% sarcoma, 18% NSCLC) efficacy evaluable pts by baseline CNS disease (no v yes) were:
ROS1+ (n=30 v 23):
% ORR (95% CI): 80.0 (61.4, 92.3) v 73.9 (51.6, 89.8)
CR, n (%): 3 (10.0) v 0
PR, n (%): 21 (70.0) v 17 (73.9)
mDOR, mo (95% CI): 24.6 (11.4, 34.8) v 12.6 (6.5, not evaluable [NE])
% CBR (95% CI): 80.0 (61.4, 92.3) v 73.9 (51.6, 89.8)
mPFS, mo (95% CI): 26.3 (15.7, 36.6) v 13.6 (4.5, NE)
mOS, mo (95% CI): NE v NE (10.5, NE)
Intracranial % ORR; mDOR; mPFS: NE v 55.0 (31.5, 76.9; n=20); 12.9 (5.6, NE); 7.7 (3.8, 19.3)
NTRK+ (n=42 v 12):
% ORR: 59.5 (43.3, 74.4) v 50.0 (21.1, 78.9)
CR: 4 (9.5) v 0
PR: 21 (50.0) v 6 (50.0)
mDOR: 12.9 (7.1, NE) v NE (4.2, NE)
% CBR: 61.9 (45.6, 76.4) v 75.0 (42.8, 94.5)
mPFS: 12.0 (8.7, 15.7) v 7.7 (4.7, NE)
mOS: 20.9 (16.8, NE) v 14.3 (51, NE)
Intracranial % ORR; mDOR; mPFS: NE v 54.5 (23.4, 83.3; n=11); NE (5.0, NE); 14.3 (5.1, NE)
Entrectinib was tolerable with a manageable safety profile; most treatment-related AEs were grade 1–2.
Conclusions: Entrectinib induced clinically meaningful durable responses in pts with *ROS1*+ NSCLC or *NTRK*+ solid tumors with/without CNS disease.

Conflicts of Interest:
Tobias Overbeck: Honoraria (self) from AstraZeneca, BMS, BoehringerIngelheim, Eli Lilly, Medac, MSD, Novartis, Roche/Genentech; Advisory/Consultancy for AstraZeneca, BMS, BoehringerIngelheim, Eli Lilly, Medac, MSD, Novartis, Roche/Genentech; Research grant/Funding (institution) from AstraZeneca, Eli Lilly, Roche/Genentech, Sanofi-Aventis; Travel/Accommodation/Expenses from AstraZeneca, Boehringer-Ingelheim, Eli Lilly, and Roche/Genentech.
Salvatore Siena: Advisory board member for Amgen, Bayer, BMS, CheckmAb, Celgene, Clovis, Daiichi-Sankyo, Incyte, Merck, Novartis, Roche/Genentech, and Seattle Genetics.
Robert C. Doebele: Honoraria from Genentech/Roche, Takeda/Millenium; Advisory board for Genentech/Roche, Rain Therapeutics; Travel reimbursement from Genentech/Roche, Ignyta; Licensing fees for biological materials from Genentech/Roche, Ignyta, Foundation Medicine, Loxo Oncology; Consulting for Ignyta, Loxo Oncology, Bayer, Rain Therapeutics; Sponsored research for Ignyta, Loxo Oncology; Stock ownership at Rain Therapeutics; Licensing fees from patent from Rain Therapeutics, and Abbott Molecular.
Alice T. Shaw: Consulting, honoraria, and institutional (research) support from Genentech, Roche, and Ignyta.
Christos C. Karapetis: Advisory board role for Roche, MSD, BMS, Amgen, AstraZeneca, Eisai; Honoraria from Roche, Eisai, and AstraZeneca.
Daniel S.W. Tan: Honararia (self) from Merck, Pfizer, Novartis, Boehringer Ingelheim, Roche, Takeda; Advisory / Consultancy for Novartis, Bayer, Boehringer Ingelheim, Celgene, Astra Zeneca, Eli-lily, Loxo; Research grant / Funding (self) from Novartis, Astra Zeneca, GlaxoSmithKline, Bayer, Pfizer; Travel / Accommodations / Expenses from Merck, Pfizer, Novartis, Boehringer Ingelheim, Roche,Takeda.
Byoung Chul Cho: Research funding from Novartis, Bayer, AstraZeneca, MOGAM Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono Pharmaceuticals, Dizal Pharma, MSD; Consulting role for Novartis, AstraZeneca, BoehringerIngelheim, Roche, Bms, Ono Pharmaceuticals, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, MSD; Stock ownership at TheraCanVac Inc., Gencurix, Inc., Bridge Biotherapeutics; Royalty from Champions Oncology.
Dong-Wan Kim: Research funding (institution) from Alpha Biopharma, AstraZeneca/MedImmune, Hanmi, Janssen, Merus, Mirati Therapeutics, Inc, MSD, Novartis, Ono Pharmaceutical, Pfizer, Roche/Genentech, Takeda, TP Therapeutics, Xcovery, and Yuhan.
Myung-Ju Ahn: Advisory / Consultancy for AstraZencea, Lilly, MSD, Takeda, Alpha pharmaceuticals, Roche, Yuhan.
Matthew G. Krebs: Advisory Boards for Roche, Janssen, OCTIMET Oncology, Achilles Therapeutics; Travel grants from AstraZeneca, BerGenBio; Research funding from Roche.
Koichi Goto: Honoraria (institution) from MSD, AstraZeneca, Novartis Pharma, Life Technologies Japan, Pfizer Japan Inc., Bristol-Myers Squibb., Ono Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd, Chugai Pharmaceutical Co., Ltd, Eli Lilly Japan, Nippon Boehringer Ingelheim Co., Ltd, Takeda Pharmaceutical Co., Ltd, Otsuka Pharmaceutical, Kyowa Hakko Kirin Co.,Ltd; Research grant/Funding (institution) from Taiho Pharmaceutical Co., Ltd, Chugai Pharmaceutical Co., Ltd, Ono Pharmaceutical Co., Ltd, Astra Zeneka, Sumitomo Dainippon Pharma Co., Ltd, Bristol-Myers Squibb, MSD, Astellas Pharma Inc., Eisai Co., Ltd, DAIICHI SANKYO Co., Ltd, Pfizer Inc., Kyowa Hakko Kirin Co., Ltd, Novartis Pharma, Takeda Pharmaceutical Co., Ltd, Eli Lilly Japan, Merck Serono Co., Ltd, Ignyta,Inc., Boehringer Ingelheim Japan, Inc., Janssen Pharmaceutical, Ignyta, Inc., Loxo Oncology, Sysmex Corporation Xcoo, Inc., and Medical & Biological Laboratories Co., Ltd.

Pilar Garrido: Consulting and advisory services (self) for Roche, MSD, BMS, Boehringer Ingelheim, Pfizer, AbbVie, Guardant Health, Novartis, Eli Lilly, AstraZeneca, Janssen, Sysmex, Blueprint Medicines, Takeda; Speaking, public presentations (self) from Takeda, AstraZeneca, Roche, MSD, BMS, Pfizer, Novartis, Boehringer Ingelheim, Gilead Sciences, Rovi; Financial support for clinical trials (institution) from Roche, MSD, BMS, Takeda, Eli Lilly, Pfizer, Novartis, Pharmamar, Celgene, Sanofi, Gsk, Theradex Oncology, Blueprint Medicines; Financial support for contracted research (institution) from Guardant Health, and Sysmex.
Anna F. Farago: Advisory/Consultancy for Roche, Genentech, Loxo Oncology, Bayer, Pharmamar, AstraZeneca, Bristol-Myers Squibb, AbbVie, Boehringer Ingelheim; Research grant/Funding (self) from AbbVie, AstraZeneca; Research grant/Funding (institution) from AbbVie, and AstraZeneca, Pharmamar, Merck, Bristol-Myers Squibb, Amgen, Genentech/Roche, Ignyta, Loxo, Bayer, Novartis; Travel/Accommodation/Expenses from Roche, Genentech, Loxo, Bayer, Pharmamar, AstraZeneca, Bristol-Myers Squibb, AbbVie, and Boehringer Ingelheim.
Herbert H.F. Loong: Consulting or advisory role (self) for GlaxoSmithKline, Roche/Genentech, Novartis; Speakers' Bureau (self) for AbbVie, Ignyta, Novartis; Research Funding (institution) from MSD Oncology; Travel/Accommodation/Expenses from Roche, MSD Oncology, Bayer, and Pfizer.
Diego Tosi: Travel expenses for scientific meetings from Pfizer, Astellas, MSD; Research funding from Janssen, Astellas, Ipsen; Research contract from Phosplatin Therapeutics; Research grant from Ipsen.
Minal Barve: No conflicts of interest to disclose.
Brian P. Simmons: Employment at Genentech, Inc.; Stock ownership at Roche.
Chenglin Ye: Employment at Genentech, Inc.; Stock ownership at Roche.
Xinhui Huang: Employment at Genentech, Inc.; Stock ownership at Roche.
Alexander Drilon: Honoraria or advisory boards for Ignyta/Genentech/Roche, Loxo/Bayer/Eli Lilly, Takeda/Ariad/Millenium, TP Therapeutics, AstraZeneca, Pfizer, Blueprint Medicines, Helsinn, BeiGene, BerGenBio, Hengrui Therapeutics, Exelixis, Tyra Biosciences, Verastem Oncology, MORE Health, AbbVie; Associated research paid to institution: Pfizer, Exelixis, GlaxoSmithKline, Teva Pharmaceutical Industries, Taiho Pharmaceutical Co., Ltd, Pharmamar; Research for Foundation Medicine; Royalties from Wolters Kluwer; Food and beverage from Merck, Puma; CME Honoraria from Medscape, OncLive, PeerVoice, Physicians' Education Resources, Targeted Oncology, Research to Practice, Oncology.
All authors: Medical writing and editorial support for the original abstract was provided by Gardiner-Caldwell Communications, Ashfield Healthcare Communications and sponsored by Roche in accordance with Good Publication Practice guidelines. Support for third-party editing assistance for this abstract, furnished by Helen Singleton, PhD, Sammi Cham, BA, and Niamh Gould, BA, of Health Interactions, was provided by Roche Pharma AG. This study was funded by F. Hoffmann La-Roche, Basel, Switzerland.

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Regorafenib in Advanced High Grade Glioma

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Purpose: The REGOMA phase II trial has recently reported an overall survival benefit of the oral multikinase inhibitor regorafenib in progressive glioblastoma1. We analyzed retrospectively the clinical efficacy of regorafenib and treatment-related adverse events in a series of patients with advanced stages of glioma.
Methods: Patients with progressive glioma received 80-160 mg regorafenib daily (3 weeks on, 1 week off) until tumor progression or dose-limiting toxicity.
Results: We treated 24 patients with regorafenib (21 glioblastoma, 1 astrocytoma, 1 midline glioma, 1 oligodendroglioma). Median progression-free survival was 2.1 months, median overall survival 4.1 months. The occurrence of hand-foot-syndrome correlated with longer median survival. Adverse events of CTCAE grades 1-3 included fatigue (13/24, 54%), dermatological toxicity (8/24, 33%), increased lipase (5/24, 21%) and endocrinological events (4/24, 17%). One patient developed a treatable corticosteroid-responsive aseptic meningitis during regorafenib.
Conclusions: In the absence of further available treatment strategies, regorafenib could be evaluated as an option in progressive glioblastoma2. Dermatological toxicity might be useful as a clinical marker for patient stratification and could be investigated in future prospective trials. Given the broad application of regorafenib beyond the field of neuro-oncology, the occurrence of a treatable aseptic meningitis3 might be of interest for the general clinical management during regorafenib treatment.

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2. Tzaridis et al., Neuro Oncol 2019
3. Gepfner-Tuma et al., Neuro Oncol Practice 2019

Disclosure Statement: IG-T: speaker's fees from Novocure; grant from Medac. UH: grants and personal fees from Roche; personal fees and nonfinancial support from Medac; personal fees from Novocure; Novartis; Daichi Sankyo; Riemser; Noxxon; Abbvie; Bayer. GT served on Advisory Boards of BMS; MSD; AbbVie; received research and/or travel grants from Roche; Novocure; Medac; speaker's fees from Medac; Novocure.

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Targeting of CSF1R and PD1 in Experimental Glioma

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Purpose: Glioblastoma is an aggressive primary tumor of the central nervous system. The median overall survival of patients is in the range of 1.5 years even in selected clinical trial populations investigating multimodal therapies. Novel therapeutic strategies are urgently needed. Therapeutic targeting of the glioblastoma-associated microenvironment is a promising approach in this regard. Particularly macrophages represent a highly abundant population of tumor-infiltrating host cells. The colony stimulating factor-1/colony stimulating factor-1 receptor (CSF1/CSF1R) axis plays an important role for macrophage differentiation and survival.
Methods: To assess CSF1R in human glioblastoma, we performed CSF1R staining in human tissue samples from primary and recurrent glioblastoma. For targeting the tumor microenvironment (TME) we performed an anti-CSF1R approach in experimental glioma using the antibody clone 2G2[1] syngeneic preclinical glioma mouse models. TME-associated treatment patterns were evaluated by histology and immunochemistry.
Results: CSF1R is present in human samples of primary and recurrent glioblastoma. Monotherapy with anti-CSF1R antibody increased latency until the onset of neurological symptoms in SMA560-bearing VM/Dk mice and CD204 and CD11b positive cells were reduced suggestive after treatment. A combination of anti-PD1 and anti-CSF1R antibodies further prolonged the symptom-free survival and led to higher $CD8^+/CD4^+$ ratios *in vivo*.
Conclusions: Our results identify CSF1R as a promising therapeutic target for glioblastoma, probably in combination with PD1 inhibition.

Reference:
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Disclosure Statement: HB received funds from a Siegmund Kiener doctoral fellowship. GT received grants from Roche Diagnostics. GT received research and/or travel grants from Roche, Novocure, Medac; speakers` fees from Medac, Novocure.

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Argyrin F Leads to Targetable Treatment-Induced Vulnerabilities in Experimental Glioma

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Purpose: Glioblastoma is an aggressive primary tumor of the nervous system with limited efficient treatment options. The proteasome inhibitor Argyrin A and its recently developed analogue Argyrin F display anti-tumor activity [1, 2]. Proteasome inhibition is a promising therapeutic strategy in glioma. In fact, the EORTC 1709 trial investigates Marizomib in newly diagnosed glioblastoma. We consequently aimed at exploring the anti-glioma activity of Argyrin F in experimental glioma to evaluate its suitability for further clinical development in glioblastoma.
Methods: We performed an in-depth characterization of Argyrin F induced effects in LN229, LNZ308, SMA560, and GL261 cell lines by acute cytotoxicity (24 h and 48 h) and clonogenicity assays. We determined $p27^{KIP1}$ levels by immunoblot, proteasome activity by fluorometry, and cell cycle progression by flow cytometry. We investigated the HLA ligandome with an EC_{20} dosage and conducted *in vivo* treatments in the syngeneic SMA560/VMDk glioma model.
Results: We observed treatment-related reductions of proteasome activity, cell viability and clonogenic survival (> 50% reduction at 0.5 mg/mL) and an increase of $p27^{KIP1}$ levels. Argyrin F induces the presentation of immunogenic peptides on the cell surface. *In vivo* analysis and histological characterizations are ongoing and will be presented.
Conclusions: Argyrin F has anti-glioma activity and might, therefore, be an interesting therapeutic approach for clinical translation in glioblastoma, potentially in combination with immunotherapeutic strategies.

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1. Chen X *et al*, *Cancer letters* 2017
2. Nickeleit I *et al*, *Cancer Cell* 2008

Disclosure Statement: GT served on Advisory Boards of BMS; MSD and AbbVie; received research and/or travel grants from Roche Diagnostics; Novocure and Medac; received speaker's fees from Medac; Novocure.

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The Influence of an Infection with S. Aureus on Growth and Cytokine Secretion of Glioblastoma Multiforme (GBM)

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Purpose: The relationship between postoperative infections and a prolonged survival in patients with GBM remains controversial. Nevertheless, there are no studies on the influence of infections of GBM cells on survival and proliferation of these cells. There is evidence to suggest that pathogens may stimulate the tumor cells to secret cytokines. To test these hypotheses, we established an in vitro infection model with Staphylococcus aureus.
Methods: Four primary GBM cultures and one culture of human brain astrocytes (HBA) were infected with the strain 6850 of S. aureus and observed for 7 days. At different timepoints the number of intracellular bacteria was determined. A gene expression analysis was performed by qPCR and the secretion of proinflammatory cytokines (IL6, IL8) was measured by ELISA.
Results: All cell cultures expressed factors to enable bacterial internalization and were infectable with S. aureus. The GBM cells ingested up to 4.7% of the bacteria, the HBA up to 0.3%. The HBA eliminated the bacteria very quickly and survived better than the GBM, but also the GBM showed a quick elimination and recovered. There was a significant increase ($p<0.01$) in expression of the proliferation markers MKI67 (6.7fold), PLK1 (2.9fold) and the transcription factor c-Jun (3.0fold) in all infected GBM cells, compared to uninfected cells. 24h after infection, there was an increase in secretion of the proinflammatory cytokines IL6 (7.2fold, $p<0.001$) and IL8 (1.8fold) in the GBM cells, compared to uninfected cells. The HBA also showed an increase in IL6 and IL8 secretion, but to a lower extent (IL6: 5.6fold, IL8: 1.1fold). Interestingly, the uninfected HBA showed a significantly higher IL6 (up to 10.2fold) secretion than the uninfected GBM cells.
Conclusions: In summary, both GBM and HBA could be infected by S. aureus, whereby the GBM proved to be more vulnerable to the infection. Furthermore, there was an increased secretion of proinflammatory cytokines in GBM, comparable to uninfected HBA, indicating a stimulation of the GBM cells.

Disclosure Statement: There are no conflicts of interest.

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Radiotherapy for Glioblastoma – Feasibility, Results and Correlation of Target Volumes and Location of Relapse in a Monoinstitutional Sample

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Purpose: Glioblastoma is the most common primary brain tumor. Radiotherapy is a well-established adjuvant treatment modality. However, nearly all patients suffer from a relapse of the tumor. The aim of this survey was to document the feasibility and results and to correlate the location of the relapse with the target volumes and isodoses.
Methods: All patients, which received RT or RCT at the University Hospital Regensburg for glioblastoma from 2004 to 2012 were included.
94 patients could be identified. The median age was 57 years with 60.6% male and 39.4% female patients. For 30 patients we could perform a fusion of the MRI scan showing the relapse with the treatment plans and correlate the localization.
The median follow-up was 16 months (IQR 9 to 24 months).
Results: The feasibility of radiotherapy was good.
The median overall survival was 14 months. After 12 months 62% and after 24 months 20% of the patients were alive.
The median progression free survival was 8 months. After 6 months 40%, after 12 months 75% and after 24 months 93% suffered from a tumor relapse.
In most of the cases the main volume of the recurrent tumor occurred within the initial high dose area (60 Gy). Only one recurrent glioblastoma was completely outside the initial target volumes.

Conclusions: The feasibility of radiotherapy was good, but the survival data are still unsatisfying. The main challenge is the avoidance of local relapse inside the target volumes.

Disclosure Statement: On behalf of all authors, the corresponding author declares that there are no conflicts of interest.

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Inhibiting BHLH Transcriptional Networks Using Dominant Negative E47 Leads to a Strong Anti-Glioma Activity in Vitro and in Vivo

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Inhibiting bHLH transcriptional networks using dominant negative E47 leads to a strong anti-glioma activity in vitro and in vivo
Purpose: The transcription factor E47 forms heterodimers with helix-loop-helix (HLH)/basic helix-loop-helix (bHLH) proteins such as ID-1 and Olig2, both of which are frequently overexpressed in gliomas. The dominant negative variant of E47 (dnE47) lacks a nuclear translocation signal and eventually leads to sequestration of HLH and bHLH factors into the cytoplasm. In this study, we investigated a combination of this approach with standard of care (SOC) temozolomide and irradiation to explore its therapeutic efficacy and molecular mechanisms.
Methods: Doxycycline-inducible dnE47 lentivirus was used to transduce long-term and stem cell glioma cell lines. In vitro experiments including immunoblots, immunocytochemistry stainings, cytotoxicity and clonogenic assays were performed for functional evaluation of the dnE47 approach. Effects upon latency of symptom onset were investigated in vivo. CAGE and RNA-seq were used to study transcriptional changes upon dnE47 induction.
Results: dnE47 induction led to cytoplasmatic sequestration of HLH/bHLH proteins, reduced proliferation, increased cytotoxicity and reduced clonogenic survival in vitro. In vivo experiments showed a longer latency for symptom onset. CAGE and RNA-seq analysis pointed to alterations in several cancer-related pathways.
Conclusions: dnE47-mediated inhibition of HLH/bHLH networks induced actionable molecular alterations in glioma that could be exploited to develop novel therapies.

Disclosure Statement: MK received funds from Elfriede Kröner Stiftung, GT served on Advisory Boards of BMS, MSD and AbbVie; received research and/or travel grants from Roche Diagnostics, Novocure and Medac; received speaker's fees from Medac, Novocure

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Pretreatment with the mTOR Inhibitor Everolimus Enhances Glioblastoma Sensitivity to Temozolomide in Vitro

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Purpose: Glioblastoma (GBM) is the most invasive and devastating primary brain tumor with a median overall survival time of 18 months despite aggressive multimodal therapy. New therapeutic strategies, potentially involving multistage chemotherapy regimens, are needed to enhance survival. This applies not only in the setting of progressive disease but also in frontline protocols.
Methods: Four distinct primary GBM cell cultures were treated with the mTOR inhibitor everolimus and/or the tyrosine kinase inhibitor axitinib. Untreated cell cultures and cultures treated with the corresponding vehicle (ethanol and/or DMSO) acted as controls. Treatment was applied to each culture once and the IC10, IC25 and IC50 concentrations previously determined by MTT assay were used. Surviving cells were cultured for three passages and then tested for chemosensitivity to lomustine and temozolomide.
Results: Cells resistant to the initial treatment could be cultivated in all study groups. However, cells treated with the combination of everolimus and axitinib, and with axitinib alone (IC25 and IC50), showed the strongest treatment effects. Cells in these groups no longer adhered to the substrate of culture vessels after two passages. Cells that could be cultured showed no significant difference in chemosensitivity to lomustine after pretreatment. However, cells treated with everolimus were significantly more sensitive to temozolomide. Vehicle pretreatment was also associated with a trend towards increased temozolomide sensitivity.
Conclusions: Everolimus pretreatment strongly enhances GBM cell chemosensitivity to temozolomide. This finding may have relevance for GBM treatment strategies and should now be explored in vivo.

Disclosure Statement: The authors report no conflicts of interest.

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Analysis of Possible Influence of Cortex Temperature on Patient Cognition during Awake-Surgery

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Purpose: During skull trepanning, it is possible to observe an intraoperative heat loss at the brain surface due to convection as well as thermal radiation. This effect is intensified involuntarily, when rinsing fluid adapts to room temperature during surgery, or intentionally, when cerebral seizures are stopped by active ice-water rinsing. However, the patient's active cognitive cooperation is essential, especially during awake phase. The aim of this pilot study is to investigate the influence of cortex temperature on cognition during awake-surgery.
Methods: During an awake-surgery, the complete course of the cortex's temperature was analysed continuously by an imaging camera. This was performed with 8 patients at a total of 52 measuring points. The body's core and the cortical temperature changes were determined over time – split into phases where no water, warm flush (36°C) or ice water was used. As a surrogate for the cognitive performance of patients, a reaction time test was performed intraoperatively on the patient.
Results: During the first measurement the cortex's temperature was 37.1°C (36.2-37.5°C). The cortex's surface temperature approached room temperature (median: 26.2°C) without proper regular irrigation (mean - 1.1°C in the first 10 min, mean - 2.4°C in the first 15 min).
Average reaction time was 742 milliseconds. At the same time, average reaction time at a cortex temperature < 35°C was 1421 milliseconds, at a cortex temperature 35°C 572 milliseconds ($p < 0.05$). At a cortex temperature < 35°C, reaction time improved again after rinsing with warm liquid.

Conclusions: Our pilot study suggests a continuous drop in the cerebral cortex's temperature during (awake) phase of surgery. Furthermore; the average reaction time correlated with the temperature of the cortex significantly. The brain's temperature may have significant impact on the cognitive performance of patients during the awake phase. This possible connection should be investigated in further studies.

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Evaluation of MRI-Artefacts After Removal of Cerebral Applied Iron Oxide Particles in a Sheep Brain Model

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Purpose: A possible adjuvant therapy method for patients with recurrent glioblastoma multiforme is the intra-tumoral application of magnetic iron oxide particles and the excitation of these particles by an alternating magnetic field. By using this method cancer-killing mechanism should be induced. An obvious problem is the fact that further MRI follow-up checks are no longer possible after insertion of metal into the skull because of artefacts. Our study's aim is to evaluate the possibility of post-interventional removal of iron oxide particles *ex-vivo* that would allow subsequent morphological imaging.
Methods: A precisely defined amount of iron oxide particles (applied via carrier material) was injected into *ex-vivo* sheep brains. Subsequently, brains were heated to 45°C in water for 30 minutes, approaching heat-generating activation mechanism and demonstrated on the MRI. Subsequently, the particles (1) were removed by rinsing (0.9% NaCl) and (2) by means of ultrasonic aspirator. In a third group, only the carrier material was removed. The completeness of the iron oxide particles' removal was quantified on the MRI.
Results: The experiments were performed on a total of three sheep brains. When particles were enclosed, pronounced artefacts were found on the MRI. After removal via extensive irrigation or usage of an ultrasound aspirator, the MRI could no longer detect any iron oxide induced artefacts. By selective removal of the carrier material, pronounced artefacts remained afterwards.
Conclusions: A complete removal of iron oxide particles *ex-vivo* allowing an artefact-free MRI imaging seems to be possible. Further studies must show whether this is possible *in-vivo*.

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Comparison of the Cerebral Thermal Ambient Temperature During the Use of Conventional Coagulation Forceps and Coagulation Forceps with Active Heat Conduction

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Purpose: Bipolar coagulation forceps are currently used as standard during (neuro-) surgical operations. Principle of the forceps is based on heat production that effects a thermally induced tissue coagulation. At the same time, a heat-related environmental reaction occurs, which can also be accompanied by damage to the surrounding physiological tissue. The aim of our study is to compare ambient temperatures after coagulation with conventional coagulation forceps and coagulation forceps with active heat conduction.
Methods: We used an *ex-vivo* sheep brain model developed at our laboratory: for this purpose, an area of sheep brains encompassing 4mm² was coagulated *ex-vivo* (with a surface temperature of 28°C), within a fixed time of 5 seconds, using 1.) conventional coagulation forceps (Bipolar) and 2.) coagulation forceps with active heat conduction (Iso). Throughout the process, the temperature of the coagulation area and surrounding tissue was documented by means of a thermal imaging camera during and after coagulation, being subsequently evaluated electronically.
Results: The experiments were carried out on a total of four sheep brains. We were able to show that during the use of conventional coagulation forceps temperatures above the previously measured surface temperature could still be measured several centimetres away from the coagulation area (mean T_{max}: 86.75°C, ambient reaction 1cm: 42.8°C). Compared to that result, the rise of the ambient temperature was significantly lower when coagulation forceps with active heat conduction were used (mean T_{max}: 46.9°C), ambient reaction 1cm: mean 34.0°C.
Conclusions: Our thermography measurements have proven that even several centimetres away from the actual coagulation area, increased and thus potentially harmful temperatures can be found and shown on the tissue. Since heat has a toxic effect on brain tissue; the application and intensity of coagulation forceps should be used carefully. More recent surgical instruments with active heat conduction seem to be helpful in reducing collateral damage due to heat exposure.

Developmental Therapeutics: Cytotoxic Chemotherapy

Poster

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High Throughput Drug Screening on Pleural Effusion for Optimizing Cytotoxic Treatment in Metastatic Breast Cancer

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Purpose: Finding the optimal beyond 2nd line therapeutic strategy in metastatic breast cancer (mBC) is challenging. *Ex vivo* drug tests on patient´s cancer cells may help to identify effective substances, however despite of a good correlation between *ex vivo* test results and *in vivo* therapy response, the required time for drug testing (cell isolation, expansion and drug response test) is far beyond the possibilities of clinical utilization, in combination with a low number of candidate drugs tested. We introduce here a novel approach for *ex vivo* high throughput drug screening on malignant pleural effusion to identify substances for an effective beyond 2nd line cytotoxic treatment.
Methods: For an optimal analysis of *in vitro* drug response a suspension of single cells with high number of tumor cells is required. Malignant pleural effusion of 5 mBC patients was analyzed for eligibility. Drug response assays using a drug library of 133 agents were tested at 5 concentrations in duplicates using an *in vitro* viability assay for reproducibility and correlation to the retrospective clinical course of the patients.
Results: Malignant cell count in the analyzed pleural effusions (>200ml) was sufficient in all cases to generate a standardized single cell suspension for drug testing. Drug response assays were successfully carried out in all 5 cases, providing results within 96 hours after pleural puncture. The *in vitro* reproducibility was 100% in repeated tests. We also detected a 100%

correlation between the *in vitro* test results of non-responding drugs and retrospective clinical progress under the corresponding cytotoxic agent.
Conclusions: High throughput drug response screens can be successfully carried out on pleural effusion within 4 days. The high number of cytotoxic agents and the rapid testing allow the identification of drug candidates for beyond 2nd line treatment in rapidly progressing mBC. Further investigations are required for the assessment of the prospective prognostic value. The need for pleural effusion is also a current limitation.

Disclosure Statement: no conflict of interest

Developmental Therapeutics: Immunotherapy/Cellular Therapy

Best-of-Abstracts-Vorträge

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CAR-T Cells Directed Against B Cell Surface Antigens for the Targeting of B Cell Non-Hodgkin's Lymphoma

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Purpose: Chimeric antigen receptor (CAR)-T cell therapy is a new type of cellular immunotherapy that is based on the adoptive transfer of autologous T cells genetically modified with an engineered immunoglobulin-derived receptor that recognizes tumor-associated antigens. CAR-T cell therapies targeted at the CD19 antigen on leukemia and lymphoma B cells showed substantial clinical efficacy, currently, more than 40 CD19 CAR-T cell studies are registered at the FDA for the treatment of B-NHL and B-ALL. However, anti-CD19 CAR-T cell therapy can become ineffective due to CD19 antigen loss. This signifies the development of immunotherapies for additional tumor-associated targets, either for salvage therapy, or as an alternative to anti-CD19 CARs.
Methods and Results: Here, we identified a B cell homing receptor as an alternative target for CAR-T cell immunotherapy of mature B cell lymphomas by demonstrating strong surface expression of CXCR5 on B-NHL cell lines but also on primary tumor samples. Based on an anti-human CXCR5 antibody, we designed a humanized scFv that was incorporated into a second-generation CAR backbone to generate the anti-human CXCR5 CAR. The CXCR5 CAR endows T cells with high avidity, necessary for anti-tumor efficacy on lymphoma cell lines, and on primary patient-derived B-NHL cells. Also, the CXCR5 CAR confers T cell-reactivity against benign mature B cells, and concomitantly reacts towards lymphoma-supportive Tfh cells. No unwanted T cell-reactivity against myeloid cells and various non-hematopoetic cells from human tissues were observed. A syngeneic mouse model of anti-CXCR5 CAR-T cell therapy was used to further prove absence of unexpected on-target/off-tumor effects in-vivo. Finally, CXCR5 CAR-T cells exhibit a robust *in-vivo* antitumor activity in a mouse xenograft model of human B-NHL.
Conclusions: We propose CXCR5-targeted CAR-T cells as an attractive alternative treatment strategy for B-NHL through combined elimination of lymphoma and tumor-supporting Tfh cells.

Disclosure Statement: All authors declare that they have no competing interests.

Vorträge

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Feasibility of Autologous Lymphocyte Apheresis in Heavily-Pretreated Patients Intended to Undergo Therapy with Chimeric Antigen Receptor (CAR)-T Cells

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Purpose: One of the essential steps in manufacturing CAR-T cells is the apheresis of autologous CD3+ lymphocytes. However, due to previous cytotoxic therapy, lymphopenia or disease status it is not always possible to perform a sufficient collection. Here we evaluated the feasibility of collecting adequate apheresis products.
Results: Between February and August 2019, we performed 15 collections in 12 patients with relapse/refractory diffuse large B cell Lymphoma (DLBCL) for subsequent scheduled CAR-T cell therapy (Kymriah®). The median age was 56 (30-71) and 3 patients were female. In median the patients had received 4 prior treatments (3-6). Prior to apheresis the mean white blood cell count (WBC) was 5500/µl (2000-14000) while absolute lymphocyte count (ALC) was 640/µl (240-1390). All patients underwent a large volume apheresis (4 x total blood volume) on a Spectra Optia device. In 14/15 patients the target numbers of CD3+ cells were collected. The total count of collected CD3 cells was mean $6{,}8x10^9$ (2,2-16,2), the yield was mean $0{,}8x10^8$/kg body weight (0,06-1,91). In 1 patient the collection was performed in severe lymphopenia (240/µl) thus not reaching the minimal yield of CD3+ cells. A consecutive collection after one month was successful. Vitality after thawing reached >50% in all collections, median 82,1% (68,8-94,2). Nevertheless, proliferation of lymphocytes after transduction in 3 collections (2 patients) was insufficient thus terminating the production of CAR T product.
Conclusions: In most patients intended to undergo real-life CAR T-cell therapy adequate numbers of CD3 cells can be collected.

Reference:

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Poster

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Modulation of Antibody-Dependent Phagocytosis by Macrophages under Metabolic Regulation in the Tumor Microenvironment

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Purpose: Therapy response in B-cell lymphoma by chemoimmunotherapy largely depends on the tumor microenvironment and the functional status of macrophages as important effector cells. Within the tumor microenvironment a limited supply of nutrients leads to metabolic alterations in malignant cells as well as an altered immune system.
Methods: As macrophage function is sensitive to metabolic alterations, we addressed macrophage lymphoma cell co-cultures to assess the impact of metabolic pathway inhibition (using several pathway inhibitors) on antibody-dependent cellular phagocytosis (ADCP). We particularly aim to improve macrophage effector cell function in the context of immunotherapy.
Results: Inhibition of AMP kinase, glycolysis or the ATP-production had no positive effect on the phagocytosis rate. However, inhibiting the pentose phosphate pathway (PPP) by Oxythiamine, p-Hydroxyphenylpyruvate, Physcion and 6-Aminonicotinamide leads to an increased target cell phagocytosis and Fc-receptor expression in independent effector cell types (J774A1 and THP1). In this line metabolites of the PPP could be shown to similarly affect ADCP by adding educts and products of the PPP significantly altering the macrophage-mediated target cell depletion. These changes could also be seen in PPP-enzyme knockdown (transketolase and 6-PGD) in macrophages and by inhibiting the PPP in primary murine and human macrophages.
We subsequently performed a proteomic analysis of PPP inhibition in macrophages identifying metabolism and immune regulation related effects. Specifically under PPP-inhibition, Seahorse analysis showed increased oxygen consumption and glycolysis of macrophages. Furthermore, the effector cells showed enlarged morphology and developed an activated phenotype.
Conclusions: We hypothesize the PPP as a regulator of macrophage activity determining therapy outcome and aim to identify specific modulators of macrophage polarization and function in tumor immunotherapy.

Disclosure Statement: No conflict of Interest. A.B. was supported by Köln fortune scholarship

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A Phase 3 Randomized, Open-Label, Multicenter Study Comparing Isatuximab, Pomalidomide, and Low-Dose Dexamethasone Versus Pomalidomide and Low-Dose Dexamethasone in Patients with Relapsed / Multiple Myeloma Refractory (RRMM)

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Purpose: To demonstrate the benefit of isatuximab (Isa), a novel anti-CD38 monoclonal antibody, combined with pomalidomide (P)/dexamethasone (d) versus (vs) Pd, on progression free survival (PFS) in RRMM patients (pts).
Methods: Pts who received ≥2 prior lines, including lenalidomide (len) and a proteasome inhibitor (PI), refractory to last therapy were enrolled in this phase 3 trial (NCT02990338). IsaPd arm received Isa 10 mg/kg IV weekly for first 4 weeks (wks), then every 2 wks. Both arms received approved schedules of P and d (4mg PO days 1-21; 40mg [20mg if >75 yrs] PO or IV weekly) every 28 days until progression or unacceptable toxicity.
Results: 307 pts (154 IsaPd, 153 Pd) were randomized and analyzed (ITT). Patient characteristics were well balanced across treatment arms. Median age: 67 (36-86) yrs; median prior lines of therapy: 3 (2-11); estimated GFR: <60ml/min in 33.9% pts; 92.5% refractory to len, 75.9% to PI; and 19.5% pts had high-risk cytogenetics. At median follow-up (11.6 months [mos]), median PFS was 11.5 mos IsaPd vs 6.5 mos Pd; HR 0.596 (95% CI 0.44-0.81), P=0.001. PFS benefit was consistent across all major subgroups. ORR (≥PR) was 60.4% IsaPd vs 35.3% Pd, P<0.0001. VGPR rate or better was 31.8% IsaPd vs 8.5% Pd, and MRD negativity (NGS, 10^{-5}) was seen in 5.2% IsaPd pts vs 0% Pd. At analysis date, overall survival (OS) was immature (99 events) but a trend to OS improvement in IsaPd vs Pd was observed (HR 0.687; 95% CI 0.461-1.023). Median treatment duration was 41 wks IsaPd vs 24 wks Pd; median Isa infusion (inf.) duration was 3.3h at 1st inf. and 2.8h at subsequent inf. Grade ≥3 AEs were observed in 86.8% IsaPd vs 70.5% Pd; 7.2% IsaPd and 12.8% Pd pts discontinued due to AEs; 7.9% IsaPd and 9.4% Pd pts died due to AEs. Inf. reactions were reported in 38.2% (2.6% grade 3-4) IsaPd. Grade ≥3 infections were seen in 42.8% IsaPd and 30.2% Pd, grade ≥3 neutropenia in 84.9% (febrile 11.8%) IsaPd and 70.1% (febrile 2.0%) Pd.
Conclusions: IsaPd significantly improved PFS and ORR vs Pd, with a manageable safety profile. IsaPd is an important new treatment option for the management of RRMM.

This abstract was previously presented atAmerican Society of Clinical Oncology (*ASCO*) *2019* Annual Meeting, May 31–June 4, Chicago IL, and encored at the European Hematology Association (*EHA*) June 13–16, *2019,* Amsterdam, Netherlands

Disclosure Statement
DIETGER W. NIEDERWIESER: No conflicts of interest.
PAUL G. RICHARDSON: Consulting or Advisory Role – Karyopharm; Oncopeptides; Celgene; Janssen; Takeda; Sanofi; Research Funding - Oncopeptides, Celgene; Takeda, BMS.
MICHEL ATTAL: Research Funding – Sanofi.
S. VINCENT RAJKUMAR: No conflicts of interest.
JESUS SAN-MIGUEL: Consulting or Advisory Role - Amgen; Bristol-Myers Squibb; Celgene; Janssen; MSD; Novartis; Roche; Sanofi; Takeda.
MERAL BEKSAC: Consulting or Advisory Role - Amgen (Inst); Celgene (Inst); Janssen-Cilag (Inst); Takeda (Inst); Speakers' Bureau - Amgen; Bristol-Myers Squibb; Celgene; Janssen-Cilag.
IVAN SPICKA: Consulting or Advisory Role - Amgen; Bristol-Myers-Squibb; Celgene; Janssen-Cilag; Novartis; Takeda; Speakers' Bureau - Amgen; Bristol-Myers-Squibb; Celgene; Janssen-Cilag; Novartis; Takeda.
XAVIER LELEU: Honoraria - Abbvie; Amgen; Bristol-Myers Squibb; Carsgen Therapeutics Ltd; Celgene; Janssen-Cilag; Karyopharm Therapeutics; Merck; Mundipharma; Novartis; Oncopeptides; Pierre Fabre; Roche; Sanofi; Takeda; Consulting or Advisory Role - Abbvie; Amgen; Bristol-Myers Squibb; Carsgen Therapeutics Ltd; Celgene; Gilead Sciences; Janssen-Cilag; Karyopharm Therapeutics; Merck; Mundipharma; Novartis; Oncopeptides; Roche; Takeda; Travel, Accommodations, Expenses – Takeda.
FREDRIK SCHJESVOLD: Honoraria - Abbvie; Amgen; Celgene; Janssen China R&D; Novartis; Takeda; Consulting or Advisory Role - Adaptive Biotechnologies; Amgen; Bayer; Bristol-Myers-Squibb; Celgene; Janssen China R&D; Oncopeptides; Takeda; Research Funding - Amgen; Janssen China R&D.
PHILIPPE MOREAU: Honoraria - Amgen; Celgene; Janssen-Cilag; Novartis; Takeda; Consulting or Advisory Role - Amgen; Celgene; Janssen; Novartis; Takeda.
MELETIOS A DIMOPOULOS: Honoraria - Celgene, Takeda, BMS, Janssen and Amgen; Consulting or Advisory Role - Amgen; Bristol-Myers Squibb; Celgene; Janssen-Cilag; Takeda.
JEFFREY SHANG-YI HUANG: Research Funding – Sanofi.
JIRI MINARIK: Consultancy and Honoraria - Amgen, BMS, Celgene, Janssen, Takeda Clinical trials investigator - Amgen, Janssen, Karyopharm, Oncopeptides, Sanofi.
MICHELE CAVO: Honoraria - Abbvie; Adaptive Biotechnologies; Amgen; Bristol-Myers-Squibb; Celgene; GlaxoSmithKline; Janssen China R&D; Takeda; Consulting or Advisory Role - Abbvie; Adaptive Biotechnologies; Amgen; Bristol-Myers-Squibb; Celgene; GlaxoSmithKline; Janssen China R&D; Takeda; Speakers' Bureau - Celgene; Janssen China R&D.
H. MILES PRINCE: Honoraria - Amgen; Celgene; Janssen China R&D; Novartis; Takeda; Consulting or Advisory Role – Amgen; Celgene; Janssen China R&D; Novartis; Takeda; Research Funding – Sanofi; Takeda.
KENNETH C. ANDERSON: Stock and Other Ownership Interests - C4 Therapeutics; OncoPep; Consulting or Advisory Role – Bristol-Myers Squibb; Celgene; Gilead Sciences; Janssen Oncology; Millennium; Sanofi; Patents, Royalties, Other Intellectual
Property - C4 Therapeutics; Oncopep.
SANDRINE MACÉ, KATHRYN P. CORZO, FRANK CAMPANA, SOLENN LE-GUENNEC, FRANCK DUBIN are employees of Sanofi.

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CAR T-Cell Therapy in the Real World Setting: Predictive Factors for Successful Bridging between Apheresis and Car T-Cell Infusion

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Purpose: CAR T-cells directed against CD19 are a newly approved cellular therapy for treating patients (pts) with relapsed or refractory (r/r) pediatric and adolescent acute lymphoblastic leukemia or diffuse large B-cell lymphomas (DLBCL). Bridging pts from lymphapheresis (LA) to infusion of CAR T-cells remains challenging given the aggressive nature of the disease. Little is known on predictive factors affecting this period of manufacturing in the real-world population.
Methods: We evaluated the potential of clinical variables affecting success of CAR-T reinfusion in pts receiving CD19 CAR tisagenlecleucel at our CAR T-cell center.
Results: Nine pts were allocated to receive CARs and underwent apheresis between May to August 2019 for r/r DLBCL. 3 pts died prior to infusion. 6 pts received CARs after a median time of 49 days after LA. Pts not receiving the CAR infusion presented with higher lactate dehydrogenase (LDH) and C-reactive protein (CrP), worse ECOG performance status (PS) at the time of LA, had obtained more lines of therapy and were more likely treated in an external hospital than patients receiving the CARs. We developed a scoring system in order to predict outcome based on these factors. CrP and LDH above the median were assigned 2 points (p.) each, the ECOG PS at the time of LA were added, and each line of therapy after 1st salvage was assigned 1 p. and referral from an external hospital therapy 1 p. Pts achieving a score of 5 or higher were at high risk to die prior to infusion: 3 out of 4 patients did not undergo CAR T-cell infusion. In contrast, pts receiving the CARs had a median score of 2.5 (range 1-6).
Conclusions: Bridging eligible patients to from LA to CD19 CARs infusion remains a challenge. The proposed score may help to identify pts at high risk for complications rendering the CAR T-cell infusion impossible. We aim to evaluate the score in a larger group of pts.

Disclosure: the authors have nothing to disclose

Developmental Therapeutics: Molecular Therapeutics

Best-of-Abstracts-Vorträge

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Identification of Novel Notch1-Regulated Therapeutic Targets in Multiple Myeloma through Functional shRNA-Based Screening

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Purpose: Aberrantly activated Notch signaling promotes multiple myeloma (MM) onset, progression and drug resistance. As inhibition of Notch activation using γ-secretase inhibitors is impeded by serious side effects, there is still the need for the development of novel specific therapeutic strategies. The present study aims to address this challenge and identify novel druggable downstream effectors of the Notch1 pathway by employing shRNA-based functional high throughput (HT) screening.
Methods: First, we performed transcriptome profiling in MM.1S cells to identify Notch1-regulated genes. Of 842 genes differentially expressed after Notch1 inhibition, we selected 40 consistently and strongly downregulated genes for a tailored shRNA library. Negative selection screens employing the library were carried out in U266 cells modified to exclusively express the Notch1 intracellular domain (NIC) or the Notch1 variant NΔE. After cultivation for 12 days under the selective pressure of melphalan, bortezomib or lenalidomide, treated cells and controls were harvested. Subsequently, shRNA sequences were recovered from genomic DNA using PCR and changes in their representation were analyzed bioinformatically after HT sequencing.
Results: Analysis of differential shRNA representation of the first screen with lenalidomide was recently completed. Based on standard deviation scores (z-scores; cut-off>-2), we ranked the shRNAs and further evaluated the druggability of the corresponding target gene/protein. Finally, we chose 4 candidate genes - 3 transcription factors and one enzyme - druggable with already available small molecule inhibitors. *In vitro* validation of candidate genes will comprise treatment of MM cell lines with a chemical inhibitor or specific shRNAs in combination with lenalidomide. Results of the bioinformatic analysis of the screens and *in vitro* validation of screen hits will be presented in detail at the DKK 2020.
Conclusions: Study results hold the potential for the development of novel MM treatment strategies.

Disclosure Statement: No conflicts of interest.

Poster

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NTRK Fusion-Tumors in Adult Cancer Patients – Single Center Report on Screening and Treatment

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Purpose: Neurotropic tropomyosin-related kinases (NTRK) are involved in neuronal processes. Oncogenic NTRK gene-fusions are rare but promising targets for tyrosine kinase inhibitors (TKI). We report on feasibility of screening and treatment of NTRK-fusions during oncology routine.
Methods: Patients (pts) with malignant diseases of mainly Head and Neck (HNSCC), salivary glands (SGT), thyroid (TC), soft tissue (STS), bone (BS), kidney (RCC), melanocytes (MM) were screened. Primarily, NTRK-immunhistochemistry (IHC) (EPR17341, Abcam) and FISH analyses were done for ETV6 (Abbott Vysis). Once screening was positive, RNA based NGS analyses was performed (RNA-Oncomine-Focus-Assay, Thermo Fisher). NTRK positive pts were treated with TKI larotrectnib, if applicable.
Results: From 12/18-8/19 108 pts were screened. Pts were at median 53.7 (range (r), 15.8 - 89.9) years old and received 1.5 lines (r, 0 – 8) of chemotherapy at time of screening. 3 (2.7 %) pts were NTRK-IHC positive, and NGS confirmed NTRK-fusion in 2 pts (1.85 %) (TPM3-NTRK1 and ETV6(5)-NTRK3(15)). One NTRK positive TC-pts received larotrectinib, resulting in an ongoing good response.
Conclusions: NTRK testing is feasible during oncological routine upon interdisciplinary established screening strategy. In 1.85 % of screened pts NTRK-fusion-tumour was proven. This incidence is higher than expected, which might result from our selected screening cohort. However, in one pts without therapeutic options NTRK screening enabled TKI administration resulting in highly effective treatment. Testing algorithm needs to be discussed interdisciplinarily in particular when several NTRK inhibitors will be available, to ensure NTRK-inhibition as a therapeutic option for patients with NTRK-fusion-tumours.

Dislosure Statement: FL, VG, PI received lecture honoraria and advisory fees from Bayer and Roche.

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Tumor-Biological Effects of Acetylsalicylic Acid and Ascorbic Acid Regarding the HIF1 Level

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Purpose: Treatment with acetylsalicylic acid (ASA) positively affects the prognosis of various tumor entities (Rothwell et al., 2012). A similar benefit for tumor patients was found for a treatment with ascorbic acid (vit c) (Kuiper et al., 2014). It appears that the activity of the transcription factor

HIF1 could be reduced by these treatments. HIF1 is a regulator of genes involved in hypoxic metabolism/glycolysis but also influences normoxic metabolism/glutaminolysis. In addition, HIF1-level is associated with a poorer outcome of tumor patients and drives the process of metastasis (Rankin et al., 2016).
Methods: We examined in tumor cell lines the effect of ASA and vit c on the expression of HIF1 and/or its tumor biological/metabolic influence.
Results: We found that ASA and vit c reduced the expression level of normoxic HIF1 and ASA even reduced the hypoxic HIF1 level. This is caused by the ability of ASA to alter the acetylation status and thus the stability of proteins (Tatham et al., 2017) like HIF1. Vit c appears to impair the functionality of mitochondria and affected the normoxic HIF1 stability and the amino acid metabolism, also independently of HIF1.
Conclusions: Both substances are able to inhibit the activity of HIF1. This inhibition could partly explain the tumor-therapeutic effect of ASA and vit c. A possible support of tumor therapies with ASA & vit c appears to be a useful adjunction for the treatment of both normoxic and hypoxic tumors.

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Endocrine Tumor (e. g. Thyroid Cancer, Adrenal Tumor, Neuroendocrine Tumor)

Poster

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Characterization of Epigenetic Modulation in Pancreatic Neuroendocrine Neoplasms

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Purpose: Pancreatic neuroendocrine tumors (pNETs) represent a rare and heterogeneous tumor entity. Despite surgery, several therapeutic approaches involving biotherapy, target therapy or chemotherapy are applicable. However, cancer progression and resistance mechanisms are still challenging. Recent genome wide sequencing analyses in pNETs identified a large number of mutated genes involved in epigenetic modulation. Targeting epigenetic regulation in tumor cells in combination with specifically triggered immune cells could be a new therapeutic avenue.
Methods: The human pNET cell lines BON-1 and QGP-1, the murine insulinoma cell lines beta-TC-6 and RIN-T3 and the human monocyte-like THP-1 cells were treated with Panobinostat (PB) and analyzed for functional effects and affected signaling pathways performing Western blot, FACS and qPCR analyses. Additionally, the impact of PB on microRNA and lncRNA expression in BON-1 and QGP-1 cells was investigated by RNA sequencing.
Results: Beside hyper-acetylation, PB clearly induces an apoptotic phenotype as well as cell cycle arrest in neuroendocrine cells from various species. Thereby, the effect of PB tends to be mediated by a cluster of differentially regulated microRNA and lncRNA. In THP-1 monocytes PB induces altered macrophage polarization into a more pronounced M1 phenotype, which additionally enhances its tumor-repressing impact in co-cultivation studies.
Conclusions: Beside its cytotoxic effect on tumor cells, PB also showed tumor cell-independent influence due to alteration of the inflammatory stroma. These results play an important role on tumor progression.

Disclosure Statement: No conflict of interest

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"Routine Usage of Molecular Targeted Therapies (Everolimus and Sunitinib) and Temozolomide Based Chemotherapy in Neuroendocrine Neoplasia and Its Outcome"

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Purpose: Orally applied targeted therapies everolimus (EV) and sunitinib (SUN) as well as a temozolomide (TEM) mono- or combination chemotherapy (CTx) with capecitabine (CAP) are of increasing importance in the treatment of neuroendocrine neoplasia (NEN).
Methods: In a multicentric cohort from the German NET-Registry routine data of NEN pts. with initial diagnosis since 1988 were analyzed with regards to the usage and outcome of EV, SUN and TEM-based therapies. Statistical analysis was performed using SPSS version 20.0.
Results: From a total of 3521 patients (pts.) registered within the NET-Registry database 219 received EV, 61 received SUN and 94 a TEM-based CTx during the course of the disease. Subgroup analyses due to sufficient follow-up information were possible for 81 pts on EV, 36 on SUN and 66 on a TEM-based CTx. In pts with EV, SUN or a TEM-based CTx median age was 54 years, 56 years and 54 years, respectively. Primary tumor localization were pancreatic (66%), bronchopulmonal (10%), intestinal (13%) and other localizations (n=4%) or unknown (n=7%). Initial therapy consisted of EV, SUN or TEM-based CTx in 9%, 6% or 10%, while 31%, 14% and 26% received them as second line treatment. In later therapeutic lines EV was used in 60%, SUN in 77% and a TEM-based CTx in 64% of pts.. Partial remission (PR) as best radiologic response was seen in 7% of pts. on EV, 23% of pts. on SUN and 24% of pts on a TEM-based

CTx. Stable disease (SD) was achieved in 64%, 60% and 46% treated with EV, SUN or a TEM-based CTx. Disease progression was documented in 29%, 17% and 30%, respectively. Median overall survival was 43 months (m) in the EV group, while 44 m and 43m in the SUN or TEM-based CTx group. Median time to documented progression (mTTP) was 8, 10 and 8 months in pts. with EV, SUN or a TEM-based CTx and 9 months in a subgroup of pts. with NET-G2.
Conclusions: Routine treatment of EV; SUN and TEM-based CTx showed a reasonable response and sufficient disease control in advanced and in part heavily pretreated pts. with neuroendocrine Neoplasia G1/G2 as well as G3.

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Peritoneal Carcinomatosis Manifestation within the Hernia Sack of an Inguinal Hernia (Representative Case)

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Purpose: Periop. management & surgical treatment of inguinal hernia are routinely provided.
Method: Scientific case report
Results (case presentation)**:** A 65-years old patient w/ a med. history significant for a pararenal gland carcinoma (PRG-Ca) (treated w/ radiation) w/ hepatic metastases & multiple ulcerations of the posterior gastric wall showed reduced clinical (palpable & painful tumor resistance at the right lower abdomen) & nutritional status (cachexia). CT scan showed advanced tumor growth of a PRG-Ca infiltrating surrounding organs. A multivisceral resection was performed comprising adrenalectomy/left nephrectomy, resection of the pancreatic tail, splenectomy, partial gastric resection, resection of the left renal vein w/ tumor thrombectomy within the inferior V. cava & patch plasty (xenograft), omentectomy & local excision of peritoneal tumor lesions. Postoperatively, patient underwent re-laparotomy to suture a sudden intestinal lesion. During further course, an irreducible inguinal hernia was diagnosed which was confirmed by ultrasound & subsequently repaired by Shouldice's procedure. The intraop. suspicion of a peritoneal tumor lesion of the PRG-Ca within the hernial sac was confirmed by histopathological investigation. Further postop. course was uneventful.
Conclusions: An irreducible inguinal hernia w/ manifest nodes of a peritoneal carcinomatosis can be assessed a rare but instructive disease in the broad spectrum of differential diagnoses of inguinal hernia.

Epidemiology

Poster

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Socioeconomic Differences and Lung Cancer Survival in Germany: Investigation based on Population-Based Clinical Cancer Registration

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Purpose: Studies from several countries reported socioeconomic inequalities in lung cancer survival. Hypothesized reasons are differences in cancer care or tumor characteristics. We examined associations of small-area deprivation and lung cancer survival in Germany and the possible impact of differences in patient, tumor or treatment factors.
Methods: Patients registered with a primary tumor of the lung (ICD-10 C34) between 2000-2015 in three German population-based clinical cancer registries were included. Area-based socioeconomic deprivation on municipality level was measured with the categorized German Index of Multiple Deprivation (GIMD). Our main outcome, survival after cancer diagnosis, was analyzed with Cox regression and we repeated the analysis for subgroups receiving chemotherapy, radiotherapy or surgery. The main models included age, sex, histologic subtype, grading and stage at diagnosis. All analyses were conducted in SAS 9.4.
Results: Overall, 22,905 patients were included of whom 72.9% were male, 23.8% were over 75 years of age, 49.5% were diagnosed with stage IV cancer and 82.7% with non-small-cell lung cancer. Kaplan-Meier five year overall survival estimates from the least to the most deprived quintile were 17.2% [95%-Confidence Interval (CI): 15.8-18.5], 15.9% [14.8-17.2], 16.7% [15.5-17.9], 15.7% [14.5-16.9], and 14.4% [13.3-15.5], respectively. Our main Cox model showed lower survival in the most deprived group compared to the most affluent group (Hazard Ratio (HR) 1.06, 95% confidence interval (CI) 1.01-1.11). Subgroup analyses showed lower survival in the most deprived compared to the least deprived quintile for stage I-III patients [HR: 1.14, 95% CI: 1.06-1.22]. The association persisted when restricting to patients receiving surgery but was attenuated for subgroups receiving either chemotherapy or radiotherapy.
Conclusions: Our results indicate differences in lung cancer survival according to area-based socioeconomic deprivation on municipality level in Germany.

Disclosure Statement: The authors declare no conflict of interest.

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Establishing a Valid Approach for Estimating Familial Risk of Cancer Explained by Common Genetic Variants

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Purpose: To critically examine existing approaches for the estimation of the excess familial risk of cancer which can be attributed to identified common genetic risk variants and to propose an alternative, more

straightforward approach for calculating this proportion using well-established epidemiological methodology.
Methods: The underlying equations of the traditional approaches and the new epidemiological approach were applied for colorectal cancer (CRC) in a large population-based case-control study in Germany with 4447 cases and 3480 controls, who were recruited from 2003-2016 and for whom interview, medical and genomic data were available.
Results: Having a family history of CRC (FH) was associated with a 1.77-fold risk increase in our study population (95% CI 1.52-2.07). Traditional approaches yielded estimates of the FH-associated risk explained by 97 common genetics variants from 9.6% to 23.1%, depending on various assumptions. Our alternative approach resulted in smaller and more consistent estimates of this proportion, ranging from 5.4% to 14.3%.
Conclusions: Commonly employed methods may lead to strongly divergent and possibly exaggerated estimates of excess familial risk of cancer explained by associated known common genetic variants. Our results suggest that familial risk and risk associated with known common genetic variants might reflect two complementary major sources of risk.

Disclosure Statement: The authors have nothing to disclose.

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Manifestation of Secondary Malignancies of the Hematopoietic (HP) System in Patients with Tumors of the Genitourinary (GU) Tract

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Purpose: There are reports on the increased risk of double malignancies in patients with GU cancer and lymphomas (1,2). Since immunological reactions play an important role in the control of tumor growth and since the immune system is part of the HP system it seems of interest to look more intensively on double malignancies arising in both systems to eventually detect common disturbances behind.
Methods: We searched the data base of our hospital over a period of 15 years for the documentation of double malignancies within the HP system and the GU tract. The HP system was represented by acute leukemias / myelodysplasias (n=12), lymphomas / CLL (n=33), paraproteinemias / multiple myelomas (n=12), and myeloproliferative diseases (n=2), and the GU tract by cancer of the prostate (n=35), the bladder (n=19), and the kidney (n=5).
Results: We identified 59 patients with double malignancies detected both in the GU tract and in the HP system either synchronously or metachronously (interval of diagnosis <3 or > 3 months). 66% of patients started with a primary neoplasm of the GU tract followed by a HP malignancy metachronously with a median interval time of 6 years. In 19 % of patients the diagnosis of the HP and GU neoplasm was made synchronously. A primary malignancy of the HP system was found in 15 % of patients. Rare patients developed a HP malignancy within the GU tract. A group of 8 patients exhibited 3 malignancies of different entities.
Conclusions: Considering the multifactorial background of tumor growth the occurrence of double malignancies may be associated to cytogenetic aberrations, therapeutic interventions, and perhaps immunosuppressive conditions due to chronic infections residing outside the tumor itself in the tumor adjacent microenvironment. The analysis of patients with multiple malignancies deserves special interest due to an advanced cancer prone status.

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Disclosure Statement: The authors declare no conflict of interest.

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Trends in Cancer Survival in Germany from 1991 to 2016

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Purpose: Survival rates estimated using data from epidemiological cancer registries in Germany are difficult to interpret due to regional and temporal variability. One source of uncertainty is the substantial proportion of cases notified by death certificate only (DCO cases). DCO cases are usually excluded from survival estimation, but this can lead to biased survival rates.
Methods: This study is based on data from 4.6 million cancer patients from 13 federal states diagnosed between 1990 and 2016 and expands upon previous work [1]. First, relative survival rates were estimated excluding DCO cases for each registry and year. Then, a mixed linear model controlling for DCO proportions was fitted to those estimates. Finally, based on this model, survival rates and time trends for Germany were estimated at a DCO proportion of 0%.
Results: The age standardized 1-year relative survival rates for all cancers combined increased from 47% in 1991 to 73% in 2016, 5-year survival rates increased from 1995 to 2016 by 25 percentage points to 60%. For lung cancer, 1-year survival increased by 19 percentage points to 46% and 5-year survival increased from 9% to 18%. For pancreas cancer, 1-year survival increased from 15% in 1991 to 40% in 2016 and 5-year survival increased from 2% (1991) to 11% (2016).
Conclusions: The method presented here allows long-term survival rate estimation based on data from several registries with varying DCO proportions. Furthermore, the modelling approach uses recent data from a large number of registries to strengthen estimates could be extended to the time periods during which only three small registries were in operation.

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Disclosure Statement: This research did not receive any specific grant from funding agencies in the public; commercial; or not-for-profit sectors

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Educational Inequalities and Regional Variation in Colorectal Cancer Survival in Finland

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Purpose: Previous studies reported lower colorectal cancer (CRC) survival in patients with lower educational levels. We investigated the impact of regional variation on educational inequalities in CRC survival by using both individual and aggregated area-based information on education.
Methods: Patients diagnosed with colorectal cancer (ICD-10 C18-20) in Finland in 2007-2016 were followed up for death until end of 2016. Age-standardized relative survival and relative excess risk of death (RER) were estimated by sex using the period approach (Ederer II). RERs were adjusted for follow-up time, age, stage at diagnosis, cancer site, urbanity and region by using piecewise constant Poisson excess hazard models. All analyses were conducted separately including individual (basic, secondary, high) and aggregated area-based (quartiles Q1-Q4 based on the proportion of population with basic education) information on education, respectively.

Results: Altogether 24,462 CRC patients diagnosed in 2007–2016 were included in the analyses. There was a clear gradient in 5-year relative survival across education groups (Men: Basic 61%, Secondary 64%, High 68%; Women: Basic 61%, Secondary 68%, High 71%). Compared to the basic education group, RER in the high education group was 0.73 (95% Confidence Interval (CI) 0.65–0.82) in men and 0.67 (95% CI 0.59–0.76) in women. Accounting for regional variation had no effect on the RERs, but the effects were slightly attenuated when stage was adjusted for (RER 0.77 in men and 0.69 in women with high education). No association between area-based education and 5-year relative survival in men (Q1 63%, Q2 64%, Q3 65%, Q4 63%) and women (Q1 61%, Q2 67%, Q3 69%, Q4 65%) was observed.
Conclusions: Educational inequalities in CRC survival are still present in Finland and could not be explained by regional variations neither for individual nor area-based education. Individual education information should be preferred over area-based if interested in survival differences by education.

Disclosure Statement: The authors declare no conflict of interest.

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Record Linkage of 76,026 Cancer Cases Notified by Death Certificate Only

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Purpose: The federal cancer registry data act tasks the Robert Koch Institute (RKI) with conducting an interstate data linkage to identify individual cases reported by multiple epidemiological registries. The linkage uses pseudonym control numbers based on patient names and dates of birth. Because not all registries send control numbers to the RKI; a nationwide linkage has not yet been possible. Methods: The current linkage focused on matching cases notified by death certificate only (DCO cases) in the years 2014 and 2015 with previously diagnosed cases. Data from 12 federal states covering 77% of the population were included. Due to the limited identifying information available; a probabilistic approach was applied to identify likely matches. Results: A total of 76;026 DCO cases were linked with approximately 8.5 million other cases. Of these DCO cases; 421 (0.6%) were identified as likely matches. Niedersachsen had the largest proportion of likely matched DCO cases (1.4%). Analyses by county (Landkreis) suggested particularly large numbers of likely matches in Berlin and at the border between Lower Saxony and North Rhine-Westphalia. Considering these cases as duplicates would reduce the estimated total cancer incidence in Germany by far less than one percent. Conclusions: Although the identification and elimination of duplicate records has only a small impact on nationwide statistics; regional analyses – particularly at state borders – may be affected to a greater extent. By focusing on DCO cases; not only can duplicate records be identified; but vital status can be updated for survival analyses.

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Socioeconomic Deprivation and Burden of Cancer in Baden-Württemberg

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Purpose: Socioeconomic disparity (SD) has been linked to differences in access to health care, cancer incidence, mortality, and prognosis but the association between SD and stage at diagnosis is less well established [1-5].
Methods: Data from the Cancer Registry Baden-Württemberg on newly diagnosed primary cancers between 2011 and 2017 were linked with community level SD from the German Index of Socioeconomic Deprivation [6]. Differences in cancer incidence were analyzed using multilevel Poisson regression models, in stage distribution (regional/distant vs. local/in-situ) using chi^2-test, and in age-adjusted survival using Cox proportional hazards model with and without stage adjustment.
Results: Overall, there was a negative association between cancer incidence and socioeconomic deprivation, i.e. lower rates were observed in more deprived areas. This pattern was mostly pronounced for melanoma and female breast cancer. Higher rates in more deprived areas were observed for stomach cancer (males). The proportion of advanced tumors was higher in socially more deprived areas for melanoma, colorectal (males), breast and prostate cancer. Case fatality was higher in socially more deprived areas for all cancers combined. Site and sex specific analysis revealed higher case fatality rates in more deprived areas for melanoma, stomach, prostate and thyroid cancer in males and for breast cancer in females. Differences in survival disappeared after adjustment for differences in stage distribution.
Conclusions: Stage-adjusted prognosis does not vary according to socioeconomic deprivation in Baden-Württemberg. The differences in cancer incidence and stage distribution are most likely due to differences in screening behavior.

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Disclosure Statement: Nothing to disclose.

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Human Papillomavirus Infections (HPV) in Young Women Ten Years after the Introduction of HPV Vaccination in Germany: The Nation-Wide HPV Prevalence Study

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Purpose: Persisting infections with high-risk human papillomavirus (HPV) can lead to cervical cancer. In 2007, routine HPV vaccination of girls was introduced into the national vaccination schedule in Germany. Vaccine coverage reached 44.6% in 2016. The two HPV vaccines on the German market confer protection against two or seven high-risk HPV types. Aim of our study was to investigate HPV prevalence in women aged 20-25 years and to estimate the effects of HPV vaccination ten years after the introduction of HPV vaccination.
Methods: We performed a nation-wide representative cross-sectional study in 2017-18 using a two-step stratified sampling design to recruit at least 1,173 women aged 20-25 years from population registries in Germany. Participants used self-sampling kits (Evalyn brush; Rovers, Oss, The Netherlands) to collect cervico-vaginal samples and completed questionnaires. Samples were tested for 18 high-risk and eight low-risk HPV types (genotyping HPV test; Optiplex; Diamex, Heidelberg).
Results: In 1,202 of 1,226 study participants HPV test results as well as data on sociodemographic characteristics and HPV vaccination status were available. Overall response rate was 15%, ranging from 10 to 18% locally. Of 1,134 participants, 597 (53%) had received a full course of HPV vaccine. Further analyses on HPV type prevalence and vaccine effectiveness are in preparation and will be presented at the conference.
Conclusions: Our study will generate estimates of HPV type distribution and assess the impact of HPV vaccination in Germany. These data will contribute to the evaluation of the national vaccination strategy and improve prevention of HPV-associated carcinoma in Germany (supported by BMG; grant no. 321-4471-02/158).

Disclosure Statement: All authors have nothing to disclose.

Gastrointestinal (Colorectal) Cancer

Best-of-Abstracts-Vorträge

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High Microsatellite Instability (MSI-H) is Associated with Distinct Clinical and Molecular Characteristics and an Improved Survival in Early Colon Cancer (CC): Real Life Data from the Aio Molecular Registry Colopredict Plus

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Purpose: MSI-H is a known positive prognostic factor in early CC observed retrospectively in numerous clinical trials. A prospective validation in real life cohorts, also compared to other molecular and clinical factors, is still lacking.
Methods: From Sep 2013 to Jan 2019 patients (pts.) with UICC stage II/III CC were registered in 70 German cancer centers. MS status was tested by immunohistochemistry (IHC) of mismatch repair proteins. Loss of protein expression was confirmed by fragment length analysis (FLA) defining MSI-H and MSS tumors. Mutational status in RAS, BRAF, PI3K was determined by next generation sequencing (NGS). Disease free survival (DFS) and overall survival (OS) were estimated using COX regression. Relapse rates (RR) were calculated as a percentage of the subgroup.
Results: Tissue of 1787 pts. was analyzed by IHC and NGS. 423 pts. were MSI-H upon FLA (23.7%). Association of MS status with clinical and molecular factors is shown in Table 1. Rate of MSI-H increased with age with BRAF mutations (MT) more often detectable in older MSI-H pts. (%BRAF MT ≤70/70-75/>75y: 16.9/ 19.2/63.9%). DFS was significantly longer in MSI-H versus (vs.) MSS pts. (hazard ratio (HR) 0.702; confidence interval (CI) 0.547-0.900; p=0.005), while the HR for OS was not significant due to few events recorded (0.781; CI 0.595-1.0x26; p=0.076). DFS/OS in right vs. left sided primary tumors were not different (HR 1.003 CI 0.844-1.192; p=0.971/ HR 1.134; CI 0.930-1.383; p=0.213). In the BRAF MT subgroup, RR was substantially lower in MSI-H vs. MSS pts. (5.2/19.7%) albeit RR in MSI-H pts. did not differ between BRAF MT/WT (3.5/3.2%).
Conclusions: MSI-H tumors were more frequently detected in our cohort compared to reported data, presumably related to the older age of our pts. The high incidence of BRAF MT point to a sporadic etiology of most cases. We could also confirm MSI-H as a strong prognostic marker in early CC independent of BRAF MT.

Disclosure Statement: The authors state no disclosures.

Vorträge

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Longitudinal Investigation of Circulating Tumour Cells in Liquid Biopsies of Colorectal Cancer Patients - Analysis of the Clinical Benefit of a New Biomarker of Tumour Burden and Relapse

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Purpose: Previously, we established a semi-quantitative RT-PCR against CK20 and were able to identify colorectal cancer (CRC) patients at risk. Ongoing to this work, we now want to report on our recent longitudinal data on serial CK20 mRNA analysis of CRC patients. For the first time this allows us to monitor the burden of the CTC over a course of time and especially after surgery and absence of the tumour.
Methods: In total 126 serial blood samples from 50 patients were analysed. Blood was drawn prior to surgery (t0), one month (t1), three (t2), six (t3), nine (t4) and twelve months (t5) after surgery. Blood samples were analysed by CK20 RT-PCR. The PCR data was assessed regarding the previously published clinically relevant cut off value.
Results: At t0 17 (34.0%) patients were above the cut-off. At t1 a significant decrease of the CTC load was monitored (p<0.001). Also, at t2, t3 and t4 less CTC were measured (p=0.015, p<0.001, p=0.019, respectively). These results show, that the CTC load does correlate with the tumour burden – after macroscopically tumour free resection, the CTC load decreases as no more tumorous tissue enables the release of CTC.
Analysing individual patients we exemplarily identified two patients. (A) Stage II sigmoid carcinoma. Ongoing increase of mRNA expression over the postoperative course of 12 months. At t6 the cut-off was passed. 14 months after surgery a local relapse was diagnosed. (B) Stage III sigmoid carcinoma. Adjuvant treatment was started. No elevated CTC in the first blood sample. T2: significant increase of CTC passed the cut-off. Six months postoperative, iliacal CRC metastasis.
Conclusions: We successfully implemented a protocol of obtaining and analysing serial blood samples as liquid biopsies. By this, we might be able to identify CRC patients who potentially benefit of a more thorough aftercare at an earlier stage of follow-up. The detection of CK20-positive CTC may be a promising tool to detect a tumour recurrence prior to routine radiological diagnostics.

Disclosure Statement: No conflict of interest.

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Laparoscopic and Open Resection of Rectal Cancer—is Age an Effect Modifier for Short- and Long-Term Survival?

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Purpose: Various studies proofed the oncologic safety of laparoscopic resection of rectal carcinoma. However, there does not exist a clear recommendation on whether age should influence the choice of the surgical approach.

Methods: This population-based retrospective cohort study compares outcomes of laparoscopic and open surgery in rectal cancer patients. Perioperative mortality, 5-year overall, relative, and recurrence-free survival rates were analyzed separately for three age groups (< 60 years, 60–69 years, 70–79 years). Data originate from 30 regional German cancer registries that cover approximately one quarter of the German population. All primary nonmetastatic rectal adenocarcinoma cases with surgery between 2005 and 2014 were eligible for inclusion. To compare survival rates, Kaplan–Meier analysis, a relative survival model, and multivariable Cox regression were used; a sensitivity analysis assessed bias by exclusion.
Results: 10,754 patients fulfilling all inclusion criteria without missing data in important variables were included in the analysis. The mean laparoscopy rate was 23.0% and increased over time. Uni- and multivariable regression analysis of 30-day postoperative mortality revealed advantages for laparoscopically treated patients, although the significance level was not reached in any age group (for age group 70–79, it was missed only slightly: odds ratio, OR 0.559; 95% confidence interval, 95% CI 0.296–1.058). Regarding 5-year overall survival, laparoscopy generally seems to be the superior approach, whereas for recurrence-free survival patients under 60 years benefited more from the minimally invasive approach than older patients (< 60 years: hazard ratio, HR 0.703, 60–69 years: HR 0.787, 70–79 years: HR 0.923).
Conclusions: Laparoscopy shows similar results to the open approach in terms of postoperative mortality in all age groups. Concerning long-term outcomes, younger patients benefitted most from the minimally invasive approach. Increased use of laparoscopy for rectal cancer should be considered in this group.

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Somatic Alterations and Tumor Mutational Burden (TMB) in Patients with Metastatic Colorectal Cancer (mCRC) Treated with FOLFiRI Plus Bevacizumab or Cetuximab (Fire-3 Trial)

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Purpose: Molecular biomarkers and primary tumor sidedness guide treatment decisions in mCRC. Precision oncology is a novel model to identify targetable alterations and TMB.
Methods: FoundationOne® next generation sequencing (NGS) identified single nucleotide variants (SNV), copy number alterations (CNA), TMB and microsatellite instability (MSI-H) in patients treated in FIRE-3. Data was correlated with overall response (OR), progression free survival (PFS) and overall survival (OS). Multivariate regression analyses confirmed prognostic and predictive biomarkers for OR.
Results: 373 of 754 patients (49.4 %) provided eligible material for this analysis. Frequent known SNVs were found in *TP53* (72.4 %), *APC* (66.0 %), *KRAS* (27.3 %), *PIK3CA* (16.1 %), *BRAF* (12.1 %), *SMAD4* (8.0 %), *FBXW7* (7.0 %), frequent CNAs were found in *FLT3* (5.6 %) and *MYC* (6.7 %). *RAS* wildtype (WT) had significantly longer OS (27.9 vs. 20.6 months, HR = 0.62 [95% CI 0.50 – 0.78], p = 0.0001) and PFS (10.4 vs 8.9 months, HR = 0.75 [95% CI 0.60 – 0.94], p = 0.01) compared to RAS mutant (MUT) patients. OS (26.4 vs. 15.9 months, HR = 0.57 [95% CI 0.41 – 0.80], p = 0.001) and PFS (10.5 months vs 7.6 months, HR = 0.62 [95% CI 0.45 – 0.85], p = 0.003) were longer in *BRAF* WT vs. MUT patients. *SMAD4* WT vs. MUT patients showed significantly longer OS (HR = 0.59 [95% CI 0.34 – 1.01], p = 0.05) and higher probability of response [odds ratio *SMAD4* SV vs. WT = 0.32 [95% CI 0.10 – 0.98], p = 0.05] when treated with cetuximab. Multivariate regression confirmed *BRAF*, *KRAS* and *SMAD4* SNV as prognostic biomarkers and *KRAS* and *SMAD4* MUT as predictive biomarkers for OR. High TMB (> 8 mutations / MB) and MSI-H were detected in 56 and 10 patients, respectively, and showed a trend towards better OR in patients receiving cetuximab.
Conclusions: *RAS*, *BRAF* and *SMAD4* MUT were identified as poor prognostic biomarkers in patients of FIRE-3. *SMAD4* MUT might provide predictive relevance for cetuximab efficacy.

Poster

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Dissemination of Intestinal Epithelial Cells in Inflammation-Associated-Colorectal- Carcinogenesis

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Purpose: Cellular markers for the detection of circulating tumor cells (CTC) in patients with colorectal carcinoma (CRC) have been shown to have a high predictive and prognostic relevance. Patients suffering from inflammatory bowel diseases (IBD) have an increased risk to develop colorectal cancer particularly after long duration of disease. Thus, this study investigated whether markers used for CTC detection in CRC patients can be already determined in blood of IBD patients. Moreover, detection levels were correlated with clinicopathological data such as severity of inflammation.
Methods: CK20, PLS3, LAD1, DEFA5 -mRNA expression was analyzed by qRT-PCR in total RNA from peripheral blood mononuclear cell fraction from patient blood samples provided by the biobank of Comprehensive Cancer Center Kiel, Germany. In order to model the impact of an inflammatory microenvironment on malignancy-associated alterations and expression of CTC markers, the intestinal epithelial cell line NCM-460 was indirectly co-cultured with primary M1-like polarized human macrophages *in vitro*.
Results: Markers used for CTC detection in CRC patients (n=100), particularly CK20 and PLS3, were also elevated in IBD patients (n=75) compared to healthy donors (n=40). No difference could be seen in the levels of these markers in CRC or IBD patients. Current statistical analysis aims at identifying a correlation between detection levels and clinical parameters. Results from the *in vitro* co-culture system indicate that proinflammatory macrophages influence CTC marker expression as well as foster a motile and mesenchymal phenotype in NCM-460 cells.
Conclusions: These data suggest that dissemination of intestinal epithelial cells into the blood is promoted by inflammation and occurs already in IBD patients. Further analyses are needed to understand the role and evaluate the prognostic value of these CTC markers in IBD patients.

Disclosure Statement: The Authors declare no conflict of interest.

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The Influence of Postoperative Complications on Long-Term Prognosis in Patients with Colorectal Carcinomas

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Purpose: The impact of postoperative complications (POCs) on long-term prognosis in patients with colorectal carcinomas was analyzed with respect to the severity of complications according to the Clavien-Dindo classification (CDC).
Methods: The data of 2158 consecutive patients with curative elective resection of a colorectal carcinoma (CME or TME/PME) without distant metastases between 1995 and 2014 were analyzed. POCs were documented in a standardized form and retrospectively assigned to the CDC. Patients who died postoperatively (CDC grade V, 1.7%) were excluded. The influence of CDC on locoregional and distant recurrence, disease-free and overall survival was examined.
Results: 990 patients with colon carcinoma and 1168 with rectal carcinoma were analyzed. 467 patients (21.6%) had POCs: CDC I 141 (6.5%), CDC II (pharmacological treatment) 162 (7.5%), CDC III (surgical, endoscopical or radiological intervention) 112 (5.2%) and CDC IV (intensive care) 52 (2.4%). A higher rate of POCs and a higher grade of CDC were found in men, ASA III-IV patients, rectal carcinomas, abdominoperineal excisions and multivisceral resections. The 5-year rate of locoregional recurrences was 5.6% and was highest in CDC grade III patients (12.9%). The 5-year rate of distant metastases was 16.7% and increased continuously to 23.7% in CDC grade IV patients. In disease-free survival, the 5-year rate was 73.4% and decreased to 55.4% in CDC IV patients. In overall survival, the 5-year rate was 81.3% and decreased to 63.1% in CDC IV patients. This was confirmed in multivariate Cox regression analysis. We found a significantly higher risk for locoregional recurrences (HR 2.2; p=0.005) and distant metastases (1.7; p=0.020) in CDC III patients, while patients with CDC grade IV were associated with significantly worse disease-free (HR 1.8; p=0.002) and overall survival (HR 1.9; p=0.001).
Conclusions: Patients with POCs after colorectal surgery have worse long-term prognosis. With increasing CDC grade, survival deteriorates.

Disclosure Statement: The authors declare no conflict of interest.

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The Influence of Body Mass Index on Long-Term Prognosis in Patients with Colon Carcinomas

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Purpose: Obesity is an established risk factor for a number of chronic diseases, including diabetes, cardiovascular diseases and cancer with an unfavorable influence on life expectancy. A crude measure of obesity is the body mass index (BMI). Here, we analyze the impact of the preoperative BMI on long-term prognosis in patients with colon carcinomas.
Methods: The data of 694 consecutive patients with curative resection of a colon carcinoma (CME, complete mesocolic excision), no distant metastases, between 2003 and 2014 were analyzed. BMI was categorized according to the proposal of the WHO: <18.5 underweight, 18.5-24.9 normal weight, 25.0-29.9 overweight, ≥30.0 obesity.
Results: 13 patients (1.9%) were underweight, 221 patients (31.8%) were normal weight, 309 patients (44.5%) were overweight and 151 patients (21.8%) were obese. Men were found to be significantly more frequently overweight or obese (p<0.001). The 5-year rate of locoregional recurrences was 2.1%, no influence of any risk factor including BMI was found. The 5-year rate of distant metastases was 13.4%. It was significantly higher in advanced stage and emergency patients, but was not influenced by the patients' BMI. The 5-year rate of disease-free survival was 72.4%, the 5-year rate of overall survival was 78.1%. Both were significantly influenced by age, ASA classification, emergency presentation, tumor site, stage and preoperative BMI. Obese patients had a significantly better 5-year disease free survival than normal weight patients (78.5% vs 69.8%; p=0.045). This could be confirmed in multivariate Cox regression analysis (HR 0.7; p=0.034). In addition, obese patients had a significantly better overall survival than normal weight patients (82.4% vs 73.4%; p=0.027), which also could be confirmed in multivariate Cox regression analysis (HR 0.6; p=0.019).
Conclusions: In a cohort of 694 colon carcinoma patients treated with CME, obese patients at the time of surgery were not found to have worse prognosis than normal weight patients.

Disclosure Statement: The authors declare no conflict of interest.

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Prognostic Value of BRAF, KRAS and MSI Status in Patients with Advanced Left- and Right-Sided Colorectal Cancer: A Retrospective Evaluation Based on Data from the Tumor Documentation of the UCT Frankfurt

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Purpose: In recent years, a large number of studies have dealt with the prognostic difference between advanced left- and right-sided colorectal cancer (CRC). It became clear that patients with left-sided primarius have a higher survival probability. Further studies linking certain molecular markers such as KRAS, BRAF or MSI to the location showed an increase in mutations on the right side. This issue will be further investigated using data from the tumor documentation of the UCT Frankfurt.
Methods: For our study, we considered routine data from the UCT tumor documentation on patients with advanced CRC (ICD-10 C18-20, UICC III/IV) from 2008 until July 2019. We assigned flexura linealis, colon descendens, colon sigmoideum and rectum to the group of left-sided carcinomas; caecum, appendix, colon ascendens, flexura hepatica, colon transversum were assigned to the right-sided tumors. Endpoint was the overall survival after 5 years (OS).
Results: 612 (78 %; total: 785) had a primary tumor on the left side. OS was determined for patients with left-sided CRC at a rate of 47.2 % (95 % CI: 0.41 to 0.53), for patients with right-sided CRC at a rate of 37,2 % (95 % CI: 0.28 to 0.46). In general, mutations could be detected more frequently in the right-sided tumors. The survival could only be determined in patients with mutated KRAS due to the small number of cases. There was no significant difference between left and right side.
Conclusions: As already proven in various other sources, the data of the UCT tumor documentation also confirms the better prognosis for patients with left-sided CRC. As our results show, this could be associated with a lower mutation rate compared to right-sided tumors. To confirm this theory and for a more meaningful evaluation of the survival time of the individual mutations, a further study with an increased number of cases will be added.

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Disclosure Statement: All authors have declared no conflicts of interest.

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Farkor: Evaluating a Screenig Program for Familial Colorectal Cancer Risk

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Purpose: Colorectal cancer (CRC) screening in Germany starts at age 50. As there is evidence that individuals with a family history of CRC have an increased risk of developing CRC before age 50, screening for this group should start earlier. This study evaluates the clinical and economic effects of a risk-adapted screening program for CRC in individuals between 25 and 50 years of age.
Methods: An interim analysis assess the effects of the screening program FARKOR (Family Related Colorectal cancer Risk) in a population-based prospective cohort study. The program is open to members of the statutory health insurance in Bavaria between October 2018 and March 2020. Participants enter the study through their physicians or a public campaign. Additionally, insurances contact patients recently diagnosed with CRC to inform them that their relatives may have an increased risk of developing CRC. Trained doctors classify participants as potential risk carriers or as inconspicuous. Potential risk carriers are *invited* to a shared decision making shared decision making on 1) immunological test for fecal occult blood or 2) colonoscopy. Assessment of long-term benefits, harms and cost-effectiveness of FARKOR uses decision-analytic modeling from the perspective of the German health care system.
Results: After 11 months, 4823 patients have joined the program. Among the 1675 identified potential risk carriers, 1201 participated in a shared decision making after which 421 (635) decided to undergo an immunological test for fecal occult blood (colonoscopy). Adenoma were detected in 17% of screening colonoscopies. No complication occurred.
Conclusions: The preliminary results of an interim analysis suggest good adherence to the proposed screening measures. Further evaluations will follow to assess its overall clinical and economic effects.

Disclosure Statement: The "German Innovation Fund" of the Federal Joint Committee (G-BA) supports this work: 01NVF17026. The author declare no conflict of interest.

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IVOPAK II Study: Morbidity Following Secondary Resection of Colorectal Liver Metastases

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Purpose: In the IVOPAK II study, patients with unresectable metastatic colorectal carcinoma (CRC) receiving palliative chemotherapy and biological agents after expanded RAS-analysis are regularly re-staged by imaging with subsequent tumor board decision every 2 months to identify patients becoming secondary resectable.
Methods: Between 7/2016 and 7/2019, 40 patients were included into the study. 50% (n=20) had a RAS mutation, 50% (n=20) an All-RAS-wildtype. To date, 14 patients received a secondary curative therapy, including 9 patients with liver metastases only (HEP), 1 patient with resection of HEP and primary tumor (PT), 2 patients with resection of HEP and pulmonary metastases (PUL) and PT, 1 patient with resection of PUL, 1 patient with peritoneal metastases.
Results: Median age of the 12 patients with HEP was 65 years (range: 56-72), including 10 men and 2 women. RAS wildtype was diagnosed in 67% (n=8), RAS mutations in 33% (n=4). Patients underwent secondary curative surgery in median 6 months after starting palliative treatment (range 3-18). The 12 patients with HEP (+/- PUL) were treated by surgical resection (n=7), radiofrequency ablation (n=3), both (n=2). Liver resections included 2 atypical and 4 segmental resections, 2 right hemihepatectomies and 1 extended right hemihepatectomy. Postoperatively, the following complications occurred in liver-resected patients (Clavien-Dindo classification): Grade 0 (n=2), Grade I (n=1), Grade II (n=1), Grade III (n=2), Grade III (n=3). Median follow-up of the 12 patients is currently 6 months (0-28). 11 of 12 patients are still alive. 4 patients (30%) remain with no evidence of disease.
Conclusions: Even in patients with unresectable metastatic CRC receiving palliative therapy, regularly restaging for evaluation of secondary curative treatment options is meaningful. The high response rate of All-RAS wildtype population is important for secondary resection.

Disclosure Statement: The authors declare no conflict of interest.

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Case of Two Patients with MSI-High Metastatic Colorectal Cancer Treated with Pembrolizumab

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Purpose: Immune checkpoint inhibitors (ICI) have become a standard treatment in everyday oncological practice. In clinical trials, pembrolizumab and nivolumab as well as the combination of nivolumab and ipilimumab have demonstrated efficacy in patients with microsatellite instability-high (MSI-high) metastatic colorectal cancer (mCRC). The underlying mismatch repair deficiency seems to correlate with the level of neoantigen and consecutively with high immunogenicity- this may explain the treatment effect derived from ICI in MSI-high mCRC. Unlike the FDA, the EMA has not yet approved ICI for the treatment of MSI-high mCRC.
Methods: We present a scientific report on the clinical courses of two male patients with RAS-wildtype, MSI-high mCRC, who received off-label pembrolizumab (200 mg every 3 weeks) in our department after failure to first- and third-line treatment, respectively.
Results: A 42-year old patient with synchronous hepatic mCRC received pembrolizumab after tumor progress to first-line treatment with FOLFIRI and Cetuximab. The patient developed significant clinical symptoms and corresponding radiological tumor progression after four administrations of ICI. We administered pembrolizumab as fourth-line treatment to another 49-year old patient with mCRC, that metastasized per continuitatem to the right-sided thoracic wall. After three applications, a CT-scan revealed significant shrinkage of the bulky tumor mass. The radiological re-assessment five months after initiation demonstrated further decreasing tumor size. The clinical performance status improved significantly and therapy with pembrolizumab is still ongoing.
Conclusions: ICI are able to provide durable tumor response in pretreated MSI-high mCRC patients. Therefore, we emphasize the importance of testing for MSI. Further clinical studies are needed in order to verify efficacy and safety of ICI in mCRC patients and to identify those patients with MSI-high mCRC that do not benefit from ICI therapy.

Disclosure Statement: No conflict of interest.

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Age-Specific Sequence of Colorectal Cancer Screening offers in Germany: Model-Based Critical Evaluation

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Purpose: The current offer of the organized screening program for colorectal cancer (CRC) in Germany implies that both sexes can have up to five annual fecal immunochemical tests (FITs) between ages 50-54, followed by a first screening colonoscopy at age 55 in case all of these FITs were negative. We sought to assess the performance of this offer.
Methods: Using a multistate Markov model, we quantified the expected prevalences of neoplasms in a population perfectly adhering to annual FIT screening between ages 50-54 to assess the detection rates and numbers needed to scope one case of (non-)advanced adenoma or cancer (NNS) of colonoscopic screening at age 55. We additionally modelled the diagnostic performance of such consecutive annual FIT testing.
Results: In subjects with five consecutive negative FITs, expected colonoscopy detection rates (NNS) of any neoplasm, any advanced neoplasm and cancer at age 55 are 10% (10), 1.9% (52) and 0.05% (2,089), respectively, in women, and 17% (6), 3.5% (28) and 0.09% (1,058), respectively, in men. Positive predictive values (PPVs) for advanced neoplasms drop from 14.0% and 22.4% in year 1 to 8.4% and 13.9% in year 5, and PPVs for cancers from 2.4% and 3.9% to 0.6% and 1.0%, for women and men, respectively.
Conclusions: Our findings suggest that the current screening offer in Germany of five consecutive FITs from ages 50-54, followed by screening colonoscopy at age 55 after five negative FITs, may be highly inefficient as perfect adherence would go along with very low PPVs of repeat annual FITs and very high NNS of screening colonoscopy at age 55. The design of the FIT screening offer should be re-evaluated.

Disclosure Statement: The authors declare that they have no conflict of interest.

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Outcomes at Follow-Up of a Negative Colonoscopy in the Average-Risk Population: a Systematic Review and Meta-Analysis

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Purpose: To review and summarize the evidence on the prevalence of colorectal adenomas and cancers at a follow-up screening colonoscopy after negative index colonoscopy, stratified by interval between examinations and by sex.
Methods: We systematically searched the electronic databases of PubMed, Web of Science and EMBASE and performed meta-analyses of all available studies. Published studies were eligible for inclusion if they assessed the outcome of a follow-up colonoscopy in subjects at average risk for CRC with a negative previous colonoscopy (no adenomas).
Results: 28 studies were identified, including 22 cohort studies, 5 cross-sectional studies and 1 case-control study. Findings for an interval between colonoscopies of one to five, five to ten, and more than ten years were reported by 17, 16 and 3 studies, respectively. Summary estimates (95% confidence intervals) of rates of any neoplasms were 20.7% (15.8% to 25.5%), 23.0% (18.0% to 28.0%) and 21.9% (14.9% to 29.0%) for one to five, five to ten, and more than ten years between colonoscopies. Corresponding summary estimates of rates of advanced neoplasms were 2.8% (2.0% to 3.7%), 3.2% (2.2% to 4.1%) and 7.0% (5.3% to 8.7%). Seven studies also reported findings stratified by sex. Summary estimates stratified by interval and sex were consistently higher for men as compared to women.
Conclusions: Although detection of any neoplasms was observed in >20% of subjects within five years of a negative screening colonoscopy, detection of advanced neoplasms within ten years was rare. Our findings suggest that ten-year colonoscopy screening intervals after negative colonoscopy (as currently recommended) may be adequate, but more studies are needed to strengthen the empirical basis for pertinent recommendations and to investigate even longer intervals.

Disclosure Statement: The authors declare that they have no conflict of interest.

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Long Term Survival of Patients with Stage IV Rectal Cancer - Due to Targeting the Tumor Associated Inflammatory Process?

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Purpose: The median overall survival time of patients with stage IV rectal cancer is less than 3 years. We present cases of 2 patients with rectal cancer who survived initial diagnosis of metastasis for 9 and more than 11 years, respectively. We speculate on the possible reason for this favorable course.
Case reports: Patient 1 was a 66 year old lady who was operated because of rectal cancer UICC stage I. 18 months later she developed skin and hepatic metastasis, received resection and was treated with regimens containing FOLFOX, bevacizumab, FOLFIRI, cetuximab, irinotecan, CAPOX, panitumumab, mitomycin, and aflibercept. She died 9 years after diagnosis of metastasis. Patient 2, aged 61 years, initially presented with metastasis to the peritoneum and later on to abdominal wall and lung. During the course she was treated with regimens containing bevacizumab, FOLFIRI, capecitabine, FOLFOX, cetucimab, and ramucirumab. She received several tumor resections and irradiation. Currently she is living more than 11 years after diagnosis of metastasis.
Discussion: A survival of more than 9 years in stage IV rectal cancer is remarkable. Based upon animal studies a strategy combining antiangiogenic therapy with long term applcation of capecitabine has been proposed (1). In the human situation single cases of the beneficial effects of long term metronomic capecitabine have been reported. The patients described here received a long term therapy with regimens containing anti-VEGF, or VEGFR-2 directed modalities, and drugs targeting endothelium and tumor supporting myeloid cells.
Conclusions: Besides targeting tumor cells itself the long lasting inhibtion of angiogenesis proves to be an important factor to achieve long term disease stabilisation.
The spectrum of drugs targeting cells of the intra- and peritumoral inflammatory rection is wide and aggravates the interpretion of single factors responsible for a benefical course.
Report more of those cases with a noticeable survival time.

Reference:

1. Zhang Y et al, PNAS 2017, PMID: 28607065

Disclosure Statement: The authors declare no conflict of interest.

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Real-World Testing Patterns for Braf-Mutations and Treatment of Patients with Braf-Mutated Metastatic Colorectal Cancer: Results from The German Tumor Registry Colorectal Cancer (TKK Registry)

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Purpose: *BRAF*-mutations have been reported in approximately 8-12 % of patients (pts) with metastatic colorectal cancer (mCRC), with V600E being the most common mutation. Despite major improvements in survival for mCRC overall, *BRAF*-mutant mCRC typically appears refractory to standard chemotherapy for mCRC and is associated with a poor prognosis with a median overall survival of less than 12 months. Real-world data on the identification and treatment of this high medical need population are scarce.
Methods: Since 2006, the Tumor Registry Colorectal Cancer (TKK) prospectively documents treatment of CRC pts in clinical routine in Germany. Pts are treated according to physician's choice. Data on pts and tumor characteristics, all systemic treatments including first-line and subsequent line treatments, outcome and quality of life are collected. In addition, since 2018 data on *BRAF* testing are documented. Here, we analyzed BRAF-mutation testing patterns and treatment of pts with BRAF-mutant mCRC. Analyses were ongoing at the time of submission.
Results: Until data base cut 31.03.2019, 4334 pts with mCRC had been enrolled at initiation of palliative first-line treatment, 474 pts from 91 sites since data on BRAF testing is collected. Of those, 65% (310 pts) were tested for BRAF mutation with positive results documented in 48 patients (10% of all, 15% of tested pts). Results will be presented regarding characteristics (age, gender, ECOG performance status, tumor localization, RAS status, MSI status, time between primary diagnosis until start of first-line therapy) and treatment patterns (1st, 2nd, 3rd line) of pts with and without *BRAF* mutation testing and with and without BRAF mutation.
Conclusions: This analysis of the TKK data provides important insights into the testing and treatment patterns of patients with BRAF-mutant mCRC treated in clinical routine in Germany.

Disclosure Statement: None of the authors has declared a conflict of interest regarding the subject of this work.

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Perioperative Therapy of Locally Advanced Adenocarcinoma in the Upper Third of The Rectum - Long-Term Results of Different Therapeutic Approaches

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Purpose: The German S3-guideline's recommendations for the perioperative treatment of stage II and III rectal cancer in the upper third of the rectum have recently changed. Between 2008 and 2017 it was up to the treating physician whether to follow the guideline's recommendations on rectum- or on colon carcinoma; nowadays, there is a clear statement in favor of the colon line of treatment.
Methods: Based on a cohort of 5,312 patients diagnosed with stage II/III upper third rectum cancer between 2000 and 2016, gathered by 30 clinical cancer registries in Germany, we performed a comparison of 462 cases of neoadjuvant radiochemotherapy and adjuvant chemotherapy combined and 1,049 cases of adjuvant chemotherapy only, with regard to the outcome quality of the different perioperative therapeutic approaches for locally advanced upper third rectum cancer in clinical practice. Using Kaplan-Meier, uni- and multivariable Cox-regression analyses, overall survival, disease-free survival, local and distant recurrence rates were calculated.
Results: Patients in UICC stage II/III who received neoadjuvant radiochemotherapy and adjuvant chemotherapy combined had, according to the multivariable analyses, no significant differences concerning overall survival, disease-free survival or local and distant metastases rates as compared to patients receiving adjuvant chemotherapy only. The corresponding cumulative 5-year local recurrence rates were 4,1% and 5,6% respectively. In contrast, patients with UICC stage III and an elevated risk profile (subgroup analyses for: stage III T4 and stage III N2) showed a significantly worse disease free survival when they had obtained adjuvant chemotherapy only (HR=3,225, 95%-CI=1,140-9,123, p=0,027 / HR=2,352, 95%-KI=1,153-4,798, p=0,019).
Conclusions: The recommendations of the German S3-guideline of 2017 to refrain from neoadjuvant radiation therapy in low-risk patients with a tumor in the upper third of the rectum are supported by the results of this study.

Disclosure Statement: The authors declare no conflict of interest.

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The Influence of Diabetes Mellitus (DM) on Morbidity and Mortality as well as Oncological Outcome in Colon Cancer (CA) Surgery – Interims Analysis

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Purpose: To investigate the influence of DM as well as the factors associated with this metabolic disease, on early postop. & long-term oncological outcomes following colon Ca surgery.
Methods: Patients with colon Ca -/+ DM were registered in this prospective multi-center observational study. Early postop. & long-term oncological outcome was specifically characterized by morbidity/in-hospital mortality & 5-yr-overall survival (5-yr-OS), 5-yr-disease-free survival (5-yr-DFS) & 5-yr-local recurrence rate (5-yr-LRR), resp.
Results: In total, 9167 patients were enrolled who were subdivided as follows: 20.5% w/ DM (insulin-dependent, 37.8%) & 79.5% w/o DM (age range of +/- DM patients, 34-97 *vs.* 18-98 yr; sex ratio [m/f], 52.9/47.1% *vs.* 56,2/43,8%). The initially higher progression rates of tumor (Tu) disease (P=0.018) as well as the more advanced Tu stages according to the UICC classification was found in DM patients (P=0.293). Furthermore, DM patients showed significantly worse ASA scoring (P<0.001). With a total morbidity of 35.8%, DM patients had significantly more general postop. complications (P<0.001). However, the slightly higher rate of special postop. complications in DM patients was not significant (P=0.224). With a total in-hospital mortality of 4.2%, DM patients showed a significantly higher rate (P<0.005). DM patients had a significantly lower 5-yr-OS (DM, 49.8% *vs.* non-DM 59.7%; P<0.001). A clearly worse 5-yr-DFS was also found in the DM category (DM, 57.7% *vs.* non-DM, 67.6%, P<0.001). The surprisingly lower 5-yr-LRR of DM *vs.* non-DM patients was not significant (2.4% *vs.* 2.8%, P=0.664).

Conclusions: The highest postop. complication rates as well as the worst 5-yr-OS and the lowest 5-yr-DFS were found in the DM patients.

Disclosure Statement: Nothing to be disclosed.

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Body Mass Index (BMI) Dependent Outcome in Colon Cancer(CA) Surgery – Interims Results of a Prospective Multi-Center Observational Study

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Purpose: To verify the impact of BMI onto immediate post-op. & long-term oncological outcomes following colon Ca surgery.
Methods: Patients (n_{Total}=8,574; mean age, 71 [range, 18-98] yrs; sex ratio, m:f=53.7:46.3%) were classified according to WHO definitions for BMI into under-/normal-/overweight & obese (<18.5/18.5-24.9/25-29.9/≥30 kg/m^2, resp.).
Early postop. outcome comprised morbidity & hospital mortality.
Long-term oncological outcome was specifically characterized by 5-yr-overall survival (5-yr-OS), 5-yr-disease-free survival (5-yr-DFS) & 5-yr-local recurrence rate (5-yr-LRR).
Results: The relative portions for the BMI categories were as follows: Under-, 2.1%; normal-, 36.5%; overweight, 40.3% & obese, 21.2%. The highest progression of the Tu disease was found in the underweight patients. More advanced Tu stages (according to UICC classification) were detected in the normal weight group compared to overweight & obese patients (P<0.001 each). In addition, both underweight & obese patients showed worse ASA scoring (P<0.001). With a total morbidity of 35%, obese patients suffered most from surgical complications (P<0.001) *vs.* underweight category was associated with the highest rate of general complications after surgical intervention (P=0.183). The overall in-hospital mortality was 3.7%. Obese subjects had better 5-yr-OS (63.1%) than normal weight individuals (54.4%; P<0.001). In addition, overweight cases were not different compared to obesity (P=0.205). The lowest 5-yr-OS rates were found in the underweight group of patients (38.9%; P<0.001 - overall 5-yr-OS, 58.8%). With the lowest proportion of local recurrences (5-yr-LRR, 1.4%), only the obesity category had a significant influence on 5-yr-LRR (P<0.016; LRR in total, 2.88%). Despite the higher 5-yr-LRR in the underweight cases, it was not significantly different (P>0.264).
Conclusions: Results are similar to previously obtained rectal Ca data on long-term outcome emphasizing the obesity paradox.

Disclosure Statement: Nothing to be disclosed.

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Multicenter Study Results on Colon Cancer Conducted by a Single Research Group – an Overview

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Purpose: To summarize results on the surgical management of colon cancer(Ca), its quality assurance & their consequences for daily surgical practice.
Methods: Prospective multicenter observational study data on diagnostic, treatment & outcome of patients with colon Ca over a defined study period.
Results (selective):

1) Case load in general does not provide necessarily a significant impact onto the outcome.
2) Age can be considered a risk factor, however, it can not be considered a contraindication for surgcial treatment of colon Ca.
3) Hartmann's procedure is still indicated in high-risk patients & emergency cases to reduce morbidity & mortality.
4) Hospital volume does not provide a significant impact onto the early postop. outcome.
5) Implantation of self-expanding stents (SEMS) can be considered an efficient measure in endoscopic palliation of the malignant colonic stenosis – it reduces postop. complications in bridging of stenosing tumor growth of colon Ca until surgical intervention.
6) Laparoscopic approach in resection of colon Ca is reasonable in a well defined portion of patients; it should be performed by experienced surgeons since conversion to open surgery is associated with a significant increase of morbidity, mortality & hospital stay.
7) Anastomotic insufficiency in colon resection is a rare but severe complication, which is associated with specific risk factors.

Conclusions: The aquisition of such data can provide important hints & knowledge for future care.

Disclosure Statement: Nothings has to be disclosed.

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Quality Assurance in Rectal Cancer - Multicenter Study Results Obtained By One Research Group

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Purpose: To analyze data on diagnostic & treatment profile, outcome as well as quallity assurance of surgical care in the management of rectal cancer(Ca).
Methods: Prospective multicenter observational study (design) in patients with rectal Ca over a defined study period.
Results:

- Hospital volume did not have a significant impact onto the oncosurgical long-term outcome.
- Neoadjuvant radiochemotherapy did not increase the risk of a postoperative anastomotic insufficiency or dysfunction of the urinary bladder after sphincter-preserving rectal resection with curative intention.
- Creation of a protective enterostoma did not reduce the frequency of a postop. anastomotic insufficiency but it lowered the frequency of following surgical or interventional consequences.
- Quality of TME depends on patient- & treatment-associated factors.
- Patient's age is a risk factor but it can not be considered a general contraindication for resection of rectal Ca.
- Oncological outcome after laparoscopic rectum resection is comparable with that after open resection (worsening after conversion).
- Limited resection of pT1-low-risk carcinoma may provide an acceptable oncosurgcial outcome.
- Rate of abdominoperineal rectum exstirpation (APR) has been reduced in routine surgical care down to approximately 20%.

Conclusions: The results i) reflect real situation in abdominal surgery in Germany, ii) have influenced disease-specific clincial management, and iii) may define novel subjects of up-coming studies.

Disclosure Statement: Nothing to be diosclosed.

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Colorectal Cancer Screening with Fecal Immunochemical Tests – The Impact of Anatomical, Morphological and Histopathological Adenoma Characteristics on Test Sensitivity: Systematic Review and Meta-Analysis

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Purpose: Fecal immunochemical tests (FIT) are recommended for colorectal cancer (CRC) screening. Different adenoma characteristics can affect FIT sensitivity. We aimed to systematically investigate adenoma characteristics influencing FIT sensitivity and leading to false-negative results.
Methods: Literature search was conducted in MEDLINE, Cochrane Library and EMBASE databases. Included studies had to provide quantitative information on FIT sensitivity with regard to different specific adenoma characteristics. We limited our search to articles published 2010-2019 in English language. Evidence tables were used to systematically combine study characteristics. The differences between sensitivity of distal and proximal adenomas were pooled using a fixed effects meta-analysis model and 95% confidence intervals (CI) were calculated.
Results: 11 studies were included in our review. Study designs varied with 8 prospective and 3 retrospective studies. Identified characteristics leading to low FIT sensitivity are proximal localization, non-polypoid morphology and serrated type. The pooled absolute difference in FIT sensitivity between proximal and distal adenomas was 15% (95% CI: 11%-19%). FIT sensitivity was significantly lower for flat as compared to non-flat adenomas (11%). The largest statistically significant difference between sessile serrated (SSA/P) and conventional advanced adenoma was 20%. FIT results in high proportion of false-negative results (16%) for patients with proximal and small (≥10 mm) or flat adenomas.
Conclusions: Our findings suggest that localization in the proximal colon, flat adenomas and SSA/Ps are the most unfavorable for detection in early stages when the curative treatment could prevent CRC development.
Imperiale TF, et al. 2019.
Niedemaier T, et al. 2018.

Disclosure Statement: No conflict of interest.

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Integrated Biobanking and Tumor Model Establishment of Human Colorectal Carcinoma Provides Excellent Tools for Modern Precision Medicine

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Purpose: Over the time period from 2006 to 2017, consecutive patients operated on at the University Medical Center Rostock participated in this comprehensive biobanking and tumor-modelling approach: the HROC collection. Samples were collected using strict SOP including blood (serum und lymphocytes), tumor tissue (vital and snap frozen) as well as adjacent normal epithelium. Patient and tumor data including classification, molecular type, clinical outcome and results of model establishment are the essential pillars.
Methods: Overall 149 patient-derived xenografts, 34 primary and 35 secondary cell lines were successfully established and encompass all colorectal carcinoma anatomic sites, grading and staging types and molecular classes. The HROC collection represents one of the largest model assortments from consecutive clinical CRC cases worldwide.
Results: Statistical analysis identified a variety of clinicopathological and molecular factors associated with model success in univariate analysis; several of them not identified before: localization, mutational status of K-Ras and B-Raf, MSI-status as well as grading and staging parameters. Surprisingly, in multivariate analysis model success solely correlated positively with the nodal status N1 and mutations in the genes K-Ras and B-Raf. These results imply that generating CRC tumor models on the individual patient level is worth considering especially for advanced tumor cases with a dismal prognosis.
Conclusions: In sum, this study succeeded in generating CRC *in vitro* and *in vivo* models from all subtypes of CRC with the exception of FAP. To the best of our knowledge, the HROC collection represents the largest single-center integrated biobanking activity of CRC-patient biomaterial plus individual-patient-derived *in vitro* and matching *in vivo* models worldwide. Several clinical and molecular factors significantly influencing success of model generation were identified – many for the first time. All models are available upon reasonable request.

Disclosure Statement: none to declare

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Beacon Crc: a Randomized, Phase 3 Study of Encorafenib (ENCO) and Cetuximab (CETUX) with or without Binimetinib (BiNI) vs. Choice of Either Irinotecan or Folfiri Plus Cetux in BRAF V600E–Mutant Metastatic Colorectal Cancer (mCRC)

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Purpose: BRAF V600E mutations are identified in up to 15% of mCRC patients (pts) and confer a poor prognosis. Objective response rates (ORR) to chemotherapy in ≥ 2 line are generally less than 10%, with median progression-free survival (PFS) and overall survival (OS) of approximately 2 and 4-6 months, respectively. A 30-patient safety lead-in with ENCO+BINI+CETUX showed acceptable safety and encouraging activity in these pts.
Methods: The BEACON CRC Study (NCT02928224) was a multicenter, randomized, open-label, phase 3 study to evaluate ENCO+CETUX with/without BINI (triplet or doublet) vs. choice of irinotecan or FOLFIRI + CETUX (control) in pts with BRAF V600E–mutant mCRC who had progressed after 1 or 2 prior palliative regimens. The primary endpoints were OS and ORR (by blinded central review) comparing triplet to control arm; secondary end points included OS for the doublet arm as well as PFS and safety.
Results: 665 pts were randomly assigned to the triplet (n = 224), doublet (n = 220), or control arm (n = 221). Median OS was 9.0 months (95% CI, 8.0-11.4) for the triplet and 5.4 months (95% CI, 4.8-6.6) for the control regimen (HR, 0.52; 95% CI, 0.39-0.70, p < .0001). Confirmed ORR of the triplet was 26% and 2% for the control (p < .0001). Median OS for the doublet combination was 8.4 months (95% CI, 7.5-11.0) (HR vs. control, 0.60; 95% CI, 0.45-0.79; P = .0003). Adverse events were as anticipated based on prior trials with each combination. Grade 3 or 4 adverse events were seen in 58%, 50% and 61% of pts in the triplet, doublet and control arm, respectively.
Conclusions: ENCO+BINI+CETUX improved OS and ORR in pts with BRAF V600E-mutant mCRC when compared with current standard of care chemotherapy and had a safety profile consistent with the known safety profile of each agent. This targeted therapy regimen should be a new standard of care for this patient population.
The study was published at ESMO World GI congress 2019.

Conflicts of Interest: AV: honoraria from Pierre Fabre.; GP: speaker, advisory board member, other type of consultant: Celgene, Bayer, Roche, Shire, Halozyme, Lilly, BMS, Pierre Fabre, Amgen, Servier, MSD, Merck, Taiho; GF: honoraria from Merck, Roche, Sanofi-Aventis, Lilly, Bayer, Servier, Mundipharma, BMS, MSD; Research funding: Merck; SK: Stock and Other Ownership Interests: Molecular-Match, Navire Consulting or Advisory Role: Roche, Genentech, EMD Serono, Merck, Karyopharm Therapeutics, Amal Therapeutics, Navire Pharma, Symphogen, Holy Stone, Biocartis, Amal Therapeutics, Amgen, Novartis, Eli Lilly, Boehringer Ingelheim; AG: Honoraria: Elsevier, Aptitude Health Consulting or Advisory Role: Genentech (Inst), Bayer (Inst), Bristol-Myers Squibb (Inst), Eli Lilly (Inst), Boston Biomedical (Inst), Amgen (Inst), Array BioPharma (Inst), Guardant Health (Inst), Daiichi Sankyo (Inst), Research Funding: Genentech (Inst), Bayer (Inst), Pfizer (Inst), Eisai (Inst), Eli Lilly (Inst), Boston Biomedical (Inst), Daiichi Sankyo (Inst), Array BioPharma (Inst); Travel, Accommodations, Expenses: Genentech, Bayer, Bristol-Myers Squibb, Boston Biomedical, Amgen, Boehringer Ingelheim, Merck Sharp & Dohme; EVC: Consulting or Advisory Role: Bayer, Eli Lilly, Roche, Servier, Bristol-Myers Squibb, Celgene, Merck Sharp & Dohme, Merck KGaA, Novartis, AstraZeneca; Research Funding: Amgen (Inst), Bayer (Inst), Boehringer Ingelheim (Inst), Eli Lilly (Inst), Novartis (Inst), Roche (Inst), Celgene (Inst), Ipsen (Inst), Merck (Inst), Merck KGaA (Inst), Servier (Inst), Bristol-Myers Squibb (Inst); RY: Research Funding: Array BioPharma, GlaxoSmithKline, Novartis; Travel, Accommodations, Expenses: Array BioPharma; Speakers' Bureau: Sysmex; Research Funding: Symphogen; Patents, Royalties, Other Intellectual Property: Patent licensed by Biocartis (Inst); HW: Honoraria: Merck KGaA, Celgene, Sirtex Medical, Servier, Array BioPharma, Shire, Genentech, ERYTECH Pharma; Consulting or Advisory Role: Roche Pharma AG, SITEX Medical, ERYTECH Pharma, Shire, Incyte; Speakers' Bureau: Sirtex Medical, Celgene, Merck KGaA, Servier; Research Funding: Sirtex Medical (Inst), Merck KGaA (Inst), Pfizer (Inst), Merck Sharp & Dohme (Inst); TY: Research Funding: Chugai Pharma (Inst), Sanofi (Inst), Sumitomo Dainippon (Inst), GlaxoSmithKline (Inst); JD: Consulting or Advisory Role: Bionomics, Eli Lilly, Eisai, BeiGene, Ignyta (Inst); Research Funding: Roche (Inst), GlaxoSmithKline (Inst), Novartis (Inst), Bionomics (Inst), MedImmune (Inst), BeiGene (Inst), Eli Lilly (Inst), Bristol-Myers Squibb (Inst); FC: Consulting or Advisory Role: Genentech, Merck KGaA, Bayer, Amgen, Pfizer; Research Funding: Merck KGaA (Inst), Genentech (Inst), Servier (Inst), Symphogen (Inst), Amgen (Inst), Bayer (Inst), Merck Sharp & Dohme (Inst), Bristol-Myers Squibb (Inst), Ipsen (Inst); AG: Employment: Array BioPharma, Alnylam (I), Bluebird Bio (I); Stock and Other Ownership Interests: Array BioPharma, Alnylam (I); Honoraria: Bluebird Bio (I); Patents, Royalties, Other Intellectual Property: Receives royalties from Yale University on an antibody used in nephrology basic research (I); KM: Employment: Array BioPharma; Stock and Other Ownership Interests: Array BioPharma; Travel, Accommodations, Expenses: Array BioPharma; NS: Research funding (inst): ompany: AstraZeneca/MedImmune, Bayer, Bristol-Myers Squibb, Novartis, GlaxoSmithKline, Pfizer, Roche, Genentech/Roche, Boehringer Ingelheim, Blueprint Medicines, AB Science, Deciphera, Blueprint Medicines, Genentech, Merck Sharp & Dohme, Amgen, Merus, Lilly, Incyte; VS: Employment: Array BioPharma; Leadership: Array BioPharma; Stock and Other Ownership Interests: Array BioPharma; JCB: Employment: Array Biopharma; Stock and Other Ownership Interests: Array Biopharma, Gilead Sciences; LA: Array employee; Employment: Array BioPharma; Stock and Other Ownership Interests: Array BioPharma; Travel, Accommodations, Expenses: Array BioPharma; JT: Consulting or Advisory Role: Bayer, Boehringer Ingelheim, Eli Lilly, MSD, Merck Serono, Novartis, Sanofi, Taiho Pharmaceutical, Merrimack, Peptomyc, Rafael Pharmaceuticals, Symphogen, Chugai Pharma, Ipsen, Merus, Pfizer, Seattle Genetics, Array BioPharma, AstraZeneca, BeiGene, Genentech, Genmab, Halozyme, Imugene Limited, Inflection Biosciences Limited, Kura, Menarini, Molecular Partners, Pharmacyclics, ProteoDesign SL, Roche, Seattle Genetics, Servier, VCN Biosciences, Biocartis, Foundation Medicine, HalioDX SAS, Roche Diagnostics; FT, YH, TG, TA, PGA have nothing to dislose.

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Are Visceral Obesity and Sarcopenia Postoperative Risk Factors for Patients Undergoing Hepatic Resections for Synchronous Colorectal Liver Metastases?

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Purpose: The impact of body fat composition on surgical outcomes is controversial. This study examined whether sarcopenia or visceral obesity were risk factors after hepatic resection of synchronous colorectal liver metastases.
Methods: 94 consecutive patients with primary hepatic resections for synchronous colorectal metastases were identified from a single cancer center database between January 2013 and August 2018. Body fat distribution and sarcopenia were retrospectively calculated from single-slice CT images at the level of L3.
Results: 63,8% (n=60) of patients had postoperative complications, whereas only 18,1% (n=17) had major complications (Clavien-Dindo grade IIIb and above). 36,2 % (n=34) of patients had sarcopenia and 70,2% (n=66) were viscerally obese. Different definitions for visceral obesity included visceral fat area (VFA) > 100cm², VFA >168cm² for men and >80 cm² for women and visceral to subcutaneous fat ratio (V/S) >0,4. All definitions of visceral obesity showed a significant impact on postoperative complications (p=0,002, p=0,014, p=0,015, respectively). Higher grades of complications were observed with viscerally obese patients (p=0,002). BMI was not a predictor for postoperative outcomes (p=1,0). Sarcopenia was not significantly associated with postoperative complications (p=0,461), however, it was shown to increase the length of hospital stay (p=0,028). Neither sarcopenia nor visceral obesity had an impact on overall survival.
Conclusions: Visceral obesity but not sarcopenia correlates with short-term postoperative outcomes after hepatic resections and may thus serve for better preoperative risk stratification.

Disclosure Statement: No Disclosures.

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Beyond Proximal or Distal Location: Colonoscopy and Reduction of Colorectal Cancer Risk By Molecular Subtypes and Pathways

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Purpose: In previous studies, the protective effect of colonoscopy was generally stronger for distal than for proximal colorectal cancer (CRC) (1,2). This study aimed to investigate whether the association of colonoscopy and CRC risk varies according to major molecular pathological features and pathways of CRC.
Methods: Population-based case-control study from Germany, including 2132 patients with a first diagnosis of CRC and information on major molecular tumor markers, and 2486 control participants without CRC. Detailed participant characteristics were collected by standardized questionnaires and information on previous colonoscopy was derived from medical records.
Results: Overall, we observed strong risk reduction of CRC after colonoscopy that was weaker for microsatellite instable (MSI) than for non-MSI CRC (p for heterogeneity <0.0001), for CpG island methylator phenotype (CIMP) high CRC than for CIMP low/negative CRC (p het=0.0011), for BRAF-mutated than for BRAF non-mutated CRC (p het <0.0001), for KRAS non-mutated than for KRAS-mutated CRC (p het=0.0415), and for CRC classified into the sessile serrated pathway than for CRC of the traditional pathway (p het=0.0009). After colonoscopy with detection of adenomas, no risk reduction was found for sessile serrated pathway CRC.
Conclusions: Our study extends the molecular understanding of existing differences in risk reduction of proximal and distal CRC reported by previous studies, and may imply relevant information for improving strategies for timely detection of relevant precursors.

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Disclosure Statement: The authors declare that they have no conflict of interest.

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Utilization of Repeat Colonoscopies and Polypectomies in Germany within 10 Years: a Claims Data Analysis Based on More Than 2 Million Index Colonoscopies

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Purpose: In Germany, >6 million colonoscopies are performed per year, but longer-term follow-up data to monitor colonoscopy use at the individual level are lacking. We aimed to explore the potential of German claims data to describe the utilization and the diagnostic yield of repeat colonoscopy.
Methods: We used the German Pharmacoepidemiological Research Database (GePaRD), containing claims data with information on ~25 million persons, to identify patients who underwent at least one colonoscopy between 2006 and 2015. We only included persons with ≥2 years of continuous health insurance before the index colonoscopy. We excluded all patients with a diagnosis code for colorectal cancer within 2 years before index colonoscopy. We defined 3 sub-cohorts according to procedure/diagnosis codes at index colonoscopy: Patients with a code for snare polypectomy (cohort 1), patients with no snare polypectomy but a diagnosis code for polyps (cohort 2) and patients without such codes (cohort 3). We described the sub-cohorts regarding utilization of and snare polypectomies performed at repeat colonoscopy. All analyses were stratified by type of index colonoscopy (diagnostic vs. screening).
Results: Overall, 2,520,445 persons with at least one colonoscopy were included (cohort 1: 15%; cohort 2: 14%; cohort 3: 71%). The proportions of persons entering cohorts with a screening colonoscopy were 47%, 39% and 35%, respectively. Among these, the proportions with at least one repeat colonoscopy in cohort 1, 2 and 3 were 70%, 59% and 36%, and a snare polypectomy at first repeat colonoscopy was performed in 30%, 15% and 10%, respectively. Among persons entering cohorts with a diagnostic colonoscopy, the proportions with at least one repeat colonoscopy were 71%, 66% and 48%, and a snare polypectomy at first repeat colonoscopy was performed in 32%, 14% and 8% of these, respectively.
Conclusions: Claims data can provide useful information on utilization of repeat colonoscopy in Germany and – although histological data are lacking – provide an estimate on polyp detection.

Disclosure Statement: None.

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KRAS Mutation Status Concordance Between the Primary Tumor and the Corresponding Metastasis in Patients with Rectal Cancer

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Purpose: KRAS is a negative predictive indicator for *EGFR*-treatment-response in patients with colorectal cancer. We have shown KRAS mutation status concordance in patients with locally advanced rectal cancer treated preoperatively indicating no relevant heterogeneity within and between multiple pre- and posttherapeutic samples of the primary tumor. The aim of this study was to evaluate the heterogeneity of KRAS mutation status between the primary tumor and the corresponding metastasis in the same collective and to evaluate the ideal representative tissue for KRAS mutation testing.
Methods: *KRAS* mutation status analyses were performed in a previous study from 47 patients with rectal cancer to evaluate the intratumoral heterogeneity. In this study 6 patients were excluded due to missing follow up data. 15 patients showed recurrence during the follow up. DNA from representative areas of metastatic tissue was obtained from FFPE specimens from 11 metastatic rectal cancer patients. Mutations in KRAS codons 12, 13, and 61 were analyzed by the therascreen® *KRAS* test.
Results: The mean age was 64.13 ± 10.64 years. 19 patients showed a *KRAS* mutation. Of the 11 patients with a metastatic disease or local recurrence, 5 patients showed a KRAS mutation. A significant *KRAS* mutation status concordance was detected in 81.18% (9/11) of the patients (p=0.03271). Only 2 patients showed intertumoral heterogeneity, which harbored in one patient a *KRAS* G12C mutation status in the primary tumor, but a G12V *KRAS* mutation status in the corresponding lung lesion, and in the other patient a G12A mutation in the primary lesion and a WT in the lung metastasis.
Conclusions: We show a significant concordance of the *KRAS* mutation status between tumor samples obtained from the primary tumor and the metastasis in patients with rectal cancer indicating no relevant intertumoral heterogeneity. Our data suggest that sampling either the primary or metastatic lesion is valid for the initial evaluation of *KRAS* mutation status predicting the response to anti-*EGFR* treatment and guiding clinical decisions.

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Epigenome Mapping Identifies Tumor-Specific Gene Expression in Primary Rectal Cancer

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Purpose: Epigenetic alterations play a central role in cancer development and progression (1). The acetylation of histone 3 at lysine 27 (H3K27ac) specifically marks active genes (2). While chromatin immunoprecipitation (ChIP) followed by next-generation sequencing (ChIP-seq) analyses are commonly performed in cell lines, only limited data are available from primary tumors. We therefore examined whether cancer-specific alterations in H3K27ac occupancy can be identified in primary rectal cancer
Methods: Tissue samples from primary rectal cancer and matched mucosa were obtained. ChIP-seq for H3K27ac was performed and differentially occupied regions were identified. The expression of selected genes displaying differential occupancy between tumor and mucosa were examined in gene expression data from an independent patient cohort. Differential expression of four proteins was further examined by immunohistochemistry.
Results: ChIP-seq for H3K27ac in primary rectal cancer and matched mucosa was successfully performed and revealed differential binding on 44 regions. This led to the identification of genes with increased H3K27ac, i.e., RIPK2, FOXQ1, KRT23, and EPHX4, which were also highly upregulated in primary rectal cancer in an independent dataset. The increased expression of these four proteins was confirmed by immunohistochemistry.
Conclusions: This study demonstrates the feasibility of ChIP-seq-based epigenome mapping of primary rectal cancer and confirms the value of H3K27ac occupancy to predict gene expression differences.

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Disclosure Statement: Data has recently been published:
Flebbe, H.; et al. Epigenome Mapping Identifies Tumor-Specific Gene Expression in Primary Rectal Cancer. Cancers 2019; 11(8);1142.

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Therapy-Dependent Survival in Patients with Colorectal Peritoneal Carcinomatosis - a Population-Based Study

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Purpose: Various studies showed a significant survival benefit for cytoreductive surgery (CRS) with HIPEC (hyperthermic intraperitoneal chemotherapy) compared to surgery and systemic chemotherapy in patients with peritoneal carcinomatosis (PC). However, a recent prospective randomized study reported no superiority of CRS and HIPEC to CRS with chemotherapy, so that now, independent of the CRS, the effectiveness of HIPEC is unclear. The aim of this multicenter, retrospective cohort study was the analysis of treatment-dependent overall survival (OS) after CRS with HIPEC compared to surgery and subsequent chemotherapy in patients with PC.
Methods: Based on the clinical cancer registry of the Regensburg Tumor Center, a retrospective, multicenter cohort study was performed on 941 patients diagnosed with colorectal PC between 2004 and 2018. Primary endpoint was the therapy-dependent OS estimated using Kaplan-Meier method and multivariable Cox-regression. Risk adjustment was performed for age, sex, primary tumor stage and localization, extraperitoneal tumor spread, syn- and metachronous PC.
Results: In the included 941 cases, 63 cases were treated with CRS and HIPEC (6.7%), 176 cases (18.7%) with surgery followed by chemotherapy. Median OS after CRS and HIPEC was 40.5 months, after surgery with chemotherapy 21.4 months. Two-year OS after CRS and HIPEC was 58.2% (surgery with chemotherapy 41.8%); 3-year OS 50.1% and 21.4%, resp. (log rank p<0.001). After risk adjustment, CRS and HIPEC persisted to prove superior to surgery with chemotherapy (HR 0.529, CI 95% 0.363-0.770, p<0.001). In addition, significant factors influencing OS were age, tumor histology and grading, presence of extraperitoneal metastases, T and N status, onset of PC.
Conclusions: In line with most randomized and retrospective studies to date, this population-based analysis shows a significant survival benefit of CRS with HIPEC versus surgery and subsequent chemotherapy.

Disclosure Statement: no conflict of interests

Gastrointestinal (Noncolorectal) Cancer

Best-of-Abstract-Vorträge

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FOLFiRI Plus Ramucirumab Versus Paclitaxel Plus Ramucirumab for Patients with Advanced or Metastatic Adenocarcinoma of The Stomach or Gastroesophageal Junction As Second-Line Therapy – Interim Safety and Efficacy Results from The Phase II Ramiris Study (AIO-STO-0415) of the German Gastric Group at AIO

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Purpose: Ramucirumab as monotherapy and in combination with paclitaxel is a proven second-line option for advanced gastroesophageal adenocarcinoma (GEA). More and more patients (pts) are pretreated with docetaxel in the perioperative or first-line setting. For those pts, the benefit of a combination of ramucirumab and paclitaxel is unclear, and physicians would choose an irinotecan-based regimen as second line treatment. This provides a rationale for the evaluation of FOLFIRI + ramucirumab.
Methods: This is a multicenter, randomized, investigator initiated, phase II trial, planned to include 111 pts with advanced GEA to receive 2:1 either FOLFIRI plus ramucirumab every two weeks (Arm A) or paclitaxel (days 1, 8, 15 of a 28-day cycle) plus ramucirumab every two weeks (Arm B). Primary endpoint is 6-months OS rate. This abstract displays interim results of safety and overall objective response (ORR) in docetaxel pre-treated group from up to 65 randomized pts. The results were needed to decide on conducting a subsequent phase III study.
Results: 58 (A, 36; B, 22) pts were included in the safety analysis and 50 pts with tumor assessment in the response analysis. Main ≥ grade 3 adverse events were respectively in arms A/B: neutropenia (20%/22%), fatigue (6%/0%), diarrhea (8%/3%), and related SAEs (14% v 23%). Twenty-nine of 50 pts (58%) were pre-treated with docetaxel. In these pts, ORR was 30% in Arm A (5/17) and 8% (1/12) in Arm B. Disease control rate (DCR) was 65% and 50% for Arm A and B respectively.
Conclusions: The interim safety analysis of the RAMIRIS trial has demonstrated feasibility of the combination of FOLFIRI and ramucirumab. Docetaxel pre-treated pts had higher ORR and DCR when ramucirumab is combined with FOLFIRI, instead of paclitaxel.

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Pancreatic Tumor Remission in PDX-Models By Treatment with Gemcitabine in Combination with The Oxathiazine GP-2250

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Purpose: The oxathiazine GP-2250, a newly defined anti-tumor agent, displays anti-neoplastic activity on pancreatic cancer tissue as shown both in cell culture *in vitro* and in patient derived xenograft (PDX) models *in vivo* (1). In the present study, GP-2250 was tested in PDX models in combination with the standard chemotherapeutic agent gemcitabine in view of a potential antineoplastic synergy of the combination treatment *in vivo*.
Methods: Using nine different PDX models of pancreatic cancer, tumors were grown up to a size of 200 mm^3 in nude mice [NMRI-Fox1 nu/nu] prior to treatment with 500 mg/kg*BW substance GP-2250 three times a week and twice a week with 50 mg/kg*BW gemcitabine either alone or in combination for up to 60 days.
Results: While gemcitabine and GP-2250, given as monotherapy, showed only a limited antineoplastic response, the combination treatment of gemcitabine with substance GP-2250 resulted in a significantly higher antineoplastic activity than gemcitabine or GP-2250 monotherapy. Eight out of nine tumors showed a response towards this combination treatment. The tumor growth in five out of the nine PDX models treated with the drug combination was characterized by a partial remission via RECIST criteria. Three of the remaining PDX models showed an outcome of stable disease. Remarkably, in one PDX model, which was immediately resistant to gemcitabine, the combination therapy nevertheless achieved a reduction in the tumor growth rate which exceeded that of GP-2250 monotherapy.
Conclusions: The partial remission of pancreatic cancer tumor growth in mice, which was achieved by the combination of gemcitabine with GP-2250, is strongly relevant towards clinical practice providing a new therapeutic strategy in pancreatic cancer treatment. These results provide the basis for initial clinical studies with this promising combination of gemcitabine and GP-2250.

Reference:

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Vorträge

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Classification of Barrett's Carcinoma Specimens by Hyperspectral Imaging (HSI)

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Purpose: Hyperspectral imaging (HSI) technology combines imaging with spectroscopy and can be used for the classification of malignant and non-malignant cells. Thereby HSI combined with artificial intelligent algorithms can be used to predict tumor cells in in Barrett's carcinoma specimens.
Methods: HSI imaging records light between the visual and near-infrared light (500-1000nm). For a first feasibility study, this technique was used to discriminate between squamous epithelium and esophageal adenocarcinoma and 45 specimens from Barrett's carcinoma patients were recorded. In 22 of the 45 investigated specimens contained also squamous epithelium. The specimens were fixed routinely after resection in paraformaldehyde, were sliced to 3µm, and were stained by haematoxylin and eosin (HE). A non-parametric supervised classification learning algorithm (K-nearest neighbours (k-NN)) was used for discrimination.
Results: Barrett's adenocarcinoma cells were recorded by HSI in all 45 investigated cases. Squamous epithelium and Barrett's adenocarcinoma cells displayed differences in the absorbance between the wave lengths of 500 to 700 nm. For both, the squamous epithelium and the Barrett's adenocarcinoma cells, the intra group variances of the investigated specimens were quite low. 333,275 and 74,000 spectra could be measured from Barrett's adenocarcinoma and from squamous epithelium, respectively. Specificity, sensitivity and precision with a k-NN (k=5) classifier were 0.74, 0.92 and 0.94 for the presence of Barrett's adenocarcinoma cells.
Conclusions: HE-stained squamous epithelium and Barrett's adenocarcinoma cells showed specific spectral alterations, when measured by HSI. These characteristics could be used in the future to develop a computer-assisted algorithm to discriminate semi-automated for tumor cells Barrett's carcinoma specimens, which will help to foster decision-making support in histopathological diagnosis.

Disclosure Statement: None

Poster

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Alpha Fetoprotein (AFP) Response and Efficacy Outcomes in the Phase 3 Celestial Trial of Cabozantinib (C) Versus Placebo (P) in Advanced Hepatocellular Carcinoma (HCC)

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Purpose: AFP response, defined as a decrease in serum levels of the tumor marker AFP after therapy, has been associated with improved survival of patients (pts) with HCC treated with locoregional therapy; high baseline (b) AFP levels are associated with poor prognosis. In the phase 3 CELESTIAL trial (NCT01908426), C significantly improved overall survival (OS) and progression-free survival (PFS) vs P in pts with previously treated advanced HCC. Here we evaluate clinical outcomes with C in the CELESTIAL trial based on AFP response or progression on treatment.
Methods: 707 pts were randomized 2:1 to receive C (60 mg qd) or P. Eligible patients had a pathologic diagnosis of HCC, Child-Pugh score A, and ECOG PS ≤1. Pts received prior sorafenib and up to 2 lines of prior systemic therapy for HCC. Serum AFP levels were measured centrally at b and every 8 weeks thereafter. Outcomes were evaluated for pts with elevated b serum AFP (≥20 ng/mL) based on AFP response (≥20% decrease from b) or progression (≥20% increase from b) at week 8.
Results: Overall, 331 pts (70%) in the C arm and 160 (68%) in the P arm had elevated b AFP levels, and 236 (50%) and 111 (47%), respectively, were evaluable for AFP response at Week 8. Among evaluable pts, 117 pts (50%) in the C arm vs 14 (13%) in the P arm had an AFP response and 72 (31%) vs 75 (68%), respectively, had AFP progression. Median OS with C was 16.1 mo for AFP responders vs 9.1 mo for non-responders (HR 0.61, 95% CI 0.45-0.83), and median PFS with C was 7.3 mo vs 4.0 mo (HR 0.55, 95% CI 0.41-0.75). For pts with AFP progression, median OS with C was 8.1 mo, and median PFS with C was 3.6 mo. Hazard ratios for OS and PFS with C also favored AFP responders over non-responders when analyzed according to best response through week 24 or using 50% decrease from b as the cutoff for response.
Conclusions: AFP response rate was higher with C vs P, and AFP response was associated with longer OS and PFS with C for pts with previously treated advanced HCC. Response assessment in HCC may be improved by evaluating on-treatment AFP changes in addition to radiographic response.

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Association of Adverse Events (AES) with Efficiacy Outcomes for Cabozantinib (C) in Patients (PTS) with Advanced Hepatocellular Carcinoma (AHCC) in the Phase 3 Celestial Trial

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Purpose: Class-specific AEs occurring with tyrosine kinase inhibitors have been associated with improved efficacy outcomes in several tumor types including aHCC. In the CELESTIAL trial C improved overall survival (OS) and progression-free survival (PFS) vs placebo (P) in pts with previously treated aHCC. Here, we retrospectively evaluate the association of palmar-plantar erythrodysaesthesia (PPE) and hypertension (HTN) with OS and PFS for C in the CELESTIAL trial.
Methods: 707 pts with aHCC were randomized 2:1 to receive 60 mg C or P once daily. Eligible pts had Child-Puqh score A, ECOG PS ≤1, must have received prior sorafenib and could have received up to two prior regimens of systemic therapy for HCC. OS and PFS with C were evaluated for pts with any grade PPE or ≥ grade 3HTN within the first 8 weeks of study treatment.
Results: Overall, 374 (80%) pts in the C arm and 179 (76) pts in the P arm completed ≥ 8 weeks of treatment. In the first 8 weeks, 188 (40%) of C-treated pts developed any grade PPE vs 11 (5%) of P-treated pts and 61 (13%) of C-treated pts developed grade ≥3 HTN vs 3 (1%) of P-treated pts. Median OS with C was 14.4 mo for pts with any grade PPE vs 3.4 mo for pts without PPE (HR 0.59, 95% CI 0.47-0.74) and median PFS with C was 6.5 mo vs 3.7 mo, respectively (HR 0.63,95% CI 0.51-0.78). Median OS with C was 16.1 mo for pts with grade ≥3 HTN vs 9.5 mo for pts without grade ≥3 HTN (HR 0.56, 95 CI 0.39-0.80), and median PFS with C was 7.4 mo vs 4.4 mo, respectively (HR 0.59, 95% CI 0.43-0.82). Some imbalances in baseline (BL) characteristics were present. Pts with PPE had better ECOG PS (60% vs 47% ECOG 0), better liver function (48% vs 34% ALBl grade 1), and less macrovascular invasion (24% vs 30%) than those without. Likewise, pts with grade ≥3 HTN had better ECOG PS (61% vs 51% ECOG 0), better liver function (56% vs 37% ALBI grade 1), and less macrovascular invasion (20% vs 29%) than those without.
Conclusions: The development of PPE or grade ≥3 HTN with C was associated with prolonged OS and PFS in pts with previously treated aHCC although some imbalances in BL characteristics between comparator qroups were present.

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Matching-Adjusted Indirect Comparison of Cabozantinib (C) Versus Regorafenib (R) in Advanced Hepatocellular Carcinoma (HCC)

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Purpose: C and R have demonstrated survival benefit in second-line treatment of advanced HCC. The aim of this matching-adjusted indirect comparison (MAIC) was to compare the safety and efficacy of C and R for patients with HCC who have received sorafenib (S) as the only prior systemic therapy.
Methods: Data from two pivotal trials with C (CELESTIAL (CT) or R (RESORCE (RT)) in patients with HCC were used. Using MAIC, individual-level data (ILD) from patients enrolled in CT who had received S as the sole prior therapy (N=495) were adjusted to match the average baseline (BL) characteristics of the 573 patients enrolled in RT, for which ILD are not available. To compare survival outcomes, ILD were simulated for regorafenib using the published Kaplan-Meier (KM) curves for the RT. Parametric distributions were fitted to the ILD to model progression-free survival (PFS) and overall survival (OS). Grade 3/4 treatment-emergent drug-related adverse events (AEs) affecting >5% of patients in any arm of either CT or RT were compared.
Results: After balancing BL characteristics, the weighted KM curves for patients receiving C or R were associated with a median (95% Confidence Interval) PFS of 5.59 (4.90–7.26) months and 3.19 (2.78–4.14) months, respectively ($p<0.05$, log-rank test); median OS were 11.37 (8.90–16.95) months for C and 10.79 (9.18–12.30) months for R ($p>0.05$, log-rank test). Upon fitting and extrapolating the selected models, C treatment was associated with longer median PFS and OS than R. The median PFS estimate was 5.49 (4.92–6.13) months for C vs 3.39 (3.05–3.78) months for R, median OS was 11.40 (10.01–12.96) months for C vs 10.29 (9.15–11.56) months for R. R was associated with lower rates of diarrhea.
Conclusions: In patients who received second-line treatment after S and were matched for BL characteristics, C was associated with prolonged median PFS and OS compared with R, whereas R was associated with lower rates of diarrhea than C. However, even after matching, bias may still occur in MAIC due to imbalance in unobserved factors, and it cannot replace a head-to-head randomized control trial.

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Quality-Adjusted Life Years Accrued with Cabozantinib in Patients with Advanced Hepatocellular Carcinoma (AHCC) in the CELESTiAL Trial

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Purpose: In patients previously treated for aHCC, cabozantinib (C) led to longer overall survival and progression-free survival vs placebo (P) in the randomized, phase 3 CELESTIAL trial (NCT01908426; N=707). CELESTIAL was stopped early for benefit at the second interim analysis. This post hoc analysis estimated the incremental quality-adjusted life years (QALYs) accrued in CELESTIAL.
Methods: Health utility was elicited at each study visit using the EQ-5D-5L quality of life questionnaire. (completed by 82-100% of patients overall). UK crosswalk tariffs were applied for health states. Cumulative QALYs by patient were calculated by linear interpolation; for patients who were censored (31% of patients; including 9% within 100 days of randomization), the last observed utility value was carried forward to study end. The difference in restricted mean QALYs was calculated using generalized linear models, accounting for baseline utility, and with 0.06-0.08 QALYs considered the minimal important difference.
Results: At day 50 after randomization (acute treatment phase), C was associated with a small reduction in mean total QALYs vs P (difference −0.003; 95% CI −0.005 to −0.002; p≤0.001; n=601 [C n=389; P n=212]). At day 100, there was a numerical benefit in mean total QALYs for C (difference +0.007; 95% CI −0.001 to 0.015; p=0.103; n=627 [C n=410; P n=217]), and at day 150 the difference was +0.032 QALYs (95% CI 0.017 to 0.047; p≤0.001; n=629 [C n=412; P n=217]) in favor of C. Over the entire follow-up, patients randomized to C accrued a mean of +0.092 (95% CI 0.016 to 0.169; p=0.018; n=700 [C n=465; P n=235]) additional QALYs compared with those receiving P. Using alternative Devlin weights for health states, the mean accrued QALYs with C was +0.115 vs P (95% CI 0.032 to 0.198; p=0.007).
Conclusions: Cabozantinib was associated with an initial, small reduction in health utility. However, with continued treatment, health utility increased and at the end of the study there was a clinically and statistically significant benefit in mean QALYs in favor of C.

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Pet-Directed Combined Modality Therapy for Gastroesophageal Junction Cancer: First Results of the Prospective Memori Trial

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Purpose: We evaluated a PET-guided treatment stratification for improvement in obtaining negative surgical margins (R0) in resectable gastroesophageal junction (GEJ) adenocarcinoma. According to sequential 18F-FDG PET, only 40–50% of patients (pts) respond to neoadjuvant chemotherapy (CTX). Early PET non-responders (P-NR) after induction CTX might benefit from chemoradiation (CRT).

Methods: 75 pts with resectable GEJ adenocarcinomas were enrolled in this interventional, prospective, non-randomized multicenter trial. Pts underwent baseline ^{18}F-FDG PET scan followed by 1 cycle of CTX (e.g. EOX, XP, mFOLFOX6). PET was repeated at day 14-21 and responders (P-R), defined as ≥ 35% decrease in SUVmax from baseline, continued with CTX. P-NR switched to CRT (41.4 Gy/23 fractions with weekly carboplatin/paclitaxel). Pts underwent surgery 4-6 weeks post-CTX/CRT. Primary objective was improvement of R0 resection rates in P-NR above a proportion of 70% based on results from the MUNICON1/2 trials. Secondary endpoints include disease-free survival (DFS), overall survival (OS), and translational endpoints.
Results: 160 pts with resectable GEJ adenocarcinomas were screened with PET in three German university centers. Overall, 85 pts (53%) could not be included due to previously undetectable metastases (40/25%), no or too low FDG uptake of the primary tumor (21/13%), other reasons (24/15%). 75 eligible pts were enrolled in the study and 69 were evaluable. Based on PET criteria, 47 (68%) and 22 (32%) were P-R and P-NR, respectively. R0 resection rates were 94% (44/47) for P-R and 91% (20/22) for P-NR. Pathologic complete remission (pCR; <10% vital tumor cells), was 33% (15/46) in P-R and 55% (12/22) in P-NR. With a median follow-up time of 19 months (mo), estimated 18 mo DFS was 71%/61% for P-R/P-NR, respectively. Observed median 18 mo OS was 95% for P-R and 75% for P-NR.
Conclusions: Alternative CRT for GEJ adenocarcinoma improved R0- and pCR rates among pts who were P-NR after induction CTX. PET response was prognostic for a prolonged OS and DFS.

Disclosure Statement: No conflicts of interest

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Does Inflammation or Malignancy have Specific Impact onto the Early Postoperative Outcome – Comparison of Pylorus-Preserving Pancreatic Head Resection by Traverso-Longmire in Chronic Pancreatitis vs. Cancer of the Pancreatic Head – Initial Results of a Tertiary Center

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Purpose: To investigate the impact of various diagnoses (chronic pancreatitis ["Pan."] *vs.* cancer of the pancreatic head ["Ca"]) & interindiv. differences such as age & accompanying diseases onto the early postop. outcome in comparable interventional invasiveness, surgical trauma & surgical intervention(Op)-induced SIRS-associated alterations.
Methods: All consecutive pats. who had undergone Op in Pan. & Ca were registered & various outcome parameters such as postop. morbidity (general/specific complication rates) & 30-d-mortality were determined.
Results: From 2003-2015, overall 315 pats. were registered out of whom only *n*=295 (sex ratio: m/w=181:114 [1.59:1]; median age: 59 [range: 20-82] yrs.) could be evaluated - 197 cases with Ca (66.8%) & 98 individuals with Pan. (33.2%). In comparison, median age was 68.5 (37-82) *vs.* 51 (20-72) yrs. in Ca & Pan. ($p<0.001$), resp.; mean ASA scoring was 2.3 (Ca [1-4]) & 2.1 (Pan. [1-4]; $p=0.084$), resp. Median preop. hospital stay was 2 [0-17] d in both diseases whereas median postop. stay was 18 (Ca [2-88]) & 15 (Pan. [6-48]) d, resp. ($p=0.029$).
Surprisingly, there were similar general & specific complication rates of 21.3% (Ca) *vs.* 21.4% (Pan.) & 40.1% (Ca) *vs.* 43.9% (Pan.) ($p=0.274$; $p=0.616$), resp.; in addition, there was only a marginal difference of the 30-d-mortality: 3.6% (Ca) *vs.* 2.0% (Pan.) ($p=0.723$).
Univariate analysis resulted in ASA class with a signif. impact onto morbidity ($p=0.013$).
In pats. with postop. morbidity, the No. of intraop. transfused red cell packs was signif. greater than in subjects with no morbidity (1.156 *vs.* 0.304; $p=0.000$). Morbidity itself had a signif. effect onto mortality ($p=0.000$).
Multivariate analysis using logistic regression did not show any signif. associations.
Conclusions: The initially hypothesized disadvantageous impact of a malignancy compared with chronic inflammation can not be confirmed based on the morbidity & mortality despite signif. older pats. & a longer postop. hospital stay.

Disclosure Statement: The authors do not have anything to be disclosed.

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Does Splenectomy Play a Significant Role in the Surgical Outcome of Gastric Cancer?

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Purpose: Splenectomy can be associated with an increase of postop. complications but a worse 5-yr survival.
Methods: From 01/01/2007-12/31/2009, all patients ($n_{\text{in total}}$=2,897; surgical depts., *n*=141) with primary gastric Ca/Tu lesion of the esophagogastric junction (AEG-Tu) who underwent surgery were registered.
Results: Overall, 2,545 patients (=group[gr.] 1) underwent Tu resection. Gr.2/3/4/5: AEG-Tu (*n*=475)/distal gastric Ca (*n*=2,070)/intraop. spleen injury (*n*=127)/splenectomy (*n*=94) due to Tu infiltration *vs.* injury.
Splenectomy rate was 11.1% (*n*=283) with the highest proportion in AEG-Tu (19.4%; no signif. differences among the groups regarding age, sex ratio & ASA).
Surgical procedures: The highest splenectomy rate was found in transhiatally ext. gastrectomy (in total, 30.2%; AEG-Tu, 27.3%; distal gastric Ca, 38.6%).
Morbidity in case of splenectomy was higher overall & depending on Tu site (the same in *general postop. complication rate*; *specific postop. complication rate*, no difference).
Lethality post-splenectomy: Only in AEG-Tu, it was signif. higher (15.2 *vs.* 5.0%).
All splenectomized patients showed a shorter long-term survival ($p<0.001$; 18 *vs.* 36 months with preservation of the spleen).
The lowest 5-yr-survival rates were observed in splenectomized AEG-Tu patients (25%) & in those with splenectomy due to Tu infiltration (20%).
Logistic regression: Spleen preservation – signif. independent variable regarding lower postop. morbidity whereas splenectomy was associated with higher postop. complication rate. Overall, splenectomy did not provide a signif. impact onto lethality. However, splenectomy as part of resection in AEG-Tu was associated with a signif. higher lethality. A tendential impact of splenectomy onto a lower overall survival was only seen in the group of AEG-Tu.
Conclusions: Splenectomy – negative predictor for a worse early postop. & long-term oncosurgical outcome; therefore, it can only be justified by direct Tu infiltration or irreparable spleen injury.

Disclosure Statement: There is nothing to be disclosed.

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Anal Cancer – Population-Based Data from the Munich Cancer Registry

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Purpose: Anal cancer is rare and linked to HPV infections similar to cervical and some oropharyngeal cancers. In Germany, the incidence differs clearly between men and women (1.3/100,000 vs. 2.0/100,000). Objective was to reveal sex-related differences.
Methods: The number of anal cancer diagnoses between 1998 and 2016 registered in the catchment area of the Munich Cancer Registry were analyzed by sex, and prognostic factors. Cumulative incidence of tumor progression, and secondary tumors in consideration of competing risks as well as survival analyses by Kaplan-Meier method and multivariate Cox regression analysis were conducted.
Results: A total of 1 815 malignant anal tumors were recorded. After exclusion of in situ cases, mucosal and skin melanomas, lymphomas, sarcomas,

and neuroendocrine neoplasia the age-adjusted incidence (European Standard Population) was 1.2/100,000 in men and 2.0/100,000 in women without changes since 1998. Excluding death certificate only cases, 1 564 invasive anal carcinoma were finally analyzed. Median age at initial diagnosis accounted for 65.1 years, men were 2 years younger than women. Age and male/female ratio of 1:2 did not change over the observed time. TNM-categories were similar frequent in men and women. Whereas G3 tumors were significantly more in women (39% vs. 28%) and adenocarcinomas were more in men (7.8% vs 3.2%).
Conclusions: Women have a better outcome in anal cancer; although no tumor-specific characteristics were attributed to this difference.

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Induction Chemotherapy in Locally Advanced Pancreatic Cancer (LAPC) - Final Results of a Multicenter Randomized Phase 2 AIO Trial (NEOLAP)

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Purpose: The best preoperative treatment for LAPC is unknown. NEOLAP is the first prospective, randomized trial to compare nab-Paclitaxel and Gemcitabine (nPG) with FOLFIRINOX-based induction chemotherapy in LAPC.
Methods: In this open-label, randomized, two-arm, phase 2 trial, treatment-naive patients (pts) with histologically/cytologically proven non-resectable LAPC were recruited from 33 German centers. After two cycles of nPG induction pts without progressive disease or unacceptable adverse events (AEs) were randomly allocated (1:1) to receive either two additional cycles of nPG or four cycles of sequential un-modified sqFOLFIRINOX. Secondary resectability was assessed by surgical exploration in all pts with at least stable disease (SD) after completion of induction chemotherapy. The primary endpoint was conversion rate (R0/R1 resection). Secondary endpoints included overall survival (OS), safety, CA 19-9 response and central radiological review.
Results: 168 pts were registered and 130 were randomly allocated (64 to nPG and 66 to sqFOLFIRINOX). Conversion rate was 30.6 vs 45.0% (Odds ratio 0.54; 95% CI, 0.26 to 1.13; P = 0.135), OS 17.3 vs 22.5 months (adjusted HR 0.73; 95% CI, 0.42 to 1.28; P = 0.268), AEs ≥ grade 3 54,7 vs 53,0%, (investigator assessed) ORR 22.6 vs 21.7%; DCR 82.3 vs 75.0%, CA 19-9 response (baseline to week 16); -62.2 % vs -56.7 %, major pathological response (<10% viable tumor cells) 15 vs 9.5% in the nPG (n=62) and sqFOLFIRINOX (n=60) arm, respectively. Among all ITT-pts (N=165) conversion was associated with significant improved OS (27.4 vs. 14.2 months; P = 0.0035). First results from central radiological review with regard to primary and secondary resectability status and tumor response will be presented.
Conclusions: Secondary resection after 4 months of induction chemotherapy followed by surgical exploration is feasible in about 1/3 of pts with LAPC and associated with markedly prolonged OS without significant difference in safety or efficacy endpoints between nPG and sqFOLFIRINOX arm.

Disclosure: Supported by Celgene + AIO-Studien-gGmbH

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Immunohistochemical Profiling of Liver Metastases and Matched-Pair Analysis in Patients with Metastatic Pancreatic Ductal Adenocarcinoma

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Purpose: The purpose of the current study was to investigate the immunohistochemical (IHC) profile of liver metastases (LM) from patients with pancreatic ductal adenocarcinoma (PDAC).
Methods: Liver biopsies from seventy-seven (n = 77) patients with PDAC diagnosed between 2010 and 2014 were evaluated regarding expression of 15 IHC markers. In a separate subgroup analysis (n = 12), paired samples (LM and primary tumor) from the same patient were investigated for discordance in the IHC profile.
Results: LM were classified as pancreatobiliary-type (PB-type) in 72 cases (93.5%), intestinal-type (INT-type) in four cases (5.2%) and squamous in one case (1.3%). There was no significant difference in overall survival (OS) between LM of PB-type or INT-type (p = 0.097). In multivariate analysis, age < 70 years (p = 0.047), absence of SMAD4 mutation (p = 0.026), absence of CDX2 expression (p = 0.003) and well to moderate differentiation were significant prognostic factors for better OS in patients with LM (p = 0.031). Analysis of paired tissue samples from LM and primary tumor revealed marked discordance in CDX2 (50% gained, p = 0.125) and SMAD4 (33% loss of SMAD4, p = 0.375).
Conclusions: CDX2 expression and SMAD4 mutation indicate poor outcome in patients with LM of PDAC. Matched-pair analysis reveals discordance in expression of distinct IHC markers.

References:
Not applicable.

Disclosure Statement: The authors declare no conflicts of interest.

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Patient with Severe Symptomatic Aortic Valve Insufficiency and Multiple Small Strokes Due to Nonbacterial Thrombotic Endocarditis (NBTE) Diagnosed with Metastatic Pancreatic Cancer

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Purpose: Patients with metastatic cancer diseases tend to have a hypercoagulopathy with risk of thrombosis, arterial embolization and, in consequence, ischemic strokes. One of the known causes is NBTE.
Methods/Patient characteristics: A 51-year old athletic man with metastatic pancreatic adenocarcinoma presented with aphasia and memory gaps for four days after initiation of chemotherapy (FOLFIRINOX regimen).
Results: A cerebral MRI showed a pattern of multiple small ischemic lesions. A transesophageal echocardiography revealed a severe aortic valve insufficiency with mobile vegetation. An empiric antibiotic treatment with ampicillin, flucloxacilline and gentamicin was initiated. The patient had to undergo biological aortic valve replacement. As a possible source of infection, the port catheter was removed. Microbiology showed no pathological evidence of infective endocarditis. Therefore, the duration of an antibiotic treatment was limited to 22 days.
Pre-medical history showed that the patient already had previous peripheral venous thrombosis one month ago. During the current treatment, multiple thrombophlebitic events occurred despite anticoagulation. Further inspections regarding different causes of NBTE showed no pathological findings. However, a histopathological examination of the aortic valve had not been done.
During the management period, CA19-9 levels rose and CT scan showed disease progression of the pancreatic tumor and the hepatic metastases. Therefore, chemotherapy was re-induced and a new port catheter was implanted.
Conclusions: This is a rare but manageable consequence of paraneoplastic hypercoagulopathy in metastatic pancreatic cancer despite oral anticoagulation.

Disclosure Statement: The authors have no conflict of interest.

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Analysis of Central versus Local Deviating HER2 Test Results in Gastric Cancer in the Multicenter Varianz Study

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Purpose: VARIANZ is a non-interventional study funded by BMBF (01ZX1610E) recruiting patients (pts) receiving treatment for stage IV gastric cancer. The primary objective of VARIANZ is to investigate resistance factors of HER2 target therapy. Locally assessed HER2 status was re-assessed centrally using immunohistochemistry (IHC) and in situ hybridization. In 22.2% of all pts HER2 status was not confirmed. Only pts with confirmed HER2+ status seem to benefit from trastuzumab. Here, we aimed to investigate causes of HER2 discrepancies between local and central pathologies.
Methods: Information about HER2 test procedures, antibodies for IHC and participation in round robin tests was collected from participating pathologies (n=105). Tumor samples with central and local HER2 tests (n=375) were grouped: central HER2+ concordant to local HER2 status (HER2+/HER2+) and central HER2- deviating from local HER2 status (HER2-/HER2+).
Results: Type of antibody used in local pathology and participation in round robin tests did not influence HER2 deviation rate. In central testing, cytoplasmatic HER2 staining of tumor cells was detected in 60.3% of HER2-/HER2+ probes compared to 40.6% in HER2+/HER2+ ($p< 0.05$, Chi^2 -test). Concordant to this result the percentage of HER2 membrane stained tumor cells was low in HER2-/HER2+ (13.97 ± 21.87%) vs. HER2+/HER2+ (61.19 ± 31.31%; $p< 0.001$, Mann-Whitney-test). 32% of tumor samples originated from surgical resection specimens in HER2-/HER2+ vs. 9% in HER2+/HER2+ ($p< 0.001$, Chi^2 -test). The majority of pts undergoing surgery received neoadjuvant chemotherapy (54% of HER2-/HER2+, 66.7% of HER2+/HER2+ pts).
Conclusions: Identification of pts who benefit from HER2 targeting therapy remains challenging. The extent of cytoplasmatic HER2 staining and potential misinterpretation as HER2+ status may influence test results. Beyond that, the use of surgical resection specimens for assessment of HER2 seems to lead to less robust results compared to the use of biopsy material.

Disclosure Statement: none

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Treatment of HER2 Positive Advanced Gastric Cancer: Deviations in HER2 Results and Its Impact on Survival

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Purpose: Trastuzumab is the only approved target therapy for HER2 positive (HER2+) gastric cancer (GC) and used in stage IV 1st line treatment. Not all treated HER2+ patients respond and most initial responders experience progression. The resistance mechanisms for trastuzumab in GC are poorly understood. The aim of the VARIANZ study (NCT02305043, grant: BMBF 01ZX1610E) was to investigate the biological background of resistance to HER2 directed target therapy in GC.
Methods: Patients (pts) receiving medical treatment for stage IV GC were recruited in 34 German sites and followed up to 48 months. HER2 status was verified centrally using immunohistochemistry and chromogenic-in-situ hybridization. In addition, HER2 gene expression was assessed using qPCR.
Results: 548 pts were enrolled and 521 samples were characterized for HER2. 89 of 521 samples were found HER2+ in central testing. In 78 samples the locally assessed HER2+ status could not be centrally confirmed. The deviation rate between local and central testing was 22.2%. In confirmed HER2+ GC more tumor cells stained positive for HER2 (61.19 ± 31.31% [SD] vs. 13.97 ± 21.87% [SD]; p< 0.001) and a higher HER2/CEP17 amplification was found (7.31 ± 5.58 [SD] vs. 1.78 ± 0.80 [SD]; p< 0.001). Furthermore, HER2 gene expression (ΔCt) was significantly higher in confirmed HER2+ GC (41.83 ± 1.63 [SD] vs. 39.05 ± 1.78 [SD]; p< 0.001).
Pts with a confirmed HER2+ status had a significantly longer overall survival when treated with trastuzumab plus chemotherapy (18.6 months [95%-CI 15.7 - 21.5; n=62] vs. 9.6 months [95%-CI 6.6 – 12.6, n=67], HR for death 0.45, p< 0.001).
Conclusions: Discrepancies in HER2 assessment in GC between central pathology and local sites were significant and mostly found in tumor specimens with intermediate HER2 levels. Borderline HER2-positivity and heterogeneity of the marker expression should be considered as a resistance factor for HER2-directed therapy. HER2-cut-offs should be reconsidered and detailed HER2 reports including quantification of stained tumor cells and HER2 amplification levels might be of value.

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Somatostatin and Chemokine CXCR4 Receptor Expression in Pancreatic Adenocarcinoma Relative to Pancreatic Neuroendocrine Tumours

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Purpose: Pancreatic adenocarcinoma (PAC) represents one of the most devastating types of cancer with an exceptionally poor prognosis. Therefore, improved diagnostic and treatment approaches are urgently needed. An over-expression of somatostatin receptors (SST) as well as of the chemokine receptor CXCR4 has been shown for many tumor entities. Respective expression data for PAC, however, are scarce and contradictory.
Methods: Overall, 137 tumor samples from 70 patients, 26 of whom were diagnosed with PAC and 44 with pancreatic neuroendocrine tumor (PanNET), were compared in terms of SST and CXCR4 expression by immunohistochemical analysis using well-characterized rabbit monoclonal antibodies.
Results: In PAC tumors, only SST1 and CXCR4 expression was detectable. SST1 was present in 42.3% and CXCR4 in 7.7% of the cases. The overall staining intensity, however, was very weak. In contrast to the tumor cells, in many PAC cases, tumor capillaries showed strong SST3, SST5 or CXCR4 expression. In PanNETs, SST2 was the most-prominently expressed receptor. It was observed in 75.0% of the tumors at medium-strong intensity. SST5, SST1 and CXCR4 expression was detected in 20.5%, 15.9% and 11.4% of PanNET cases, respectively, but the staining intensity for these receptors was only weak. SST2 positivity in PanNET, but not in PAC, was associated with favorable patient outcomes.
Conclusions: In contrast to PanNET, SST or CXCR4 expression in PAC is clearly of no therapeutic relevance. However, indirect targeting of these tumors via SST3, SST5 or CXCR4 on tumor microvessels may represent a promising additional therapeutic strategy.

Disclosure Statement: Daniel Kaemmerer received funding and support for travel to meetings from IPSEN and PFIZER. All other authors have nothing to declare.

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Periampullary Cancer - Survival Among Patients with Resistant Bacteribilia

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Purpose: In pancreatic surgery preoperative biliary drainage is associated with bacteribilia, which is more and more frequently caused by resistant microorganisms. Resistant microorganisms increase the risk for postsurgical complications, which may delay recovery and adjuvant therapy. The question if resistant microorganisms also reduce long term survival is not answered, yet.
Methods: We performed a prospective survival analysis among all patients with periampullary cancer who underwent pancreatic head resection or biliary bypass surgery at St. Josef Hospital, Ruhr University Bochum, from January 2011 until December 2015. The final date for survival evaluation was August 31st 2016. Intraoperative bile duct cultures were collected among all patients immediately after bile duct transection.
Results: 430 patients were included. The frequency of bacteribilia was 66 %, bacteribilia with resistant microorganisms was 17 %. In 41 % patients with resistant microorganisms had undergone preoperative antibiotic therapy, vs. 20 % in patients without resistant microorganisms (p<0.001). There were significantly more postsurgical infectious complications (33 % vs. 17 %; p=0.003), wound infections (10 % vs. 3 %; p=0.019) and sepsis

(7 % vs. 2 %; p=0.049) among patients with resistant microorganisms. The overall survival was 35 % for patients with resistant microorganisms, vs. 51 % for patients without resistant microorganisms (p=0.024). After palliative bypass surgery the 3 year survival rate was 25 % for patients with resistant microorganisms, vs. 34 % for patients without resistant microorganisms (p=0.540). After R0 resection the 3 year survival rate was 33% for patients with resistant microorganisms, vs. 62 % for patients without resistant microorganisms (p=0.055).
Conclusions: Bacteribilia with resistant microorganisms is associated with higher risk for postsurgical complications with reduced long term survival. Strategies to avoid bacteribilia with resistant microorganisms include avoidance of preoperative biliary drainage and rational use of antibiotics.

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Histone Deacetylases Expression and Activity in Esophageal Adenocarcinoma Cells in Vitro

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Purpose: The response of EAC patients to common chemotherapeutic regimens is relatively low (approx. 50%). Improving the response rate in cancer patients is challenging and novel therapeutic treatment options are needed. Histone deacetylases (HDAC), an enzyme class with promising novel features, are involved the regulation of gene expression affecting the epigenom.
Methods: The expression of Zn^{2+}-dependent HDACs and the endogenous HDAC activity were characterized in a Berrett's esophagus *in vitro* model, containing cells from squamous epithelium, Barrett's metaplasia, dysplasia and EAC. Proliferation assays were carried out in EAC cells to determine cell response to an experimental, HDAC1-3 specific, HDAC inhibitor (HDACi) in comparison to vorinostat (pan HDACi). The HDAC activity, the p21 expression, and the histone H3 acetylation were investigated under HDACi treatment.
Results: All Zn^{2+}-dependent HDACs were expressed by each stage of the Berrett's esophagus *in vitro* model. However, the expression intensity was variable. Vorinostat showed an inhibition of proliferation in the EAC cells OE33 and OE19 (IC_{50} of 1.1µM and 1.8µM), while the experimental HDACi DDK137 revealed an increased anti proliferative effect (IC_{50} of 0.4µM and 0.6µM), a higher HDAC activity reduction, and higher increase in H3 acetylation. The p21 mRNA-expression showed a cell line, time and inhibitor specific increase. The highest increase was determined in OE33 cells (2.5fold) by DDK137 after 48h, while no increase in p21 was measured under vorinostat treatment.
Conclusions: We could show a pharmacological more potent HDACi than vorinostat in EAC cells in vitro. However, further studies are necessary to evaluate the significance of HDACi and whether HDACi are able to increase chemosensitivity in EAC patients.

Disclosure Statement: None.

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Intratumoral Bacterial Lipopolysaccharide (LPS) Detection as Negative Predictor of Gemcitabine Efficacy in Advanced Pancreatic Cancer: Translational Results from the AIO-PK0104 Phase 3 Study

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Purpose: A recent pre-clinical study provided evidence that intratumoral bacteria may mediate gemcitabine resistance by the expression of a long isoform of the bacterial enzyme cytidine deaminase. This study was conducted in order to determine whether intratumoral LPS detection by IHC (as surrogate for gram-negative bacterial colonization) is associated with outcome in advanced pancreatic ductal adenocarcinoma (PDAC) treated with gemcitabine and non-gemcitabine containing 1st-line chemotherapy.
Methods: Retrospective analysis of archival tumor tissue from 130 patients treated within the randomized, crossover phase 3 trial AIO-PK0104 (NCT00440167); validation in a second patient cohort (n=113) from a prospective biomarker study. The correlation of intratumoral LPS to progression free survival (PFS) and overall survival (OS) was calculated using the Kaplan-Meier method. Hazard ratios were estimated by Cox proportional hazards regression.
Results: In 31 out of 130 patient samples (24%) from the AIO-PK0104 study intratumoral LPS was detected; in patients with LPS positive tumors median OS was estimated with 4.4 months, compared to 7.3 months in patients with LPS negative tumors (HR 1.732, p=0.010). This difference in OS was also detected in the subgroup of patients treated with 1st-line gemcitabine-based treatment (n=71; HR 2.377, p=0.002), whereas no difference in OS was observed in the non-gemcitabine subgroup (n=59; HR 1.275, p=0.478). Within the validation cohort, the LPS positivity rate was 23% (26 out of 113 patient samples) and LPS detection equally correlated with impaired OS in the gemcitabine-based treatment subgroup (n= 94; HR 1.993, p=0.008) whereas no difference in OS was observed in the smaller non-gemcitabine-based treatment subgroup (n=19; HR 2.596, p=0.219).
Conclusions: The detection of intratumoral bacteria by LPS immunohistochemistry may serve as a negative predictor for gemcitabine efficacy; this finding indicates a potential role of antibiotic pre-/co-treatment to overcome bacteria-mediated chemotherapy resistance.

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Nivolumab versus Chemotherapy in Advanced Esophageal Squamous Cell Carcinoma (ESCC): The Phase 3 attraction-3 Study

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Purpose: We report the final analysis from the phase 3 ATTRACTION-3 study of the programmed death (PD)-1 inhibitor nivolumab (NIVO) vs chemotherapy (CT) in patients (pts) with unresectable advanced or recurrent ESCC refractory or intolerant to 1 prior fluoropyrimidine/platinum-based CT.

Methods: Pts were enrolled regardless of tumor PD-ligand 1 (PD-L1) expression and randomized 1:1 to either NIVO (240 mg Q2W) or investigator's choice of paclitaxel or docetaxel. Primary endpoint was overall survival (OS).

Results: 419 pts were randomized (NIVO = 210, CT = 209). At a minimum follow-up of 17.6 months (mo), NIVO showed a statistically significant improvement in OS vs CT (HR for death 0.77 [95% CI 0.62–0.96; $P = 0.02$]; median OS [95% CI], 10.9 mo [9.2–13.3] vs 8.4 mo [7.2–9.9]). The proportion of pts alive at 18 mo was numerically larger with NIVO (31%) vs CT (21%). HRs for the risk of death favored NIVO over CT across tumor PD-L1 expression levels (PD-L1 ≥ 1%, HR 0.69 [95% CI 0.51–0.94]; PD-L1 < 1%, HR 0.84 [95% CI 0.62–1.14]). Objective response rates (95% CI) were 19% (14–26) with NIVO and 22% (15–29) with CT. Responses (median [95% CI]) were more durable with NIVO (6.9 mo [5.4–11.1] vs CT (3.9 mo [2.8–4.2]). Median (95% CI) progression-free survival was 1.7 mo (1.5–2.7) with NIVO and 3.4 mo (3.0–4.2) with CT; 12-mo rates were 12% and 7%, respectively. Fewer treatment-related adverse events (TRAEs) were reported with NIVO (any grade, 66%; grade 3–4, 18%) vs CT (any grade, 95%; grade 3–4, 63%). NIVO showed significant overall improvement in quality of life vs CT through on-treatment week 42 in the EQ-5D visual analog scale (least square mean, 6.9; 95% CI 3.0–10.9; $P < 0.001$).

Conclusions: NIVO demonstrated superior OS and a favorable safety profile vs CT in pts with previously treated advanced ESCC, with survival benefit observed regardless of tumor PD-L1 expression. NIVO may represent a new standard second-line treatment option for pts with advanced ESCC.

Disclosure Statement: PT-P has been on ad boards and received personal fees from Lilly, Roche, MSD, BMS, Pfizer, and Merck. KK reports serving as a consultant for ONO Pharmaceutical, Oncolys BioPharma, BeiGene, and MSD Oncology; and receiving research funding from ONO Pharmaceutical, BeiGene, MSD Oncology, and Shionogi, outside the submitted work. B-CC reports receiving honoraria from ONO Pharmaceutical, during the conduct of this study; and stock ownership of TheraCanVac, Inc.; holding patents for Champions Oncology; serving as a consultant for ONO Pharmaceutical and Bristol-Myers Squibb; receiving research funding from Novartis, Bayer, AstraZeneca, Mogam Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, ONO Pharmaceutical, Dizal Pharma, and MSD; receiving honoraria from AstraZeneca, Novartis, Bayer, Mogam Institute, Champions Oncology, Janssen, Yuhan, Dizal Pharma, and MSD; and serving as a consultant for AstraZeneca, Novartis, Janssen, Yuhan, MSD, Boehringer-Ingelheim, Roche, Pfizer, Eli Lilly, and Takeda, outside the submitted work. MT reports receiving research funding from ONO Pharmaceutical, during the conduct of this study; and serving as a speaker for ONO Pharmaceutical, Bristol-Myers Squibb, Daiichi Sankyo, and Taiho Pharmaceutical, outside the submitted work. MO reports serving as speaker for Taiho Pharmaceutical, Chugai Pharma, Covidien, Johnson & Johnson, and Lilly; and receiving research funding from Taiho Pharmaceutical, Nippon Kayaku, Chugai Pharma, Covidien, Johnson & Johnson, Daiichi Sankyo, Yakult Honsha, Lilly Japan, Nihon Medi-Physics, Pfizer, Mochida Pharmaceutical Co., Ltd., and Shionogi, outside the submitted work. SK reports receiving research funding from ONO Pharmaceutical and Bristol Myers-Squibb during the conduct of this study; and receiving research funding from Lilly Japan, Taiho Pharmaceutical, and Boehringer Ingelheim; and receiving personal fees from Chugai Pharma, Merck Serono, Bayer, Eisai, and Yakult Honsha, outside the submitted work. M-JA reports receiving honoraria from AstraZeneca, Lilly, MSD, and Takeda; serving as a consultant for Alpha Pharmaceuticals; and serving as an advisor with AstraZeneca, Roche, Lilly, MSD, and Takeda, outside the submitted work. YH reports receiving grants from ONO Pharmaceutical and Bristol-Myers-Squibb, during the conduct of this study. YD reports receiving personal fees from ONO Pharmaceutical, during the conduct of this study; and receiving grants from Taiho Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, MSD, Daiichi Sankyo, Yakult Honsha, Takeda Pharmaceutical, Kaken Pharmaceutical, Abbott Japan, Eisai, Shionogi, Otsuka Pharmaceutical, Ajinomoto Pharmaceutical, Astellas Pharma, Tsumura, AstraZeneca, Johnson & Johnson, Nippon Kayaku, Novartis Pharma, Pfizer Japan, CSL Behring, and Nestle; receiving personal fees from Taiho Pharmaceutical, Chugai Pharmaceutical, Eli Lilly, MSD, Daiichi Sankyo, Yakult Honsha, Takeda Pharmaceutical, Kaken Pharmaceutical, Abbott Japan, Eisai, Shionogi, Otsuka Pharmaceutical, Ajinomoto Pharmaceutical, Teijin Pharma, Sanofi, Astellas Pharma, Tsumura, AstraZeneca, Asahi Kasei Pharma, Medtronic, Johnson & Johnson, Olympus, and Intuitive Surgical; and receiving conference fees from the Japanese Gastric Cancer Association, the Japan Esophageal Society, and the Japan Surgical Society, outside the submitted work. C-CY reports receiving research funding from ONO Pharmaceutical, during the conduct of this study; and receiving honoraria from Lilly, Merck Sharp & Dohme, Amgen, and Eisai; receiving research funding from Eisai, Effective Pharmaceuticals, and Deciphera Pharmaceuticals; and holding consulting roles with Lilly and Merck Sharp & Dohme, outside the submitted work. S-BK reports receiving researching funding from Novartis, Genzyme, and Dongkook Pharma, outside the submitted work. C-HH reports receiving honoraria from ONO Pharmaceutical and Bristol Myers-Squibb, during the conduct of this study; and serving as a consultant for ONO Pharmaceutical; receiving research funding from ONO Pharmaceutical; serving in a consulting role for Novartis, Lilly, and MSD; receiving honoraria from Merck Sharp & Dohme; and receiving research funding for MSD, AstraZeneca, and Genentech, outside the submitted work. IX reports employment with Bristol-Myers Squibb and ownership of stock in Bristol Myers-Squibb, outside the submitted work. MK reports employment with ONO Pharmaceutical and ownership of stock in ONO Pharmaceutical, outside the submitted work. YK reports receiving honoraria from ONO Pharmaceutical, during the conduct of this study; and receiving honoraria from Ethicon, Olympus, Taiho Pharmaceutical, Chugai Pharma, Nippon Kayaku, and Asahi Kasei; and receiving research funding from Astellas Pharma, Otsuka, Kyowa Hakko Kirin, Kowa, CSL Behring, Kaken Pharmaceutical, Shionogi, Daiichi Sankyo, Taiho Pharmaceutical, Takeda, Chugai Pharma, Tsumura & Co., Teijin Pharma, Medtronic, Boehringer Ingelheim, Merck Serono, Novartis, Asahi Kasei, Kureha, Sanofi, Sumitomo Dainippon Pharma, Taisho Toyama Pharma, Nippon Kayaku, Lilly, Pfizer Yakult Honsha, GlaxoSmithKline, Medicon, EA Pharma, Otsuka, ONO Pharmaceutical, KCI Licensing, Inc., Nihon Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Eisai Co., Ltd., Bayer Yakuhin, Ltd, Abbot Japan Co., Ltd., and FUJIFILM Toyama Chemical Co., Ltd., outside the submitted work. All other authors report no competing interests.

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TGFB1 and TGFB2 Mediated Epithelial-Mesenchymal Transition in Esophageal Adenocarcinoma Cells

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Purpose: The esophageal adenocarcinoma (EAC) is characterized by an early lymphogenic dissemination and a poor prognosis. The tumor biology and the impact of autocrine, paracrine and endocrine mediators are involved in these mechanisms. For dissemination, the tumor cells need to escape the solid tumor and invade into new target structures. This mechanism is described as epitheliale-mesenchymal transition (EMT), which could be initiated by TGF-beta.
Methods: Two proliferation and motility of the esophageal adenocarcinoma cell lines (OE33, OE19) were analyzed after TGF-beta1 and TGF-beta2 treatment. EMT marker gene expressions (e.g. vimentin) were assessed by qRT-PCR.
Results: TGF-beta2 led to a deceased proliferation rate compared to untreated and TGF-beta1 treated cells in OE33 cells. In OE19 cells both, TGF-beta1 and TGF-beta2 treatment resulted in an increased proliferation compared to untreated cells. In OE33 cells the motility was affected by TGF-beta1 only, while in OE19 cells the motility was increased by TGF-beta1 and TGF-beta2 compared to untreated cells. The vimentin mRNA-expression in OE33 cells was increased by TGF-beta1 and TGF-beta2 (14.7-fold and 25.9-fold). However TGF-beta1 and TGF-beta2 only led to a moderate increase in the vimentin mRNA-expression (4.0-fold and 1.8-fold) in OE19 cells.
Conclusions: TGF-beta1 and TGF-beta2 induce EMT and cellular motility in a cell line specific pattern. The responsible intracellular signaling cascades addressed by TGF-beta1 and TGF-beta2 and their contribution for dissemination in EAC patients need to be investigated with full details.

Disclosure Statement: None.

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POLO: Efficacy and Health-Related Quality of Life (HRQOL) with Maintenance Olaparib Following First-Line Platinum-Based Chemotherapy (PBC) in Patients (PTS) with a Germline BRCA Mutation and Metastatic Pancreatic Cancer (MPC)

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Purpose: Pancreatic cancer (PC) pts with germline BRCA1 and/or BRCA2 mutation (gBRCAm) have shown response to PARP inhibitor olaparib (O) (Kaufmann et al. JCO 2015). HRQoL assessment was a predefined sec. objective.
Methods: POLO is an international, randomized, double-blind, placebo (P)-controlled trial of pts with gBRCAm and PC who had received ≥16 wks of 1L PBC for metastatic disease without progression. Pts were then randomized 3:2 to maintenance O tablets (300 mg bid) or P. Treatment continued until investigator-assessed disease progression or unacceptable toxicity. Primary endpoint was progression-free survival (PFS) by blinded independent central review (modified RECIST 1.1). HRQoL was sec. endpoint, assessed using EORTC QLQ-C30 questionnaire at baseline and every 4 wks until disease progression, discontinuation and 30 days after last dose. Scores ranged from 0 to 100; ≥10-point change or difference between arms was considered clinically meaningful.
Results: We screened 3315 pts, identified 247 with gBRCAm, randomized 154 (O 92, P 62), and treated 151 (O 90, P 61). Pt characteristics (O/P): age, median (range) 57 (37–84)/57 (36–75); male, 58%/50%; ECOG performance status 0, 71%/61%. With 104 events, PFS was significantly improved with O vs P (hazard ratio [HR] 0.53; 95% CI 0.35, 0.82; P=0.0038; median PFS 7.4 vs 3.8 mo, respectively). At interim overall survival analysis (46% maturity), HR was 0.91 (95% CI 0.56, 1.46; P=0.68). Grade ≥3 adverse events occurred in 40% of O- and 23% of P-treated pts. HRQoL was preserved with O, no diff. between arms. Additional HRQoL data will be presented.
Conclusions: Maintenance O provided a statistically significant and clinically meaningful improvement in PFS in mPC pts with gBRCAm whose disease had not progressed on PBC. Safety was consistent with the known profile for O. POLO is the first Phase III trial to validate a biomarker-driven treatment in PC.

Disclosure Statement: Study was funded by AstraZeneca and is part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, Usa (MSD).

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Long-Term Survival Following Pancreaticoduodenectomy for Pancreatic Ductal Adenocarcinoma of the Pancreatic Head

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Purpose: Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease most commonly diagnosed at an advanced stage presenting with distant metastases or being irresectable. Therefore, 5-year overall survival is extremely poor being estimated at 2.5%. Less than 20% of patients present with a resectable tumor. Pancreaticoduodenectomy (PD) is the treatment of choice in cases of PDAC located in the pancreatic head.
Methods: All patients suffering from PDAC of the pancreatic head who underwent a PD in the period from 2007 – 2014 underwent a chart review. Follow-up investigations were performed at least 5 years to detect long-term survival (LTS). Univariate and multivariate analyses were performed to identify factors influencing LTS.
Results: Of 152 patients in the study period, 33 patients (22%) were identified as long-term surviving patients, surviving at least 5 years after PD. Median age was 65 (42-80). Male to female ratio was 22 (66.7%) / 11 (33.3%).
Median carbohydrate antigen (CA) 19-9 level was 87 U/ml (2 - 1136 U/ml) in the LTS-group being significantly lower than in the remaining cohort (131 U/ml; 1 – 9897 U/ml; p = 0.012).
Univariate analyses of pathohistological features between the LTS – group and the non - LTS-group showed significant differences in lymph node invasion (16x [48.5%] vs. 94x [61.9%]; p = 0.014), lymph node ratio (p = 0.029), perineural invasion (24 [72.7%] vs. 129 [84.9%] and tumor grade (p < 0.001).
Multivariate analysis identified CA 19 – 9 levels, lymph node metastasis and tumor grade as independent factors contributing to LTS.
Conclusions:
Pathohistological features such as low lymph node ratio, minimal to no perineural invasion or low tumor grade as well as low levels of CA – 19 - 9 have a significant impact on long-term survival after PD in PDAC.

Disclosure Statement: The authors declare no conflict of interests.

Genito-urinary Cancer, including Prostate Cancer

Best-of-Abstracts-Vorträge

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Health-Related Quality of Life in Long-Term Prostate Cancer Survivors After Nerve-Sparing and Non-Nerve-Sparing Radical Prostatectomy – Results from The Multiregional Procas Study

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Purpose: Nerve-sparing (NS) surgery was developed to improve postoperative sexual and potentially urological outcomes after radical prostatectomy (RP). However, it is largely unknown how NSRP affects health-related quality of life (HRQoL) including urinary and sexual outcomes in prostate cancer (PC) survivors 5-10 years after diagnosis in comparison to Non-NSRP.
Methods: The study population included 382 stage pT2-T3N0M0 PC survivors 5-10 years post-diagnosis, who were identified from the multiregional *Prostate Cancer Survivorship in Switzerland* (PROCAS) study. Briefly, in 2017/2018, PC survivors were identified via six population-based cancer registries based in both German- and French-speaking Switzerland. HRQoL and PC-specific symptom burden was assessed using the EORTC QLQ-C30 and EORTC QLQ-PR25 questionnaires. Differences in HRQoL outcomes between survivors treated with NSRP (uni- & bilateral) and Non-NSRP were analysed with multivariable linear regression adjusted for age, years since diagnosis, cancer stage, comorbidities at diagnosis and further therapies, if appropriate. Multiple imputation was performed to minimize the bias due to missing data.
Results: 5-10 years after diagnosis, PC survivors treated with NSRP and Non-NSRP reported similar symptom burden and comparable HRQoL function scores. The only significant differences were reported for sexual activity, whereas PC survivors who underwent NSRP reported statistically significant (p=0.031) higher sexual activity than those on Non-NSRP. NSRP and Non-NSRP reported similar scores for urinary symptoms and all other HRQoL outcomes.
Conclusions: NSRP and Non-NSRP were generally associated with comparable long-term HRQoL outcomes, but NSRP was linked with significantly higher sexual activity scores than Non-NSRP. Our results support nerve-sparing techniques as an option to improve post-operative sexual but not urinary outcomes after RP in long-term PC survivors.

Disclosure Statement: The authors have nothing to disclose.

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Immune Cell Gene Expression Signature is Associated with Improved Outcome in Muscle-Invasive Urothelial Bladder Cancer Patients Treated with Radical Cystectomy

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Purpose: Recently, distinct immune phenotypes in muscle-invasive bladder cancer (MIBC) correlating with improved outcome were defined. This study was conducted to develop a diagnostic assay to assess the immune status of MIBC and to predict patient outcome after curative treatment.
Methods: Gene expression of *CD3Z*, *CD8A* and *CXCL9*, different immune cell (IC) populations including stromal tumor infiltrating lymphocytes (sTILs), T-cells, NK-cells, macrophages and PD-1$^+$ IC, and intrinsic subtypes (MDACC-approach) were assessed in a cohort of 187 curatively treated MIBC patients (CCC-EMN-cohort). A gene expression signature was derived by hierarchical-clustering and further validated in the TCGA-cohort. IC populations in the TCGA cohort were assessed via CIBERSORT. Benefit of platinum-containing adjuvant chemotherapy was assessed in a pooled cohort of 125 patients.
Results: The gene expression signature of *CXCL9*, *CD3Z* and *CD8A* correlates with quantitative amounts of specific IC populations and sTILs (CCC-EMN: ρ-range: 0.44-0.74; TCGA: ρ-range: 0.56-0.82) and allows stratification of three different inflammation levels in both cohorts (Inflamed high, Inflamed low, Uninflamed). Highly inflamed tumors are preferentially of basal differentiation and show favorable 5-year survival rates of 67.3% (HR=0.27; CCC-EMN) and 55% (HR=0.41; TCGA). Uninflamed tumors are predominantly of luminal differentiation and low 5-year survival rates of 28% (CCC-EMN) and 36% (TCGA). Inflamed tumors exhibit higher levels of targetable immune checkpoints PD-1 and PD-L1. Patients undergoing adjuvant platinum-based chemotherapy with "inflamed high" tumors showed a favorable 5-year survival rate of 64% (HR=0.27; merged CCC-EMN and TCGA cohort).
Conclusions: The gene expression signature of *CD3Z*, *CD8A* and *CXCL9* is reliable to assess the immune status of MIBC and to stratify the survival of MIBC patients undergoing curative treatment and adjuvant platinum-based chemotherapy. It identifies tumors with high expression of immune checkpoints which are targetable by immunotherapy.

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The Pure High-Grade Papillary Urothelial Carcinoma of the Urinary Bladder: A Luminal Lesion Characterized by Frequent Alterations in Genes Encoding Chromatin-Modifying Proteins

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Purpose: Non-muscle-invasive bladder cancer is characterized insufficiently. It is accepted that high-grade papillary tumors (pTaHG) develop from a precedent low-grade (LG) lesion. Based on clinical data it is hypothesized that pTaHG tumors might also develop de novo. In this study we aimed to characterize potentially de novo pTaHG cancers by immunohistochemistry (IHC) and NGS, especially focussing on potential targeted therapies.
Methods: 78 samples from 48 patients presenting with pTaHG cancer without a history of previous or concomitant pTaLG or muscle-invasive disease (44 pTaHG, 34 papillary pT1a/pT1HG samples) were analyzed for protein expression of luminal and basal markers. The presence of genetic alterations with therapeutic potential was studied by targeted sequencing in a cohort of 23 samples from 23 patients (19 pTaHG/papillary pT1HG tumors, four smooth muscle controls). For analysis only the exophytic tumor area was considered.
Results: Potential de novo pTaHG/papillary pT1a/pT1HG tumors were characterized by a luminal IHC-based phenotype (KRT20+: 74% (58/78), GATA3+: 99% (77/78), ERbeta+: 96% (75/78), HER2 Dako score 3+: 28% (22/78)), while lacking in basal marker expression in the majority of cases (KRT5/6+: 3% (2/78), KRT14+: 9% (7/78)). At least one alteration in genes potentially impacting the selection of targeted therapies, including frequent alterations in genes encoding chromatin-modifying proteins (e.g. *KDM6A* in 47%, *ARID1A* in 37% of cases), was detected in 95% (18/19) of cases. Noteworthy, *TP53* (21%) and *FGFR3* (16%) mutational rates were similar.
Conclusions: Potential de novo pTaHG tumors are luminal lesions characterized by frequent alterations in genes encoding chromatin-modifying proteins and a similar rate of *TP53* and *FGFR3* alterations. The vast majority of cases harbored alterations in genes potentially impacting the selection of targeted therapies.

Reference:
1. Pathologe (2019) 40(Suppl 2): 41. https://doi.org/10.1007/s00292-019-0616-1

Disclosure Statement: All contributing authors have no conflicts of interest to declare.

Vorträge

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Checkmate 214 Post Hoc Analyses of Nivolumab Plus Ipilimumab or Sunitinib in IMDC Intermediate/Poor-Risk Patients with Previously Untreated Advanced Renal Cell Carcinoma (ARCC) with Sarcomatoid Features (SRCC)

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Purpose: Patients (pts) with aRCC with sRCC have poor prognosis and suboptimal outcomes with anti-VEGF targeted therapy. Nivolumab plus ipilimumab (N+I) demonstrated superior objective response rate (ORR) and overall survival (OS) vs sunitinib (S) in previously untreated pts with

IMDC intermediate/poor (I/P)-risk, clear cell, advanced RCC in the phase 3 CheckMate 214 trial.
Methods: We performed a post hoc exploratory analysis of N+I vs S in CheckMate 214 sRCC pts. The presence of sarcomatoid features was assessed by keyword search for "sarcomatoid" in pts with available local pathology reports accompanying pretreatment tumor samples.
Results: 842 (77%) of 1096 intention-to-treat pts had local pathology reports available, including 112 randomized pts with I/P-risk sRCC (N+I, n=60; S, n=52). Baseline characteristics of sRCC pts were balanced between arms. Notably, 47% vs 53% of I/P-risk sRCC pts in the N+I and S arms had baseline tumor PD-L1 expression ≥1%, which was higher than in all I/P-risk pts (N+I, 26% vs S, 29%). In descriptive analyses performed at a minimum follow-up of 30 months, confirmed ORR (56.7% [95% CI 43.2–69.4] vs 19.2% [95% CI 9.6–32.5]; *P*<0.001) and complete response rate per investigator (RECIST v1.1; 18.3% vs 0%), OS (median [95% CI] 31.2 [23.0–not estimable] vs 13.6 [7.7–20.9] months; HR [95% CI], 0.55 [0.33–0.90]; *P*<0.0155), and progression-free survival (median [95% CI] 8.4 [5.2–24.0] vs 4.9 [4.0–7.0] months; HR [95% CI], 0.61 [0.38–0.97]; *P*<0.03) per investigator were improved with N+I vs S in I/P-risk pts with sRCC. No new safety signals were seen in sRCC pts.
Conclusions: In this post hoc descriptive subgroup analysis of CheckMate 214, N+I demonstrated promising efficacy and prolonged survival vs S, with consistent safety, in untreated, I/P-risk, advanced clear cell RCC with sarcomatoid features. Prospective studies of N+I that include pts with sRCC are ongoing.

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Apalutamide (APA) and Overall Survival (OS) in Patients (PTS) with Nonmetastatic Castration-Resistant Prostate Cancer (NMCRPC): Updated Results from The Phase 3 Spartan Study

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Purpose: In the Ph3 PBO-contr. SPARTAN study, APA with ongoing ADT signifi. improved metastasis-free survival (MFS) (HR, 0.28; 95% CI, 0.23-0.35; p < 0.001), time to symptomatic progress., and progress.-free survival on 2nd therapy compared with PBO with ongoing ADT in pts with nmCRPC. At the primary analysis for MFS, APA was associa. with improved OS (HR, 0.70; 95% CI, 0.47-1.04; p = 0.07) and time to initiation of cytotoxic chemotherapy. OS results were immature, with only 104 of 427 events (24%) required for the prespecified final OS analysis. We report a second interim analysis (IA2) for OS after 285 events (65% of required events).
Methods: Pts with nmCRPC and PSA doubling time of ≤ 10 mths were random. 2:1 to APA (240 mg QD) or PBO, with ongoing ADT. The OS effect of APA vs PBO was assessed using a group sequential testing procedure with O'Brien-Fleming-type alpha spending function. The required p value for stati. signifi. at IA2 was 0.0121. OS was analyzed by Kaplan-Meier method and Cox model.
Results: At 41 mths' med. follow-up and 285 OS events, APA was associa. w/ improved OS compared with PBO (HR, 0.75; 95% CI, 0.59-0.96; p = 0.0197). The 4-yr OS rates for APA and PBO were 72.1% and 64.7%, respect.. After unblinding the study and prior to IA2, 76 nonprogressing PBO pts (19%) crossed over to open-label APA. At IA2, the proportion of pts who received subsequent life-prolonging therapy was 68% in the PBO group and 38% in the APA group. Rates of disconti. due to progressive disease and AE were 34% and 14%, for the APA group, and 74% and 8% for the PBO group. Rates of treatment-emergent AEs for APA at IA2 were similar to the rates previously reported at IA1.
Conclusions: At IA2, APA was associa. w/ a 25% reduc. in risk of death compared with PBO. This OS benefit for APA was observed desp. crossover of PBO pts to APA and higher rates of subsequent life-prolonging therapy for PBO pts. APA safety profile remained unchanged. These results further support APA as a standard of care option for pts with high-risk nmCRPC.

Reference:
1. ESMO Congress Barcelona 27 Sep - 01 Oct 2019

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Profound: Phase III Study of the Efficacy and Safety of Olaparib versus Enzalutamide or Abiraterone Acetate in Men with Metastatic Castration-Resistant Prostate Cancer (MCRPC) and Homologous Recombination Repair Gene (HRR) Alterations

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Purpose: mCRPC is a molecularly heterogenous disease. Tumors in a sizable proportion of patients with mCRPC harbor loss-of-function alterations in genes involved in HRR (eg *BRCA1*, *BRCA2* and *ATM*). HRR alterations have been associated with increased sensitivity to the PARP inhibitor olaparib in mCRPC. The PROfound study (NCT02987543) evaluates olaparib efficacy and safety versus either enzalutamide or abiraterone acetate, in mCRPC patients with an HRR alteration.
Methods: PROfound is a randomized, open-label, Phase III study in men with mCRPC, for whom prior new hormonal agent treatment for metastatic prostate cancer and/or CRPC had failed. Eligible patients had

a qualifying tumor HRRm in 1 of 15 genes, prospectively and centrally determined in tumor tissue using an investigational next-generation sequencing test (Foundation Medicine, Inc.). Two cohorts were enrolled: Cohort A (n=245) included patients with alterations in *BRCA1*, *BRCA2* or *ATM*; Cohort B included patients with an alteration in 12 other HRR genes (n=142). Patients were randomized (2:1) to olaparib tablets (300 mg bid) or physician's choice of either enzalutamide (160 mg orally od) or abiraterone acetate (1000 mg orally od + 5 mg bid prednisone). Treatment continued until radiographic progression (assessed by blinded independent central review or lack of treatment tolerability. The primary endpoint of radiographic progression-free survival (rPFS) in Cohort A was assessed by BICR using RECIST 1.1 and PCWG3 criteria and analyzed via stratified log-rank test.
Results and conclusions: The abstract will be updated with results and conclusions pending data availability.

Funding Source: AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA

Poster

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Prediction of Response Rate and Long-Term Survival in Polychemotherapy for Metastatic Penile Cancer by the Glasgow Prognostic Score

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Purpose: The Glasgow Prognostic Score (GPS) is defined by a combination of elevated C-reactive protein serum level (> 10 mg/L) and of hypoalbuminemia (< 35 g/L). It is considered in a variety of tumor entities as an independent prognostic marker, which predicts the biological behavior of malignant tumors. The survival rates for metastatic penile carcinoma are low. There is increasing evidence that patient-related prognostic factors, such as a persistent systemic inflammatory response, lead to low survival rates in tumor patients. The aim of the current study was to clarify the value of GPS in metastatic penile carcinoma in terms of response rate and long-term survival.
Methods: The correlation of GPS and long-term survival and response rate was studied in 68 patients with metastatic penile carcinoma. For this purpose, a score of C-reactive protein and albumin was determined prior to systemic treatment in order to correlate this consecutively with the follow-up.
Results: The survival and response of GPS-1 patients was significantly worse than that of GPS-0 patients (p = 0.006) and the survival and response of GPS-2 patients was significantly worse than that of GPS-1 patients (p <0.0001). Multivariate analysis showed that GPS (p <0.0001), tumor stage (p = 0.004), venous and lymph vessel invasion (p = 0.011) were factors that were independently associated with a worse prognosis.
Conclusions: The GPS can stratify the clinical outcome of penile cancer and can be used as a prognostic indicator.

Disclosure Statement: none

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Quantification of Lymphedema of the Lower Extremity and the External Genitals After Inguinal Lymphadenectomy in Penile Cancer Patients and Its Impact on the Quality of Life

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Purpose: Lymphedema of the lower extremity and the external genitals as a result of penile cancer treatment is a chronic disease that can significantly impair the quality of life. In the present study, various aspects of lymphedema associated with penile cancer were examined, including measurement methods, definitions, risk factors and, in particular, the effects on the physical, psychological and emotional well-being of affected men.
Methods: In a retrospective cohort study, we investigated the relationship between lymphedema, quality of life and surgical factors (radical vs. modified lymphadenectomy, LND). A total of 76 men, surgically treated for penile cancer, were evaluated at least 1 year after LND.
Results: In 29% of men lymphedema was detected (leg volume difference > 200cm^3). Affected men have a reduced self-esteem due to a distorted body image. Negative emotions reported include anxiety, frustration, sadness, anger, anxiety, and reduced self-esteem.
Conclusions: Lymphedema as a result of penile cancer treatment continues to be a significant quality of life problem with consequences for physical, mental and emotional well-being. The development of lymphedema leads to physical impairment, including impaired function, diminished strength, fatigue and pain in the affected limb.

Disclosure Statement: none

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Traumatic Spinal Cord Injury Confers Bladder Cancer Risk: Lessons from a Comparison of Clinical Data with the National Database

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Purpose: Life expectancy for people with traumatic spinal cord injury (TSCI) is increasing due to advances in treatment methods and in neuro-urology. Thus, developing urinary bladder cancer (UBC) is gaining importance.
Methods: Single-center retrospective evaluation of consecutive in- and out-patient data with spinal cord injury between January 1, 1998 and December 31, 2018 was carried out and data were compared with publicly available UBC data of the German population from the Center for Cancer Registry Data of the Robert Koch-Institute.
Results: A total of 37 (4 female, 33 male) out of 7004 patients with TSCI were diagnosed with histologically proven urinary bladder cancer. Median follow-up of TSCI patients with UBC was 85 months. Median age at bladder cancer diagnosis was 54.0 years, which is well below the average

for bladder cancer cases in the general population in Germany (male: 73, female: 77 years).
All but two patients had a latency period between the onset of TSCI and tumour diagnosis of more than 10 years (median: 30.0 years).
Of the 37 patients, 30 (81%) had muscle invasive bladder cancer at ≥T2 at the time of diagnosis, 27 out of 37 patients showed a histologically poorly differentiated G3 carcinoma. Both frequency distributions differ significantly between TSCI patients (p <0.0001 each) and the normal German population.
Median survival for all patients was 12.0 months (transitional cell carcinoma (n=31) 13 months; squamous cell carcinoma (n=5) 4 months, p = 0.0039). The prognosis of the 24 cystectomized patients was 15.0 months and thus significantly better than in those without cystectomy (p = 0.0148)
32 patients suffered from urodynamically confirmed neurogenic detrusor overactivity while 5 patients (all male) had detrusor acontractility.
Long-term suprapubic or indwelling catheterization was found in only 8 patients for a total of only 5.09% (median: 15.5 months) of the latency of all patients.
Conclusions: The results indicate that the neurogenic bladder caused by traumatic SCI itself is the main risk factor for bladder cancer.

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Clinical Outcome of PSMA-Guided Radiotherapy for Patients with Oligorecurrent Prostate Cancer

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Purpose: First line treatment of patients with recurrent, metastatic prostate cancer is a combination of hormone therapy with or without chemotherapy/ abiraterone, as a systemic, palliative treatment. A new perspective is given by PSMA-PET/CT-guided irradiation, which demonstrated promising efficacy in recent trials. The current study aimed to classify the type and localization of metastases after primary treatment and its clinical outcome.
Methods: Between 2011 and 2019, 86 patients (mean age of 69 years) with recurrent, oligometastatic prostate cancer received a PSMA-PET/CT followed by a precise irradiation of their metastases. 60 patients underwent a clinical follow-up including a quality of life status. Data were analyzed retrospectively regarding the region of relapse and the primary endpoints overall survival (OS), biochemical progression free survival (bPFS) and androgen deprivation therapy (ADT)-free survival.
Results: The median follow- up was 24 months (range 4-72). According to the d'Amico risk classification, 90.7% of all patients were categorized as high-risk. A median amount of 1.0 metastases per patient could be identified. In total, 49.4% of the metastases were considered as metastases of the bone, 34.1% were nodal metastases within and 16.5% nodal metastases outside of the pelvis. A 2-year OS rate of 95.7% and a 2-year bPFS rate of 85.1% were calculated. The data analysis revealed a mean ADT- free time of 15.9 months (range 3-40). Biochemical response was detected in 83.3% of the cohort. If a progress monitoring via PSMA-PET/CT was implemented, the standard uptake value (SUV) of the irradiated metastases was reduced significantly.
Conclusions: PSMA-guided radiotherapy is a promising, novel therapeutic approach for oligorecurrent prostate carcinoma to extent OS and bPFS in comparison to systemic therapy and should be more considered in the recurrent situation. However, prospective, randomized trials are necessary to confirm and validate the analyzed data with a larger cohort of patients.

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Clinical Outcomes According to PD-L1 Status and Age in the Prospective International Saul Study of atezolizumab (ATEZO) for Locally Advanced or Metastatic Urothelial Carcinoma (UC) or Non-UC of the Urinary Tract

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Purpose: Atezo, a monoclonal antibody targeting PD-L1, is an approved therapy for locally advanced/metastatic UC based on IMvigor210 and IMvigor211 phase II and III trials. The single-arm SAUL study (NCT02928406) with a broader patient (pt) population demonstrated median overall survival (OS) of 8.7 months and a safety profile consistent with previous atezo trials.
Methods: Pts with locally advanced/metastatic UC or non-UC of the urinary tract received atezo 1200 mg every 3 weeks until disease progression or unacceptable toxicity. Populations excluded from IMvigor211 (renal impairment, ECOG PS 2, treated asymptomatic CNS metastases, stable controlled autoimmune disease, concomitant steroids, HIV positive, non-UC) were eligible. The primary endpoint was safety; OS and overall response rate (ORR) were secondary endpoints. Predefined subgroup analyses included outcomes according to PD-L1 status (VENTANA SP142) and age in the overall population (and the IMvigor211-like subgroup for PD-L1).
Results: Between Nov 2016 and Mar 2018, 1004 pts were enrolled; 997 received atezo. Median (95% CI) OS was overall IC 0/1 vs IC 2/3: 7.9 (6.8–9.1) vs. 11.6 (8.8–18.8); IMvigor211-like IC 0/1 vs 2/3: 9.0 (7.8–10.4) vs 14.5 (9.5–18.8). ORR (95% CI) was overall IC 0/1 vs IC 2/3: 10% (8–13) vs 21% (16–26); IMvigor211-like IC 0/1 vs 2/3: 10% (7–13) vs 23% (17–30). Treatment response was observed in all age groups (ORR [95% CI], ≥65 y:

14% [12–17]; ≥75 y: 13% [9–18]; ≥80 y: 8% [3–16]). Incidences of grade ≥3 treatment-related adverse events were similar irrespective of PD-L1 status (overall IC 0/1 vs 2/3: 11% vs 16%; IMvigor211-like IC 0/1 vs 2/3: 11% vs 15%) or age (≥65 y: 13%; ≥75 y: 12%; ≥80 y: 10%).
Conclusions: OS and ORR appear more favorable in IC2/3 vs IC0/1 subgroups (overall and in the IMvigor211-like population). Atezo was effective and well tolerated across subgroups including elderly pts.

Reference:
1. Sternberg et al. ASCO 2019

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Association Between Depth of Response (DepOR) and Overall Survival (OS): Exploratory Analysis of Nivolumab + Ipilimumab (N+I) vs Sunitinib (S) in Patients with Previously Untreated Advanced Renal Cell Carcinoma (ARCC) in Checkmate 214

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Purpose: DepOR (max % reduction from baseline in sum of target lesion diameters) has shown prognostic value for long-term survival in multiple malignancies. Among aRCC intention-to-treat patients (pts) in CheckMate 214 superior efficacy was recently shown with N+I over S at 30-mo min follow-up. The relationship between DepOR and OS was evaluated in CheckMate 214 to determine a potential DepOR threshold predictive of long-term OS with N+I.
Methods: Pts were randomized 1:1 to N+I (3 mg/kg + 1 mg/kg IV) Q3W for 4 doses, followed by N (3 mg/kg IV) Q2W, or S 50 mg/day orally for 4 wk (6-wk cycles). An exploratory analysis of OS by DepOR quartiles was conducted (Q0, no reduction; Q1, >0–≤25%; Q2, >25–≤50%; Q3, >50–≤75%; Q4, >75–≤100%).
Results: Of 550 and 546 pts randomized to N+I or S, 479 and 459, respectively, had postbaseline target lesion measurements. Among Q0 pts, median OS was longer and OS probabilities were notably higher with N+I vs S. Overall, greater DepOR was associated with improved OS in both arms. The OS probability HR (95% CI) vs Q0 was 0.63 (0.43–0.93) for Q1, 0.65 (0.42–1.01) for Q2, 0.22 (0.13–0.38) for Q3, and 0.18 (0.11–0.32) in the N+I arm (all $P<0.0001$). The OS probability vs Q0 progressively decreased with greater DepOR in arm S; however, N+I pts with >50–≤75% (Q3) tumor reduction had similar OS benefits as those with >75% (Q4) reduction, whereas only Q4 pts achieved comparable OS with S (203/550 [37%] N+I vs 46/546 [8%] S randomized pts). Receiver operating characteristic analysis supported a >50% DepOR threshold for greatest OS benefit with N+I. Additional analyses of the relationship between DepOR and outcomes across arms will be presented.
Conclusions: The relationships between DepOR and OS are distinct for N+I vs S, with a greater percentage of N+I pts having prolonged OS. Similar notable OS benefits in N+I DepOR Q3 and Q4 suggest that a DepOR threshold >50% may be a useful indicator of potential for long-term survival with N+I in aRCC pts. Prospective analyses to determine clinical applications are needed. Previously presented at Esmo 2019, Fpn 950P, Grünwald et al. Reused with permission.

Disclosure Statements:
Viktor Grünwald reports grants and personal fees from Pfizer; grants, personal fees and non-financial support from Bristol-Myers Squibb; personal fees and non-financial support from Roche; personal fees and non-financial support from Novartis; personal fees and non-financial support from EISAI; grants, personal fees, and non-financial support from Ipsen; and grants and personal fees from EUSA Pharm, during the conduct of the study and grants, personal fees, non-financial support, and stock ownership from MSD; grants from Novartis; grants, personal fees, and stock ownership from AstraZeneca; grants, personal fees, non-financial support, and stock ownership from Bristol-Myers Squibb; personal fees and non-financial support from Merck Serono; personal fees from Roche; personal fees from Pfizer; personal fees from Lilly; personal fees and non-financial support from PharmaMar; personal fees from Nanobiotix; and personal fees from Janssen, outside the submitted work.
Toni K. Choueiri reports research funding (institutional and personal) from AstraZeneca, Alexion, Bayer, Bristol-Myers Squibb/ER Squibb and Sons LLC, Cerulean, Eisai, Foundation Medicine Inc., Exelixis, Ipsen, Tracon, Genentech, Roche, Roche Products Limited, F. Hoffmann-La Roche, GlaxoSmithKline, Lilly, Merck, Novartis, Peloton, Pfizer, Prometheus Labs, Corvus, Calithera, Analysis Group, Sanofi/Aventis, and Takeda; honoraria from AstraZeneca, Alexion, Sanofi/Aventis, Bayer, Bristol-Myers Squibb/ER Squibb and Sons LLC, Cerulean, Eisai, Foundation Medicine Inc., Exelixis, Genentech, Roche, Roche Products Limited, F. Hoffmann-La Roche, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, EMD Serono, Prometheus Labs, Corvus, Ipsen, Up-to-Date, National Comprehensive Cancer Network, Analysis Group, Michael J. Hennessy (MJH) Associates, Inc (healthcare communications company with several brands such as OnClive, PeerView and PER), L-path, Kidney Cancer Journal, Clinical Care Options, Platform Q, Navinata Healthcare, Harborside Press, American Society of Medical Oncology, New England Journal of Medicine, Lancet Oncology, Heron Therapeutics, and Lilly; consulting or advisory role with AstraZeneca, Alexion, Sanofi/Aventis, Bayer, Bristol-Myers Squibb/ER Squibb and Sons LLC, Cerulean, Eisai, Foundation Medicine Inc., Exelixis, Genentech, Heron Therapeutics, Lilly, Roche, GlaxoSmithKline, Merck, Novartis, Peloton, Pfizer, Emd Serono, Prometheus Labs, Corvus, Ipsen, Up-to-Date, National Comprehensive Cancer Network, and Analysis Group; patents, royalties or other intellectual properties: International Patent Application No. PCT/US2018/12209, titled "PBRM1 Biomarkers Predictive of Anti-Immune Checkpoint Response," filed January 3, 2018, claiming priority to U.S. Provisional Patent Application No. 62/445,094, filed January 11, 2017, and International Patent Application No. Pct/US2018/058430, titled "Biomarkers of Clinical Response and Benefit to Immune Checkpoint Inhibitor Therapy," filed October 31, 2018, claiming priority to U.S. Provisional Patent Application No. 62/581,175, filed November 3, 2017.
Brian I. Rini reports research funding to institution from Pfizer, Merck, GNE/Roche, Peloton, Aveo, AstraZeneca, and Bristol-Myers Squibb; consulting fees from Bristol-Myers Squibb, Pfizer, GNE/Roche, Aveo, Novartis, Synthorx, Peloton, Compugen, Merck, Corvus, and Exelixis; and stock holding with PTC Therapeutics.
Thomas Powles reports research funding from AstraZeneca/MedImmune and Roche/Genentech; consulting/advisory roles with Genentech/Roche, Bristol-Myers Squibb, Merck, Novartis, and AstraZeneca; honoraria from Roche/Genentech, Bristol-Myers Squibb, and Merck; and other relationships with Ipsen and Bristol-Myers Squibb.
Saby George reports consulting/advisory roles with Bayer, Bristol-Myers Squibb, Novartis, Exelixis, Janssen, Corvus, Genentech, Sanofi/Genzyme, Pfizer, and EMD Serono; and grants from Acceleron, Merck, Agensys, and Eisai.
Marc-Oliver Grimm reports research funding and consulting/advisory fees from Novartis; research funding, consulting/advisory fees, and honoraria from Bristol-Myers Squibb; consulting/advisory fees and honoraria from Pfizer, Bayer HealthCare, Sanofi Aventis, AstraZeneca, MSD, Janssen Cilag, and ONO Pharmaceutical; honoraria from Astellas, Hexal, Apohepha, Ipsen Pharma, and Medac; consulting/advisory fees from Intuitive Surgical and Amgen, outside the submitted work.
M. Brent McHenry reports employment with and stock ownership in Bristol-Myers Squibb.
Matthew Maurer reports employment with and stock ownership in Bristol-Myers Squibb.
Robert J. Motzer reports research funding paid to institution from Bristol-Myers Squibb, Pfizer, Novartis, Eisai, Exelixis, and Genentech/Roche; and consultancy roles with Bristol-Myers Squibb, Pfizer, Novartis, Eisai, Exelixis, Genentech/Roche,

Merck, Incyte, and Lilly.
Hans J. Hammers reports clinical trial support and advisory board roles with Bristol-Myers Squibb and Merck; and advisory board roles with Pfizer, Exelixis, Armo Biosciences, and Novartis.
Nizar M. Tannir reports research funding and advisory board roles with Bristol-Myers Squibb, Pfizer, Novartis, and Exelixis Inc; research funding from Calithera Bioscience; advisory board roles with Nektar Therapeutics, Oncorena, and Eisai Medical Research; and a speakers bureau role with ONO Pharmaceutical.
Laurence Albiges reports consulting (by institution) for Pfizer, Novartis, Bristol-Myers Squibb, Ipsen, Roche, MSD, and AstraZeneca.

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Nora: Real World Evidence in Renal Cell Carcinoma; A National, Prospective, Non-Interventional Study in Patients with Advanced/Metastatic Renal Cell Carcinoma Starting 1st Line Nivolumab and Ipilimumab Combination Therapy or Nivolumab Monotherapy After Prior Therapy

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Purpose: The pivotal Ph3 trials CM 214 (NCT02231749) and CM 025 (NCT01668784) showed long term overall survival benefit for patients with advanced/metastatic RCC treated with nivolumab + ipilimumab combination therapy compared to sunitinib and for nivolumab alone vs. everolimus. Real world data is needed to further evaluate the effectiveness and tolerability in routine clinical care, as well as the quality of life associated with the treatment in a broader patient population.
Materials: NORA (NCT02940639) is an ongoing, non-interventional study (NIS) in Germany. Overall, 490 adult patients diagnosed with advanced/metastatic RCC, who start a new systemic 1st line therapy with nivolumab + ipilimumab with intermediate/poor risk (cohort-2, n=260) or nivolumab after prior therapy (cohort-1, n=230) according to marketing authorization in Germany, will be enrolled. Patients are followed for 5 years from treatment initiation until death, withdrawal of consent, loss to follow-up or end of study. The primary endpoint is overall survival. Secondary endpoints include progression free survival, response rates, adverse events (AE), AE management and patient reported outcomes with EQ-5D and FKSI19.
Results: At the September 30th 2019 data cut, 36 months after start of enrollment, interim data of 233 patients of cohort-1 describe baseline characteristics and outcome of patients with a minimum follow-up of 6 months. The data also shows demographic and disease characteristics, ECOG performance status and patient reported outcomes for 1st line patients documented until data cut.
Conclusion: We provide the first effectiveness data of the NORA observational study in patients treated with nivolumab monotherapy in routine care in Germany. Furthermore, information about baseline characteristics in 1st line patients and the management of immune related adverse events in clinical practice is shown. Taken together, these data give valuable insight in the current treatment landscape and outcome in patients with advanced/metastatic RCC.

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Successful Targeting of the Warburg Effect in Prostate Cancer by Novel 1,4-Naphthoquinone Sulphomethylene Carbohydrate Conjugates

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Purpose: The ability of prostate cancer (PCa) cells to consume large amounts of glucose due to overexpression of GLUT1[1] (Warburg effect) can be used to enhance selectivity of anticancer drugs by their conjugation to carbohydrates. 1,4-naphtoquinones exhibit cytotoxic effects by exerting oxidative stress on cancer cells.[2] Here, we characterize a series of novel semi-synthetic molecules containing a 1,4-naphthoquinone conjugated with glucose via S-CH_2 bond.
Methods: A cytotoxicity screen was performed for the 34 novel compounds in 22Rv1 cells by MTT assay. The two most active compounds were evaluated in human PCa cells, as well as non-malignant cells to confirm selectivity. Apoptosis induction, mitochondrial damage, oxidative stress and glucose uptake were assessed by Western Blot and FACS analysis.
Results: Two promising derivatives with IC_{50}s of low micromolar concentrations and high selectivity for PCa cells were identified in the screen. Glucose depletion in media resulted in increased cytotoxicity of the compounds, while GLUT1-inhibitors antagonized these effects, suggesting a GLUT1-mediated uptake of the derivatives. Up-regulation of cleaved caspase-3, cleaved PARP and Bax indicate an apoptotic character of drug-induced cell death. At the same time, pro-survival pathways (Bcl-2, Survivin) were suppressed under treatment. The compounds reduced mitochondrial membrane potential, increased ROS levels and the antioxidant N-acetylcysteine rescued treated cells from cell death, suggesting oxidative stress to contribute to the cytotoxic activity. Strong synergistic effects were observed in combination with PARP inhibitors.
Conclusions: We identified two novel compounds exhibiting potent activity and selectivity in human PCa cells due to GLUT1-mediated uptake. The mode of action comprises caspase-dependent apoptosis, suppression of pro-survival processes and induction of oxidative stress. Effects on AR- and MAPK-signaling, cancer cell proteome and autophagy are currently investigated.

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Survival Improvement in Metastatic Renal Cell Carcinoma (MRCC) Patients Over Time: Do Elderly Patients Participate?

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Purpose: The incidence of RCC is increasing and prognosis of mRCC is still limited. However, new approaches have changed our therapeutic landscape dramatically over the last two decades and overall survival (OS) for mRCC is improving. Nonetheless, little is known about the outcome of elderly mRCC patients. Therefore, this monocentric retrospective analysis addresses changes in overall survival between treatment periods and age groups.
Methods: Patients with mRCC treated at Hannover Medical School from 01/2003 - 12/2018 were identified by retrospective chart review. Treatment periods were defined from 01.01.2003 – 31.12.2009 (Period 1) and 01.01.2010 – 31.12.2018 (Period 2). Age groups were defined according to WHO (age <61 years = not old, age 61-75 = older, age >76 = old). Descriptive statistics, Kaplan-Meier analysis and logistic regression were administered.
Results: Overall, 314 patients showed a median OS of 40.1 months (95%-CI: 32.8-47.4 month). Median OS is significantly longer for patients treated in period 2 vs. period 1 (59.1 vs. 35.1 months, p=0.003). Median OS does not differ between not old vs. older and older vs. old. Subgroup analysis of age groups within treatment periods showed no difference, but increase of median OS was more profound in age group old vs older comparing treatment periods (period 1 older 36.7, period 1 old 18.8, period 2 older 59.1, period 2 old 45.7 months).
Conclusions: While the increase in OS between treatment periods might reflect the advance of our therapeutic armamentarium, there is no difference in OS comparing age groups. Improvement of OS was comparable between age groups, but with the largest increase in median OS across treatment periods. Surprisingly, the old seem to profit particularly.

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Prognostic Role of Docetaxel-Induced Reduction of Free Testosterone Serum Levels in Metastatic Prostate Cancer Patients

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Purpose: We have recently demonstrated that carboplatin plus weekly docetaxel is effective in docetaxel-refractory prostate cancer (PC) and interferes with testosterone biosynthesis (Reuter et al.; Oncol Res & Treat. 2018, 41 (suppl.1): p.10). In this study, the impact of docetaxel monotherapy on free and total testosterone (fT, TT) serum levels and the prognostic role of fT and TT were analyzed in mPC patients.
Methods: 59 consecutive mPC patients were treated with at least two cycles of docetaxel (75 mg/m2 q3w; 50 mg/m2 q2w, or 35 mg/m2 q1w) until disease progression, occurrence of intolerable adverse effects or completion of the planned cycle number. Efficacy measures were done following PCWG2 recommendations. FT and TT were measured before and during chemotherapy.
Results: At the current analysis, the median follow-up time was 20.8 months. Response of prostate-specific antigen (PSAR; ≥50% PSA reduction) was observed in 39/59 (66.1%) and 11/37 (29.7%) patients with measurable disease exhibited a partial remission (PR). Median progression-free survival (PFS) for all patients was 7.8 months (CI 95% 3.8, 11.8) and median overall survival (OS) was 25.1 months (CI 95% 17.6, 32.7). The most common reversible grade 3/4 toxicity was leukopenia/neutropenia (29.3/34.5%). Median fT and TT serum levels were reduced below the detection limit during docetaxel treatment (fT: from 0.37 pg/mL to <0.01 pg/mL and TT: from 0.12 to <0.05 ng/mL, respectively). Multivariate Cox regression analyses identified fT nadir values <0.01 pg/mL, PSAR>50%, number of organs involved and previous prednisone treatment as independent prognostic risk factors for PFS and fT reduction >90%, number of organs involved and previous prednisone as independent prognostic risk factors for OS. FT nadir values <0.01 pg/mL and PSAR >50% were associated with longer PFS (p<0.05).
Conclusions: These data demonstrate that fT is an important prognostic factor for PFS and OS in mPC patients.

Disclosure Statement: The authors declare no potential conflicts of interest.

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Advanced Renal Cell Carcinoma: First Results from the Prospective Research Platform Carat for Patients with MRCC in Germany

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Purpose: The Tumor Registry Renal Cell Carcinoma (TNK) analyzed treatment and outcome of patients (pts) treated in Germany from 2007-17. CARAT is the successor registry, which continues to assess longitudinal real world clinical outcome, incl. patient-reported outcomes (PROs) and decentralized biobanking. Today, we introduce CARAT and report on current changes of the treatment landscape in mRCC in Germany.
Methods: Since Dec 2017 150 pts have been enrolled in CARAT, expanding the previous TNK (2007-17, 1500 pts). CARAT is an observational, prospective, open, multicenter clinical research platform aiming to enroll 1000 pts by 150 sites. Pts with mRCC who start systemic 1stline treatment are eligible. Treatment characteristics, clinical outcome and physician-reported factors on treatment decision making are collected. Changes of the treatment landscape are shown descriptively.
Results: By August 2019 >1700 pts with mRCC have been recruited. Median age is 68 years. 60% had intermediate risk (MSKCC) at start of 1st-line. Median OS for pts with start of 1st-line 2007-17 is 19 months (>60% events). If selected by trial eligibility criteria, the median OS is 27 months. Pts who started treatment in 2018 mostly received pazopanib or sunitinib (38%/34%). Since the approval (May 2018) 18% are treated with cabozantinib. Preferred 2nd-line treatment changed from sorafenib/temsirolimus (35%/21%, 2007-09), everolimus (33% 2010-12), everolimus/axitinib/sunitinib (29%/19%/18%, 2013-15) to nivolumab (>60% since 2016). The impact of new treatment options on OS will be analyzed.
Conclusions Pts in routine care in Germany are older and have inferior prognosis than trial-eligible pts. CARAT complements results of RCTs

with prospective data on clinical and PROs for pts with mRCC in routine care. CARAT will show changes in the choice of treatment due to new approvals, applied sequences and investigate the effectiveness in a "real world" setting.

Disclosure Statement: None of the authors declare conflicts of interests regarding the topic of this abstract.

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Early Mortality of Prostatectomy vs. Radiotherapy as a Primary Treatment for Prostate Cancer: a Population-Based Study from The United States and East Germany

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Purpose: To assess the extent of early mortality and its temporal course after prostatectomy and radiotherapy in the general population.
Methods: Data from SEER-database and East German epidemiologic cancer registries were used for the years 2005-2013. Metastasized cases were excluded.
Analysing overall mortality, year-specific Cox regression models were used after adjusting for age (including age squared), risk stage and grading. To estimate temporal hazards we computed year-specific conditional hazards for surgery and radiotherapy after propensity-score matching and applied piecewise proportional hazard models.
Results: In German and US-American populations we observed higher initial three-month mortality odds for prostatectomy (USA: 9.4, 95% CI: 7.8–11.2; Germany: 9.1, 95% CI: 5.1-16.2) approaching the null effect value not before 24 months (estimated annual mean 36 months in US data) after diagnosis.
During the observational period we observed a constant hazard ratio for the 24-month mortality in the US-population (2005: 1.7, 95% CI: 1.5–1.9; 2013: 1.9, 95% CI: 1.6–2.2) comparing surgery and radiotherapy. The same was true in the German cohort (2005: 1.4, 95% CI: 0.9–2.1; 2013: 3.3, 95% CI: 2.2–5.1). Considering low-risk cases, the adverse surgery effect appeared stronger.
Conclusions: There is strong evidence from two independent populations of a considerably higher early to midterm mortality after prostatectomy compared to radiotherapy extending the time of early mortality considered by previous studies up to 36 months (at least 24 months).

Disclosure Statement: All authors declare that there is no conflict of interest.

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TKI Induction Followed by a Randomized Comparison between Nivolumab or TKI Continuation in Renal Cell Carcinoma (NiVOSWiTCH)

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Background: Treatment with tyrosine kinase inhibitors (TKI) or Nivolumab (NIVO) are standard treatment options in metastatic renal cell carcinoma (mRCC). We tested whether TKI with early switch to NIVO improved outcome in mRCC.
Patients and methods: Key inclusion criteria: measurable advanced or metastatic ccRCC, ECOG PS: 0-2, adequate organ function. Patients with PR or SD to sunitinib or pazopanib after 10-12 weeks of treatment were 1:1 randomized to continue TKI treatment or switch to NIVO 240 or 480 mg IV q2-4wks. Imaging was performed q12wks. 49 of 244 planned patients were randomized between December 2016 and August 2018 and poor accrual led to premature closure of the trial. Efficacy and safety parameters were analyzed descriptively.
Results: 25 and 24 pts. received NIVO or TKI, respectively. Median age was 65 years (range: 35-79), 40 pts. (82%) were male and 2 pts. (4%) had an ECOG PS of 2. MSKCC risk categories were: favorable (31%), intermediate (65%), and poor (4%). Best objective response rate (ORR) from start of 1st line therapy was not significantly different between groups (64 vs. 70%, P=0.76). However, when measured from time of randomization ORR for NIVO vs. TKI was 16 vs. 48% (P=0.029). All grades adverse events (AE) occurred in 96% (NIVO) and 100% (TKI) and grade 3-5 were 44% vs. 67%, respectively. Serious AE (SAE) were 10 (40) and 9 (38), respectively.
Conclusions: Our results indicate that TKI-sensitive pts. have less benefit from early switch to NIVO treatment than from TKI continuation. The major limitation of our trial is the premature closure and the limited sample size.

Disclosure Statement: The authors declare no conflict of interest.

Sponsor & funding source: AIO-Studien-gGmbH, financial support: BMS
Clinical trial registry: Eudra-CT: 2016-002170-13. NCT02959554

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Erdafitinib Compared with Vinflunine or Docetaxel or Pembrolizumab in Patients (PTS) with Metastatic or Surgically Unresectable (M/UR) Urothelial Carcinoma (UC) and Selected FGFR Gene Alterations (FGFRALT): Phase 3 THOR Study

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Purpose: Pts with M/UR UC have poor prognoses. Programmed death (ligand)-1 (PD-[L]1) inhibitors have improved outcomes in some pts, but responses vary based on genotypic subtype. *FGFRalt* are present in 20% of pts with UC and may reflect an immunologically cold tumor that does not respond well to immunotherapy.[1] In early phase 2 study, erdafitinib (ERDA, 8 mg/d continuous), a pan-FGFR (1-4) inhibitor demonstrated tolerability and favorable objective response rate (ORR, 42%) in pts with M/UR UC and *FGFRalt*; uptitration to 9 mg/d was feasible. Activity of single-agent ERDA will be compared with chemo or pembrolizumab in pts with M/UR UC in this randomized phase 3 study.
Methods: Adult pts (ECOG status ≤ 2, adequate bone marrow, liver, and renal function; no uncontrolled cardiovascular disease, known HIV, hepatitis B or C, or baseline phosphate persistently above upper limit of normal allowed) with stage 4 M/UR UC and specific pathogenic *FGFRalt* (*FGFR3* mutations or *FGFR2/3* fusions), who have received 1 or 2 lines of prior systemic therapy are eligible. Pts will be screened for *FGFRalt* and randomized in 2 cohorts (1:1). Cohort 1 (n ~280): pts with prior chemo and PD-L1 inhibitor (prior PD-[L]1 inhibitor -as monotherapy or combo; no more than 2 lines of prior allowed for cisplatin-ineligible pts) in combination or in maintenance setting will receive 8 mg/d continuous ERDA vs chemo (1:1) with docetaxel or vinflunine. Cohort 2 (n ~350): pts with prior chemo but no prior PD-(L)1 inhibitor will receive 8 mg/d ERDA vs pembrolizumab (1:1). Uptitration of ERDA to 9 mg/d is recommended in pts with serum phosphate ≤ 9 mg/dL. Primary end point: overall survival. Secondary end points: progression-free survival, ORR, duration of response, pt-reported outcomes, safety, and pharmacokinetics. PD-L1 expression level per immunohistochemistry and UC subtype per RNA sequencing or other methods as exploratory end points. Pts are being enrolled at sites in 25 countries. For additional information on specific sites/countries refer clinicaltrials.gov (NCT03390504).

Reference:

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Activity of Two Routine Cabazitaxel Treatment Sequences in Patients with Metastatic Castration- Resistant Prostate Cancer (mCRPC) – Interim Analysis of The Non-Interventional Scope Study

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Purpose: Cabazitaxel (CAB) and new hormonal therapies (HT: abiraterone or enzalutamide) have demonstrated a survival benefit in the

post-docetaxel setting. Optimal sequencing of these agents is unknown. SCOPE is the first multinational, non-interventional study evaluating prospectively the activity of CAB according to different sequences.
Methods: SCOPE is aimed at recruiting 900 patients (pts.) starting treatment with CAB in daily practice. Medical history, previous life-extending therapies received and outcome during CAB therapy (PSA response, clinical benefit, pain relief, tumor response as per RECIST) are collected. Pts are followed for up to 24 months after start of CAB therapy. Treatment outcomes (PSA, clinical including pain or radiological) are collected. For the current interim analysis (cut-off FEB 04, 2019) preliminary treatment outcomes of 2 sequences of therapies (DOC-CAB-HT and DOC-HT-CAB) are provided. It is funded by Sanofi-Aventis Germany.
Results: Of 734 enrolled pts., 273 pts. currently completed CAB therapy and are included in this interim analysis. 150 pts. (55%; med. age 70 yrs) received DOC-CAB-HT and 123 received DOC-HT-CAB (45%, med. age 73 yrs). Of these 273 pts, 146 (53.5%) responded to CAB (DOC-CAB-HT, n=87; DOC-HT-CAB, n=59), 76 (27.8%) had no response - outcome was missing for 51 (18.7%). Responses to CAB (n=146) documented were mainly a PSA decrease (≥30% or ≥50% in 92 or 63 pts, respectively) , pain relief (n=18), clinical (n=36) and RECIST responses (n=13; PR n=6 ; SD n=7). Med. PFS with CAB was 4.9 mo (95% CI 4.0-5.5) with DOC-CAB-HT and 4.6 mo (95% CI 3.9-5.4) with DOC-HT-CAB (p=0.24). OS data are not yet mature. TEAE were observed in 141 pts. (51.7%). Main AE of CAB ≥ 5% were nausea (7.3%), fatigue (6.3%), anemia (5 %) and diarrhea (4.7%).
Conclusions: Preliminary results of SCOPE prospective registry suggest that under routine conditions, CAB is active (even after new HT) and shows manageable tolerability.

Reference:

1. Oncol Res Treat 20149;42(suppl 4):51. Published and presented Oktober 2019 by same authors

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Anticancer Activity and Mechanism of Action of Derivatives of The Marine Alkaloid Ascididemine in Drug-Resistant Prostate Cancer

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Purpose: Marine organisms have served as a source for new potent anticancer drugs. The marine natural compound Ascididemine, a pentacyclic aromatic alkaloid, is known to exhibit antineoplastic activity.
Methods: Chemically optimized synthetic Ascididemine derivatives were generated and screened for selective cytotoxicity against human prostate cancer (PCa) cells. Most promising compounds were chosen for further investigations *in vitro*. Effects on cell compartments, intracellular signaling, proteome and kinome were investigated. Combinational treatment with established and preclinical drugs were performed. Androgen-independent, docetaxel-resistant PC3 cells and AR-V7 positive, BRCA2- mutated 22Rv1 cells were investigated.
Results: Two out of 24 derivatives were identified to selectively and potently inhibit drug-resistant PCa cells, while non-malignant cells were less affected. The compounds induced a mitochondrial membrane- permeabilization followed by increase of reactive oxygen species levels and Ca^{2+} release by the endoplasmatic reticulum. Decreasing levels of intracellular androgen receptor and its splice variant ARV7 were found. Kinome and proteome analysis revealed a general upregulated kinomic activity, specifically for the PI3K-Akt-pathway and PIM1 kinase. Coherently, combinations with specific Akt inhibitors as well as PARP inhibitor Olaparib in BRCA2-deficient PCa cells revealed strong synergism. Moreover a synergism in drug-resistant PCa cells was found for abiraterone, enzalutamide and docetaxel, indicating a reconstitution of sensitivity to these anticancer drugs.
Conclusions: We identified two potent marine-derived anticancer substances with high potential to overcome resistance mechanisms alone and in combination with established drugs in PCa, thus filling a medical demand. The mechanism of action includes the induction of mitochondrial damage leading to Ros generation and activation of endoplasmatic reticulum stress with consequent caspase-dependent apoptosis. *In vivo* examinations are ongoing.

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Efficacy of Anti-PD(L)1 Treatment in Patients with Metastatic Urothelial Cancer Based on mRNA- and Protein- Based PD-L1 Determination: Results from the Multicentric, Retrospective Fosmic Trial

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Purpose: Immunotherapy (IO) against PD1 or PD-L1 has been approved for treatment of metastasized urothelial bladder cancer (mUC). Here we evaluated efficacy in a retrospective Real-World-Phase IV trial based on molecular subtypes and PD-L1 status.
Methods: Cancer specific survival (CSS) from start of IO treatment to death was analyzed in a multicenter cohort of 65 patients having received IO for mUC in 1st and 2nd line setting. Intrinsic molecular subtypes were assessed by CK5, CK20, GATA3, FOXA1 and CD44 immunohistochemistry and RT-qPCR of CK5 and CK20. PD-L1 status was determined using the 28-8 Dako-assay. Stromal tumor infiltrating lymphocytes were assessed on HE slides. Survival analyses were performed by applying clinically relevant cut-offs and using Kaplan-Meier analysis and logistic regression for CSS.
Results: Altogether, 43% of tumors presented with basal differentiation, 57% were luminal. As expected, basal tumors exhibited significantly higher levels of PD-1 and PD-L1 gene expression, higher amounts of sTILs and PD-L1+ immune and tumor cells. Hierarchical clustering of all immunological biomarkers revealed three cluster: "Inflamed high" (n=13, 20%), "Inflamed low" (n=22, 33.8%), and "Uninflamed" (n=30, 46.2%). There were no significant CSS differences for any of these groups. However, patients with good performance status (ECOG0) and low PD-L1 expression showed significantly better CSS compared to those with ECOG0 / PD-L1 high and ECOG1 or ECOG2, respectively.

Conclusions: Immunological determinants of mUC show comparable distributions and correlations with subtypes of localized curatively treated MIBC patients. Interestingly, data indicate improved CSS after PD-1/PD-L1 treatment in patients with good performance and low PD-L1 expression, which warrants validation in larger cohorts.

Disclosure Statement: Stratifyer carried out gene expression analysis, RW is owner and employee of Stratifyer. Janssen Pharmaceutical gave research support for this work. This abstract was submitted at Esmo 2019.

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Prognostic Role of FGFR Mutations and FGFR mRNA Expression in Metastatic Urothelial Cancer Treated with Anti-PD(L1) Inhibitors in First an Second Line Setting

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Purpose: In the era of individualized oncological therapy in bladder cancer, FGFR3 mutations, FGFR2 and FGFR3 gene fusions as well as FGFR mRNA expression as potential oncological targets and their association to anti-PD-1 and anti-PD-L1 (IO) treatment outcomes in patients with metastatic urothelial cancer of the bladder (mUCB) was studied in a German patient cohort.
Methods: Within a cohort of 72 patients with mUCB from 5 academic centers in Germany (2016-2018) FGFR3 mutations, FGFR2 and FGFR3 gene fusions as well as FGFR expression in formalin-fixed, paraffin embedded tumour samples and its association to survival was examined using SNaPshot PCR, RT-qPCR as well as Next Generation Sequencing. Statistical analyses comprised Kaplan-Meier survival analyses, Spearman rank correlations, non- parametric testing.
Results: In 17% of all patients, FGFR3 mutations or gene fusions could be detected. Patients with FGFR3 alterations did not have better outcome after IO treatment (p=0.201). All alterations of FGFR3 resulted in overexpression of FGFR3 mRNA. Combination of FGFR mutation analysis and FGFR mRNA assessment improved IO outcome prediction. Overexpression of FGFR3 mRNA was negatively associated with PDL1 expression (mRNA and protein level). High FGFR2 mRNA expression in primary tumors predicted better disease specific survival of mUCB patients receiving IO therapy, whereas high FGFR3 mRNA expression was associated with tumor specific death in patients exhibiting of low FGFR2 mRNA expressions ($p<0.05$). This high risk group of mUCB patients exhibiting high mRNA levels FGFR3 comprises 40% of the total cohort.
Conclusions: The assessment of FGFR mRNA by standardized RT-qPCR identified a high risk mUCB patient cohort, which has inferior disease specific survival despite IO treatment and overexpresses FGFR3 mRNA. The assessment of FGFR mRNA levels by using this standardized, locally applicable FGFR testing could identify an FGFR inhibitor target population with poor response to IO treatment which is twice the size as currently detected by FGFR genomic alterations alone.

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Objectively Assessed Physical Activity and Sedentary Behavior in Patients with Advanced Renal Cell Carcinoma

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Purpose: Increased levels of physical activity are associated with decreased cancer risk and mortality in many cancer types. Moreover, physical activity is known to reduce several side effects of cancer and its treatment thereby improving patients' quality of life (QoL). So far, most studies have focused on frequently observed types of cancer, such as breast-, prostate-, lung- and colorectal carcinoma. Recent data from epidemiological studies also reported such relationships for renal cell carcinoma (RCC). Observational studies have included heterogenous populations in view of stage of disease and treatment. Further, collected data on physical activity have been based on self-reported assessments, a major limitation of these trials.
Methods: Against this backdrop we have initialized the multicenter observational CABOCARE trial in Germany and Austria. Patients with advanced RCC (n = 105) are recruited after treatment decision for cabozantinib has been made. Cabozantinib is an inhibitor of receptor tyrosine kinases c-MET, VEGFR and AXL, which has proven to prolong progression free survival (PFS) compared to standard care with sunitinib. Patient characteristics, state of disease, occurrence of adverse events (AE), quality of life (FACT NFKSI-19), self-reported physical activity (newly developed visual analogue scales) as well as objective physical activity, sedentary behavior and sleep data (Actigraph® GT9X Link device) are recorded at baseline, and each three months thereafter.
Results: Until data cut-off, baseline physical activity data were available for three patients showing that the patients' subjective and objective physical activity results were similar. The patients recorded predominately light physical activity, and the mean time of moderate to vigorous physical activity was below the recommended value of 150 minutes per week.
Conclusions: CABOCARE (NCT03647878) will be the first observational trial collecting objective physical activity and sleep data and their associations with PFS, AE and QoL in patients with advanced RCC in a longitudinal fashion.

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Different Diagnostic Methods for Identification of FGFR Alteration in Advanced Urothelial Carcinomas: Proficiency Results Based on Multiple RNA Extraction Kits and Mutation Detection Methods

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Purpose: *Pan FGFR* inhibitors such as Erdafitinib are approved in patients with advanced urothelial carcinoma (aUC) harboring *FGFR* alterations. Based on the necessity of sensitive and reproducible identification of these alterations in diagnostic routines this study aimed to compare different RNA isolation techniques and the QIAGEN *therascreen® FGFR* RGQ RT-PCR Kit with the SNaPshot mutational analysis.
Methods: Nucleic acids were extracted from 47 UC patients using the QIAGEN RNeasy DSP FFPE Kit, STRATIFYER Xtract or Maxwell RNA (Promega) isolation kit. Mutations of the *FGFR3* gene were detected using the SNaPshot method as well as via the QIAGEN *therascreen® FGFR* RGQ RT-PCR Kit. Intrinsic molecular subtypes were assessed using immunohistochemistry (IHC) of GATA3, FOXA1, CK20, CK5 and CD44 as well as RT-qPCR for gene expression of CK20 and CK5.
Results: All three different RNA isolation kits showed comparable amount of extracted RNA (Median 290, 177 and 226 ng/ul). Six hotspot *FGFR3* mutations were identified with 100% concordance. The main difference were the necessary working hours: per 10 samples, 4 vs. 4.5 vs 8 hours were needed for Stratifyer, Maxwell or QIAGEN RNA isolation. In addition, of 47 analyzed samples 100% concordance between QIAGEN *therascreen® FGFR* RGQ RT-PCR Kit and SNapShot analysis were achieved with 18 mutations identified (14 S249C, 2 R248C and 2 Y375). Immunohistochemical basal marker profile (CD44 and CK5) as well as high CK5 expression was observed in 28 (6/28 *FGFR3*-altered). Luminal marker profile (IHC markers: GATA3, FOXA1 and CK20 as well as expression of CK20) was detected in 37 samples (5/37 with *FGFR3* alteration, n.s.).
Conclusions: Different RNA extraction methods presented with comparable amount of nucleic acids with variant working hours. Moreover, a 100% concordance between the well established SNaPshot analysis compared to the QIAGEN *therascreen® FGFR* RGQ RT-PCR Kit for *FGFR3* mutations was observed. So far, the frequency of *FGFR3* mutations in aUC was not related to the type of UC as defined by marker profiles.

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Central, Prospective Detection of Homologous Recombination Repair (HRR) Gene Alteration in Tumor Tissue From> 4000 Men with Metastatic Castration-Resistant Prostate Cancer (MCRPC) Screened for The Profound Study

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Purpose: A proportion of patients (pts) with mCRPC have tumor cells harboring HRR gene alterations that may confer sensitivity to PARP inhibition. The PROfound study (NCT02987543) is a phase III, randomized, multicenter trial evaluating the efficacy and safety of the PARP inhibitor olaparib versus physician's choice of enzalutamide or abiraterone acetate in pre-treated mCRPC pts with a qualifying alteration in 15 predefined genes with a direct or indirect role in HRR. Here, we report the prevalence of single and co-occurring HRR alterations in pts screened for PROfound.
Methods: An investigational next-generation sequencing assay developed in partnership with Foundation Medicine Inc. (FMI) was used to prospectively select patients harboring HRR gene alterations in their tumor tissue reporting deleterious or suspected deleterious qualifying alterations in 15 HRR genes. Samples were clinically heterogenous regarding location and timing. Pts with a qualifying alteration who met the eligibility requirements were randomized to the trial. The study comprised two cohorts; Cohort A: pts with alterations in *BRCA1*, *BRCA2* or *ATM* (assigned regardless of any co-occurring mutation in other genes); Cohort B: 12 other HRR genes.
Results: Of 4425 screened pts, 4047 had samples tested at FMI, of whom 2792 (69%) yielded a biomarker status result. A qualifying HRR alteration was detected in 778 (27.9%) pts. Among the Cohort A genes, alterations in *BRCA2* were the most common (9.7%) followed by *ATM* (6.3%) and *BRCA1* (1.3%). *CDK12* alterations (7.1%) were the most common among the other HRR genes. *A* co-occurring qualifying HRR alteration in more than 1 gene was detected in 59 (7.6%) patients, most commonly *BRCA2* (n=30), *CDK12* (n=24) or *ATM* (n=13).
Conclusions: This is the largest study to date with central prospective HRR gene alteration tissue testing in prostate cancer. HRR alterations were most common in *BRCA2*; followed by *CDK12* and *ATM*. Further analyses are warranted to help understand whether there is a correlation between clinical/demographic characteristics and HRR alterations.

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Role of Free Testosterone Serum Levels During Salvage Chemotherapy with Carboplatin Plus Weekly Docetaxel in Patients with Docetaxel-Refractory, Metastatic Castration-Resistant Prostate Cancer (MCRPC)

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Purpose: Carboplatin plus docetaxel (CD) may be effective in mDRPC. Platinum(II)-complexes interfere with steroid biosynthesis lowering testosterone levels. In this study, the impact of CD on free and total testosterone (fT, TT) serum levels and the prognostic role of fT and TT were analyzed in mPC patients.
Methods: Docetaxel failure/resistance was defined according to the Prostate Cancer Working Group (PCWG2 2007) criteria. Treatment consisted of at least 2 cycles of carboplatin AUC5 iv for 30 min on day 1 every 4 weeks (q4w), docetaxel (35 mg/m2) iv for one hour on days 1, 8, (15) plus prednisone 2x5mg/day orally after receiving informed consent until disease progression or occurrence of intolerable adverse effects. Efficacy measures were done following PCWG2 recommendations.
Results: Of the 118 pts. treated since February 2005, 95.8% had bone, 47.5% lymph node, 28.0% liver and 20.3% lung metastases. At the time of the current analysis, the median follow-up time was 14.4 months. The objective response rate (ORR) was 46.4% in the 69 pts. with measureable disease (58.5%). Response of prostate-specific antigen (PSAR ≥ 50%) was observed in 56 (47.9%) patients. Median progression free survival (PFS) was 7.6 months (CI 95% 6.0, 9.1) and median overall survival (OS) was 15.7 months (CI 95% 12.2, 19.2). The most common reversible grade 3/4 toxicity was leukopenia/ neutropenia (36.4/28.8%). Median FT serum levels were 0.35 pg/mL before and < 0.18 pg/mL during CD treatment (nadir levels, $p < 0.001$; detection limit < 0.18 pg/mL). In multivariate analyses, LDH>2xULN, PSAR≥50% and FT nadir levels below the detection limit (< 0.18 pg/mL) during CD treatment were associated with longer PFS ($p < 0.05$).
Conclusions: These data suggest that CD may be an important salvage treatment option for DRPC patients by inhibition of the testosterone biosynthesis.

Disclosure Statement: The authors declare no potential conflicts of interest.

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A Phase 3, Randomized, Open-Label, Multicenter, Global Study of Efficacy and Safety of Durvalumab in Combinationwith Gemcitabine+CiSPLATiN (G+C) for Neoadjuvant Treatment Followed By Durvalumab Alone for Adjuvant Treatment in Muscle-Invasive Bladder Cancer (MiBC) (NiAGARA)

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Purpose: In the management of MIBC, neoadjuvant cisplatin-based combination chemotherapy has demonstrated improved pathologic complete response (pCR), event-free survival (EFS), and OS compared with radical cystectomy alone. Many patients still develop recurrence, including progression to metastasis. The combination of chemotherapy and immunotherapy in a neoadjuvant setting and consolidating response post-cystectomy in the adjuvant setting may improve clinical outcomes. PD-L1 inhibition with durvalumab, in combination with a standard neoadjuvant regimen (G+C), may improve immune-mediated antitumor response and increase the rates of pathologic responses and long-term survival.
Methods: NIAGARA is a Phase 3, randomized, open-label, multicenter, global study (~1050 patients) with 1:1 randomization to durvalumab and G+C combination (Arm 1) or G+C (Arm 2) as neoadjuvant chemotherapy prior to radical cystectomy. Following radical cystectomy and during adjuvant therapy, patients in Arm 1 will receive durvalumab monotherapy for 8 cycles; patients in Arm 2 will receive no adjuvant treatment. Patients with resectable MIBC (clinical stage T2N0M0-T4aN0M0) with transitional cell histology planning to undergo a radical cystectomy will be included. Primary endpoints are pCR rates at time of cystectomy following neoadjuvant treatment and EFS. Secondary and exploratory endpoints include proportion of patients who achieve pathologic response <P2 (stages Pa, P1, and CIS) at time of cystectomy following neoadjuvant treatment, EFS at 24 months, metastasis-free survival, proportion of patients who undergo cystectomy, and OS at 5 years. Enrollment opened in Dec 2018. Clinical trial information: NCT03732677.
Results: Not yet available.
Conclusions: Not yet available.

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Disclosure Statement: Funded by AstraZeneca.

DE-21760/19

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Comparison of Online Information About Prostatectomy, Radiotherapy and High-Intensity Focused Ultrasound for Prostate Cancer Patients

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Purpose: While the importance of the Internet as information source for prostate cancer patients is increasing, there is little knowledge about the relation between the prostate cancer treatment modality and the website's quality, readability and popularity.
Methods: By using the search engine Google, an Internet search for the English terms "prostate cancer prostatectomy", "prostate cancer radiotherapy" and "prostate cancer hifu" as well as for the corresponding German terms "Prostatakrebs Prostatektomie", "Prostatakrebs Strahlentherapie" and "Prostatakrebs HIFU" was conducted. The website's quality of the first 30 search results was assessed by validated instruments such as the DISCERN Plus score, the JAMA benchmark criteria and the Health on the Net Code of Conduct (HONcode) certification. The readability of the websites was analyzed with the Flesch-Reading-Ease, and the average usage time was assessed using Alexa Internet.
Results: Regarding the DISCERN Plus instrument and JAMA benchmark criteria, the website's quality was moderate with no differences between English and German websites. Using the JAMA benchmark criteria, the quality of German radiotherapy websites was significantly increased compared to German HIFU websites. Similarly, there were significantly more websites with HONcode certification in the German radiotherapy group than in the HIFU group; however, the majority of websites exhibited no HONcode certification. Based on the Flesch-Reading-Ease, both English and German websites were difficult to read with no differences between the surgery, radiotherapy and HIFU group. Likewise, the average user time did not differ among the groups.
Conclusions: As the overall quality of the investigated websites is moderate, the internet may be helpful in the treatment decision process of prostate cancer patients. However, regarding the insufficient readability of many websites, a significant number of patients have difficulties to obtain the relevant information highlighting the importance of high-quality medical consultations by physicians.

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A Prospective Phase 2A Study of Focal HDR Brachytherapy for Low to Intermediate Prostate Cancer - Profocal

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Purpose: An interim report on the feasibility of the technique and results on tolerability and PSA course.
Methods: Single fraction interstitial HDR brachytherapy was performed in patients with biopsy proven low to intermediate risk prostate cancer (PC) of 1 lesion with an encompassing dose of ≥20Gy. Catheters were placed into the lesions in a 3T-MRI system in local anesthesia. Follow up was planned for PSA levels after 3, 6, 12 and 24 months, a multiparametric (mp) MRI examination after 6, 12 and 24 months and a re-biopsy 12 months after HDR brachytherapy.
Results: The first 9 patients with a follow-up for 6 months had tumors exclusively located in the anterior part of the prostate mostly in the apical region. Overall procedure time was 52 min and actual intervention time 34 min for the placement of the catheters. Median time of radiotherapy was 8.3 min. Median encompassing dose was 27.4 Gy, median dose to 2 mL of rectum and bladder were 4.9 Gy and 8.5 Gy respectively. Using the VAS scale the pain reported for the intervention ranged from 2 to 3. No other complications were reported except for mild hematuria the day after the procedure in one patient. Short term follow up of at least six months demonstrated no acute genitourinary or gastrointestinal toxicity. Despite of the absence of antibiotic prophylaxis none of the patients developed post-interventional signs of infection. PSA levels in all patients decreased significantly (from 8,9 to 1,7ng/ml on average). No residual or recurrent prostate carcinoma was imaged at follow-up multi-parametric MRI. Imaging results were confirmed by transrectal ultrasound (TRUS) guided biopsies (n=4/9) showing no residual or recurrent prostate carcinoma in the treated region at 12 months after therapy.
Conclusions: HDR brachytherapy for localized PC is feasible and safe. Catheters can be placed accurately and maximum therapeutic dose distribution can be restricted to the tumour, no general anesthesia or antibiosis is necessary.

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Surgical Treatment of Synchronous and Metachronous Metastatic Adrenal Tumors in Patients with Renal Cell Carcinoma

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Purpose: A comparative analysis of surgical treatment results in patients with synchronous and metachronous solitary metastatic adrenal tumors renal cell carcinoma origin.
Methods: Between 1997 and 2018, 93 patients (66 men and 27 women; median age 60 years (28-78)) underwent surgical treatment, 58 patients underwent simultaneous surgery for synchronous metastasis in the adrenal gland, and 35 patients underwent adrenalectomy due to a solitary metachronous lesion.
Results: The sensitivity of ultrasound in the diagnosis of adrenal tumors is 80.6%, and computed tomography - 93.5%. Adrenal biopsy was successful in 73.9%. Progression free survival (adrenal metastasis) after the previous primary surgical treatment was 44 months (5-204). During surgical treatment of metachronous metastases, a decrease in the volume of blood loss ($p = 0.006$), the average length of stay ($p < 0.0001$), and the frequency of postoperative complications ($p = 0.022$) were observed. During pathology report study, clear cell RCC was observed in 84.9% (n = 79), papillary in 9.7% (n = 9), chromophobe in 2.2% (n = 2), and Collecting duct carcinoma (Bellini) in 3.2 % (n = 3).
The median follow up time was 42.0 ± 13.4 months (in the synchronous lesion group - 24.0 ± 5.4 months, the median in the metachronous lesion group was not achieved). The one-year survival of patients with a metachronous lesion of adrenal was 82.3 ± 76.6% versus 52.8 ± 7.1% in the synchronous lesion group, three-year survival was 79.2 ± 7.0% versus 32.3 ± 7.6% and five-year - 57.0 ± 10.0% versus 16.2 ± 12.0%. Metachronous adrenal lesion ($p < 0.0001$) and time to metastasis ≥24 months ($p = 0.007$) were favorable prognosis factors. In a multivariate analysis, only a metachronous lesion affected survival ($p = 0.002$).
Conclusions: Performing adrenalectomy among patients with a solitary metachronous lesion can improve OS and PFS.

Disclosure Statement: no conflict of interest

Geriatric Oncology

Poster

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Changes in Survival Rates and Tumor Characteristics with Increasing Age: Results from Population-Based Cancer Registries

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Purpose: A high proportion of cancers affect individuals of older age, for whom guidelines are applicable only to a limited extent due to comorbidities or other factors. It has frequently been shown that cancer survival rates are considerably lower for patients aged 75 and older, even when taking age related life expectancy into account (relative survival). Still, little is known about how these results evolve with advancing age and if they correspond to changes in tumor characteristics. We therefore investigated how relative survival rates, distribution of tumor stage and grading change with advancing age for selected common cancers. In addition, we examined the use of adjuvant chemotherapy in stage III colorectal cancer according to age and sex.
Methods: Analyses were based on data from German population-based cancer registries for the period 2012–2016, including patients aged 60 years or older with cancer of the bowel, bladder, lung, stomach, prostate or breast as well as mature B-cell neoplasms. All results were calculated by tumor site, sex and 5-year age groups (60-64 to 90+ years).
Results: Although the relative survival rates for all investigated entities decreased continuously, particularly in the age groups from 65–69 to 85–89 years, the results were inconsistent in terms the distribution of tumor stages and grading: invasive bladder cancer showed a trend toward earlier stages with increasing age, while the proportion of poorly differentiated tumors in gastric and lung cancer decreased. The proportion of adjuvant chemotherapies for colorectal cancer with lymph node involvement recorded in the registries declined significantly, particularly after the age of 75.
Conclusion Overall, the drop in relative survival rates with advancing age cannot be explained by changes in tumor characteristics alone. Less aggressive treatment strategies due to a higher prevalence of comorbidities, different patient preferences and lower degrees of scientific evidence are likely to have an influence on these results.

Disclosure Statement: No conlict of interest

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TrainIng Programs Promoting Daily Activity and Physical Function of Older Patients with Cancer – a Questionnaire Based Survey Regarding Individual Needs and Preferences

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Purpose: Physical function of older patients with cancer often decreases during cancer therapy. This study aims to explore individual needs and preferences of older patients with cancer in order to promote their physical activity (PA.)
Methods: The study is designed as a multi-center questionnaire-based survey including a convenience sample of patients aged ≥ 60; ≥70 and ≥80 years with heterogeneous cancer diagnoses and stages; either receiving therapy or after care. The questionnaire covers: gender; age; diagnosis and life situation; previous and recent PA; changes of PA due to the cancer diagnosis; individual goals for exercising; preferred type of PA; preferred physical and social environment for exercising (e.g. individual training vs. group based; home based vs. sport-center); aspects of motivation; need for support; self-efficacy and the use of digital media. Data are analyzed descriptively.
Results: In four centers 64 patients with a mean age of 69 ± 6.4 years; n=34 male; participated. The main cancer sites were hematological (n=17); lung (n=9); breast (n=8) and pancreas (n=7). Patients stated their interest in exercising to improve their mobility and physical performance (n=38) to prevent falls (n=26); to relax (n=15) and reduce fatigue (n=14). Patients preferred outdoors activities e.g. walking (n=48); cycling (n=38) and gymnastics either at home (n=36); in a group (n=26) or with a partner providing motivational support (n=23). For independent exercises at home; personalized recommendations and instructions (paper-based or video-based) were considered helpful (n=40). Digital media are used regularly (n=31) or sometime by (n=12) patients.
Conclusions: The study provides useful insights into preferences; needs and motivational factors for PA in older patients with cancer. Digital media seem to be feasible to reach this target group.To improve representativeness; the survey is currently expanded to n=280 participants including three more oncological centres.

Disclosure Statement: The authors do not have any conflicts of interest relevant to the topic to declare.

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Development of a Multimodal Supportive Intervention to Promote Physical Functioning of Older Patients with Cancer

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Purpose: Physical function (PF) of older patients with cancer may decline during therapy and endanger selfcare, independence and health related quality of life (HRQOL). To prevent deterioration of PF and maintain independence, targeted strategies considering the heterogeneity of older people are needed. This study aims to develop and evaluate a multimodal supportive intervention to maintain PF and nutritional status of older cancer patients undergoing outpatient radiotherapy.
Methods: The approach is based on the UK MRC Framework for the development and evaluation of complex interventions involving clinical experts and cancer survivors aged >60 years in development and pretest. Assessments: comprehensive geriatric assessment, objective and subjective assessments of PF, nutrition, HRQOL, specific needs, goals, individual barriers and facilitators. Subsequent pilot-testing will be accessible via digital media or paper based to examine which mode results in better motivation and adherence.
Results: Each patient will receive tailored exercise and nutritional recommendations according to his/her baseline assessments' results. Pretest including exercising and focus group interviews indicates feasibility and potential usefulness of the exercises for maintaining everyday-functionality. Participants appreciated the flexibility of the programme, which includes exercises in sitting and standing position. They reported having stopped rehabilitation classes since these were too strenuous. They valued coordination and balance exercises for increasing confidence and preventing falls. Participants rated their relatives' help as a cornerstone for overcoming their weaker self.
Conclusions: There is a need in this target group for individually tailored exercises that can be implemented in everyday life. The home-based intervention comprises feasible exercises relevant for everyday functioning addressing endurance, coordination, balance and fine motor skills in sitting or standing positions and nutritive advice.

Disclosure Statement: No conflicts of interest

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Social Relations of Older Patients with Cancer - Development During the Disease Trajectory. A Retrospective, Qualitative Study

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Purpose: Social support is a domain of the geriatric assessment. However, little is known about the development of social relationships during the course of the disease, especially among older people with cancer. The aim of this study was to explore the experiences of older patients with cancer regarding the development of their social relationships during disease trajectory.
Methods: A qualitative retrospective approach was chosen. People with cancer aged ≥65 years at diagnosis, at least 6 months after treatment were interviewed using a semi-structured interview guide and asked to depict their social relations at four given time points using the Family Board a non-verbal method to visualize social relations. The audiotaped interviews were transcribed, the Family Board constellations were documented and qualitative content analysis was conducted. Ethical approval was obtained.
Results: Six women and four men (mean age: 74.5 years) participated. The tumor sites were prostate, gastric, pancreas, esophagus, lymphatic glands, and brain. Analyses revealed that all participants experienced changes in their social network. Disease-related reduction of physical function was experienced to lead to the loss of social and role function. Grandchildren were perceived as supporting the fighting spirit and the return to everyday life. Comparisons of the Family Board constellations showed growing closeness of familial relations especially during treatment which remained later on. Frequent changes in number, closeness or distance related to other non-family ties. Participants valued these ties as another important source of emotional and instrumental support.
Conclusions: Findings underline the importance of repeated assessments of social relations and the availability of social support. The Family Board was well accepted and provided useful additional information especially regarding the perceived development of social relations.

Disclosure Statement: No conflicts of interest.

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Supportive Needs and Burden of Older Patients with Cancer and their Spouses- a Qualitative Analysis of Semi-Structured Interviews

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Purpose: Cancer and cancer therapy may cause burden of illness for patients and spouses likewise. This study aimed to explore needs and burden of older cancer patients and their spouses during the disease trajectory.

Methods: Within a qualitative retrospective design with semi-structured interviews experiences of patients and their partners were explored. Patients 65 years and older having completed therapy and their partners (dyads) were eligible. The interview transcripts were analyzed according to qualitative content analysis (Mayring).
Results: Nine dyads were included. Mean age of patients was 74 years, of partners 73 years, main tumor sites were: prostate (n=4), gastrointestinal (n=3), breast (n=2). Patients were treated with: operation (n=10), chemotherapy (n=4) and radiotherapy (n=6), the most frequent comorbidity was hypertension (n=9). Data analysis revealed positive and negative experiences regarding 6 main themes: 1. Information of patients and partners about illness and treatment: "My husband is still grateful. The doctor took his time to explain everything." 2. Empathic communication: "Tell your wife: Sex is over", 3. Trans-sectoral care: "I got discharged and did not know what to do", 4. Burden of illness regarding symptoms, side effects or late effects (e.g. fatigue, impotence, incontinence): "Everything is different than before, I got weaker, 5. Effects of illness and therapy on partnership and sexuality including emotional burden and supportive needs of partners: "it was not easy, I missed it (sexuality), there was a big gap, 6. Dyadic coping: "my wife always backed me, she endured more than I can think of", "I worry about him (partner with cancer), but I do not talk about my feelings because I do not want to burden him".
Conclusions: The importance of empathic communication, information, participation in decision making, the need for support regarding dyadic coping and issues of intimacy and sexuality became evident. Due to the qualitative design, these findings should be examined in further studies.

Disclosure Statement: No conflicts of interest

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Meaningfulness of a Biological Marker (Advanced Glycation Endproducts) Measured By Noninvasive Skin-Scan (Autofluorescence Measurement) in Geriatric-Oncological Patients

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Purpose: Older patients with cancer differ regarding their biological age, functionality, organ reserve and comorbidities. Therefore, a comprehensive geriatric assessment (CGA) e.g. to assess physical and cognitive functioning, nutritionals status, mood, self-care and social support is recommended before planning oncological therapies[1]. In addition, a valid assessment of the biological age could add valuable information. To investigate the possible benefit of the autofluorescence measurement of advanced glycation endproducts in the skin (AGE value) in the clinical context of geriatric oncology.
Methods: The Analysis of AGE data of a heterogeneous sample of older cancer patients to generate hypotheses regarding the clinical relevance of AGE. The AGE value of the skin was determined by autofluorescence measurement in n=100 cancer patients. Based on of age-specific reference values, AGE values were categorized as age-appropriate or pre-aged. Descriptive analyses regarding sex, comorbidities, cancer diagnoses and results of geriatric assessments were performed. To explore the predictive properties of AGE values survival data were analyzed with simple Kaplan-Meier estimates and Cox regressions with log-rank tests.
Results: The analyses of the AGE values were performed on 97 patients (47 women and 50 men) with a mean age of 75 ±5 years. Main cancer sites comprised lung n = 27 (28%), hematological n = 16 (17%), breast n = 14 (14%), head/neck n= 14 (14%), skin n = 12 (13%) and other =14 (14%). AGE values were Ø 3.1 Arbitrary Units (AU) ±0.8 (min. 1.7, max. 6.1). According to the age-specific reference values n =38 patients were categorized as age-appropriate and n =59 as the pre-aged. The survival time analyses indicated a survival advantage for tumor patients with high AGE values (p = 0.036, KI =1.038- 2.937, n = 97).
Conclusions: Due to the exploratory design, the results are not generalizable. To the best of our knowledge the result that high AGE value were associated with a better survival of older cancer patients have so far not been puplished elsewhere.

Reference:
1. Schmidt et al. 2017.

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How to Deal with Senescent Patients in the Field of Visceral Surgery?

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Purpose: Senescence is considered a risk factor for surgery. Due to a lack of scientific evidence, therapeutic decisions are often based on the clinical experience of the individual surgeon. The Center of Geronto-Surgery Thuringia was founded to improve the outcome after surgery for this growing group of patients at risk. To better characterize the age-dependent risk profile, we performed a retrospective analysis of the in-hospital results after visceral surgery performed in the last 5 years (y).
Methods: Using the clinic patient information system data from patients being treated in our department were extracted. Out of this cohort two groups were formed containing either patients below the age of 35y or older than 65y of age. Using an Access database all clinically relevant parameters (e.g. age, sex, comorbidities, duration of hospital stay, complication rate…) were assembled. Statistical analyses were performed using R.
Results: The total number of patient older than 65y as well as in relation to the cohort of patients below 35y was rising significantly in the study period. Geriatric surgery patients more often suffering from postoperative complications such as cardiovascular, pulmonary or neurological complications. Even the morbidity rate was significantly higher in the older patient cohort, no difference was detected in the mortality rate (30days post-operative). The length of hospital stay was significantly longer in the geriatric patients.
Conclusions: Facing the problem of an ageing population yet no solutions are available for this complex patient cohort especially in surgery manners. Keeping in mind the elevated postoperative morbidity avoiding a higher postoperative mortality is one of the challenging problems in the field of geriatric surgery. In our mind it is ethically not feasible to refuse an operation in elderly patients in principle. On the other hand; these elderly patients are in need for an individual pre-; peri- and postoperative course. The formation of geriatric surgery units is one promising way to treat these patients optimized.

Gynecological Cancer

Best-of-Abstracts-Vorträge

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Carboplatin/Pegylated Liposomal Doxorubicin/Bevacizumab (CD-Bev) vs. Carboplatin/Gemcitabine/Bevacizumab (CG-BEV) in Patients with Recurrent Ovarian Cancer: a Prospective Randomized Phase iii Engot/GCiG-Intergroup Study (Ago Study Group, Ago-AUSTRiA, ANZGOG,GiNECO, SGCTG)

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Purpose: In patients with recurrent ovarian cancer (ROC) suitable for platinum based retreatment (PBT) standard therapy comprises CG-BEV and Carboplatin(C)/pegylated liposomal-Doxorubicin (D). CG-BEV significantly increases progression-free-survival (PFS) over CG alone whilst CD has one of the best therapeutic indices for ROC-PBT. The aim of this trial was to evaluate whether CD is superior to CG when given in combination with BEV with investigator-determined PFS as primary objective.
Methods: Between 2013 and 2015 682 pts. with ROC-PBT were randomized to CG-BEV (n=337) or CD-BEV (n=345). Secondary objectives were overall survival (OS), biological progression-free survival (PFSBIO) by serum CA125, quality of life (QoL) assessed by EORTC-QLQ-C30 and QLQ-OV28, safety and tolerability.
Results: Mean age was 61.1 (SD 10.3) years, 87.4% had serous histology, 83.1% were high grade, 41.5% were pretreated with BEV as part of first-line treatment. CG-BEV was associated with 359 (53.3%) serious adverse events vs. 314 (46.7%) for CD-BEV (p=0.083). Median PFS in the standard arm CG-BEV was 11.7 months (95% CI 11.1-12.8) vs. 13.3months (95% CI 11.7-14.3) in the arm CD-BEV (HR 0.80; 95% CI 0.68-0.96, p=0.0128). Median OS in the standard arm CG-BEV was 27.9 months (95% CI 25.6-30.3) vs. 32.0 months (95% CI 26.6-34.9) for CD-BEV (HR 0.810; 95% CI 0.668-0.983, p=0.0319).
In the stratum with previous anti-angiogenic treatment (n=309) median PFS was 10.1 months (95% CI 8.5-11.2) for CG-BEV vs. 11.3 months (95% CI 10.1-13.8) for CD-BEV (HR 0.73; 95% CI 0.57-0.94, p=0.0126).
Conclusions: CD-BEV provided a significant PFS improvement compared to CG-BEV in patients with ROC suitable for PBT and resulted also in superior OS compared to CG-BEV. CD-BEV was associated with fewer serious adverse events. The global Quality of life status was not worsened by CD-BEV. Thus CD-BEV is a new standard of care for patients with ROC PBT.

Disclosure Statement: There are no disclosures.

Vorträge

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Prevalence of BRCA1 and BRCA2 Mutations in Patients with Primary Epithelial Ovarian Cancer Based on Family History of Breast and Ovarian Cancers using The German Checklist – a Single Center Experience

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Purpose: *BRCA1/2* are the major susceptibility genes involved in hereditary epithelial ovarian cancer (EOC). Genetic testing for EOC pts in Germany was recommended if validated family history (FH) based criteria were fulfilled that confer a probability of a pathogenic *BRCA1/2* mutation >10%. The German checklist (CL) is a scoring tool developed and further validated by the consortium based FH criteria including type of cancer and ages at diagnosis of a detailed 3-generation FH. In the past, pts with EOC lacking a FH (singular EOC) were not classified at risk according to the checklist. Since results of the AGO TR1-study revealed mutation prevalences of >10% also in singular EOC patients irrespective of the familial predisposition, testing is now recommended in all pts with EOC by the German S3 guideline. Our aim was to evaluate the prevalence of *BRCA1/2*-mutation(s) by CL score.
Methods: Between 01/11-05/19 1206 primary EOC pts were treated at Kliniken Essen-Mitte. A total of 537 patients were tested for *BRCA1/2* only (cohort A), in 445 cases multigene testing (TruRisk® panel) including non-BRCA genes was performed (cohort B). For each pts, the CL score was evaluated based on personal and familial BC/OC history.
Results: In cohort A, 23.6% (127/537) of pts had a *BRCA1* (n=92) or *BRCA2* (n=35) mutation. In cohort B, 6.2% (22/356) of the patients without *BRCA1/2*-mutation had other mutation (*RAD51C* (6), BRIP1 (4), *PALB2* (3), *MSH6* (2), *RAD51D* (2), others (5). In 40.6% (218/537) of the pts the CL score was 2 (singular EOC). The prevalence for *BRCA1/2* mutation in cohort A was 11.0%, 17.4%, 25.5%, 35.1%, 51.4%, and 66.7% for pts with CL score 2, 3, 4, 5, 6, and ≥7, respectively. The prevalence for total mutations in the panel testing cohort B was 15.3%, 16.7%, 28.6%, 39.1%, 44.8%, and 62.5% for pts with CL score 2, 3, 4, 5, 6, and ≥7, respectively.
Conclusions: The *BRCA1/2* mutation prevalence in EOC pts positively correlated with increasing CL scores. However, the prevalence of mutation was >10% even in singular EOC cases confirming the necessity for offering genetic panel testing independent of FH to all pts with EOC.

Poster

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Olaparib Routine Clinical Practice in Germany – Interim Results of The Non-Interventional C-Patrol Study with a Focus on Patients who Switched from The Olaparib Capsule to the Tablet Formulation

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Purpose: Olaparib (50 mg hard capsules, HC) was the 1st PARP inhibitor approved in the EU in 12/2014 as monotherapy for maintenance treatment of adult patients (pts) with platinum-sensitive relapsed BRCA-mutated ovarian cancer (PSR-OC) who are in response to platinum-based chemotherapy. In addition, film-coated tablets (FT, 100/150 mg) were approved in the EU in 05/2018 regardless of BRCA status. Here, we report real-world olaparib treatment data from pts who switched from olaparib HC to FT.
Methods: The German prospective, non-interventional study C-PATROL collects real-world clinical and patient-reported data of pts treated with olaparib according to label. Data of 255 pts were analyzed in this interim analysis (data cut-off: 01 April 2019) using descriptive statistics.
Results: The most commonly used olaparib HC starting dose was 800 mg (in 85% of pts with HC (n=177), and in 77% of pts who started on HC and switched to FT (n=47)). Most pts who started olaparib FT maintenance therapy (n=28) received an initial daily dose of 600 mg olaparib (89%). At the switch from the capsule to the tablet formulation, most pts started with a FT daily dose of 600 mg olaparib (68%). In the 3 subgroups (HC, switcher, FT), the median treatment duration was 9, 17.4 and 2.9 months, respectively. Adverse events (AEs) ≥ grade 3 occurred in 38% (HC), 32% (switcher) and 18% (FT) of patients; and AEs leading to discontinuation of olaparib therapy in 11% (HC), 0% (switcher) and 7% (FT).
Conclusions: This interim analysis provides first RWE data for the switch from olaparib capsule to tablet formulation. The data indicate that switching was well tolerated by pts under routine conditions. The observed toxicity profile is in line with data from clinical trials and prior interim analyses of this study with olaparib as maintenance therapy in PSR-OC and primary advanced OC.

Disclosure Statement: Study funded by AstraZeneca

Frederik Marmé: honoraria received for speaker, consultancy or advisory role, travel, from AstraZeneca, Tesaro, Roche, Novartis, Pfizer, PharmaMar, GenomicHealth, CureVac, Amgen, Eisai, MSD,Celgene, Clovis
Felix Hilpert: Honoraria: Astra Zeneca, Clovis, Roche, Tesaro, MSD, PharmaMar, Pfizer, Novartis
Advisory Board: AstraZeneca, Roche, Tesaro, Clovis, MSD, PharmaMar
Manfred Welslau: No conflict of interest
Andreas Hartkopf: Andreas Hartkopf has received honoraria (speakers bureau and consulting fees) from AstraZeneca, Eisai, GenomicHealth, Lilly, MSD, Novartis, Pfizer, Roche, Tesaro, Teva.
Ahmed El-Balat: Ahmed El-Balat: membership on advisory councils, speaker's activities for AstraZeneca, Roche, PharmaMar, Olympus
Regina Glowik: Angestellte der Firma AstraZeneca
Jalid Sehouli: J. Sehouli: Advisory and expert activities for PharmaMar, Clovis, Tesaro, Roche, Roche Diagnostics, Astra Zeneca,Merck, Bayer,Eisei, Johnson and Johnson, MSD, Novocure, Amgen, Lilly; Receipt of professional fees from PharmaMar, Clovis, Tesaro, Roche,Astra Zeneca, receipt of research grant support (institution) from PharmaMar, Clovis, Tesaro, Roche, Astra Zeneca, Medimmune, Bristol Myers, Lilly.

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G Protein-Coupled Estrogen Receptor (GPER-1) and Agonist G-1 Inhibit Growth of Ovarian Cancer Cells by Activation of Anti-Tumoral Transcriptome Responses

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Purpose: Previous studies addressing the role of G-protein coupled estrogen receptor (GPER-1) in ovarian cancer yielded contradictory results. On the one hand, GPER-1 was suggested to act as tumor suppressor; on the other hand, this receptor was reported to mediate oncogenic effects on ovarian cancer cells in vitro and to predict poor survival of ovarian cancer patients. The present in vitro study intended to further elucidate the role of this receptor in ovarian cancer cells comparing the effects of a GPER-1 knockdown and treatment with its agonist G-1 on cell growth, apoptosis and the transcriptome of two ovarian cancer cell lines.
Methods: GPER-1 expression in OVCAR-3 and OAW-42 ovarian cancer cells was knocked down by RNAi. The effects on cell growth were measured by means of the fluorimetric Cell Titer Blue assay and on the transcriptome by Affymetrix GeneChip analysis.
Results: Knockdown of GPER-1 and treatment with its agonist G-1 exerted converse effects on growth and the transcriptome of ovarian cancer cells. GPER-1 knockdown resulted in a significant growth stimulation of both cell lines, with a maximum increase by 37% (OVCAR-3) or 28% (OAW-42), (both $p<0.01$). In contrast, treatment with GPER-1 agonist G-1 decreased growth of both cell lines in a dose-dependent manner, with a maximum inhibitory effect of 1 µM of this drug of about 80% 6 days after treatment. To address the question of off-target actions of this high G-1 concentration, we found both GPER-1-dependent and -independent effects on the transcriptome. Generally, treatment with this drug led to a transcriptome response associated with growth inhibition. In contrast, knockdown of GPER-1 exerted opposite effects, stimulating pathways activating mitosis, transcription and translation, but inhibiting pathways associated with apoptosis or interferon signaling.
Conclusions: Our data suggest that GPER-1 is able to inhibit growth of ovarian cancer cells and support the hypothesis that this gene acts as a tumor suppressor. Further studies are required to examine the significance of our data in the in vivo situation.

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Revised FIGO Classification for Cervical Carcinoma 2019 - What´s New and What are the Problematis Issues?

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Purpose: Numerous therapeutic and prognostic studies of cervical carcinoma have made a revision of the FIGO classification necessary.
Methods: Evaluation of the new FIGO classification and comparison with previous classification dated back on 2009 und with the current TNM classification from 2017.
Results: For microinvasive carcinomas, the horizontal dimension is no longer considered, and diagnosis and staging will solely be made by the depth of cervical stromal invasion. Lymphovascular invasion beyond the

deepest point of stromal infiltration by tumor cells does not alter the stage. There will be a new subclassification of macroinvasive carcinoma confined to the uterine cervix which will be made by largest tumor extension as followed: FIGO IB1/T1b1: invasive carcinoma ≥0.5cm depth of stromal invasion and <2cm in largest dimension, FIGO IBII/T1b2: invasive carcinoma ≥2cm and <4cm, FIGO IBII/T1b3: invasive carcinoma ≥4cm. Pelvic as well as para-aortic lymph nodes will be defined as regional nodes. Pelvic lymph node metastases only will be categorised as FIGO IIIC1/pN1a and para-aortic lymph node involvement with or without concomitant pelvic involvement will be FIGO IIIC2/pN1b. Uterine corpus as well as adnexal involvement are disregarded for staging purpose as they does not alter itself either the prognosis or the management at time.
Conclusions: the new definition of microinvasive carcinoma may result in stage migration which impact treatment decisions. The same issue will occur for the definition of regional lymph nodes. An open question is still the classification of ovarian involvement.

Disclosure Statement: There are no disclosures.

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Mesonephric-Like Endometrial Carcinoma May Represent an Aggressive Tumor with Characteristic KRAS-Mutation

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Purpose: Very rarely mesonephric-like features are seen in ACs of the endometrium and account for about 1% of all endometrial AC. Here we report three cases with clinical, histopathological and molecular analyses.
Methods: Case description with immunohistochemical and molecular analyses. Review of the literature of mesonephric-like AC of the endometrium for porgnosis.
Results: The mean age of the patients was 60.0 years (range range 31 to 91 years). Vaginal bleeding is the leading symptom. More than 50% showed local advanced disease, i.e. ≥FIGO stage II, one third lymph node involvement. About 10% of the patients died of the disease and 40.0% were alive with evidence of the disease. Most common site of distant recurrent disease was pulmonary. Positive immunostaining of at least two of the mesonephric markers, like CD 10, GATA-3 and TTF with negative results for ER and PR allows the correct diagnosis in line with mixed growth patterns on H&E. Almost all cases represented KRAS-mutation at codon 12.
Conclusions: Uterine ML-AC are likely of Müllerian origin but represent mesonephric features at the histopathologic, immunophenotypic and molecular level. The immunohistochemical panel of GATA-3, TTF-1, CD 10 (luminal staining), calretinin, p53 and p16 in addition to KRAS-mutation allows the correct diagnosis of ML-AC in the majority of cases. ML-AC may represent an aggressive subtype of endometrial cancer with pulmonary involvement.

Disclosure Statement: There are no disclosures.

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The Use of miRNA in the Early Detection of Cervical Intraepithelial Neoplasia

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Purpose: Today, one of the biggest challenges in cancer therapy and prevention is the latter, which includes the difficulty to predict progression of early lesions or pre-stages to invasive disease. In this context, the characterization and categorization of pre-neoplastic lesions of squamous cell carcinoma called cervical intraepithelial neoplasia (CIN) is an important task.
Methods: Using small molecular markers extracted from cervical mucus saves the patient the discomfort of a colposcopy with biopsies. We utilized miRNAs extracted from cervical mucus samples from healthy patients and patients with CIN 3 lesions.
Results: We can show that miRNA analysis from cervical mucus of 49 patients allowed us to distinguish between healthy patients and patients with a CIN 3 lesion. The miRNA panel used in combination allowed for highly significant testing (p<0,0001) of CIN 3 status. In parallel, HPV status of the patients, which is an important criteria for screening as well as treatment strategies in the therapy of cervical cancer, significantly correlated with the miRNA markers hsa-miR-26b-5p, hsa-miR-191-5p and hsa-miR-143-3p, a subpanel of the original six miRNAs.
Conclusions: We provide here the first proof-of-concept for a cervical mucus-based testing for pre-neoplastic stages of cervical squamous cell carcinoma.

Disclosure Statement: no conflict of interest

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Histotype-Specific Analysis of Acid Ceramidase Expression in Ovarian Cancer

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Purpose: Acid ceramidase (ASAH1) is a key player in sphingolipid metabolism and signalling. It has prognostic value for several cancers, but histotype-specific analyses of ovarian cancer are not yet available.
Methods: We used three retrospective TMA cohorts encompassing a total of 1106 ovarian cancers with follow up data for immunohistochemical analysis of acid ceramidase (ASAH1) expression. Patients with sub-optimal debulking and persistent residual tumor after surgery introduced bias in the prognostic analysis and were excluded from further studies.
Results: Overall, we detected an association of ASAH1 expression with improved prognosis in ovarian cancer patients. ASAH1 expression differed between histological ovarian cancer histotypes with most frequent expression in endometrioid and clear cell ovarian cancer, which are both associated with good prognosis. Stratified subgroup analyses within these histotypes did not reveal significant survival differences, but the power of the analysis may be limited by smaller sample sizes. In contrast to breast cancer, we found only a modest concordance between estrogen receptor status and ASAH1 expression within the endometrioid ovarian cancer histotype. In an exploratory analysis of estrogen receptor negative endometrioid ovarian cancer, ASAH1 expression was associated with significantly improved overall survival (P=0.007).
Conclusions: Acid ceramidase is most frequently expressed in endometrioid and clear cell histo-types and could add independent prognostic value to estrogen receptor in endometrioid ovarian cancer. Modulating sphingolipid metabolism may lead to novel therapeutic intervention strategies for this disease.

Disclosure Statement: Nothing to disclose.

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Claudin1 Expression in Border Line Epithelial Tumors of the Ovary

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Purpose: To evaluate the integral transmembrane protein Claudin 1 as marker for borderline ovarian tumors (BOTs).
Methods: We analyzed a retrospective cohort of 114 BOTs with validated diagnosis by an independent pathologist. Immunohistochemical detection of Claudin 1 was quantified as combined immunoreactive score blinded to clinical patient data. Analyses were performed for Claudin 1 positive versus negative.
Results: We detected Claudin 1 positivity in 26.3% of patients. There was no significant correlation between the different histological subtypes and Claudin 1 expression. The expression of Claudin1 was less frequent in patients with FIGO Stage I (p<0.045). Claudin1 expression was more

frequent in cases with micropapillary pattern (p=0.047) and was highly associated with the presence of implants (p=0.003).
Conclusions: Our analysis links Claudin 1 with micropapillary pattern. Positive expression is associated with the presence of implants, which is related to elevated risk of recurrence. Accordingly, Claudin 1 is an interesting marker and worth further analyses of its prognostic value in BOTs.

Disclosure Statement: Nothing to disclose.

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Influence of Lymph Node Status and Treatment Strategy on Overall Survival in Advanced Cervical Cancer

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Purpose: The lack of prognosis data hinders the implementation of an optimal therapy for cervical cancer. Because surgery is associated with higher morbidity, we examined the overall and relapse-free survival after various treatments in patients with cervical carcinoma in the FIGO stages IIB, IIIA, IIIB and IVA with or without affected lymph nodes using data from a clinical cancer registry in a retrospective cohort study.
Methods: Between 2002 and 2015, the Register of the Tumor Center Regensburg documented 389 patients with cervical carcinoma in the FIGO stages IIB, IIIA, IIIB and IVA. The results of the Kaplan-Meier analyzes were given in 5-year survival and recurrence probabilities as well as the median survival time. We estimated the hazard ratios for overall survival after various therapies with univariable and multivariable Cox regression for risk adjustment.
Results: We have demonstrated the need for a thorough assessment of lymph node status in order to obtain reliable data for the treatment strategy. Our analysis showed significant differences in overall survival in FIGO IIB as a function of therapy and nodal status. Overall survival was lower with radiochemotherapy without surgery for patients with N0 compared to a combination of surgery and chemoradiotherapy (HR = 3.012, 95% CI 1.075 - 8.441, p = 0.036). However, in patients with affected lymph nodes (N1), chemoradiation without surgery resulted in a comparable result (HR = 0.808, 95% CI 0.188 - 3.403, p = 0.765), while surgery alone resulted in a poor outcome (HR = 2.889, 95% CI 1,356 - 6,156, p = 0.006). Regardless of nodal status, advanced cervical cancer chemotherapy (FIGO III) was superior to surgery.
Conclusions: Our study indicates that FIGO IIB patients with cervical cancer benefit from a combination of surgery and chemoradiotherapy for long-term oncologic outcome. In the case of a lymph node involvement, however, surgery did not result in improvement of overall survival. In patients with stage FIGO III disease chemotherapy shows the best results.

Disclosure Statement: The authors declare no conflict of interest.

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Is there an Advantage of Lymphadenectomy for Overall and Recurrence-Free Survival in Endometrial Carcinoma Type I FiGO IB G1-2? A Retrospective Population-Based Cohort Analysis

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Purpose: The recommended therapy for patients with type I FIGO IB endometrial carcinoma is hysterectomy and adnexectomy. However, the therapeutic benefits of additional pelvic and para-aortic lymph node dissection (LND) are still under discussion. In this study, we retrospectively studied overall survival (OAS) and relapse-free survival (RFS) in patients with endometrial carcinoma type I FIGO IB who have undergone a systematic or elective lymphadenectomy compared to patients without LND.
Methods: We included 299 patients from the registry database of the Regensburg Tumor Center, who were diagnosed with endometrial adenocarcinoma of type I FIGO IB between 1998 and 2015. A multivariable Cox regression was applied to the selected patient data and the hazard ratios for OAS and RFS for the interventions performed were estimated. Furthermore, we have made risk adjustments with respect to clinicopathological parameters.
Results: We observed significant benefits of LND in univariable survival without risk adjustment. However, we have not seen this effect confirmed in the multivariable regression analysis after risk adjustment. In this case, the hazard ratio (HR) for OAS in patients without LND decreased to 1.214 (95% CI 0.771-1.911, p = 0.402) compared to patients with LND, the HR for RFS to 1.059 (95% CI 0.689). 1.626, p = 0.795). Similarly, a benefit of systematic versus elective LND after risk adjustment could not be confirmed.
Conclusions: Contrary to previous observations in patients with high-grade endometrial carcinoma, our study provides evidence that LND, and in particular systematic lymphadenectomy, is not beneficial in patients with type I FIGO IB endometrial carcinoma in terms of overall and recurrence-free survival.

Disclosure Statement: The authors declare no conflict of interest.

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Prognostic Factors and Outcomes of Cervical Cancer Patients (2007-2016): a Population-Based Analysis

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Purpose: Cervical cancer incidence is decreasing both globally and in Germany. The objective of this study was to analyse prognostic factors and outcomes of invasive cervical cancer in a population-based setting.
Methods: 2,291 cervical cancer patients diagnosed between 2007 and 2016 within the catchment area of the Munich Cancer Registry (MCR) were analysed regarding prognostic factors and outcomes. Cumulative incidence was used to calculate time to locoregional recurrence and distant

metastases. Survival was assessed using the Kaplan–Meier method, relative survival (RS) analysis, and a Cox proportional hazards model.
Results: The majority (48.7%) of the comparatively young (median age: 52 years) cervical cancer patients was diagnosed at an early tumor stage (IA1,IA2,IB1), while 14.3 % presented with metastatic disease at the time of diagnosis. The proportion of patients with positive lymph nodes increased with stage, with no lymph node involvement in stage IA1, and up to 42.8 % in stage IIB. The analysis of time to locoregional recurrence and metastasis showed a respective 5-year cumulative incidence rate of 10.1 % and 13.4 %. There was only a slight improvement in overall (5-year: 68.1 %) and relative (5-year: 71.5 %) survival rates over time. Stratified by stage the 5-year overall survival ranges from 98.9 % in stage IA1, to 61,6 % in IIB, and 16,6 % in patients with metastases (M1). A cox model revealed, as expected, a statistically significant association of age (p<0.001), stage (p<0.001), grade (p<0.01), lymph vessel invasion (p<0.01), and histology (p<0.01) with survival.
Conclusions: The prognosis in cervical cancer is comparatively good, caused by the high percentage of patients diagnosed at an early stage. Unfortunately there is only a slight improvement in prognosis over time.

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Trends in Prognostic Factors and Outcomes of Ovarian Cancer Patients Over a 20-Year Period (1997-2016)

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Purpose: Significant effort has been made to improve the poor prognosis of invasive ovarian cancer patients. The objective of this study was to analyse prognostic factors and invasive ovarian cancer patient outcome over time in a population-based setting.
Methods: 6,984 ovarian cancer patients diagnosed between 1997 and 2016 within the catchment area of the Munich Cancer Registry (MCR) were analysed. Patients diagnosed 1997-2006 and 2007-2016 were compared. Cumulative incidence (CI) was used to calculate time to progression. Survival was analysed using the Kaplan–Meier method (Overall survival, OS), calculation of relative survival (RS), and a Cox proportional hazards model (OS).
Results: The incidence rate of invasive ovarian carcinoma decreased over time from 23.8 (1997) to 16.5 (2016) / 100,000. The majority of the patients continued to be diagnosed at an advanced stage of FIGO III or IV. Furthermore, there was a slight increase (p=0.04) in the proportion of patients diagnosed with FIGO III (45.4 vs 47.9%) and FIGO IV (23.1 vs 24.1%). While the proportion of patients that underwent surgery did not change significantly over time (87.0 vs 88.0%, p=0.25), an increase in patients without residual disease was observed (50.2 vs 58.5%, p<0.001). In patients with surgery, there was a slight improvement in time to progression (5-year CI: 43.2 vs 41.0%, p=0.11), as well as in overall (5-year OS: 41.2 vs 44.8%, p=0.04)) and relative (5-year RS: 44.6 vs 48.4%) survival rates. The cox model revealed a significant association of survival with age (≥80 vs <50 HR 3.78, p<0.001), stage (FIGO IV vs I HR 5.54 p<0.001), residual disease (>1cm vs no residuals HR 2.09, p<0.001), and chemotherapy (no chemo vs chemo HR 1.44, p<0.001).
Conclusions: Ovarian cancer remains a very challenging disease that needs to be treated with highest standards. Patients undergoing successful treatment, especially with regard to surgery, showed an improvement in survival over time. This may primarily be due to the significant increase in the proportion of patients that underwent surgery without residual disease.

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Combined Assessment of 3Q26 Amplification and Promoter Methylation in Patients with High Grade Cervical Lesions Show Age Specific Differences

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Purpose: A considerable proportion of high grade cervical intraepithelial lesions (CIN2/3) are known to resolve on their own especially among young women. However, since reliable prognostic markers are still lacking, the diagnosis "CIN3" is still an indication for surgery which may result in overtreatment. It is conceivable that a combination of different, ideally independent molecular markers may provide more reliable results. In the present cross-sectional study two established triage markers, 3q26 amplification and a methylation signature, were evaluated in an age-dependent manner.
Methods: The patient cohort comprised 60 patients with histologically confirmed CIN2/3 in two equally sized age groups (<30 years, ≥30 years). Cervical scrapes were analyzed by interphase fluorescence in situ hybridization for 3q26 amplification and methylation specific PCR (GynTect®) for six different genome regions.
Results: Both assays showed a significantly different pattern of test outcome independent of age (P=0.001). Moreover, the combination of both assays differed significantly for double positive and double negative cases when comparing the two age groups: In patients <30 years there were clearly less cases with positive methylation signature and amplification of 3q26 as in women ≥30 years (23% versus 63%, Bonferroni adjusted P=0.016). Of particular interest is the finding that double negative results were exclusive for the young age group (0% versus 27%, Bonferroni adjusted P=0.020).
Conclusions: Since regression of CIN2/3 characteristically occurs among young women it is tempting to speculate that a double negative test result could be prognostic for regression of CIN2/3. This will have to be investigated further in a prospective longitudinal intervention study.

Disclosure Statement: no conflicts of interest to disclose

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A Real-World Experience of Multiple Lines of Bevacizumab-BASED Therapy in Patients with Pretreated Recurrent Tuboovarian Carcinoma

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Purpose: This retrospective study sought to yield more concise data on multiple lines of Bevacizumab (Bev)-based therapy (Tx) in patients (pts) with recurrent tuboovarian carcinoma (TOC).
Methods: 90 pts with recurrent TOC were included. 37 (41.1%) pts had one, 20 (22.2%) had two, 13 (14.4%) had three and 20 had (22.2%) 4-9 lines of Bev. A total of 225 courses of Bev-based treatment were administered: 58 (25.8%) as monotherapy (Bev), 63 (28.0%) in combination with conventionally dosed Ctx (Bev+cCtx), and 104 (46.2%) in combination with metronomic Ctx (Bev+mCtx). Time to progression (TTP) was calculated from the start of each Bev-based Tx until progression, overall survival was calculated from the start of the first Bev-based Tx until death from any reason or loss to follow-up. Adverse effects in regard to Bev Tx were scored according to CTCAE vs 4.02.
Results: Bev-related G3-4 toxicities comprised hypertension in 2.2%, bowel obstruction in 0.9%, small bowel perforation in 0.9%, nephrotic syndrome in 0.4% and infection seen in 1.3% of treatments. Both TTP and OS were not significantly different between different types of Tx. TTP: Bev, 5.4 months (ms); Bv+cCtx, 6.1 ms; Bev+mCtx, 6.3 ms. OS: Bev, 28.6 ms, Bev+cCtx, 31 ms; B+mCtx, 21.4 ms. TTP was comparable between one and multiple lines of Bev: one line, 6.6 ms; two lines, 6.3 ms, three lines 5.9 ms, and ≥4 lines 3.7 ms (p=0.130). However, OS increased significantly with the number of Bev-based lines of Tx: one line, 8.8 ms; two lines, 16.8 ms; three lines 25.4 ms; ≥4 lines, 36.6 ms (p=0.0001).
Conclusions: Retreatment with Bev is safe and effective in a real-world population of pts with recurrent TOC. The number of Bev-based lines had a significant impact on overall survival.

Disclosure Statement: All authors declare no conflicts of interest

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Tissue Factor Expression of Extracellular Vesicles from Ascites of Ovarian Cancer Patients Correlates with Venous Thrombembolic Events (VTE)

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Purpose: As malignant effusions (e.g. ascites) contain cells, cellular components, growth factors, and cytokines, they mirror the microenvironment of tumors. Often, patients with ovarian carcinoma suffer from both deregulated immune mechanisms and systemic hyper coagulation. As a molecular link, tissue factor-bearing small Extracellular Vesicles (EVs) may play a decisive role in the systemic coagulation *via* activation of the extrinsic tenase as well as in tumor cell activation *via* the PAR2/G-protein/ERK-pathway[1].
Methods: Here, we obtained ascites from ovarian carcinoma patients from the Clinic for Gynecology of the University Medical Center Schleswig-Holstein collected during surgery or paracentesis. EV subgroups (exosomes, ectosomes) were isolated and separated using sequential centrifugation as described elsewhere[2]. Using annexin-V coated magnetic beads, phosphatidylserine$^+$ EVs were specifically enriched[3]. EV subpopulations were then characterized using high-resolution flow cytometry as well as electron microscopy and analyzed regarding their procoagulant properties (PS, TF activity). Results were correlated with clinically overt VTEs.
Results: Ascites from patients with ovarian cancer contained high amounts of EVs that exposed varying amounts of PS and TF on their surface. Interestingly, PS and TF were co-expressed. Isolation using annexin-V coated magnetic beads resulted in a significant enrichment of TF$^+$EVs. Notably, TF expression on EVs significantly correlated with clinically reported VTEs[4].
Conclusions: This small study indicates the clinical value of EV diagnostic in human body liquids. However, standardized methods for the isolation of EV subpopulations (exosomes, ectosomes), as well as for quantification and characterization have to be used in order to get reliable and comparable results.

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Disclosure Statement: The Authors declare no conflict of interest.

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Analysis of Methylation Marker for Circulating Tumor DNA of Epithelial Ovarian Cancer (EOC) – The Assurer Project

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Purpose: The lack of early detection assays and the occurrence of unspecific symptoms are causative for the late diagnosis of EOC. Aberrant DNA methylation of cell-free DNA (cfDNA) may be a potential biomarker for EOC.
Methods: Genome wide methylation analyses of tissue-derived gDNA and cfDNA from blood were used to identify candidate regions. Marker validation was realized with two sample sets by methylation specific PCR (MSP) using bisulfite-treated cfDNA (set 1: benigne controls n=67 and EOC n=68 (FIGO III/IV); set 2: EOC n=43 (FIGO I-IV) and age matched healthy women n=14).
Results: Analyses of tissues (EOC n=33, normal ovaries n=3, white blood cells n=4) lead to the identification of potential candidates for cfDNA analysis. The comparison with published data resulted in the selection of 50 candidate regions for validation. Three top candidates reached a sensitivity and specificity of 27-57% and 91-100%, respectively. The best two-marker combination exhibited 63.2% sensitivity and 95.5% specificity. For one of these three markers a low methylation level in the tumor tissue can explain the absence of methylation in cfDNA. Intratumoral heterogeneity and the methylation state in early stage disease point to hypermethylation of one candidate as potentially late event in EOC development. To identify additional markers the genome wide analysis of cfDNA was established and is presently conducted.
Conclusions: The specific and sensitive detection of EOC-specific aberrant DNA methylation in cfDNA is possible. The direct analysis of cfDNA for marker identification should result in an improved diagnostic performance to enable the early detection with DNA-methylation-based biomarkers.

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Safety and Effectiveness of Bevacizumab (BEV)-ContainIng Therapy in Patients (PTS) with Primary Ovarian Cancer (OC): Interim Analyses of The Otilia German Non-Interventional Study

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Purpose: BEV combined with carboplatin plus paclitaxel (CP) is approved as front-line therapy for FIGO (1998) stage IIIB–IV OC. The ongoing single-arm non-interventional OTILIA study (NCT01697488) was initiated to assess the safety and effectiveness of front-line BEV-containing therapy in the real-world setting in Germany. Here we present results of the 2nd and 3rd interim analysis.
Methods: Pts with FIGO stage IIIB–IV OC received front-line BEV + CP. Adverse events were recorded at each cycle and graded using CTCAE v4.0. Investigators assessed response according to local practice. Patients were followed for 12 months after disease progression, discontinuation of BEV or completion of 15 months of BEV therapy. Exploratory analyses compared safety and efficacy according to age, Eastern Cooperative Oncology Group performance status (ECOG PS), and comorbidities.
Results: 808 pts were analyzed, of whom 704 had completed documentation. Estimated median BEV treatment duration was 13.4 months (95% CI 12.8–13.8). 433 (62%) had discontinued therapy prematurely. Median progression-free survival (PFS) was 21.3 months (95% CI 20.3–22.5) in the overall population. There was no apparent difference in PFS according to age, ECOG PS, or between comorbidity subgroups and the overall population. Comorbidities were more common in pts aged ≥70 (47%) than <70 years (53%). Tolerability was similar in subgroups aged ≥70 versus <70 years (all grades, 74% vs. 70%; grade 3/4, 35% vs. 32%; serious AE, 31% vs. 24%).
Conclusions: The interim analyses of this large observational trial indicate the favorable effectiveness and tolerability of BEV- maintenance therapy for pts with newly diagnosed OC treated in a real-world setting. Exploratory analyses of OTILIA showed no association of age with worse outcome with respect to (preliminary) efficacy or tolerability. PFS results of patients with comorbidities were in line with those of the overall population, despite older age and worse ECOG PS. This study underlines that BEV is a safe and effective treatment option independently of age and comorbidities.

Conflicts of Interest: J. Sehouli: Honoraria: AstraZeneca, Clovis Oncol, Eisai, Johnson & Johnson, MSD Oncology, Olympus Medical Systems, Pfizer, PharmaMar, Tesaro, Teva; Consulting or Advisory Role: AstraZeneca, Clovis Oncology, Lilly, Merck, MSD Oncology, Pfizer, PharmaMar, Tesaro; Research Funding: AstraZeneca (Inst), Bayer (Inst), Clovis Oncology (Inst), Merck (Inst), MSD Oncology (Inst), Pfizer (Inst), PharmaMar (Inst), Tesaro (Inst); Travel, Accommodations, Expenses: AstraZeneca, Clovis Oncology, MSD Oncology, PharmaMar, Roche Pharma AG, Tesaro.
A. Mustea: Consulting or Advisory Role: AstraZeneca. Roche
G. Oskay-Özcelik: Honoraria: Roche, Novartis, AstraZeneca, AMGEN, Riemser; MSD; Consulting or Advisory Role: Roche, Novartis, AstraZeneca, MSD
M. Keller: No Relationships to Disclose
R. Richter: No Relationships to Disclose
O. Tomé: No Relationships to Disclose
H. Woopen: Travel, Accommodations, Expenses: Medac
A.-K. Sommer: Employee of Roche
J.P. Grabowski: Honoraria: AstraZeneca, Clovis Oncology, Pfizer, RIEMSER, Roche, Tesaro. Consulting or Advisory Role: AstraZeneca, Clovis Oncology, Pfizer, RIEMSER, Roche, Tesaro; Research Funding: AstraZeneca (Inst), MSD (Inst), RIEMSER (Inst), Tesaro (Inst); Travel, Accommodations, Expenses: Molecular Health, Tesaro.
R. Armbrust: No Relationships to Disclose
P. Wimberger: Honoraria: Roche; AstraZeneca; Clovis Oncol; Eisai; Novartis; Amgen; MSD; Merck; Oncology; Pfizer; PharmaMar; Tesaro; Teva; Research Funding: Amgen; Novartis; RocheConsulting or Advisory Role: Roche; MSD; Tesaro; Novartis; Amgen; Clovis; Pfizer; AstraZeneca; Eisai

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Phase III PAOLA-1/ENGOT-OV25 Trial: Olaparib Plus Bevacizumab (BEV) As Maintenance Therapy in Patients (PTS) with Newly Diagnosed, Advanced Ovarian Cancer (OC) Treated with Platinum-Based Chemotherapy (PCH) Plus Bev

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PAOLA-1 Study
Purpose: PAOLA-1/ENGOT-ov25 (NCT02477644) is the first Phase III trial to evaluate the efficacy and safety of a PARP inhibitor with bev as first-line (1L) maintenance therapy for advanced OC, regardless of BRCA1/2 mutation (BRCAm) status. Please copy and paste the
Methods: PAOLA-1 is a randomized, double-blind, international Phase III trial. Eligible pts had newly diagnosed, FIGO stage III–IV, high-grade serous or endometrioid OC, fallopian tube or primary peritoneal cancer. Pts had received standard PCh plus bev and were in clinical complete or partial response. Pts were randomized (2:1) to Olaparib tablets (300 mg bid for up to 24 months [m]) plus bev (15 mg/kg, d1, q3w, for 15 m including when combined with PCh) or placebo (pbo) plus bev, stratified by 1L treatment outcome and tumour BRCAm status. The primary endpoint was investigator-assessed progression-free survival in the intent-to-treat population (PFS; modified RECIST v1.1).
Results: The primary endpoint in the intent-to-treat population showed a statistically significant and clinically meaningful improvement in progression-free survival (PFS). The safety and tolerability profiles observed in PAOLA-1 were generally consistent with those known for each medicine.
Conclusions: In patients with advanced primary ovarian cancer, maintenance Olaparib resulted in a statistically significant PFS improvement. This is the first time this was demonstrated regardless of BRCA mutation status.

Literature: not applicable

Disclosures: will be shown in the final presentation with updated information on disclosures of all 20 authors

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Laparoscopic Radical Hysterectomy in Cervical Cancer: Is Peritoneal Contamination with Tumor Cells an Underestimated Event?

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Purpose: Peritoneal dissemination of cervical cancer cells during intracorporal colpotomy might be responsible for reduced disease free survival after laparoscopic radical hysterectomy as shown in the LACC study. However, data on the frequency or mechanisms of peritoneal contamination are missing. Therefore, we aimed to analyze peritoneal contamination of cervical secretion during intracorporal colpotomy with a novel indocyaningreen (ICG) -based technique.
Methods: In this prospective study, we evaluated patients undergoing routine laparoscopic or robot-assisted hysterectomy for benign indications. Routine surgery was performed after application of ICG specifically to the cervical surface. During and after colpotomy pictures under white and fluorescence light were taken in order to evaluate frequency and extent of peritoneal contamination.
Results: Peritoneal contamination during intracorporal colpotomy occurred in 9/12 (75%) patients undergoing routine laparoscopic hysterectomy. Laparoscopic instruments were contaminated in 60% of all cases. Extent of contamination varied between individual patients with a median grade of 2.75 (range 1-4.5; 1 no contamination - 5 strong contamination) at posterior colpotomy. There were no adverse effects during surgery.
Conclusions: Peritoneal contamination with cervical secretion is a frequent event during intracorporal colpotomy. We describe a promising tool for feasible and direct visualization of peritoneal contamination during laparoscopic colpotomy. This may be easily implemented in further studies on laparoscopic radical hysterectomy and serve as a quality assessment tool for surgeons and surgical techniques.

Disclosure Statement: All authors declare no conflict of interest.

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Sentinel Lymph Node Dissection in Vulvar Cancer. A Survey About Knowledge, Status and Counseling in Outpatient Sector

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Purpose: Sentinel lymph node dissection is an alternative to radical lymph node dissection (LND) for early vulvar cancer. Patient selection and counseling is key for a safe use of SLND (1). Our aim was to evaluate how gynecologists in an outpatient setting think about SLND, counsel patients and select hospitals for further treatment.
Methods: A questionnaire containing 29 questions about SLND in vulvar cancer was sent to gynecologists in Lower Saxony via mail and letter. The questionnaire contained multiple choice questions and open questions. The study was approved by the local ethics committee.
Results: The median age of the 80 respondents was 54.5 (26-66) years. Most (86%) participants reported to only treat one to five patients with vulvar cancer per year. Interestingly, 70% and 64% of the gynecologists send their patients to university hospitals or hospitals offering maximum care, respectively. Of all, 33% replied that SLND was performed rarely or never in their patients. The gynecologists answered that only 40% of the patients are well informed about advantages and possible disadvantages of SLND. Most (95%) felt responsible to counsel patients on treatment decisions independently from or additionally to the hospital. Of all, 78% replied that they are not completely sure about the exact recurrence rates after SLND. Of notice, 68% believe that SLND for vulvar cancer is safe if applied in specialized centers and 92% stated that focusing patients on specialized centers is required for best results.
Conclusions: Gynecologists in the outpatient setting play a crucial role for counseling and admission of patients to the hospitals. A close communication between hospital and outpatient gynecologists appears to be essential to select optimal treatment strategies for individual patients.

Reference:

1. Diagnosis, Therapy, and Follow-Up Care of Vulvar Cancer and its Precursors. National Guideline of the German Society of Gynecology and Obstetrics (S2k-Level, AWMF Registry No. 015/059, August 2015).

Disclosure Statement: All authors have no conflicts of interest.

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Characterization of Tribbles 1 in Epithelial Ovarian Cancer

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Purpose: We have identified TRIB2 a member of the Tribbles protein family as mediator of cisplatin sensitivity in epithelial ovarian cancer (EOC; Ref.1). The aim of the presented project is the characterization of Tribbles 1 (TRIB1).
Methods: Gene expression analyses of clinical samples (EOC type II, FIGO III/IV, n=38) and cell lines were done by qRT-PCR. In-vitro analyses were conducted after stable overexpression of TRIB1 using retroviral transduction of A2780 (parental and resistant cultures) and OVCAR3 cells. Functional readouts consist of IC50 determination against cisplatin, proliferation and colony formation assays.
Results: TRIB1 RNA expression was significantly higher in parental cell lines or platin sensitive EOC patients compared to resistant sub-cultures and patients, respectively. Moreover, parental sensitive cell lines revealed a time and concentration dependent upregulation of TRIB1 under cisplatin treatment, whereas resistant cells exhibited a more stable TRIB1 expression. EOC patients stratified by the median TRIB1 expression resulted in groups with significantly different PFS and OS. Patients with TRIB1-high tumors had a longer survival than patients with TRIB1-low tumors ($p<0.05$, LogRank test). The successful overexpression of TRIB1 in parental and resistant A2780 cells (>10-fold increase of transcript level) did not result in changed IC50 values for cisplatin.
Conclusions: Although TRIB1 gene expression is potentially prognostic for EOC and is affected by cisplatin exposure similarly to the TRIB2 expression, its overexpression cannot reverse the resistant phenotype in A2780. Presently, both the validation in other EOC cell lines and the exploration of the molecular differences between TRIB1 and TRIB2 are conducted.

Reference:

1. Kritsch et al. Tribbles 2 mediates cisplatin sensitivity and DNA damage response in epithelial ovarian cancer. Int J Cancer. 2017 Oct 15;141(8):1600-1614

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Adapted Adjuvant TC Chemotherapy in Primary Tubal Cancer After Renal Transplantation and Chronic Hepatitis C Infection - A Case Report

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Purpose: Application of a platinum-based chemotherapy in patients with impaired renal function or taxanes in case of liver disorders is challenging. Strategies suggested applying platinum at a GFR <15ml/min include a dose reduction with subsequent dialysis (DIA). Considering taxanes, due to a possible hepatitis C reactivation a close monitoring with temporary discontinuation and subsequent dose reduction is suggested.
Methods: Presentation 74-year old patient with renal impairment following a renal transplantation and a chronic hepatitis C infection with the

clinical picture of an ovarian cancer. Following an exploratory laparotomy, a primary high-grade serous fallopian tube cancer was confirmed, FIGO IIIb, with the operative achievement of a macroscopic disease-free status (R0). The adjuvant chemotherapy with paclitaxel (TAX) and carboplatin (CAR) was adapted to the impaired renal function and hepatic status: TAX 140mg/m^2, followed after 48 hours by CAR 125mg/m^2 with a subsequent DIA after 20 hours (AUC 3-5 mg·min/ml) (d1[TAX], d3[-CAR], d4[DIA] / q3w).
Results: Hematotoxicity with anemia and thrombocytopenia, without signs of leukopenia appeared after 3 cycles resulting in a further dose reduction of TAX. Anemia was treated with regular blood transfusions during DIA. The treatment was discontinued after 5 cycles due to a severe thrombocytopenia. Relapse occurred after 10 months. 2nd line treatment was initiated with liposomal doxorubicin in monotherapy (d1/q4w), which was discontinued after 3 cycles due to a severe thrombocytopenia and disease progression, followed by best supportive care.
Conclusions: : In case of a combined renal and hepatic impairment we suggest during a combined TC treatment TAX in reduced dose and the time-delayed application of CAR along with a hemato-nephroprotective dialysis within 24 hours. According to the observed hematological toxicity of TC, apart from transfusion of red blood cells, the continuous application of thrombopoietin during the cytotoxic treatment should be considered.

Disclosure Statement: no conflict of interest

Head and Neck Cancer

Poster

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Nivolumab Adjuvant in Combination with Postoperative Radiotherapy and as Maintenance in Patients with Intermediate Risk Locally Advanced Head and Neck Cancer – The NadiHN Trial

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Purpose: Adjuvant radiotherapy is the standard of care in postoperative patients with locally advanced head and neck squamous cell carcinoma (HNSCC) and adequate R0 resection in the absence of extracapsular lymph node extension (ece). Immunotherapy with the check point inhibitor Nivolumab has significantly improved the outcome of relapsed/refractory HNSCC patients. Preclinical data suggest that the combination of photon radiation with PD-1 targeting immunotherapies may strengthen immune responses. This two-armed, randomized, open-label phase II trial evaluates the efficacy of combined adjuvant immunotherapy and radiation therapy.
Methods: 176 patients with locally advanced stage HNSCC (R0, ece-) will be included. 88 patients will be randomized to receive standard of care adjuvant 60 Gy IMRT (standard arm). 88 patients will additionally receive Nivolumab (experimental arm). Nivolumab will be given once prior to radiotherapy (RT), concurrently to RT and over 3 months every 2 weeks after RT. Then, Nivolumab will be additionally applied as maintenance therapy over the course of additional 9 months every 4 weeks. Therapy will be stopped in case of progression or unacceptable toxicity.
Results: The primary endpoint will be disease free survival. Secondary endpoints will be overall survival, safety and quality of life. An extensive exploratory translational research program attached to this trial will focus on mechanisms of the immune-stimulating effect of radiotherapy and the identification of potential biomarkers predicting response to Nivolumab. 40 patients have been recruited by July 2019. The detailed treatment protocol and accrual data will be presented.
Conclusions: The NadiHN trial will contribute prospective data to the level of efficacy of adjuvant immunotherapy with Nivolumab and safety data on the combination of photon radiation and immunotherapy with Nivolumab in the postoperative setting where single adjuvant radiation therapy would be the standard of care.

Disclosure Statement: EudraCT 2016-004787-20; Funding: Bristol-Myers Squibb GmbH & Co. KGaA.

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Oncogenic BTK Promotes Growth and Vascularization of Head and Neck Squamous Cell Carcinoma (HNSCC) in Vitro and in Vivo

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Purpose: Recently, two novel BTK (Bruton's Tyrosine Kinase) isoforms of 80 and 65 kDa have been described to be expressed in solid carcinoma entities and therein BTK expression seemed to be linked with tumor growth and protection from apoptosis resulting in a poor prognosis of these cancer patients. Until these observations, no BTK expression outside the hematopoietic system has been reported. Therefore, we aimed to investigate whether BTK isoforms are also expressed in HNSCC and to further elucidate the molecular and cellular consequences of BTK expression for HNSCC tumorigenesis.

Methods: HNSCC-derived cell lines as well as tumor samples were analyzed for BTK-p65 and –p80 expression. The consequences of pharmacological and genetic inhibition of BTK activity for proliferation, cell cycle progression, transmigration, apoptosis and vascularization were analyzed *in vitro* and *in vivo*. BTK-promoter methylation studies were performed.
Results: BTK-p65 and -p80 isoforms are expressed in HNSCC cell lines as well as in primary HNSCC samples. Pharmacological or genetic targeting of BTK activity leads to inhibition of cell proliferation, transmigration as well as VEGF secretion *in vitro*. These effects were associated with cell cycle arrest and induction of apoptosis. Moreover, in *in vivo* xenograft experiments, chemically abrogation of BTK activity impaired tumor growth and was associated with decreased tumor vascularization. BTK-promoter methylation studies revealed a regulation of oncogenic Btk expression by epigenetic alterations.
Conclusions: Together, our data characterize BTK-p65 as well as BTK-p80 as novel HNSCC-associated oncogenes representing crucial players in the maintenance of HNSCC. Thus, targeting BTK-activity appears to be a promising therapeutic option for patients suffering from BTK-expressing HNSCC.

Disclosure Statement: Nothing to disclose

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Hanna - Real-World Data from a Non-Interventional Study Assessing Routine Use of Nivolumab in Patients with Recurrent or Metastatic Cancer of the Head and Neck (R/M SCCHN) in Germany

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Purpose: Nivolumab (a fully human IgG4 monoclonal antibody targeting the PD-1 receptor on activated T-cells), is indicated in the EU for the treatment of patients with R/M SCCHN progressing on or after platinum-based therapy. Results from CheckMate 141 (NCT02105636), the pivotal trial evaluating nivolumab versus investigator's choice (methotrexate, docetaxel, or cetuximab), demonstrated that patients treated with nivolumab had significantly improved overall survival (OS), higher response rates, reduced adverse events, and maintained quality of life (QoL) measures. The objective of this study is to assess real-world nivolumab utilization, safety and outcomes in patients with R/M SCCHN.
Methods: HANNA is collecting real-world data on the routine treatment of 385 patients with R/M SCCHN in 56 clinics and practices in Germany. Patients will be followed for 5 years from treatment initiation with Nivolumab until death, withdrawal of consent, loss of follow-up/record or to end of study. Primary objective is OS. Secondary objectives include progression free survival, response rates, baseline characteristics, safety profiles and QoL.
Results: In this interim analysis, data of 300 patients with R/M SCCHN regarding baseline-characteristics, effectiveness of the Nivolumab treatment as well as safety and QoL under treatment will be presented. The data provides information on disease and treatment characteristics, prior treatment and ECOG performance status in an unselected patient population.
Conclusions: Real-World data from HANNA reflect use of Nivolumab in routine clinical practice including patients with higher age and ECOG >2. Recent results[1] have shown that patients have a similar improvement in outcomes, the treatment with Nivolumab was well tolerated and the QoL stabilized under therapy.

Reference:
1. Dietz et al. DGHNO 2019, Oral presentation #101

Disclosure Statement: Amgen, Astellas, AstraZeneca, Bms, Celgene, Gilead, Hexal, Janssen, Lilly, Medac, Novartis, Roche, Sanofi

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Adenosine Receptor 2B Activity Promotes Autonomous Growth, Migration As Well As Vascularization of Head and Neck Squamous Cell Carcinoma Cells

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Purpose: Adenosine is a signaling molecule that exerts dual effects on tumor growth: while it inhibits immune cell function, thereby preventing surveillance by the immune system, it also influences tumorigenesis directly via activation of adenosine receptors on tumors. However, the mechanisms affecting oncogenic processes particularly in head and neck squamous cell carcinomas (HNSCC) are not fully understood. The aim was to identify the effects of ADORA2B (adenosine receptor A2B) on HNSCC-derived cell lines.
Methods: First, the expression profile was analyzed by RT-PCR and Western-Blot. Second, the effects of ADORA modulation by receptor ligands on proliferation, migration, invasion and angiogenesis were investigated. Also, the activity of ADORA2B was analyzed. *In vitro* experiments involved MTT assays, scratch assays, transwell migration assays, VEGF-ELISA and cAMP-Assays; *in vivo* experiments involved tumor xenograft on chicken chorionallantoic membranes (CAM-Assay).
Results: Targeting ADORA2B with the inverse agonist/antagonist PSB-603 leads to inhibition of proliferation, transmigration and VEGFA secretion *in vitro*. At the molecular level, cell cycle arrest as well as the induction of the apoptotic pathway were found. In addition, shRNA-mediated down-modulation of ADORA2B expression caused decreased proliferation. Moreover, in *in vivo* xenograft experiments, chemical and genetic abrogation of ADORA2B activity impaired tumor growth associated with decreased tumor vascularization.
Conclusions: We found that ADORA2B is upregulated and constitutively active in HNSCC-derived cell lines. The receptor promotes cell growth, migration and angiogenesis *in vitro* and *in vivo*. Our data suggest ADORA2B being an important biomarker as well as an interesting therapeutic target for treatment of HNSCC.

Reference:
1. Mello P de A, Coutinho-Silva R, Savio LEB. Multifaceted effects of extracellular adenosine triphosphate and adenosine in the tumor-host interaction and therapeutic perspectives. *Front Immunol* 2017;8:1–17.

Disclosure Statement: Nothing to disclose.

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Effects of Exosomes on B Cell Populations in Head and Neck Squamous Cell Carcinoma (HNSCC)

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Purpose: The tumor microenvironment (TME) of HNSCCs is highly immunosuppressive. Tumor derived exosomes are key mediators of many pro-tumorigenic effects and exhibit strong immunosuppressive properties. So far, this has been established for T cells and other leukocyte populations, but the effects of exosomes on B cells remain to be elucidated. Here we show that exosomes purified from the plasma of HNSCC patients modify the phenotype of B cells.
Methods: : Exosomes were isolated from plasma of HNSCC patients by mini size exclusion chromatography. B cells were purified from peripheral blood of healthy donors by LeukoSep and CD19-negative selection and co-cultured with HNSCC exosomes. Using flow cytometry, the expression of checkpoint receptors was determined. Adenosine production was assessed by luciferase assay. The activity of the B cell receptor (BCR) pathway was inferred by measuring the expression of phosphorylated Bruton's tyrosine kinase (p-BTK).
Results: Co-cultivation with HNSCC exosomes inhibited cluster formation of stimulated B cells. This was accompanied by a decrease in the expression of the co-stimulatory checkpoint receptor GITR and CD39, an ATP-hydrolyzing ectoenzyme. In line with this, ATP hydrolysis and adenosine production by exosome-treated B cells were decreased. Furthermore, the expression of p-BTK was reduced.
Conclusions: These results demonstrate that exosomes derived from HNSCC patients have direct effects on B cells in vitro. We suspect a global inhibitory effect; since exosomes inhibited cluster formation; reduced the expression of a co-stimulatory receptor and decreased the activity of the BCR pathway.

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Feasibility and Results of a Definitive Radiotherapy (RT) or Chemoradiation (RCT) for Elderly Patients with Squamous Cell Carcinoma of The Head and Neck (SCCHN) – a Retrospective Monoinstitutional Survey

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Purpose: SCCHN belong to the frequent malignancies worldwide. In an aging society, also the incidence of SCCHN in elderly patients is rising. Worldwide definitive RT or RCT is widely used as first line therapy.
Nevertheless, elderly patients are underrepresented in clinical trials. The aim of this survey was to evaluate the feasibility of a definitive RT/RCT and the treatment results in a collective of elderly patients with SCCHN.
Methods: All patients older than 70 years, which received a definitive RT or RCT at the University Hospital Regensburg from 2004 to 2018 were included.
110 patients could be identified with a median age of 75 years. Most patients suffered from a SCCHN UICC stadium IVa. 46 patients received a concomitant chemoradiation, 64 patients were just irradiated. The median pretreatment Karnofsky Performance Status was 70 %.
The median follow up was 16 months (IQR 7 to 30 months).
Results: The feasibility of radiotherapy was good. Only for 18 patients radiotherapy had to be interrupted for more than one day. 46 % of the patients could receive at least 75 % of the planned dose of the chemotherapy. 66 % of the patients suffered from any acute toxicity of CTC grade III or IV.
The overall survival was 59 % after 12, 33 % after 24 and 15 % after 60 months. The local control was 85 % after 12 months, 63 % after 24 and 50 % after 60 months.
Conclusions: We could find a good feasibility of a definitive radiotherapy and a reasonable feasibility of concomitant chemotherapy for elderly patients with SCCHN. Also in comparison with collectives of younger patients the overall survival is reasonable, particularly regarding the reduced pretreatment general condition of the patients. Because of our results concerning feasibility, a de-intensification of radiotherapy just due to age seems not to be justified.

Disclosure Statement: On behalf of all authors, the corresponding author declares that there are no conflicts of interest.

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The Role of Tertiary Lymphoid Structures in Adenoid Cystic Carcinoma

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Purpose: Adenoid cystic carcinoma (ACC) is a rare malignancy of salivary glands in the head and neck. The prognosis remains poor and late recurrences often occur after 5 years and later.[1] To date, there are no reliable prognostic markers for ACC. In several solid tumors, tertiary lymphoid structures (TLS) are associated with improved survival. This study aims to investigate the role of distribution patterns of tumor infiltrating immune cells (TIL) in ACC.
Methods: Our screening cohort consisted of 10 ACC patients where formalin-fixed paraffin embedded (FFPE) tissue of the primary tumor were available. The validation cohort comprised further 25 patients. All patients were treated at the Ulm University head and neck cancer center. Sections were stained for CD3, CD4, CD8 and CD20 and evaluated with regard to their distribution of TIL. Patterns were determined as infiltrated-excluded, infiltrated-inflamed and presence of tertiary lymphoid structures as published before.[2]
Results: In the screening cohort 8 of 10 tumors presented with an infiltrated-excluded TIL pattern by infiltrating ≤ 5% of the tumor. Two cases showed an infiltrated-inflamed phenotype with more CD3+ cells (80% and 60%) than CD20+ (20% and 40%) and additionally formed TLS. These two cases had no relapse, whereas 50% of the infiltrated-excluded tumors relapsed. Due to the limited case number in the screening cohort, these results were not statistically significant and are currently being verified in the validation cohort.
Conclusions: TIL patterns in ACC represent a promising prognostic tool and could identify patients at risk of relapse. These patients should be monitored more closely and possibly treated more aggressively.

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Disclosure Statement: Nothing to declare.

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Feasibility and Results of a Postoperative Radiotherapy (RT) or Chemoradiation (RCT) for Elderly Patients with Squamous Cell Carcinoma of the Head and Neck (SCCHN) – a Retrospective Monoinstitutional Survey

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Purpose: SCCHN belong to the frequent malignancies worldwide. In an aging society, also the incidence of SCCHN in elderly patients is rising. Nevertheless, elderly patients are underrepresented in clinical trials. The aim of this survey was to evaluate the feasibility of a postoperative RT/RCT and the treatment results in a collective of elderly patients with SCCHN.
Methods: All patients older than 70 years, which received a definitive RT or RCT at the University Hospital Regensburg from 2004 to 2018 were included.
71 patients could be identified with a median age of 75 years. Most patients suffered from a SCCHN UICC stadium IVa. 9 patients received a concomitant chemoradiation, 62 patients were only irradiated.
The median follow up was 27 months (IQR 18 to 62 months).
Results: The feasibility of radiotherapy was good. Radiotherapy had to be interrupted for more than one day for 18 patients. 6/9 patients could receive at least 75 % of the planned dose of the chemotherapy.
52 % of the patients suffered from any acute toxicity of CTC grade III or IV.
The overall survival was 87 % after 12, 67 % after 24 and 41 % after 60 months. We could only identify the pretreatment general condition as predictive factor for overall survival.
The local control was 99 % after 12 months, 88 % after 24 months and 75 % after 60 months.
Conclusions: We could find a good feasibility of a postoperative RT or RCT for elderly patients with SCCHN. Especially the local control was quite satisfactory. There seems to be no obvious difference in overall survival in comparison with other collectives of younger patients or unselected patients regarding age. Our results show, that a de-intensification of treatment just because of age seems not to be justified.

Disclosure Statement: On behalf of all authors, the corresponding author declares that there are no conflicts of interest.

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Improved Detection of Promising Epigenetic Biomarkers for Head and Neck Cancer in Saliva

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Purpose: Head and neck squamous cell carcinoma (HNSCC) is a heterogeneous disease. Two thirds of patients are diagnosed with advanced tumour stages.[1] Therefore, we currently conduct a feasibility study with the aim to prove that our validated cancer-specific markers, detected in DNA from primary tumour tissue, may also be detectable in non-invasive saliva samples.
Methods: HNSCC-specific DNA methylation markers (Z1-Z5; reference ACTB) were validated using fresh-frozen tissue samples (20x HNSCC; 20x controls) by methylation-specific multiplex QPCR on the cobas z 480 analyzer (Roche). The aim is to include 200 patients in the study. For multiplex QPCR testing both, tissue and saliva are collected from each HNSCC patient at the Department of Otorhinolaryngology, Jena University Hospital. Isolated genomic DNA is bisulfite-converted before use.
Results: Validation of Z1 – Z5 by multiplex QPCR yielded 100 % clinical sensitivity and 95 % specificity, if 1/5 markers were positive, in HNSCC and control tissues. Single marker sensitivity ranged from 30 % to 70 % and specificity from 95 % to 100 % in this validation sample set. In samples collected from the first six HNSCC patients, the markers Z1, Z3-Z5 were detected in the six available tissue samples. Z1 showed matching results between all six tissue and saliva samples. Z5 showed positive detection in 6/6 tissue and 5/6 saliva samples. Z2 – Z4 had weak detection rates in saliva samples so far. Results from the control group are not yet available.
Conclusions: Preliminary results support our study hypothesis to robustly detect HNSCC markers in both, tissue and saliva. Utilization of saliva samples for cancer-specific diagnostic assays based on epigenetic markers will be useful in *in vitro* diagnostics aiming at secondary and tertiary prevention.

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Disclosure Statement: This study was supported by oncgnostics GmbH; Jena; Germany.

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Effects of Decitabine on the Expression of Immune Checkpoints Molecules (ICM)

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Purpose: Decitabine (DAC) reduces DNA methylation unspecifically. DNA demethylation increases the expression and repertoire of cancer-testis antigens (CTA) in cancer cells, potentially enhancing immunogenicity. DAC effects on immune cell (IC) phenotype and function in the tumor microenvironment need to be taken into consideration. To this end, we set out to characterize DAC induced changes in IC.
Methods: Peripheral blood mononuclear cells (PBMC) of patients with oropharyngeal carcinoma and healthy controls were cultivated and treated at 1µmol/l for 5 consecutive Days. Changes in ICM expression were analyzed by flow cytometry. Four panels were designed with five backbone markers (CD3,4,8,39,19) each. Expression of ICMs (PD-1, CTLA4, BTLA, CD137, CD27, GITR, LAG-3, OX40, TIM3, VISTA, ICOS, TIGIT) was analyzed. Cytotoxicity was monitored with Annexin V / 7AAD staining plus CD3,4,8,39&19.
Results: Variations in different immune cell populations' susceptibility to DAC's cytotoxicity were observed. CD19+ B cells were depleted by 78%, CD39+ cells were depleted by 29%, CD8+ cells increased by 19% and CD4+ cells by 38% compared to control treated cells. DAC evokes a shift in the expression pattern of immune checkpoint molecules: In healthy controls DAC reduced the expression of PD1 and CTLA4 in CD4+ cells, whereas tumor patients showed increased expression of these ICMs in CD8+ and CD4+ cells. CD19+ cells show an increase in OX40 and decrease in CD27 expression. CD39+ cells show decreased levels of PD1, CD137, CD27, ICOS and TIGIT.
Conclusions: DAC treatment alters the expression of ICM and lymphocyte subpopulations proportions. This needs to be considered when combining DAC with immunotherapy. Further experiments are ongoing to validate and extend our findings.

Disclosure Statement: P.J.S.: Advisory Boards: BMS; MSD. T.K.H.: Advisory Boards: MSD; BMS; MSD. Honoraria: Merck Serono; BMS. S.L.: Advisory Boards: Merck Sharp & Dohme (MSD); Bristol Myers Squibb (BMS); Astra Zeneca (AZ). Honoraria: MSD; BMS; AZ; Merck Serono. All other authors indicated no potential conflict of interest.

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Cell-Free DNA in Plasma or Saliva for Minimally Invasive Monitoring of Head and Neck Cancer Patients

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Purpose: In patients with head and neck cancer (HNC), disease monitoring and recurrence detection are currently based on clinical examination and imaging. Liquid profiling of tumor-derived nucleic acids such as cell-free tumor DNA (ctDNA) in plasma and in saliva could provide better monitoring and earlier recurrence detection. Here, we aim is to determine to which extent ctDNA and HPV DNA can be detected in plasma and saliva, and which sample material is more suitable for liquid-based HNC profiling.
Methods: In 92 HNC patients, blood plasma and saliva samples were prospectively collected after surgery and analyzed with digital droplet PCR (ddPCR) assays to detect two *TERT* promoter hotspot mutations. In the subgroup of 50 patients with HPV-associated tumor localizations, cell-free DNA (cfDNA) was tested for HPV16 *(E7)* in plasma and saliva. To increase the detection rate, mutations in the primary tumor were identified with NGS (45 genes) and ctDNA was quantified using individually designed mutation-specific ddPCR assays.
Results: In 33% (30/92), ctDNA was detected in plasma, in 38% already in early tumor stages (I/II). In saliva, ctDNA was detected in 52% (17/33). In the course of disease, a tumor progression could be detected by increasing ctDNA concentrations in plasma or saliva on average 5 months (2 weeks to 13 months) earlier than by clinical imaging. In p16-pos. patients (n=16), HPV16 cfDNA was detected in plasma in 39% (6/16), in 50% already in early tumor stages (I/II). P16-pos. HPV-neg. patients (10/16) showed an unfavorable clinical course compared to p16-pos. HPV-pos. patients (30% died, 79% had a relapse or progressive disease).
Conclusions: Liquid profiling with ddPCR-based detection of ctDNA in blood and saliva is a promising tool for disease monitoring and early recurrence detection in HNC patients. In HPV-associated tumors, HPV cfDNA could be a complementary marker for disease monitoring and for identifying a subgroup of p16-pos. tumors that are not driven by HPV infection.

Disclosure Statement: no conflict of interest

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Intrathecal Ziconotide and Morphine Using Cervical Catheters for Cancer Analgesia

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Purpose: Pain remains the first symptom in cancer population at an advance stage of the disease (1). Intrathecal drug delivery systems (IDDS) is efficient to relieve pain refractory to comprehensive medical management (2). However, IDDS through cervical catheters with Ziconotide for Head and Neck Cancer (HNC) pain is a new option never described on literature. This prospective follow up study was designed to evaluate results of cervical IDDS with Ziconotide for Cancer pain at the ICO.
Methods: Patients were treated from 2010 to 2017, after selection for IDDS based on multidisciplinary meeting discussion. After a complete withdrawal of systemic opioids, IDDS-treated patients were prescribed a combined intrathecal regimen (morphine, ropivacaine and ziconotide) through a catheter placed behind the cervical spinal cord. Post-implant assessment of pain was determined using a numeric rating scale (NRS).
Results: 43 patients were included from 2010 to 2017, total therapy duration accounts for 9013 IDDS-days. Implanted patients suffered from severe pain (mean presurgical NRS 8.6±0.8) despite a mean 566 +/-112 mg oral morphine equivalent daily dose. Median survival time after IDDS was 125 ± 176 days. IDDS provided great pain relief with significant difference ($p < 0.01$) after 1 week (2.4+/- 0,46), 1 month (2.7 +/- 0,44) and 2 months (2.8+/- 0.55) 50%. Only one serious adverse effect was observed with ziconotide.
Conclusions: Long-term IDDS using a multidrug regimen including ziconotide for HNC pain through cervical intrathecal catheters reduce pain scores and seems safe in our study population, using mainly a percutaneous lumbar approach.

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Disclosure Statement: Dr Dupoiron is consultant for Medtronic and RIEMSER Pharma GmbH.

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Expression of the Immune Modulators of the PD-1: PD-L1 Axis in oral Leukoplakia

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Purpose: PD/PD-L1 Immune Checkpoint overexpression is involved in immunosuppression and the failure of an immune response against tumor cells. Cancer immunotherapy using antibodies targeting this axis has become a new therapeutic approach also for patients suffering from OSCC. Little is known about its expression in oral precancerous lesions like oral leukoplakia (OLP). The aim of the study was to check whether altered PD/PD-L1 expression already exists in OLP and whether it is associated with malignant transformation.
Methods: PD-1 and PD-L1 expression were immunohistologically analyzed separately in the epithelium and the subepithelium of OLP that transformed malignant within 5 years (T-OLP), in OLP without malignant transformation (N-OLP), in corresponding OSCC and in healthy oral mucosa (NOM). Additionally, RT qPCR analysis for PD-L1 expression was done in the entire tissues. The expression rates were compared and statistical significance of the expression change between the groups

and the association between overexpression and malignant transformation was determined.
Results: PD-1 was overexpressed in the epithelial and subepithelial compartment of T-OLP compared to N-OLP (P_E=0.001; P_S=0.005). No significant difference in PD-L1 mRNA expression between transforming and non-transforming OLP could be demonstrated (P=0.10). However, the PD-L1 protein was significantly overexpressed in the epithelial section of transforming OLP (p=0.007), but not in the subepithelial compartment (p=0.25) compared to N-OLP. Additionally, this overexpression was significantly associated to malignant transformation within 5 years.
Conclusions: PD-1/PD-L1 may represent a prognostic indicator to determine the risk of malignant progression of OLP. Local immunosuppression in the epithelium could be induced by PD-L1 overexpression in epithelial cells and trigger malignant transformation. Hence, checkpoint inhibitors could counteract tumor development and serve as therapeutic agents in patients with high-risk OLP lesions.

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Zoledronate Shifts Macrophage Polarization towards M1 in Vivo - An Animal Study on Wistar Rats

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Purpose: Clinical studies and in vitro analyses indicate that immunomodulatory properties of bisphosphonates contribute to the development of medication associated osteonecrosis of the jaw (MRONJ) as well as to the anti-metastatic effect observed in certain groups of breast cancer patients. Macrophages are precursor cells of osteoclasts and could be potential candidates for the mediation of immunological effects of bisphosphonates. Aim of the study was to investigate the influence of zoledronate on density and polarization of macrophages in different tissues of the Wistar rat.
Methods: A total of 120 animals (6-month-old male Wistar rats) were divided into 4 groups, 56 of which were treated with 8x 40mg/kg body weight zoledronate i.p. After 2, 4 and 8 weeks the tissues skin, lung, spleen and tongue were removed and immunohistochemically examined for the expression of CD68, CD163 and iNOS positive cells using a tissue microarray.
Results: In bisphosphonate treated animals a significantly increased macrophage cell count (increased CD68 expression) as well as significantly increased iNOS expression and significantly decreased CD163 expression was observed.
Conclusions: Bisphosphonate application leads to a shift of macrophage polarization towards M1 *in vivo*. This provides a possible explanation for the clinically observed anti-tumor effect of bisphosphonates.

Disclosure Statement: The authors declare no conflict of interest.

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A Randomized Phase II Study on the Optimization of Immunotherapy in Squamous Carcinoma of the Head and Neck (SCCHN) – OPTiM (AiO-KHT-0117)

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Purpose: The OPTIM trial investigates whether dual checkpoint blockade is superior to docetaxel chemotherapy as early salvage therapy in recurrent or metastatic SCCHN (R/M-SCCHN). The primary endpoint is overall response rate after randomization, hypothesizing that dual checkpoint blockade improves ORR to 25% compared to 10% with docetaxel. Secondary endpoints are overall survival, progression-free survival, safety, and quality of life.
Methods: 280 patients with R/M-SCCHN progressing after platinum-based chemotherapy or within 6 months after RCT will initially receive nivolumab monotherapy (240 mg Q2W). They are closely followed for tumor progression by radiologic assessment at increased frequency (i.e. every 4-6 weeks). Patients who progress during the first 24 weeks of nivolumab monotherapy are randomized 1:1 between intensified immunotherapy (nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W) and chemotherapy (docetaxel 75 mg/m^2 Q3W). 154 patients are planned to be randomized. Patients who do not progress continue nivolumab monotherapy according to standard of care. After randomization, study treatment continues until disease progress or for up to 12 months.
Results: Recruitment started in July 2018 and is ongoing. Results will be published after finalization of study.

Disclosure Statement: All authors have no relevant financial or nonfinancial relationships to disclose.
OPTIM (EudraCT 2017-003349-14) study sponsor is AIO-Studien-gGmbH; Berlin. The study is financially supported by Bristol-Myers Squibb.

Health Economy/Public Health

Vorträge

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Health Economic Effects of Biosimilars: The Potential for the Long-Term Financing of Oncological Care and Therapeutic Innovations

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Purpose: Several new options for individualized and targeted therapies in oncology and immunology are available or in development. However, these are cost intensive, in particular in view of healthcare systems with limited resources. Hence, new financing approaches are warranted. Biosimilars are biological drugs containing the active substance of an already approved reference biological drug. The introduction of biosimilars can relieve the burden on healthcare and thus finance new therapies. However, existing data shows that the saving potential in Germany is far from exhausted.
Methods: Based on available health economic analyses, the actual use and effects of biosimilars were determined using the examples of trastuzumab, rituximab and G-CSF. The associated costs of the originator and biosimilar were compared to determine the saving potential in the real world for the German healthcare system. Incidence calculations were based e.g. on data from the Robert-Koch-Institution, Munich cancer registry, quality indicators of the certified centers and calculations of the IQWiG benefit assessments. Cost calculation was based on Lauer tax (15/12/2018).
Results: According to the example of trastuzumab and calculations based on various sources, the number of patients with HER2-positive breast cancer receiving trastuzumab in the adjuvant and metastatic setting ranges from 8,199 to 14,380 and 4,643 to 4,670 cases/year, respectively. This corresponds to a range of 118,745 to 208,250 cycles/year in the adjuvant setting and 236,793 to 238,170 cycles/year in the metastatic setting. The annual saving potential would amount from 87,883,705 EUR to 120,496,027 EUR if all patients received the least expensive trastuzumab biosimilar compared to the original drug.
Conclusions: The available data show that potential savings are far from exhausted and that, if the option of biosimilars is fully exploited, enormous resources can be released in the healthcare system in order to offset financing new innovative forms of therapy. Additional calculations for rituximab and G-CSF will be provided.

Poster

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Assessment of Metastatic Colorectal Cancer Patient Preferences for Biologic Treatments in Germany Using a Discrete Choice Experiment – Study in Progress

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Purpose: This is an ongoing discrete choice experiment (DCE) that aims at understanding patient preferences in the systemic biologic treatment of metastatic colorectal cancer (mCRC), focusing on the perception of adverse event risk relative to the expected treatment benefits.
Methods: This ongoing multicenter cross-sectional study is a based on patient interviews using a DCE framework. It aims to include 150 patients with mCRC from 15-20 sites in Germany. It includes adult patients (≥18 years) with a physician-reported diagnosis of mCRC actively or previously (within the previous 3 months) receiving or about to be initiated on a first-line mCRC therapy. All participants must provide written informed consent. Patients are asked to make several stated (hypothetical) choices in deciding between two alternative treatment options to quantify their preferences for different mCRC treatment attributes, specifically attributes related to efficacy (e.g., overall survival) in relation to safety (e.g., risk of rash, infusion reactions, or gastrointestinal hemorrhage).
Results: This study is currently recruiting patients and results are expected in December 2019. In a conditional logit regression model, the influence of different attribute levels on the probability of a patient's choice for or against a specific treatment alternative will be estimated. In an additional analysis, utility values will demonstrate marginal willingness to accept a given attribute if a specific treatment with a more favorable attribute level could be received. Furthermore, relative importance of each attribute for the overall decision for or against an option in the DCE will be provided. Additionally, a latent class analysis to identify and describe patient subgroups will be done.
Conclusions: There is a lack of research focusing on patient preferences with a biological mCRC treatment and there are no existing data for Germany so far. Therefore, this study will facilitate a better understanding of trade-offs related to the existing treatment of the disease from the perspective of the German population.

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Development of a Telemedical Software for the Organisation of Oncological Councils and Tumor Conferences within the Project "Tumornetzwerk Sachsen"

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Purpose: Strategies for Cancer patients need to be discussed within interdisciplinary tumor conferences. The development of the software "eTumorkonsil" for telemedical consultation of oncological patients will allow physicians of various disciplines and medical facilities to network digitally wherever located. This will improve the medical care of cancer patients, also for patients in structurally weak areas.

Methods: The application "eTumorkonsil" is going to be developed on an established telemedicine platform and will allow physicians to share oncological councils using electronical (e-) councils or to take part in e-tumor conferences, two possible functions within the software. Furthermore, all clinical information will be made available directly to a digital patient record. The user of the application, defined by a login, may request second opinions on oncological issues and discuss patients digitally using a high quality phone and video conferencing system. The program is web based and therefore capable of running independent and free of any connection into operating systems.
Results: Uniform processes ensure a fast procedure of the digital councils without media disruption. The transmitted patient data is encrypted in agreement with the data protection requirements. The application is user friendly, so that the preparation and follow-up as well as the execution of the tumor conference are logically organized. Therapy recommendations are provided on the platform by standardized digital paths within 24 hours.
Conclusions: In the Free State of Saxony physicians who are responsible for outpatient and inpatient treatment are able to be networked with the telemedical application "eTumorkonsil" in a multidirectional way. Hereby it is possible to optimize the care of cancer patients; especially in structurally weak regions; by connecting them to certified cancer centers. „eTumorkonsil" offers an innovative and time-efficient support in oncological care for everyday medical practice and stand for a continuous quality assurance in the context of patient care.

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Measuring Utilities in Cancer Patients - The EORTC QLU C10D

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Purpose: Health economic analysis and therefore cost-utility studies are becoming more prominent in cancer research. Generic utility instruments may not address cancer patients in a suitable way due to the complexity of the disease [1]. The EORTC QLU C-10D is a new multi-attribute utility instrument derived from the cancer-specific EORTC QLQ C-30, which is one of the most widely-used quality of life instruments for assessing cancer patients' quality of life. The aim of this project was to develop cancer-specific utility weights derived from the EORTC QLQ C-30 for five European countries.
Methods: A professional marketing company set up the DCEs with a general population of 1000 participants in each country. Discrete Choice Experiments (DCEs) from a general population in five European countries (Austria, Germany, France, Italy and Poland) were used to derive utilities from the C-30. The key dimensions used for the discrete choice experiments have been identified in previous studies.
Results: The dimension that impacted most on choice was physical functioning followed by pain for all five European countries. Regarding the order of impact for the other dimensions, slight variations were seen across the countries. Relevant cancer-related symptoms with a moderate effect were nausea and bowel problems. A small impact across all five European countries was seen for fatigue, sleep problems, and appetite loss. The highest utilities were seen for Italy, while the lowest were obtained for France.
Conclusions: This project provided the first country-specific European utility weights for the QLU C-10D in five EU countries. These utilities can be applied in future clinical trials using the EORTC QLQ C-30. Further valuations for European and Asian countries are performed.

Reference:

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Disclosure Statement: The authors have nothing to disclose.

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Time-Dependent Risk Predictions As Novel Method to Improve Screening Efficiency

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Purpose: Risk-prediction tools allow to classify patients into risk-groups based on risk thresholds. The usage of information concerning an individual's risk development over time would facilitate further tailoring of screening schemes.
Methods: In a simulation analysis, three screening approaches (risk-based, time-independent: cumulative approach CA; risk-based, time-dependent: cumulative approach with interval-specific reevaluation CAIR, interval-specific approach ISA) are compared regarding their impact on screening-efficiency. For this purpose, 81 scenarios featuring 5,000 patients with time-dependent risk estimations for a hypothetical disease D and five consecutive intervals of one year are simulated, using different parameters to model disease progression, risk-distribution, risk-correlation, and target detection rate of screening (tdr). The results of these simulation analyses are validated using a real-world clinical case-study based on German breast cancer patients and the INFLUENCE-nomogram for locoregional breast cancer recurrence.
Results: If individual, time-dependent risk estimations were used to personalize screening at a fixed tdr of 90%, the percentage of saved screening examinations relative to an uninformed approach could exceed 20%, depending on the simulated scenario. Whereas the time-independent approach CA is associated with acceptable saving potentials in case of a relatively homogenous risk distribution, the time-dependent approaches CAIR and ISA are superior when risk-variation increases. With slowly progressing diseases, approach CAIR yields the highest efficiency on population level, for rapidly progressing diseases, approach ISA is superior. The possible benefits of time-dependent risk-based screening were confirmed in the real-world clinical case-study.
Conclusions: An appropriate usage of time-dependent risk-predictions may considerably enhance screening efficiency. Therefore; predicting risk development over time should be incorporated in future prediction-tools and decision-algorithms.

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Gera: a Health Economic Trial to Analyze the Impact of eHealth in Breast Cancer Care

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Purpose: In breast oncology, the increasing number of oral drug therapies poses great challenges for patient management. Numerous studies demonstrate that well-informed patients develop higher confidence in their treatment and a greater sense of disease control, resulting in increased adherence and persistence as well as potentially better outcome. The electronic Patient Reported Outcome (ePRO) tool CANKADO is designed to help oncologists to bridge the gap between good, personalized care and a time and resource-saving treatment for cancer patients.
Methods: Aim of GERA is to assess the economic impact of an ePRO tool in breast cancer care. It is a prospective, single arm, non-interventional trial, based on questionnaires that answered by patients via the CANKADO Patient App. All patients undergoing systemic therapy for breast cancer with access to CANKADO will be included in the evaluation. This study will take place in 10 German centers and 337 patients will be included in the study. The enrollment phase of patients will last 6 months, while the individual patient observation and accompaniment phase through

CANKADO will continue for 3 months. Primary objective is to gain knowledge on the health economic impact of CANKADO resource utilization in breast cancer care including the evaluation of physicians' time and patient experience. As secondary objectives, exploratory analysis of all collected information is planned. This includes the socio-demographic patient information, clinical characteristics, quality-of life and patient documentation behavior.
Results: The GERA trial is ongoing. Results will be presented at the conference.

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Disclosure Statement: None declared

Imaging

Poster

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A Deep Learning-Based Pipeline for The Automation of the HER2 Gene Amplification Status Detection on Digitalized Whole Fluorescence in Situ Hybridization (Fish) Slides in Breast and Gastric Cancer

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Purpose: The human epidermal growth factor receptor 2 (HER2) gene amplification status is important for therapy assessment in breast and gastric cancer. It is visually assessed by pathologists based on FISH imaging using a fluorescence microscope or fluorescence scanner. To automatize this daily clinical routine in terms of speed, accuracy and objectivity, a multi-step deep learning (DL) based pipeline was developed to mimic the evaluation steps performed by pathologists.
Methods: The DL pipeline relies on (1) the prediction of the image-wide HER2 gene amplification status via image classifier convolutional neural networks (CNNs), (2) the detection, localization and classification of interphase nuclei and their HER 2 and CEN17 fluorescence signals based on (2a) object detection and (2b) pixel-wise segmentation networks and (3) the visualization of the decision making of the networks to enable interpretability by pathologists.
Results: We demonstrate that the accuracy of our DL pipeline is on par with a team of pathologists for the classification of whole FISH slides. Moreover, by classifying each nucleus independently by different networks, our system provides deep medical reports increasing both robustness and interpretability.
Conclusions: Our pipeline is a large step in automating the evaluation of the HER2 status of tumors using whole FISH slide scans and in optimizing the documentation of each tumor sample by automatically annotating and reporting of the HER2 gene amplification status. This system is in principle also transferable to all current FISH-based analyses which are routinely performed at pathology institutes.

Disclosure Statement: *Falk Zakrzewski, Martin Weigert and Torsten Wenke are founders of the startup company ASGEN.*

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Sodium MRI at 7 Tesla as a Potential Biomarker for Tumor Infiltration and IDH Status in Glioma Patients

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Purpose: These are the first data from a prospective trial investigating sodium (^{23}Na) MRI at 7 Tesla (T) as a potential biomarker for tumor infiltration and isocitrate dehydrogenase (IDH) mutation.
Methods: 30 glioma patients underwent ^{23}Na MRI on a 7 T scanner (Siemens Healthineers, Erlangen, Germany) parallel to standard 3T MRI before chemoradiation. A self-developed density-adapted 3D radial projection pulse sequence [1] with consecutive iterative 3D-DLCS reconstruction [2] was employed. Areas of gadolinium contrast enhancement (gdce), non-enhancing T2 hyperintensity (regarded as edema) as well as necrosis were segmented, and regions of interest were placed inside normal-appearing white matter (nawm) on 3T MRI. All segmentations were registered to the ^{23}Na images in MITK (http://mitk.org). The median ^{23}Na signal of all areas was compared by pairwise t-tests, and the difference in median ^{23}Na signal of the whole tumor was compared between IDH-mutated (mut, N=6) and IDH-wild-type (wt, N=18) gliomas by a Mann-Whitney U test.
Results: The ^{23}Na signal increased successively from nawm to necrosis (mean ± sd [mM]: nawm = 37.8 ± 5.9, edema = 54.7 ± 10.6, gdce = 61.7 ± 13, necrosis = 81.9 ± 17.5) and the signal differences between all areas proved significant (p-values for all pairwise comparisons < 0.01). Furthermore, IDH-mut gliomas showed significantly higher ^{23}Na signal than IDH-wt gliomas (median (interquartile range) [mM]: wt = 52.4 (46 – 58.6), mut = 65 (58.9-67.1), p = 0.0094).
Conclusions: The continuous gradient of ^{23}Na signal from central necrosis to white matter suggests a correlation with tumor infiltration. Considering the additional correlation with IDH status, ^{23}Na MRI could enhance identification of biopsy sites and assist image-guided surgery and radiotherapy.

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Disclosure Statement: N.G.R.B. currently works for Siemens Healthineers.

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Development of a Convolutional Neural Network (CNN)-Based Classifier for Automated Tissue and Tumor Annotation of Matrix-Assisted Laser Desorption/Ionization (MALDI) Data

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Purpose: Proteins and peptides represent the phenotype of the tumor at the time of treatment. Consequently, the tumor proteome is a promising target to define novel biomarkers. MALDI combines the identification of the proteome by means of mass spectra according to time-of-flight masses (m/z), and the macroscopic anatomy of the tissue compartments. Deep Learning is largely suitable for addressing the complex MALDI data for automation of tumor classification by identification of tumor-specific peptide features. Therefore, a complementation of MALDI with Deep Learning pipelines will largely bring forward automated pathological tumor slide analysis.
Methods: Regions of interest (ROI) of human cancer tissue slides are defined by pathologists and are translated into mass spectra patterns used for protein/peptide composition and quantification by MALDI. The data is then transferred into Convolutional Neural Networks (CNNs) for extracting ROI-specific features. These trained CNNs are subsequently applied for autonomous prediction of the tumor content and tumor tissue localization in previously uncharacterized tissue slides from tumor samples on the basis of their MALDI spectra.
Results: Trained CNNs can be used to automatically classify, quantify and mark tumor regions in MALDI imaging data. Morphologically indistinguishable tumors can be subdivided and analyzed regarding their molecule-dependent heterogeneity at a very high resolution (down to 5x5 micrometer).
Conclusions: Our mission is to offer MALDI imaging as a diagnostic complement for immunohistochemically analysis. We will provide our MALDI pipeline as a broad application in CNN-based automated tumor diagnostics and cancer research projects to enable the identification of new protein/peptide biomarkers.

Leukemia, Myelodysplasia, Transplantation

Best-of-Abstracts-Vorträge

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Nilotinib (NIL) vs. NIL Plus Pegylated Interferon alpha2B (IFN) Induction and Nil or IFN Maintenance Therapy for Newly Diagnosed BCR-ABL1+ Chronic Myeloid Leukemia (CML) Patients (PTS) in Chronic Phase

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Purpose: The TIGER-study (NCT01657604) is a multicenter, randomized phase III trial to evaluate efficacy and tolerability of NIL 2*300mg/d monotherapy vs NIL 2*300mg/d + IFN and the option to discontinue therapy after IFN maintenance as first line therapy for chronic phase CML pts.
Methods: 717 pts (429 male; median age 50.3 yrs, range 18-85) were recruited from 109 sites in Germany, Switzerland, and the Czech Republic. 692 pts were randomized to receive NIL monotherapy (n=353) or NIL/IFN combination therapy (n=339). Median observation time was 41 mo. 477 pts concluded the induction phase (confirmed major molecular response, MMR, BCR-ABL1 $\leq$0.1% IS, after $\geq$2 yrs of therapy) and reached the maintenance phase of the study (NIL vs IFN monotherapy). 199 pts achieved and maintained MR^4 (BCR-ABL1 $\leq$0.01% IS) for at least one year and discontinued all therapy.
Results: IFN significantly improved rates of MR^4 and $MR^{4.5}$ (BCR-ABL1 $\leq$0.0032% IS). Median time to MMR was 5.4 vs 5.7 mo, to MR^4 12.5 vs 20.9 mo and to $MR^{4.5}$ 23.2 vs 33.8 mo for NIL vs NIL/IFN, respectively. From 199 pts who discontinued all therapy (MR^4 for at least one year) 63 showed a molecular relapse (BCR-ABL1 >0.1%). Relapse free survival by 18 mo after treatment discontinuation was 61% in the total cohort. 15 pts (2.1%) progressed to advanced disease; 22 pts (3.1%) received allogeneic stem cell transplantations.
Conclusions: This per protocol interim analysis demonstrates feasibility of 1st-line treatment with NIL combined with IFN. High rates of early molecular responses indicate an option of treatment-free remission. The addition of IFN to NIL significantly improved rates of deep molecular response (MR^4 and $MR^{4.5}$) at 12 and 18 mo of therapy.

Disclosure Statement: none

Poster

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Selective Dependency of MLL-Rearranged Leukemia on Immunoproteasome Function

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Purpose: Several pathways control the balance between self-renewal and differentiation to maintain leukemia stem cell (LSC) function. To identify dependencies of oncogenic fusion proteins, we performed global proteome profiling using MLL-AF9 (MA9) or AML1-ETO9a (AE) murine cells. In MLL-rearranged (MLLr) cells, GSEA revealed enrichment of pathways related to proteasome function. This enrichment is present in MLLr-leukemia but not in AE-LSCs. That may indicate an oncogene specific vulnerability. In published AML datasets, immunoproteasome (IP) subunits showed higher expression in MLLr compared to non-MLLr-AML. IP is a proteasome variant constitutively expressed in hematopoietic cells. It is relevant for mediating stress-responses during inflammation.
Methods: To assess for functional dependency of MLLr cells on IP subunits we performed a CRISPR/Cas9 dropout screen in MLLr MOLM13 cells. Inactivation of LMP7 (IP subunit) resulted in outcompetition with 3/5 sgRNAs. Specificity of this finding was confirmed in 5 different cell lines by RNAi using 2 shRNAs against LMP7. To confirm these findings in primary cells, we used a previously published conventional LMP7 knockout mouse model.
Results: LSK cells of LMP7 ko and wildtype mice were retrovirally infected with either MA9 or NUP98-HOXA9 (non-MLLr control) to assess for disease development by serial plating in methylcellulose. Only in MA9 cells LMP7-deficiency limited re-plating capacity. When we injected MA9-infected LSK cells into recipient mice, recipients of MA9-LMP7-/- cells and MA9-LMP7+/+ showed development of AML. However, recipients of MA9-LMP7-/- cells had a significant delay in AML development.
Conclusions: Taken together, our studies uncover a selective dependency of MLLr-leukemia on IP function and identify LMP7 as a tractable target.

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Disclosure Statement: Nothing to disclose.

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Cytoreductive Treatment in 'Real Life' – Analysis of 434 Polycythemia Vera Patients in Germany

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Purpose: The aim is to evaluate the use of phlebotomy and cytoreductive therapy in patients with polycythemia vera.
Methods: For this analysis 11 centers provided data on 434 patients - 211 (48.6%) male and 223 (51.4%) female.
Results: Most patients were of older age (mean 71.4 years; 62.7 years at diagnosis and 63,4% over 60 years).
100 patients (23.0%) had thromboembolic complications at time of diagnosis and 61 (14.1%) during treatment. Cardiovascular (CV) risk-factors were reported for 320 patients (73.7%). Hypertension (86.9%) was the most prevalent CV risk factor, followed by hypercholesteremia (18.8%), diabetes mellitus (16.2%) and smoking (15.9%).
Phlebotomy was primary therapy in 301 patients (69.4%). Triggers to start pharmacologic cytoreduction included the presence of high-risk criteria (53.2%) and insufficient disease control (22.6%). Asymptomatic iron deficiency (5.6%), symptomatic iron deficiency (9.3%) and intolerance to phlebotomy (5.3%) contributed to the limitation of phlebotomy treatment.
Cytoreductive agents included hydroxycarbamide (n=320; 73.3%), JAK-inhibitors (n=80; 18.4%), Interferon alpha (n=15; 3,5%), IMIDEs (n=2; 0.5%) and other cytoreductive agents (n=6; 1.4%). While 11 patients (2.5%) required combination, 137 (31.3%) patients had a persistent need for phlebotomy.
Conclusions: Age was main factor for the majority of patients being categorized as 'high risk'. Although the majority of patients (>60%) presented as 'high risk' according to international guidelines, 69.4% of patients received phlebotomy as primary therapeutic approach. The low number of primary cytoreductive treatment and occurrence of symptomatic iron deficiency and of intolerance indicates the need to reconsider indication and limitations of phlebotomy.
Phlebotomy as a prophylactic measure of risk reduction should result in mild iron-deficient erythropoiesis and hematocrit control. Pharmacologic cytoreduction is necessary for high risk patients older than 60 years or with previous thromboembolic complications.

Disclosure Statement:

Regine Wunschel - Nürnberg; Novartis Inc.; Nürnberg; Deutschland
- Beschäftigungsverhältnis als Mitarbeiterin bei Novartis
Andreas Hochhaus - Jena; Klinik für Hämatologie und Onkologie; Universitätsklinikum Jena; Jena; Deutschland
- Kongresspräsident

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Prevalence and Dynamics of BCR-ABL Independent Gene Mutations in Chronic Phase CML Patients

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Purpose: Living without treatment has become a realistic aim for patients with chronic myeloid leukemia (CML) who achieved durable deep molecular remission under treatment with tyrosine kinase inhibitors (TKI). Recently, we have identified novel BCR-ABL independent gene mutations in newly diagnosed CML patients whereby mutations in epigenetic modifier genes were most common. The prevalence, kinetics and prognostic significance of such mutations need to be investigated in a well-characterized patient cohort.
Methods: 100 chronic phase CML patients from the German CML-V (TIGER) trial were investigated by targeted deep next-generation sequencing covering 54 genes frequently mutated in myeloid malignancies. Paired samples at diagnosis, 12 months, 24 months and 36 months of therapy were investigated.
Results: Forty-six different mutations were detected in 39/100 patients affecting the genes ASXL1, BCOR, CALR, CUX1, DNMT3A, FBXW7, IKZF1, JAK2, KDM6A, NOTCH1, RUNX1, STAG2, TET2, TP53, U2AF1 and WT1. ASXL1 (n=13) and DNMT3A (n=9) were most commonly affected. Nine patients carried more than one mutation. For 26/100 patients at least one mutation was present at diagnosis. Follow-up samples revealed that in 22 patients mutations disappeared during TKI treatment. In 3 patients the mutation persisted indicating that the mutation preceded the BCR-ABL translocation. In 2/97 patients the initial mutation re-emerged at month 24 after disappearance at month 12. In 6/100 patients a new mutation occurred at month 12; 4 of which persisted in further follow-up samples. Seven mutations were initially detected at month 24 with 2 persisting, and five mutations at month 36.
Conclusions: BCR-ABL independent gene mutations were frequently identified in chronic phase CML patients at diagnosis. In a minority of patients such mutations seem to precede the BCR-ABL translocation indicating a multistep pathogenesis of CML. BCR-ABL independent gene mutations were found to vary in their dynamics during TKI treatment and may function as important cofactors in the evolution and persistence of the disease.

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Outcome of Refractory and Relapsed Patients with Acute Myeloid Leukemia

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Purpose: Outcome of patients (pts) with refractory Aml or following relapse is usually reported as refractory/relapsed and considered dismal.
Methods: A total of 1621 pts from the OSHO AML 2002 ≤60 y (n=740) and AML 2004 >60 y (n=881) with newly diagnosed AML (except APL) eligible for chemotherapy were analyzed. Pts with partial remission (PR) or non-response (NR) to two induction cycles were considered refractory. Pts achieving CR and relapsing thereafter were considered relapses and treated with MitoFlag or Flag-Ida.
Results: A total of 238 (14.7%) pts were refractory (PR 60.1%, NR 39.9%). OS of refractory pts was 11.4 (7.9-16.6)% @5y, and dependent upon PR [13.1 (8.1-21.1) % @10y] and NR [5.2 (2.1-12.6)% @5y; p=0.0003]. Intensive chemotherapy ± HSCT and hypomethylating agents (HMA) were able to induce CR in 24.8%. CR pts had an OS of 42.7 (31.4-58.2) % @5y. Risk factors for OS in refractory pts were age and type of therapy (p<0.0001). Younger patients with FLT3 mut had a trend for inferior OS (p=0.1). Almost all long term survivors were treated with HSCT.
Of the 1144 CR/CRi pts, 582 relapsed 1-121 months (mts) after CR. Age, cytogenetic risk, type of AML, interval CR to relapse and HSCT were the dominant factors for relapse. A total of 198 pts received palliative treatment. CR2 was achieved after intensive chemotherapy ± HSCT, ± DLI and HMA in 227 pts (39.0%). OS of relapsed pts was 13.8 *(11.1 – 17.3)* % @5y. Pts with CR2 had a LFS of 24.9 (19.5-31.7) % @5y and was highest in patients when intensive chemotherapy followed by HSCT was involved.
Conclusions: Outcome of pts with refractory and relapsed AML is consistent >10% @5y. Age, proportion of palliative treatment and in younger pts FLT3 mut was recognized as a determinant for OS. However, refractory and relapsed pts have different outcomes and results depend upon PR, NR and CR. Increase of CR rate in younger but especially in elderly pts with second generation TKI, reduction of TRM using FLT3-inhibitor monotherapy and the option to treat pts ineligible to chemotherapy promise better outcome.

Disclosure Statement: Cellectis and Daichii

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Unfavorable Prognosis of Patients with Acute Myeloid Leukemia and Central Nervous System Involvement

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Purpose: Central nervous system (CNS) involvement in acute myeloid leukemia (AML) is rare and associated with a poor outcome. Systematic data is scarce and cerebrospinal fluid puncture (CFP) is not recommended in current guidelines at any time point of the disease. However, distinct signs and symptoms should raise awareness of CNS involvement in AML patients (pts).
Methods: In this retrospective single center analysis, we analyzed 18 AML pts identified by screening our in-house database using the keywords "meningeosis" and "AML" diagnosed between 2006 and 2019. All pts received CFP and blasts were detected in all samples by microscopy and/or flow cytometry. Further characterization was performed by clinical, molecular and pathological parameters.
Results: 18 pts (6 female/ 12 male) with a median age of 55 years at diagnosis (range, 27-77) were identified. Clinical symptoms were headache, lack of vigilance, nausea or distinct neurological symptoms like cranial or peripheral nerve palsies. Besides meningeal involvement, 5 pts (28 %) also had solid CNS manifestations. 6 pts (33 %) presented with CNS involvement at initial diagnosis, 12 (66 %) at relapse. 9 pts (50 %) underwent allogeneic stem cell transplantation (SCT), 6 (33 %) had meningeal relapse after allogeneic SCT and 3 pts (17%) showed CNS involvement before allogeneic SCT. Only 2 pts (11 %) are still alive, both of them had CNS involvement before allogeneic SCT. Median survival after diagnosis of CNS involvement was 205 days (range, 2-3475). 16 of 18 pts (88 %) received intrathecal chemotherapy; in individual cases radiation was applied. The majority of pts were categorized into adverse and intermediate risk group according to current ELN guidelines (7 (38%) and 9 pts (50%), respectively).
Conclusions: There is an unmet need for a more vigorous screening for risk factors of CNS involvement in AML pts due to its poor prognosis. Several risk factors have been identified that might be associated with the occurrence of CNS involvement in AML pts. Intensified treatment strategies might be beneficial to improve outcome in this patient cohort.

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Novel Circulating Tumor Dna (CTDNA) Based Ddpcr Drop-OFF Assays for Improved Minimal Residual Disease (MRD) Monitoring in Acute Myeloid Leukemia (AML)

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Purpose: MRD assessment is important for early relapse detection in AML. MRD monitoring by bone marrow (BM) aspiration is more sensitive than analyses of peripheral blood (pB), yet it is invasive. Moreover, both fail to detect extramedullary disease (EMD). Analyses of ctDNA may address these limitations.
Methods: Plasma samples were collected in Streck tubes. CtDNA was isolated using the QIAampCNA Kit and quantified by Agilent 2100 Bioanalyzer High Sensitivity DNA Kit. Mutations in *IDH2* and *NPM1* were detected using custom drop-off ddPCR assays (BioRad QX200). Mutations in *IDH1* and *DNMT3A* were detected using commercially available ddPCR assays (Biorad). All assays achieved <0.1% sensitivity. All patients provided written informed consent.
Results: We regularly monitored ctDNA, bulk pB cell and BM gDNA in 13 patients with previously untreated AML during induction therapy with the following mutations: *NPM1* (Type A, n=7; Type V, N=1), *DNMT3A* (R882H, n=4), *IDH1* (R132H, n=1) and *IDH2* (R140Q, n=2; R172K, n=2). Variant Allele Frequencies (VAF) of BM- and ctDNA-samples correlated closely. Sensitivity of ctDNA samples was similar to ddPCR analyses of BM gDNA, and superior to pB cell gDNA. Mutations were detectable in ctDNA beyond pB blast clearance, and in one case a mutation present in EMD but not in BM was detected in ctDNA, indicating that ctDNA noninvasively captures relevant disease compartments. Absolute ctDNA levels correlated closely to known causes of cell turnover such as infections or BM regeneration. However, in cases in which both mutation VAF and absolute ctDNA levels rose, AML progressed.
Conclusions: We are currently investigating the prognostic value of response kinetics during treatment. Patient recruitment is ongoing, and updated data will be presented. ddPCR-based ctDNA analysis allows minimally invasive AML monitoring. ctDNA analyses may be more sensitive than pB-cell gDNA and may capture EMD.

Disclosure Statement: The authors have no conflicts of interest to disclose.

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MARS: Mutation-Adjusted Risk Score for Advanced Systemic Mastocytosis

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Purpose: With the aim to establish a prognostic score for advanced systemic mastocytosis (AdvSM), we evaluated a large cohort of clinically and genetically well characterized patients who were enrolled within the 'German Registry on Disoders of Eosinophils and Mast Cells'. The proposed mutation-adjusted risk score (MARS) was subsequently validated in an independent cohort of AdvSM patients derived from several centers within the European Competence Network on Mastocytosis (ECNM).
Methods: A total of 383 AdvSM patients were included. The diagnosis of AdvSM was established according to the WHO classification. Molecular analyses were performed at diagnosis. Targeted Next-Generation Sequencing (NGS) was performed to investigate mutation status of *KIT* and 32 myeloid genes.
Results: In multivariable analysis, the following risk factors were identified as being associated with overall survival (OS): age greater than 60 years, anemia (hemoglobin < 10 g/dL), thrombocytopenia (platelets < 100 < 10^9/L), presence of one high molecular risk gene mutation (ie, in *SRSF2*, *ASXL1*, and/or *RUNX1*), and presence of two or more high molecular risk gene mutations. By assigning hazard ratio–weighted points to these variables, the following three risk categories were defined: low risk (median

OS, not reached), intermediate risk (median OS, 3.9 years; 95% CI, 2.1 to 5.7 years), and high risk (median OS, 1.9 years; 95% CI, 1.3 to 2.6 years; P < .001). The MARS was independent of the WHO classification and was confirmed in the independent validation set. During a median follow-up time of 2.2 years (range, 0 to 23 years), 63 (16%) of 383 patients experienced a leukemic transformation to secondary mast cell leukemia (32%) or secondary acute myeloid leukemia (68%). The MARS was also predictive for leukemia-free survival (P < .001).
Conclusions: The MARS is a validated, five-parameter, WHO-independent prognostic score that defines three risk groups among patients with AdvSM and may improve up-front treatment stratification for these rare hematologic neoplasms.

Disclosure Statement: nothing to disclose

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Accurate and Reproducible Measurement of BCR-ABL1 (IS) Using Digital PCR: Results from a EUTOS Ring Trial

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Purpose: BCR-ABL1 positive chronic myeloid leukemia is monitored by quantitative PCR (RTqPCR). To compare results between different laboratories alignment to the International Scale (IS) using a conversion factor (CF) is required, involving a cumbersome process of sample exchange or lyophilized cell reference material (the LYO-panel)[1]. We evaluated digital PCR (dPCR) for monitoring BCR-ABL with regards to interlaboratory variation, ability to detect deep molecular responses and the CF within the European Treatment and Outcome Study for CML (EUTOS) consortium.
Methods: Assays for BCR-ABL1 and the reference genes (RG) ABL1 (provided by Bio-Rad) and BCR (provided by NP) were shipped to 7 laboratories together with the LYO Panel. Samples were prepared and measured in quadruplicate on two days using local RNA extraction and reverse transcription and the provided assays. Valid results were returned from 6 labs for central analysis.
Results: Mean %BCR-ABL1/ABL1 for MR1 to MR4.5. was 14.99% (range, 12.23 – 16.95%), 1.36% (0.97 – 1.68%), 0.109% (0.080 – 0.139%), 0.0128% (0.0105 – 0.0143%) and 0.0081% (0.0022 – 0.0182%), respectively, and 17.11% (14.09 – 23.46%), 1.25% (1.08 – 1.42%), 0.111% (0.090 – 0.135%), 0.0095% (0.0080 – 0.0120%) and 0.0064% (0.0032 – 0.0089%) for BCR-ABL1/BCR, respectively. %CV for ABL1 and BCR as RG, ranged from 11.3 for MR1 (%BCR-ABL/RG< 10%) to 78.9 for MR4.5 samples. CF to IS could be calculated for 4/6 labs for BCR and was 0.954 (mean, range 0.868 – 1.097), compared to only 2/6 labs for ABL1 with a mean CF of 1.023 (range 0.851-1.204). The main reason for not being able to calculate a CF was non-linearity at MR4.5.
Conclusion: Digital PCR reliably detects deep molecular responses. Interlaboratory variation was low and the calculated CFs for individual labs lay within a very narrow band, suggesting that digital PCR might overcome the need for a lab specific CF. This needs to be tested in a larger trial using optimized PCR settings for both assays.

Reference:
1. Cross NCP et al. Leukemia 2016

Disclosure Statement: The authors have nothing to disclose.

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Prognostic Significance of BAALC and MN1 Expression Levels During Disease Course in Acute Myeloid Leukemia (AML) Patients Receiving Allogeneic Stem Cell Transplantation (HSCT)

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Purpose: High pre-treatment expression of the AML-associated genes *BAALC* (brain and acute leukemia, cytoplasmic) & *MN1* (meningioma-1) links to adverse outcomes in patients (pts) receiving chemotherapy. The prognostic significance in pts receiving allogeneic HSCT for consolidation remains to be elucidated.
Methods: We analyzed 138 AML pts receiving non-myeloablative (3x30 mg/m^2 Fludarabine & 2 Gy total body irradiation) allogeneic HSCT (median age 64, range 32-76 years [y]) in complete remission (CR) or CR with incomplete recovery (CRi). Digital droplet PCR was applied to quantify absolute pre-treatment bone marrow *BAALC* & *MN1* copy numbers. For 66 pts, pre-HSCT peripheral blood *BAALC* & *MN1* copy numbers were assessed in CR/CRi. R's OptimalCutpoint package defined high & low expressers, pre-treatment & pre-HSCT respectively. At diagnosis recurrent mutations by next generation sequencing & flow cytometry patterns were analyzed. Median follow up was 6.3y.
Results: High pre-treatment *BAALC* & *MN1* copy numbers associated with a higher CD34 (*P*<.001 & *P*<.001, respectively) & CD34+/CD38- surface antigen expression on mononuclear cells at diagnosis (*P*<.001 & *P*<.001), lower incidence of normal karyotype (*P*=.008 & *P*=.04), worse ELN risk (*P*=.02 & *P*=.05), *NPM1* wild type (*P*<.001 & *P*<.001) & *RUNX1* mutations (*P*=.03 & *P*=.01). There was no correlation between pre-treatment & pre-HSCT *BAALC* (*r*=.14) or *MN1* copy numbers (*r*=-.06). High pre-treatment *BAALC* & *MN1* copy numbers associated with higher cumulative incidence of relapse (CIR, *P*=.05 & *P*=.05) while overall survival (OS) was not significantly different (*P*=.61 & *P*=.41). In contrast, we observed a significantly higher CIR for pts with high pre-HSCT *BAALC* (*P*=.05) or *MN1* copy numbers (*P*=.01) which also translated into shorter OS (*P*=.003 & *P*=.004).
Conclusions: While the adverse prognostic effects of high *BAALC* & *MN1* expression at AML diagnosis might be mitigated after allogeneic HSCT, high *BAALC* or *MN1* expression in CR/CRi prior to allogeneic HSCT may detect residual disease & identify patients at high risk of relapse & shorter survival.

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TET2 Mutation Associated Clonal Hematopoiesis is Linked to a TET2 Polymorphism in Acute Myeloid Leukemia Patients

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Purpose: *TET2* mutations (mut) can be detected in complete remission (CR), as persistent clonal hematopoiesis (CH), in about 16% of acute myeloid leukemia (AML) patients (pts). Several *TET2* single nucleotide polymorphisms (SNPs) represent missense variants and are linked to altered gene expression. We analyzed the *TET2* coding region for CH associated SNPs in AML.
Methods: Using a next-generation targeted amplicon sequencing (TAS) approach we analyzed *TET2* exons 3–11 in bone marrow samples at

diagnosis (dx) in 111 AML pts (median age 64, range 33-75 years) on the MiSeq platform (Illumina). In a subset of 75 pts in CR or CR with incomplete recovery (CRi) peripheral blood was tested for CH associated mut (*i.e.* in *ASXL1*, *DNMT3A*, *IDH1*, *IDH2*, *IKZF1*, *JAK2*, *PPM1D*, *SF3B1*, *SRSF2* & *TET2*) applying TAS. Mut with variant allele frequency (VAF) <3% were excluded from further analyses. Outcome analyses were performed in 102 of these pts; receiving allogeneic hematopoietic stem cell transplantation (HSCT) in CR/CRi. Median follow up was 6.0 years.
Results: In *TET2* SNP rs34402524 (c.5162T>G; p.Leu1721Trp) minor allele (G) presence vs absence associated with *TET2* CH mut (26% vs 5%, P=.02), but not with the presence of CH mut in one of the other analyzed genes, *e.g.* in *DNMT3A*. *TET2* SNP rs34402524 allele distribution was 86% T & 14% G. The minor allele SNP frequency in AML was comparable to healthy caucasians (12% GnomAD; P=.18). The incidence of *TET2* mut at dx did not differ between pts with minor allele (G) presence vs absence (18% vs 26%, P=.41). The mean VAF of *TET2* CH mut did not vary for pts with minor allele (G) presence vs absence (21% vs 32%, P=.49). Pts with minor allele (G) undergoing HSCT were by trend less likely to suffer relapse (32% vs 53%, P=.08), but had no different overall survival (P=.70).
Conclusions: We found the minor allele (G) in *TET2* SNP rs34402524 to be linked to *TET2* mut associated CH in AML pts, but not to the presence of *TET2* mut at dx. Further analyses of a larger set of pts and functional studies will improve our understanding of *TET2* mut associated CH in AML.

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Comparison of Four Different Humanized Hematopoietic Niche Xenotransplantation Models to Engraft Myelodysplastic Syndromes (MDS)

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Purpose: Xenograft models in NSG mice have emerged as versatile preclinical platforms for investigation of functional pathomechanisms in MDS ([1] Medyouf et al., 2014, [2] Rouault-Pierre et al., 2017). The limiting factor of these models is the low engraftment of patient-derived CD34+ hematopoietic stem cells (HSCs). Efficient humanized 3D scaffolds in NSG mouse models have been established, enabling to increase engraftment rates of normal and malignant hematopoiesis ([3] Reinisch et al., 2016current models do not fully mimic the components of the human bone marrow (BM, [4] Abarrategi et al., 2017). Therefore, we evaluated engraftment ability of IPSS low-risk, int-1 and high-risk-patient samples, in four different 3D scaffolds.
Methods: We transplanted samples from 10 MDS patients in parallel into NSG mice testing the following conditions: A) Intrafemoral co-injection of CD34+ HSCs and MSCs according to [1]. Subcutaneous implantation of 3D scaffolds. Gelfoam (B) and Bio-OSS (C) [4], Matrigel ossicles (D) [3] and primary human bone isolated after hip replacement, inserted with Gelfoam, preseeded in vitro with MSCs and mononuclear cells (MNCs) and injected in vivo with CD34+ HSCs 8 weeks after implantation (human bone ossicles = HBO) (E).
Results: Gelfoam and HBO showed significantly higher hCD45+cell numbers compared to intrafemoral injection analyzed by flow cytometry. We found systemic engraftment of hCD45+cells outside the injected bone fragment in the BM and spleen solely in mice, which received HBO. This could possibly be explained due to transplantation of MNCs in this condition. That was supported by another set of experiments using HBO (n=10), which showed that colonization of the scaffold was similar when transplanting either CD34+ cells + MSCs, MNCs + MSCs or MNCs only but systemic engraftment could only be seen in MNC transplanted mice.
Conclusions: Our data show that hCD45+cells and MSCs from MDS BM were able to colonize humanized ossicle scaffolds. Gelfoam and HBO were the most promising novel methods to improve MDS xenograft models. For systemic engraftment, application of MNCs seems to be necessary.

Disclosure Statement: nothing to disclose

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Treatment with Romiplostim in Patients with Lower-Risk Myelodysplastic Syndrome (MDS) and Thrombocytopenia - Results of the Europe Trial By the Emsco Network

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Purpose: The thrombopoietin receptor agonist (TPO-RA) romiplostim has shown safety and efficacy in a poorly-defined subset of lower-risk (LR) myelodysplastic syndrome (MDS) patients with thrombocytopenia.
Methods: The *EUROPE* multicenter phase 2 trial investigated the impact of endogenous thrombopoietin (TPO) level and platelet transfusion events (PTE) on the efficacy of romiplostim treatment in patients with LR-MDS (IPSS low/int-1). Patients were eligible if baseline bone marrow blast count was <5% and platelet counts were ≤30 G/L or ≤50 G/L in case of bleeding history. Patients were assigned into 3 different cohorts at the time of screening based on their previous PTE and TPO serum levels (cohort A TPO<500 ng/l, PTE<6U/past year; cohort B: TPO<500 ng/l, PTE≥6U or TPO≥500 ng/l, PTE<6U, cohort C: TPO≥ 500 ng/l, PTE≥6U). Primary endpoint of the study was the rate of hematologic improvement of platelets (HI-P) according to IWG 2006 criteria after 16 weeks of romiplostim treatment.

Results: A total of 68 patients with a median platelet count of 25 G/L (range 1-50 G/L) were included and stratified into cohort A (n=47), B (n=17) or C (n=4), respectively. Two patients had transient increases in peripheral blasts to >10% and 1 patient progressed to AML after 1 month of treatment. HI-P was observed in 26 of 68 (38%) patients, while response was ongoing in 24 of them beyond week 16. Rate of HI-P lasting for at least 8 weeks was higher in cohort A (45%) compared to patients in cohort B and C (24%) (p=0.11). Explorative analysis showed a correlation between pretreatment PTE and endogenous TPO-levels (p=0.034). Evaluation of the mutational profile in a subgroup of 49 patients demonstrated that 67% of responders exhibited spliceosome mutations compared to 35% in non-responders (p=0.06).
Conclusions: The EUROPE study confirms that romiplostim treatment is effective in a subgroup of LR-MDS patients, neither baseline PTE nor baseline TPO levels were significantly associated with response. Further translational studies are ongoing to elucidate biomarkers of response.

Disclosures: Study funding from Amgen

Lung Cancer

Poster

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Treatment Patterns of EGFR MT+ NSCLC IV PTS: Real World Data of the Nowel Network

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Purpose: The percentage of pts switching from 1st gen TKI in 1st line to 3rd gen TKI in 2nd line seems to be low with 30% and it is questionable whether these data represent real world treatments[1]. Therefore, we investigated the treatment pattern and especially the attrition rate between 1st and 2nd line therapy in EGFR mt+ pts.
Methods: 965/1536 (63%) pts with non-squamous NSCLC IV were tested for EGFR mt+. 148/965 (15%) pts with an EGFR mt+ were identified. To calculate PFS and OS we used Kaplan Meier and the log rang test for p-values.
Results: 144/148 pts were treated with TKI on 1st or 2nd line (after chemotherapy). 14/144 pts are still on 1st line, 9 pts were lost to follow-up and 3 pts died while on 1st line. We identified 118/144 candidates for 2nd line therapy (because of progression on 1st line TKI) and only 84/118 (70%) pts received a 2nd line therapy. 30% (36/118) of pts did not receive a 2nd line therapy because of bad PS (n=26), pts refusal (n=2), fast progression (n=6) and death (n=2). After accessibility of 3rd gen TKI 72 pts were candidates for 2nd line treatment and 51/71 pts (71%) received a 2nd line therapy. mOS of pts receiving 2nd line therapy after access to 3rd gen TKI was 35 mo for pts with 2nd line therapy vs. 10 mo without 2nd line (p<0.000). 32/51 pts (63%) were tested for T790M and 20/32 (62%) were T790M+. Highest T790M test rate in one center was 22/28 (79%). 16/20 (80%) T790M+ pts received 3rd gen TKI for 2nd line therapy. mOS of pts receiving 3rd gen TKI (n=31) was 51 mo vs. 25 mo for pts without 3rd gen TKI (p<0.002).
Conclusions: A significant number of pts treated with 1st or 2nd gen TKI do not reach 2nd line therapy even with broad accessibility of 3rd gen TKI. Reasons for not receiving 2nd line therapy are in most cases deterioration of PS, death and no testing for T790M in a minority of cases. These data are important for the interpretation of the OS data of the FLAURA study[1] as they reflect real world treatment algorithms in dedicated German lung cancer centers.

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Conflicts of Interest:
Julia Roeper: Honorarium: Roche, Boehringer Ingelheim
Markus Falk: The authors declare no potential conflict of interest.
Ursula Stropiep: The authors declare no potential conflict of interest.
Markus Tiemann: Honorarium: Astra Zeneca, Boehringer Ingelheim, Novartis, Roche, Pfizer, Takeda, BMS, MSD
Travel costs: Boehringer Ingelheim, Roche, Takeda, BMS, MSD
Lukas C. Heukamp: Honararium: NEO New Oncology, BMS, Bayer, Roche, Pfizer
Advisory board: NEO New Oncology, BMS, Bayer, Roche, Pfizer
Class Wessler: The authors declare no potential conflict of interest.
Sandra Sackmann: The authors declare no potential conflict of interest.
Frank Griesinger: Honorarium: Astra Zeneca, Boehringer Ingelheim, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Ariad, Abbvie, Siemens
Advisory board: ASTRA, Boehringer, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Ariad, Abbvie, Siemens
Research fund: Astra Zeneca, Boehringer, BMS, Celgene, Lilly, MSD, Novartis, Pfizer, Roche, Takeda, Siemens

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Sophisticated Epitope Quality-Based Approach Reveals Patient's Suitability for Immune Checkpoint Inhibition

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Purpose: Immune checkpoint inhibition, especially the blockade of PD-1 and PD-L1, has developed into one of the most prosperous therapeutic approaches in modern oncology. Despite promising clinical results, resistance acquirement remains a perpetual problem[1]. One possible escape mechanism, which mediates therapy failure might be linked altered epitope processing (processing escapes)[2]. In the present study, we aim to demonstrate the effects of processing escapes on immunotherapy outcome in NSCLC-patients.
Methods: The cohort was comprised of primary tumor samples from 48 NSCLC-patients. Everyone received Nivolumab at one point of their treatment. Mutations were identified by targeted amplicon-based sequencing including hotspots and whole exomes of 22 genes. Convolutional neural networks were utilized to examine the effect of mutations on proteasomal processing. The algorithm was previously trained on 1260 known MHC-I ligands. Possible influences on Overall survival were calculated by Cox-regression.

Results: In the validation cohort, patients displaying both processing escapes and high expression rates PD-L1 (n=8/48) showed significantly shortened overall survival, independent of mutational load or PD-L1 status alone in multivariate analysis.
Conclusions: The concept of altered epitope processing might broaden our horizon in understanding immune therapy failure. Especially when combined with PD-L1 status, this method could provide important negative predictive value, potentially becoming a foundation in the I/O therapy decision process.

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Disclosure Statement: All authors formally declare that there are no conflicts of interest

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Long Time Remission in NSCLC Stage iv After Stopping Immunotherapy Due to Severe Side Effects - a Report of Two Cases

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Purpose: Immunotherapy is an important element in the treatment of NSCLC. Side effects of immunotherapy due to autoimmune reactions can lead to severe problems.
Methods: We report two cases with long time remission after stop of Immunotherapy due to side effects
Results:
Case 1: A 62 y old male was diagnosed with NSCLC; adeno cancer stage IV in September 2017. No targetable mutations were found, PDL1 was 50%. An Immunotherapy with Pembrolizumab was initiated in October. CT scan in December 2017 demonstrated PR. Brain metastases were irridiated in November and December 2017. In December, the patient developed interstitial pneumonia WHO grade 3 and was treated with high dose corticosteroids. The immunotherapy was therefore terminated after 2 cycles in 2017. The patient shows still stable disease without progression until August 2019.
Case 2: A 61 y old male was diagnosed with NSCLC; adeno cancer stage IV in January 2017. No targetable mutations were found, PDL1 was 60%. An immunotherapy with Pembrolizumab was initiated in February 2017. The CT Scan showed PR after 4 cycles in May 2017 and SD after 12 cycles in November 2017. In November 2017 the patient developed autoimmune colitis WHO grade 3 and was treated with high dose corticosteroids. The immunotherapy was therefore terminated after those 12 cycles. The patient shows still stable disease without progression until August 2019.
Conclusions:
When immunotherapy has reached a remission and has to be terminated due to immunologic complications, the complications have to be treated with immunosuppressive therapy. After the remission of the side effects, the patients might be followed up without systemic therapy under close clinical observation. In some cases, SD persists. Further tumor-specific therapy should be only considered, if PD is documented.

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Delays and Delaying Factors from Symptoms to Diagnosis in Lung Cancer

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Purpose: The majority of lung carcinomas are diagnosed and treated in a late stage. One reason might be long delays between first symptoms, diagnosis and treatment. This study was conducted to identify delays during the management of patients with lung cancer to assess possible causes for these delays and to analyze the impact of delays on survival.
Methods: Patients with recently diagnosed lung cancer were prospectively included. Delays were calculated as: patient's delay (first symptom to first general practitioner visit); GP delay (first GP visit to specialist appointment); specialist's delay (specialist appointment to hospital referral); hospital delay (hospital referral to diagnosis) and treatment delay (diagnosis to therapy initiation). Delays were analyzed in relation to clinical characteristics and factors for delays were assessed by uni- and multivariate analyses.
Results: 220 patients were included (60.9% male; median age of 63.5 years; 30.3% SCLC, 77.7% ex-smokers). The median patient's delay, GP delay, specialist's delay, hospital delay and treatment delay was 5 days (mean 20.9), 15 days (mean 38.9), 11 days (mean 27.2), 8 days (mean 14.3) and 15 days (mean 21.4) respectively. Diagnostic intervals were shorter for patients with SCLC vs NSCLC (median 10.5 vs 16 days, p=0.004) and for late-stage vs early-stage cancer (median 6 vs 9 days, p=0.025). Patients <65 years had longer total delay vs those ≥65 years (median 66 vs 49 days, p=0.035). Patients with dyspnea, cough or hemoptysis had longer patient's delay than those without (median 5 vs 3 days, p=0.020), but a shorter treatment delay (median 14 vs 19 days, p=0.048). No significant effect on survival was observed in this cohort.
Conclusions: There are varieties of causes leading to delays during the diagnosis of lung cancer. This study provides some insights, which may help to reduce waiting times by raising awareness of certain demographics and symptoms and shortening the referral times to improve the overall outcome for lung cancer patients.

Disclosure Statement: The authors declare that there is no conflict of interest.

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Relay: a Multinational, Double-Blind, Randomized Phase 3 Study of Erlotinib (ERL) in Combination with Ramucirumab (RAM) or Placebo (PL) in Previously Untreated Patients with Epidermal Growth Factor Receptor Mutation-Positive (EGFRM) Metastatic Non-Small Cell Lung Cancer (NSCLC)

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Purpose: RELAY evaluated efficacy and safety of erlotinib (ERL)+ramucirumab (RAM) or placebo (PL) in 1L epidermal growth factor receptor mutation-positive (EGFRm) metastatic non-small cell lung cancer (NSCLC).
Methods: Eligibility: untreated metastatic NSCLC patients (pts) with Exon19 deletion (del) or L858R and no CNS metastasis. Randomized (1:1) pts received ERL (150mg/day) +RAM (10mg/kg q2w) or ERL+PL, stratified by gender, geographic region (East Asia vs other), EGFRm type (Ex19del vs L858R) and EGFR testing method. Primary endpoint was investigator-assessed progression free survival (PFS). Other objectives: overall response rate (ORR), duration of response (DoR), PFS2, overall survival (OS), safety and plasma T790M mutation.
Results: 449 pts were randomized. Baseline characteristics were balanced between treatment arms: Asian 77%, Females 63%, Ex19del 54%. PFS was significantly prolonged in the RAM-ERL vs PL-ERL group (medians 19.4 months [mos; 95%CI 15.4, 21.6] vs 12.4 mos [95%CI 11.0, 13.5], stratified hazard ratio [HR] .591; 95%CI .461, .760; p<.0001). ORR was similar between groups (76.3% [95%CI 70.8, 81.9] vs 74.7% [95%CI 69.0, 80.3]). DOR was longer for pts responding in the RAM-ERL group (medians, 18.0 mos [95%CI 13.9, 19.8] vs 11.1 mos [95%CI 9.7, 12.3], unstratified HR .619; 95%CI .477, .805; p=.0003); OS data were immature (82% censoring, medians not reached [NR], HR .832 [.532-1.303]; p=.4209). PFS2 favored RAM-ERL (69% censoring rate, medians NR, HR .690, 95%CI .490, .972; p=.0325). Grade≥3 treatment-emergent adverse events were greater with RAM (72%) vs PL (54%), largely driven by hypertension (24 vs 5%, no Grade 4), with 1 treatment related on study death (hemothorax) in RAM vs 0 PL. EGFR T790M+rates at progression are forthcoming.
Conclusions: RAM+ERL led to superior PFS in 1L EGFRm metastatic NSCLC. Safety was consistent with the established safety profiles of the individual compounds.

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NAB-Paclitaxel Plus Carboplatin As First-Line Therapy for Patients with Advanced NSCLC in the Real-World Setting: Safety Results of the Non-Interventional Neptun Study

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Purpose: In patients with non-small cell lung cancer (NSCLC), the combination of nab-paclitaxel plus carboplatin is a standard first-line regimen. The favorable efficacy and safety profile of this combination has been shown in a pivotal phase 3 trial and was confirmed for various patient subpopulations in the consecutive ABOUND studies. The prospective non-interventional study NEPTUN was designed to analyze effectiveness, safety and tolerability of this regimen in the real-world setting in Germany.
Methods: In total, 400 patients with stage IIIB/IV NSCLC scheduled to receive nab-paclitaxel and carboplatin as first-line therapy were planned to be recruited in 100 outpatient centers and hospitals across Germany. Primary endpoint was the six-month progression-free survival rate. Key secondary endpoints included further effectiveness parameters, safety and quality of life (QoL). Descriptive statistics were used to analyze data. The second interim analysis of the NEPTUN study was scheduled to analyze effectiveness and safety data as well as QoL. Here, we will focus primarily on the safety results.
Results: Between 08/2016 and 06/2019 408 patients have been enrolled at 74 active sites. Baseline patient and tumor characteristics including age, ECOG, co-morbidities, histology, and treatment details including dose modifications and reasons will be presented. Safety and tolerability data will be analyzed including incidence of (severe) adverse events, adverse drug reactions and use of supportive care.
Conclusions: The NEPTUN study demonstrates an acceptable safety profile of nab-paclitaxel and carboplatin in patients with advanced NSCLC in a real-world setting. Toxicity is generally mild and manageable, supporting the use of this regimen as a first-line treatment option.

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Single-ARM Phase II-STUDY in Patients with Extensive Stage Small-Cell Lung Cancer (ES-SCLC) with Poor Performance Status Receiving atezolizumab-Carboplatin-Etoposide (Space; AiO-TRK-0119)

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Purpose: Small-cell lung cancer (SCLC) is an aggressive tumor with an unfavorable prognosis that accounts for approximately 15% of all lung cancers. Two in three patients (pts) diagnosed with SCLC have metastases (extensive disease, ED) at primary diagnosis. Platinum-based doublet chemotherapy has been the palliative standard of care in these pts for over 30 years[13].
Addition of the PD-L1-antibody atezolizumab results in a significant and meaningful OS benefit in patients with ED-SCLC, as shown in the IMpower133 trial[4]. The trial excluded pts with low performance status, that account for approximately one-third of all SCLC pts; therefore, to date no

data is available regarding safety and efficacy of the triplet combination in this population.
The SPACE study plans to include 70 pts with low performance status to provide a reasonable estimate of the primary study endpoint of the 1-year survival rate; secondary endpoints are response rate, progression-free survival, safety and quality of life.
Methods: Treatment naive pts with ECOG=2 will receive induction treatment consisting of four 21-day cycles of carboplatin (AUC of 5 mg/mL/min, IV, d1) and etoposide (cumulative total dose of ≥300 mg/m², IV on 3 consecutive days) with atezolizumab (1200 mg IV, d1), followed by a maintenance phase during which pts receive atezolizumab (Q3W) until the occurrence of unacceptable toxicity, disease progression or withdrawal of consent or death.
Results: Recruitment not yet started.

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Disclosure Statement: SPACE (EudraCT 2019-001707-21) study sponsor is AIO-Studien-gGmbH; Berlin. The study is financially supported by F. Hofmann-la Roche.

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Neoadjuvant Immune Checkpoint Inhibition in Resectable Lung Cancer

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Purpose: Pharmacological inhibition of programmed cell death (PD-1) protein improves survival in patients with advanced non-small-cell lung cancer (NSCLC) [1]. The clinical effect of neoadjuvant immune checkpoint inhibition (ICI) in patients with resectable or oligometastatic disease is scarcely explored.
Methods: Retrospective single-center cohort analysis. Tissue biopsies of NSCLC in advanced stage were tested for PD-L1 expression. In patients with PD-L1 expression > 50%, ICI were administered before surgery with surgery planned approximately 4 weeks after the first dose. Clinical tolerance, radiological and histological tumor response and oncological outcome were analyzed.
Results: Between 2017 and 2019 four patients (2 male, 2 female; age 56-78 years) received ICI before tumor resection. Tumor histology was adeno carcinoma in 3 and squamous cell carcinoma in 1 case. All patients had locally advanced tumors T3 or T4. Mediastinal lymph nodes were positive in 3 cases. In one patient, a single brain metastasis was present that was treated by radiotherapy. All patients received at least 2 cycles ICI before surgery (Pembrolizumab in 3 cases, Atezolizumab in 1 case). ICI therapy was well tolerated and did not delay surgery. According to RECIST criteria, 3 tumors showed partial remission and 1 patient progressive disease. All tumors were resected completely. Pathological workup of the surgical specimen confirmed complete pathologic response (CPR) in 2 and partial pathologic response (PPR) in 2 cases. Mean follow up is 12 months (1-24). PPR patients developed either distant metastasis after 6 months or local recurrence after 4 months.
Conclusions: ICI is well tolerated in the neoadjuvant setting for NSCLC and may induce total tumor remission in selected patients. Therapy does not interfere with surgery and is well tolerated by patients. Prognosis is very promising in CPR and limited in PPR.

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Disclosure Statement: The authors declare no conflict of interest.

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Non-Invasive Molecular Profiling for Therapy Monitoring of ALK+ Lung Cancer

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Purpose: Non-small cell lung cancer (NSCLC) patients with *ALK* rearrangements are routinely treated with tyrosine kinase inhibitors (TKIs), leading to improved survival. However, clinical courses vary widely as the tumors inevitably develop resistance. Thus, early detection and molecular characterization of treatment failure is important for patient outcome.
Methods: To identify indicators of therapy response and progression, we performed an analysis of circulating tumor DNA (ctDNA) from serial plasma samples (n=278) of 73 NSCLC patients with *ALK* rearrangements. Using targeted sequencing and shallow whole genome sequencing (sWGS), we achieved mean unique coverages of >4000x and 0.5x, respectively.
Results: Variable mutation levels were marked in all patients and correlated with clinical features. For example, mutant ctDNA levels were low in cases of stable disease, but increased at the time of TKI failure. Targeted sequencing identified known and novel mutations indicating TKI resistance. We also found mutated *TP53* at the time of progression in patients with initially *TP53* wildtype tumors. The progression-free survival of patients with acquired *TP53* mutations was comparable to that of primarily *TP53* mutated and shorter than that of persistently *TP53* wildtype cases. sWGS of ctDNA identified copy number variations, some of which might contribute to tumor progression. We also measured miRNA abundances in corresponding serum samples and noted fluctuating miRNA levels during therapy that correlated with the clinical course in several cases.
Conclusions: Our data suggest that liquid biopsies can improve ALK⁺ NSCLC patient care through early detection of progression and tailored treatment of resistant tumors. ctDNA and miRNA can indicate the need to switch treatment and provide information to guide the next-line therapy. Detection of acquired *TP53* mutations in liquid rebiopsies at the time of disease progression identifies additional high-risk cases and suggests potential clinical utility of ctDNA monitoring for this disease beyond profiling of *ALK* resistance mutations.

Conflicts of Interest:
SD reports speaker's honoraria from Roche;
PC reports research funding from Novartis, Roche, AstraZeneca and Takeda as

well as advisory board and/or lecture fees from Boehringer, Pfizer and Chugai;
AV reports speaker's honoraria from Astra Zeneca;
VE reports advisory board and lecture fees from AstraZeneca and ThermoFisher;
MT reports advisory board honoraria from Novartis, Lilly, BMS, MSD, Roche, Celgene, Takeda, AbbVie, Boehringer, speaker's honoraria from Lilly, MSD, Takeda, research funding from AstraZeneca, BMS, Celgene, Novartis, Roche and travel grants from BMS, MSD, Novartis, Boehringer;
AS reports advisory board honoraria from BMS, Bayer, AstraZeneca, ThermoFisher, Novartis, Seattle Genomics speaker's honoraria from BMS, Bayer, Illumina, AstraZeneca, Novartis, ThermoFisher, MSD, Roche, as well as research funding from Chugai, Bayer and BMS;
HS reports advisory board and speaker's honoraria from Roche.

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Patients with Metastatic Non-Small Cell Lung Cancer and Targetable Molecular Alterations in Germany. Treatment and First Outcome Data from The Prospective German Registry Platform Crisp (AIO-TRK-0315)

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Purpose: Guidelines for stage IV NSCLC recommend stratified treatment by biomarker test results. We used CRISP to evaluate treatment and outcome of patients (pts) with targetable molecular alterations.
Methods: Currently 163 sites in Germany have recruited >4255 pts at start of 1st-line who will be followed until death or end of project. Data from 2204 pts recruited by 133 sites from 12/2015 to 06/2018 was analyzed. Progression-free survival (PFS) was determined in pts observed ≥1 year (recruited <06/2017 (n=906), outcome sample (ous)).
Results: 94%/65% of 1732/472 pts with non-squamous/squamous tumors were tested for any biomarker. In 2018 test rate was 96%/75% and 49%/33% were tested for all biomarkers (EGFR, ALK, ROS1, BRAF) with approved targeted therapies (aTT). An alteration in EGFR, ALK, ROS1 or BRAF was detected in 9%, 3%, 2%, and 2% of pts, respectively. Of pts with druggable EGFR mutation (EGFR+ pts, n=149) 78% received EGFR-aTT in 1st-line. In 2nd-line, 20% received EGFR-aTT, 15% something else, 11% died prior to 2nd-line, 54% were still in 1st-line. Median PFS of EGFR+ pts was 7.1 months (n = 67, 61% events, 95%-CI 5.2-10.1), in total 46% (n=31) of pts had died (ous). Of pts with druggable ALK alteration (n=55), 47% received ALK-aTT in 1st-line. In 2nd-line, 22% received ALK-aTT, 11% something else, 13% died prior to 2nd-line, 54% were still in 1st-line. In the ous (n=29), 55% (n=16) of tumors had already progressed, in total 24% (n=7) of pts had died. All 6 pts with druggable ROS1 alteration received chemotherapy, while 6 of the 9 pts with druggable BRAF mutation and start of treatment in 2017/18 received a BRAF-ATT in 1st-line.
Conclusions: Pts are frequently tested for molecular alterations. While EGFR-aTT is well established as 1st-line and first data are promising for BRAF-aTT, pts with ALK/ROS alteration are not routinely treated with 1st-line aTT, reasons are not yet clear.

Disclosure Statement: None of the authors has declared a conflict of interest regarding the subject of this work.

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Patients with Metastatic Non-Small Cell Lung Cancer and PD-L1 Expression in Germany. Treatment and First Outcome from the Prospective German Registry Platform Crisp (AIO-TRK-0315)

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Purpose: Treatment guidelines for stage IV NSCLC recommend stratified treatment according to biomarker testing results. We used CRISP to evaluate treatment and outcome of patients (pts) with PD-L1-expressing tumors.
Methods: Currently 163 centers in Germany have recruited over 4255 pts at start of 1st-line who will be followed until death or end of project. Data from 2204 pts recruited by 133 centers between 12/2015 and 06/ 2018 was analyzed regarding PD-L1 testing, treatment and outcome. Progression-free survival (PFS) was determined in patients being ≥1 year under observation (recruited until June 30th 2017 (n=906), outcome sample, (ous)).
Results: Test rates for PD-L1 increased from 25% (2016) to 75% (2018) in pts with non-squamous tumors (n=1732), and from 20% (2016) to 62% (2018) in pts with squamous tumors (n=472). PD-L1 TPS was ≥50% in 16% of pts, 1-49% in 18% of pts, and <1% in 7% of pts, while 3%/12% of pts were classified by pathologists as PD-L1 positive/negative with TPS not specified. In 9% and 4% an EGFR or ALK alteration was also detected, respectively.
Of all pts with PD-L1 TPS≥50% 70% received pembrolizumab-based 1st-line treatment, 21% chemotherapy and 9% another/targeted therapy. At database cut, 20% had started 2nd-line, 19% had died prior to a 2nd-line and remaining pts were still in 1st-line. In the ous, median PFS of all pts with PD-L1 positive tumors was 4.4 months (62% events, 95%-CI 3.5-5.5 months, n=185), in pts with PD-L1 TPS≥50% (n=83) so far 53% had a progression after 1st-line. In total, 49% of pts with PD-L1 positive tumors and 41% of pts with PD-L1 TPS≥50% had died (ous).
Conclusions: Testing for PD-L1 has been quickly integrated into routine care diagnostics. The majority of pts with PD-L1 positive tumors and a TPS≥50% receive an immune-oncology therapy. The impact of these

novel targeted treatment approaches on the outcome of pts will be subject of future analyses.

Disclosure Statement: None of the authors has declared a conflict of interest regarding the subject of this work.

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Patients with Metastatic Non-Small Cell Lung Cancer without Molecular Alterations or PD-L1 Expression in Germany. Treatment and First Outcome from The Prospective German Registry Platform Crisp (AIO-TRK-0315)

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Purpose: Guidelines for stage IV NSCLC recommend stratified treatment by biomarker test results. We used CRISP to evaluate treatment and outcome of patients (pts) in whom neither targetable molecular alterations nor any PD-L1 expression were detected.
Methods: Currently 163 sites in Germany have recruited >4255 pts at start of 1st-line who will be followed until death or end of project. Data from 2204 pts recruited by 133 sites from 12/2015 to 06/2018 was analyzed. These pts started treatment prior approval of immune checkpoint inhibitors (ICI) for this group of pts. Progression-free survival (PFS) was determined in pts ≥1 year under observation (recruited until 06/2017 (n=906), outcome sample (ous)).
Results: 6% of pts with non-squamous (nsq) and 35% with squamous (sq) tumors received no type of biomarker testing prior to start of 1st-line, and in 49% and 36% no targetable alterations or any PD-L1 expression were detected. Thus, 55% and 71% of pts (nsq/sq) were eligible for chemotherapy (ctx) but no type of targeted therapy at start of 1st-line.
In 1st-line, pts received carboplatin- (55%) or cisplatin-based ctx (24%), 13% targeted therapy (e.g. ICI in trial, switch to TKI but test result not yet documented).
At database cut, 33% of all pts had started 2nd-line, 24% had died prior to a 2nd-line and remaining pts were still in 1st-line. In the ous, median PFS was 5.0 months (66% events, 95%-CI 4.5-5.5 months, n=457) for nsq tumors and 4.5 months (66% events, 95%-CI 3.4-5.3 months, n=154) for sq tumors. In total 55% of pts with nsq and 53% of pts with sq tumors had died.
Conclusions: Despite break-throughs with targeted therapies and high test rates in routine care, the majority of pts do not qualify for targeted therapy. First outcome results indicate that prognosis is poor in these pts. Outcome will hopefully improve in the cohort now treated with ctx-ICI combination.

Disclosure Statement: None of the authors has declared a conflict of interest regarding the subject of this work.

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Caspian: Os Results from a Randomised Phase 3 Study of First-Line Durvalumab ± Tremelimumab + Chemotherapy in ES-SCLC

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Purpose: Immune checkpoint blockade targeting the PD-1/PD-L1 pathway in combination with platinum-based chemotherapy (CT) has demonstrated improved clinical outcomes in patients (pts) with extensive-stage small-cell lung cancer (ES-SCLC). Treatment with durvalumab (D), a selective, high-affinity, human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80, and tremelimumab (T), a selective human IgG2 mAb against CTLA-4, may provide possible additive or synergistic effects. Durvalumab demonstrated durable clinical activity and had a manageable safety profile both as monotherapy and in combination with tremelimumab in pts with pretreated ES-SCLC (NCT01693562; NCT02261220; NCT02937818). CASPIAN (NCT03043872) is a randomised, multicentre, open-label, sponsor-blind, Phase 3 study of Durvalumab ± Tremelimumab in combination with etoposide and platinum-based CT (EP) as first-line treatment for pts with ES-SCLC.
Methods: In total, 804 pts were randomised 1:1:1 to receive D 1500 mg + T 75 mg + EP q3w for 4 cycles, followed by D 1500 mg q4w until disease progression (PD), with one additional dose of T given post EP (Arm 1); D 1500 mg + EP q3w for 4 cycles, followed by D 1500 mg q4w until PD (Arm 2); or EP q3w for 4–6 cycles with prophylactic cranial irradiation if indicated (Arm 3). Randomisation was stratified by platinum-based CT in cycle 1 (carboplatin vs cisplatin). Pts had histologically or cytologically documented ES-SCLC, WHO/ECOG PS 0 or 1 and were suitable to receive first-line platinum-based CT. The primary endpoint was overall survival (OS) for D ± T + EP versus EP. Secondary endpoints included progression-free survival (PFS); objective response rate; landmark OS and PFS rates; safety and tolerability; pharmacokinetics; immunogenicity; quality of life.
Results: Results will be presented at WCLC 2019 including OS, key secondary endpoints, safety and tolerability.
Conclusions: Not applicable.

Reference:
1. Paz-Ares, L. et al., WCLC 2019, Barcelona, #2265

Disclosure Statement: Funding by AstraZeneca

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Clinical and Molecular Predictors for The Development of EGFR T790M at Failure of First- or Second-Generation EGFR Inihibitors

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Purpose: Approximately half of epidermal growth factor receptor (EGFR)$^+$ non-small cell lung cancer (NSCLC) patients failing first- or second-generation EGFR inhibitors (TKI) feature *EGFR* T790M mutations and sensitivity to osimertinib, but it is unclear at present which factors determine this constellation.
Methods: We retrospectively analyzed EGFR$^+$ NSCLC patients that underwent T790M testing at the time of TKI failure at our institutions.
Results: *EGFR* T790M testing was performed for 182 cases using liquid biopsies (n=53), tissue rebiopsies (n=110) or both (n=19). Median age was 64 years with a predominance of female (65%) never-/light-smokers (69%). A positive T790M result was noted in 101/182 patients (55%) and followed by treatment with osimertinib in 75/101, resulting in a significantly longer overall survival (52 vs. 30 months from start of first-line treatment, logrank p=0.001). Detection of T790M was positively associated with presence of *EGFR* exon 19 deletions (67% vs. 35% in del19$^+$ *vs.* del19$^-$ cases, p<0.001), and negatively associated with *EGFR* L858R (48% *vs.* 65%, p=0.047), "rare" *EGFR* mutations (18% *vs.* 60%, p=0.001) and presence of co-mutations at baseline in the 38-42 genes covered by our NGS panel, including *TP53* (42% *vs.* 58%, p=0.042). No significant relationship was noted with patient sex, age, smoking status, initial ECOG performance status, histology, previous nonmetastatic NSCLC, pattern of metastatic spread, lymphocyte-to-neutrophil ratio, use of palliative radiotherapy or surgery, but T790M$^+$ cases were slightly enriched among patients with first-line TKI treatment duration > 1 year (63% *vs.* 48%, p=0.035).
Conclusions: Acquired *EGFR* T790M mutations under first- or second-generation EGFR inihibitors are an important prognostic factor with major therapeutic relevance, but their development cannot be reliably predicted at present. Their associations with the type of *EGFR* mutation and presence of co-mutations suggest that deeper molecular profiling might facilitate identification of more accurate biomarkers.

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Osimertinib vs Comparator EGFR-TKI As First-Line Treatment for EGFRM Advanced NSCLC (Flaura): Final Overall Survival Analysis

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Purpose: Osimertinib, a 3rd generation, irreversible, oral EGFR-TKI potently and selectively inhibits both EGFRm and EGFR T790M and has demonstrated efficacy in NSCLC CNS metastases. The phase III FLAURA study (NCT02296125) compared 1st line osimertinib vs comparator EGFR-TKI in EGFRm advanced NSCLC. Median progression-free survival (PFS; primary analysis, DCO 06/12/2017) was significantly longer with osimertinib than comparator EGFR-TKI (18.9 vs 10.2 months; p<0.001). Overall survival (OS) data were immature (25% maturity) at the time of the primary publication.
Methods: Patients (pts; 556 globally) were randomised 1:1 to osimertinib 80 mg once daily (qd) orally (po) or comparator EGFR-TKI (gefitinib 250 mg qd or erlotinib 150 mg qd po) and stratified by race (Asian/non-Asian) and mutation status (Ex19del/L858R). Inclusion criteria: ≥18 years (Japan: ≥20); treatment-naïve with Ex19del/L858R EGFRm advanced NSCLC; WHO PS 0–1; neurologically stable pts with CNS metastases were allowed, provided definitive treatment/steroids were completed for ≥2 weeks. Treatment beyond progression (RECIST 1.1, per investigator) was allowed if clinical benefit continued; pts randomised to the comparator arm could crossover to osimertinib if T790M positive on progression (BICR confirmed). Primary endpoint: PFS by RECIST 1.1, per investigator. OS is a secondary endpoint. Safety and tolerability measures included adverse events (CTCAE v4), clinical and physical assessments.
Results: The data for final OS analysis (app. 60% maturity across both arms) is anticipated by 08/2019. At ESMO 2019 median OS, 2- and 3- year survival rates will be reported for each arm as well as OS across predefined subgroups including race and EGFR mutation type as well as updated safety data. We will for the first time provide FLAURA data on the prevalence of T790M mutations in different molecular subgroups (Ex19del/L858R) after progression on 1st line EGFR-TKI.
Conclusions: Not applicable.

Reference:

1. Ramalingam, SS et al., ESMO 2019, Barcelona, LBA to be submitted

Disclosure Statement: Funding by AstraZeneca

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Clinical Characteristics and Outcome of BRAF-Mutated Advanced NSCLC in Two Large German Lung Cancer Centers

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Purpose: BRAF-mutated non-small cell lung cancer (NSCLC) has been established as a molecularly defined subentity with specific clinical and biological characteristics. BRAF mutations can be functionally classified[1] (class I: V600x, constitutively active monomer; class II: constitutively active dimers; class III: low kinase activity, heterodimers amplifying the RAS signal). Available kinase inhibitors are effective only for V600x mutations. Recently, class II/III mutations were associated with adverse prognosis[2]. We set out to clinically characterize a cohort of BRAF mutated NSCLC and compare functional class-specific outcome, including the time before kinase inhibitors became available.
Methods: Retrospective study in two German lung cancer centers. Patients were identified by database query and clinical data collected from the electronic patient charts.
Results: We identified 72 patients (m/f 53/47%, median age 64.7y) diagnosed 2010-2019 with advanced NSCLC. Median follow up was 23.9 months. 43% of patients had V600x mutations, 32% class II, 25% class III. Most patients had a positive smoking history, with a trend towards a higher proportion in class II/III patients (81% vs 97%, p=0.1). Only a minority of patients with V600x mutations received kinase inhibitors (16%), which have been available only since 2017. Median overall survival (OS) was 13.1 months and differed significantly compared to a reference control group of 748 NSCLC patients without BRAF mutations (median OS 22.0 months, HR 1.39, p=0.043). In contrast, median OS upon beginning of palliative therapy (OSpall) was identical (HR 1.03, p=0.9). In this cohort with only little influence of targeted therapy, overall survival by functional class of the mutation was identical (class I vs. II/III, HR 1.02, p=0.95).
Conclusions: The availability of targeted therapy solely for class I mutations appears to be a major factor contributing to the reported superior outcome compared to class II/III cohorts.

References:

1. Yao, Z. et al. Nature 548, 234–238 (2017)
2. Dagogo-Jack; I. et al. Clin. Cancer Res. 25; 158–165 (2019)

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Registrational Results of Libretto-001: a Phase 1/2 Trial of LOXO-292 in Patients with RET-Fusion-Positive Lung Cancer

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Purpose: LOXO-292 is a highly selective RET inhibitor with activity against *RET* fusions, activating *RET* mutations and brain metastases.
Methods: This phase 1/2 study (87 sites, 16 countries) enrolled patients (pts) with advanced *RET*-altered solid tumors including *RET* fusion-positive (*RET*+) NSCLC (NCT03157128). LOXO-292 was dosed orally in 28-day cycles. Phase 1 established MTD/RP2D (160mg BID). Phase 2 enrolled pts to 1 of 6 cohorts based on tumor type, *RET* alteration & prior therapies. Primary endpoint: ORR; secondary endpoints: DoR, CNS ORR, CNS DoR, PFS, and safety.
Results: As of 17-06-19, 253 *RET*+ NSCLC pts were treated. Primary analysis set (PAS): first 105 consecutively enrolled *RET*+ NSCLC pts who received prior platinum-based chemotherapy (PBC); 58 pts also received prior anti-PD-1/PD-L1 agents. Majority of PAS responders were followed for ≥6 months (m) from first response. Of remaining 148 pts, 79 were previously treated with PBC, 55 did not receive prior PBC & 14 did not have measurable disease at baseline.
Investigator-assessed ORR in PAS: 68% (95%CI 58-76%, n=71/105, 2 PRs pending confirmation). Responses did not differ by prior therapy (e.g. anti-PD-1/PD-L1, multikinase inhibitors). Median DoR: 20.3m (95%CI 13.8-24.0) with median follow-up of 8m; as evidenced by wide CI, DoR estimate is not statistically stable due to low event number (16/69 confirmed responders). Intracranial ORR: 91% (n=10/11:2 confirmed CRs, 8 confirmed PRs) for pts with CNS target lesions at baseline.
ORR in treatment-naïve *RET*+ NSCLC pts: 85% (95%CI 69-95%, n=29/34, 7 PRs pending confirmation). In safety data set of 531 pts, 5 treatment-related AEs occurred in ≥15% pts: dry mouth, diarrhea, hypertension, increased AST & ALT. Most AEs: Gr 1-2. Nine (1.7%) pts discontinued LOXO-292 for treatment-related AEs.
Conclusions: LOXO-292 had marked antitumor activity in *RET*+ NSCLC pts & was well tolerated. These data will form the basis of an FDA NDA submission later this year.

Disclosure Statement: Previously presented at WCLC 2019.
Jürgen Wolf is author on behalf of the LIBRETTO-001 Investigators

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Enlarge-Lung: Two-Year Follow-Up of Real-World Patients with Locally Advanced or Metastatic (Stage IIIB/IV) Squamous and Non-Squamous Non-Small Cell Lung Cancer (NSCLC) from a National, Prospective, Non-Interventional Study (NiS Enlarge) of Nivolumab after Prior Chemotherapy in Germany

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Purpose: In two registrational trials, nivolumab showed overall survival (OS) benefit versus docetaxel in pretreated locally advanced or metastatic NSCLC. These results have been confirmed by initial data disclosure of

the German NIS ENLARGE. Here we report mature OS data from the first 300 patients enrolled in the trial.
Methods: 882 patients with pretreated, locally advanced or metastatic NSCLC recruited from 79 cancer care facilities in Germany will be followed for a period of 5 years from initiation of nivolumab until death, withdrawal of consent, loss of follow-up/record or end of study. The primary endpoint is OS. Baseline characteristics are reported using descriptive statistics. OS from the time of first nivolumab dose is estimated using the Kaplan–Meier method. Study was initiated in July 2016.
Results: With the data cut off on July 31st 2019, interim data of the first 300 patients from the ENLARGE study describe baseline characteristics and OS of patients with a minimum follow-up of 25 months. We report OS and response rates for the total population, by histology and other subgroups of interest (biomarker, ECOG Performance Status, elderly, metastases).
Conclusions: Real world data provide complementary information about special patient populations underrepresented in interventional clinical trials (elderly; poor performance status; comorbidities) and outcomes of treatment with nivolumab in accordance with the market authorization approval in Germany.

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Real World Molecular Testing in Patients with EGFR Mutation-Positive (EGFRM+) Locally Advanced or Metastatic NSCLC in Routine Practice in Germany – Interim Results of The Clinical Registry Panorama

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Purpose: Epidermal Growth Factor Receptor mutations (EGFRm) are among the most common in patients (pts) with non-small cell lung cancer (NSCLC) and can be targeted with EGFR tyrosine kinase inhibitors (TKIs). Appr. 50% of the pts will acquire resistance by the T790M mutation (T790M). Osimertinib (OSI) is a 3rd generation TKI and standard of care for pts who developed the acquired resistance by T790M during the prior TKI treatments.
Methods: PANORAMA (NCT02777658) is a prospective, clinical registry for pts with EGFRm+ locally advanced or metastatic NSCLC, who progressed after prior TKI therapy. Besides others the 2nd interim analysis (cut-off: 1APR2019) reflects data on routine clinical, molecular testing using descriptive statistics.
Results: Data of 148 evaluable pts were analysed: At diagnosis median age was 67.5 yrs (min-max 38.4-84.5 yrs), 49 (33%) pts were male and 98 (66%) were diagnosed with NSCLC Stage IV. 124 pts (84%) were tested for EGFRm at diagnosis, the remaining pts at later time points. At time of progression on/after TKI 74/148 pts were tested again, overall re-test rate after progression at any time was 76% (113 pts). 107 (95%) out of these 113 re-tested pts were tested for T790M thereof 73 pts (64%) were T790M pos (14 pts not yet documented). 55 (75%) pts who were tested T790M pos after progression (n=73) were treated with OSI. No difference in T790M positivity in the EGFRm subgroups (Ex19Del, L858R) was apparent. Further details on molecular testing will be shown.
Conclusions: The results will help to understand evolving Real World pts management, treatment patterns and associated outcomes among pts with EGFRm locally advanced or metastatic NSCLC who have progressed on/after TKI therapy. These data help validating the growing number of data sets suggesting that only a minority of EGFRm NSCLC pts benefit from sequential TKI-treatment with OSI after TKI-progression.

Reference:

1. Schumann, C. et al., DGHO-2019, Berlin, #A-1089-0026-00488

Disclosure Statement: Sponsor AstraZeneca

Christian Schumann: Beratungs- bzw. Gutachtertätigkeit & Honorare: AstraZeneca
Reinhard Büttner: Honoraria (alle „minor"); Lectures and Advisory boards for AbbVie, AstraZeneca, Bayer, Bms, Boehringer-Ingelheim, Illumina, Lilly, MSD, Novartis, Qiagen, Pfizer, Roche; Firmenanteile: Co-Founder and Scientific Advisor for Targos Mol. Pathology Inc; Zulassungsverfahren: Testifying Advisor for MSD in GBA-assessment for Pembrolizumab, Advisor for Durvalumab
Karl-Matthias Deppermann: Advisory/Consultancy: AstraZeneca, MSD, Boehringer, Roche, Takeda; Speaker bureau/Expert testimony: AstraZeneca, MSD, Boehringer, Roche
Niels Reinmuth: AstraZeneca: Advisory/Consultancy; Speaker bureau/Expert testimony, Travel/Accommodation/Expenses
Unabhängig vom Abstract habe ich Speaker honoraria / advisories and travel support erhalten von: Bms, Msd, Roche, Abbvie, Takeda und Böhringer erhalten.
Michael Thomas: Advisory/Consultancy: AbbVie, BMS, Boehringer, Celgene, Lilly, MSD, Novartis Roche, Takeda; Speaker bureau/Expert testimony: Lilly, MSD, Takeda; Research grant/Funding (institution): AstraZeneca, BMS, Celgene, Roche; Travel/Accommodation/Expenses: BMS, Boehringer, MSD, Novartis
Mark Wroblewski: Angestellt bei der Firma AstraZeneca
Frank Griesinger: Beratungs- bzw. Gutachtertätigkeit: Astra Zeneca, Boehringer Ingelheim, Novartis, Pfizer, Roche, Bms, Msd, Celgene, Lilly, Takeda, Siemens, Abbvie, Bayer
Honorare: Astra Zeneca, Boehringer Ingelheim, Novartis, Pfizer, Roche, BMS, MSD, Celgene, Lilly, Takeda, Siemens, Abbvie, Bayer, Finanzierung wissenschaftlicher Untersuchungen: Astra Zeneca, Boehringer Ingelheim, Novartis, Pfizer, Roche, BMS, MSD, Celgene, Lilly, Takeda, Siemens

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First-Line Immunotherapy in Elderly Patients with Stage iv Non-Small Cell Lung Cancer: an Early Efficacy and Safety Assessment

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Purpose: Clinical trials have shown benefits on both PFS and OS of adding pembrolizumab to standard chemotherapy (CT) in patients with previous untreated stage IV NSCLC without EGFR or ALK mutations, leading to approval of first-line immunotherapy (IO) regardless of the PDL-1 status. Elderly patients are still underrepresented in main clinical trials, thus there is an unmet need of evaluating safety, efficacy and predictors for toxicity of novel therapies in this challenging population.
Methods: We retrospectively evaluated clinical features, response rate (RR) and toxicities of 58 patients aged ≥70 years diagnosed with stage IV NSCLC treated in our clinic with first-line IO, both as monotherapy and in combination with CT, from January 2017.
Results: The mean age was 75.8 years. 17 patients (29%) were treated with IO plus CT. Among all patients the RR was 59% and the mean time to response was 6.3 weeks with no significant differences between the two treatment groups (p=0.32 and p=0.07, respectively). 27 patients

(47%) experienced immune-related adverse events (irAE), 22% of which reached grade 3, with no significant differences comparing the two groups (p=0.6). The most frequent early-detected irAEs involved thyroid (17% of patients), lungs (10%) and liver (9%). Neutropenia of grade ≥ 3 occurred in 4 patients treated with the combination therapy. Treatment was discontinued due to toxicity in 7 cases (14%) and 8 patients needed a chemotherapy dose reduction. Both Charlson Comorbidity Index (CCI) and age-adjusted CCI were identified as significant predictors for toxicity of any type (p=0,026 and p=0,008, respectively).
Conclusions: In this early assessment no significant differences regarding efficacy or toxicity in patients ≥ 70 years old with stage IV NSCLC treated with either first-line IO alone or in combination with CT were revealed. Notably, these preliminary data show a higher irAE rate than expected based on previous publications. The presence of comorbidities can predict the toxicity occurrence. We will extend this study to gain deeper insight into these issues.

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Mortality After Radiotherapy or Surgery in The Treatment of Early Stage Non-Small-Cell Lung Cancer: a Population Based Study on Recent Developments

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Purpose: Stereotactic body radiotherapy (SBRT) can achieve high tumour control with limited toxicity for inoperable early stage non-small-cell lung cancer (NSCLC) patients. This study aims to assess alterations in the survival of early stage lung cancer in relation to therapy across recent years.
Methods: The German Epidemiologic Cancer Registries were assessed. Periods according to availability of SBRT: (1) 2000-2003 (pre-SBRT), (2) 2004-2007 (interim) and (3) 2007-2014 (broad availability of SBRT). To assess the association of cancer related parameters with mortality, hazard ratios (HR) from Cox proportional hazards models were computed. To evaluate the change of treatment related mortality, we performed interaction analyses and the relative excess risk due to interaction (RERI, additive scale) was computed.
Results: 16,292 patients with UICC stage I NSCLC diagnosed between 2000 and 2014 were analysed. Radiotherapy utilization increased from 5% in pre-SBRT era to 8.8% after 2007. In univariate analyses survival in the whole cohort improved only marginally when 2000-2003 is compared to 2004-2007 (HR=0.92, 95% CI: 0.85-1.01) or 2008-2014 (HR=0.93, 95% CI: 0.86-1.01). Comparing surgery and radiotherapy the interaction analysis revealed a stronger improvement for radiotherapy (multiplicative scale for 2000-2003 vs. >2007: 0.78, 95% CI: 0.62-0.98), while risk of death was lower in the surgery group irrespective of period. On an additive scale, treatment*period interaction revealed a RERI for 2000-2003 vs. >2007 of -1.18 (95% CI: -1.84, -0.52).
Conclusions: Using population-based data, we observed a survival improvement in stage I lung cancer over time. With an increasing utilization of radiotherapy, a stronger improvement occurred in patients treated with radiotherapy when compared to surgery.

Reference:

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Disclosure Statement: no conflict of interest

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Deciphering The Tumor Immune Microenvironment Based on CD8+ TiL Density and PD-L1 Expression in Locally Advanced NSCLC Treated with Concurrent Chemoradiotherapy

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Purpose: The prognostic value of the tumor immunity microenvironment (TIME) in multimodal treatment for locally advanced non-small cell lung cancer (LA-NSCLC) is controversal. The aim of this study was to investigate the prognostic value of PD-L1 expression on tumor cells in combination with CD8+ tumor stroma-infiltrating lymphocytes (TILs) density in inoperable LA-NSCLC treated with concurrent chemoradiotherapy (CRT).
Methods: Data of 31 inoperable LA-NSCLC patients treated with concurrent CRT with tumor biopsy samples at initial diagnosis were evaluated. PD-L1 expression on tumor cells (0% versus ≥1%), CD8+ TILs density (0-40% vs. 41-100%) and TIME according to classification of Zhang et al. [1] were evaluated for potential prognostic value in terms of local control, progressions-free (PFS) and overall survival (OS) as well as correlations with clinicopathological features investigated.
Results: Median OS was 14months (range: 3-167 months). The OS rates at 1- and 2 years were 68% and 20%. Local control of the entire cohort at 1 and 2 years were 74% and 61%, respectively. Median and PFS at 1 and 2 years were 13±1,4 months, 58% and 19%. PD-L1 expression <1% on tumor cells was associated with improved OS, PFS and local control in patients treated with concurrent CRT. Evaluation of TIME appears to be an independent prognostic factor for local control, PFS and OS. The longest and shortest OS were achieved in patients with typ I (PD-L1neg/CD8low) and type IV (PD-L1pos/CD8low) tumors (median OS: 57±37 vs. 10±5months, p=0.05), respectively.
Conclusions: Assessment of the tumor immunity microenvironment (TIME) by PD-L1 expression on tumor cells and CD8+ TILs density is a predictive biomarker in patients treated with concurrent CRT for inoperable LA-NSCLC.

Reference:

1. Zhang Y, Chen L (2016) Classification of advanced human cancers based on tumor immunity in the MicroEnvironment (TIME) for cancer immunotherapy. JAMA Oncol 2:1403–1404

Disclosure Statement: Nothing to declare

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First Subsequent Treatment After Discontinuation of Durvalumab in Unresectable, Stage III NSCLC Patients from PACIFIC

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Purpose: In the phase 3 PACIFIC trial of unresectable, stage III NSCLC patients (pts) without progression after concurrent chemoradiotherapy (cCRT), durvalumab (durva) significantly improved PFS and OS with similar safety compared to placebo (pbo). We performed exploratory analyses to characterize 1st subsequent treatment (Tx) after discontinuation of durva.
Methods: Pts with WHO PS 0/1 and any tumor PD-L1 status were randomized (2:1) 1–42 days after ≥2 cycles of platinum-based cCRT to durva 10 mg/kg IV or pbo Q2W up to 12 months. Pts were classified by the use or not of 1st subsequent Tx and category of 1st systemic Tx.
Results: As of Mar 22, 2018, 216/476 (45.4%) and 153/237 (64.6%) in the durva and pbo arms, respectively, had a RECIST-based PFS event per BICR (5.7% and 8.4% due to death). 195 (41.0%) and 128 (54.0%) received 1st subsequent Tx, most of which were systemic Tx (158 [33.2%] and 109 [46.0%]): PDCT (16.4% and 19.0%), SCT (8.6% and 8.4%), IT (4.2% and 13.5%) or TT (3.8% and 5.1%); 7.8% and 8.0% received RT only. Time to 1st subsequent therapy or death (TFST) was longer with durva vs pbo (HR 0.58; 95% CI 0.47–0.72; median 21.0 vs 10.4 months). Baseline characteristics of pts with or without 1st subsequent Tx were similar, and similar across durva or pbo arms. Best overall response to 1st systemic Tx will be presented.
Conclusions: Due to longer PFS and fewer progression events with durva vs pbo, fewer pts on durva required subsequent Tx and, per TFST, much later. Baseline characteristics were similar for pts with or without 1st subsequent Tx and pts who received 1st systemic Tx, except for pts who received TT, as expected due to their molecular profile.

Disclosure Statement: funding by AstraZeneca

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PD-L1 Expression in Primary Tumour vs Metastatic Samples in The Phase 3 MYSTiC Study in First-Line Metastatic (m) NSCLC

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Purpose: PD-L1 expression determined by immunohistochemistry (IHC) can be a useful biomarker to assess the likelihood of benefit with anti-PD-1/PD-L1 therapies in pts with mNSCLC. MYSTIC (NCT02453282) was an open-label, Phase 3 study of durvalumab (D) ± tremelimumab vs chemotherapy (CT) as first-line treatment for mNSCLC; stratification factors for randomisation included tumour cell (TC) PD-L1 expression (≥25% vs <25%). While not statistically significant, D showed a clinically meaningful improvement in OS compared with CT (HR 0.76 [97.54% CI 0.56–1.02], p=0.036) in pts with PD-L1 TC ≥25%. We investigated whether the use of a primary tumour or metastatic site biopsy to determine PD-L1 status impacted prevalence of TC ≥25% or clinical benefit.
Methods: All pts enrolled in MYSTIC were assessed centrally for TC staining for PD-L1 from tissue samples acquired <3 months (mo.) prior to randomisation from either the site of the primary tumour or a distant metastasis. Testing was performed using the VENTANA PD-L1 (SP263) IHC assay. A post-hoc analysis evaluated prevalence, OS, ORR and duration of response (DoR) in pts with PD-L1 TC ≥25% as determined using either a primary tumour or a distant metastatic sample.
Results: Of 1118 pts randomised, 716 (64.0%) provided a primary tumour sample and 402 (36.0%) provided a metastatic sample. The prevalence of PD-L1 TC ≥25% assessed using primary vs metastatic samples was 43.0% vs 44.8% (p=0.569). According to primary or metastatic site, median OS for D vs CT was 15.8 vs 13.0 mo. (HR 0.81 [95% CI 0.59-1.11]) and 20.5 vs 12.6 mo. (HR 0.65 [95% CI 0.41-1.01]), respectively.
Conclusions: In MYSTIC, PD-L1 TC ≥25% prevalence was similar using primary or metastatic samples. Favourable HRs for OS with D vs CT were seen in pts with TC ≥25% expression as determined in either the primary tumour or a metastatic site. Results should be interpreted with caution given the retrospective nature of the analysis.

Reference:

1. NCT02453282 (release date: 25 May 2015)

Disclosure Statement: Funded by AstraZeneca

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Nationwide Tumor-Biological Testing Survey in Patients with NSCLC in Germany – Current Results and Development of Testing Behavior Since 2012

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Purpose: Tumor-biological testing of patients with stage IV non-small-cell lung cancer (NSCLC) is clinically indicated and endorsed by guidelines (with only few exceptions) because it enables the use of companion diagnostic guided drug therapy from which many patients benefit considerably. Molecular testing for the biomarkers EGFR, ALK, ROS and BRAF and immunohistochemical testing for PD-L1 should therefore be mandatory. We want to determine whether testing in Germany is performed as per guideline recommendation.
Methods: Experienced oncologists in different types of health care institutions (certified lung cancer centers, university and non-university hospitals and office-based physicians) are asked to answer a questionnaire on the details of testing. Data are analyzed by explorative analysis. The current results are broken down by institution and compared with those from previous years to analyze the development of test behavior.
Results: Previous surveys by us (in 2012 and in 2016) have shown that EGFR mutation analysis was employed in clinical routine in 2012 and increased significantly by the end of 2016, when the last survey was conducted. However, there is still potential for improvement in Germany in terms of the optimal use of therapy options. In the last survey the number of patients tested was 75% for EGFR, 66% for EML4-ALK, 41% for ROS1, and 14% for BRAF. These data will again be examined in the new survey which is currently ongoing. We will present the results and discuss the development of testing in Germany from 2012 to 2019.
Conclusions: Despite guideline recommendations it appears that there is still a significant number of patients in whom tumor-biological testing is not done and, therefore, access to optimal treatment may not be possible. The results that will be presented will clarify whether important improvements in the rate of testing have occurred.

Disclosure Statement: This study was supported by Astra Zeneca
Dieter Ukena received honoraria for speaker activities from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, MSD, Roche. He received honoraria for consulting activities from AstraZeneca, Boehringer Ingelheim, MSD, Takeda.
Alexander Freitag is an employee of AstraZeneca.

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Evaluation of Combined Biomarkers for Tumor Response to Immunotherapy (I/O) in Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)

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Purpose: Immune checkpoint inhibitors have revolutionized NSCLC treatment. At present, the only established predictive biomarker for I/O therapy stratification are PD-L1 expression and MSI status. However, the expression of PD-L1 is limited by heterogeneous expression and even high expressors not always respond to I/O therapy. The aim of the study is to evaluate the value of combinations of positive (Tumor Mutational Burden, PD-L1) and negative (a.o. CD73 expression and inactivating STK11 mutations) predictive markers in patients (pts) with advanced NSCLC on I/O therapy.
Methods: A retrospective study was performed on a cohort of 54 pts with advanced NSCLC that have been treated with I/O between 2015/2018. Pts were selected by the availability of tumor tissue and based on tumor response evaluated by RECIST v1.1 criteria: only patients with durable tumor response (CR,PR $\geq$ 6 months) and patients with no tumor response (PD as best response) were analyzed for biomarkers: hybrid capture NGS assay for TMB (New Oncology) including STK11 mutations and IHC tests for PD-L1, CD73 and VISTA. Adjusted Cox regression and ROC analysis will be performed to evaluate the predictive value of the different biomarkers.
Results: 43/54 pts received nivolumab, 11/54 pembrolizumab in different therapy lines (1st to 5th). 24 pts were defined as having a durable tumor response (median PFS 44 months, median OS 53 months; $p<0.0001$) 30 pts as primary progressors (median PFS 2 months, median OS 12 months; $p<0.0001$). In 30/54 pts enough material was available for TMB testing. In 13 durable responders median TMB-value was 13.28 mt/Mb versus 11.00 mt/Mb in 17 primary non-responders. STK11 mutations were observed in 3/17 primary non-responders (10%) vs. 0/13 in durable responders (0%). Additional analyses of the biomarkers will be presented at the meeting with correlative data of the parameters analyzed.
Conclusions: Our results suggest that integrating several biomarkers including positive and negative predictive markers may correlate better with responses to I/O than PD-L1 and TMB alone.

Disclosure Statement: no COI

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Screening of Pleural Mesothelioma Cell Lines for Kinase Activity May Identify New Targets to Overcome of Therapy Resistance in Patients Receiving Platin-Based Chemotherapy

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Purpose: Malignant pleural mesothelioma (MPM) is a rare, predominantly asbestos-related and biologically highly aggressive tumor leading to a dismal prognosis. Platin-compounds are standard chemotherapeutic agents and still a hallmark of chemotherapy for MPM. The reasons for the rather poor efficacy largely unknown. Kinase activity might influence cellular response to these regimes.
Methods: We screened different MPM cell lines for overall phosphorylation signatures as well as kinase activity with respect to cellular response to cisplatin-based therapeutics in a high-throughput manner using the highly innovative technique PamGene. Cell state analysis including apoptosis, necrosis as well as cell viability was performed by using enzyme-activity and fluorescent-based assays.
Results: Cisplatin alters phosphorylation affecting cell cycle, migration, adhesion, signal transduction, immune modulation and apoptosis of cells. High phosphorylation, especially of ESR1, LAT, PTPN12 and PTPN6 affecting proliferation and the RAS-MAPK-Pathway, leads to platin resistance. In cisplatin-responsive cell lines, phosphorylation of AKT1 and GSK3B was reduced. Cisplatin-responsive cell lines showed elevated

phosphorylation levels of JNK1/2/3, but decreased phosphorylation in cisplatin-resistant NCI-H2452 cells.
Conclusions: Kinase phosphorylation and activity might play a crucial role in cellular response to cytostatic agents. Cisplatin influences phosphorylation patterns in tested cell lines with distinct features in cisplatin-resistant cell lines. Based on our results, the induction of p38 or JNK1/3, or inhibition of AKT1 by e.g. BIA-6, might have synergistic effect with platin-based strategies and therefore be a therapeutic approach to induce apoptotic response to cisplatin treatment, thus potentially enhancing patients' outcome.

Disclosure Statement: The authors have no conflicts of interest to disclose.

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Impact of Metallothionein-Knockdown on Cisplatin Resistance in Malignant Pleural Mesothelioma

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Purpose: Malignant pleural mesothelioma (MPM) is an aggressive tumor with dismal prognosis. Platinum-based chemotherapy is standardly used for treatment. The expression of metallothioneins (MT) has been identified as a reason for cisplatin resistance in MPM. We hypothesized that knockdown of MT expression might improve response to cisplatin treatment.
Methods: MT expression of three MPM cell lines and the lung fibroblast cell line MRC 5, and their sensitivity to cisplatin treatment have been evaluated. Knockdown of MT1A, 1B and 2A expression was induced by RNA interference and subsequently, MT expression was measured using qPCR. Cell viability, necrosis and apoptosis before and after incubation with cisplatin was analyzed.
Results: MT2A gene expression was observed in all MPM cell lines, with highest expression in NCI H2452 and NCI H2052. Gene expression levels of MT1A and MT1B were very low or absent. The immunohistochemical protein expression of MT-I/II correspond to MT2A gene expression levels. Especially for MSTO 211H, a strong induction of MT2A expression was observed during cisplatin treatment, indicating a platin-dependent adaption mechanism. Additionally, a MT2A dependent response to cisplatin treatment was observed, leading to three different MT based phenotypes. Knockdown of MT2A significantly induced apoptosis during cisplatin treatment with strongest induction of apoptosis in each of the MPM cell lines, but in different phenotypes. We observed a therapeutic meaningful effect of MT2A knockdown and subsequent cisplatin treatment in MSTO 211H cells.
Conclusions: MT2A seems to be part of the underlying mechanism of cisplatin resistance in MPM. Especially in MSTO 211H cells, major effects by knockdown of MT2A expression could be observed, verifying our hypothesis of an MT driven resistance mechanism in MPM. Inhibition of MT2A could be used as a powerful tool to boost response rates to cisplatin-based therapy *in vitro*. These data carry the potential to boost clinical outcome and management of MPM in the future.

Disclosure Statement: The authors have nothing to disclose.

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Early Clearance of Plasma EGFR Mutations As a Predictor of Response to Osimertinib and Comparator EGFR-TKiS in the Flaura Trial

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Purpose: In the FLAURA trial, osimertinib showed superior efficacy to comparator EGFR-TKIs as first line treatment for EGFR mutation-positive (EGFRm) advanced NSCLC. In an exploratory analysis, we investigated clinical outcomes associated with detection of plasma EGFRm at 3 or 6 weeks (wks) after start of treatment.
Methods: Treatment-naive patients (pts) with EGFRm locally advanced or metastatic NSCLC were randomized 1:1 to receive osimertinib 80 mg or comparator EGFR-TKIs (gefitinib 250 mg QD or erlotinib 150 mg QD). Plasma EGFR mutation analysis was conducted at baseline (BL), wks 3 and 6 by droplet digital PCR. Clearance was defined as undetectable levels of EGFRm in ctDNA at wks 3/6, where they were detectable at BL. PFS was investigated based on early clearance of EGFRm.
Results: In total 489/556 (88%) pts (osimertinib: 244/279; comparator: 245/277) had evaluable ctDNA at BL and wks 3/6. Of these, 342/489 (70%; osimertinib: 168/244; comparator: 174/245) had detectable BL EGFRm and were included in this analysis. See table.
Conclusions: Clearance of plasma EGFRm after 3/6 wks of EGFR-TKI therapy was associated with a numerical improvement in PFS. The efficacy of osimertinib was superior to comparator EGFR-TKIs regardless of clearance status

References:

Disclosure Statement: funding AstraZeneca

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Integrated Biobanking and Tumor Model Establishment from Lung Cancer Patients Provides Excellent Tools for Modern Precision Medicine

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Purpose: The first tumor cell line was established in the 1950s, in vivo models followed suit in the 1960s. The current focus is on patient-derived models; especially the patient derived xenografts (PDX) are very popular for preclinical drug development to mimicking clinical trials. In parallel, the generation of large biobanks, enabling individualized therapy approaches, at least on a patho-molecular level of the tumor, has become standard in comprehensive cancer centers.
Methods: Patients operated on at the University Medical Center Rostock from 2010 onward participated in the HROLu collection (HRO: Hansestadt Rostock; Lu: lung cancer). Samples were collected using strict SOP including blood, tumor tissue as well as adjacent normal epithelium. Patient and tumor data including classification, sub-type, and results of model establishment are the essential pillars.
Results: In total, 39 patients with either a primary lung tumor (n=27) or a metastasis (n=12) of a primary brain tumor were included so far. The male-to-female ratio was 1.6: 24 male and 15 female patients. The mean age at time of surgery was 61 years, ranging from 36 to 80 years. The subtype distribution in the primaries was: one small cell carcinoma and 20 adenocarcinomas, 1 squamous cell carcinomas, 1 large cell carcinoma and 1 adenosquamous and in the metastases: 5 adenocarcinomas, 3 squamous cell carcinomas, 1 large cell carcinoma and 3 not further defined metastases. Patient-derived tumor model establishment attempts in vitro were successful for 3/33 (9%); however 12 are still ongoing. A PDX could be established in 3/5 (60%). Sensitivity of the PDX towards a variety of therapeutics commonly used in tumor therapy was tested. One PDX was highly sensitive towards most of the therapeutics tested; one PDX was highly sensitive towards Gemcitabine and Bevacizumab, the third PDX was highly sensitive towards Paclitaxel.
Conclusions: These patient individual tumor models and biobanked materials represent a valuable basis for translational and preclinical studies.

Disclosure Statement: none to declare

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Predicting Response and Outcome After Platin-Based Chemotherapy and New, Targeted Approaches in Malignant Pleural Mesothelioma

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Purpose: Platin-analoga are the drug of choice for the treatment of malignant pleural mesothelioma (MPM), resulting in response rates of merely 6 to 16%. The reasons for the rather poor efficacy largely unknown. Against the unsatisfactory background, we investigated the impact of platinum uptake, -metabolism as well as DNA-damage response on therapy outcome.
Methods: FFPE samples of 236 MPM patients and healthy tissue from 20 patients with spontaneous pneumothorax were used. For functional validation, 6 cell lines were analyzed in the same manner. Specimens were screened by digital gene expression analysis for 366 mRNAs and 800 important miRNAs using NanoString technology. Additionally, 48 selected candidate genes were analyzed in a multiplex manner using the PlexSet chemistry. Complementary, we discovered gene expression levels of significant targets via qPCR and protein expression levels via IHC. Methylation patterns were analyzed of 284 different CpG sites via mass spectrometry (MassARRAY EpiTYPER). To proof casuistic association, viability, necrosis and apoptosis of all cell lines were analyzed before and after incubation with cisplatin. Knock-down of target genes was induced by RNA interference.
Results: mRNA levels of DDR pathway members (MMR, BER, NER) are significantly associated with response to chemotherapy as well as OS and PFS in MPM patients. Especially genes involved in TP53-mediated DNA damage recognition, those compiled under the term "BRCAness" as well as metallothioneins have been identified to mediate tumors' response rates against cisplatin-based chemotherapeutic regimes.
Conclusions: Beside modern therapeutic concepts, biomarker stratification is urgently needed concerning nowadays state-of-the-art chemotherapeutic to improve and individualize MPM-therapy, saving non-responders from inefficient and side-effect loaded therapy. Our results will hopefully find their way into clinical and pathological practice, resulting in a benefit for patients and improved clinical outcome.

Disclosure Statement: The authors have nothing to disclose.

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Using German Claims Data to Characterize Real-World Treatment Patterns in Cancer Patients – The Example of Crizotinib

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Purpose: To explore the potential of German claims data for characterization of real-world treatment patterns in oncology, exemplified by patients treated with crizotinib which is approved for a certain subtype of non-small cell lung cancer (LC).
Methods: We used claims data from the German Pharmacoepidemiological Research Database (short: GePaRD, information on ~25 million persons), to identify patients with at least one crizotinib dispensation. Each individual was followed as long as possible, longest 2004 until 2016. We defined first line therapy as the first antineoplastic therapy (inpatient or outpatient) and subsequent therapies as second or later line therapy. We described patients regarding age, sex, codes for LC and metastases, number of crizotinib dispensations, as well as sequence of oncologic therapies and death.
Results: In total, we identified 348 patients under crizotinib (56% female, mean age: 58 years). 96% of the patients had a LC diagnosis code and 88% had metastases coded within 6 months after the first LC diagnosis coded in GePaRD. The mean time between first LC diagnosis and first crizotinib dispensation was 16 months. On average, there were 8 crizotinib dispensations per patient. 25% of patients received crizotinib as first line therapy, 77% received a non-targeted chemotherapy during the study period and 14% received a non-targeted chemotherapy after crizotinib discontinuation. 11% of patients died while treated with crizotinib and 16% died within 3 months after discontinuing crizotinib therapy.
Conclusions: Using GePaRD we found treatment patterns regarding crizotinib consistent with other studies and could provide detailed information on its utilization. The results underline the potential of German claims data for real-world monitoring of oncologic drug utilization.

Disclosure Statement: None.

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Mutations in CTDNA Associated with Sensitivity or Resistance to Immunotherapy in mNSCLC: Analysis from The Mystic Trial

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Purpose: Tumour mutational burden (TMB) is associated with improved overall survival (OS) to immunotherapy in patients with metastatic non-small cell lung cancer (mNSCLC). Prior studies suggest that mutations in STK11 (LKB1) are associated with resistance to PD-1/PD-L1 inhibitor monotherapy but the associations between a broader panel of genomic alterations and response to anti-PD-L1 monotherapy or anti-PD-L1/anti-CTLA-4 combination therapy are not well characterised. MYSTIC was a Phase 3 trial of first-line durvalumab (anti-PD-L1) ± tremelimumab (anti-CTLA-4) versus platinum-based doublet chemotherapy in patients with mNSCLC without EGFR mutations or ALK rearrangements. In MYSTIC, while not statistically significant, a clinically meaningful improvement in OS was observed with first-line durvalumab versus chemotherapy in patients with mNSCLC and PD-L1 expression in ≥25% of tumour cells (TC ≥25%). Durvalumab + tremelimumab did not improve OS versus chemotherapy in patients with PD-L1 TC ≥25%, but showed promising OS and PFS in an exploratory analysis in patients with blood TMB (bTMB) ≥20 mut/Mb. Associations between selected gene mutations and outcomes are being explored in MYSTIC.
Methods: Circulating tumour DNA from baseline blood specimens was profiled using the GuardantOMNI platform. Samples were available from 1003 patients [89.7% of ITT]; of these 943 samples were sequenced. Survival outcomes and response rates will be analysed in patients with or without nonsynonymous somatic mutations in KRAS, STK11 (LKB1), KEAP1 or ARID1A and in association with bTMB status.
Results: Results will be presented on frequency of gene mutations in the total population. OS and objective response rates will be reported based on the presence of gene mutations for both the overall population and for patients who had bTMB above and below designated thresholds.
Conclusions: Conclusions will be based on findings.

Disclosure Statement: funding by AstraZeneca

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Adriatic: a Phase III Trial of Durvalumab +/- Tremelimumab After Concurrent Chemoradiation for Patients with Limited Stage Small Cell Lung Cancer

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Purpose: Limited stage small-cell lung cancer (LS-SCLC), which represents 30% of newly diagnosed SCLC, remains an area of high unmet medical need. Standard of care, which has not changed for several decades, consists of curative intent platinum-based chemotherapy concurrent with radiotherapy (cCRT) followed by prophylactic brain irradiation (PCI) and observation. Despite good response to cCRT, outcomes remain poor, with median progression-free survival (PFS) 15 months and overall survival (OS) 25 months. Durvalumab (D) is a selective, high-affinity, human IgG1 monoclonal antibody (mAb) that blocks programmed cell death ligand-1 binding to programmed cell death-1 and CD80. Tremelimumab (T) is a selective human IgG2 mAb against CTLA-4. D demonstrated a PFS and OS advantage over placebo in locally advanced NSCLC following cCRT. D and D + T demonstrated a tolerable safety profile and antitumour activity in pretreated extensive stage SCLC. The ADRIATIC trial (NCT03703297) will assess if treatment with D + T is beneficial vs placebo in patients (pts) with LS-SCLC who have not progressed following cCRT.
Methods: ADRIATIC is a Phase 3, randomised, double-blind, multicentre, placebo-controlled international trial. Pts (N600) will be randomised 1:1:1 to receive D + placebo T, D + T, or dual placebo, stratified by Stage (I/II vs III) and receipt of PCI at the investigator's discretion (yes vs no). Eligible pts must have confirmed inoperable Stage I–III LS-SCLC; WHO/ECOG PS 0/1; and completed 4 cycles of cCRT with a response of stable disease or better within 1–42 days prior to randomisation. Pts will receive the assigned treatment until clinical, RECIST v1.1-defined progressive disease, intolerable toxicity or for a maximum of 24 months, whichever comes first. Primary objectives are PFS and OS for D + T vs placebo. Key secondary endpoints include health-related quality of life, and safety and tolerability. Recruitment is ongoing.
Results:
Conclusions:

Reference:

1. Clinical trial identification: NCT0370329

Disclosure Statement: Funded by AstraZeneca

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Frequency of Epidermal Growth Factor Receptor (EGFR) Mutations in Stage IB–IIIA Egfr Mutation Positive Non-Small-Cell Lung Cancer (NSCLC) After Complete Tumour Resection

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Purpose: Data on the frequency of EGFR mutations in patients (pts) with NSCLC potentially eligible for adjuvant therapy are limited. Osimertinib, a 3rd-generation, irreversible, oral EGFR-tyrosine kinase inhibitor (TKI), potently and selectively inhibits both EGFR-TKI sensitising (EGFRm) and EGFR T790M mutations and has shown efficacy in the CNS. The ADAURA study (NCT02511106) will assess osimertinib as adjuvant therapy in early-stage NSCLC after complete resection. Here we report frequency of the most common EGFR activating mutations from pts screened for ADAURA.
Methods: ADAURA is a Phase III, double-blind, randomised, placebo-controlled study assessing efficacy and safety of osimertinib vs placebo in adult pts with mainly non-squamous histology, stage IB–IIIA EGFRm NSCLC, following complete tumour resection, without or after adjuvant chemotherapy. At screening, EGFR mutations associated with EGFR-TKI sensitivity (ex19del, L858R), alone or in combination with exon 20 insertion, G719X, S768I, T790M or L861Q were centrally assessed from resected tumour samples using the cobas® EGFR Mutation Test (Roche).
Results: In total, 2447 pts were screened. Median age was 63 years (range 23–88), 54% were female, and 61% were non-Asian. At screening, 1087 (44%) pts were EGFR mutation positive; 110/2447 (4%) pts had an unknown/unevaluable test result. Of pts EGFR mutation positive, the most common mutations were ex19del and L858R in 572 (53%) and 458 (42%) pts, respectively; exon 20 insertion, G719X, T790M, S768I, and L861Q mutations occurred in 28 (3%), 24 (2%), 19 (2%), 11 (1%) and 8 (1%) pts, respectively. Mutations occurred alone or in combination. A higher proportion of EGFR mutation positive pts were Asian vs non-Asian (681 [63%] vs 402 [37%]; 4 pts missing) and female vs male (755 [69%] vs 331 [30%]; 1 pt missing).
Conclusions: This analysis shows a high prevalence of EGFRm mutations in Asian and female pts with stage IB–IIIA NSCLC following complete resection, which is consistent with the advanced setting.

Reference:
1. NCT02511106

Disclosure Statement: Funded by AstraZeneca

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Predictors and Effects of Reduced Chemotherapy Dosing in Patients with Non-Small Cell Lung Cancer IIIB

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Purpose: Dose reductions in chemotherapy occur frequently due to various reasons. The ubiquitous opinion is that dose reductions favor a negative outcome. However, there are only few studies that test this opinion in respect to lung cancer patients. The aim of this retrospective single-center study is to identify the most common predictors of dose reductions in NSCLC IIIB patients and to evaluate the effects thereof.
Methods: The study includes 132 patients treated at the Klinikum Nürnberg between 2008 - 2015. Predictors of dose reductions were evaluated using uni- and multivariate methods and survival statistics were analyzed using Kaplan-Meier and logrank method.
Results: 48% of the patients (n = 63) experienced dose reductions. Male gender (p = 0.029), age (p = 0.042), comorbidities (CCI) (p = 0.00) and palliative intent (p = 0.021) were identified as predictors of initial dose reductions. Initial dose reductions were independent of ECOG status and initial laboratory values. Dose reductions later in chemotherapy were linked to hematologic toxicities. The most common hematotoxicites were leucopenia (45%) and bi-/pancytopenia (23%). 59% of patients with leukopenia and 33% of patients with bi-/pancytopenia had chemotherapeutic doses reduced consecutively. The comparison between patients with and without dose reduction showed no significant difference in overall survival (OS) (p = 0.598) and progress-free survival (PFS) (p = 0.340). The OS of patients with reduced doses was 18.86 (± 18.65) vs. 17.51 (± 16.61) months and PFS was 15.03 (± 18.14) vs. 12.71 (± 17.60) months.
Conclusions: This study supports the view that hematotoxicities are considered the most serious side effects. In particular, leukopenia was related to frequent dose reductions. Contrary to expectations, a reduction in chemotherapy dosage did not seem to be associated with a worse prognosis. A possible explanation is that most studies focus on chemotherapy-sensitive tumor types. In addition, when several cycles of chemotherapy were performed individual dose reduction only slightly influenced the cumulative dose.

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Predictive and Prognostic Role of Pretherapeutic Bodyplethymography in SCLC Patients

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Purpose: About 15 % of all newly diagnosed lung cancers are Small Cell Lung Cancers (SCLC). Despite intensive research in the last 20 years no relevant improvement of survival has been achieved for these patients. Estimation of prognosis is essential for treatment planning and patient guidance. Lung function testing including bodyplethymography and measurement of diffusion capacity has been shown to be a predictive and prognostic marker in several malignancies. In this context, this project aims at investigating the predictive and prognostic role of lung function testing in SCLC patients.
Methods: 209 SCLC patients diagnosed and treated at a German tertiary care lung cancer were analysed regarding anthropomorphic characteristics. Pretherapeutic lung function tests (spirometry, bodyplethymography and diffusion capacity) were analysed regarding their impact on response to first line treatment and survival. Descriptive and comparative uni- and multivariate analyses were performed
Results: Pretherapeutic elevated values of total lung capacity as well as residual volume are significantly associated with first line treatment failure and early mortality. Airway obstruction did not show any significant impact of treatment response or survival.
Conclusions: Emphysematic lung disease and hyperinflation seemed to be a negative pretherapeutic marker regarding treatment response and survival. These easy to obtain and cost-effective parameters allow an additional prognostic estimation in patients with SCLC. Thus, pretherapeutic bodyplethymography should be performed in pretherapeutic assessment of SCLC patients rather than sole spirometry.

Disclosure Statement: No conflicts of interest

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Inflammational Scores Predict Survival in Advanced Lung Cancer Patients

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Purpose: Newly found correlations between inflammation and lung cancer have expanded the possibilities for patient therapy and prognosis. Prognostic scores such as mGPS, CAR, NLR, MLR, PLR, SII, LIPI, PIL or PNI have already proven their validity in the prognosis of patients.
Methods: We retrospectively analyzed 130 lung-cancer-patients treated at a German tertiary care lung cancer center between 2015 and 2016. We extracted data sets from electronic records, analyzed anthropometric data, pre-therapeutic blood values and prognostic scores. Discriminant analysis was performed to predict Overall Survival (OS) and Progression Free Survival (PFS).
Results: For PFS the factors albumin (p<0,001), clinical response (p<0,001), CAR (p<0,001), CRP (p<0,001), ECOG-PS (p<0,001), MCV (p<0,001), mGPS (p<0,001), MLR (p<0,001), PIL (p<0,001), platelets (p=0,001), LDH (p=0,003), LIPI (p=0,003), lymphocytes (p=0,018), NLR (p=0,023), PLR (p=0,026), protein (p=0,035), sex (p=0,035) und SII (p<0,044) were significant. Significant prognostic factors of the OS proved to be Albumin (p<0,001), clinical response (p<0,001), CRP (p<0,001), ECOG-PS (p<0,001), LDH (p<0,001), LIPI (p<0,001), MCV (p<0,001), mGPS (p<0,001), PIL (p<0,001), CAR (p=0,002), protein (p=0,002), MLR (p=0,009), platelets (p=0,017), PNI (p=0,034) and a found driver mutation (p=0,048) in a univariate analysis. In a multivariate analysis MCV, protein, MLR and PIL were found as independent predictors for OS.
Conclusions: New, inflammation-based prognosis scores have shown that they can be used to make reliable and independent statements about the prognosis of patients with advanced lung cancer. Since they can be calculated easily and cost-effectively, they are an ideal complement to classical prognostic parameters.

Disclosure Statement: Declarations of interest: none; this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Development of A Drug-Related Case-Finding Algorithm for Identifying Patients with NSCLC and SCLC in a German Claims Database

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Purpose: In total, 80–85% of all lung cancer (LC) are classified as non-small cell LC (NSCLC) and the remaining 15–20% as small cell LC (SCLC). Histological findings are not included within ICD.
Methods: Aim of this retrospective survey based on claims data of the InGef database was to find an algorithm to separate NSCLC from SCLC cases. The analysis period was 2015/16. LC patients were identified based on ICD-10 codes C33. & C 34.
Results: An analysis population of 3.972 primary LC cases was identified. Since it is not possible to determine the tumor type of LC with the help of the ICD, in this analysis an attempt was made to assign each case based on the drug therapy (tx) received. Many of the drugs and its combinations are only approved or prescribed for the tumor of one or the other cell type. If no differentiation was possible, the tumor was classified "undifferentiated". The following drugs were documented: (i) NSCLC: 5-fluoruracil, avelumab, cetuximab, ipilimumab, folic acid, gemcitabine, mitomycin, nab-paclitacel, paclitaxel, pemetrexed, vinorelbine, atezolizumab, bevacizumab, necitumumab, nivolumab, pembrolizumab, afatinib, ceritinib, crizotinib, dabrafenib, erlotinib, gefitinib, nintedanib, osimertinib, tremetinib. (ii) SCLC: irinotecan, liposomal irinotecan, trofosfamid, carboplatin, cyclophosphamide, doxorubicin, epirubicin, etoposide, ifosfamid, lomustin, topotecan, vincristin. Cisplatin is licensed and prescribed for both LC entities. For carboplatin, an off-label allowance for NSCLC exists. 780 of the cases could be allocated to NSCLC, and 253 to SCLC, respectively, but 2.939 cases had to be classified "undifferentiated".
Conclusions: This case-finding algorithm is a starting point to separate between NSCLC and SCLC based on drugs prescribed. However; a lot of patients remain undifferentiated. Reasons are the wide range of approvals of older chemotx; off label use and undetected coding errors. An amendment of the DRG System; e.g.; more specific LC codes for NSCLC and SCLC; is suggested to allow for more specific LC research based on German claims data.

Lymphoma and Plasma Cell Disorders

Vorträge

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Elevate Tn Phase 3 Study of Acalabrutinib Plus Obinutuzumab or Acalabrutinib Monotherapy vs Chlorambucil Plus Obinutuzumab (ClbO) in Subjects with Previously Untreated Chronic Lymphocytic Leukemia (CLL)

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Purpose: Acalabrutinib is a highly selective, potent, covalent Bruton tyrosine kinase inhibitor that has shown clinical benefit in patients with R/R as well as treatment-naïve (TN) CLL. ELEVATE-TN (ACE-CL-007, NCT02475681), a randomized, multicenter, open-label, phase 3 study is evaluating the safety and efficacy of acalabrutinib in combination with obinutuzumab or acalabrutinib monotherapy vs ClbO in TN CLL patients.
Methods: 535 TN patients with CLL were randomized (1:1:1) into three arms. Patients in the first arm received chlorambucil (orally, 0,5 mg/kg at d1 and 15 of cycle 1 to 6) in combination with obinutuzumab (IV, 100mg on d1, 900mg on d2, 1000mg on d8 and d15 of cycle 1, 1000mg d1 of cycle 2 to 6). Patients in the second arm received acalabrutinib (orally, 100mg twice daily until disease progression) in combination with obinutuzumab. Patients in the third arm received acalabrutinib monotherapy. The primary endpoint was progression-free survival (PFS) in the acalabrutinib and obinutuzumab arm compared to the ClbO arm, assessed by an independent review committee (IRC), and a key secondary endpoint was IRC-assessed PFS in the acalabrutinib monotherapy arm compared to the ClbO arm. Other secondary endpoints include objective response rate, time to next treatment, incidence of adverse events and overall survival.
Results: Data for the primary endpoint and key secondary endpoints based on a pre-specified interim analysis will be included. The trial has met its primary endpoint; acalabrutinib in combination with obinutuzumab demonstrated a statistically-significant and clinically-meaningful improvement in PFS when compared with the chemotherapy-based combination of ClbO. The trial also met a key secondary endpoint showing acalabrutinib monotherapy achieved a statistically-significant and clinically-meaningful improvement in PFS compared to ClbO. The safety and tolerability of acalabrutinib was consistent with its established profile.
Conclusions: Forthcoming; based upon unblinded data results.

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Poster

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Collection and Utilization of Hematopoietic Stem Cell Products in Multiple Myeloma

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Purpose: High-dose (HD) chemotherapy and autologous blood stem-cell transplantation (ABSCT) is the standard of care in multiple myeloma (MM) for transplant-eligible patients. Up to three HD/ABSCTs may be given during the course of disease, including late-onset relapse.[1] Therefore, many transplant centers routinely collect more than one peripheral blood stem cell (PBSC) graft.[2] However, subsequent HD/ABSCTs are often not performed for a variety of reasons.[3]
Methods: The collection, storage and disposal practice of PBSC products in a large cohort of MM patients (n=1,114) during a 12-year period was analyzed (minimum follow-up time 7 years).
Results: The median number of sufficient PBSC transplants per patient was 3 (range 0-6), those were stored in a median of 3 (range 1-11) cryopreserved bags (overall n=3,644). 95% of all patients (n=1,059) underwent at least one HD/ABSCT. However, more than one ABSCT was performed in 48% (n=532) of patients. Only a small proportion of PBSC bags (3%, n=109) was used after a storage of >5 years. Overall, 23% (n=830) of the

products were discarded and 16% (n=566) were kept in storage until reference date (March 2019).
Conclusions: We identified considerable discrepancies between the collection/storage and utilization of PBSCs. This is on the one hand associated with significant efforts and costs, on the other hand the disposal may raise legal and ethical questions. We therefore implemented comprehensive guidelines for systematic re-evaluation of stored PBSC grafts at our institution.

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Simultaneous Occurrence of Castleman's Disease and Plasmocytoma with Progression Into Multiple Myeloma Associated with POEMS Syndrome

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Purpose: Castleman's disease (CD) is a rare heterogeneous group of lymphoproliferative disorders. We present an unusual case of a patient with simultaneous CD and plasmocytoma followed by progression into multiple myeloma with POEMS syndrome and discuss the diagnostic criteria as well as the treatment options.
Methods: Case report and review of the literature.
Results: A 67-year old woman presented with weight loss, generalized sensory neuropathic pain, disseminated hemangiomas of the skin and enlarged mediastinal lymph nodes. On histology the typical morphology of CD with hyperplastic lymphoid follicles in combination with a lambda light chain plasmocytoma was found. Additionally monoclonal gammopathy of uncertain significance of the lambda light chain type was demonstrated. In the bone marrow plasma cells were below 10 %. The criteria for POEMS (polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder and skin changes) syndrome were initially not met, due to the absence of peripheral neuropathy on electrophysiological studies. VEGF serum levels were increased with > 1000 pg/ml (NR <445 pg/ml). HIV and HHV8 were negative. Because of the multicentric presentation of CD a systemic therapy with the anti-Il-6 antibody siltuximab was started. After 13 months of treatment the patient experienced multiple cerebral thrombembolic events. At the same time progressive disease was diagnosed and treatment was changed to immunochemotherapy with 6 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone). During the 6th cycle of R-CHOP lambda light chains increased noticeably. Restaging with lymphadenectomy proved a good response with complete remission of CD. However bone marrow biopsy showed progression into multiple myeloma with an increase of plasma cells up to 60 % and electrophysiological studies revealed peripheral neuropathy corresponding to POEMS syndrome.
Conclusions: This unusual case demonstrates the diagnostic challenges as well as treatment options in Castleman´s disease and POEMS syndrome.

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Ascend Phase 3 Study of Acalabrutinib vs Investigator's Choice of Rituximab Plus Idelalisib (IDR) or Bendamustine (BR) in Patients with Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL)

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Purpose: In this randomized, global, multicenter, open-label Phase 3 study (CL-309; ASCEND; NCT02970318), the efficacy and safety of acalabrutinib, a highly selective, potent, covalent Bruton tyrosine kinase inhibitor, was evaluated vs investigator's choice of IdR or BR in R/R CLL.
Methods: Eligible patients (pts) with R/R CLL were randomized 1:1 to 100 mg oral acalabrutinib BID until progression vs IdR (Id 150 mg oral BID and up to 8 IV infusions of R [375 or 500 mg/m2]) or BR (70 mg/m2 IV B on d1 and 2 and R [375 or 500 mg/m2 IV] on d1 for up to 6 cycles). The primary endpoint was progression-free survival (PFS) assessed by independent review committee (IRC).
Results: 310 pts were randomized to acalabrutinib (n=155) or IdR/BR (n=155 [IdR, n=119; BR, n=36]); median age was 67 y (range, 32-90). At a median follow-up of 16.1 mo, acalabrutinib significantly prolonged IRC-assessed PFS vs IdR/BR (median NR vs 16.5 mo; HR 0.31, 95% CI 0.20-0.49, P<.0001). PFS rates at 12 mo were 88% with acalabrutinib and 68% with IdR/BR. PFS improvement with acalabrutinib (vs IdR/BR) was seen across subgroups including del(17p), TP53 mutation and Rai stage. IRC-assessed ORR was not significantly different with acalabrutinib vs IdR/BR (81% vs 75%, respectively; p<.22). 12-mo OS rates were 94% and 91% (with 15 and 18 deaths) for acalabrutinib and IdR/BR, respectively. 23% of pts randomized to IdR/BR crossed over to receive subsequent acalabrutinib. Grade ≥3 AEs with acalabrutinib (≥5%) were neutropenia (16%), anemia (12%) and pneumonia (5%); with IdR (≥15%), neutropenia (40%) and diarrhea (24%); with BR (≥5%), neutropenia (31%), anemia (9%) and constipation (6%). AEs of interest were atrial fibrillation (5.2% of pts on acalabrutinib vs 3.3% on IdR/BR), bleeding AEs (26% vs 7.2%; including major hemorrhage [1.9% vs 2.6%]), Grade ≥3 infections (15% vs 24%), and 2nd primary malignancies (excluding NMSC; 6.5% vs 2.6%).

Conclusions: Acalabrutinib monotherapy significantly improved PFS with a more tolerable safety profile compared with IdR/BR in pts with R/R CLL.

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Treatment Reality of Myeloma Patients 2012-2018 in Germany

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Purpose: Survival of Multiple Myeloma (MM) patients has improved in prospective randomized trials. Real world data concerning treatment and outcome from unselected patients who receive routine care are not known.
Methods: Multicentre retrospective analysis of 1,000 unselected MM patients who were treated between 01/2012 and 12/2018 in 9 community-based oncology group practices in Germany. Data were extracted from patient files into a database and analyzed statistically using SPSS.
Results: So far 770 patients have been documented, 45% were female, 55% male. Median age was 69 years (25-92). 651 patients (85%) fulfilled CRAB criteria for cytoreductive treatment. 1st line treatment consisted of bortezomib+dexamethasone (VD) in 15%, bortezomib+melphalan+dexamethasone (VMP) in 14%, bortezomib+cyclophosphamide+dexamethasone (VCD) in 10% and lenalidomide+dexamethasone (Rd) in 6%. 23% received other therapy combinations. 32% were treated with high dose melphalan and stem cell transplantation (SCT). 2nd line therapy consisted of Rd in 26%, VD in 13%, VMP in 6%, thalidomide+dexamethasone in 6%, VCD in 5%, carfilzomib+lenalidomide+dexamethasone (KRd) in 4% and bendamustine+dexamethasone in 4%. 13% had high dose melphalan and SCT. 3rd line therapy consisted of Rd in 25%, VD in 10%, VMP in 5%, VCD in 4%, KRd in 3%, daratumumab in 3%, lenalidomide+daratumumab+dexamethasone in 3% and pomalidomide+dexamethasone in 3%. Median overall survival (OS) of the whole cohort was 95.4 months (0.6-304.8). OS was strongly dependent on age, comorbidities and ECOG performance status. Median OS of the age cohorts 25-60, 61-70, 71-75 and 76-92 was 146.5 (2.1-340.8), 112.8 (0.6-201.5), 80.8 (0.6-199.8+) and 52.6 (1.2-124.6) months respectively (p<.001).
Conclusions: MM patients who are treated in routine care receive therapy as suggested by international recommendations. Survival has improved compared to historical controls and is strongly dependent on age, comorbidities and performance status.

Disclosure Statement: All authors report no conflicts of interest

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Obesity is Associated with an Impaired Survival in Lymphoma Patients Undergoing Autologous Stem Cell Transplantation

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Purpose: In relapsed and refractory lymphomas, autologous hematopoietic stem cell transplantation (auto-HSCT) provides a possibly curative treatment option.[1,2] Obesity displays an emerging epidemic risk factor for global mortality and is associated with an increased mortality in cancer patients.[3,4] To date, there is no uniform data on the impact of obesity on the outcome of lymphoma patients undergoing auto-HSCT.
Methods: We conducted a retrospective single-center study assessing 119 lymphoma patients who underwent auto-HSCT. Overall survival (OS) served as primary endpoint whereas progression free survival (PFS), cumulative incidence of non-relapse related mortality (NRM) and cumulative incidence of relapse were analyzed as secondary endpoints.
Results: Obese patients (BMI≥30) unveiled a significant lower OS (45.3% vs. 77.9%; p=0.005) and PFS (29.8% vs. 67.2%; p<0.001) compared to non-obese patients at 48 months. The cumulative incidence of NRM displayed no significant differences while the cumulative incidence of relapse was significantly increased in patients with BMI≥30 (66.2% vs. 21.5%; p<0.001). There was no significant difference in OS between patients with a BMI<25 and overweight patients (BMI 25-30; 76.1% vs. 80.9%; p=0.585) whereas patients with BMI≥30 exhibited significant lower OS when compared to either of both groups (76.1% vs. 45.3%; p=.0.021 and 80.9% vs. 45.3%; p=0.010). Furthermore, in a multivariate analysis, obesity was identified as an independent risk factor for death (HR 2.231; 95% CI 1.024 to 4.860; p=0.043).
Conclusions: In the present study, we demonstrate that obesity is associated with an impaired outcome in lymphoma patients undergoing auto-HSCT. Further studies are needed to evaluate the reasons for the higher relapse rate causing higher mortality in obese patients.

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Disclosure Statement: The authors declare no conflict of interest.

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Pomalidomide, Cyclophosphamide and Dexamethasone (PCD) is an Effective Salvage Regimen for Multiple Myeloma (MM) Patients Relapsed and/or Refractory to Daratumumab

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Purpose: Daratumumab (dara) alone or in combination with lenalidomide (daraRd) or bortezomib (daraVd) is approved for the treatment of relapsed and/or refractory MM patients (pts). However, treatment options for pts progressing on dara are limited, and little data are available on the efficacy of salvage treatment after dara.
Methods: The aim was to evaluate the efficacy of PCD as salvage therapy after dara. Progression free survival (PFS) and overall survival (OS) were

calculated from the start of PCD. The median follow-up was 16 months (mo).
Results: Thirteen pts treated at Jena University Hospital and at the Seragnoli Institute of Hematology in Bologna who received at least 1 cycle of PCD after dara-failure were included. Median age at the start of PCD was 64 years (range 51-84). Three pts had extramedullary (EM) disease. The median number of previous lines of therapy was 5 (range 2-9). Twelve pts had previously been treated with melphalan, 2 pts had received allogeneic SCT. All patients had previously received IMiDs (12/13 lenalidomide, 4/13 thalidomide), with 11 pts progressing on IMiD therapy. Twelve pts received bortezomib and 7/13 carfilzomib; 9/12 pts were refractory to proteasome inhibitors. Dara combinations were: 6 pts dara alone, 5 pts daraRd and 2 pts daraVd. Seven pts (including 2 pts with EM disease) had a disease refractory to dara. The median daily dose of pomalidomide was 4 mg (range 1-4), median doses per cycle of cyclophosphamide was 700 mg/m2 (range 0-1800) and of dexamethasone 160 mg (range 0-320). The median number of cycles of PCD was 5 (range 1-31); 6 patients are still on treatment. Overall response rate (≥PR) to PCD was 62% (8/13), including 2 pts with VGPR and 2 pts with CR. Of the 3 pts with EM disease, 1 achieved a CR and 1 a minimal response. Responses occurred after a median of 2 cycles (range 1-5). Median duration of response was 3 mo (95% CI 0-9), median PFS and OS were 9 (95% CI 3-15) and 16 (95% CI 9-23) mo, respectively. Toxicity of grade ≥3 was limited and mainly hematologic (6/13 pts).
Conclusions: PCD is an effective regimen for dara refractory pts, including those with EM disease.

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Rare Lymphomas – Epidemiology from the Munich Cancer Registry

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Purpose: Rare cancers are defined as cancers with an incidence of less than 6/100,000. In total they represent 22% of the new cancer cases. Lymphomas in total are not rare, but they fragment into many different entities which therefore count as rare. The population-based data herein is presented to weigh in on the results of randomized clinical trials and to clarify expectations in the treatment of sporadic diagnoses.
Methods: Nine different rare lymphoma entities registered in the catchment area of the Munich Cancer Registry (MCR) 1998-2016 were selected for presentation: lymphocyte predominant Hodgkin lymphoma, hairy cell leukemia, Mantle cell lymphoma, Burkitt's lymphoma, MALT lymphoma, M. Waldenström, primary lymphoma of the central nerve system, cutaneous T-cell lymphoma, and peripheral mature T-cell lymphoma. Incidences, distributions of patient and tumor characteristics, and survival were computed per entity, sex, and period of initial diagnosis.
Results: The incidences (ASR ES) range between 0.6/100,000 in Mantle cell lymphoma and 0.15/100,000 in lymphocyte predominant Hodgkin's lymphoma. Men account for 62% of all patients. The median age differs between 44 years in Burkitt's lymphoma and 68 years in Morbus Waldenström. The 5-year relative survival (as estimation for cancer specific survival) lies between 35.6% in primary CNS lymphoma and 94.7% in hairy cell leukemia (94.2% in lymphocyte predominant Hodgkin lymphoma, 61.3% in Mantle cell lymphoma, 64.9% in Burkitt's lymphoma, 89.8% in MALT lymphoma, 82.3% in M. Waldenström, 70.7% in cutaneous T-cell lymphoma, and 42.4% in peripheral mature T-cell lymphoma). Apart from MALT lymphoma and lymphocyte predominant Hodgkin lymphoma men have a better prognosis than women. A noteworthy improvement in survival over time cannot be shown.
Conclusions: Incidence; age; and outcome in rare lymphomas vary extremely. The treatment of rare diseases such as these lymphomas should be expanded by the knowledge of "real-life" population-based data to adjust and deliver the patients' expectations.

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The Prospective Intersectoral National Cohort Study Myriam to Study Characteristics, Treatment and Outcome of Patients with Multiple Myeloma in Germany

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Purpose: Therapeutic options for multiple myeloma (MM) have markedly increased over the last decade and a number of new treatments may be approved in the near future. MYRIAM is a prospective, intersectoral, national, longitudinal, multicenter cohort study to document patient and disease characteristics, treatments, course of disease, including clinical and patient-reported outcomes and consent to perform translational research.
Methods: Between 2017 and 2021 about 2.000 patients with MM giving informed consent at the start of their first or second systemic treatment will be prospectively recruited in 150 different sites, including university and community hospitals and office-based practices and will be followed until death or for a maximum of 5 years. Data will be collected in electronic case report forms with implemented completeness and plausibility checks, regularly examined by data managers and randomly monitored. Patient-reported outcomes will be assessed at the time of recruitment, every 3 months for the first 24 months and every 6 months thereafter, for a maximum of 5 years altogether using the EORTC-QLQ-C30+MY20 and the Brief Pain Inventory. Patients will be asked to give informed consent for future translational research of their unused tumor samples. Annual interim analysis will be performed. The study was approved by local ethics committees and is registered under clinicaltrials.gov (identifier: NCT03308474).
Results: The first patient was recruited in September 2017. At the time of abstract submission (August 2019), 788 patients had been recruited in 103 sites. First results on patient and disease characteristics and initial treatments will be presented.
Conclusions: MYRIAM will for the first time present prospective, intersectoral, longitudinal data on MM patients in Germany. Data will shed light to the current state of care and allow identification of unmet medical needs.

Disclosure Statement: None of the authors has declared a conflict of interest regarding the subject of this work.

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Diffuse Large B-Cell Lymphoma Patient-Derived Xenograft Models: Establishment and Treatment Study

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Purpose: About 30-40% of the patients diagnosed with diffuse large B-cell lymphoma (DLBCL) will not be cured by standard R-CHOP therapy. Despite intense molecular profiling efforts, the treatment standard remains unchanged so far. Thus, new models such as patient-derived xenografts (PDX) are pivotal to develop molecularly guided treatment alternatives.
Methods: DLBCL PDX were derived from lymph node extirpations or core needle biopsies, transplanted subcutaneously into immunodeficient NOG mice, and subsequently passaged to NMRI nu/nu mice. Each graft was passaged 4 to 5 times to generate a stable model. In addition to histological analysis, whole genome sequencing (WGS) and RNA sequencing was performed. Stable PDX models were used for treatment studies.
Results: We successfully established 6 DLBCL PDX models from patients routinely admitted to our center and exposed to standard induction (*i.e.* R-CHO[E]P) or salvage therapy in case of progress, as well as patients treated within the actively recruiting investigator-initiated trial ImbruVeRCHOP (ibrutinib, bortezomib, R-CHOP; PI: Clemens A. Schmitt; multi-center first-line trial). We performed WGS and gene expression profiling to monitor lymphoma heterogeneity and clonal evolution at primary PDX establishment and during subsequent serial passaging. Reminiscent of our ImbruVeRCHOP trial, we conducted a treatment study. In the cyclophosphamide-resistant models, we were able to show that the addition of ibrutinib and bortezomib to cyclophosphamide delayed tumor growth. Next, panel-based targeted re-sequencing will be applied to serial samples obtained upon treatment exposure to investigate therapy-driven clonal evolution and emerging drug resistance.
Conclusions: The DLBCL PDX models reflect histological and genetic heterogeneity of the primary DLBCL sample from which they were derived from, and present with varying response patterns to ImbruVeRCHOP compounds. Response associations with the clinical outcome of the respective patients, and with distinct molecular profiles will be discussed at the conference.

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Non-Interventional Optimob-Study: a Nationwide Evaluation of Mobilization and Collection of Hematopoietic Stem and Progenitor Cells in Patients with Multiple Myeloma (MM) and Lymphoma in Clinical Practice

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Purpose: Autologous stem cell transplantation (ASCT) remains a standard therapy for MM and lymphoma in eligible patients (pts). A sufficient yield of stem cells is necessary for a successful ASCT. In clinical routine est. 15% (1) of pts are classified as poor mobilizers (PM) requesting several apheresis sessions (aph). Stem cells are mobilized with chemotherapy + G-CSF +/- plerixafor (PLX) or G-CSF +/- PLX.
Methods: Pts. with MM, Non-Hodgkin lymphoma or Hodgkin lymphoma eligible for ASCT are included in OPTIMOB. Mobilization and collection parameters are documented and analyzed in detail. Primary endpoint of the study is the proportion of PM pts. reaching ≥ 2 mio $CD34^+$ cells / kg body weight with the 1st apheresis. Pts. are defined as PM if they did not reach ≥ 20 $CD34^+$ cells / µL before 1st aph., receive PLX at any time point, did not reach the initially planned stem cell yield or terminated collection early due to poor mobilization. It is planned to include 1.500 pts to identify 210 PM pts.
Results: Up to now 189 pts from 16 centers are documented. About two thirds of pts have MM and one third malignant lymphoma. Mean age is 61 years and 40 % of pts are female. Half of pts are classified as PM (n=39) and 21 out of 80 pts received PLX + G-CSF +/- chemotherapy for mobilization. Furthermore, 19 AEs were reported incl. 2 SAEs.
Conclusions: This ongoing large prospective observational study evaluates stem cell mobilization rates in pts with MM and lymphoma who are candidates for ASCT. Updated data will be presented at the meeting.

Reference:
1. Wuchter et al. Biol Blood Marrow Transplant 16: 490-499 (2010)

Disclosure Statement: This study is supported by Sanofi.

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Gender Differences in Hematological Malignancy: The Experience of Jena University Hospital

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Purpose: Cardiological studies showed that female (F) patients (pts) might be undertreated. Data in hematological malignancies are lacking.
Methods: Aim was to investigate gender differences in multiple myeloma (MM) and diffuse large B-cell lymphoma (DLBCL) pts treated at one center**.** The MM and DLBCL databases were retrospectively interrogated. Analysis included descriptive statistics and survival analyses.
Results: Pts included were: 655 (MM) and 304 (DLBCL). Median observation was 48 months (mo) in MM and 41 mo in DLBCL. F were 43% (MM) and 51% (DLBCL). Median age was 62 years (yr) (MM, range 35-89) and 65 yr (DLBCL, range 20-92), and similar between F and men (M) (MM p=.14, DLBCL p=.33)
At diagnosis (dg) MM pts had no difference in disease risk (p=.49), stage (p=.52), MM type (p=.62), or bone involvement (p=.79). F had lower Hb (p<.001), less coronary heart disease (p=.006) and COPD (p<.001). In DLBCL, pts status and disease stage were similar: ECOG ≥2 p=.99, stage ≥III p=.14, IPI ≥3 p=.64. More F had B symptoms (p=.04).
MM pts had no difference in therapy (tp) administered (number/type) at dg or at first relapse, in overall response rate (ORR, F 71% vs M 72%, p=.43) and in overall survival (OS, F 83 vs M 72 mo, p=.45, 95% CI [63-89]). This applies to all age groups. High dose tp (HDT) was not affected by sex. More F had mucositis grade ≥3 (p=0.001). Progression free survival (PFS) (F 27 vs M 26 mo, p=0.37, 95% CI [23-29]) and OS from HDT (F 83 vs M 74 mo, p=0.90, 95% CI [59-95]) were similar.
In DLBCL, 257 pts received CHOP-like tp. There was no difference in ORR (F 72% vs M 69%, p=.56) or OS (F not reached (NR) vs. M 83 mo, p=.89, 95% CI [54-112]). Elderly F (60-79 yr) had R-CHOP14 in 40% vs 58% elderly M (p=.04). ORR (F 77.5% vs M 73%, p=.83), OS (F NR vs M NR, p=.94) and PFS (F NR vs M 72 mo p=.64, 95% CI [17-127]) did not differ, but R-CHOP14 was superior to 21 in elderly F (PFS NR vs 18 mo, p=.007 95% CI [9-28]).
Conclusions: Gender does not impact on biology, tp and outcome of MM pts. In Dlbcl, data suggests that elderly F might be undertreated with a possible effect on outcome.

Disclosure Statement: AB received honoraria from Takeda; Celgene; Sanofi and Janssen; Travel support from Celgene; Takeda; Janssen and Gilead and research founding from Celgene; MvLT received travel support and research founding from Janssen; Celgene; Takeda; Gilead; MSD; Oncopeptides and Novartis; the other authors have no conflict of interest to declare

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Treatment of Patients WiT Refractory Hodgkin Lymphoma

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Purpose: The anti-CD30 immunotoxin brentuximab-vedotin and checkpoint inhibitors Nivolumab and Pembrolizumab has being used for refractory HL patients as monotherapy and in different combinations.
Methods: This presentation summarizes our experience in the treatment of refractory HL.
Results: We have treated a total of 8 patients with refractory Hodgkin Lymphoma with Nivolumab or Brentuximab, 6 men and 2 female, 16 to 56 years of age. All patients had ECOG 0, 3-4 lines of therapy, 5 patients had previous radiation therapy, and 4 patients have been treated with autologous peripheral blood stem cell transplantation (PBSCT). Previous allogeneic PBSCT has been performed in one patient, and 4 patients have been treated with brentuximab-vedotin prior to nivolumab. The patients have been treated with 1-8 cycles of Nivolumab 3mg/kg b.w. two weekly according to the recommendation from CHECK Mate 205 Phase II Study. The overall response was excellent, CR in 4 patients and PR in 3 patients. In one patient, the treatment with Nivolumab was terminated due to Liver toxicity Grade 2.
Conclusions: Encouraging durability of response in our patients of 75% at median follow up of 25 months has been described. The safety profile with AEs mostly grade 1 or 2 was acceptable. Nivolumab is an important new therapy in patients with refractory HL.

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2. Armand P, Engert A, Younes A, et al. Nivolumab for relapsed/refractory classic Hodgkin Lymphoma after failure of autologous hematopoietic cell transplantation: Extendedn Follow-up of multicohort Single-Arm Phase II Checkmate 205Trial J Clin Oncol 2018; 36:1428

Disclosure Statement: no disclosure

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Acquired Hemophagocytic Lymphohistiocytosis as Paraneoplastic Syndrome in Lymphoma (LA-HLH): atypical Presentation of Rare Lymphoma Subtypes Requires an Aggressive Diagnostic Approach

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Purpose: Acquired hemophagocytic lymphohistiocytosis (HLH) can be the initial paraneoplastic syndrome at lymphoma onset. Hyperferritinemic fever, cytopenia and splenomegaly are diagnostic hallmarks.
Methods: Three patients registered in www.hlh-registry.org with LA-HLH requiring emergency diagnostic splenectomy are presented.
Results: 1) A 56 y/o patient with relapsing pneumo-pleuritis without specific histopathologic features developed full blown HLH. PET-CT showed no accessible hypermetabolic mass. Respiratory failure requiring ICU-treatment triggered etoposide application leading to clinical stabilization. Diagnostic splenectomy was performed revealing T-cell rich diffuse large B-cell lymphoma (DLBCL). The patient was cured by 6 x CHOEP and auto-PBSCT. 2) A 53 y/o male organ transplant patient presented with HLH. PET-CT indicated dim splenic hypermetabolism. HLH-directed treatment stabilized the patient to allow diagnostic splenectomy. Splenic T-cell lymphoma was found and T-NHL-directed CHOEP treatment was initiated. Follow-up will be presented. 3) A 32 y/o male patient presented with worsening hyperferritinemic fever, neutropenia, splenomegaly, hypofibrinogenemia, bone marrow phagocytosis. Abdominal probe excision revealed hemophagocytosis without specific lymphopathology. Due to

respiratory failure, dexamethasone/etoposide was initiated. After stabilization, diagnostic splenectomy was performed revealing T-cell/histiocyte-rich DLBCL. The patient was cured with 8 x R-CHOEP and high dose chemotherapy with auto-PBSCT.
Conclusions: Rare lymphoma phenotypes, inflammatory tissue infiltration and severely compromised patients with multiorgan failure make lymphoma diagnosis in HLH-patients an extra challenge. To overcome grim prognosis in LA-HLH, resolute diagnostics on concurrent HLH-treatment require interdisciplinary coordinated interventions[1].

Reference:
1. La Rosée et al., Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019

Disclosure Statement: The authors declare no COI.

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Comparative Effectiveness of Triplets ContainIng Bortezomib (B), Carfilzomib (C), Daratumumab (D), or Ixazomib (I) in Relapsed/Refractory Multiple Myeloma (RRMM) in Routine Care in The US

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Purpose: Lack of head-to-head trials of novel agents vs bortezomib-based triplet regimens (TpRs) renders treatment choice for RRMM difficult, highlighting a need for real-world (RW) evidence. We conducted a RW comparative effectiveness analysis of bortezomib (B), carfilzomib (C), daratumumab (D), and ixazomib (I) based TpRs in RRMM.
Methods: Patients (pts) with ≥1 prior line of therapy (LOT) initiating a TpR on/after 1/1/2014 were followed retrospectively in Optum's de-identified US electronic health record database (2007-2018), a general population-representative dataset. Duration of therapy (DOT) and time-to-next-treatment (TTNT) were estimated using Kaplan-Meier methods and compared using Cox models.
Results: Among 1432 pts with 1902 pt-LOTs in the B/C/D/I groups (n=746/522/418/216) median age was 70/65/68/69 yrs; pts with CRAB symptoms: 82/87/82/64%; pts with high risk disease (del 17p and/or t(4;14) and/or t(14;16) and/or 1q21 gain): 16/26/20/14%; IMID and/or PI refractory: 38/84/85/65%, respectively. B/C/D/I TpRs consisted of an alkylator in 36/26/5/5% or an IMID-backbone in 54/70/60/91%, respectively; 81/60/44/64% pts received B/C/D/I TpRs in LOT 2-3. At median f/u of 16.3/13.3/8.6/10.2 mos in the B/C/D/I groups, unadjusted median DOTs were: 6.0/6.0/6.2/8.4 mos and TTNTs were: 9.8/6.7/7.2/11.1 mos, respectively. In LOT 2-3, unadjusted median DOTs in the B/C/I groups were: 8.4/6.3/8.4 mos and TTNTs were: 10.8/7.8/12.7 mos, respectively; and not estimable in the D-triplet group. Adjusted risk of next LOTinitiation/death were statistically comparable for all groups overall; in LOTs 2-3, a trend toward lower risk of next LOTinitiation/death for I- vs B-triplet groups (adjusted HR: 0.77; P=0.09) was noted.
Conclusions: The adjusted risk of starting next LOT/death for C-, D- or I- vs B-based triplets was not significantly different in LOTs 2+ overall, but showed a lower trend in LOTs 2-3 for I-based triplets. Limitations include residual confounding due to unobserved treatment selection biases that are inherent to any non-randomized, observational study.

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Acquired Hemophagocytic Lymphohistiocytosis in Cancer Patients: Initial Presenting Paraneoplastic Syndrome of de novo Malignancy or Complication of Immunosuppressive Cancer Treatment?

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Purpose: Acquired hemophagocytic lymphohistiocytosis (HLH) is a complicating syndrome in cancer patients. HLH may be a paraneoplastic syndrome of de novo malignancy or a complication triggered by an infection in an immunocompromised patient. Two case reports illustrating diverse roots of HLH-origin are presented.
Methods: Case report
Results: 1) A 78 y/o male patient with chronic myelomonocytic leukemia (CMML-1) was treated with 5-azacytidine over 6 months. After RSV-pneumonia in January 2019, re-admission 4 weeks later due to aggravated dyspnea, renal failure and fever of unknown origin was required. Based on clinical and laboratory fulfillment of 5 out of 8 HLH-2004 criteria, the diagnosis of acquired HLH secondary to RSV-pneumonia was confirmed. Combined HLH- and CMML treatment with corticosteroids (dexamethasone) to suppress the cytokine storm and hydroxycarbamid to control leukemic proliferation reversed pulmonary and renal failure and allowed discharge. 2) A 53 y/o male double organ transplant patient under long-term immunosuppression presented with hyperferritinemic (39.404 ng/ml) fever, pancytopenia, splenomegaly, coagulopathy, hypertriglyceridemia (536 mg/dl), high sIL2R (4.958 U/ml) and bone marrow hemophagocytosis fulfilling HLH diagnostic criteria. Nodal status and viral replication testing were unrevealing. PET-CT indicated dim splenic hypermetabolic activity. HLH-directed treatment stabilized the patient to allow diagnostic splenectomy. Splenic T-cell lymphoma was found and T-NHL-directed treatment was initiated.
Conclusions: Acquired HLH may indicate hidden malignancy mandating intense diagnostic studies and interventions to detect malignancy. On the other hand, cancer patients are at increased risk to develop acquired HLH after infectious complications. Individual treatment tailoring adapted to various trigger conditions are required[1].

Reference:
1. La Rosée et al., Recommendations for the management of hemophagocytic lymphohistiocytosis in adults, Blood 2019

Disclosure Statement: The authors declare no COI.

Molecular Pathology

Poster

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The Expression of Genetic Variants of Cytochrome CYP2C9*2 and CYP2C9*3 and their Association with Increased Risk of Lung Cancer

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Purpose: The cytochrome P450 superfamily metabolic enzymes (P450) could have a possible role in lung cancer susceptibility. Therefore, it is important to define the overexpression profile of P450 and to establish their prognostic significance in subjects with lung cancer. The aim of this study was to investigate the possible connection among the risk of lung cancer and frequency of genetic variants of cytochrome CYP2C9 (CYP2C9*2 and CYP2C9*3).
Methods: The study was performed among 359 patients (69% males and 31% females; mean age of 59.96 ± 18.24 years) with diagnosis of stage IV small-cell (24.6% of patients) and non-small cell lung cancer (75.4% of patients) compared to 167 healthy subjects (72% males and 28% females; mean age of 69.96 ± 11.74 years). The distribution of CYP2C9 genetic variants CYP2C9*2 and CYP2C9*3 was detected using the quantitative *real-time polymerase chain reaction* (qRT-PCR) restriction fragment *length polymorphism* (RFLP) assay. The *study* was *conducted according* to the *Declaration* of *Helsinki*, the protocol was reviewed and approved by the institutional Ethics committee and all patients provided written informed consent.
Results: No statistically significant differences in the distribution of genetic allelic variants CYP2C9*2 and CYP2C9*3 were found among the patients with lung cancer compared to healthy subjects (p=0.648). The CYP2C9*2 and CYP2C9*3 genetic variants were expressed at the similar frequency in cancer and healthy bronchial tissue.
Conclusions: Our data indicate that there is no statistical significance between the occurrence of the frequencies of genetic alleles CYP2C9*2 and CYP2C9*3 and the increased risk of lung cancer.

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Disclosure Statement: No *conflicts of interest* to declare.

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Maldi-IMAGiNG - a Tool for Proteomic Characterization of Tumor Cells

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Purpose: Matrix assisted laser desorption/ionization (MALDI) imaging is a recently developed molecular imaging method. It simultaneously reveals the label-free detection of numerous molecules in-vitro. In this study, the method is used in an exemplary way to obtain molecular characterization of oropharyngeal cancer tissue and fine-needle aspiration cytology (FNAC).
Methods: From 20 patients with SCC located in the oropharynx, both FNAC and tissue samples from the primary tumor zone as well as from the adjacent normal tissue zones were used. Tissue sections and cell aspirates were placed on glass slides. After sample specific processing the sections and the cells were analyzed with MALDI imaging. Afterwards the MALDI data were compared with histological and cytological staining. Identification of potential tumor marker was carried out with liquid chromatography-mass spectrometry (LC-MS/MS).
Results: The assessment of the MALDI data of the tissues resulted in proteomic signatures specific to SCC allowing a clear differentiation between malign and benign tissue areas. Different, already established as well as new potential marker proteins could identified. The transfer of these data onto the aspirates leads to new approaches in the diagnostic of FNAC.
Conclusions: MALDI imaging is an appropriate tool for the comprehensive molecular characterization of tumor tissue and tumor cells of the head and neck area. The signatures can contribute to improved diagnostics of oropharyngeal carcinoma. In combination with further examinations, they can provide valuable information regarding the inhomogeneous therapy response and contribute to a better understanding of the tumor biology.

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Disclosure Statement: Franziska Hoffmann has no relevant financial or nonfinancial relationships to disclose.

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Encyclopedic Tumor Analysis Guided Personalized Treatments: a Paradigm Shift in Clinical Management of Advanced Refractory Cancers

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Purpose: Standard of Care therapies have limited efficacy in advanced refractory solid organ malignancies. Also benefits from Checkpoint Inhibitors are restricted to populations with qualifying molecular features. We assumed that molecular and cellular investigations ('Encyclopedic Tumor Analysis', ETA) can reveal unexplored features and target them using combinations of cytotoxic, targeted and endocrine agents. We report the results of the pan-cancer RESILIENT trial, where patients with advanced refractory malignancies received ETA-guided treatments.
Methods: Fresh tumor tissue was obtained from 200 patients and used for ETA, which included molecular profiling (MP: gene alterations/expression), immunohistochemistry (IHC), and *in vitro* chemoresistance and response (CRR) profiling against approved anti-tumor agents. MP, IHC and CRR datasets were integrated to generate patient specific drug priority lists with projected efficacy and safety. Patients received individualized combinations, and treatment response was evaluated by FDG PET-CT to determine Objective Response Rate (ORR), Disease Control Rate (DCR) and Progression Free Survival (PFS).
Results: Among the 143 patients who received ETA-guided treatments, 126 were evaluable for response *per protocol*. PR was observed in 54 patients (ORR = 42.9%) and 114 patients continued to exhibit PR or SD at study termination (DCR = 90.5%). Median PFS was 134 days. Median PFS rate at 90 day was 93.9%. No significant therapy related adverse events were observed. Most patients reported stable to improved Quality of Life.

Conclusions: Eta-guided treatments offered meaningful pan-cancer Orr and Pfs benefits in this heavily pretreated population and thus outperformed other systemic treatment options incl. Checkpoint Inhibitors.

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Characterisation of Clonal and Subclonal Allelic Imbalance at The Hla Locus in a 31 Patient Multi-Region Profiled Primary / Metastasis Clear Cell Renal Cell Carcinoma Cohort

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Purpose: Metastasis is the primary cause of death in cancer. Large-scale studies of metastatic disease have not included analysis of matched primary tumours, which are required to distinguish tumour clones with and without metastatic potential. Although the treatment of primary tumours has become more successful, 5 year survival rates for metastatic renal cancer remain at 8%. An improved understanding of the genetic differences between primary and metastatic tumours could reveal distinct therapeutic vulnerabilities between local and metastatic disease, which if exploited could improve treatment or prevent metastasis. Immune evasion is required for tumour progression and metastasis. We investigated whether genomic alterations causing the loss of human leukocyte antigen (HLA) alleles would facilitate immune evasion and subsequently promote proliferation and metastasis.
Methods and Results: We acquired the ability to decipher potential modes of metastatic progression through simultaneous analysis of 418 primary and 278 metastatic biopsies from 31 renal cell carcinoma patients. Multiple regions from each tumour were biopsied giving us clonal resolution. AI was investigated using fluorescently labelled STR oligonucleotides that were polymorphic within the HLA locus. We showed AIHLA was significantly selected for within the metastases. The detection of genomic alterations in tumour biopsies is confounded by infiltration from stromal DNA. Therefore, we developed a novel bioinformatics tool that purified and Characterised Allelic Imbalance in Tumours (CAIT). This was achieved through mathematical deduction of signals originating from stromal DNA. CAIT increased AIHLA detection, providing insights on AIHLA's prevalence and timing.
Conclusions: These results suggest AIHLA could promote metastatic progression. The characterisation of AIHLA could increase our understanding of drug-resistance mechanisms and inform the development of immunotherapeutic agents targeting neoantigens.

Novel Agents/Early Clinical Trials

Poster

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Entrectinib in Neurotropic Tropomyosin Receptor Kinase Fusion Positive (NTRK-FP) Gastrointestinal (GI) Cancers: Integrated Analysis of Patients (PTS) Enrolled in Three Trials (STARTRK-2, STARTRK-1, and ALKA-372-001)

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Purpose: *NTRK1/2/3* gene fusions cause expression of chimeric TRK proteins with constitutively activated kinase activity, leading to oncogenic potential across several histopathologies. Entrectinib is a CNS-active, potent TRKA/B/C and ROS1 inhibitor. We present integrated efficacy and safety data from phase 1/2 trials for entrectinib in *NTRK*-fp solid tumors, focusing on pts with GI cancers.
Methods: Pts with locally advanced/metastatic *NTRK*-fp solid tumors (± baseline CNS disease) confirmed by nucleic acid-based methods were enrolled in global (>150 sites, 15 countries) trials (ALKA-372-001 [EudraCT 2012-000148-88], STARTRK-1 [NCT02097810], STARTRK-2 [NCT02568267]). Tumor assessments were by blinded independent central review (BICR) using RECIST v1.1. Primary endpoints (BICR): objective response rate (ORR), duration of response (DOR). Key secondary endpoints: progression-free survival (PFS), overall survival (OS), safety.
Results: In the total efficacy-evaluable *NTRK*-fp population (n=54; 10 tumor types), ORR (BICR) was 57.4% (95% CI 43.2–70.8), with 4 complete responses (7.4%). Responses occurred in all tumor types. Median (95% CI) DOR, PFS, OS were 10.4 (7.1–NR), 11.2 (8.0–14.9), 20.9 (14.9–NR) months, respectively. In the cohort of 8 pts with *NTRK*-fp GI cancers, responses by BICR were observed in 1/4 colorectal, 2/3 pancreatic, and 1/1 cholangiocarcinoma pts; all were partial. Investigator-assessed responses in this GI cohort were seen in 2 colorectal and 1 pancreatic pt, and 1 cholangiocarcinoma pt. In the safety population (n=68 pts with *NTRK*-fp solid tumors who received ≥1 entrectinib dose), 47% had grade 1/2 treatment-related AEs (TRAEs), 38% had grade 3, 4% had grade 4; there were no grade 5 TRAEs. TRAEs led to dose reductions in 39.7%, interruptions in 30.9%, and discontinuations in 4.4% of pts.
Conclusions: Entrectinib was well tolerated and induced clinically meaningful, durable responses in pts with *NTRK*-fp solid tumors, including pts with a variety of different GI cancers.

Conflicts of Interest:
Gunnar Folprecht: Honoraria (self) from Merck, Roche, Sanofi-Aventis, Bayer, Mundipharma, Bms, MSD, Servier; Advisory/Consultancy for Merck, Roche, Sanofi-Aventis, Bayer, Mundipharma, BMS, MSD, Servier; Research grant / Funding (institution) from Merck.
Salvatore Siena: Advisory board member for Amgen, Bayer, BMS, CheckmAb, Celgene, Clovis Oncology, DaiichiSankyo, Incyte, Merck, Novartis, Roche-Genentech, and Seattle Genetics.
George Demetri: Grants, personal fees, non-financial support, and travel support for consulting meetings from Novartis, Bayer, Roche, Epizyme and Daiichi-Sankyo; Grants, personal fees, and travel support for consulting meetings from Pfizer; Personal fees and travel support for consulting meetings from EMD-Serono; Personal fees from Sanofi; Grants and personal fees from Ignyta; Grants, personal fees, and travel support for consulting meetings from Loxo Oncology; Grants, personal fees, and non-financial support from AbbVie; Personal fees and travel support for consulting meetings from Mirati Therapeutics; Personal fees and travel support for consulting meetings from WIRB Copernicus Group; Personal fees from ZioPharm; Personal fees from Polaris Pharmaceuticals; Personal fees and travel support for consulting meetings from M.J. Hennessy/OncLive; Grants, personal fees, and travel support for consulting meetings from Adaptimmune;

Grants from GlaxoSmithKline; Personal fees, minor equity, and travel support to Board meetings from Blueprint Medicines, where he serves as a member of the Board of Directors; Personal fees and minor equity options from Merrimack Pharmaceuticals, where he serves as a member of the Board of Directors; Personal fees and minor equity from G1 Therapeutics; Personal fees, minor equity options, and travel support to consulting meetings from Caris Life Sciences; Minor equity options from Bessor Pharma; Minor equity options from Erasca Pharmaceuticals; Personal fees and travel support to consulting meetings from Champions Oncology; Grants and personal fees from Janssen; Grants, personal fees, travel support for consulting meetings and non-financial support from PharmaMar; Use of patent on imatinib for GIST, licensed to Novartis with royalties paid to the Dana-Farber Cancer Institute.
Robert Doebele: Honoraria from Genentech/Roche, Takeda/Millenium; Advisory board for Genentech/Roche, Rain Therapeutics; Travel reimbursement for Genentech/Roche, Ignyta; Licensing fees for biological materials from Genentech/Roche, Ignyta, Foundation Medicine, Loxo Oncology; Consulting for Ignyta, Loxo Oncology, Bayer, Rain Therapeutics; Sponsored research from Ignyta, Loxo Oncology; Stock ownership at Rain Therapeutics; Licensing fees from patent from Rain Therapeutics and Abbott Molecular.
Young Kwang Chae: Research grants from AbbVie, BMS, Biodesix, Lexent Bio, and Freenome; Honoraria from Roche/Genentech, AstraZeneca, Foundation Medicine, Counsyl, NeoGenomics, Guardant Health, Boehringer Ingelheim, Biodesix, ImmuneOncia, Lilly Oncology, Merck, and Takeda.
Paul Conkling: Research funding from Roche, BMS, and US Oncology Research.
Ignacio Garrido-Laguna: Ad-hoc scientific advisory boards for Array, Ignyta, Glycyx; Financial support to the Huntsman Cancer Institute from Agios, Bayer, BMS, Eli Lilly, Halozyme, Incyte, MedImmune, Novartis, OncoMed, Pfizer, Taiho Pharmaceutical, RedHill Biopharma, Glenmark, GSK, NewLink Genetics, ARMO Biosciences, Amgen, and Rafael Pharmaceuticals.
Pilar Garrido: Consulting and advisory services (self) from Roche, MSD, BMS, Boehringer Ingelheim, Pfizer, AbbVie, Guardant Health, Novartis, Eli Lilly, AstraZeneca, Janssen, Sysmex, Blueprint Medicines, Takeda; Speaking, public presentations (self) from Takeda, AstraZeneca, Roche, MSD, BMS, Pfizer, Novartis, Boehringer Ingelheim, Gilead, Rovi; Financial support for clinical trials (institution) from Roche, MSD, BMS, Takeda, Lilly, Pfizer, Novartis, Pharmamar, Celgene, Sanofi, GSK, Theradex Oncology, Blueprint Medicines; Financial support for contracted research (institution) from Guardant Health and Sysmex.
Christian Rolfo: Speaker fees from MSD and GuardantHealth; Scientific advisor for Mylan; Institutional research collaboration with Biomark, Inc.; Non-remunerated collaboration with OncoDNA; Steering scientific committee for Oncopass.
Darren Sigal: Speakers Bureau for Celgene, Bayer; Scientific Advisory Board for Celularity, Molecular Stethoscope, CureMatch; Patent on using TRK inhibitors to treat neuroendocrine tumor.
Xinhui Huang: Employment at Genentech, Inc.; Stock ownership at Roche.
Brian Simmons: Employment at Genentech, Inc.; Stock ownership at Roche.
Chenglin Ye: Employment at Genentech, Inc.; Stock ownership at Roche.
Fortunato Ciardiello: Honoraria or consultation fees for speaker, consultancy or advisory roles from Amgen, Bayer, Bristol-Myers Squibb, Celgene, Merck Serono, Pfizer, Pierre Fabre, Roche, Servier; Direct research funding as the principal investigator for institutional research projects from
Amgen, Bayer, Merck KGaA, Pierre Fabre, Roche, Ipsen; Institutional financial interests, financial support for clinical trials or contracted research from Merck KGaA, Roche, Symphogen, Array, Servier, AstraZeneca, and MSD.
All authors: Medical writing and editorial support for the original abstract was provided by Gardiner-Caldwell Communications, Ashfield Healthcare Communications and sponsored by Roche in accordance with Good Publication Practice guidelines. Support for third-party editing assistance for this abstract, furnished by John Carron, PhD, Sammi Cham, BA, and Niamh Gould, BA, of Health Interactions, was provided by Roche Pharma AG. This study was funded by F. Hoffmann La-Roche, Basel, Switzerland.

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Identification of Novel HDAC-Inhibitors Targeting Epigenetic Dysregulations in MDA-MB-231 Cell Differentiation

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Purpose: Targeting tumor specific epigenetic deregulations by activating silenced cellular differentiation programs is a promising strategy for tumor treatment. Epigenetic-acting agents are supposed to potently reduce solid cancer cell tumorigenicity and to render cells more prone to common therapies. Histone deacetylase (HDAC) inhibitors represent one innovative class of epigenetic drugs known to induce differentiation in distinct cancer cells.
Methods: We analysed an in-house library of 20 newly developed HDAC-inhibitors by a cell-based phenotypic high-throughput screening system which allows the identification of potential epigenetic-acting agents via the quantification of two innovative differentiation markers. MDA-MB-231 cells were used as *in vitro* model for complex epigenetic deregulations leading to an early differentiation arrest. Differentiation-inducing potency of the identified compounds was validated by quantifying the expression of characterized differentiation markers by qRT-PCR analysis and compared to clinically relevant HDAC inhibitors.
Results: Testing a databank of 20 novel HDAC inhibitors identified two compounds as possible hit-candidates. These compounds showed a higher pharmacological efficacy *in vitro* compared to current clinical HDAC inhibitors.
Conclusions: We have successfully discovered two new HDAC inhibitors inducing differentiation in triple negative MDA-MB-231 cells. Further studies will be performed to optimize pharmacological potency and to investigate their potential suitability for anti-tumor drug development.

Oncological Pharmacy

Poster

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Pharmacist in a Multidisciplinary Cancer Care Team in Germany – Exception or Well-Established Model?

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Purpose: There is an increasing demand for better management of patients with cancer due to high numbers of newly diagnosed patients and the increasing complexity of new chemotherapeutics. Pharmacists are able to ensure the patient's safety and quality of life.[1] The objective of this study is to evaluate the current number of pharmacists embedded in a multidisciplinary cancer care team in Germany.
Methods: A survey was conducted using a web-based questionnaire. It addressed all clinical pharmacists in Germany who are ADKA (Federal Association of German Clinic Pharmacists) members. It was distributed *via* ADKA mailing list together with some basic information to ensure comparability of the answers. It was pointed out that only one response per hospital pharmacy is allowed.
Results: The ongoing study was started at 8th of August 2019. Up to now the overall response rate is 34.7% (130 of 375 hospital pharmacies[2]). Pharmacists are involved in the management of clinical studies (66.9%) and supportive care (42.3%), as well as in establishing chemotherapy schemes (66.9%). Although 90.8% of all participants are preparing ready-to-administer cytostatics, only 15.4% are on ward routinely. Even less (four pharmacists) are implemented five days per week for at least four hours at an oncology ward. Only two (of these four) are involved in the entire patient care process from admission to discharge counselling patients ensuring medication safety.
Conclusions: Although the positive impact of a ward pharmacist was reported by some hospitals abroad and clinicians recommend pharmacist's support, the implementation in Germany is still insufficient. Therefore, we encourage every clinician to consider a close cooperation with pharmacists to improve safe medical treatment.

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Disclosure Statement: S.D., A.F., and R.R. declare no conflict of interest.

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Medication Safety in Patients Treated with New Oral Antitumor Agents: A Prospective, Randomized Investigation on the Impact of Intensified Clinical Pharmaceutical/Clinical Pharmacological Care on Patient Safety and Well-Being (AMBORA). Supported by the German Cancer Aid (70112447) within the Comprehensive Cancer Center Erlangen-EMN

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Purpose: The increasing use of oral anticancer drugs leads to a higher responsibility for the patient and requires close management to handle Drug related problems and non-adherence. The main objective of this study is to investigate the effect of an intensified clinical pharmaceutical/ pharmacological care on medication safety and treatment satisfaction in patients treated with new oral anticancer drugs.
Methods: 200 patients will be randomized to receive either standard clinical care or intensive care over 12 weeks. A structured clinical pharmaceutical/pharmacological care program including patient counseling, medication reconciliation, and side effect management was established. Primary outcome parameters are the number of drug related problems (DRP) regarding the oral anticancer drug and patient treatment satisfaction. Further outcome parameters are for example the number of serious side effects, hospitalization and treatment discontinuation rates.
Results: These are the results of an interim analysis of 129 patients. Patients` satisfaction with anticancer treatment is significantly higher in the intervention group (TSQM questionnaire 92 vs. 78, $p<0.001$). The number of DRP in the control group was higher than in the intervention group (7.9 vs. 6.8 DRP per patient, n.s.). In particular, serious side effects were significantly reduced in the intervention group (1.3 vs. 0.7 side effects per patient; $p<0.05$). Rates of hospitalization and discontinuation of anticancer treatment due to toxicity were higher in the control group (12 vs. 2 hospitalizations; $p<0.01$, 9 vs. 4 discontinuations; ns).
Conclusions: The data of this interim analysis show that an intensive clinical pharmaceutical /pharmacological counseling can reduce the number of drug related problems associated with new oral anticancer drugs. The early intervention reduced serious side effects as well as therapy discontinuation and hospitalization rates due to toxicity. Patients´ satisfaction was significantly higher.

Disclosure Statement: The authors have no conflicts of interest to disclose.

Pediatric Cancer

Poster

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Impairments in Cardiovascular Health and Physical Activity Early after Treatment for Pediatric Cancer

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Purpose: Cardiovascular diseases in pediatric cancer survivors are known late sequelae[1]. Cardiovascular health is usually related to physical activity (PA). Reduced PA during cancer treatment results in impaired motor performance[2]. Therefore, reintegration into sports structures might be affected.
Methods: Participants (6-18 yrs, mixed entities) were recruited during follow-up care from April to June 2019. Peripheral and central systolic/diastolic blood pressure (pSBP/pDBP/cSBP) and pulse wave velocity (PWV) were assessed using the Mobil-O-Graph®. The MOON test scaled motor performance. PA aspects were quantified with the KiGGS study questionnaire. All data was compared to reference values.
Results: 40 children (11.3±3.8 yrs, 50% ♀) were recruited 1.6±1.8 years post-treatment. PSBP (z-score 0.9±1.7, p = 0.003), pDBP (0.8±1.9, p = 0.033) as well as cSBP (≥8 yrs: 0.6±1.3, p = 0.011) were significantly increased compared to reference values. PWV was elevated (<8 yrs: 1.2±2.9, p = 0.374; ≥8 yrs: 0.6±1.9, p = 0.127). Motor performance was reduced in nearly all dimensions. 17% reported 60 min of daily PA as recommended by the WHO. 50% were active sports club members, but 1/3 did not resume their former membership.
Conclusions: Early after treatment, children show increased blood pressure, a risk factor for cardiovascular diseases. Impaired motor performance and low PA underline the support needed regarding engagement in PA to potentially counteract risk factors and improve cardiovascular health. Implementation of sports offers during and after treatment should be considered as a meaningful, cost-effective preventive approach in terms of late effects associated with physical inactivity.

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Short and Long Term Outcome for Patients with Surgical Removal of Sacrococcygeal Teratoma in Newborns and Infancy

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Purpose: This study evaluates the short and long term outcomes of newborn and infant cases with sacrococcygeal teratoma removal. We examined the physical and neurological impairment affecting these patients.
Methods: A total of 21 patients underwent surgical procedure between July 2001 and July 2019 in our pediatric surgery department. We gathered information from the patient medical records, postoperative medical interviews, and performed physical examinations. We used this information to evaluate the status and the extent of the impairment of the patients. The patients received follow up treatment in according to the MAKEI recommendations for duration of 10 years.
Results: 21 patients had surgical procedure through our department due to sacrococcygeal teratoma (male: n = 5, female n = 16). SCT are more common in females with a 3 to 4:1 ratio. Pre-operative assessment included prenatal ultrasound (n = 20), prenatal MRI (n = 7), neonatal MRI (n = 10). The distribution of our Altman classification was: 14% Altman I (n = 3), 57% Altman II (n = 12), 10% Altman III (n = 2), 10% Altman IV (n = 2), 10% Altman unknown (n = 2). The surgery was performed at the age of diagnosis which was on average the 3nd day of life (range: 0 to 13 day of life). The weight median was by 2800g with a range of 2570 g. Out of the 21 patients, 12 tumors were completely removed with R0 surgical resection (n = 12), 3 tumors with R1 (n = 3) and 6 tumors with RX (n = 6) surgical resections. Histological findings included predominantly chondroid (n = 12) and neuroectodermal (n = 10) parts. The maturity level was evaluated: 33% GC 0 (n = 7), 24% GC 1 (n = 5), 14% GC 2 (n = 3), 5% GC 3 (n = 1), 14% GC unknown (n = 6). Post-operative complications included surgical site infections (n = 6), bowel perforation (n = 1), and post-operative mortality (n = 2).
Conclusions: Sacrococcygeal teratoma is a heterogeneous entity of the germline tumors and the prognosis is significantly better for patients who had R0 surgical resection and low GC scores. Postoperative and long term complications are tolerable. Follow ups are necessary to determine future reoccurrence of the tumor.

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A Comprehensive Map of Genetic Vulnerabilities in ATRT Subgroups

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Purpose: Brain tumors are the leading cause of cancer-related deaths in children and adolescents. Embryonal brain tumors are a group of high-grade neoplasms which primarily affect young patients, and atypical teratoid rhabdoid tumors (ATRTs) are the second most common type of tumor within this group. In spite of intensive research efforts and the knowledge of molecular mechanisms driving subgroup-specific heterogeneity within ATRTs, survival estimates stay relatively low as compared to other tumor entities with a median survival of around 17 months. More efficacious and durable therapies are urgently needed to improve the situation of patients.
Methods: We investigated genetic, epigenetic, and transcriptional features of seven distinct human ATRT cancer cell lines in order to assign those cell lines to three molecular subgroups described for ATRTs. Subsequently, we will perform genome-wide CRISPR/Cas9 knockout screens for these ATRT cell lines in order to identify genetic vulnerabilities and novel therapeutic targets for this tumor entity.
Results: Detailed analyses including mRNA expression- and DNA methylation-based prediction approaches provide evidence that our selection of ATRT cell lines (BT12, BT16, CHLA02, CHLA04, CHLA05, CHLA06, CHLA266) recapitulates features of all three molecular subgroups of

ATRT, namely ATRT-TYR, ATRT-SHH, and ATRT-MYC. Dependencies discovered in the first screen using BT12 cells were highly enriched for fundamental cellular processes such as transcription and translation, thereby validating our approach. We identify 190 BT12-specific cell essential genes, including 44 genes in potentially druggable categories and seven genes representing clinically actionable targets. We are preparing to screen additional ATRT cell lines of all molecular subgroups in order to establish a comprehensive overview of ATRT vulnerabilities.
Conclusions: Our data will provide a comprehensive map of dependencies for distinct ATRT subgroups which will serve as a starting point in the development of targeted therapies for this tumor entity.

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Feasibility of Indoor-Wall Climbing with Pediatric Cancer Survivors

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Purpose: To assess feasibility of an indoor-wall climbing intervention for pediatric cancer survivors.

Methods: Eight pediatric cancer survivors (6.50 – 20.67 years, mixed diagnoses) (patient group, PG) and five healthy controls (7.42 – 20.67 years) (healthy group, HG) participated in an indoor-wall climbing intervention for 8-9 weeks. Supervised training was offered once a week for 60 min. Feasibility was assessed by adverse events leading to study drop-out. Additionally, side effects like temporary muscle pain/ injuries and compliance were evaluated. An evaluation questionnaire was used to determine training acceptance by participants and parents.
Results: No adverse events or side effects were documented. Only one child reported that the climbing intervention was too exhausting due to insufficient breaks. Participants completed an average of 56,78% (25% – 100%) of the offered training sessions. Reasons for non-participation were reported in 28 cases which were lack of time (80%) and medical issues like infections (20%). Overall, 13 children (PG and HG) and 9 parents (PG and HG) completed the questionnaire. Children generally liked the climbing intervention and stated to feel stronger and more confident. They were interested in continuing indoor wall-climbing.
Conclusions: Indoor-wall climbing with pediatric cancer survivors is feasible and well-accepted. Study results encourage to assess potential effects of indoor-wall climbing in pediatric oncology.

Disclosure Statement: The authors declare nothing to disclose.

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Secondary Malignancies following Ewing Sarcoma Treatment

Isabelle Kaiser

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Purpose: Ewing Sarcoma (EwS) is an aggressive, bone- and soft tissue sarcoma found in children, adolescents and young adults. Due to intense multimodal therapy, survival rates have increased to 75% in patients with localized disease[1]. Consequently, long-term surveillance of late effects has gained importance. We investigated secondary malignant neoplasms (SMNs) following EwS-treatment. This study investigated relative risk and prognostic factors of SMN development and compared different SMN risk characteristics. Time of latency between EwS and SMN diagnosis was also examined.
Methods: The following GPOH studies supplied data: CESS 86, CESS 91P, EICESS 92 and Euro-Ewing 99; data from a total of 3097 patients were included. Time to SMN occurrence and survival rates after EwS diagnosis were analyzed. Cumulative incidences and Odds ratios for cause-specific risks were computed.
Results: Median age of EwS diagnosis was 16 years (2–68 years). Notably, 35% had been diagnosed with metastatic EwS. Metastases were localized mainly in the lung, bone marrow and other bones. A total of 75 patients (54% female, 46% male) with 76 SMNs were identified. Two patients developed two different SMNs. SMNs manifested as hematological neoplasms (42%) and solid tumors (58%) at a mean latency time of 7.8 years following primary EwS diagnosis. In total, 58/74 (78%) patients received radiation treatment. Twelve out of 15 (80%) observed Osteosarcomas were localized within a previously irradiated field.
Conclusions: Ewing Sarcoma survivors are at risk of developing SMNs. In particular, hematological neoplasms (AML and MDS), as well as Osteosarcomas were recorded following EwS treatment.

Reference:

1. Grünewald T., Cidre-Aranaz F., Surdez D. et al. (2018). Ewing sarcoma. Nature Reviews. Disease Primers 4(5). doi: 10.1038/s41572-018-0003-x

Palliative Care

Poster

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Parental Dealing with Diffuse Intrinsic Pontine Glioma in Children

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Purpose: Diffuse intrinsic pontine glioma (DIPG) in children is a dismal disease with median overall survival (OS) of less than a year. Usually palliative care is involved. Open communication about death eases dying for children and surviving for parents. This study establishes case reports based on parental confrontation with DIPG. During the course of DIPG designated key points exist. We determine specific needs of parents and children as well as typical problems in interaction between families and care givers. The results lead to recommendations and improvements for existing treatment concepts.
Methods: We conducted a problem-oriented guided interview followed by a qualitative content analysis according to Mayring.
Results: 13 parents of 7 children (aged 5-16 years) were interviewed. The children's median OS was 8 months and 4 days. Palliative home care was involved in 5 families. Palliative care generally met the needs of the examined families. Parents stated overall satisfaction and comfort regarding to most subjects (management of physical symptoms and support, provision of information, family support, patient psychological care). Communication about death is a relevant inductive category. Out of 7 children it was assumingly spoken openly to only one child. Two families remained in mutual pretense. Two children were actively prevented by their parents to have open communication. In two other cases the concept remains unclear. All parents regret that they have not talked to their children about death.
Conclusions: Parents are less burdened when palliative care is involved in the treatment of their children's DIPG. The overall load of statements about not talking with children about their death meets the relevance of

this topic in literature. Concepts need to be established on how to rise attention to the chances that open communication about death offers for both children with life-limiting diseases and their families.

Reference:
1. Radlanski K., Hartwig M., Kordes, U. (2019) Parental Dealing With Diffuse Intrinsic Pontine Glioma in Children. EAPC Abstracts, Palliat Med

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Dealing with Desire to Die in Patients with Incurable Cancer: Recommendations of the German S3 Guideline Palliative Medicine

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Purpose: Desire to die (DD) is common in palliative patients. Medical advance and improved therapy options do not cancel out DD, but on the contrary many patients think about dying and ask about the meaning of life. Health practitioners are often confronted with these thoughts. The current national and international state of knowledge and experience in dealing with DD offers orientation and assurance in responding to it in an appropriate manner.
Methods: Development of evidence and consensus based recommendations with the participation of more than 60 professional societies.

Medline, PsycInfo, and Cochrane Library databases were systematically searched for relevant publications on proactively addressing DD, and selected according to defined inclusion criteria. Findings were assessed and built the base for developing recommendations. Evidence based and consensus based statements were consented in a formal process.
Results: The expert panel agreed on 19 statements and recommendations dealing with DD issues such as differential diagnosis, potential background and meaning, how to deal with DD, possible options for action and legal framework. The handling of DD within the treatment team, possible support from external experts and the involvement of relatives are also covered within the guideline.
Conclusions: The guideline aims to support decision-making in practice and provides systematically developed recommendations on the basis of the best available evidence and clinical experience of a large number of experts. The recommendations concerning DD aim at helping with (proactively) addressing potential DD as well as dealing with them. Therefore they should be considered a contribution to the advancement of multi-professional competence in palliative care.

Disclosure Statement: The authors declare no conflict of interest.

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Stability of Cancer Patients´ Unmet Spiritual Needs and Spiritual Wellbeing in Palliative Care Units

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Purpose: Duration of patients´ stay in palliative care units (PCU) is decreasing, and thus options to profoundly provide spiritual care. Aim was thus to analyze patients´ unmet spiritual needs at the beginning and end of their PCU stay.
Methods: Pre-post analysis (paired t-test) of 65 patients´ spiritual needs (SpNQ-20), spiritual wellbeing (FACIT-Sp), life satisfaction (BMLSS), satisfaction with team support (BMLSS) and perceived health status (VAS) with standardized questionnaires in two PCUs. IRB-Approval 316/14.
Results: Patients´ primary diagnosis was cancer (99%; 62% women, mean age was 64±11 years; 73% Christians, 2% Muslims, 24% without religious affiliation). The Meaning component of their spiritual wellbeing scored highest (3.19±0.70), followed by Peace (2.45±0.78) and Faith (1.80±1.34). Among unmet spiritual needs, Inner Peace needs (1.59±0.91) and Giving/Generativity needs (1.42±0.93) scored highest, Religious needs (0.88±0.93) and Existential needs (0.72±0.83) scored rather low. Most stayed for 2-3 weeks at the PCU (65%). Within this time frame, neither spiritual needs nor spiritual wellbeing nor life satisfaction changed significantly, while their perceived health status improved (M -8.7±18.6; p<.001). Within the sample, 66% felt that their spiritual needs were supported 'very well' by the hospital staff (which is not specifically trained in spiritual care issues), 21% stated 'quite well', and 13% were not satisfied.
Conclusions: The time frame to provide profound spiritual care support is rather limited. Although most felt supported in terms of their spiritual needs, neither their needs nor their wellbeing scores changed significantly. Nevertheless, the individual development of spiritual needs and spiritual wellbeing might be very different, and thus hospital staff has to be aware that also an 'aggravation' of unmet needs could be expected (indicating either stronger awareness or increase of fear and burden).

Disclosure Statement: The authors disclose any conflicts of interest.

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Development of a Training Program to Enhance Communication Skills Regarding Early Referral to Palliative Care in Advanced Cancer Patients – The Palli-Kom Study

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Purpose: To develop a communication training for physicians who treat cancer patients to promote an early referral to palliative care in advanced cancer patients. The training aims to strengthen the ability to address palliative care related topics constructively and early during disease trajectory. The basis of the training development will be focus groups, literature and expert discussions.

Methods: In addition to an intensive literature search to identify relevant training contents, we conducted four focus groups with a total of 28 physicians of varied specialization and levels of experience (*M* age = 39.5, *SD* = 8.92). Discussed topics were professional and communicative competencies, personal barriers and the desired training structure. The talks were audiotaped, transcribed and analyzed via qualitative content analysis.
Results: Due to the focus groups (average length: 90 minutes) we identified numerous aspects, which the participating physicians considered to be crucial to the training. The need for a rectification of the understanding of palliative care including its benefits was especially emphasized. Also, knowledge about symptom control and palliative care structures seem of particular importance. Highlighted communication skills were an adapted language, the balance between honesty and hope, and the consideration of individual information needs. Crucial personal barriers are a high emotional involvement, especially in young patients, and the difficulty of being unable to heal. Participants desire a realistic training with a high practical part. Personal aspects like coping shall be addressed.
Conclusions: The daily experience of physicians is a valuable source to identify necessary competencies for early integration. Physicians have precise expectations towards a training on communicating palliative care related topics. Results of the focus groups were supplemented by findings from literature search. This will now be used to specify content and didactics of the training.

Disclosure Statement: The authors declare no conflict of interest.

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Full Local Control in a Giant Ulcer of Advanced Breast Cancer by Definitive Radiotherapy Only

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Purpose: Female patient, *1931 with satisfying health conditions, Karnofsky index (KI) 70%. Patient is widowed with no children and lives in her own home with the support of a local care team. She was acutely hospitalized with delirium due to exsiccosis and a suspected mild stroke. Accidentally a large high risk tumor of the left mamma was found (cT4 cN0 cM0, triple negative hormone receptor status, Ki67 index 90%). Interdisciplinary oncologic tumor conference advised surgery followed by chemotherapy. Both declined by patient, she primarily consulted radiotherapy. Clinical examination showed a giant ulcer of 10 x 12 x 8 cm in upper quadrants of left breast with spontaneous bleeding, fibrinous slimy coat/secretion and strong odour. Patient's only distress was caused by ulceral staining of her clothes.
Methods: Ambulatory radiotherapy (RT) of left mamma with 48 Gray (Gy) photons in 3 Gy single fractions, five days a week with the use of a 8 mm moulage. Wound care with Octenilin® and manual necrosis ablation. Weekly doctor's visits.
Results: 36,0 Gy: bleeding has stopped, yellowish fibrinous coat. 48,0 Gy: much more compact findings, no spontaneous bleeding/secretion. Modest erythema of treated mamma (common toxicity criteria, CTC=2), two small epitheliolyses (CTC=0-1), no edema of mamma or arm. KI 70%. Very satisfied patient. Wound care is to be continued. 1. follow-up, 3 months after RT: mild erythema, significantly smaller tumor. Ulcer almost healed, 5 cm residuum with slimy coat. Mild edema of treated mamma. Very satisfied patient, KI 90-100%. 2. follow-up, 7 months after RT: intact skin, former ulcer is fully healed. No edema. Very satisfied patient, KI 90-100%.
Conclusions: Definitive RT as sole treatment can be considered as a sufficient palliative strategy to achieve local control in advanced breast cancer with ulceration. We controlled local symptoms and reached full healing of the ulcer. We were able to not only sustain but raise the quality of life of a self-sufficient senior in the severe health condition of advanced breast cancer. She experiences no impairment of daily life.

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Music at the Palliative Care Unit (PCU) – A Volunteer Project with Young Adults

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Purpose: Music could help to vercome social isolation at palliative care institutions. Young volunteers have combined swim sports with this social idea.
Methods: Since 2006 the Swim Club Nordhausen 1990 is taking part in 24-h-competitions in order to fundraise the project of our PCU. The club donated an e-piano in 2014 and from then every 2-3 month concerts were given to our patients. Each concert has 20-30 visitors and patients listening the young artists. In 2018 we were able to engage a professinal guitarrist making active music together with the individual patients every month.
Results: 167 young volunteers have taken part in the fundraising project. 26 concerts were organized presenting piano, guitar or choral music since March 2014. 289 patients were able to take part in these concerts. More than 600 family members were guests of the young artists. Active music offer was used by 53 patients at 11 sessions, e.g. 40% of possible patients have had benefit from this new apporach since January 2018.
Conclusions: Palliatve patients consume music in passive as well as active way. Its integration helps to overcome their isolation. Furthermore young artists become embassadors of hospice ideas.

Disclosure Statement: The authors disclose any conflict of interest.

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"But you need a Questionnaire Like This": Real Life Experience of Quality of Life Assessment in Outpatients with Lung and Prostate Cancers – A Longitudinal Cohort Study

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Purpose: Quality of life (QoL) assessment with patient-reported outcome measurements (PROMs) improves patients' QoL. It is a prerequisite in the certification process for oncology centers of the German Cancer Society (DKG). The aim of the study was to test the feasibility of PROMs (Integrated Palliative Outcome Scale IPOS, and Distress Thermometer DT) in outpatients with advanced lung and castration-resistant prostate cancer, both diseases beyond recovery.
Methods: The process of longitudinal QoL assessment with IPOS and NCCN-DT was observed for 15 months. Besides patients' distress we also analyzed the numbers of requests for supportive services as a consequence of the patients' findings in the questionnaires. Focus group interviews with patients, informal caregivers and health care professionals (HCP) were thematically analyzed.
Results: Ninety-seven percent (n=125) out of 129 eligible patients received a questionnaire for one time at least. However, quarterly assessment as recommended was achieved only in 60% of prostate cancers, and 48% of lung cancer patients. IPOS showed a high face and content validity and both questionnaires were well accepted. Patients did not feel uncomfortable with filling in the questionnaires. HCP found the instruments helped to focus and structure the time for the doctor-patient-contact. Some patients pointed out difficulties with the DT in terms of comprehension. Due to lacking process and to organizational challenges the achieved response rates were low as were the rates of consultations

with supportive services. Monitored hand-over of the questionnaires improved their implementation.
Conclusions: PROMs were regarded as important by lung and prostate cancer outpatients as well as HCP. To facilitate consequences they should be realized as standardized intervention rather than pure assessment. The results must be accessible in a straightforward way to gain the maximum benefit for patients and health care processes. The effects on a direct data input into the electronic patient chart, such as results from laboratory tests, should be tested.

Pflege

Poster

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Anwendung des Niedrigenergielaser (Low Level Laser LLL) Zur Prävention und Behandlung der oralen Mukositis bei onkologisch erkrankten Erwachsenen und Überprüfung der Wirksamkeit – Eine prospektive Beobachtungsstudie

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Zweck: Orale Mukositis (OM) ist eine der Nebenwirkungen der Transplantation hämatopoetischer Stammzellen(HSCT), die zu erheblicher Morbidität führt. Ziel dieser Studie war es, die Wirkung eines speziellen Mundpflegeprogramms mit Lasertherapie bei der Behandlung von Patienten, die eine HSCT erhalten zu überprüfen.
Methoden: Bei den Patienten wurden ab dem Tag der Behandlung einmal täglich beide Wangen vorbeugend von außen für maximal 5:20 Minuten mit dem Low Level Lasergerät Twin 21+ mit den Einstellungen 21x100mW, 16,0J/LD Multifrequenz bestrahlt
Ergebnisse: Die hier vorgelegte Arbeit zeigt die positive Wirkung des Lasers für das beschriebene Patientenklientel. Die Schwere der Mukositis nach WHO konnten über alle Schweregrade hinweg reduziert werden.
Fazit: Eine Einführung der prophylaktischen Behandlung von onkologischen Patienten mittels der Lasertherapie kann somit zugestimmt werden. Auch eine Kostenreduktion ist zu erwarten.

Quellenangaben:

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2. Blijlevens, et al. (2008): Prospective Oral Mucositis Audit. Oral Mucositis in Patients Receiving High-Dose Melphalan or BEAM Conditioning Chemotherapy--European Blood and Marrow Transplantation Mucositis Advisory Group. In: *Journal of Clinical Oncology* 26 (9), S. 1519–1525.
3. Curra, M.; et al. (2018): Chemotherapy protocols and incidence of oral mucositis. An integrative review. In: *Einstein (Sao Paulo, Brazil)* 16 (1), eRW4007.
4. Bezinelli, L., et al. (2014): Cost-effectiveness of the introduction of specialized oral care with laser therapy in hematopoietic stem cell transplantation. In: *Hematological oncology* 32 (1), S. 31–39.
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Offenlegungserklärung: Die Fa. MKW Laser hat keinerlei Einfluss auf die Ergebnisse oder anderweitig ausgeübt

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Immuntherapie: Herausforderung für Pflegefachkräfte in Der Thorax-Onkologie

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Zweck: In der Thorax-Onkologie, insbesondere beim nichtkleinzelligen Lungenkarzinom, findet eine rapide Entwicklung neuer Therapien statt. Diese Entwicklung stellt die onkologische Pflege vor immer neue Herausforderungen. Hier ist ein Wissensdefizit zu verzeichnen, was die Wirkweise und die immunbedingten Nebenwirkungen angeht.
Methoden: Der Aufsatz erklärt die Wirkungsweise der Immunonkologie und geht auf die immunbedingten Nebenwirkungen ein. Es wird eingegrenzt, bei welchen Entitäten in der Thorax-Onkologie diese Therapieform hauptsächlich zum Einsatz kommt. In einer Reihe von Patienteninterviews wurde beispielhaft der Wissensstand von einzelnen Patienten ermittelt. Viele Informationsmaterialien, die für die Patientenedukation zur Verfügung stehen, werden im Aufsatz verglichen. Es werden Themen für Beratungsgespräche herausgearbeitet. Um eine gute Beratungskompetenz in der Pflege zu gewährleisten, ist die Mitarbeiterschulung ein wichtiger Aspekt.
Ergebnisse: Den besten Schutz vor unerwünschten Nebenwirkungen könnten Krebspatienten haben, wenn sie selbst Experten für ihre Behandlung wären. Der Schwerpunkt in der Patientenedukation sollte daher auf dem Beratungsgespräch liegen. Wenn Patienten Fragen haben, sind Pflegende häufig die ersten Ansprechpartner. Deshalb spielen sie eine wichtige Rolle als Informationsgeber. Um das Wissen der Pflegenden zu erweitern, ist die innerbetriebliche Fortbildung als fester Bestandteil der Mitarbeiterschulung unverzichtbar.
Fazit: Eine gelungene Immuntherapie bedeutet für unsere Patienten eine deutlich längere Überlebenszeit bei relativ guter Lebensqualität. Das Expertenwissen von Patienten und Pflegenden kann dazu einen entscheidenden Beitrag leisten.

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Umgang mit dem Fatigue-Syndrom bei Krebspatienten

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Zweck: Um Aufschluss über die Einstellung zum Erscheinungsbild des Fatigue-Syndroms zu bekommen und zu sehen, wo noch Informationsbedarf besteht, wurde eine Befragung durchgeführt.
Ziel der Befragung war:
- den Wissenszustand der ärztlichen und pflegenden Kolleg*innen festzustellen
- eine Fatigue-Prophylaxe auch in anderen Bereichen des onkologischen Zentrums zu etablieren
- den Wissensstand zu verbessern und Weiterbildungen gezielt planen zu können

Methoden: Es wurde in einem Zeitraum von 4 Wochen auf 13 Stationen erfragt, wie das Wissen über das Fatiguesyndrom selber eingeschätzt wird und durch welche Symptome Betroffene am meisten beeinträchtigt sind. Weiterhin wurde erfragt, ob auf Zeichen eines Fatigue-Syndroms geachtet wird und wie der weitere Umgang bei Erkennen von Symptomen erfolgt.
Ergebnisse: Es wurden 322 Bögen ausgeteilt, von denen 115 ausgefüllt wurden. Zwischen den Stationen gibt es erhebliche Unterschiede hinsichtlich des Wissens über das Fatigue-Syndrom., wobei das Wissen dort größer eingeschätzt wird, wo bereits eine Fatigue-Beratung durch das PIZ erfolgt/e.

Insgesamt gesehen geben jedoch nur 13,1% der Antwortenden – und zwar unabhängig von ihrer Berufserfahrung – an, sehr gutes oder gutes Wissen zum tumorbedingten Fatigue-Syndrom zu besitzen.

Bei der Einschätzung, wie viele Patientinnen und Patienten ein Fatigue-Syndrom entwickeln, gibt es erhebliche Unterschiede in den Abteilungen: Insgesamt gesehen glauben die Befragten, dass weniger als die Hälfte der Patientinnen und Patienten Fatigue-Symptome zeigen. Dabei verlassen sich die Befragten überwiegend auf die eigene Einschätzung, Screeninginstrumente werden selten genutzt.

Insgesamt gesehen sind die Beratungsmöglichkeiten des PIZ in Bezug auf das Fatigue-Syndrom nur bei ca. 30% aller Befragten bekannt, wobei hier ein deutlich höherer Bekanntheitsgrad in den Kliniken vorliegt, in denen bereits eine Beratung erfolgt.

Fazit: Der Wissenstand zum Thema Fatigue muss ausgebaut werden.

Quellenangaben:

1. FIBS- Fatigue individuell bewältigen

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Die Rolle von Krebserkrankungen bei der Langzeitpflege durch Angehörige

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Zweck: Die Versorgung bei Pflegebedürftigkeit erfolgt in Deutschland meistens durch Angehörige, nur teilweise unterstützt durch ambulante Pflegedienste und nur rund 25% in stationären Einrichtungen. Sie haben somit in der pflegerischen und sorgenden Begleitung in der häuslichen Umgebung eine besondere Rolle. Zur Unterstützung dieser Situation haben Pflegekassen nach §45 SGB XI den Auftrag Pflegekurse anzubieten, in denen man praktische Pflege und weitere Pflegekompetenzen lernen kann. Für Pflegekassen ist von besonderem Interesse, ob für diese Kurse zukünftig besondere Aspekte der Pflege von Menschen mit einer Krebserkrankung zu berücksichtigen sind. Da schon lange nicht mehr jede Krebserkrankung tödlich verläuft, aber trotz guter Heilungschancen Spuren hinterlässt, ist sie nicht mehr nur für die Akutpflege, sondern auch für die Langzeitpflege von zunehmender Bedeutung. Neue Angebote zu onkologischen Themen und zur Begleitung von Sterben und Tod sollen ggf. im Spektrum der Pflegekurse ergänzt werden.

Methoden: Pflegebedürftigkeit wird über einen Leistungsanspruch zur Unterstützung in der Pflegesituation über die Pflegekassen erfasst. Die Voraussetzung ist nach Antragstellung die Zuordnung eines Pflegegrades. Die Daten der AOK Nordost zur Pflegebedürftigkeit der Pflegekasse wurde in Verbindung mit Krebsdiagnosen aus der Krankenkasse betrachtet. Ergänzt wurden diese durch den jeweiligen Versorgungsort zum Lebensende.

Ergebnisse: Bei der AOK Nordost gab es 2018 n=47.399 Pflegebedürftige mit einer Krebsdiagnose. Von diesen werden 23% stationär, 42% zu Hause ohne und 36% zu Hause mit Pflegedienst versorgt. Ein Drittel davon sind im Laufe des Jahres 2018 verstorben. Davon sind 2/3 der zu Hause Gepflegten auch zu Hause gestorben.

Fazit: Es wird daher ein Bedarf gesehen, die Pflege von Menschen mit Krebserkrankungen und zur Begleitung am Lebensende, als Themen für zukünftige Pflegekurse für Angehörige zu implementieren.

Quellenangaben:

1. Daten zu Versicherten der AOK Nordost - Die Gesundheitskasse 2018

Offenlegungserklärung: kein Interessenskonflikt

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Pflegerisches Beratungsprogramm in der ambulanten Nachsorge stammzelltransplantierter Patienten

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Purpose: Um angemessen auf das Problemprofil stammzelltransplantierter Patienten reagieren zu können, wurde ein pflegerisches Beratungsprogramm entwickelt (6 Module): (1) Körperpflege, (2) Aktivität/Ruhe, (3) Ernährung/Sicherheit, (4) Therapiekooperation, (5) Soziale Interaktion und (6) Integrität der Person. Ziel der Studie ist es, die Wirksamkeit des Programms zu überprüfen.

Methods: Das Programm soll sich fördernd auf die (a) Selbstpflegekompetenz der Patienten auswirken, deren (b) Pflegeabhängigkeit senken und die (c) individuelle Lebensqualität steigern. Die Intervention wird über eine RCT evaluiert. Die Interventionspatienten (IG) nehmen am komplementären Beratungsprogramm teil. Die Kontrollpatienten (KG) werden kliniküblich versorgt. Für alle drei Studienendpunkte (a, b, c) werden zur Entlassung (T1), nach 3 Monaten (T2) und nach 6 Monaten (T3) Messwerte (ASA-A, PAS, SEIQoL-DW) erfasst.

Results: 62 Patienten wurden in die Studie aufgenommen. Die Ergebnisse belegen von T1 nach T3 einen größeren Anstieg der Selbstpflegekompetenz (ASA-Punkte: IG 8,9 vs. KG 0,1; $P < 0,01$) und einen stärkeren Abfall der Pflegeabhängigkeit (PAS-Punkte: IG 8,5 vs. KG 4,4; $P < 0,01$) unter Intervention. Effekte bezüglich der Lebensqualität waren nicht nachweisbar.

Conclusions: Die Studienergebnisse bestätigen die positiven Auswirkungen der Pflegeberatung auf das Patientenoutcome. Damit werden Untersuchungsergebnisse unterstützt, welche den Nutzen vergleichbarer Interventionen in der Intermediär- und Spätphase nach HSCT belegen. Zur Ergebnisbekräftigung gilt es, Replikationen in größeren Stichproben zu planen.

Disclosure Statement:

1. Anstellungsverhältnis oder Führungsposition
   Keine
2. Beratungstätigkeit
   Keine
3. Aktienbesitz
   Keine
4. Honorare
   Keine
5. Finanzierung wissenschaftlicher Untersuchungen
   Keine
6. Gutachtertätigkeiten
   Keine
7. Andere finanzielle Beziehungen
   Keine

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Pflegerische Interventionen bei einem Hand-Fuß-Syndrom bedingt durch eine Target- oder Chemotherapie: Eine systematische Literaturübersicht

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Zweck: Menschen, die aufgrund einer onkologischen Erkrankung eine Chemotherapie erhalten, leiden oft unter einem Hand-Fuß-Syndrom

(HFS). In diesem Zusammenhang steigt die Bedeutung an unterstützenden Maßnahmen, die der Reduktion und Prophylaxe der Symptome dienen. Diese internationale Literaturübersicht stellt die identifizierten, evidenzbasierten Pflegeinterventionen bei einem HFS dar.
Methoden: Eine systematische Literaturrecherche erfolgte in Literaturdatenbanken aus unterschiedlichen Disziplinen für den Zeitraum 01.2010 – 09.2019. Eingeschlossen wurden deutsch- oder englischsprachige wissenschaftliche Publikationen. Die Qualitätsbewertung sowie Analyse und Synthese der Studien, erfolgte von den Mitgliedern der Sektion der Deutschen Gesellschaft für Pflegewissenschaft e. V.
Ergebnisse: Für die Qualitätsbewertung konnten n=38 Publikationen in die systematische Literaturübersicht eingeschlossen werden. Die Hauptthemen der Literaturanalyse waren zum einen, allgemeine Vorgehensweisen pflegerischer Intervention in der Prävention und Behandlung und zum anderen spezifische Planung von präventiven Maßnahmen je nach Therapieregime bzw. Medikamentengabe.
Fazit: Die Prävention und die Behandlung von HFS in der onkologischen Therapie ist in der Literatur sichtbar. Die Umsetzung dieser Interventionen in der direkten Interaktion und durch edukative Konzepte sind elementar für die bildende und begleitende Rolle der Pflegefachkraft. Grundlage hierfür bilden therapienagepasste Interventionen sowie gute kommunikative und agogische Kompetenzen der Pflegenden.

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Offenlegungserklärung: Es sind keine relevanten finanziellen Verbindungen offenzulegen.

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Versorgung von Patienten mit kolo-rektalem Karzinom: Der Einsatz einer „Advanced Nursing Practice" (ANP) Als ergänzende Praxisoption

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Purpose: Jährlich steigt die Zahl der diagnostizierten und behandelten Patienten mit kolo-rektalem Karzinom. Um den Bedürfnissen dieser Patienten gerecht zu werden, werden sie durch ein spezialisiertes interdisziplinäres Team versorgt, das auf eine systematische Beratung, Diagnostik, Behandlung und Nachsorge abzielt. Um die Behandlung dieser Patienten auf pflegerischer Seite zu optimieren, könnte eine „Advance Nursing Practice" (ANP) eingeführt werden. Dies erfordert jedoch eine strategische Entwicklung, Implementierung und Evaluation dieses Versorgungskonzeptes und -modells. Das PEPPA-Framework bietet ein Modell dafür. Gut funktionierende Konzepte oder Modelle sollen in die Praxis umsetzen und durch weitere Forschung optimiert werden.

Das Ziel ist die Identifizierung und Zusammenfassung von Tätigkeitsfeldern einer ANP im Rahmen der Versorgung von Patienten mit kolo-rektalem Karzinom.
Methods: Zu diesem Zweck wurde eine systematische Literaturrecherche in CINAHL durchgeführt. Diese ergab 22 Studien. Anhand der Abstrakte konnten vier geeignete Studien identifiziert werden, in welchen die Bedeutung der ANP in der Patientenversorgung deutlich wurde, dennoch fokussierten sich nur zwei auf das kolo-rektale Karzinom.
Results: Die Komplexität der Patientenversorgung und der Krankheitsverlauf und die Bedeutung eines multidisziplinären Teams setzt die Entwicklung neuer Versorgungsmodelle voraus, wie zum Beispiel die Einführung der ANP.
Conclusions: Eicher et. al. 2006 weisen darauf hin, dass ANP Interventionen einen positiven Einfluss auf die Patientenversorgung haben kann. Dennoch mangelt es an primären Evidenzen hinsichtlich der Versorgung von Patienten mit kolo-rektalem Karzinom.

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Sensibilisierung von Pflegenden auf tägliche Phänomene. Eine Prozessoptimierung am Beispiel orale Mucositis

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Zweck: Der Zweck dieser Arbeit ist die Sensibilisierung der Pflegefachpersonen auf ihre Kernkompetenzen und die Abbildung dieser Ergebnisse in Rahmen von sichtbaren Instrumenten. Hierbei soll der Pflege die Möglichkeit gegeben werden, Erfolge zu zeigen und diese präsentieren zu können.
Methoden: Methodisch wurde in mehreren Schritten vorgegangen. Zunächst wurde eine Literaturanalyse zum Thema Orale Mucositis durchgeführt und die neusten Erkenntnisse zusammengetragen. Im nächsten Schritt wurde das Assessmentinstrument „Oral Mucositis Dayli Questionare" durch die Pflege ausgewählt und entsprechend in die Praxis implementiert. In einer ersten Pilotphase von Vier Wochen wurde dies getestet und dann evaluiert und anschließend ausgeweitet. Im letzten Schritt wurden Fortbildungen in Form von „One Minute Wonder" erstellt sowie getestet und evaluiert.
Ergebnisse: Für die Pflege hat sich schnell eine Zufriedene Haltung entwickelt, ihre Qualifikationen abbilden zu können. Ebenso wurde im interdisziplinären Kontext eine hohe Akzeptanz erreicht und das Assessment für die tägliche Visite zur Evaluation genutzt. Das Assessment konnte mit wenigen Veränderungen eingeführt werden und hatte eine leichte Anwendungsmöglichkeit.
Fazit: Als Fazit lässt sich deutlich aufzeigen, dass die Pflege sich durch Visualisierung der eigenen Ergebnisse motivieren lässt, sich diesem Phänomen zu widmen und entsprechend an der Weiterentwicklung mitzuarbeiten. Durch die Mitbestimmung an der Auswahl von Assessment und Themen für die OMW wird eine hohe Akzeptanz erwartet. Das Thema hat auch interdisziplinär einen anderen Stellenwert erreicht, wofür die Pflege Vorreiter ist.

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Offenlegungserklärung: Der Autor erklärt hiermit, keinen Interessenskonflikt zu haben

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Basale Stimulation in der Onkologie. Wer profitiert davon?

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Viele der Patienten mit denen wir täglich arbeiten, sind hoch betagt oder leiden unter dementiellen Veränderungen. Sie haben cerebrale Metastasen oder Tumoren des ZNS, sind durch einen Aufenthalt auf einer Intensivstation beeinträchtigt, haben ein Delir, eine schwere Infektion, Elektrolytverschiebungen oder befinden sich am Lebensende. Es gibt aber auch Patienten, welche aufgrund ihrer Fatigue oder ihrer ausgeprägten körperlichen Schwäche tagsüber wie auch nachts schlafen. Alle haben sie oft eins gemeinsam: Sie verlieren die Orientierung. Der Alltag hat einen ungewohnten Rhythmus, viele fremde Menschen sind um sie herum, unbekannte Prozeduren müssen durchgeführt werden, der Lebensmittelpunkt ist das Krankenbett. Der Patient und seine Angehörigen benötigen in dieser krisenhaften Lebenssituation Unterstützung durch Pflegende. In diesem Vortrag möchte ich das Konzept der Basalen Stimulation® vorstellen und anhand von Beispielen, Möglichkeiten für eine kompetente und empathische Pflege und Begleitung dieser Menschen aufzuzeigen.

Psychooncology

Poster

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Study on the Relationship between Patients with Advanced Prostate Cancer and their Partners

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Purpose: The aim of the study is to identify possible differences between patients in an advanced stage of prostate cancer and their partners in the areas of therapy decision, treatment goals, perception of cognitive changes, stress and partnership. The results should contribute to a better understanding of this special life situation.
Methods: The study is a non-interventional explorative study. We investigated in 100 patients with advanced prostate cancer and their partners who completed their own questionnaires. Anamnestic, psychological (distress thermometer, PHQ-4, EORTC:global quality of life, ASKU, PA-F) and partnership (QMI-D) questionnaires are used.
Results: The partners are younger than the patients (64.6 vs. 69.2 years). No significant differences were found in quality of life, subjective competence expectation and depressiveness. However, the partners reported higher distress (5.7 vs. 4.8), anxiety (1.9 vs. 1.4) and fear of progression (33.9 vs. 30.8). Trends toward worsening are reported in all 13 questions on core symptoms of dementia. The most pronounced deteriorations are in the area of emotional balance, motivation to do something, to perform movements correctly and to organize everyday things. Partners rate the limitations in 9 of the 13 questions more highly than the patients themselves. With regard to the therapy decision, a decision based on partnership is usually preferred, with the emphasis on the patient's will. Only 6% of the patients state that they make the therapy decision without involving their partner. The quality of the partnership is rated better by the patients (42.4 vs. 40.6) than by the partners.
Conclusions: Apart from the fact that both groups are psychologically highly stressed, the partners show a pronounced anxiety symptomatology while the patients suffer from a deterioration of cognitive abilities. Due to the high stress of these couples and the involvement of the partners in the therapy decision, it is important that the attending physician provides detailed information and support to both.

Disclosure Statement: None

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Identifying Subtypes of the Psycho-Neurological Symptom Cluster in Long-Term Prostate Cancer Survivors – Results from the Multiregional Procas Study

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Purpose: Aside from common urological and sexual problems, long-term (≥5 years after diagnosis) prostate cancer (PC) survivors might suffer from pain, fatigue and depression. These symptoms are collectively known as the psycho-neurological symptom (PNS) cluster. No research has been done to 1) identify possible subtypes of this cluster, 2) classify cancer survivors accordingly, and 3) explore associations between subtypes of the PNS cluster and health-related quality of life (HRQoL) in long-term PC survivors.
Methods: The study sample included 653 stage T1-T3N0M0 long-term PC survivors, identified from the multiregional *Prostate Cancer Survivorship in Switzerland* study. Briefly, in 2017/2018, PC survivors were identified via six population-based cancer registries based in both German- and French-speaking Switzerland. Fatigue was assessed with the EORTC QLQ-FA12, mental health with the MHI-5, and pain with the EORTC QLQ-C30 questionnaire. Latent class analysis was used to derive PNS cluster classes. Factors associated with the derived classes were determined with multinomial logistic regression analysis.
Results: Three PNS classes were identified: class 1 (n=394, 61.4%) – 'low pain, physical and emotional fatigue, moderate mental distress'; class 2 (n=98, 15.1%) – 'low physical fatigue and pain, moderate emotional fatigue, high mental distress'; and class 3 (n=151, 23.5%) high scores for all symptoms. Survivors in class 2 and 3 were more likely to be less physically active, having a comorbidity, being treated with radiation therapy, and having worse HRQoL outcomes compared to class 1 (reference).
Conclusions: Three distinct classes of the PNS cluster were identified, which could be distinguished by treatment, comorbidities, lifestyle factors and HRQoL outcomes. Therefore, improving classification of PC survivors according to severity of multiple symptoms could assist in developing interventions tailored to survivors' needs.

Disclosure Statement: The authors have nothing to disclose.

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Expectations and Experiences with the term "Immunotherapy" in the Context of Cancer

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Purpose: The aim of our study was to describe expectations and experiences of patients, physicians and employees of the cancer information service with immune checkpoint inhibitors (ICIs) in cancer therapy.
Methods: In this mixed methods study we investigated knowledge, ideas and believes of 108 cancer patients and 53 patients without cancer about ICIs. For this purpose we used a structured questionnaire. We also interviewed 12 patients which were currently receiving ICI therapy. In order to examine the health professionals´ perspective we performed focus groups with 8 physicians and 9 employees of the cancer information service.
Results: In the patient groups we could identify a lack of knowledge regarding the ICIs. 38% of the patients with ICI therapy were not able to describe the mechanism of the therapy without relevant false contents. In patients without ICI therapy this percentage was even 87%. Furthermore, the results suggest that the image of immunotherapy is noticeably better than that of CT. Immunotherapy is considered to be more expensive, but also in lesser time, more promising and with a lower spectrum of side effects. In patients´ opinion, the future rather belongs to immunotherapy than to CT. In the qualitative interviews, the patients focused on the topics "prognosis", "quality of life", "therapy decision" and "side effects". The participants of the focus groups discussed more about topics such as "creation of an information base" and "how immunotherapy is portrayed in the media".
Conclusions: Personal conversation between patients and physicians should have the highest priority to create an information base for the patient. Furthermore, evidence-based tools, which provide information on ICIs to patients, would be desirable. Based on the good rating of the ICI therapy, it might be useful during therapy education to ensure that possible side effects are not underestimated by the patients.

Disclosure Statement: There are no financial conflicts of interest to disclose.

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Loh-Fear: Determination of Subjectively Perceived Anxiety of Patients in Oncological Abdominal Surgery

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Purpose: For many patients visceral oncological surgery is associated with anxiety, such as fear of heteronomy, pain, injury, physical disfigurement, complications and death. The present study measures anxiety in patients both in intensity and over time.
Methods: In N= 100 persons with a malignant gastrointestinal tumor (62 men, 38 women; age: *M* = 68.4 years; *SD*=10.8; 36-89) anxiety, depression and distress was assessed at 4 time points: first contact (T1), inpatient admission (T2), hospital discharge (T3) and 30 days post inpatient discharge (T4).
Results: Subjectively perceived anxiety and depression was highest at T1 and at T3. 30% of patients showed increased values above the cut-off, regarding anxiety and depression at T1. Higher values of fear at T1 did not correlate in regards to levels of fear at T4 in comparison with patients exhibiting low values of fear at T1. In the framework of a logistical regression a high subjectively perceived burden at T1 was attached to elevated levels of fears at T3 and T4. A multifactor analysis was performed.
Conclusions: Anxiety and depression appear to be an ongoing problem. The identification of persons at risk for clinically relevant anxiety or depression is a particular challenge. Since the extent of anxiety varies over time, a one- off assessment of anxiety at the beginning is not sufficient. However, the subjectively perceived level of distress seems to be a valid predictor for anxiety at the end of treatment. In the course of treatment, the highest anxiety and depression values were found at initial contact and inpatient discharge. Reasons for a lower expression during the treatment phase may be due in the medical and nursing care and competence and the subjective feeling of "being cared for". The results verify the relevance of screening tools for psychological burden also in oncological visceral

surgery. Furthermore the question arises as to which psycho- oncological interventions appear to be indicated and feasible in the pre- and perioperative setting.

Disclosure Statement: The authors declare that they have no conflict of interest.

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Benefit-Finding in Long-Term Prostate Cancer Survivors

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Purpose: Benefit-finding (BF) refers to positive effects that may arise in the aftermath of a cancer diagnosis. It involves disease-induced changes in different aspects of personal and social life such as enhanced interpersonal relationships or growing acceptance of life's deficiencies. The aim of the current study was to investigate the extent of BF and its determinants in prostate cancer (PC) survivors.
Methods: 4,252 PC survivors (97.9% radical prostatectomy) from the German database "Familial PC" were available for analysis. Association between BF (German version of the Benefit-finding-scale) and sociodemographic and clinical variables was analyzed using bivariate analysis.
Results: Mean age at survey was 77.4±6.2 years with a mean follow-up of 14.8±3.8 years. 29.4% of the respondents owned a university degree, 85.4% were living with a partner and 25.1% perceived the severity of the disease as high. 19.6% had a biochemical recurrence at time of survey and 13.5% were under PC-treatment. Mean BF-score was 3.1±1.0 (range 1-5), 59.7% had a BF-score ≥3, 22.6% had score of ≥4. Highest BF-scores emerged for the items "taught me to adjust to things I can`t change" (3.6±1.2), "has helped me take things as they come» (3.6±1.2), and "has shown me that all people need to be loved" (3.5±1.4). Higher BF-level was associated with lower educational level and with higher perceived severity of the PC ($p<0.001$). Time since diagnosis, biochemical recurrence, ongoing treatment as well as anxiety and depression (patient health questionnaire-4) showed statistically significant but negligible associations with BF.
Conclusions: 60% of long-term PC survivors expressed moderate-to-high levels of BF. Higher perceived severity of the disease as well as a lower educational level were associated with higher levels of BF. In contrast, the clinical course of the PC (past or present biochemical recurrence, ongoing treatment) had no clinically meaningful effect on the amount of found benefit.

Disclosure Statement: No conflict of interest.

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Physical Exercize, Coping, and Survival in Cancer Patients

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Purpose: A growing number of studies supports the positive connection between physical exercise training programs and improved quality of life in cancer patients. Some studies even suggest that an increased physical activity may contribute to a better survival of such patients. We report results of an exercise intervention program in patients by also controlling for psychological and coping ressources with regard to survival time.
Methods: 82 patients with advanced cancer diseases of various kinds received an individually tailor-made exercise training over six weeks. Gain in lung capacity (VO_2max) was controlled by comparing pre and post VO_2max. Patients completed the EORTC QLQ-C30 questionnaire, Profile of Mood Scales (POMS), SCL-K and were interviewed with a semi-structured interview with regard to their coping ressources at baseline and after the exercise intervention. Independent blind raters objectively rated the interviews sentence by sentence using the Ulm Coping Manual (UCM). Survival time was followed for more than eight years.
Results: Linear mixed-model analyses revealed that specific active coping ressources and sufficient role functions predicted gain in VO_2max and VO_2max in turn predicted survival time besides significant increases in two active coping dimensions: information seeking and anticipation.
Conclusions: Psychological and personality variables such as coping ressources are essential predictors for cancer patients' benefit from exercise training.

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Integration of Cross-Sectoral Psycho-Oncological Care into Inpatient and Outpatient Cancer Therapy

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Purpose: The National Cancer Plan describes the objective of cross-sector, integrated oncological care (field of action 2, objective 7). Cooperation and coordination in oncological care across sectors and occupational groups should be improved and self-help more closely integrated. The isPO project (integrated, cross-sectoral psycho-oncology), funded by the Innovation Committee of the Federal Joint Committee, aims to integrate psycho-oncology into inpatient and outpatient care through vertical and horizontal coordination and cooperation.
Methods: In the isPO project, a psycho-oncological care programme will be developed, implemented and evaluated by 2021. The integration of the programme into oncology will be implemented through the establishment of psycho-oncological care networks consisting of an oncological centre and registered doctors (vertical cooperation) as well as the (horizontal) cooperation of doctors, nurses/medical assistants, psychotherapists, psychosocial specialists and self-help. A network coordinator takes over the central control of the processes and is the contact person for all professional groups.
Results: The program will be integrated at four locations (Cologne, Troisdorf, Neuss, Mönchengladbach) as part of a contract pursuant to § 140a SGB V. It is presented in the form of organization charts with defined tasks and powers and is implemented on the basis of formal administrative SOP´s . The programme has been undergoing testing since the beginning of 2019. It is evaluated and optimized within the framework of a quality management system. The main outcome criteria for integration are (timely) patient enrolment and cross-sector networking of care.
Conclusions: The establishment of cooperation and coordination structures integrated into the oncological care routine is essential if all cancer patients are to be offered psycho-oncological care, as required by the National Cancer Plan.

References: not applicable

Disclosure Statement: The authors declare that they have no conflict of interests.

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Factors Influencing Psychosocial Distress in Persons with Hereditary Cancer Predisposition Syndromes and their Relatives - "Gemeinsamgen"

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Purpose: Persons with hereditary cancer predisposition syndromes carry a mutation in individual genes and hence are at increased risk for the

development of specific tumors (e.g., HBOC, HNPCC, Gorlin Syndrome). Typically the age of onset is earlier and a familial accumulation of the syndrome-specific tumor spectrum is seen. The knowledge of a genetic disposition can relieve affected families, providing the possibilities of prophylactic surgeries and intensified surveillance for early detection. As well as precipitate psychological stress. Specific factors that can lead to increased distress involve, e.g., coping behavior, psychosocial problems, familial issues, feelings of guilt and fear of developing cancer. Whether and to what extent relatives experience distress has not yet been sufficiently investigated. This study therefore aims to gain knowledge about stress inducing factors in mutation carriers and relatives.
Methods: Within the scope of a nationwide, cross-sectional online survey mutation carriers and relatives will be asked about their subjectively experienced psychological distress via patient reported outcomes N=236 individuals will be included. In addition, questionnaires are used to record individual and family factors for which a correlation is assumed.
Results: For the statistical analysis we assume a final N of 118 per group (N=236). Besides descriptive evaluations, such as mean values, standard deviations and frequencies, regression analyses are planned. First results will be presented at the conference.
Conclusions: The research findings can help towards identifying predictors of psychosocial distress as well as determining specific risk groups. Consequently, feasible deficits in the quality of care can be detected. Furthermore the results can be implemented in the development of further psychosocial care services and interventions. In particular this study can make an important contribution to assessing the psychosocial burden of relatives, given that only little research on these individuals has been conducted so far.

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"And Now, Am I Ill or Still Healthy?" Psychological and Medical Need for Assistance in Women with Increased Risk for Hereditary Breast- and Ovarian Cancer – A Qualitative Analysis

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Purpose: Healthy women recognized to carry a pathogenic BRCA1/2 mutation bear a significant psychological burden, e.g. due to uncertainty how to deal with an increased risk to develop breast (BC) and ovarian cancer (OC). Mutation carriers may experience significant levels of distress in the short time, and genetic testing distress can remain elevated in the longer term, especially among younger women and women with higher levels of distress at testing. Only one-third of the counselees who reported a request for psychological assistance had attained help. This study aims to identify whether, and if so, in which extent women with hereditary BC and OC need psychological and medical assistance and which contents could be additionally of interest for them.
Methods: N = 21 women were asked by in-depth interviews if a genetic burden exists and if psychological assistance were requested. In addition, topics of interest were identified. Moreover, N = 5 interviews were conducted with experts (physicians, psycho-oncologists) to identify themes of interest for women with a pathogenic mutation.
Results: Preliminary analysis indicates that 33.3% requested for psychological help because of the genetic mutation and/or their consequence in the past (divorce, depression). Further, 52.4% of the interviewed women show an interest in psychological help. At this point main topics are communication within relatives, anxiety, decision-making processes, dealing with genetic- and family-related distress. Relatives and their way to cope with the mutation are of particular importance for affected people. More extensive analyses are planned.
Conclusions: In particular this study takes first step toward understanding patients' psychological and medical need for assistance and suggested main themes of interest. A long-term goal could be the development of further psychosocial care services and interventions. In Addition further research is needed which focus on relatives, because whether and to what extent relatives experience distress has not yet been sufficiently investigated.

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Spiritual Care in Oncology: Cancer Patients' Unmet Spiritual – Data from a Pilot Project

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Purpose: As part of the AG PRIO project on spiritual needs of cancer patients, we analyzed their unmet spiritual needs and related these to their interpretations of illness (IoI) and quality of life.
Methods: Cross sectional survey in a defined time frame among patients with cancer (N=171; 62% women; 61±12 years of age; 53% R-S-) from centers in East and West Germany with standardized questionnaires. Unmet spiritual needs (SpNQ-20) were categorized as Religious (RN), Existential (ExN), Inner Peace (IPN), Generativity (GN) needs with intensity scores ranging from 0 to 3.
Results: RN (0,8±0,9) and ExN (0,8±0,8) scored low, IPN (1,6±0,9) and GN (1,4±0,9) higher. There were no significant differences between East and West. Their needs were moderately (r 0.3-0.5) related to positive IoI, while negative IoI were related moderately to ExN and IPN only. IPN were weakly (r 0.2-0.3) related to lower wellbeing (WHO5) and life satisfaction (BMLSS-10), and positively with under pressure feelings (VAS); RN and GN were not significantly related. Patients with higher tumor stages had significantly higher ExN, IPN and GN, but not RN.
Conclusions: Identifying cancer patients´ unmeet spiritual needs requires a reaction from health professionals and pastoral workers. These needs were related to higher tumor stages, how they perceive their illness and lower wellbeing - but not RN. Thus, health professionals do not have to fear responding to strictly religious issues they may feel less competent to address.

Disclosure Statement: The study was supported by a grant of German Cancer Society. The authors disclose any conflict of interest.

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Dimensionen Der Patientenkompetenz Bei Krebsbetroffenen: Ergebnisse Einer Replikationsstudie im Vergleich

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Purpose: Advancing Patient Competence (PC) represents an important goal of Germany's National Cancer Plan. However, no consensus has yet been reached as to which dimensions may constitute PC. Therefore, this study asked whether the 8 dimensions of PC derived by Giesler and Weis[1] would replicate in other samples of cancer patients.
Methods: Based on a sample of N = 424 breast, colorectal, and prostate cancer patients (mean age 62 years, 53% female) undergoing either oncological rehabilitation or treatment in specialized oncology practices, confirmatory factor analyses were performed for the problem- and the emotion-focused items of the Patient Competence Questionnaire 57.[1]

Results: Using conventional fit criteria, 7 factors were identified for problem-focused items (e.g. seeking information, self-regulation, and assertively interacting with physicians; CFI = .921, RMSEA = .054). For emotion-focused items 3 factors were identified (managing distress, dealing with threat, and (low) avoidance; CFI = .961, RMSEA = .055).
Conclusions: This study partially confirms the dimensions of PC found by earlier research.[1] Studies of similar intent report comparable results, including a splitting of factors.[2,3] Thus, the factors listed in the results section appear to be replicable dimensions of PC with some restrictions. Future research should focus on refinements of the concept of PC and on interventions to advance it.

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Disclosure Statement: The authors have no conflict of interest.

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Correlation of Psychooncological Support and Quality of Life in Patients with Oral Cancer: A Study Based on an Electronic Psychooncological Screening Instrument and Quality of Life Questionnaire

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Purpose: Cancer patients suffer from severe distress, and oral cancer patients report some of the highest distress levels of all cancer patients[1]. The German S3-Guidline and the certified Head and Neck Cancer Centres recommend psychooncological support for these patients. This study analysed the need for psychooncological support with an electronic screening instrument (ePOS) and measured the Quality of Life (QoL) up to one year after therapy.
Methods: The ePOS instrument included the DISTRESS questionnaire (DT), the Hornheider Screening Instrument (HSI), Hospital Anxiety and Depression Scale (HADS), and inquiries for personal support need. These patients were also monitored with the EORTC QLQ-C30 and H&N35 QoL questionnaires.
Results: A total of 66 patients were screened including 37 patients with QoL surveys completed after one year: 76% of patients reached the pre-therapeutic QoL level. Patients who opted for psychooncologial support had a significantly worse QoL after one year compared to patients who tested positive for treatment need but did not request psychooncological support. The HADS was a predictive marker for a lower QoL after 1 year.
Conclusions: Generally, a positive ePOS test for psychooncological support was not a significant predictor for lower QoL outcome after one year. Patients who requested support showed a lower outcome in QoL. Consequently, these patients should be supported more intensively. Patients with a positive HADS may also benefit from more intensive psychooncological support[2]. Our study was one of the first analysing the pre-therapeutic distress and QoL outcome after surgical cancer treatment.

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Disclosure Statement: Nothing to disclose

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Prognostic Awareness Regarding the Treatment Intensity in Cancer Patients

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Purpose: Higher levels of patients´ prognostic awareness (PA), crucial for early integration of palliative care in oncology, lead to better decision making about further treatment and care options. However, previous studies have found mostly low levels of PA in patients. Focussing on PA regarding the treatment intensity (PATI) as one facet of PA, the patients´ perception of the treatment intensity and possible discrepancies between them and their oncologists regarding PA were explored.
Methods: Five cancer patients of a large German university hospital were interviewed about their perception of the treatment intensity. The interviews were analysed with Kuckartz´s thematic content analysis. The patients and their oncologists completed questionnaires assessing the patients' PA, too.
Results: The questionnaires showed moderate to high levels of congruence between patients' and oncologists' answers, indicating moderate to high levels of PA in patients. The following factors were reportedly impacting their perception of the treatment intensity: the physical condition, hope for recovery and normality, conditions in the hospital, interaction with oncologists, social and financial factors and psychological condition.
Conclusion: Knowing the patients´ individual background and their perception of the treatment intensity is a key factor for improving PATI. The factors influencing the perception of treatment intensity can be assessed via tailored questions. If healthcare professionals address these topics, they may meet specific communication needs of the patients, leading to higher levels of PATI.

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Disclosure Statement: No conflicts of interest.

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Development and Evaluation of an Unguided Psychosocial Online-Intervention for Caregivers of Cancer Patients (OAse): Results of a Feasibility Study

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Purpose: Informal caregivers (family and friends) of cancer patients provide support to the patient and at the same time they experience an increased burden or distress - often unprepared for their caregiving role. Due to shame, uncertainty or lack of time, psychosocial face-to-face services are rarely used by cancer caregivers. The aim of this study is therefore to develop and evaluate an unguided psychosocial online-intervention for caregivers of cancer patients (OAse).
Methods: From June 2018 to April 2019, n=41 caregivers of cancer patients (spouse, children, friends) were included in the study. Participation in the study was independent of patients' tumour site and treatment stage.

OAse is a resource-oriented, web-based unguided self-help program comprising four modules (understanding and providing effective support, understanding the patient's feelings, dealing with own burdensome feelings, strengthening own resources). Qualitative and quantitative data were collected at the beginning (T1) and at the end (T2) of the intervention to assess the feasibility and acceptance of OAse as well as patient satisfaction with the program.
Results: Of the 41 caregivers 65,9% (n=27) were female. Most of the participants were spouses (70,7%, n=29), followed by adult children (19,5%, n=8) and friends (9,8%, n=4). The age of participants ranged from 19 to 69 years (M=44,59, SD=13,75). Of the 41 participating caregivers, n=28 (62.2%) fully completed the OAse intervention. The qualitative and quantitative data show a high degree of caregivers' satisfaction.
Conclusions: Up to now specialised psychological internet interventions for caregivers of cancer patients are rare. In the present study OAse has proven feasible and acceptable. Compared to other unguided online interventions in this field, the completion rate was very high. Therefore, the intervention could make a significant contribution to improve caregivers' psychological condition and to increase their competency and self-efficacy.

Disclosure Statement: Authors have no conflicts of interests.

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Is the Spectrum of Mental Disorders in Cancer (Ca) Patients Changed by Time?

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Purpose: In a previous study, the spectrum of mental disorders of long-term cancer(Ca) survivors (LCS; time since initial diagnosis, 5 years[yr] as minimum) and patients with acute Ca pain (acpp; initial diagnosis, 1-2 yr ago) was compared. There were differences in the total number of mental disorders (LCS: 65.6%; acpp: 53.8%) as well as, among them, organic mental disorders (9.8% *vs.* 2.2%) and addictions (13.1% *vs.* 2.2%). Ca of the urogenital tract (uro-Ca) were more frequent in LCS and gastrointestinal(GI) Ca in acpp. Since uro-Ca in general has usually a longer survival time, the question arose whether the different prevalences are a function of the duration.
Hypothesis: If the different numbers were a consequence of the type of Ca, this distribution would also be apparent in acpp of the urogenital tract.
Methods: "acpp" of the GI and urogenital tract were compared. The occurrence and distribution of mental disorders (F1-F4 according to ICD-10, as well as psychologically normal ones) were investigated.
Results: Within the same period of time since initial diagnosis (GI=1.10 yr, Uro=1.37 yr), 50% of the GI patients had abnormal psychological findings, however, only 38.2% of the uro-patients. Addictions were found in only 2.3% of uro Ca patients (ucp). Organic mental disorders were found in 11.6% of ucp.
Conclusions: The acute ucp had less psychological disorders than the acute GI-patients and, in particular, than LCS. This also applies to addictions. Derived from this, it can be assumed that mental disorders as a specific group of patients as well as the individual diagnosis of addiction develop to higher proportions over time.

This is in contrast to organic mental disorders, which already occur as often in acute ucp as in LCS. Here, the influence of Ca diagnosis must be assumed.

Disclosure Statement: Patients with a long history of Ca need to be examined for the spectrum of various mental disorders, especially for addiction.

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How Do Cancer Patients Experience Molecular Diagnostics?

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Purpose: Research findings within molecular diagnostic (MD) raise hope for new effective cancer treatments. At the same time, evidence of a treatment benefit of MD is still limited for many malignancies. However, patients may hold high expectations nonetheless. To support these patients sufficiently, deeper insight into their individual experience with MD is needed. Thus, this study examines cancer patients' perceived level of information and expectations regarding MD.
Methods: In two German Comprehensive Cancer Centers, 30 cancer patients undergoing MD participated in semi-structured interviews on their subjective level of information and expectations regarding their MD participation. Additionally, socio-demographic, medical, and distress data was collected.
Results: While most patients understood their program's procedures, many found the background of tumor genomic profiling to be too complex. In the tension between limited understanding and uncertainty about a personal benefit, they emphasized the importance of trusting their doctor. Overall, patients mentioned three expectations of participating in MD: 1) improving their treatment, 2) contributing to research and 3) learning more about their tumor. Moreover, they described feeling individually appreciated and maintaining hope for recovery by participating in the MD program.
Conclusions: The results underline the significance of the relationship between patients and their oncologist within MD: Trusting their treating physician can buffer incomprehensible or missing information as well as the uncertainty whether they will benefit from MD at all. Also, patients felt they were treated in a more "personalized" way. To balance patient hopes and potential outcomes, oncologists and psycho-oncologists should regularly and openly discuss treatment expectations as well as realistic goals with their patients, thereby providing support and enabling an individual and truly "personalized" treatment.

Disclosure Statement: The authors have nothing to disclose.

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Distress in Patients with Non-Melanoma Skin Cancer

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Purpose: Non-Melanoma Skin Cancer (NMSC) is often not regarded as cancer by patients and considered less dangerous than malignant melanoma. Usually NMSC is treated curatively by surgical excision of the affected area. So far, there is no reliable study examining the NMSC patient's distress. The aim of this study was to examine the patient's distress during the often several tumor surgeries to reach R0 resection.

Methods: From 1/2018 to 2/2019 we examined N=168 inpatients at the university skin clinic Tuebingen. To evaluate the distress, we used Hornheider Screening Instrument (HSI), Patient-Health-Questionnaire (PHQ-2), General Anxiety Disorder Screening (GAD-2), Distress Thermometer (DT) and subjective need for support. Besides we used BFI-K personality variables (based on the Big Five model) as possible predictors and a self-developed questionnaire to investigate the patient's awareness of the disease. A diagnostic interview (based on QLQ-C30) and somatic data from the clinical history completed the data collection. Follow-up 6 months after the hospital-stay queried data on any changes of distress.
Results: Mean patient age was 62.9 years, 47.6% were female. The histologically confirmed tumor type was in 79% (n_1=133) basal cell carcinoma and in 17% (n_2=28) squamous cell carcinoma. In 68.4% tumor localization was the facial area. The mean size of the largest operated defect was 5.5 cm². Patients with NMSC reported extremely low subjective support needs (0.6%). Still, we identified an above-threshold value of DT in 46.1 %. In HSI 31.8% showed abnormal stress values, 11.7% indicated an anxiety disorder (GAD-2) and 4.9% indicated depression (PHQ-2). Worries, anxieties and sleep were most frequently mentioned in DT problem list.
Conclusions: Our data show that patients hardly express any subjective need for psycho-oncological support, although a remarkable amount of patients has increased distress levels. This could be due to the subjectively lower threat attributed to NMSC. The follow-up was completed in 8/2019, so that further results will be available at the congress.

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Patientenkompetenz bei Krebspatienten: Welche Wirkung haben Zeit seit Diagnose und eine kurative vs. palliative Behandlungssituation?

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Purpose: Germany's National Cancer Plan designates promoting Patient Competence (PC) as one of its goals, while acknowledging a considerable need of clarifying this concept itself and identifying potential determinants and health-related outcomes. Against this background, we explored potential effects of time since diagnosis (TSD) and a palliative treatment situation on PC, coping self-efficacy, and quality of life.
Methods: In a study with three measurement points, we included 424 patients with breast, colorectal or prostate cancer in either oncological rehabilitation or out-patient treatment (mean age 62 years, 53% female, 34% under palliative treatment, median TSD 9.8 months). At each time point, PC was measured with the Patient Competence Questionnaire 57 (PCQ-57) that covers 8 PCs.[1] To test for effects of TSD and treatment situation, we computed 2 (TSD below median vs. TSD above median) x 2 (curative vs. palliative treatment situation) ANOVAs on PC, coping self-efficacy (CBI-B) and quality of life (QLQ-C30) as measured at baseline.
Results: Longer TSD was associated with significantly stronger competencies for seeking information, striving for autonomous decisions, and using social benefits, and also with better role functioning. Compared to patients under curative treatment, patients under palliative treatment reported dealing explicitly with the life-threat posed by cancer to a significantly larger extent. Also, they reported significantly lower coping self-efficacy and physical functioning. Effect sizes were generally small, however.
Conclusions: The findings suggest that a longer TSD and a palliative situation may independently impact on PC, coping self-efficacy and quality of life. They thus underline the need for supporting patients under these conditions in their striving for autonomy and their coping efforts.

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Disclosure Statement: The authors have no conflict of interest.

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EPOS: Development and Evaluation of an Emotion-Based Psychosocial Online Self-Help Program for Cancer Patients

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Purpose: A cancer diagnosis is associated with considerable psychosocial burdens and losses in quality of life. Many patients have problems to find adequate outpatient psycho-oncological help after discharge from the clinic. Internet-based interventions are regarded as a promising opportunity for cancer patients to overcome existing barriers to the use of psychosocial support and to improve their psychological well-being, regardless of time or place.
Methods: Based on extensive literature research, focus groups with health care professionals and interviews with cancer patients, we developed the 8-week online intervention *epos* (emotion-based psycho-oncological online self-help). The program was designed for patients with all types of cancer and follows the theoretical concepts of emotional mindfulness, resilience and positive psychology. It aims to reduce psychological distress by (1) providing orientation and information (2) promoting their social relationships and (3) strengthening their resilience.
Results: *Epos* includes an introductory module on mindfulness, followed by seven modules on a specific psychosocial issue (e.g. talking about cancer, dealing with mental complaints, dealing with cancer in the social context). Each module consists of psycho-educative elements as well as emotion- or mindfulness-based exercises. Videos of fictional cancer patients and psycho-oncological experts guide through the program.
Conclusions: With *epos*, an emotion-based online intervention has been developed that complements conventional psycho-oncological treatment. We assume that *epos* helps cancer patients to better cope with the major psychological, social and physical challenges of the disease. In a randomized controlled trial (online self-help program + treatment as usual vs. only treatment as usual) enrolling N=325 cancer patients, the efficacy and acceptance of *epos* will be investigated.

Disclosure Statement: The authors declare no conflict of interest.

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Work Ability of Employed Cancer Survivors

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Purpose: The aim of the study was to analyze work ability and its relationship with possible determinants, in particular with fatigue, occupational self-efficacy and job crafting. It was examined, if self-efficacy and job crafting are helpful strategies to cope with fatigue at work and sustain work ability.
Methods: A cross-sectional sample of individuals diagnosed with cancer who finished primary treatment and have continued work filled out an online questionnaire. Variables were assessed with common self-report questionnaires. For consideration of the target group, a shortened version of the Work Ability Index was used. Multiple regressions were executed to examine associations while controlling for gender (female), working hours and time since continuation of work. Additionally, participants were asked which symptom was most hindering after return to work.
Results: Participants (N = 69, female = 91.3%) were mostly diagnosed with breast cancer (68.1%) and have reassumed work more than three years ago. Fatigue was most frequently mentioned as a barrier after return to work. It was inverse related to general, physical and mental work ability. Women and participants with a greater workload evaluated their work ability higher. Moreover, participants with Fatigue reported a lower self-efficacy, but more job crafting. Job crafting and self-efficacy did not moderate the relationship between fatigue and work ability nor did job crafting mediate it (p >.05).

Conclusions: Quantitative and qualitative findings implicate the burden of fatigue at work. Employed cancer survivors suffering from fatigue are at risk to rate their work ability lower. Special attention should be directed to mental work ability. The relevance of self-efficacy and job crafting for work ability should be investigated in larger studies.

Disclosure Statement: No conflict of interest or financial ties.

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Distress Experiences and Acceptance of a Computer Based Screening in Neuro-Oncological Patients

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Purpose: Psycho-oncological screening is mandatory for patient-centered care in oncology. This is challenging in neuro-oncology as motor and mental dysfunctions are common.

From 2/2018 to 2/2019 we examined n = 100 patients who were in the neurosurgical department of the University Hospital Tübingen for surgical tumor therapy. The aim of the study is to investigate the patient's distress experiences as well as their individual stress factors and the feasibility of a computer-based screening.

Methods: The Electronic Psycho-oncological Screening (ePOS) was used to assess patient's distress. It includes the Hornheider Screening Instrument (HSI), Patient Health Questionnaire (PHQ-4), Distress Thermometer (DT) and a question assessing the subjective need for support. The Resiliency Scale (RS-13), the Helping Alliance Questionnaire (HAQ-S) and the Barthel Index as an clinician reported outcome, were also surveyed. Patients were assessed postoperatively by using a tablet. A follow-up measurement is scheduled 6 months after the first measurement date and will be completed by 9/2019.

Results: The average patient age was 52 years (SD:14). 53% of the patients were female. Subjective need for psycho-oncological support was reported by 21% of the patients. In DT 65% showed increased values. In the HSI, 34% had a need for psycho-oncological treatment. Indications of an anxiety disorder were found in 24% and depression in 19%. In RS-13 87% showed moderate to high values. About 80% indicated the family doctor as their outpatient primary care provider. Overall, 74% were able to handle the tablet on their own.

Conclusions: Our data show that about every fifth neuro-oncological patient indicates a subjective need for psycho-oncological support. Outpatient family doctors play the most important role in primary care. Overall, there is a high acceptance of the electronic screening in the perioperative situation.

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The Need for Psycho-Oncological Support in Colorectal Cancer Patients during different Treatment Phases

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Purpose: Colorectal cancer is frequently associated with psychooncological burden for the affected patients. Severity and temporal dimension are often not readily assessable.The aim of this study was to identify patients in need of psychooncological support and to monitor these patients in the long-term.

Methods: The present study was conducted in 25 German hospitals. 604 colorectal cancer patients were asked to answer the self-assessment *Questionnaire on Stress in Cancer Patients – short form* (Herschbach & Weis, 2010) [1] at least twice throughout the observation period.

Results: Among all colorectal cancer patients included, 35,6% suffered from psychooncological distress at the time of the first survey. There was no significant difference between women (39,3%) and men (33,3%). The average lead time between the first and the second survey was 33,4 weeks. 94 patients completed at least the 2nd survey. During the second survey, 39,3% of the 28 initially burdened patients were still identified to require psychooncological support. Among the 66 (70,2%) initially burden-free patients, 78,8% still showed no psychooncological distress at the time of the second survey. However, fourteen individuals out of this group (21,2%) exhibited significant signs of psychooncological impairment.

Conclusions: Psychooncological burden was observed in 35,6% of the colorectal cancer patients at an early stage during the course of the disease and during the second survey in approximately 20% of all patients who initially did not show any signs of psychological impairment. This argues in favor that psychooncological burden may well occur in a small but significant subset of initially unaffected colorectal cancer patients after a prolonged period of time.

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Disclosure Statement: There is no conflict of interest.

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Influence of a Rehabilitative Treatment after Resection of a Benign Meningioma

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Purpose: The BReMen Study (Belastung und Rehabilitation bei Meningeompatienten) concentrates on the (neuro)psychological burdens and limitations of patients with benign meningiomas and examines which influence a rehabilitation has and whether there is an indicator of when rehab is necessary.

Methods: In a prospective longitudinal trial, 80 patients with benign meningiomas will be examined over a period of 2 years. Test time points included pre- (T1), post-surgery (T2), 3, 6, 12 and 24 months post-surgery.

In addition to sociodemographic data, localization/size of the meningioma, use of rehabilitation and its duration, time of reintegration will be recorded.

Questionnaires used to assess quality of life and affect: Short-Form Health Questionnaire (SF-36), EORTC Quality of Life Questionnaire - C30, EORTC QLQ for brain tumor patients, PHQ-9 depression score, GAD-7 general anxiety score and distress thermometer.

Neuropsychological tests used to examine cognitive functioning: Verbaler Lern- und Merkfähigkeitstest, Wechsler Memory Scale Revised, Regensburger Wortflüssigkeitstest, Trail Making Test A+B, Stroop-Test and d2-R Aufmerksamkeits- und Belastungstest.

Results: This interim analysis focused on PHQ-9, GAD-7 and distress levels.

So far, 61 patients were recruited, 23 dropped out. From 38 patients which were examined one year post-surgery 80% claimed rehab.

While both groups show increased distress values, patients receiving rehab show an earlier distress decrease with lower long-term values.

Patients with higher depressiveness and anxiety have a stronger desire for rehab; a medium-term drop of these values can be observed, followed by a renewed increase to T5.

Conclusions: Increased depressiveness levels appear to be an indicator of rehab need.

The stronger reduction of distress, depressivity and anxiety in the rehab group indicate a positive rehab effect, while the later increase in depressiveness and anxiety levels seems to mark the need for further (neuro) psychological care.

Disclosure Statement: No conflicts of interest or financial ties.

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A Clinical Trial of Group-Based Body Psychotherapy to Improve Bodily Disturbances in Cancer Patients in Combination with Randomized Controlled Smartphone-Triggered Bodily Interventions – First Results

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Purpose: Disturbances in bodily well-being represent one key source of suffering and impairment related to cancer. There is growing evidence that body psychotherapy (BPT) is efficacious for the treatment of various mental health problems. However, with regard to cancer patients, evidence is scarce. Our aim was to evaluate whether group BPT can improve bodily disturbances in post-treatment cancer patients.
Methods: Pre-post convergent parallel design of group BPT (6 weekly sessions) using a waiting-period comparator, including a nested RCT: During the BPT phase, either a smartphone-triggered bodily intervention or a smartphone-triggered control intervention is provided at random over 5 consecutive weeks, on 6 days weekly. Assessment took place at three times (baseline, pre- and post-intervention), and on a daily basis for the smartphone-triggered interventions. Inclusion criteria: Patients who had received curatively intended treatment for any malignant neoplasm (treatment being completed ≥3 months) and were suffering from bodily disturbances. Primary outcome: bodily disturbances assessed using the 'Body Image Scale'. For the secondary outcomes standardized questionnaires are used to assess changes in experience of presence and vitality, mood, body mindfulness, somatic symptoms and somatic symptom disorder, quality of life, anxiety, and depression including suicidal tendency, vitality and mental health, as well as group cohesion.
Results: 171 patients were screened for eligibility; 40 patients attended the group BPT and were randomized on a daily basis. 7 groups were conducted. Median age was 51.7 (22-77)y. 35 (87.5%) were female. 23 (57.5%) had a malignant neoplasma of breast, 7 (17.5%) a lymphoma, 10 (25%) were spread over various cancer types. Data analysis is ongoing at the time of submission. First results will be presented at DKK.
Conclusions: Our trial has strong potential benefits for cancer patients, as it may introduce new therapeutic approaches to treat bodily disturbance that persist despite curative tumor therapy.

Quality of Life

Poster

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The Relationship between Posttraumatic Growth and Health-Related Quality of Life in Adult Cancer Survivors: A Systematic Review

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Purpose: Studies reported different results on the relationship between posttraumatic growth (PTG) and health-related quality of life (HRQOL) in cancer survivors. This review aims to give an overview of current studies and to identify factors that potentially contribute to the heterogeneity of the results on this topic.
Methods: This systematic review was registered in the International Prospective Register of Systematic Reviews (ID: CRD42019121828), and conducted and reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Eight literature databases were systematically searched using the concepts 'posttraumatic growth', 'cancer', and 'health-related quality of life'. Eligible studies (published until 2018) were reviewed, quality-assessed, and effect sizes were extracted and synthesized.
Results: Of the 37 included articles, 22 received a rating of 'weak', 11 'moderate' and 4 'strong' in study quality assessment. Thirty-five independent samples, mainly assessed in cross-sectional studies, were identified. The overall sample comprised 7954 individuals, mean age of 55.3 years, >50% females, predominantly breast cancer, and mainly focused on short-term survivors (<5 years post-diagnosis). Variations in HRQOL measurement and methodological inconsistency contributed to study-level differences of effect sizes. Sample-level factors were gender, cancer diagnosis, mean age at study and geographic origin. Excluding studies of prostate cancer survivors led to a decrease in heterogeneity regarding gender and diagnosis.
Conclusions: Studies assessing the relationship between PTG and HRQOL were heterogeneous and results were difficult to combine. Overall, most studies found a positive relationship between the factors. However, studies of higher quality and longitudinal design are needed to better understand the mechanisms behind that relationship, and to determine whether PTG in cancer survivors can be modified by intervention in order to improve HRQOL.

Disclosure Statement: None.

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HELP (Heidelberger Entscheidungshilfen für Lungenkrebs-Patienten) – Decision Aids for Lung Cancer Patients

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Purpose: Preference for patient participation increased over the past 30 years. Especially cancer patients with a limited prognosis have a strong wish for information and participation. Decision aids (DA) are useful instrument to meet these needs. They increase patients' knowledge regarding options and reduce decisional conflicts. Benefits of DA, relative to usual care, are better knowledge of options, outcomes and more accurate perceptions of outcome probabilities. Nonetheless, the use of DA by oncologists is still highly improvable. In the setting of limited prognosis that comprises not only physical and psychosocial burden but also confronts the patients and their relatives with an existential threat, many possible barriers may hinder the adequate use of standardized aids. Therefore the aim of our project is the qualitative exploration, development and successful implementation of DA for lung cancer patients.
Methods: 25 structured interviews with patients and their relatives will be conducted regarding their wishes, needs and ideas in the decision

making process. The healthcare-professionals perspective will be collected through focus groups and all data will be analyzed with content analysis. Based on these results and a thorough literature search, DA will be developed and tested with the help of patient representatives. After a trial period, the DA will be implemented in daily clinical practice following an implementation plan. The success of the implementation will be measured in the dimensions adherence and acceptance.
Results: Mainly focusing on the development of patient oriented DA and their implementation first preliminary results will be available up to the time of the congress.
Conclusions: Through the integration of DA in clinical practice patients and their family care-givers can be more actively involved in therapy- decisions and patient's competency and autonomy will be enhanced. The implementation in daily clinical practice will be particularly challenging as it also implicates dealing with important barriers perceived by the professionals.

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Prevalence and Intensity of Cancer-Related Fatigue Across a Variety of Cancer Entities

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Purpose: To systematically assess and compare prevalence and intensity of fatigue across the 16 most frequent cancer entities.
Methods: The FiX study enrolled cancer patients 1-2 years after diagnosis via the Epidemiological Cancer Registry of Baden-Württemberg. Fatigue was assessed with the multidimensional EORTC QLQ-FA12 questionnaire. Age, sex, tumor and treatment data were derived from the cancer registry. For calculating prevalence, patients with scores higher than the age- and gender-specific 75th percentile from a representative sample of the German general population were considered fatigued [1].
Results: A total of n=2,256 patients (50% male, 5% metastasized) with a mean age of 66 ± 12 years were included in this analysis. The median (Q1, Q3) raw scores of physical fatigue ranged from 26.7 (13.3, 53.3) among prostate and 33.3 (16.7, 66.7) among breast to 46.7 (26.7, 66.7) and 46.7 (26.7, 73.3) among stomach and pancreas cancer patients, respectively. Prevalence was calculated for all fatigue dimensions and entities. For example, physical fatigue was prevalent in 34% of prostate and 54% of lung cancer patients. After adjusting for determinants of fatigue, i.e. sex, age, BMI, type and timing of therapy, the intensity of physical fatigue still differed among tumor entities (p = 0.018) with highest values among patients with stomach, lung, pancreas, and kidney cancer and lowest values among patients with prostate and breast cancer. Breast cancer patients also showed lowest adjusted levels of emotional fatigue.
Conclusions: Fatigue occurs across a large variety of cancer entities. Intensity and prevalence of fatigue in breast and prostate cancer patients were in the lowest range among the 16 entities studied. As the majority of observational and interventional research on fatigue is based on breast cancer patients, the scope of this burdensome problem is probably not fully ascertained.

Reference:
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Disclosure Statement: none

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Top 10 Living with and Beyond Cancer Research Priorities

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Purpose: Currently 2.5 million people in the United Kingdom (UK) live with a diagnosis of cancer and it is projected that by 2030 it will be over four million [1]. Despite this, investment in research that aims to help people live better with and beyond a cancer diagnosis has remained consistently low and is currently only around 6% of UK cancer research spend [3]. To address this, the 2015 National Health Service (NHS) England's Independent Cancer Taskforce report recommended identifying research priorities on long-term patient needs and survivorship issues. Subsequently, the National Cancer Research Institute (NCRI), a partnership of major cancer research funders, formed a Priority Setting Partnership (PSP) with the James Lind Alliance to develop a list of priorities for Living With and Beyond Cancer (LWBC) research.
Methods: The PSP had several stages, beginning with a UK-wide survey to gather questions about uncertainties in living with and beyond cancer. These were further prioritized through an interim analysis and a second survey before the top 10 list was decided during a final stakeholder workshop. PSP participation was open to any adult first diagnosed with cancer over the age of 16, their carers and health & social care professionals. Questions on new cancer treatments solely aimed at extending life or only relevant to end of life care were excluded.
Results: The first survey had 1492 respondents who proposed 3500 unanswered questions and through an 18-month established rigorous process, the questions were prioritized down to the Top 10 LWBC research priorities (www.ncri.org.uk/lwbc).
Conclusions: This is the first time that clear research priorities have been identified in the UK to address questions that matter most to people affected by cancer. The NCRI is working with funders, researchers, the NHS and others to translate the priorities into research and patient benefit, as well as raise awareness of them internationally.

References:
1. Maddams J et al. (2012) BJC;107:1195–1202.
2. NCRI Cancer Research Database [Online, last accessed 18 March 2019].

Disclosure Statement: None

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Impact Of Darolutamide (DARO) On Pain and Quality of Life (QoL) in Patients (PTS) with Nonmetastatic Castrate-Resistant Prostate Cancer (NMCRPC)

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Purpose: DARO is a structurally distinct androgen receptor antagonist for which *in vitro* and phase 1/2 studies suggest low risk of adverse events (AEs) and drug–drug interaction. In the ARAMIS study of DARO in nmCRPC, metastasis-free survival (MFS) was significantly prolonged vs placebo (PBO) (40.4 vs 18.4 mo; hazard ratio [HR] 0.41; 95% confidence interval [CI] 0.34–0.50; P < 0.001) and interim overall survival (OS) favored DARO (HR 0.71; 95% CI 0.50–0.99; P = 0.045).

Methods: 1509 pts were randomized 2:1 to DARO 600 mg (two 300 mg tablets) twice daily (n = 955) or PBO (n = 554) while continuing androgen deprivation therapy (ADT). Primary endpoint was MFS. Secondary endpoints included OS and time to pain progression. QoL was assessed by EORTC-QLQ-PR25 at baseline (BL) and every 16 wks until end of treatment. Analysis of time to deterioration (TTD) in EORTC-QLQ-PR25 subscales, defined as first occurrence of a minimally important difference.
Results: DARO significantly delayed pain progression vs PBO (40.3 vs 25.4 mo; HR 0.65; 95% CI 0.53–0.79; P < 0.001); this was maintained beyond end of study treatment. TTD showed statistically and clinically significant delays with DARO vs PBO for urinary symptoms (25.8 vs 14.8 mo; HR 0.64; 95% CI 0.54–0.76; P < 0.01). TTD of hormonal treatment-related symptoms was comparable with DARO vs PBO (18.9 vs 18.4 mo; HR 1.06; 95% CI 0.88–1.27; P = 0.52). DARO was well tolerated. Exposure-adjusted incidences of AEs of interest were similar/lower with DARO vs PBO (fatigue/asthenic conditions [11.3 vs 11.1], hypertension [4.7 vs 5.1], hot flush [3.7 vs 4.1], fracture [3.0 vs 3.5], falls [2.7 vs 4.1], cognitive disorder [0.3 vs 0.2], and seizure [0.2 vs 0.2]).
Conclusions: For nmCRPC pts, DARO prolongs MFS, is well tolerated, maintains QoL, and delays worsening of pain and disease-related symptoms compared with PBO.

Disclosure Statement: Clinical trial information: NCT02200614. This abstract was accepted and previously presented at the 2019 ASCO Annual Meeting.

Tilman Todenhöfer reports personal fees from Bayer Healthcare, Janssen, Astellas outside the submitted work.
Karim Fizazi reports personal fees from Amgen, Astellas, Bayer, Clovis, AstraZeneca, Janssen, Curevac, ESSA, Orion Pharma, Roche/Genentech, and Sanofi outside the submitted work.
Neal D. Shore reports personal fees from Ferring, Bayer, Amgen, Janssen, Dendreon, Tolmar, Astellas, Pfizer, AstraZeneca, Genentech/Roche, Myovant Sciences, Merck, AstraZeneca, Bristol Meyers Squibb, and Nymox outside the submitted work.
Teuvo Tammela reports personal fees from Janssen, grants and personal fees from Bayer, Lidds AB and Astellas, outside the submitted work.
Iris Kuss reports employment by and stock ownership in Bayer
Marie-Aude Le Berre is an employee of Bayer.
Ateesha F. Mohamed is an employee of Bayer.
Dawn Odom is a full time salaried employee of RTI Health Solutions. RTI Health Solutions was retained by Bayer to conduct the analysis which is the subject of this abstract.
Jennifer Bartsch is a full time salaried employee of RTI Health Solutions. RTI Health Solutions was retained by Bayer to conduct the analysis which is the subject of this abstract.
Amir Snapir reports personal fees from Orion Pharma during the conduct of the study.
Toni Sarapohja reports to be an employee of Orion Corporation.
Matthew Raymond Smith reports personal fees from Amgen, Astellas, Bayer, Clovis, Gilead, Janssen, Lilly, Novartis, and Pfizer, outside the submitted work.

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Association of Laparoscopic Colectomy Versus Open Colectomy on the Long-Term Health-Related Quality of Life of Colon Cancer Survivors

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Purpose: Laparoscopic colectomy (LC) is promoted as a less invasive alternative to open colectomy (OC) in the treatment of stage I-III colon cancer. Research on the long-term (5-years post-diagnosis) health-related quality of life (HRQOL) of LC patients is scarce. Our study aimed to compare the long-term HRQOL and psychological well-being of stage I-III colon cancer survivors treated either with LC or OC.
Methods: This study used a German population-based cohort of 1066 patients who underwent either LC (n=86) or OC (n=980). LC patients were matched to OC patients with a propensity score using a 1:2 nearest-neighbor algorithm. The propensity score is derived from a set of baseline sociodemographic, clinical, and lifestyle covariates. At 5-year follow-up, patients completed assessments on HRQOL (EORTC-QLQ-C30 and EORTC-QLQ-CR29) and psychological well-being (distress and disease/treatment burden). Least square mean scores of HRQOL were derived using linear regression. Proportions of patients with moderate/high distress and disease/treatment burden versus low were compared with chi-square tests.
Results: In total, 81 LC patients could be matched to 156 OC patients. More LC patients experienced disease progression (16% versus 7%, p=0.02). On HRQOL, LC patients reported significantly better body image (87.1 versus 81.0, p=0.03) and generally less symptom burden, albeit differences were not significant. Distress levels were generally low and comparable between the two groups. OC patients were more likely to feel moderate/high levels of burden associated with the treatment (72% versus 56%, p=0.01) and the time after treatment completion (43% versus 28%, p=0.02).
Conclusions: LC was associated with higher risk of disease progression among stage I-III CRC patients, but LC patients reported comparable or better long-term HRQOL outcomes and higher levels of psychological well-being than OC patients 5 years after diagnosis.

Disclosure Statement: No conflict of interest declared.

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Depression in Long-Term Breast Cancer Survivors Compared to Female Population Controls in Germany: Age-Specific Prevalence and Determinants

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Purpose: Depression is more prevalent in breast cancer (BC) patients and survivors than in general population. However, little is known about depression in (very) long-term survivors. The study objectives were (1) to compare the age-specific prevalence of depressive symptoms (a) in BC survivors vs. female population controls, (b) in disease-free BC survivors vs. those who self-reported progression after treatment vs. controls, and (2) to explore determinants of depression in BC survivors.
Methods: 3010 BC survivors (stage I-III, 5-16 years post-diagnosis, mean age 65 years at survey), and 1005 cancer-free population controls (mean age 59 years) were recruited in German multi-regional population-based studies. Depression was assessed by the short form of the Geriatric Depression Scale (GDS-15). Prevalence differences between subgroups were assessed via logistic regression, controlling for age and education. Multinomial logistic regression was used to explore determinants of depression in BC survivors.

Results: A GDS-15 score suggestive of mild or severe depression (cut-off: ≥5) was found in 30.4% of BC survivors and in 23.8% of cancer-free controls (p<0.0001), and a score suggestive of severe depression (cut-off: ≥10) in 4.7% of BC survivors and 3.8% of controls (p=0.2107). At all ages <80 years, prevalence of mild/severe depression was significantly higher in BC survivors than controls, while at ≥80 years BC survivors showed lower rates of severe depression than controls. BC survivors with progression showed significantly higher prevalence of mild/severe depression than disease-free survivors and controls. Age, employment, income, partnership, living situation and BMI were significant predictors of depression in BC survivors.
Conclusions: Long-term BC survivors <80 years report slightly but significantly higher depression prevalence than controls, which might be explained by disease progression. Clinicians should refer survivors to psychological care when needed, especially in the case of disease progression.

Disclosure Statement: No conflict of interest.

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Validation of the Cancer Fatigue Scale in a Geriatric Population

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Purpose: Cancer related Fatigue (CRF) is a burdensome symptom both generally and particularly in geriatric cancer patients. A variety of validated questionnaires exist to assess CRF, either unidimensional, e.g. Functional Assessment of Chronic Illness Therapy-Fatigue or multidimensional, e.g. Multidimensional Fatigue Inventory or the Cancer Fatigue Scale (CFS-D). The CFS-D is validated in German for cancer patients from 30 to 83 years with robust validity. Since there is no validation specifically for a geriatric population older than 83 years we conducted this geriatric validation study.
Methods: Reliability of the CFS-D has been assessed by Cronbach-α, and test-retest reliability (with a test-retest time-span of 2–4 weeks) by Spearman rank correlation. Additionally, a factor analysis and a structural equal modeling (SEM) has been conducted. The cumulative illness rating scale (CIRS), physical self-maintenance scale (PSMS), geriatric depression scale (GDS), sleep quality (DGSM), health-related quality of life (SF-12), Karnofsky performance index (KPI) and actigraphy have been recorded as external validity criteria.
Results: We included 104 participants between 70 and 96 years (31 cancer, 22 diabetes mellitus type 2, and 51 age-matched comparatively healthy controls. The 15-item CFS-D questionnaire revealed good internal consistency (Cronbach's-α r = 0.88) and satisfying test-retest reliability (r = 0.68). Concordant construct and convergent validity with correlations to CIRS, PSMS, GDS, SF-12 and actigraphical rest/activity rhythm variability were documented (r = 0.28–0.49, all p<0.05). The factor analysis revealed a 3-factor structure. Although the subscales differed in item loading from the published CFS-D the SEM confirmed the initial validation subscales structure (physical, cognitive, affective fatigue) to be robust and usable for a geriatric sample.
Conclusions: The Cancer Fatigue Scale (CFS-D) is a reliable and valid questionnaire to measure fatigue up to 96 years, however subscale differences demand clarification for highly aged individuals.

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Influencing Factors on the Development of Physical Functioning of Older Cancer Patients During and 12 months After Cancer Therapy - A Prospective Observational Study

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Purpose: This study aims to generate hypotheses regarding modifiable factors associated with the development of physical function of older cancer patients undergoing cancer therapy.
Methods: Exploratory, prospective observational study including cancer patients ≥65 years treated with radiotherapy. Assessments of ADL, IADL, physical function (TUG, handgrip, 6 min. walk test), physical activity (PASE), nutritional status, cognition (minicog), depressed mood (PHQ9), social situation and health-related quality of life (EORTC QLQ-C30, ELD14) at baseline (t0), 6 (t2) and 12 months (t4); postal assessments at 3 (t1) and 9 months (t3). Descriptive analyses included Spearmans Rho (r_s) to examine associations between the EORTC QLQ-C30 subscale physical function (PF) and possible influencing factors.
Results: Forty patients, mean age 74.4 ±5.3 years, n=24 male, participated. Analyses show a clinically relevant change of PF over time (Ø t0: 79.8 ±8.1; Ø t1: 63.6 ±26.9; Ø t2: 65.0 ±26.7; t3: ø 60.8 ±25.7; t4: ø 61.7 ±34.0). Data show correlations of albumin (t0) with PF (t2) (r_s=0,446) and depressed mood PHQ9 (t0) with decreased PF at t2 (t2: r_s=-0,486). At 12 months the correlation of PHQ9 (t4) with PF (t4) is stronger (t4: r_s=-0.532) than the correlation of the EORTC QLQ-C30 subscale emotional function with PF (r_s=0,526). Out of the objective assessments, baseline TUG shows the strongest correlation with PF at t2 and t4 (t2: r_s=-0.523; t4 r_s=-0.605).
Conclusions: While 6 months data indicate that baseline mental health and good nutritional status are associated with the maintenance of physical function, at 12 months mental health shows the strongest association. Aiming for targeted interventions, these hypotheses should be examined in further studies.

Disclosure Statement: The authors do not have any conflicts of interest relevant to the topic to declare.

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AML Survivorship – Somatic and Psychosocial Long-Term Effects of AML Therapy

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Purpose: An increasing proportion of patients with Acute Myeloid Leukemia (AML) become long-term survivors. Somatic and psycho-social outcomes are therefore becoming increasingly important, but little is known about the long-term effects of the disease and its treatment. We therefore designed a comprehensive analysis of AML survivorship outcomes on multiple levels: somatic health status, psycho-social well-being, and genetics (clonal hematopoiesis). These data will aid in designing risk-adapted follow-up programs for long-term survivors.
Methods: We are including adult AML patients who were enrolled in AML-CG multicenter trials (AML-CG 1999, AML-CG 2004 and AML-CG 2008) or in the AML-CG patient registry, and who are alive and in remission ≥5 years after their initial diagnosis. Eligible patients receive a 14-page questionnaire with standardized instruments addressing different relevant aspects of survivorship, including quality of life, life satisfaction, fatigue, somatic health status and socio-economic status. The results will be compared to data from age-matched healthy adults to assess the impact of past AML therapy on various domains of well-being.

In a second step, we are also asking patients to also provide a peripheral blood sample, aiming to study leukemia-associated or treatment-induced genetic alterations in long-term survivors. We will use these genetic data to study associations between treatment regimens (e.g. allogeneic transplantation), clonal hematopoiesis, and relevant long-term health outcomes such as cardiovascular disease.
Results: 820 eligible potential participants have been identified. In a feasibility study, 102 of 200 persons (51%) responded to the first invitation to participate. Enrollment is ongoing, and we expect to obtain data from approximately 400 former AML patients. First results on recruitment and descriptive analysis of relevant aspects on survivorship will be presented at the meeting.
Conclusions: We will present an ongoing study of long-term health outcomes in AML survivors.

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Health-Related Quality of Life (HRQOL) Reported by Patients with Multiple Myeloma (MM) in Germany

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Purpose: Patient-focused care is the key to optimal management of multiple myeloma (MM). Novel treatment options have improved life expectancy, but real-world data on health-related quality of life (HRQoL) is still scarce. Here, we report HRQoL of patients with MM by number of treatment lines in real-world clinical practice in Germany.
Methods: An observational, cross-sectional, multicenter study was conducted in 2019 to assess overall QoL global health status (GHS), functional capacity, and symptoms using the validated European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life questionnaire (QLQ-C30) and the Quality of Life Multiple Myeloma module (QLQ-MY20). For bivariate analyses, Student´s t-tests or one-way anova were used, while Pearson´s chi-squares were applied for categorical variables. For subgroup analyses multivariate analyses have been used. Missing values have been excluded from the analyses.
Results: In total, 490 myeloma patients from 40 German centers were enrolled. The care setting included office-based practitioners (43%), cancer centers (25%), hospitals (23%) and university hospitals (10%). Median age of patients was 72 years and 62% were male. At study participation, 71% of patients were actively treated. Over a third (35%) had a previous stem cell transplantation. Most (77%) patients had ≥1 comorbidity. Mean (standard deviation [SD]) EORTC QLQ-C30 GHS scores decreased from 61.7 (19.3) in 1st line (n=101) to 46.3 (19.4) in 4th line (4L) or later (n=97). The mean difference in GHS scores was 6.4 between 2nd and 3rd line and was the highest (15.3) between supportive care and 4L. In all functional and symptom scales, HRQoL was worsening as the number of treatment lines increased. Similar results were found using EORTC QLQ-MY20 scales.
Conclusions: The observed HRQoL deterioration in later versus earlier lines, stresses the importance of maintaining HRQoL for as long as possible. As age, remission, comorbidities and therapy are interacting with HRQoL, further HRQoL analyses are needed to determine how to preserve QoL of MM patients.

Conflicts of Interest:
M. Engelhardt: ME has received educational and trial support from Amgen, Celgene, Takeda, BMS, Janssen, Novartis, Karyopharm, and has received honoraria and consultancy fees from BMS, Celgene, Amgen, Takeda, Novartis and Janssen.
G. Ihorst has received consultancy fees from Amgen.
G. Saba and M. Pellan are employees of Kantar Health who received funding from Amgen to conduct this research.
A. Rieth, M. Schoehl and A. Lebioda are employees of Amgen GmbH and hold Amgen stocks.
M. Singh is an employee of Amgen Ltd. Uxbridge.

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Development of Tumor Disease-Specific PRO-CTCAE Item Sets

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Purpose: In oncology, adverse events (AE) are mainly documented using the Common Terminology Criteria for Adverse Events (CTCAE) (1). This physicians' assessment can be supported by patient-reported outcomes (PRO) (2). For this reason, the NCI has developed a PRO version of the CTCAE criteria, consisting of a pool of 78 symptoms and 124 items (3). A core item set containing 31 items for patients with chemotherapy has already been validated in German (4). The aim of this study was to develop tumor disease-specific PRO-CTCAE item sets for different tumor entities with high content validity.

Methods: Patients treated at three outpatient centres were asked to assess the occurrence and relevance of the 78 PRO-CTCAE symptoms using a questionnaire. In order to select PRO-CTCAE items for each tumor entity, individual symptoms were ranked on the basis of occurrence and relevance.

Results: In the final evaluation 101 patients with breast cancer with and without metastases (BC) and 107 patients with multiple myeloma (MM) were analysed. The BC item set contains 39 items representing 21 symptoms, the MM item set 39 items for 19 symptoms. 32 items for 16 symptoms are included in both item sets. Four out of the five main symptoms with the highest raking in both item sets were fatigue, numbness and tingling, sleep disorders and nausea. The symptom with the highest ranking included only in one item set was blurred vision in the BC item set and anxiety in the MM item set. 24 items of the core item set were included in the MM item set, 17 items in the BC item set.
Conclusions: Based on patient-reported differences in symptom pattern, specific PRO-CTCAE item sets with high content validity were developed for breast cancer and multiple myeloma. Their psychometric criteria will be analysed in a validation study.

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Disclosure Statement: The authors do not have to disclose any conflicts of interest.

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Late Toxicities and Long-Term Health-Related Quality of Life Among Head and Neck Cancer Survivors

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Purpose: To measure the health-related quality of life (HRQoL) and extent of treatment- and disease-related toxicities in head & neck cancer (HNC)survivors more than 5 years' post-treatment. The main research questions aim to examine HRQoL differences between the survivors and reference HNC patient data from before treatment and 1 year post-treatment and to observe the frequency of toxicities among the survivors.
Methods: In this on-going, cross-sectional study coordinated by the University Hospital in Mainz, Germany, collaborators from 16 countries invite eligible survivors to their clinic, where they undergo a clinical examination for toxicities (measured with the CTCAE) and fill out questionnaires on HRQoL, productivity losses, use of medical services, and supportive care needs. This project began in September 2017 and will run until October 2021.
Results: To date, questionnaires have been robustly translated into 11 languages and ethical approval obtained at more than 10 sites. 214 survivors have been enrolled by 8 sites in 4 countries, with 5 more countries (7 new sites) expected to begin enrolment during fall 2019. Project meetings have taken place 4 times a year since the fall of 2017.
Conclusions: This project is progressing well and will provide comprehensive information on the long-term problems survivors deal with and which HRQoL issues appear to improve or worsen. Examples of frequent problems among long-term survivors include dry mouth, dysphagia, soft tissue fibrosis, and peripheral sensory neuropathy. An international effort provides an opportunity to enroll a large cohort of long-term HNC survivors using standardized instruments. To date, studies on long-term effects have often included relatively few survivors, largely limited to single countries.

Disclosure Statement: Nothing to disclose.

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Impact of Oncological Therapy and Viscum Album L. Treatment on Health Related Quality of Life in Breast Cancer Patients

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Purpose: *Viscum album L.* extracts (VA) are frequently used in integrative oncology to enhance health-related quality of life (HRQL). The key implication of this study was to evaluate the impact of oncological therapies and add-on VA applications on HRQL in breast cancer patients.
Methods: Clinical and demographic data were retrieved from the Network Oncology cancer registry. Primary non-metastasized breast cancer patients treated with oncological standard therapy alone or in combination with VA-applications were included. At first diagnosis and 24 months later the European Organization of Research and Treatment Health-Related Quality of Life Core Questionnaire (EORTC-QLQ-C30) were administered and evaluated.
Results: A total of 118 patients (median age 60 years) received standard oncological therapy, 85 patients of them (72%) endocrine therapy, 34 (29%) chemotherapy (Ctx), and 12 (10%) immunotherapy. 49 patients (42%) received additionally VA applications. Adjusted multivariable linear regression analyses revealed for the study cohort that Ctx, immuno-, and endocrine therapies had a worsening of 17, 17, and 6 point changes respectively for fatigue, while VA applications showed an improvement of 12 point change ($p = 0.0004$). A similar impact of worsening (standard oncological treatment regimens) and improvement (add-on VA) on insomnia ($p = 0.009$) and physical functioning ($p = 0.005$) were observed.
Conclusions: In the present longitudinal real-world observational analysis Ctx, immuno-, and endocrine therapies showed a negative impact while add-on VA applications in addition to standard therapy had a supportive effect on HRQL. Thus, add-on VA applications might be suited to partially alleviate discomfort symptoms during anticancer strategies in breast cancer patients.

Disclosure Statement: Grants from Helixor Heilmittel GmbH, Iscador AG and ABNOBA GmbH (FS). Lecturer Honorarium from Helixor Heilmittel GmbH (MK). No competing interests (SLO, AT, PT, HM).

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The Electronic Assessment of Patient-Reported Outcomes and Quality of Life in Radiooncology – Pilot Implementation and Process Evaluation

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Purpose: Numerous studies have shown the benefit of Patient-Reported Outcome measurements (PROM) including Health Related Quality of Life (HRQOL) in clinical practice. However, standardized assessments are still not part of clinical routine. A successful implementation in clinical practice needs a structured approach including participation of all stakeholders/parties involved as well as understanding of clinical practice, required changes, process evaluation and training.
Methods: 1. Analysis of current practice, assessment of facilitators and barriers of implementation; 2. Interprofessional focus groups to decide on PROMs, assessment times and clinical pathways; 3. Development of face to face training and e-learning for clinical staff; 4. Stepwise implementation for in-patients and out-patients; 5. Process evaluation and optimization; 6. Evaluation of impact.
Results: The still ongoing project is currently in phase 4. Staff decided on initial assessment of HRQOL (EORTC QLQ C30) followed by daily monitoring of a core set of eleven symptoms combined with few site specific questions based on EORTC single items and a final assessment of HRQOL at the end of the treatment. Developed guidelines how to react to symptoms are accessible for clinicians to ensure quality of care and to facilitate communication with patients. The electronic questionnaires are well accepted by patients and facilitate documentation and allocation of supportive measures. Process evaluation shows, that time, interprofessional communication and continuous support is needed to achieve changes of clinical routine. Support by clinic IT is crucial to guarantee success.
Conclusions: The integration of the electronic assessment of HRQOL into clinical practice is facing some challenges due to the complexity of the implementation process. A manual based on the results of the process evaluation, consisting of the many aspects that have to be considered, can support further implementations in other oncological settings.

Disclosure Statement: Bernhard Holzner holds IPRs on the PROM software CHES.

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Health-Related Quality of Life and Psychosocial Well-Being in Cancer Survivors >10 Years Past Diagnosis

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Purpose: Little is known about health-related quality of life (HRQoL) in very long-term cancer survivors >10 years past diagnosis. It is of great interest, whether these survivors' HRQoL differs from that of the general population and to which extent cancer still plays a role in their lives. Study objectives were (1) to compare cancer survivors' HRQoL to that of non-cancer controls, and (2) to assess the prevalence of (a) fear of recurrence (FoR), (b) cancer burden, and (c) the self-identity of still being a cancer patient.
Methods: The samples of 2713 breast, colorectal and prostate cancer survivors (13–23 years post-diagnosis) and 1765 controls were recruited in German multi-regional population-based studies. HRQoL was assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). Differences in HRQoL were assessed with multiple regression, controlling for age and education. FoR was assessed with PAF-KF (Progredienzangst-Fragebogen Kurzform). Patient identity and cancer burden were assessed by single item questions.
Results: Cancer survivors' **o**verall QoL/ global health status was slightly higher than that of same-age general population and they reported less pain. However, they perceived a slightly lower social function, and more dyspnea, constipation, and diarrhea. 12% of cancer survivors reported high FoR (moderate fear: 19%). Although 75% reported that their treatment had ended, 17% of those still felt as a cancer patient. A low, moderate or high burden of the cancer on their current lives was reported by 46% of all survivors.
Conclusions: Most functioning aspects of very long-term cancer survivors were comparable to same-age population controls. A majority of cancer survivors reported a low FoR and a small symptom burden. However, even many years after end of treatment, cancer-related symptoms and fears still play a role in survivors' lives. The need of continuous care after the end of regular treatment, including psychosocial aspects, seems to be warranted.

Disclosure Statement: No conflict of interest.

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Health-Related Quality of Life in Long-Term Survivors of Metastatic Cancer

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Purpose: The challenges of cancer survivors have gained increasing attention in recent years. However, most pertinent publications focused on survivors with cancer in remission. In contrast, long-term survivors with metastatic cancer have not been well studied. In this study, we describe health related quality of life (HRQoL) in long-term survivors after diagnosis of metastatic cancer in comparison to non-metastatic survivors and population controls.
Methods: 6952 long-term cancer survivors (5-16 years past diagnosis of breast [n=3045], colorectal [n=1504], or prostate cancer [n=2403]), recruited in the population-based CAESAR+study, were compared according to tumor stage with 1878 cancer free controls from the German general population. Stage at diagnosis could be classified into localized [n=3984], regional [n=1821], and localized disease [n=129] in 5934 cancer survivors. HRQoL was assessed by the EORTC QLQ-C30. The association between tumor stage and HRQoL was analyzed using multiple regression while controlling for age, gender, and education. Supplemental analyses were employed to assess the impact of disease recurrence on HRQoL.
Results: Long-term survivors with distant disease reported significantly poorer global health and quality of life across multiple dimensions including physical, role, and social functioning and more financial difficulties and symptoms such as fatigue, insomnia, and dyspnea than survivors with regional metastases or localized disease as well as population controls (all $p< 0.01$). Recurrence of disease occurred more often among survivors with distant cancer (36%) than among survivors with regional (17%) or localized disease (11%) and was strongly associated with poorer HRQOL. However, recurrence of disease did not fully explain the detriments in HRQOL in survivors with distant cancer.
Conclusions: Cancer survivors with either metastatic disease or disease recurrence suffer in particular from long-lasting detriments in HRQoL. The experience of these survivors should not be neglected in cancer survivorship research.

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Adolescents and Young Adults are at Risk for Psychosocial Sequelae after Cancer Treatment

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Purpose: Adolescents and young adults (AYA) who survive cancer are at high risk for psychological and social sequelae. Aiming to explore unmet needs and psychosocial distress, we performed a survey among all AYA treated for a haematological malignancy at our center since January 2010.
Methods: 85 AYA-survivors were invited to join the survey; at median of 36 (2-86) months after completion of therapy. A set of standardized screening instruments for psychosocial stressors (PhQ-S), symptoms of depression (PHQ-9), generalized anxiety (GAD7), fear of progression (PAF-KF), quality of life (EORTC QLQ-C30) and a self-designed questionnaire were sent to the patients.
Results: Data from a total of 47 (20 male) patients were available. Median age was 35 years. The mean on all QLQ-C30 function scales was less than published for a control group [1]. In addition, 51% of the participants reported on psychosocial stressors (PHQ-S), 45% had depression symptoms (PHQ-9) and 36% suffered from anxiety symptoms (GAD-7). Unemployment correlated with PHQ-S ($p = 0.029$), PHQ-9 ($p=0,025$) and GAD-7 ($p = 0.006$). In contrast, employment was a strong predictor for higher quality of life ($p < 0.001$). A high fear of disease progression (PAF12, cut-off 34) was reported by 36% of survivors. The fear of disease progression correlated with a lower level of education ($p = 0.026$) and with having children ($p = 0.027$). Strain was also caused by psychosocial issues emerge from daily life topics, e.g. the majority of patients (72%) reported on difficulties on resumption to work and 62% had problems with sexuality.
Conclusions: Our results clearly indicate that AYA feature a high burden for psychosocial distress after cancer treatment. In order to improve quality of life, resumption of work is of utmost importance. Therefore, psycho-oncological and social support needs to become an inherent part in the aftercare of AYA patients.

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Disclosure Statement: IH is member of the board of trustees of the German Foundation for Young Adults with Cancer.

Radiation

Vorträge

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Balloon Catheters to extend the Distance between Tumor and Adjacent Organs at Risk in Interstitial HDR-Brachytherapy of Liver Malignomas

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Purpose: Organs at risk (OAR), which are very close to a clinical target volume (CTV) can prevent an effective irradiation of the tumor without a significant risk of serious side effects. The present study investigated the extent of the dosimetric effect of distancing CTV from adjacent OAR's by means of interventionally applied balloon catheters.
Methods: Consecutive patients with peripheral, predominantly left lobular hepatic malignancies, which revealed the critical proximity of an OAR to the CTV in the assessment by gadoxetic acid-enhanced MRI-scans and the preplanning process, underwent also placement of an interventional balloon catheter during CT-guided application of interstitial brachytherapy catheters inserted into the tissue between hepatic capsule and adjacent OAR. The virtual position of the OAR without balloon catheter was anticipated and contoured in addition to contouring of CTV (which is equal to Planning Target Volume [PTV] in brachytherapy), liver and further relevant OAR. The calculated dose values for CTV as well as 1 mL of the relevant OAR (D1cc) with and without balloon were recorded. The D1cc of the realized irradiation plan was compared to the D1cc of the virtually contoured OAR and statistically evaluated.
Results: In 31 cases, one balloon catheter (in 6 cases two) was administered without any acute complications. The total duration of the application time was increased by 5 min per balloon catheter. Serious late side effects occurred in one (3%) case only. The median D1cc in the group with balloon (13.5 Gy) was significantly lower compared to the virtual OAR group without a balloon (15.5 Gy) with a corresponding median relative difference of -16.3%.
Conclusions: The achievable, significantly lower dose exposition of the adjacent OAR reduces the risk of side effects. This may be particularly important in case of oligo-metastasis since a more efficient irradiation of the CTV becomes possible consecutively.

Disclosure Statement: Nothing to be disclosed.

Poster

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Intensity Modulated Radiotherapy (IMRT) with Carbon Ion Boost in the Multimodal Treatment of Salivary Duct Carcinoma

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Purpose: To assess outcomes and treatment related toxicity following intensity-modulated radiotherapy (IMRT) and a Carbon Ion Radiotherapy (CIRT) boost for salivary duct carcinoma (SDC).
Methods: Twenty-eight consecutive patients with SDC who underwent a postoperative (82%) or definitive (18%) radiation therapy between 2010 and 2017 were assessed in this retrospective single-center analysis. CIRT boost was delivered with median 18 Gy(RBE) in 6 daily fractions, followed by an TomoTherapy®-based IMRT (median 54 Gy in 27 daily fractions). Treatment-related acute toxicity was assessed according to CTCAE Version 4.
Results: Tumors were most commonly located in the major salivary glands (n=25; 89%); 23 patients (82%) received previous surgery (R0: 30%; R1: 57%; R2: 4%; RX: 19%). Median follow-up was 30 months. Four patients (14%) patients experienced a local relapse and 3 (11%) developed locoregional recurrence. The two-year local control (LC) and locoregional control (LRC) was 96% and 93%, respectively. Median disease-free survival (DFS) was 27 months, metastasis-free survival (MFS) was 69 months, and overall survival (OS) was 93 months. Acute grade 3 toxicity occurred in 11 patients (mucositis, dermatitis, xerostomia; n=2 each (7%) were the most common) and 2 osteonecrosis of the mandibular (grade 3) occurred. No patients experienced grade ≥4 toxicities.
Conclusions: Multimodal therapy approaches with surgery followed by IMRT and CIRT boost for SDC leads to good local and locoregional disease control. However, the frequent occurrence of distant metastases limits the prognosis and requires optimization of adjuvant systemic therapies.

Disclosure Statement: Nothing to declare.

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Teaching Radiation Oncology to Medical Students in Germany – Where do we Stand?

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Purpose: To measure and analyse the teaching situation for radiation oncology (RO) in Germany.
Methods: A detailed questionnaire containing multiple-choice and free text questions covering extent and topics of RO was sent to RO departments at all university hospitals in Germany and answered by the head of departments/main lecturers.
Results: 24/35 (68.6%) of RO departments returned completed forms. Overall, RO plays a role in the curriculum from the 2nd semester onward with the majority of teaching from the 5th to 10th semester. Most faculties employ lectures (91.7%), seminars (87.5%) and practical/bedside training (75.0%), whereas training in radiation biology and medical physics are less common (25% and 33.3%, respectively). Main topics covered are general RO (100%), radiation biology (91.7%) and side effects (87.5%). Concerning different organ systems gynaecological (87.5%), urological (79.2%) and gastroenterological tumors (75%) ranked highest and were also the predominant subjects for interdisciplinary concepts. Regarding RO techniques, image-guided and intensity-modulated radiotherapy has taken centre stage being taught at all faculties, followed by palliative RO and stereotactic techniques (87.5% each). Notably, all departments offered a partial rotation ("Wahltertial") in RO in conjunction with Radiology and/or Nuclear Medicine departments in the last year of medical school, while only 70.8% offered a complete rotation in RO. In addition, 57.1% have taken measures concerning the coming National Competence-based Learning Objectives Catalogue for medical education.
Conclusions: RO has an integral role in the (clinical) medical education in Germany, but faces new challenges regarding the development of a practical, competence-based education, which may require both innovative and interdisciplinary concepts [1,2].

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Disclosures: MO and MM are members of the working group "Medizinstudium" of the DEGRO.

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Analyzing Oral Sequelae of Chemo-Radio-Therapy in the Head-Neck-Region

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Purpose: Side-effects of chemo-radio-therapy (CRT) of the head-neck-region can severely impair patients. There is limited knowledge on interdependencies of side-effects. A better understanding of underlying mechanisms, however, may help improving supportive care of these patients. We intend to study interactions of mucosal, salivary, dental and cellular parameters of patients with head-neck-cancer during and after CRT in an interdisciplinary setting. The study protocol and first results of the pilot stage will be presented.
Methods: Patients (n=50) undergoing curative CRT in the head-neck-region (cisplatinum 2x100mg/m²; 60-70 Gy; 5x2 Gy/week) are examined one week before, during, at the end, and 8 and 20 weeks after CRT. A pre-treatment oral mucosa biopsy is taken for cellular radiosensitivity testing. On exam1-5 (Ex1-Ex5) mucositis is scored (severity 0-5), saliva collected (stimulated/unstimulated; flow rate, pH, buffering capacity, microbiome, proteome), dental status assessed (plaque index, pocket depth, bleeding on probing, caries status (ICDAS)) and quality of life surveyed (xerostomia inventory, quality of life (OHIP-14), food intake frequency, oral hygiene). Age/gender matched healthy controls are also included (n=25, no CRT).
Results: First results (n=11) showed increasing mucositis during CRT (Ex3: +2.2 points) that almost completely recovered after CRT. Both, stimulated and unstimulated saliva flow rates were reduced during (Ex3: -71% and -42%) and stayed constantly low after CRT (Ex5: -75% and 50%). Caries-Scores increased constantly during and after CRT (Ex3: +9.1, Ex5: +36.9).
Conclusions: CRT impacted most investigated parameters. Our first results warrant further evaluations of these factors and their interactions to ultimately develop strategies aimed to attenuate the grievous side-effects of CRT in patients with head-neck-cancer.

Disclosure Statement: Funding: University of Freiburg. Previous presentation in parts: 96th/97th General Session of the IADR 2018/2019, 4. DGZ Tag der Wissenschaft/Universitäten 2018.

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Evaluation of High-Risk Imaging Features for Detection of Local Progression after Stereotactic Body Radiotherapy (SBRT) of Malignant Pulmonary Lesions in the Prospective Stripe -Trial

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Purpose: Detection of local progression (LP) after stereotactic body radiotherapy (SBRT) for lung lesions can be difficult because of radiation-induced lung changes in CT scans. High–risk CT-features (HRF-CT) for prediction of LP have been proposed, the role of 18F-FDG-PET remains unclear. Here previously defined HRF-CT and 18F-FDG-PET-imaging features were evaluated in a prospective SBRT-trial cohort (STRIPE) under "real-life conditions".
Methods: Four independent and blinded observers scored follow-up (FU)-CT and 18F-FDG-PET/CT images of 65 pulmonary lesions after SBRT with a structured questionnaire assessing RECIST and HRF-CT ((sequential) enlarging opacity, bulging margin, linear margin disappearance, loss of air bronchogram, craniocaudal growth). If LP was suspected, the respective18F-FDG-PET images were analyzed qualitatively, then quantitatively. Sensitivity and specificity of HRFs for detecting LP were calculated using the reference standard defined by clinical long term courses, including information on imaging and biopsy. Inter-observer Agreement (IOA) was determined using Cohen's kappa.
Results: IOA for presence of individual HRF-CT were "slight" (k=0.119 to k=0.288), for overall suspicion on LP after CT assessment k= 0.308 for HRF-CT, k= 0.289 for RECIST and k= 0.604 after qualitative additional PET assessment. Sensitivity and specificity were 0.22-0.46 and 0.73-0.92 for HRF-CT, 0.30 and 0.94 for RECIST. Additional qualitative ^{18}F-FDG-PET/CT analysis was highly sensitive (1.0; specificity 0.79), semi-quantitative evaluation using SUVmax revealed no further diagnostic benefit (sensitivity 1.0; specificity 0.67). Sensitivity / specificity of CT-assessment versus qualitative PET-assessment were 0.43 / 0,86 and 1,0 / 0,85, respectively.
Conclusions: While we could neither confirm RECIST nor defined HRF-CT as reliable predictors of LP, qualitative ^{18}F-FDG-PET/CT assessment seems to offer more diagnostically accurate information about LP after SBRT, not being improved by quantitative 18F-FDG uptake analysis.

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Immunomodulatory Effects of Photon and Carbon Ion Irradiation – A Differential in Vitro Analysis

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Purpose: We compared the immunomodulatory effects of single photon doses on the murine pancreatic ductal adenocarcinoma (PDA) cell line PDA30364/OVA to high-LET radiation with carbon (^{12}C) ions *in vitro*.
Methods: Cells were irradiated by a Gammacell 40 Exactor device (photons) or through the experimental beam line of the HIT (^{12}C ions). Biologically effective doses (BED) were established through dose dependent relative biological effectiveness (RBE), determined by clonogenic survival assay. Cell surface expression of immunomodulatory molecules as well as cell cycle analyses on PI stained cells were performed by flow cytometry. Sensitization of target cells for cytotoxic T cell (CTL) mediated lyses was analyzed via impedance-based cytotoxicity assay.
Results: Dose dependent RBE for 1, 3, 5 and 10 Gy photons were defined as 10, 7.5, 5 and 3.23, respectively, resulting in equivalent physical doses of 0.1, 0.4, 1.0 and 3.1 Gy ^{12}C ions. Irradiation induced a dose dependent G2/M cell cycle arrest and a moderate increase in cell surface expression of PD-L1, CD73 and MHC class I molecules. CTL mediated lysis of PDA30364/OVA cells was significantly increased at higher doses, however additional checkpoint blockade of PD-L1 did not further enhance target cell killing significantly. Effects of ^{12}C ions were generally milder at doses ≤ 5 Gy (BED) reaching an equivalent magnitude at 10 Gy (BED).
Conclusions: Raising single photon doses ≥ 5 Gy, PDA cells were responsive to irradiation with respect to classical radiobiology endpoints and, moreover, to enhanced CTL mediated target cell killing, thus suggesting a superiority of hypofractionation over normofractionated regimens. Irradiation with high-LET carbon ions yielded comparable results, however only at enhanced doses of 10 Gy (BED) with RBE = 3.23. Our data suggest that the discrepancies among the irradiation effects observed are most likely caused by the equivalent dose definition via clonogenic survival, strictly applying a dose dependent RBE.

Disclosure Statement: nothing to disclose.

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Carbon-Ion Beam Radiotherapy (C12 RT) as Part of a Trimodal Therapy for Non-Small Cell Pancoast Tumors: The INKA-Study

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Purpose: Pancoast-tumors are rare bronchogenic tumors arising from the lung apices and infiltrating surrounding tissue. A trimodal therapy is gold standard for locally advanced tumors. This study aims to demonstrate safety and feasibility of hypofractionated C12 RT within the trimodal approach.
Methods: INKA is an ongoing prospective, monocentric pilot-study at the University of Heidelberg. Primary endpoint is safety and feasibility, characterized by the incidence of grade 3/4 toxicities or treatment interruptions. Patients are treated with chemotherapy (CHT) according to local standard (cisplatin/vincristine). Concomitant with the second cycle, patients receive C12 RT to the primary tumor and PET-positive lymph nodes. Median dose is 39 Gy (RBE) in 13 fractions. Surgery is performed 2-3 weeks after RT. Metabolic response (PERCIST) is assessed by FDG-PET at inclusion and before surgery. Histopathological remission is judged according to the Junker classification.
Results: Since 2015, 11 patients were enrolled. 2 drop-outs were registered at the time of analysis; reasons were subsequent contraindication for CHT and insufficient tolerance of immobilization. None of the treated patients showed grade ≥3 toxicities. PET-scans performed before surgery showed partial metabolic remission, i.e. >30% decrease in SUVmax, in 6 patients (67%); 2 patients (22%) showed no change in FDG-uptake; 1 patient (11%) showed complete remission. Histopathological response was assessed on the resected tissue and showed tumor regression of at least Junker IIa in all patients. 5 patients (56%) were classified Junker IIb (<10% vital tumor cells) and 2 patients (22%) showed complete regression (Junker III).
Conclusions: First results of the ongoing INKA-trial demonstrate that hypofractionated C12 RT as part of the trimodal therapy is well tolerated and associated with excellent metabolic and histopathological response shortly after neoadjuvant therapy.

Disclosure Statement: Förderung: DFG – KFO214.

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Intracellular Brachytherapy with ^{32}P-Doped Nanodiamonds

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Purpose: Nanodiamonds (NDs) are biocompatible and are therefore suitable as carriers for drugs such as cytostatics in cancer therapy. We have investigated whether they are also suitable as carriers for a radionuclide that could be used for "intracellular brachytherapy". Therefore the nanodiamonds were doped with the strong beta-emitter 32P.
Methods: The studies were performed with cultured human breast carcinoma and glioblastoma cells. As vitality parameters proliferation, motility and clonogenic survival were determined. The intracellular localization was analyzed with commercial fluorescence-labelled NDs using a fluorescence microscope.
Results: Investigations with naked NDs showed that no impairment of the vitality parameters of the cells was observed after endocytosis. When 32P-NDs with an activity as low as 13 Bq were taken up, proliferation and especially clonogenic survival were severely reduced, but motility was not impaired. The effect was significantly more pronounced in breast cancer cells than in glioblastoma. The observed intracellular localization of NDs, which was predominantly perinuclear in breast cancer but more distant cytosolic in glioblastoma, is consistent with these findings.
Conclusions: In our model system NDs are not cytotoxic and therefore suitable for therapy. Doped with a radionuclide, they open up a promising new option in intracellular brachytherapy. 32P seems particularly suitable for this purpose due to the high-energy beta radiation and the short half-life. Targeting to the malignant cells could be achieved via coupled antibodies against specific surface markers of these cells, such as the HER2 receptor in breast cancer, where a humanized therapeutic antibody is already available.

Disclosure Statement: Nothing to declare.

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Outcome and Toxicity after Postoperative Radiotherapy in Patients with Squamous Cell Carcinoma of the Lip

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Purpose: Carcinomas of the lips are a relatively common malignancy of the head and neck region, accounting for roughly one quarter of all oral cavity cancers. Studies showed five year survival rates between 85-95% (*1*). This study summarizes our institutional experience in utilizing postoperative RT for patients with squamous cell carcinoma (SCC) of the lips.
Methods: Between 2005 and 2018, 19 patients were postoperative treated at the University Hospital of Heidelberg for SCC of the upper and lower lip with a radiotherapy. Median age at diagnosis was 67 years (58% male, 42% female). All patients received a median cumulative dose of 66 Gy (range, 60-70 Gy). Median follow-up was 5.2 years.
Results: The 2-year Kaplan-Meier estimates for OS, PFS, and LDFS were 78.9%, 85.7%, and 100.0%, respectively, and 5-year OS, PFS, and LDFS rates were 61.4%, 85.7%, and 100.0%, respectively. At the last follow-up, 13 patients (68.4%) were still alive. No patient developed locoregional relapse; distant relapse was found in two patients (10.5%, distant lymph nodes and skin metastasis), which occurred in a median of 15 months after RT. The analysis showed a significantly better OS in patients with higher total RT doses (>60Gy).
Conclusions: Our results demonstrate excellent local control and OS with acceptable toxicity when utilizing adjuvant radiotherapy in patients with SCC of the upper and lower lip, despite unfavorable characteristics (T, N, ECE+).

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Disclosure Statement: The authors declare no conflict of interest.

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The Role of Blood Biomarkers in Radiation Therapy for Thoracic Malignancies

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Purpose: Radiation (RT) of malignant tumors has the potential to induce immunomodulatory and vascular effects, which can influence anti-tumor immunity and normal tissue radiosensitivity. We prospectively evaluated the role of different chemokines and cytokines in patients treated with radiotherapy for different thoracic malignancies concerning survival (OS) and development of RT induced lung toxicity (RILT).
Methods: Fifty-six patients with lung cancer (n=41), esophageal cancer (n=14) or thymoma (n=1) treated either with conventionally fractionated (n=43) or hypo-fractionated (n=13) RT were enrolled prospectively in the study. Serum levels of IL-10, IFN-γ, IL-12p70, IL-13, IL-1β, IL-4, IL-6, IL-8, TNF-α, bFGF, Flt-1, PlGF, VEGF, VEGF-C, VEGF-D were analyzed by multiplex array (MesoScale Discovery) and measured in a USA CLIA-certified core at predefined time points: before, during and at the end of RT as well as in the first and second follow-up. Toxicities were scored according to common toxicity criteria for adverse events.
Results: We observed upregulation of IL-10, IFN-γ, PlGF, VEGF-D and downregulation of IL-8, TNF-α, VEGF, VEGF-C during and at the end of RT. IL-6 was up-, Flt-1 downregulated during RT and down- respectively upregulated at the end of treatment. A higher concentration of IL13, IL-6 (both p<0.000), IL-1β (p=0.004), IL-8 (p=0.009) and bFGF (p<0.000) during RT and of IL-6 at the first follow up (p=0.001) correlated with OS. Seventeen patients (30%) developed radiologic signs of RILT Grade ≥1 but only two of them (3.6%) developed clinical symptoms (Grade 2). We could not find any association between the different serial blood biomarkers and a higher incidence of RILT.
Conclusions: In our study early changes in blood biomarkers during RT indicate an early immune response and might play a role in the outcome of the treatment but don't seem to contribute significantly in the development of early stage (grade 1) RILT.

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Stereotactic Body Radiotherapy vs Transarterial Chemoembolisation in Locally Advanced Hepatocellular Carcinoma (Heracles: Hepatocellular Carcinoma Stereotactic Radiotherapy Clinical Efficacy Study)

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Purpose: Aim of this prospective trial (HERACLES Study) was to evaluate the role SBRT in comparison to TACE in patients with locally advanced hepatocellular carcinoma (HCC).
Methods: Patients who were discussed in a multidisciplinary tumour board over a predefined period of 12 months were included in the study. Patients received SBRT when TACE was contraindicated, in case of progressive disease after TACE or when TACE was rejected by the patient. All other patients received TACE. The impact of predefined patient and treatment related factors on QOL (EORTC QLQ-C30 and EORTC QLQ-CR29) was evaluated. Primary endpoint was feasibility.
Results: Between 06/2016 and 06/2017 19 patients received TACE and 19 patients SBRT, of whom one patient dropped out during SBRT because of lung progression. In the TACE-arm the median age was 69 years, median tumor size was 32 mm and median Child-Pugh Score (CPS) 5 points; two patients were BCLC stage A, fourteen B and two C. Patients in the SBRT-arm had a median of 73 years, median tumor diameter was 52 mm and median CPS was 5 points, 9 patients were BCLC stage B and 9 C, 3 of them had a metastatic disease. A portal vein thrombosis was present in 6 patients only in the SBRT group. Seven patients in the TACE group received further TACEs and 1 patient a liver transplantation. In the SBRT group 1 and 2-year overall survival rate was 56% and 74% in the TACE group (p=0.1). The 1-year local control rate (LCR) was 90% in the SBRT group and 70% in the TACE group (p=0.2). There was no statistically significant difference in the QOL at baseline for both groups, and no difference between baseline and follow-up. One patient had a grade 5 fistula in the SBRT group and one patient had a grade 5 hepatic failure in the TACE group, 2 a hepatic failure grade 3, 1 grade 3 pancreatitis, 1 grade 3 cholangitis and one abscess in the TACE group.
Conclusions: The primary endpoint feasibility was achieved with 38 patients included during 12 months in a single center. SBRT leads to good local control in far advanced HCC with acceptable toxicity compare with TACE despite of more advanced disease in the SBRT group.

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Local Radio-Ablation in Hepatic Malignancy – Esprit Study: A Dosimetric Comparison of Interstitial HDR-Brachytherapy (IBT) and Body Stereotaxy (SBRT)

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Purpose: To statistically compare relevant dosimetric parameters for tumor lesion and liver of the both local ablading methods such as:
- interstitial HDR-brachytherapy (iBT) and
- stereotactic body stereotaxy (SBRT)

in the treatment of primary and secundary liver malignomas.
Methods: 1) In this retrospective study **(favored by the local ethic committee)**, all patients with the characteristics mentioned above (**such as** ECOG ≤2; oligo-metastases; maximum, 6 hepatic metastases) were enrolled. After iBT, the Clinical Target Volumes (CTV = Planning Target Volume [PTV] in brachytherapy [= iPTV]) were isotropically extended to stereotactic PTV (sPTV) according to Schefter *et al*. For these sPTV, stereotactic plans were calculated, the PTV-surrounding prescription dosages were according to the iBT plans.
2) The "dose contraints" for the OAR valid for iBT were strictly taken into account during SBRT-planning. The following dosimetric parameters of the iBT- and SBRT-plans were documented for statistical analysis: V5 of the liver (absolute [cm^3] + relative [%]), D99.9 and D90 of the PTV.
Primary end point of the study was the assessment of the dosimetric differences between two relevant procedures of radiation therapy.
Results: From 12/2018 to 08/2009, 85 consecutive patients with 1–6 small and 1 single large oligometastasis (n=61), resp**ectively**, or with primary hepatic tumor lesions (n=24) were enrolled. Median iPTV was 34.66 (range, 0.63–410) cm^3, the calculated median sPTV was 73.24 (range,

6.06–593) cm³, the number of the used iBT-catheters ranged from 1 to 8. In all four parameters, there were significant differences between iBT and SBRT favoring iBT.
Conclusions: iBT provides significant advantages from a dosimetric point of view with regard to a low liver exposure and the effective PTV dosages D99.9 und D90 (taking into account the OAR – "dose-constraints"). In additon, the today's valid ICRU91 norm has not been used for the SBRT-plan calculation yet. This will be analyzed in a further study.

Disclosure Statement: Nothing to be disclosed.

Rehabilitation and Long-term Burden in Social Medicine (Survivor)

Vorträge

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Financial and Social Impact of Cancer in Adolescents and Young Adults (AYA)

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Purpose: 16,000 AYA cancer patients from 15 to 39 years are diagnosed per year in Germany. More than 80% of them can be cured but the disease and its treatment can lead to serious financial and social consequences.
Methods: Publications on the financial situation, employment, and return to work in AYAs with cancer were analyzed. Data were reviewed and put into the context of epidemiological and medical data. Furthermore questions asked in the portal "Young and Cancer" operated by the German Foundation for Young Adults with Cancer are discussed.
Results: Cancer causes a drastic reduction in the quality of life due to financial impairments because employment is reduced or absent. AYA patients are heterogeneous in diagnosis, social situation and age group. Publications differentiate often poorly due to small numbers and unspecified selections. Effects of different social security systems, legal regulations, development of economy and labor market are not considered. In Germany financial burdens arise in the early course of cancer by out of the pocket payments and co-payments as well as by gaps in the financial security in special groups such as students. Cancer-related fatigue is a major obstacle for full return to work but does not receive sufficient scientific attention. Long-term survivors experience discrimination trying to become public officers or getting housing mortgages and health insurances. Patients' questions focus on rehabilitation, stepwise reintegration into work, and disability.
Conclusions: In Germany the data base on social and financial consequences of cancer in AYA needs to be improved. Differentiated data should be obtained by a population-based approach. Data from cancer registries, social security, and health insurances have to be connected with data on economic development and working market. Relief from out of the pocket payments and co-payments is needed. Further steps include improvements of social security in some groups and steps against discrimination of long-term survivors.

Disclosure Statement: I disclose that I have no conflicts of interest.

Poster

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Learning Personalized Virtual Reality Avatars for Chemotherapy-Induced Peripheral Neuropathy Rehabilitation in Breast Cancer

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Purpose: Virtual Reality (VR) sensorimotor rehabilitation in breast cancer survivors is a promising non-opioid alternative to handle Chemotherapy-Induced Peripheral Neuropathy.
Methods: CIPN has a staggering incidence of up to 60% in taxane-based therapy, affecting as many as 83% of breast cancer patients [1]. VR rehabilitation is still in its infancy [2] but will soon provide digital alter-egos of patients (avatars) and, using Machine Learning (ML), correct and compensate for painful sensorimotor deficits [3]. Our system [4] is a first attempt at such highly-realistic adaptive VR.
Results: Our experiments show that using ML algorithms for VR avatars we are able to assess motion patterns and deficit levels. We achieve that by learning underlying correlations in patient's motion kinematics. We show that our system offers in average a 35% accuracy improvement in body joint positions estimation and 83% accuracy improvement in body joint rotation estimation over state-of-the-art. In such therapies it is assumed that the fidelity of virtual to physical world movements is vital for rehabilitation, in order to promote the recovery of movement, balance, and quality of life.
Conclusions: Our system provides a platform for personalized CIPN VR-based sensorimotor rehabilitation including an ML learnt assessment of patient motion kinematics to support clinicians to better detect CIPN symptoms compared to relying solely on patient-reported measures.

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Purdue Pegboard Test – A New Diagnostic Method for the Assessment of Chemotherapy-Induced Polyneuropathy in Breast Cancer Patients

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Purpose: Polyneuropathy is a common side effect of neurotoxic chemotherapy in breast cancer patients. Aim of this study was the evaluation of the perdue pegboard test in diagnostics of polyneuropathy induced functional deficits.
Methods: 89 patients (mean age 66,4 y) suffering on chemotherapy induced polyneuropathy manual dexterity and bimanual coordination were examined using Purdue pegboard test at the beginning and at the end of a three-week inpatient rehabilitation.
Results: For the dominant [mean score 12.3 (SD 2.6) to 13.4 (SD 2.5); effect size d=0.6] and non-dominant side [mean score 12.0 (SD 2.5) to 12.6 (SD 2.7); effect size d=0.4], the functionality during rehabilitation was significantly improved ($p < 0.001$). The two-handed test [mean score 9.9 (SD 2.6) to 10.3 (SD 2.3); effect size d=0.2] showed a significant difference only ($p = 0.05$). With the assembly test [mean score 22.7 (SD 7.8) to 23.5 (SD 8.2); effect size d=0.2], no significant difference was found ($p = 0.154$) (1).
Conclusions: Purdue pegboard test is a useful diagnostic tool in evaluation and control of functional deficits due to polyneuropathy.

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Disclosure Statement: The authors declare that they have no conflict of interest.

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Assessment of Discharge Management in Oncological Rehabilitation from the Perspective of Patients

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Purpose: Rehabilitation, with its discharge management, provides ideal conditions for long-term care for oncology patients. This study aims to analyze rehab discharge management from the perspective of oncology patients and to identify measures for a successful rehab discharge management.
Methods: Data collection was done by questionnaire (oncological inpatients, n=377) at the end and three months after rehabilitation and by telephone interviews (n = 40) one month post-inpatient. The questionnaires were analyzed descriptively and the interviews were evaluated by content analysis.
Results: 48% of oncology patients report at the end of the rehab that there was insufficient guidance about aftercare recommendations during rehab and about 44% rated the aftercare as less helpful. Overall, more occupational aftercare recommendations were desired. Three months after rehab, 54% of the participants gave the discharge management a marking of "good" or "very good" and 23% the grade "sufficient" or worse. Approximately two-thirds of the respondents felt well prepared for life at home. For about half of the participants, however, the aftercare recommendations were not sufficient. Essentials of a successful discharge management were stated: an individualized aftercare, job-related support, information or contact addresses on 'rehab-after-care services' including scheduling, cooperation between physicians and rehab-clinics and the developing of a tele rehab-aftercare.
Conclusions: In the future, the rehab-discharge management and especially the aftercare recommendations should be more tailored to the individual situation of the patient. In addition, tele-aftercare should be organized and strategies developed to promote cooperation between physicians and rehab-clinics.

Disclosure Statement: Dr. Leibbrand and Dr. Fischer are on the board of VfR e.V., Norderney.

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Reliability of Muscular Strength Assessment with the Pressure Air Biofeedback (pab®) Device in Prostate Cancer Survivors

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Purpose: Muscular strength is a key component of rehabilitation and a strong predictor of functional capacity. The pressure air biofeedback (pab®) device was developed to be easily used in a home or clinical testing environment for diagnosis of muscular strength and allows the measurement of various muscle groups. Aim of the study was to evaluate retest-reliability of different standard strength tests in prostate cancer survivors (PCS) during uro-oncologic rehabilitation.
Methods: A total of 70 PCS (64±8 yr) performed seven standardized strength tests (SCP=sit chest press, HGS=handgrip strength, TE=triceps extension, BC=biceps curl, SHA=standing hip abduction, KE=knee extension and HAD=hip adduction) with pab® in a single group 24h-test-retest design.
Results: Repeated measures ANOVA revealed no systematic error for any standard strength test with exception of TE test for the left arm ($p<0.05$). Relative reliability (ICC 3,1) was 'excellent' for HGS and HAD (ICC range>0.90), 'good' for SCP and TE (ICC range 0.75-0.90) and 'moderate' for BC, SHA and KE (ICC range 0.64-0.74). The SEM% was lowest for HGS and HAD (<10%) while the other standard tests ranged between 12-25% with the highest SEM% indicated for BC, SHA and KE (≥20%).
Conclusions: The pab® device demonstrated acceptable test-retest reliability for most of the standard strength tests except the BC, SHA and KE test. In particular, assessment of handgrip and hip adductor strength was shown to be highly reliable. With regard to the only moderate reliable BC, SHA and KE tests, a modification of the testing methodology is necessary to improve the consistency and to justify its possible application in future testing protocols.

Disclosure Statement: The authors have no relevant financial or non-financial relationships to disclose.

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Functional Status and Occurrence of Critical Prognostic Values in Prostate Cancer Survivors in Uro-Oncological Rehabilitation

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Purpose: Handgrip strength (HGS), 6-minute walk distance (6MWD) and phase angle (pA) of bioelectrical impedance analysis (BIA) have been shown to be strong biomarkers of functional status and powerful predictors of mortality in various patient groups. The aim of this study

was to find out how often prostate cancer survivors (PCS) demonstrate HGS, pA and 6MWD below predicted [1] or critical cutoff values [2,3] prior and post a 3-week uro-oncological rehabilitation program.
Methods: 125 PCS (66±7 yr) were examined at the beginning (T1) and the end (T2) of the rehabilitation program. Standardized assessment included a handgrip strength test following the Southampton protocol with a hydraulic hand dynamometer (Baseline®, HIRes™, Gauge ER™, USA), 6-minute-walk-test (6MWT) and BIA (BIA® 3 SF, EgoFit GmbH, Germany).
Results: At T1, 39.2% of PCS presented a critical HGS below individual cutoff which changed to 26.4% at T2. In 20.8% of PCS a critical pA was detected at T1 with no change of incidence at T2. A 6MWD lower than the individual predicted value was found in 67.2% of PCA at T1 and in 33.6% cases at T2. Between T1 and T2 significant improvements were obtained for HGS and the 6MWD (HGS: Cohen's d=0.5; 6MWD: d=1.1; p<0.001) but not for pA (T1: 5.2±0.8°; T2: 5.2±0.7°).
Conclusions: The data provides knowledge about the occurrence of critical prognostic values of functional status in PCS in the uro-oncological rehabilitation setting. Moreover, data has shown that a 3-week rehabilitation program is effective in improving strength and endurance but without affecting the pA. The routine assessment of HGS, 6MWD and pA may give the option to conduct a risk stratification for PCS which could affect the ongoing process of survivorship care.

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1. Enright & Sherrill: Am J Respir Crit Care Med 1998
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3. Norman et al: Am J Clin Nutr 2010

Disclosure Statement: The authors have no relevant financial or non-financial relationships to disclose.

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Domain-Specific Consideration of the FACT-P in German Prostate Cancer Survivors before and after Uro-Oncological Rehabilitation

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Purpose: Many of the treatments for prostate cancer adversely affect health-related quality of life (HRQoL). HRQoL in prostate cancer survivors is measurable by the internationally most commonly used FACT-P instrument which comprises the five domains of 'physical', 'social/family', 'emotional', 'functional' well-being and 'additional concerns' (consisting of items relating specifically to prostate cancer and/or its treatment). The aim of the study was to find out to what extent a 3-week uro-oncological rehabilitation program affects the different HRQoL domains.
Methods: 128 men (66±7ys) completed the FACT-P (version 4) prior and post the rehabilitation program. Differences were tested for statistical significance by Wilcoxon rank sum test. Effect size (r) was derived by dividing the absolute standardized test statistic z by the square root of the number of pairs. Based on the guideline given by Cohen [1], r = 0.3 was considered to be a medium and r=0.5 a large effect size.
Results: Statistical analysis revealed significant improvements with medium effect sizes for all HRQoL domains (p<0.001, r=0.3-0.4) with the exception of the 'social/family' domain (p>0.05). FACT-P total score also increased significantly (p<0.001, r=0.5).
Conclusions: Measuring and identifying issues of HRQoL in the prostate cancer survivor may create an opportunity to discuss disease-specific problems and exchange information transfer from health professional to patient and vice versa. Uro-oncological rehabilitation is very effective in improving HRQoL and should be offered to all prostate cancer survivors.

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1. Cohen: Psychol Bull 1992

Disclosure Statement: The authors have no relevant financial or non-financial relationships to disclose.

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Body Balance after Cancer Therapy – The Role of Patients Age?

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Purpose: Cancer and cancer therapies (surgery, RT, CT) have a negative impact on physical and mental well-being. The task of rehabilitation is overcoming side effects and regaining good quality of life. Physical training was proven to be very effective (1). The aim of the present prospective study was to evaluate the efficiency of a 3-week rehabilitation program on the sense of balance in dependence of patient age.
Methods: 89 patients (Ø 62 Jahre) after cancer therapy were examined. At the beginning and at the end of a 3-week rehabilitation program a Microswing Balance Test (sense of balance) was performed.
Results: The following results (pre-post-comparison) were obtained.
The stability of the right side in patients under the age of 49 years (n=9) improved from an average of 67.4% (12.8) to 76.1% (9.2) (p=0.03), between 50-59 years (n=23) from 62.0% (13.8) to 67.0% (11.6) (p=0.02), between 60-69 years (n=36) from 54.7% (19.9) to 64.7% (14.2) (p=0.001) and over the age of 70 years (n=21) from 39.4% (19.7) to 45.0% (20.3) (p=0.05).

The stability of the left side in patients under the age of 49 years (n=9) improved from an average of 71.1% (8.4) to 75.9% (6.8) (p=0.02), between 50-59 years (n=23) from 64.4% (16.0) to 69.2% (10.6) (p=0.03), between 60-69 years (n=36) from 55.6% (16.0) to 64.6% (11.8) (p=0.001) and over the age of 70 years (n=21) from 44.2% (19.1) to 50.4% (18.3) (p=0.005).
Conclusions: A significant improvement of the sense of balance could be demonstrated in all age groups. Functional training therapy to promote endurance, coordination and strength contributes improving physical function and performance. Patient of all age groups benefit form specialized oncological rehabilitation.

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Disclosure Statement: The authors declare that they have no conflict of interest.

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1H- And 24-Hour Pad Test for Incontinence Diagnostics after Prostate Cancer Surgery - Assessment of the "Minimal Clinical Important Difference" (MCID) and Test-Retest Reliability

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Purpose: The 1- (1hPT) and 24-h Pad Test (24hPT) are used as objective diagnostic methods for the assessment of postprostatectomy stress urinary incontinence. The aim of this study was to determine the "minimal clinical important difference" (MCID) and the test-retest reliability of the 1hPT and 24hPT.

Methods: 93 patients (mean age 64.0 years) were examined performing a 1hPT and 24hPT at the beginning and at the end of a three-week inpatient rehabilitation. The Pearson correlation was used for the statistical evaluation of the retest reliability. Values from 0.7 indicate a good repeatability of the test. The MCID was determined using distribution-based methods (intra-class coefficient (ICC), standard error of the mean (SEM), half standard deviation (0.5 SD).
Results: The data of all 93 patients could be evaluated. The average urine loss improved for 1hPT from 22.6g (31.2) to 8.5g (13.2) ($p<0.001$) and for 24hPT from 242.9g (269.6) to 126.7g (171.1) ($p<0.001$) before and after 21 days of rehabilitation. The test-retest reliability resulted in a value of 0.85 for the 1hPT and a value of 0.88 for the 24hPT. The standard error of the mean was for 1hPT 9.5 and for 24hPT 82.1. The half standard deviation was for 1hPT 12.6 and for 24hPT 85.7.
Conclusions: The results show that the 1hPT and the 24hPT have a very good test-retest reliability in everyday clinical practice. The minimum clinical difference (MCID) for urine loss reduction that is considered to be significant is between 9.5g to 12.6g for the 1hPT and between 82.1g to 85.7g for the 24hPT.

Disclosure Statement: The authors declare that they have no conflict of interest.

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Improvement of Coordination Skills by a Specific Sensorimotor Training as Part of Oncological Rehabilitation

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Purpose: The combination of classical continence training with oscillation rod training is an established concept in the rehabilitation of patients with post-prostatectomy incontinence (1). The aim of this study was to figure out if the sensorimotor training using an oscillating rod, originally used for incontinence therapy, also has a positive influence on the sense of balance and the reaction time in patients after radical prostatectomy.
Methods: 47 patients (Ø 64.3 years) after radical prostatectomy were examined. All study participants completed a standard therapy program, consisting of classical continence training, sensorimotor training, endurance training and a moderate strength training. The sense of balance and the reaction time were measured using Microswing Balance Test (MBT) and Traffic Light Test (TLT) at the beginning and at the end of rehabilitation. The urinary incontinence was evaluated with the 1-h and 24-h test pad.
Results: The following results (pre-post-comparison) were obtained:
1. highly significant improvement of postural stability ($p<0.001$)
   - stability right side from 51% to 57%
   - stability left side from 53% to 59%
   - overall stability from 52% to 58%
2. highly significant improvement in reaction time, by Ø 12 milliseconds ($p<0.001$)
3. significant improvement of 1-hour pad test (21.2g auf 9.4g ($p<0.05$))
4. highly significant improvement of 24-hour pad test (218.1g auf 135.1g ($p<0.001$))

Conclusions: A significant improvement of the sense of balance and the reaction time was shown. Therefore, could be concluded, that not only the continence apparatus but also the local and deep back and abdominal muscles as well as the sensory control of the arms, legs and stabilization of the trunk benefit from oscillation rod therapy.

Reference:

1. Heydenreich M, Puta C, Gabriel H, Zermann D, Oscillating pole treatment-a new effective treatment option for postprostatectomy urinary incontinence. Oncology Research and Treatment; 2016.

Disclosure Statement: The authors declare that they have no conflict of interest.

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Clinical Effects of Function-Oriented Rehabilitation on Hand Strength after Cancer Therapy?

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Purpose: Improving physical performance is one of the important expectations on uro-oncological rehabilitation. Aim of this study was the evaluation of the handgrip strength with a hand dynamometer for diagnostic during oncological rehabilitation. A comparison with normative reference values (NRV) was performed.
Methods: 109 patients (mean age 66.8 y) were examined performing a handgrip strength measurement at the beginning and at the end of a three-week inpatient rehabilitation. Rehabilitation program included endurance, moderate strength and functional training.
Results: The following results (pre-post-comparison) were obtained.
1. significant improvement of handgrip strength (37.9 kg (8.7) to 40.4 kg (9.4); $p < 0,001$)
2. significant improvement of handgrip strength in patients
   - between 40-60 years (n=20) from 41.5 kg (7.9) to 44.7 kg (8.7) ($p = 0.003$; NRV=49.7 (2.4))
   - between 61-70 years (n=53) from 39.0 kg (8.5) to 41.8 kg (9.1) ($p<0.001$; NRV=46.1 (2.7))
   - between 71-90 years (n=36) from 34.3 kg (8.3) to 37.6 kg (9.4) ($p<0.001$; NRV=39.8 (3.0))

Conclusions: Handgrip strength is a useful diagnostic tool in evaluation of general health improvements due to oncological rehabilitation. A significant increase of handgrip strength was shown however norm values are not achieved (1). Therefore, an appropriate training as learned during rehabilitation should be continued after finishing inpatient rehabilitation as a home training program.

Reference:

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Disclosure Statement: The authors declare that they have no conflict of interest.

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Manual Dysfunction after Breast Cancer Treatment - Influence of Specialized Sensorimotor Rehabilitation

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Purpose: Around one third of chemotherapy patients develop a neuropathy after their treatment. Even patients without chemotherapy have problems in their fine motor skills. The purpose of this study was to find out if breast cancer patients with and without chemotherapy benefit of a 3-week-rehabilitation program with focus on fine motor skills in occupational therapy
Methods: 162 patients (Ø 60 years) after complex breast cancer treatment were evaluated, 89 patients with chemotherapy and 73 without chemotherapy. All patients completed successfully a 3-week-rehabilitation program. This included occupational therapy (hand baths, design therapy), physiotherapy (cell baths, coordinative exercises) and sports therapy (oscillation rod therapy). Study diagnostics included a Purdue Pegboard Test (PPT) for evaluation of manual dysfunctions and the small fiber neuropathy screening list (SFNSL) for sensory and pain diagnostics (1, 2).
Results: The following results were obtained:
– All patients achieved following results
   - PPT – dominant hand (13.1 to 13.8; $p<0.001$)
   - PPT – non dominant hand (12.5 to 13.2; $p<0.001$)
   - SFNSL (18.6 to 16.3; $p<0.001$)

- Patients with chemotherapy
  - PPT – dominant hand (12.6 to 13.8; p<0.001)
  - PPT – non dominant hand (12.3 to 13.0; p=0.008)
  - SFNSL (21.2 to 18.3; p<0.001)
- Patients without chemotherapy
  - PPT – dominant hand (13.6 to 13.8; p=0.274)
  - PPT – non dominant hand (12.8 to 13.4; p=0.003)
  - SFNSL (15.5 to 13.6; p=0.006)

Conclusions: A specialized rehabilitation program after breast cancer therapy allows the improvement of manual deficits and neuropathic symptoms. Especially chemotherapy patients with polyneuropathy benefit from occupational therapy.

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Disclosure Statement: The authors declare that they have no conflict of interest.

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Body Balance, Reaction Time and Handgrip Strength in Incontinent and Continent Patients after Prostatectomy

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Purpose: Stress urinary incontinence is one of the side effects after radical prostatectomy. The identification of influencing factors for post-prostatectomy urinary incontinence is of great interest. The purpose of this pilot study was to figure out if the pre-existing body balance and the muscular situation prior to therapy have an impact on the continence situation after surgery.
Methods: 20 incontinent (1h pad test > 50g) and 20 continent (1h pad test < 1g) patients were examined. Study diagnostics included 1-h-PAD-Test, Microswing Balance Test (Posturo Kybernetik Test – PKT), a hand strength dynamometer test and a Staff-drop test (reaction time test).
Results:

1. Incontinent patients have an inferior body balance then continent patients by trend (39.26% to 44.85%; p=0.349)
2. Incontinent patients have a longer reaction time than continent patients by trend (18cm to 16.51 p=0.34)
3. Continent patients have a better muscular situation by trend (50kg to 45kg; p=0.06)

Conclusions: The results show that there are differences between continent and incontinent patients after prostatectomy relating to body balance, muscular strength and reactivity (common health condition) prior to surgery. Pelvic floor function and trunk stability are influenced by the existing body balance of the patients. Therefore, a holistic, sensorimotor (oscillation rod treatment (1)) and functional (continence training) rehabilitation program is needed.

Reference:

1. Heydenreich M, Puta C, Gabriel H, Zermann D. Oscillating pole treatment-a new effective treatment option for postprostatectomy urinary incontinence. Oncology Research and Treatment; 2016.

Disclosure Statement: The authors declare that they have no conflict of interest.

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Targets for the Prevention of Suicidality in Long-Term Childhood Cancer Survivors

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Purpose: Long-term childhood cancer survivors (CCS) are a vulnerable, understudied population group. They are at risk for physical and psychosocial late effects of the disease and its treatment. Previous research has also attested to elevated rates of suicidal ideation (SI) in CCS, an especially dangerous indicator of distress. However, there is little knowledge about potential risk factors which could inform screening and prevention efforts.
Methods: A register-based sample of 916 adult long-term CCS was drawn from the oldest German cohort (M_{age} = 34.58 years [SD = 5.53], $M_{age\ at\ diagnosis}$ = 6.15 years [SD = 4.28]). Participants underwent medical assessments and filled out questionnaires. We conducted a linear regression analysis on current SI, testing predictors of different areas: sociodemographic, social, cancer-related, physical health and health behavior, and psychological history as well as current distress symptoms.
Results: SI was reported by 73 CCS (8.0%). Besides a CNS tumor diagnosis, which was a risk factor, relevant predictors belonged to the social and psychological domain, comprising previous suicide attempts as well as current distress (loneliness, anxiety symptoms, depression symptoms, social phobia symptoms). Living together with a partner was protective.
Conclusions: Decades after having survived cancer, a subgroup of CCS is affected by (recurrent) suicidality. CCS' risk for SI was shaped by individual medical and psychological history, and by the current social environment and psychological comorbidities. There is a need for more screening efforts, e.g. in primary care settings which take account of these factors. Interventions reducing CCS' risk of suicide should target the social domain and counteract current stressors.

Disclosure Statement: CVSS is funded by the German Research Foundation (DFG) (SP 1381/2-1&2, FA 1038/2-1&2,WI 3881/2-1&2). P.S.W. is funded by the Federal Ministry of Education and Research (BMBF 01EO1503). PSYNA is funded by the German Cancer Aid (DKH, 70112165 & 70113623). There is no conflict of interest.

Sarcoma

Poster

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Core Needle Biopsy is Superior to Incisional Biopsy for Differentiation of Soft Tissue Sarcomas: A Systematic Review and Meta-Analysis

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Purpose: Incisional biopsies (IB) has long been considered the gold standard for diagnosis of soft tissue sarcomas (STS) although there is substantial evidence that core needle biopsy (CNB) offers an adequate alternative technique with less invasiveness and costs. We conducted a meta-analysis to compare the diagnostic accuracy of both biopsy techniques in STS with reference to the final histopathological result.
Methods: A systematic review of literature in the MEDLINE and EMBASE databases was performed. Pooled estimates of the diagnostic accuracy were calculated using random effects modeling. Study quality was assessed by using the QUADAS-2 checklist.
Results: 17 eligible studies (2680 patients with 1582 CNB and 241 IB) were included. CNB detected correct dignity of lesions with a pooled sensitivity and specificity of 97% (95%CI: 95-98%) and 99% (95%CI: 97-99%) compared to IB with a pooled sensitivity and specificity of 96% (95%CI: 92-99%) and 100% (95%CI: 94-100%), respectively. Estimated summary diagnostic accuracy to detect correct STS histotype were as following: CNB sensitivity 88% (95%CI: 86-90%) and CNB specificity 77% (95%CI: 72-81%) versus IB sensitivity 93% (95%CI: 87-97%) and IB specificity 65% (95%CI: 49-78%). Complications following CNB were significantly reduced compared to IB (RR 0.14; 95% CI 0.03 – 0.56; P=<0.01; I^2=0%). The quality of included studies revealed a high risk of bias.
Conclusions: CNB is the superior method to differentiate STS subtype with lower complication compared to IB.

Reference:

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Disclosure Statement: None of the authors have any conflicts or financial support to disclose.

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Ewing Sarcoma as Secondary Malignancy in a Heterogeneous Group of Cancer Patients

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Purpose: Ewing sarcoma (EWS) is the second most frequent bone associated tumor in children, adolescents and young adults [1]. Standard of care is comprised of intensive polychemotherapy, local surgery and radiotherapy [2]. Among patients with this rare malignancy, secondary EWS accounts for a small minority of all cases and data regarding EWS as a secondary malignancy are limited.
Methods: From 1991-2009, two consecutive and nationwide Ewing sarcoma trials enrolled 2422 patients. The GPOH database of these two studies was analyzed for EWS as a secondary malignancy. Kaplan Meier method was used to estimate event-free survival (EFS) and overall survival (OS).
Results: Among the 2422 patients enrolled in the EICESS 92 and EURO-EWING 99 studies, 26 cases of secondary EWS were reported. Median time of follow-up was 3.6 years (range 0.3-14.6) Median age at diagnosis of secondary EWS was 16.5 years (range 6.7-59.8) compared to 6.4 (range 0.8-53.5) at diagnosis of primary malignancy. Localized Ewing sarcoma occurred in 15 cases (58%), whereas 11 (42%) patients suffered from metastatic disease. A heterogeneous group of malignancies preceded secondary EWS; most common primary malignancies included acute lymphoblastic leukemias (6), lymphomas (5), osteosarcomas (2), and retinoblastomas (2). Three-year EFS was 0.67 (SE=0.12) for patients with localized and 0.09 (SE =0.09) for those with metastatic disease. The 3-year OS was 0.80 (SE=0.10) for patients with localized and 0.18 (SE=0.12) for patients with metastatic disease.
Conclusions: As a secondary malignancy, EWS accounts for approximately 1% of all reported EWS-cases. The most common hematologic malignancies within these age groups are consistent with those that precede secondary EWS. Patient characteristics are comparable to patients presenting with EWS as a primary malignancy.

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Impact of Surgical Margins in Patients with Soft Tissue Sarcomas of the Hand

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Purpose: The hand represents a rare but surgically challenging anatomical location of soft tissue sarcomas (STS). Maintaining the surgical aim of wide resection leads to a high rate of amputations and functional impairment while impact of resection margins on survival in distal extremity STS remains controversial. We aimed to perform a single institution analysis of long term results of hand STS to identify prognostic factors.
Methods: All patients operated for localized STS of the hand at our institution were identified. Uni- and multivariate analysis of factors associated with 5-year local recurrence free survival (5Y-LRFS), metastases free survival (5Y-MFS) and disease specific survival (5Y-DSS) were performed.
Results: 51 patients could be identified. Of these 3 received amputations of single fingers/finger rays while the rest could be treated without any amputation and marginal resections in the majority of cases and positive margins in 10% of cases. After a median follow-up of 77 months, 5Y-LRFS, 5Y-MFS and 5Y-DSS were 65%, 86% and 91% respectively. Tumor size was a predictor of all three outcome parameters but positive resection margins adversely affected LRFS only. Survival outcome was excellent and not inferior to other studies on hand STS with a more radical surgical approach.
Conclusions: Conservative surgical treatment of hand STS with marginal resection and adjuvant radiation therapy in case of high-grade STS is a viable treatment strategy leading to a better hand preservation than more radical surgical approaches at the cost of worse local control but not worse survival.

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Oncologic Impact of Wound Complications in Extremity Soft Tissue Sarcomas

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Purpose: In various malignancies, complications correlate with diminished prognosis, however literature on soft tissue sarcomas is limited and inconclusive. The aim of this study was to assess risk factors and the oncologic impact of wound complications in primary extremity soft-tissue sarcomas.
Methods: Patients with primary extremity soft tissue sarcomas without dissemination and with clear surgical margins (R0) were analyzed. Groups with and without wound complications were compared by univariate and multivariate analysis to identify risk factors. Uni- and multivariate analysis of factors associated with 5-year local recurrence free survival (LRFS), metastases free survival (MFS) and disease specific survival (DSS) were performed.
Results: 682 patients were included in the study, wound complications occurred in 94 patients (13.7%) within 90 days. Age, ASA-stage, high tumor size and grade, tumor location in the foot, neoadjuvant radiation therapy and operation time represented independent risk factors for wound complications. Patients with wound complications had a significantly worse estimated 5-year LRFS of 43.9±6.4% versus 77.1±2.1%. Wound complications could be identified as a strong independent risk factor for LRFS (HR 3.02[CI 2.03-4.49], p<0.001). 5-year MFS and 5-year DSS were significantly lower for patients with wound complications in univariate analysis but wound complications were not significant in multivariate analysis for MFS or DSS.
Conclusions: Wound complications after soft tissue sarcomas of the extremities are associated with worse local oncological outcome. Patients with high risk of wound complications should be identified and strategies implemented to reduce surgical complications and possibly improve oncologic prognosis.

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Undifferentiated Pleomorphic Sarcomas of the Extremities: A Single-Institutional Analysis of 179 Patients

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Purpose: Undifferentiated pleomorphic sarcoma (UPS) are a frequent subtype within the heterogenous group of soft tissue sarcomas and mostly occur within the extremities. Surgical resection with negative margins has been the mainstay of therapy. However, attainment of negative margins in the extremities can be complicate due to functional important structures. The aim of this study was to identify prognostic factors in patients with UPS of the extremities.
Methods: We retrospectively determined the relationship between local recurrence-free survival (LRFS), overall survival (OS) and potential prognostic factors in 179 patients with UPS of the extremities who were suitable for surgical treatment in curative intent. The median follow-up time was 4.8 years.
Results: The 5-year local recurrence-free (LRFS) and overall survival (OS) rate were 58.0% and 73.6%. Negative margin status was associated with significantly better LRFS and OS. The rates of LRFS and OS after 2 years were 75.5% and 87.0% in patients with R0-resected primary tumors and 60.0% and 75.0% in patients with R1/R2-status (LRFS: P=0.015; OS: P=0.001). Adjuvant radiotherapy significantly improved LRFS (5-year: 67.6% vs. 45.7%; P<0.001) and OS (5-year: 82.8 vs. 60.2; P=0.007). Both, negative margins and adjuvant radiotherapy were found to be independent prognostic factors in multivariate analysis.
Conclusions: The data from this study could underscore the beneficial prognostic impact of negative margins on LRFS and OS. However, the width of negative margins seemed to be not relevant. Notably, adjuvant radiotherapy was not only able to decrease the risk of local failure but also improved OS in a significant manner.

Disclosure Statement: All authors declare that they have no conflict of interest.

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Management of Patients with Gynecological Sarcoma - A Survey among Gynecologists within the Framework of the German Registry of Gynecological Sarcoma (REGSA)

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Trials in Progress:
Prospective Registry of Gynecological Sarcoma:
Management of patients with gynecological sarcoma - a survey among gynecologists within the framework of the German Registry of Gynecological Sarcoma (REGSA)
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Purpose: Gynecological sarcoma (GS) are rare neoplasms that make up 1% of all gynecological malignancies. There is a high clinical and scientific need to improve the clinical outcome. Specific data of the clinical management, including diagnostics, surgery and medical interventions are very limited.

REGSA is the largest prospective gynecological registry for sarcoma in Germany. The aim of the register has been to prospectively collect data of patients with GSs to describe their course of disease, diagnostics and therapies.
Methods: An electronic case report was designed to register clinical data from patients with gynecological sarcomas such as disease, surgery, therapy and success of therapy after informed consent. Additionally, the information about clinical management as stated by the participating physicians has also been recorded. This information is completed once per study site.

The evaluation of the register data is exploratory and descriptive. There will be a descriptive analysis of the forms of therapy according to the different types of gynecological sarcoma and their outcome. The REGSA study is registered on German Register of Clinical Trials (DRKS) with the number DRKS00009240.
Results: Patient recruitment started in September 2015 and currently is still ongoing. Up to date, 125 German study sites together with one Austrian site and one Swiss site have already enrolled 500 patients (status obtained on: 07/2019).
Conclusions: The result of the study might help to initiate multicenter trials and to improve the standard of care. Beside the collection of all medical data, the experiences and the treatment preferences of the physician are analyzed by a structured interview.

Disclosure Statement: no conflict of interest exists.

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Role of Histone Variants in Sarcoma Pathogenesis

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Purpose: Recent studies on tumor cells have suggested that altered epigenetic profiles including histone variants play a key role in modulating the functional potential at different stages of malignant transformation (Buschbeck et al. 2017). Multiple variants of the standard histones are encoded from a set of 'orphan genes' e.g. H2A.Z, H2A.X and macroH2A for H2 and specifically expression of H2A variants has been described in soft tissue sarcoma (STS) (Takahashi et al. 2014). Here we aim to investigate the role of H2A histone variants in sarcoma pathogenesis.
Methods: Expression of histone variants in 372 human STS samples was investigated by RNA-sequencing. Functional impact was investigated by RNAi and validated by CRISPR-Cas9 mediated knockout. Proliferation, cell cycle and viability of human STS-cell lines were analyzed by flow cytometry and cellular imaging.
Results: When analyzing expression of histone variants in global transcriptome analyses we found H2AFX, H2AFY and H2AFZ to be highly expressed in various STS subtypes. To assess for potential functional dependencies, we genetically inactivated H2AFX, H2AFY and H2AFZ in a RNAi-based dropout screen *in vitro* using the human STS-cell line T778. In this set of experiments especially H2AFX-depleted cells were repeatedly outcompeted by non-infected cells. These results could be confirmed by knockout of H2AFX using the CRISPR-Cas9 system. Interestingly, loss of competitive advantage was mainly caused by decreased proliferation ($n = 3$, $p \leq 0.044^*$) but did not result in higher rates of apoptosis, effects that could be recapitulated in other STS cell lines such as MLS-402-91 ($n = 3$, $p \leq 0.002^{**}$) and Fuji ($n = 3$, $p \leq 0.045^*$).
Conclusions: In Summary our findings provide first evidence for a role of H2A histone variants in STS biology. Besides differential expression in different subtypes of sarcoma, specifically H2AFX appears to be relevant for maintenance of cellular competition and proliferation *in vitro*.

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A Randomized Phase II Study of Durvalumab and Tremelimumab Compared to Doxorubicin in Patients with Advanced or Metastatic Soft Tissue Sarcoma (Medisarc, AIO-STS-0415)

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Purpose: Soft tissue sarcomas (STS) are rare tumors and exhibit substantial histological diversity. Efficacious targeted 1st line treatment for advanced/metastatic STS is not available, and the standard therapy has been anthracycline-based for decades. This strategy shows poor efficacy, as demonstrated by a median Overall Survival (OS) of 12-20 months. Several STS subtypes, however, have been shown to express PD-L1, and immune checkpoint inhibitors (ICI) have demonstrated principle anti-tumor activity in pretreated STS.
Methods: MEDISARC is a multi-center phase II trial that is enrolling adult treatment-naïve pts with histologically confirmed STS of intermediate or high grade (FNCLCC) not amenable to surgery with curative intent and ECOG status 0-2. Chemosensitive histologic STS are eligible. 100 pts will be randomized 1:1, stratified by ECOG status. Pts in the experimental arm are treated with fixed doses of durvalumab (Q4W) and tremelimumab (Q4W for 3 cycles, then Q12W) until Progressive Disease (PD) or for a maximum of 12 months. Doxorubicin treatment in the standard arm is (Q3W) limited to 6 cycles. OS is the primary endpoint. Secondary endpoints include 2-year OS rate, PFS, ORR, safety, tolerability, and health-related quality of life (EORTC QLQ-C30). The accompanying translational research aims to identify prognostic and predictive biomarkers.
Results: 14 centers in Germany are taking part. Enrollment of pts started in April 2018 and is ongoing.
Conclusions: Our ongoing clinical trial tests the activity and safety of ICI combination therapy in the 1st line setting. We hypothesize that the dual checkpoint blockade with Durvalumab (PD-L1) and Tremelimumab (CTLA-4) improves overall survival in STS when compared to the standard of care doxorubicin.
EudraCT No: 2016-004750-15, ClinicalTrials.gov ID: NCT03317457

Reference:

1. J Clin Oncol 37, 2019 (suppl; abstr TPS11075), Abstract & Poster. © 2019 American Society of Clinical Oncology, Inc. Reused with permission. This abstract was accepted and previously presented at the 2019 ASCO Annual Meeting. All rights reserved.

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Impact of Sarcopenia (SMI(+)) In Patients (PTS) with Advanced or Metastatic Soft Tissue Sarcoma (A/MSTS) during Multimodal Therapy (MT) as Risk Parameter

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Purpose: Objective parameters in a/mSTS identifying ideal pts for MT are hardly defined. Therefore, impact of sacropenia (SMI+) in MT treated a/mSTS pts were analyzed retrospectively.

Methods: 89/181 identified pts from 12/98-6/16 with a/mSTS were evaluable for analysis (CTs: -14 days before chemotherapy (CTx) onset). Within perinterventional CTs, lumbar skeletal muscle index (SMI) was measured with MeVisLab 2.7 by manual segmentation. Optimal fitting method defined SMI cut-off (SMI(+) in males (<44) and females (<38). Clinical or radiological judgment defined progression (cPFS). Descriptive statistics, Kaplan-Meier-analysis and Cox-regression were administered.
Results: Overall, at onset of CTx 28/89 pts (31%) suffered from SMI(+), and this was associated with overall less aggressive treatments, lower numbers of medical treatments, less frequently performed surgery, while radiotherapy was administered more often. SMI(+) was associated with less benefit from first line medical treatment compared to SMI(-) (clinical benefit rate: 25% vs. 49.2%, p=.032, PFS: 1 (95%-CI: .35-1.65) vs. 2 (95%CI: .67-3.32) months, p=.006). OS was shortened in SMI(+) compared to SMI(-) pts (4 (95%CI:2-6) vs. 16 (95%CI:8.8-23.2) months, p=.002). SMI(+) tends to be associated with reduced PFS (HR: 1.7 (95%CI: 0.9-2.8), p=.067) and was independently associated with reduced OS (HR: 2.53 (95%CI: 1.5-4.2), p<.001).
Conclusions: a/mSTS pts with sarcopenia tend to receive less aggressive therapies. A trend of inferior PFS and an independent risk for reduced OS was identified in SMI(+) pts. However, this analysis is limited due to its sample size. None the less, SMI(+) might reflect an attractive tool for treatment intensity modulation in a/mSTS patients, avoiding overtreatment in this cohort with dismal prognosis.

Skin Cancer, including Melanoma

Poster

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Surgical Treatment of Facial Basal Cell Carcinoma (FBCC). 30 Years of Retrospective and Prospective Studies

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Purpose: FBCC are mainly treated surgically. There are differences concerning details of the treatment, which is why own studies are summarized as decision-making aid.
Methods: Long-term analyses by means of control of the course of the disease and reevaluation of the histology. Target criterion: Recurrence (Kaplan-Meier estimate maximum 25 years).

Retrospective analysis (649 in-patient cases 1948 -1982): Excision with distance 5 mm. R1- status evaluated only in 1987. Trend to primary defect closure.

Prospective analysis (832 out-patient cases 1993 – 2007): Excision with distance 4 mm. Lateral and basal R1-status evaluated in a day. Primary defect closure.

Analysis of detailed questions (n> 2000)
Results: Controls show excellent oncological and esthetic results.
Recurrence probability for 10 years is determined by R1 and pretreatment status:
Untreated retrospective cases (n=445) R0: 1.8% R1: 48% (rate R1: 9%)
Untreated prospective cases (n=754) R0: 2% (rate R1: 3%)
Recurrences retrospective cases (n=248) R0 26% R1: 71% (rate R1: 28%)
Recurrences prospective cases (n= 83) R0: 2% (rate R1: 19%)
Detailed questions:
R1 status does not affect survival. Death as result of the tumor is rare (<0.3%). Secondary tumors occur at a rate of 30% of the patients, with 5% dying. FBCC shortens life expectancy by 5 years compared to normal population. Unfavorable are locally extended and multicentric FBCCs.

Most FBCCs can be operated on an out-patient basis. Walking disabilities, compliance and blood coagulation disorders can constitute a limitation. Age does not affect prognosis. Complications are rare (4%).

In uncertain basal R1 resections a second-look operation is better than radiotherapy.
Conclusions: FBCC can be surgically effective treated and often on an out-patient basis. Prognostically decisive is the R1-status. Sufficient safety distance as well as lateral and basal marginal cut controls leads to high oncological safety.

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Multiplex Tissue Analysis of the Tumor Microenvironment and Crucial Factors in Melanoma Pathogenesis

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Purpose: Investigation of the early events of melanocyte transformation by systematically analyzing human tissue sections by the MELC technology.
Methods: The study was made possible by applying the so-called MELC technology. With this technique, it is possible to visualize up to 100 and more individual antigens on one tissue section, while preserving the sub-cellular structure and organization of the sample.
Results: Our analysis reveals that ADAM10 activation is a key step in the transition from dysplastic nevi to a malignant cell. We detailed this mechanism and found that a change of the subcellular localization of the endopeptidase SPPL3 is the crucial event towards malignant transformation, because this event co-localized ADAM10 with its upstream activator SPPL3. To get this insight, we systematically analyzed human skin tissue sections from healthy skin to invasive melanoma. Analyzing the protein profile in the keratinocyte microenvironment surrounding melanoma cells was instrumental in our study as it reflected the individual steps of the transformation process. The molecular mechanism we uncover is plausible as we demonstrate how SPPL3-mediated activation of ADAM10

is functionally embedded in-between downstream effects of BRAFV600E and the inactivation of PTEN, two established key players in melanocyte transformation.
Conclusions: The results of our approach are remarkable not only for the introduction of novel effectors, but for the involvement of rarely described factors in the transformation process, including protein levels, their subcellular distribution and the early keratinocyte microenvironment. In summary, we demonstrate that systematic tissue antigen screening in combination with molecular analysis provides truly novel insight into melanoma development.

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Prevention of Skin Cancer among Outdoor Workers

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Purpose: Recognized as an occupational disease are squamous cell carcinoma and multiple actinic keratosis. Skin cancer is currently the second most common occupational disease.

Preventive measures have a high impact. In the AMD der BG BAU, we have conducted precautionary and advisory work on preventive measures and early detection of skin cancer since 2015.

In Germany, about 3 million outdoor workers are employed, mostly in the construction industry and agriculture sector.

Experience with preventive measures, such as head protection, sunscreen and its acceptance, as well as experience with training in training centers, using modem technologies will be presented.

The AMD der BG BAU consultations and preventive medical examinations for outdoor workers in the construction industry. In particular, carcinoma in situ, actinic keratosis and suspicious squamous cell lesions are identified and subsequent dermatological evaluation are recommended.

The current concept for the prevention of skin cancer should be put up for discussion.
Methods: Please copy and paste the corresponding text here.
Results: Please copy and paste the corresponding text here.
Conclusions: Please copy and paste the corresponding text here.

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Nico: Real World Evidence in Advanced Melanoma; A National Prospective Non-Interventional Study of Nivolumab Monotherapy or in Combination with Ipilimumab in Patients with Advanced Melanoma and in Patients with Adjuvant Nivolumab Therapy

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Purpose: Nivolumab alone (nivo) and the combination of nivolumab and ipilimumab (nivo+ipi) for first and subsequent lines of therapy have become standard treatment options for advanced melanoma. Most currently available data are from randomized clinical trials with predefined inclusion/exclusion criteria. Therefore, real-world studies are needed to evaluate the effectiveness and tolerability of nivo and nivo+ipi in a broader patient population.
Methods: NICO (NCT02990611) is an ongoing, non-interventional study in Germany associated to ADOREG.

Overall, 950 patients with advanced melanoma, who start therapy with nivo+ipi or nivo (cohort 1+2, n=750) or with nivo adjuvant therapy (cohort 3, n=200) according to marketing authorization in Germany, will be enrolled. Patients are followed for up to 5 years after initiation of therapy. The primary objectives are overall survival (OS) in patients receiving nivo+ipi and relapse-free survival in patients starting nivo adjuvant therapy. Secondary objectives include OS in patients treated with nivo, progression free survival, adverse event management and patient-reported outcomes.
Results: Baseline data of 359 nivo+ipi and 205 nivo patients are currently available, at the next data cut 30.09.2019, interim data of approx. 610 patients of cohorts 1+2 will describe baseline characteristics and outcome of patients with a minimum follow-up of 6 months. The data further provides demographic and disease characteristics of approx. 130 patients of cohort 3 and comprises safety management of more than 600 treatment-related adverse events documented so far.
Conclusion: We provide the first effectiveness data of the NICO observational study in patients treated with nivo or nivo+ipi in routine care in Germany. Furthermore, information about baseline characteristics in adjuvant patients and the management of immune related adverse events in clinical practice is shown. Taken together, these data give valuable insight in the current treatment landscape and outcome in patients with advanced melanoma.

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Topography-, Age- and Sex-Specific Incidence and Relative Survival of Cutaneous Squamous Cell Carcinoma in North Rhine-Westphalia, Germany, 2007-2015

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Purpose: Nonmelanotic skin cancer is frequently not registered by population-based cancer registries. The cancer registry of North Rhine-Westphalia (LKR-NRW) registers these tumors. The aim of this study is to assess how the incidence and survival of cutaneous squamous cell carcinoma (SCC) depends on age, sex, and topography.
Methods: With data of the LKR-NRW of the years 2007-2015, we estimated incidence rates (age-specific and age-standardized, European standard) and age-standardized relative 5-year survival of SCC (genital skin and remaining skin) by sex and topography.
Results: Overall, 83,650 cases were registered with 8.7% at the skin of the genitalia (men: 3.0%, women: 16.2%). The SCC incidence of the genital skin and the remaining skin has increased over time. Age-specific incidence rates of SCC at the genital skin were higher in women than men in each age group. At the remaining skin, men had higher SCC incidences at each subsite than women, with the exception of skin of the legs. Age-specific incidence patterns show two distinct patterns dependent on the localization. Survival was considerably lower for SCC at the genital skin (men: 71%, women: 75%) than at the remaining skin (men: 93%, women: 97%). Survival is especially low for SCC at the scrotal skin (67%) and labia majora (62%).
Conclusions: The increase of the incidence of SCC may be explained by the introduction of the skin cancer screening program and to some increase in the completeness of registration. When comparing age-specific incidences between men and women, the age-specific patterns depend on the localization of the tumors. SCC of the genital skin show a considerably lower 5-year survival than SCC of the remaining skin.

Disclosure Statement: See extra file.

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Endocrine Side-Effects in Immune Checkpoint Inhibitor Combinational (Nivolumab+Ipilimumab) Therapy for Melanoma Associate with Increased Survival

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Purpose: Although previous studies suggest that the endocrine side effects of immune-checkpoint inhibitor (ICI) combinational therapy with ipilimumab and nivolumab are underestimated, there is a lack of focused evaluations and consistent definitions in the clinical setting. The possible influence of endocrine side effects on overall survival are up to now not clearly addressed and should be evaluated in this study.
Methods: In this monocentric retrospective study, patients with ICI combinational therapy (Nivolumab + Ipilimumab) in metastatic malignant melanoma were included. Patients with start of therapy from March 2016 to September 2017 and a follow up period until July 2019 were included. The incidence, course and therapy of thyroiditis, hyperthyroidism, hypophysitis including Addisonian crisis and the effects on overall survival were analyzed.
Results: 44 patients could be included in this study. There were 27 (61.4%) different endocrine side effects in 22 (50%) patients. Mild to asymptomatic thyroiditis (27.3%) with transient thyrotoxicosis was most frequent after a median of 20.5 days (± 11.04) followed by irreversible hypothyroidism after a median of 52 days (± 21.12). Hypophysitis was observed in 11.4% of the treated patients after a median of 41 days (± 27.58) with resulting treatment pauses and irreversible adrenocortical insufficiency. Endocrine side effects significantly correlated with improved overall survival (p = 0.02). The median overall survival was 36 month in the side effect group versus 7 month in patients without endocrine adverse events.
Conclusions: Endocrine adverse events during ICI combinational therapy are more common in the clinical setting than previously thought. Due to the significantly improved survival, an increased anti-tumoral activity can be assumed when endocrine side effects occur.

Disclosure Statement: CW, KB, RK: no conflict of interest; MM: Advisory and speaker function for BMS, MSD, Merck.

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With Three-Dimensional Histology, the Area of the Studied Resection Margins of Excidates is up to 5,000 Times Higher than with Conventional Histology

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Purpose: In a conventional histology (CH) using parallel cuts, the areas between the slices remain unrepresented in the histological slides, which can lead to incomplete removal of the tumor along the resection margin (RM) and worsen the treatment results. For guaranteed detection of tumor infiltrates in the RM, the excidate should be prepared by 3D histology (3D H): separating the thin vertical lateral margin strip (marginal section (S)), then horizontal – a thin layer of the lower side (basic S) and finally – a cross section of the remaining middle part (middle S). Marginal and basic S are to be examined for the presence of tumor infiltrates, and the morphological type of the tumor is determined by the middle S. We compared the efficiency of 3D H and CH in skin cancer using a mathematical model.
Methods: 18 variants of sizes of excidates in the form of a circular cylinder were examined: 1, 2, 3, 5, 7, 10 cm in diameter and 0.5, 1 and 1.5 cm in height. It was assumed that for CH, excidates are prepared as follows: with a diameter ≤ 2 cm – in parallel S completely, starting from the center (middle S), and from it – to the margins of the excidate, and with a diameter > 2 cm, three S were made in the center and one on each sides of the excidate. The thickness of the S both in CH and in 3D H was taken to be 2 mm. After paraffinization, histological fine slices, 5 microns thick, were made and examined under a microscope: in the CH – from the center of each S, and in 3D H – from the outer margin of the S. The percentages of the studied area of RM in 3D H and CH were calculated and compared, the percentage of the area of useful examination (to determine the tumor type and to detect tumor infiltrates along the RM) in the total studied area was determined.
Results: CH provides a check of the RM by only 0.02-0.2%, and 3D H – by 85-100%. In CH with 5 S – 70-75%, and with 9 S – 87% of working time and expendable material is wasted.
Conclusions: CH does not guarantee the detection of tumor infiltrates in the RM and does not protect the patient from recurrence after surgical removal of the tumor. It is more reasonable to use 3D H for the evaluation of the excidate with skin cancer.

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Treatment Reality of Patients with BRAF-Mutant Advanced/ Metastatic Melanoma in Germany, Austria and Switzerland in the Era of Choice

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Purpose: Due to the rapid development of the treatment landscape, multiple options are available for the treatment of patients (pts) with BRAF-mutant advanced/metastatic melanoma. Targeted therapies (TT) of BRAF and MEK inhibitor combinations or checkpoint inhibitors (IO) in monotherapy or in combination are used. The present analysis shows the current treatment choices and their reasons in daily routine treatment in Germany, Austria and Switzerland.
Methods: Retrospective and anonymous documentation of the first- to third-line treatments outside of clinical trials (treatment start between January 2016 and September 2018) in pts with advanced/metastatic $BRAF^{V600E/K}$-mutant melanoma and the reasons for treatment choice.
Results: Data of 140 pts treated with 242 treatment lines at 15 clinics were analyzed (52% male; median age 59 years, ECOG PS 0 or 1: 75.7%; elevated LDH: 34.3%; stage IV M1c: 25.0%; M1d: 22.1%). 74 pts entered the second and 28 pts the third line treatment. The choice between TT and IO was well-balanced (1st: TT 50.7%; IO 49.3%; 2nd: TT 50.0%; IO: 45.9%). In general, the treatment type was switched between the treatment lines. The main reason for choosing a treatment type were remission pressure for TT and physician's preference for IO. For TT, dabrafenib + trametinib was predominantly administered (70.0%); vemurafenib + cobimetinib was used in 26.0% of the pts. For IO, more pts received monotherapy regimens (56.3%) than combination treatment (43.8%). The main reasons for choosing specific drugs were their toxicity profiles (TT) and physician's preference (IO). Main reasons for treatment discontinuation were progression (TT 45%; IO 45%) and toxicities (TT 15.0%, mostly dermatological; IO 17.9%, mostly gastrointestinal (nearly all in IO combinations)).
Conclusions: In the treatment of patients with BRAF-mutant advanced/ metastatic melanoma, modern substances were used with an equal distribution between TT and IO. The reasons for choosing between TT and IO, or substances within the groups, were different.

Disclosure Statement: Financing by Pierre Fabre Pharma.

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Single Center Experience: Use of Talimogene Laherparepvec (T-VEC) in the Elderly: A (COST)-Effective Therapy-Option with Low Side-Effects ?

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Purpose: Talimogene laherprapevec (T-VEC), a genetically modified herpes simplex virus (HSV-1), has been approved for the intralesional therapy of locally advanced malignant melanoma (AJCC IIIB- IVM1a) since 2016 in Germany. In the randomized controlled Phase III trial (OPTiM), T-VEC achieved in the above cohort a response rate (ORR) of 46.0% and a durable response rate of 28.8%. Adverse event grade 3 or higher were rare. To date, little data is available on the use of T-VEC outside of clinical trials, particularly with regard to the treatment needs of elderly patients.
Methods: In the present retrospective evaluation we examined the data of 11 elderly patients(minimum age of 65 years at the start of treatment) suffering from malignant melanoma , who were treated with T-VEC outside of clinical trials at the University Hospital Frankfurt from August 2016 to May 2019. Therapy response was measured by overall response rate (ORR) and sustained tumor response rate (DRR). Patient specific data, side effects and therapy costs were collected and evaluated.
Results: 82% (n=9) of the patients were in AJCC stage III at the start of therapy, 18% (n=2) in IVM1a. The median age was 83 years. 18% (n=2) of the patients under therapy with T-VEC achieved a complete response, 55% (n=6) had a partial remission, 9% (n=1) achieved a stable disease and 18% (n=2) showed progressive disease. Thus, the tumor control rate was 82% (n=9). Treatment related irreversible and serious side effects (≥ grade 3) were not observed. One patient died of a non-associated myocardial infarction during the observation period. The mean therapy costs in the investigated population were in the same range as the minimum annual therapy costs of T-VEC according to pharmacy retail prices.
Conclusions: In this special cohort of elderly patients, the high tumor control rate of 82% shows a good efficacy of T-VEC in the therapy of malignant melanoma under real-life conditions. With the regard to the short average duration of treatment and the low side effect rate, T-VEC offers a good therapy alternative for aged patients

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Validation of the 8th Edition TNM Classification For Stage III Melanoma Patients in a Single German Referral Center

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Purpose: In the 8th edition of the AJCC and UICC TNM classification rules for melanoma with locoregional spread (stage III) have been changed substantially. As a result, the estimated 5-year survival rates for e.g. stage IIIA have improved dramatically, making stage IIIA more favorable than stage IIB and IIC. Concerns have been raised as to the validity of the underlying outcome database, still some retrospective re-evaluations suffer from potential selection bias during follow-up.
Methods: We attempted to evaluate 5-year survival follow-up for stage III melanoma patients diagnosed between with a loss-to-follow-up rate below 10% and with a primary focus on prospectively followed primary diagnoses. We evaluated releapse-free survival (RFS) and overall survival (OS) and calculated 5-year rates using Kaplan-Meier product limit estimates.
Results: We present follow-up data on 277 patients with 7th edition stage III melanoma primarily diagnosed between January 1 2003 and December 31 2013. The estimated melanoma specific 5-year survival rates were 87.8%, 78.7%, 57.4%, and 25.0% in stages IIIA (n=49), IIIB (n=74), IIIC (n=143), and IIID (n=8), respectively.
Conclusions: The usability of the new TNM classification for stage III melanoma could be confirmed. Survival rates where higher as compared

to the corresponding 7th edition rates, but somewhat lower as published by the AJCC melanoma international database.

Reference:
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Disclosure Statement: none to disclose.

Supportive Care

Vorträge

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Institutional Strategies for Addressing Complementary or Alternative Medicine (CAM). A Qualitative Study with Health Professionals in (Pediatric) Oncology

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Purpose: This paper explores attitudes and experiences of health professionals in (pediatric) cancer care whether - and if so, how CAM consultation and/or treatment should be integrated into clinical care.
Methods: Qualitative semi-structured in-depth interviews with experts in (pediatric) oncology in Germany. Sampling started from a convenience sample with subsequent elements of snowball sampling. All interviews were audiotaped and transcribed ad verbatim. Qualitative analysis of data was conducted according to principles of content analysis by two researchers independently.
Results: Interviews were conducted with 15 pediatric oncologists, 13 physicians with clinical experience in the care of adult cancer patients, 2 nurses, 2 psychologists and 1 dietician. Interviewees understanding of CAM varied considerably. There was agreement among interviewees regarding a perceived need for institutional services on information and possible CAM treatment offers. Reported examples of individual activities to inform about or provide CAM measures were usually initiated by single professionals with strong interest in CAM but not embedded into an overall institutional strategy. Lack of evidence was not a general reason for refusal, in fact integrating CAM measures was viewed by some as a chance to create an evidence-base. Structural challenges encompassed financial resources, time and rooms allocated to the provision of such services. The acceptance by health professionals was quoted as another relevant factor furthering or hindering the institutional implementation of CAM (information) services in cancer care.
Conclusions: The interviewed experts in principle agree on the need for establishing CAM related services on an institutional level. However, there were differences regarding their understanding of CAM and the elements of CAM related services.

Disclosure Statement: This work is part of the collaborative research project "Kompetenznetz Komplementärmedizin in der Onkologie – KOKON", funded by Stiftung Deutsche Krebshilfe, Bonn, Germany (Project No. 70112458)

Poster

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Feasibility of Yoga Intervention in Curative and Palliative Cancer Patients with Fatigue

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Purpose: Yoga interventions achieve growing attention in cancer care to reduce side effects of the treatment [1]. The purpose of this pilot study was to test the feasibility of an 8-week yoga-therapy for palliative and curative oncological patients who suffer strongly from fatigue. We want to investigate the effectiveness and any necessary changes to the program or recruitment.
Methods: The eligible participants (fatigue intensity ≥4, impairment ≥ 5)[2] were randomly assigned to either the intervention group (IG) or the control group (CG). The IG received 8 units of yoga, one hour per week. At the beginning and after 9 weeks, fatigue, quality of life (QoL) and depression were assessed by questionnaire.
Results: Within a recruitment period of 5 months, 25 out of 241 eligible patients were enrolled for the study (participation rate=10.3%). The participants (12 IG, 13 CG), mean age 61.8 years (STD 13.15), were 76% women, 20% under palliative treatment and predominantly affected by breast cancer (56%). 66% of participants in IG attended more than 50% of yoga classes. 6 participants (3 IG/3 CG) discontinued the study due to overlapping appointments (33%), poor general condition (33%) or no reasons given (33%). The satisfaction regarding yoga class (5.9/6), selection of yoga poses (5.6/6) and instruction by the yoga therapists (5.8/6) was very high.

In an explorative peer-protocol analysis with participants who attended more than 50% of the yoga classes significant differences in depression score (time x group interaction) were reported (p=.007, d=1.63). No significant interactions were found in physical, emotional and cognitive fatigue and QoL.
Conclusions: These initial results suggest that yoga is well accepted and should be further explored with a larger sample size. Due to the low participation rate the inclusion and exclusion criteria must be discussed. Further research should be done into the reasons for non-participation in order to reduce it.

References:
1. Buffart et al., 2012
2. Fischer, 2013

Disclosure Statement: TZ and AR report grants from Deutsche Krebshilfe, during conduct of study

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Prio-Practical and Patient-Oriented Recipe Development for Oncology Patients

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Purpose: While nutrition recommendations play an integral role in the maintenance of nutrition status, it is important to define barriers und facilitators to the implementation of nutrition recommendations and provide practical patient-oriented, scientifically based solutions.
Methods: In this mixed methods study, the Patient Generated Subjective Global Assessment provided validated quantitative information pertaining to nutrition-related symptom burden (NRSB), and nutrition status. Qualitative methods provided criteria for development of recipes targeted at NRSB and the final questionnaire assessing barriers und facilitators to the implementation of nutrition recommendations, which will be analyzed quantitatively via SPSS v.25.
Results: Following the criteria elicited from structured interviews with patients (n=8) and professionals (n=10), 52 recipes aimed at easing the NRSB were developed, and pre-tested for taste, texture, appearance, and ease of preparation in the test kitchens by dietitians and dietetic students spread over 7 locations in Germany. Selected recipes are further being quantitatively assessed for acceptance and utility. Recruitment is ongoing (so far n=45) for the questionnaires which will be analyzed quantitatively in Autumn 2019.
Conclusions: This study will contribute to a more practicable, patient-oriented approach to managing the NRSB and provide suggestions for tailoring information aimed at malnutrition prevention. Results along with exemplary recipes will be presented at the Congress. Free access to the recipes via internet will be provided.

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1. Beehler et al. *Mil Med*. 179, 9:998, 2014.
2. Conradie et al. *S Afr J Clin Nutr* 2009;22(4):177-184

Disclosure Statement: DKG provided financial support.

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Education about Complementary Medicine: Evaluation of a Concept for Leaders of Cancer Self-Help Groups

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Purpose: Many cancer patients have a need for information about complementary and alternative medicine (CAM). The purpose of the study (KOKON subproject P7, funded by German Cancer Aid) [1] was to implement and evaluate a CAM educational concept for group leaders of cancer self-help groups, which was developed in a pilot study in cooperation with health professionals and representatives of cancer patients advocacy organizations. Its aim was to promote an open exchange of experiences with CAM, to impart reliable information sources and to sensitize for untrustworthy CAM offers.
Methods: Self-help group leaders were trained in Germany to carry out a CAM training in their groups. The trainings were evaluated in terms of acceptance and feasibility by group leaders and members. A follow-up questionnaire for the group members six months after the training to prove its sustainability and potentially changed information seeking behaviors or attitudes towards CAM will be analyzed at the end of 2019 (T_2).
Results: N=49 of N=577 trained group leaders implemented the training in their groups and felt confident to moderate it using provided material. The trained group members (N=419) were satisfied with selection and comprehensibility of contents, appreciated the possibility to exchange CAM experiences and agreed that the training imparts reliable information sources, 91% would recommend it.
Conclusions: The preliminary results indicate that this innovative educational concept could be a good option to inform cancer survivors about CAM in addition to consultation by experts.

Reference:

1. Witt, C.M., Bartsch, H.H., Güthlin, C. et al. (2017). Kompetenznetz Komplementärmedizin in der Onkologie (KOKON). Ein wissenschaftlicher Beitrag zur Verbesserung der Versorgung. Forum 2017. https://doi.org/10.1007/s12312-017-0311-1

Disclosure Statement: The authors declare that there are no conflicts of interest in terms of the contents of this publication.

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Whole Body Vibration Exercise Affects Bone Metabolism and Improves Physical Performance in Patients with Monoclonal Gammpathy of Undetermined Significance

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Purpose: Monoclonal gammopathy of undetermined significance (MGUS) is a pre-malignant condition in which abnormal monoclonal proteins are produced by plasma cells in the bone marrow. Patients with MGUS have an increased risk for bone fractures potentially due to increased cortical porosity.[1] In our clinical pilot study we evaluated the impact of whole body vibration (WBV) exercise on bone turnover, structure and physical functioning.
Methods: Fifteen MGUS patients (62.5 ± 7.8 yr; n=9 female) performed WBV two times per week for 30 minutes over twelve weeks. Ten patients continued WBV training for additional twelve weeks. Primary endpoints were changes in bone density parameters (quantitative computer tomography) and bone turnover markers. Measures of functional and activity testing served as secondary endpoints.
Results: In females (n=9) we observed a significant increase in bone structural parameters such as cortical thickness (P=0.016) at the tibia over 24 weeks. In the entire cohort a significant decrease in the bone biomarkers Dickkopf1/DKK1 (P=0.012), Alkaline Phosphatase (P=0.006), was accompanied by an increase in Sclerostin levels (P=0.015). Highly significant improvements in physical functioning were measured by the Chair Rise Test (P=0.001), Timed up and go (P=0.001) and 6-minute Walk Test (P=0.001) after 24 weeks. No exercise-related adverse events or skeletal fractures were observed during the study.
Conclusions: Our study demonstrates that WBV improves bone turnover parameters and physical functioning, particularly in females with MGUS. Future studies are needed to show whether WBV has an impact on fracture risk in cancer patients with bone disease.

Reference:

1. Farr JN et al. Blood 2014;123:647.

Disclosure Statement: Nothing to disclose.

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Ways to Cancer Counseling Centers: How do People Become Aware of these Centers?

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Purpose: Cancer counseling centers (in German: Krebsberatungsstellen – KBS) offer psychological and social (legal) support for patients and their relatives who are confronted not only with physical but also with psychosocial burdens as a result of cancer [1]. But how are people made aware of such places?
Methods: Guideline-based interviews were used in a Germany-wide qualitative study. 43 patients and relatives were interviewed face-to-face by trained staff in 10 cancer counseling centers; 30 referring physicians were interviewed via telephone by the project team. All interviews were transcribed and evaluated by content analysis [2].
Results: Flyers and information brochures are important sources that draw the attention of patients and their relatives to KBS. Websites, newspaper advertisements, and information events were also mentioned. In addition to public relations work, the personal approach - above all in the medical care system, but also in the non-clinical and social environment - was of central importance. Sometimes the referring physicians contacted the KBS directly. Sometimes they even contacted the KBS directly on behalf of the patients who were clearly struggling. Some physicians address KBS routinely, while others only do so when an explicit need arises (when those seeking advice are (very) burdened and express an increased psychosocial (legal) counseling need). Disseminated in the medical/clinical care system. As a result, closer cooperation with general practitioners, social workers, and psychologists should be sought. Informative flyers and brochures can sharpen the focus on KBS and highlight the features that distinguish it from other outpatient care services. Good public relations are essential.

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2. Mayring P (2016) Einführung in die Qualitative Sozialforschung, Beltz.

Disclosure Statement: None of the authors have anything to disclose.

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Spiritual Care in Oncology: Patients' Perceived Spiritual Support and Professionals' Perceived Responsibility to Care for their Patients´ Spiritual Needs – Data from a Pilot Project

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Purpose: As part of the AG PRIO project on spiritual needs of cancer patients and spiritual care competences of oncology staff we intended to analyze the spiritual-religious (S/R) self-categorization of patients and their health professionals.
Methods: Cross sectional survey in a defined time frame among patients with cancer from treatment centers in East and West Germany and their treatment team (i.e. physicians, nurses, psychologists, medical assistants) with standardized questionnaires.
Results: We analyzed data from 171 patients (62% women; 61±12 years of age) and from 78 health professions (78% women; 43±11 years of age; 35% physicians, 18% nurses, 47% other; 33% oncology wards, 36% hospitals, 22% university hospital, 8% other). While a majority of staff regarded themselves as religious and/or spiritual (41% R+S+, 11% R+S-, 9% R-S+, 39% R-S-), most patients stated to be non-religious (16% R+S+, 23% R+S-, 8% R-S+, 53% R-S-). There were no significant differences between East and West German centers. Among the staff, 33% of S/R and 79% of R-S- ($p<0,001$; Chi^2) do not feel responsible to care for spiritual issues. Nevertheless, 75% of S/R and 57% of R-S- patients ($p=0,056$; Chi^2) felt supported in their spiritual needs by the staff.
Conclusions: Health professionals´ and patients´ self-perception of being spiritual/religious or not differs. This may have an impact on what patients expect from the staff and how these may respond to their patients´ spiritual needs. Even in widely secularized societies, patients may be affected by unmet spiritual needs and unresponsive caregivers.

Disclosure Statement: The study was supported by a grant of German Cancer Society. The authors disclose any conflict of interest.

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PACC: Patient Centered Care

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Purpose: Investigation of efficacy of nutrition-related patient reported outcomes (NR-PRO) and their implications in clinical care.
Methods: Multicenter, multinational trial exploring the acceptability, perception, and usability of NR-PRO factors assessed using CANKADO's E-health platform.
Results: 188 patients undergoing treatment for gastrointestinal tumors in Germany and Switzerland were asked to complete 79 tablet-based questions consisting of 2 validated questionnaires related to nutrition status along with questions pertaining to acceptability. 34 Patients (18%) chose not participate.152 patients (median age 62 years; range 22-86) were willing to complete the questionnaires. While 84% perceived the tablet-based questionnaire to be not difficult, older patients tended to find the tablet-based format more unwieldy than younger patients ($p=0.052$). While age was similarly distributed between the sexes, men were significantly more likely to require help completing the questionnaires than women

(p=0.035). A high proportion (89%) largely, or completely, agreed that NR-PROs via tablet should be integrated in routine clinical care.
Conclusions: Routine assessment of NR-PROs via tablet is an acceptable approach for patients undergoing treatment for gastro-intestinal tumors and poses a simple and efficient solution for integrating these valuable assessment parameters into routine clinical care.

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Disclosure Statement: C.Riese is employed by Cankado.

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On-Site Integrative Oncology: The Bochum/Hattinger Model

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Purpose: For the last 10 years, the Clinic for True Naturopathy in Hattingen-Blankenstein has offered a consultation service for integrative oncology tot he St. Josef-Hospital. Ruhr-University Bochum, department of hematology and oncology. Since February 2019, aregular consultation service on site, twice weekly, has been conducted.
Methods: From the 20th of February to the 26th of September, 2019, N=154 male and female patients from the department of hematology and oncology, St. Josef Hospital, Ruhr-University Bochum, were treated. The diagnoses were: Pancreatic carcinoma (N=81), Breast carcinoma (N=7), Lung carcinoma (N=12), Eophageal carcinoma (N=10), Stomac carcinoma (N=2), Colon and Rectalcarcinoma (N=17), Ovarian carcinoma (N=3), Others (N=22). In addition to a therapy program consisting of the classical European natural healing remedies, to include phytotherapy, wraps compresses and cupping therapy, acupuncture and mistletoe therapy (N=26) were also offered to suitable patients.
Results: First indications show that more patients can be recruited during oncological patient visits by the presence of a qualified doctor of true naturopathy, thereby promoting the possibility for complementary naturopathic treatment such as mistletoe therapy. In this period, mistletoe therapy was discussed with N = 26 patients. Finally, N = 8 patients performed mistletoe therapy.
Conclusions: Consultation between the oncologist and a medical specialist of true naturopathic treatment would identify suitable patients. The therapy concept oft he Bochum/Hattinger model is herewith presented.

Disclosure Statement: None

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A Comparison of Physical Activity Change Patterns and Determinants between Breast, Prostate and Colorectal Cancer Patients

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Purpose: Despite well-established benefits of physical activity (PA) for cancer patients, a majority of patients do not meet recommended PA guidelines (≥150 min moderate-to-vigorous PA/week). The purpose of the study was to investigate how PA behavior changed from pre- to post-diagnosis, which sociodemographic and medical factors were associated with PA and how change patterns and determinants of PA differed between breast, prostate and colorectal cancer patients.
Methods: In a cross-sectional study, 912 cancer patients (457 breast, 241 prostate, 214 colorectal cancer; on average 15.1 months post-diagnosis) completed a questionnaire assessing sociodemographic and medical variables as well as their weekly duration of PA pre-diagnosis and within the last week. PA change patterns and differences between cancer types were analyzed with non-parametric tests. Logistic regression analyses were used to identify sociodemographic and medical determinants of sufficient post-diagnosis PA. Additionally, population subgroups more or less likely to be physically active were detected using classification tree analyses.
Results: Despite a modest decrease of PA from pre- to post-diagnosis, we found that 54% of cancer patients indicated to be sufficiently active post-diagnosis. Considerable differences in pre-diagnosis PA between cancer types disappeared post-diagnosis. While for all cancer types, post-diagnosis PA was strongly affected by pre-diagnosis PA, we detected differences between cancer types regarding further PA determinants. Our results suggest that previously inactive prostate cancer patients and recently diagnosed patients currently undergoing cancer treatment had an increased likelihood of being insufficiently active post-diagnosis.
Conclusions: The number of sufficiently active cancer patients was encouragingly high. Yet it seems important to further raise awareness of PA in the general population as well as in the post-diagnosis setting, where interventions that are more tailored to specific patient and cancer characteristics need to be established.

Disclosure Statement: The study was funded by German Cancer Aid. There is no conflict of interest.
Prof. Dr. Karen Steindorf gibt folgende Verbindungen außerhalb des eingereichten Abstracts an:
Personal fees from Pfizer Pharmaceuticals (Consulting for writing a brochure on physical activity and cancer for breast cancer patients), personal fees from Adviva Heidelberg (Lecture Fee), non-financial support from Asklepios Clinics (Travel costs), personal fees from BIG direkt health insurance (Lecture fee, travel costs), personal fees from TEVA Pharmaceuticals (Lecture fee, travel costs).

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Safety of a Combined Supervised and Home-Based Whole-Body Vibration Intervention for Childhood Cancer Survivors

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Purpose: To assess safety of a whole-body vibration (WBV) intervention, combining supervised and home-based training for childhood cancer survivors.
Methods: Eight childhood cancer survivors (mixed cancer types, age: 6-17) participated in a 12-week WBV-intervention, comprising one supervised and two home-based sessions per week. Training was performed on a side-alternating vibration platform. WBV-protocol included one warm-up (60 sec, 18 Hz, 2mm peak-to-peak amplitude) and 5-10 progressive training exercises (60-90 sec, 18-27 Hz, 2mm peak-to-peak amplitude). Adverse events leading to health deterioration and intervention drop out were evaluated. Side effects of WBV were secondarily investigated.
Results: No study dropout due to WBV-related adverse events occurred. Three patients reported pain in the feet following WBV (vibration frequencies: 22Hz and 27 Hz) that required early training stop or temporary training interruption. Itching in the feet and legs during exercising was reported in almost all patients. One patient experienced itching in the lower back.
Conclusions: Not only supervised[1] but also home-based WBV is safe for childhood cancer survivors. However, close monitoring seems necessary to detect the onset of pain. Survivors and families should be informed that common symptoms of WBV like itching[2] are possible during or immediately following WBV.

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Disclosure Statement: No conflicts to disclosure.

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Real-World Evidence of the Effectiveness and Safety of NEPA (Netupitant-Palonosetron) for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Patients (PTS) Receiving Highly (HEC) or Moderately Emetogenic Chemotherapy (MEC): Final Results of a German Prospective Non-Interventional Study

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Purpose: NEPA, the fixed combination antiemetic composed of a neurokinin-1 receptor antagonist (RA; netupitant) and a 5-hydroxytryptamine-3 RA (palonosetron), is recommended for CINV prophylaxis for HEC and MEC. This prospective non-interventional study assessed quality of life (primary endpoint), effectiveness and safety (secondary endpoints) of NEPA in HEC/MEC-treated pts under real-world conditions. Here, we report final effectiveness and safety data by chemotherapy (CT) group.
Methods: Adult pts treated with 1- or 2-day (d) HEC or MEC receiving NEPA per SmPC were enrolled. Effectiveness, including frequency and severity of nausea and vomiting and use of rescue medication (RM), was reported in pt diaries. Complete response (CR) was defined as no emesis and no RM, and non-significant nausea (NSN) as no or mild nausea. Adverse events (AEs) were reported on d1–21 of each cycle (C). All data were collected for 3 consecutive CT Cs.
Results: From 9/15 to 9/17, 2405 pts initially assessed at 162 centers across Germany, of whom 2173 were analyzed. Median age was 58 y (range 25-89); 85% were female and half of the pts had an ECOG of 0-1. Pts were diagnosed with breast (66%), gastrointestinal (10%), ovarian (7%) or lung (5%) cancer. More than half of the pts (1230, 56%) received anthracycline/cyclophosphamide-(AC), 19% carboplatin-, 8% cisplatin-, 7% oxaliplatin- and 9% other CTs. During the overall period in C1, CR rates were between 81-84% and comparable in the pt groups treated with different HEC or MEC. NSN rates varied between over 73% in the carboplatin-, cisplatin- and 45% in the oxaliplatin pt group, in the overall period in C1. Outcomes were similar for C2 and C3. Overall, 7% of pts reported drug-related AEs, with the most common (in >1% pts) being constipation, fatigue, insomnia, and nausea.
Conclusions: NEPA was highly effective at CINV control under real-world conditions in AC-, carboplatin-, cisplatin-, oxaliplatin- and other CT pts, with a predictable and favourable safety profile.

Disclosure Statement: Advisory Role, Honoraria: RIEMSER Pharma GmbH, Helsinn Healthcare SA.

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Effects of a Whole-Body Vibration Intervention in Children and Adolescents after Inpatient Anticancer Therapy on Ankle Dorsiflexion Function and Balance Control

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Purpose: Ankle dorsiflexion (DF) function (strength, range of motion (ROM)) and balance control are often impaired in children and adolescents after inpatient anticancer therapy. However, adequate functional capacity of the lower limbs is prerequisite for mobility and for being active in general. Whole-body vibration (WBV) aims to improve those variables.
Methods: Eight children after inpatient anticancer therapy (mixed diagnoses, age: 6-17) participated in a twelve-week WBV intervention. Training was offered three times a week (1x supervised, 2x home-based). Training was performed on a side-alternating vibration platform. The training sessions included one warm-up (60 sec, 18 Hz, 2mm peak-to-peak amplitude) and 5-10 progressive training exercises (60-90 sec, 18-27 Hz, 2mm peak-to-peak amplitude). Two testings were performed before and after the intervention assessing balance control (one-leg stance), ankle dorsiflexor strength (hand-held dynamometry) and active DF ROM (measured with bent and straight legs, goniometry).
Results: Positive trends were reported in balance control, strength of ankle DF and active ankle DF-ROM with straight legs. Active DF-ROM with bent legs was significantly improved.
Conclusions: The results indicate that our WBV-intervention, combining supervised and home-based training sessions, can improve all of the three focused parameters, especially active DF-ROM. Consequently, the barriers for a regained higher level of physical activity can be considerably reduced. WBV might be a promising modality to improve lower limb function in pediatric oncology.

Disclosure Statement: The authors have no conflicts to disclosure.

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Lung Cancer Patients' Expectations and Support Needs Regarding Patient Navigation

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Purpose: Lung cancer patients face a low five-years-survival rate.[1] Due to this poor prognosis, treatment with palliative intent is often initiated early after diagnosis. Navigation programs for patients aim to optimize the individual's care trajectory including early integration of palliative care, which has positive effects on patients' quality of life.[2] In Germany, there is little coordination of a patient`s continued care and patient navigation is only slowly evolving. In this study, we investigated lung cancer patients` perspectives on patient navigation.[3]
Methods: A longitudinal interview study was conducted with 20 lung cancer patients assessed at three time points (after diagnosis, at 3-6 and at 6-12 months). The interviews were audio-recorded and transcribed verbatim. We conducted a thematic analysis.
Results: Navigation needs were mainly seen in emotional and practical support, but also in linking patients to existing support services and providing information on social care issues. Patients would appreciate the continued support through one contact person. For navigation to be of interest to patients its implementation within existing care structures, such as the outpatient clinic or oncology practice, is crucial.
Conclusions: From the patients` perspectives, navigation could be a supportive approach to identify and address their individual healthcare needs and improve their journey through the complex care continuum by having one permanent contact person.

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Disclosure Statement: This work is part of the research consortium "NAVICARE – Patient-oriented health services research". NAVICARE is funded by the German Ministry of Education and Research (01GY1601).

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Patient Information, Communication and Competence Empowerment in Oncology (PIKKO) – Evaluation of a Supportive Care Intervention for Overall Oncological Patients: Baseline Data and Representativeness

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Purpose: In Saarland the supportive new consulting and information path, called PIKKO (funded by InnoFond, 01NVF17011), is implemented for all types of cancer. The evaluation study is still ongoing. The study design is presented, the participating patients are described and their representativeness discussed.
Methods: We included all cancer types (new diseases and existing ones) and used a non-randomized, comparative, multicenter superiority design. The patients assigned to a control group (usual care) or intervention group (usual care + PIKKO). The core elements of intervention are a patient navigator, oncological knowledge database, and specialized psycho-oncological counseling. In addition to patient surveys, data from statutory health insurances and usage data from the web database are collected, and interviews with patient navigators and doctors are carried out.
Results: Recruitment will be completed in October 2019. Preliminary demographic analyzes indicated that the PIKKO sample is broadly similar to other German cancer studies [1, 2, 3]. The score ranges for quality of life, depression and anxiety are comparable to Gotze [1] and Sauer [2], but a little more distressed. Dominant cancer types are breast cancer (C50), leukemia and lymphoma (C81-C96) and lung cancer (C33-C34). Final data will be available at time of the congress.
Conclusions: PIKKO is designed to improve quality of life, self-efficacy, health literacy and patient satisfaction and to reduce psychological distress, related health care costs and the days of inability to work.

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Disclosure Statement: No competing interests.

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Assessment of Body Composition with Different Methods in Breast Cancer Patients

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Purpose: Many studies have consistently shown that malnutrition is associated with higher degrees of treatment-related toxicity, reduced response to cancer treatment and worse prognosis. In particular, body mass index may be normal in patients with sarkopenic obesity. So far, screening for malnutrition, in particular the assessment of body composition is still the exception in daily practice although different well-established techniques of body composition analysis do exist.
Methods: In this study body composition of 92 breast cancer patients was analyzed at t0 and after 20 weeks. Different methods such as bioelectrical impedance analysis (BIA), near-infrared interactance (NIR) and dual x-ray absorptiometry (DXA) (considered as the current gold standard) as well as a simple body fat scale (BFS) from the discounter were compared with respect to various outcome variables (e.g. fat mass (FM), fat free mass (FFM) etc.), their validity and reliability as well as costs and handling.
Results: DXA, BIA and NIRS yielded similar results for body composition, including FM (DXA: 28,9 BIA: 28,2 kg, NIRS: 27,9kg) and FFM (DXA: 44,5kg, BIA: 46,2kg, NIRS: 46,5kg). Results, however, differed significantly between these 3 methods and a simple BFS (FM: 22kg, FFM: 50,0kg), which overestimated fat free mass and underestimated fat mass ($p<0,01$). With regard to changes in body composition over time, all 4 investigated methods yielded comparable results (FM $p=0,698$ resp. FFM $p=0,211$).
Conclusions: All investigated methods are suitable for follow-up checks in oncological patients when monitoring changes in body composition over time. This even applies for a simple body fat scale which, however, significantly overestimates FFM and underestimates FM in comparison to the other techniques. For the exact measurement of body composition NIR and BIA are rapid, safe, non-invasive and inexpensive techniques with valid and reliable results - ideal for routine body composition assessment.

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Physical Fitness and Body Composition in Breast Cancer Patients that Adhere to Different Nutritional Regimes

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Purpose: Breast cancer (BC) patients are often advised to adhere to a "healthy diet". However, this diet has not been defined yet. The aim of this study was to evaluate the effect of three different diets on physical fitness and body composition.
Methods: 152 BC patients could choose between 3 diets. They received intense training and advice during 3 wks of rehabilitation and were instructed to adhere to their diet for 20 weeks in total. Proportion of macronutrients in energy percent (fat/protein/carbohydrates) were: Ketogenic diet (KD) 80/16/4 (n = 29), Low-Carb diet (LC) 50/20/30 (n = 92) and western diet (WD) 30/15/55 (n = 31). Dual-Energy x-ray (DXA) and spiroergometry were performed at start (t0) and after 20 weeks (t20) to analyse body composition and physical fitness. Data were analyzed by non-parametric Kruskal-Wallis test or Mann-Whitney-U-Test.
Results: From t0 to t20 muscle/fat ratio increased [2.1/2.4 (KD), 1.6/1.77 (LC) ($p=0.02$) and 1.65/1.75 (WD)] and visceral fat decreased [10.0/7.9kg (KD), 14.3/12.6kg (LC) and 12.7/12.1 (WD)] in all diet groups. At t0, total fat was lowest with KD (21.8kg) ($p<0.001$) and the muscle/fat relation (2.3) was significantly higher than with LC (1.8) and WD (1.9). Subgroup analysis based on food questionnaires revealed, that 14/31 patients had used KD, 8/31 LC and only 7/31 WD before the study while 14/92 in the LC group hat used LC before and the 31/31 patients of the WD group started from WD.

With regard to physical fitness, both, Vo2/kg at VT2 (anaerobic threshold) [KD (+2.93), LC (+0.64) and WD (+0.48]) and Vo/kg Max [KD (+2.51), LC 1.43 and WD(+2,49)] increased between t0 and t20.
Conclusions: All 3 groups improved in body composition and physical fitness attesting the efficacy of the rehabilitation intervention. However, KD proved to be best for positive changes in muscle/fat ratio and physical fitness. One reason of this surprising result might be that ketone bodies may act as "super fuel" improving energy efficiency which is especially important in cancer patients.

The therapeutic potential of a KD as nutritional regime should be further evaluated.

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Phytotherapeutic Approaches for Treating Mucositis, Loss of Appetite, Xerostomia and Ageusia –An Analysis of Empirical Knowledge

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Purpose: Which empirical reports can be found regarding phytotherapeutics used traditionally to treat lack of appetite and dysphagia?
Methods: We screened 10 German books on phytotherapy for the following symptoms: mucositis/stomatitis/gingivitis, anorexia/loss of appetite, xerostomia and loss of taste. All traditional European herbs were included. Hits were registered on an Excel spreadsheet.
Results: We found 133 plants; 103 are recommended for treating oral mucositis, 75 for stimulating appetite, 10 for alleviating xerostomia and for stimulating taste. *Matricaria chamomilla* L., *Salvia officinalis* L. and the bark of *Quercus robur* L. are the most commonly mentioned herbs for treating mucositis. The following herbals were the most frequently recommended as stimulants of appetite: *Artemisia absinthium* L., *Centaurium* Hill and *Cichorium intybus* L.. *Zingiber officinale* Roscoe, *Gentiana lutea* L. und *Centaurium* Hill were mentioned several times as potent agents to alleviate xerostomia. *Gentiana lutea* L. might be also used to treat ageusia. *Gentiana lutea* L. is qualified to treat all four symptoms investigated; *Angelica archangelica* L., *Zingiber officinale* Roscoe, *Cuminum cyminum* L. and *Centaurium* Hill are recommended for treating three out these.
Conclusions: Here we summarize a canon of the 10 plants recommended by traditional (European) medicine.Clinical studies are required to investigate their therapeutic efficacy against mucositis, anorexia, xerostomia and ageusia.

Disclosure Statement: The authors declare no conflict of interest.

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Reduction of Severity of Chemotherapy-Induced Peripheral Neuropathy by Onlife: Final Results of the Breast Cancer Cohort of the Stefano Trial

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Purpose: Chemotherapy-induced peripheral neuropathy (CIPN) is a common and potentially dose-limiting side effect of neurotoxic chemotherapy, especially of platinum and taxanes, with a profound impact on patients (pts)' quality of life and survivorship. It is predominantly caused by sensory axon damage. There is no effective strategy to prevent or cure CIPN. OnLife®, a patented mixture of fatty acids (F.A.G.®) with the main component palmitoylethanolamide (PEA), is supposed to have anti-inflammatory, neuroprotective and antinociceptive properties.
Methods: STEFANO is an observational, prospective, two-cohort, multicenter study designed to evaluate the influence of OnLife® on existing CIPN in adult pts with colon or breast cancer after neo-/adjuvant chemotherapy (cohort A: colon cancer, oxaliplatin-based therapy; cohort B: breast cancer, paclitaxel therapy). Pts received OnLife® orally BID for 3 months. Neuropathy assessment before, during and after OnLife® intake included physical examination and neurophysiological testing, i.e. tendon reflexes, vibration sensitivity and CIPN grading according to CTCAE v4.03. The primary objective was the change in severity of CIPN (CTCAE v4.03) before and after 3 months of OnLife® intake. Secondary endpoints included Patient-reported outcomes (PROs; EORTC QLQ-C30, -CIPN20). Descriptive statistics were used to analyze data.
Results: In total, 74 breast cancer pts with paclitaxel-induced CIPN received OnLife®. According to CTCAE, after OnLife® intake 31% of pts had an improvement of sensory CIPN, 54% of pts experienced a stabilization, with no further worsening, 1% of pts had a deterioration and 14% of pts were not evaluable. In pts with grade 2/3 sensory CIPN (n=58), 36% had an improvement, 50% a stabilization and no deterioration occurred. According to PROs, 45% of pts had less symptoms and functional limitations related to sensory CIPN after OnLife® intake.
Conclusions: OnLife® may reduce the severity of existing CIPN in breast cancer pts treated with paclitaxel and thus appears to be a promising treatment option for CIPN.

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Administration of Pegfilgrastim Prophylaxis Via Pre-Filled Syringe (Neulasta®) or On-Body Injector (OBI): Interim Results on Patient Preference and Health Economics from the Convenience Study

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Purpose: The effectiveness of granulocyte colony-stimulating factors (G-CSFs) like pegfilgrastim depends on the optimal timing, recommended ≥24 h after chemotherapy (CTx) according to SmPC and guidelines. Return visits to the medical office for pegfilgrastim administration, however, may be burdensome and cause additional expenditure of time and costs for both, patients and medical staff.

The pegfilgrastim On-body injector (OBI) is a small injector automatically delivering a subcutaneous pegfilgrastim dose after 27 h without need of return visit to the medical office. Therewith the OBI has the potential to optimize pegfilgrastim prophylaxis. The CONVENIENCE study aims to evaluate patient's preference and health economics for pegfilgrastim administration via OBI versus pre-filled syringe (PS) in real-world in Germany.
Methods: In this randomized, multicenter study (partially funded by AMGEN GmbH) 400 patients with early breast cancer receiving 2 or 3 weekly anthracycline/cyclophosphamide or 3 weekly taxane-based CTx or patients with Non-Hodgkin lymphoma receiving 1st-line R-CHOP-14 or-21 will be enrolled at 50 sites in Germany. Patients are observed for 4 CTx cycles supported with pegfilgrastim OBI or PS in an alternating sequence with 1:1 randomization of the application form to start with. Patient's preference and influence of pegfilgrastim administration on daily life and cost factors will be evaluated using patient surveys.
Results: For this prespecified interim analysis, 200 patients were randomized between 06/2018 and 01/2019. Data on patient characteristics, time interval between CTx and pegfilgrastim administration, patient's preference before and after study including reasons for decision and influence of the different application forms on daily life (daily routine, social life, time restriction) and health economics will be presented.
Conclusions: The results of the interim analysis demonstrate the feasibility, effectiveness and convenience of administering pegfilgrastim via OBI.

Reference:

1. Metz M et al, DGHO 2019, P944.

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Motivation for an Active Lifestyle (Motiva) – Pilot Study of a Behavior-Change Module in Exercise Programs for Cancer Survivors

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Purpose: Physical Activity (PA) is associated with many benefits for cancer survivors (CS).[1] However, research has shown insufficient levels of PA for CS. Rehabilitation sport groups (RSG) are a common way to deliver exercise interventions to CS in Germany but measures to increase sustainability of PA after the end of RSG are still lacking. Therefore, the National Center for Tumor Diseases (NCT)/UCC Dresden and the NCT Heidelberg developed a behavior-change program (MotivA) as additional module for existing RSG.
Methods: MotivA teaches behavior-change-techniques (e.g. action-planning and coping) based on the Health Action Process Approach. MotivA is an additional module that can be used in CS groups. A project kit free of charge consists of a manual for trainers (incl. a CD with 7 audio-inputs) and a workbook for CS. A pilot-study with a pre-post-3 month-follow-up (FU) design without control group investigates the effects of MotivA on subjective PA, motivational determinants of PA and program acceptance with 29 participants.
Results: 76% of the participants were pleased with the additional behavior-change module being part of the exercise program. At baseline, 62% of the participating patients reported insufficient PA. Motivational barriers as 'Can't pick myself up' (47%), 'Not in the mood' (33%) and 'Comfortable at home' (33%) and 'Bad weather' (32%), were most frequent. Pre-post differences show a significant increase in subjective reported PA levels ($p < .01$, $r = .61$) and a significant decrease of motivational barriers ($p < .01$, $r = .49$). The effects in increased subjective PA and reduced motivational barriers remained stable at 3 months-FU.
Conclusions: The results of this pilot-study are promising that MotivA can support CS in developing a more active lifestyle. MotivA can be easily disseminated and integrated in any exercise program for CS.

Reference:

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Disclosure Statement: No conflicts of interest.

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Defining Criteria for Guiding Cancer Patients to Find a Reputable Complementary Medicine Provider: Results of a Mixed-Methods Study

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Purpose: Approximately half of cancer patients use complementary medicine(CM) during their cancer treatment[1]. However, even in cases of positive evidence for CM therapies [2], it is still difficult for cancer patients to identify reputable CM providers on their own. The aim of this study was to develop and evaluate a criteria list to provide guidance to cancer patients seeking a reputable CM provider.
Methods: In this mixed-methods study, results of a systematic literature review, a multi-level expert consensus procedure (n=15) and a practice evaluation from three relevant stakeholder perspectives (cancer patients (n=18), CM providers (n=26) and oncology physicians (n=20)) were combined.
Results: A total of 30 CM criteria were extracted from the literature, and 12 more were added by the experts. All criteria were assigned in their importance for cancer patients to find reputable providers, oncology physicians to establish a CM provider network and registers for quality assurance in nonmedical CM providers. A final comprehensive list of 8 criteria guiding cancer patients to find a reputable CM provider was developed in the form of a leaflet.
Conclusions: Health professionals and cancer information services might find the criteria list helpful when aiming to strengthen patients' awareness of quality-related factors associated with nonmedical CM providers. The criteria developed might support the development of standards for quality assurance in CM in oncology.

References:

1. Horneber, M., et al., *How many cancer patients use complementary and alternative medicine: a systematic review and metaanalysis.* Integr Cancer Ther, 2012. **11**(3): p. 187-203.
2. Lyman, G.H., et al., *Integrative Therapies During and After Breast Cancer Treatment: ASCO Endorsement of the SIO Clinical Practice Guideline.* J Clin Oncol, 2018. **36**(25): p. 2647-2655.

Disclosure Statement: We declare no competing interests. This project is part of the collaborative research project KOKON supported by the German Cancer Aid [grant number 109863].

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An Interdisciplinary Outpatient Clinic for Patients with Neurological Sequelae of Cancer Therapies – Results of a Pilot Project at the University Hospital of Bonn

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Purpose: Most patients with cancer experience adverse events after oncological treatment. Neurological sequelae are among the most important challenges in patient survivorship, including but not limited to muscle weakness, neuropathic pain, gait disorders and cognitive impairment, which often have a significant impact on activities of daily life. To improve diagnosis and treatment of these side effects, we started a pilot project for cancer patients with neurological symptoms.
Methods: A consultation service for cancer patients was on a trial basis implemented at the Division of Clinical Neurooncology. Consultations were requested via the clinical workstation used at a tertiary universitary medical center. Necessary information was a short description of symptoms, the assumed diagnosis and the priority in time. Contact was also possible by phone call of selected collaborators. Our experience of the pilot project was analysed in a descriptive manner.
Results: Between October 2018 and July 2019, a total of 42 patients with 65 visits were evaluable. The most frequent question was differentiation between chronic graft-versus-host-disease and neuropathy or myopathy (40,5%). The leading neurological diagnosis was peripheral neuropathy (42,9%). In 76,2% of the cases the neurological consultation led to additional examinations and in 71,4% of the cases the consultation had therapeutic implications. Usage of antiepileptic drugs or antidepressants to modify neuropathic pain was recommended in 16,7% of the cases. 17 patients had at least one follow up visit within the reported period. Successful treatment with improvement of symptoms was shown in 35,3% of patients with follow-up visits.
Conclusions: There seems to be a formerly unmet demand of neurological consultation service in neurological sequelae of cancer therapies that can be supplied by a specialized outpatient clinic. Building on the experience of this pilot project, a special outpatient clinic will now be permanently established at our Division of Clinical Neurooncology.

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Onkoaktiv-Network Evaluation: A Patient's Perspective

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Purpose: More than 700 RCTs have shown significant positive effects of exercise interventions for cancer patients and survivors; as well as clinical relevant decreases in mortality rates through exercise behavior [1]. However, there is no comprehensive provision of exercise therapy in the German medical system. Therefore, OnkoAktiv follows the idea of building a network, consisting of exercise professionals, training- and cancer treatment centers, to connect patients with quality assessed and certified exercise offers. The purpose of the project was to evaluate the work of OnkoAktiv from a patient's perspective.
Methods: Patients are recruited through OnkoAktiv at the National Center for Tumor Diseases in Heidelberg. Evaluation consists of three assessment time points (Q1: patient´s first consultation, Q2: completed connection to training facility, Q3: 8 weeks of exercise therapy) measuring QoL, self- efficacy, volume of exercise, satisfaction, structure and process quality parameters of the OnkoAktiv service and supervision by exercise professionals.
Preliminary Results: By now, 71 of 86 patients with an average age of 56 years (SD=11.52) are enrolled, of which 59 already completed Q1 and 25 Q3. The distribution presents 26 patients with breast-, 19 with prostate- and 20 with other cancer types. The mean time for patient´s placement in an exercise facility was 38 days, serving 37 different exercise facilities within the Rhein-Neckar-Region. 35 out of 55 participants already reported high satisfaction in rating the OnkoAktiv service; however training volume seems to be demanding during treatment and needs to be adjusted on a day to day basis. 14 patients dropped out after enrolment. Recruitment will be completed in Oct 2019, data analysis will be finalized Dec 2019.
Conclusions: This study is the starting point of the OnkoAktiv-network evaluation for further research in the field of oncological exercise therapy.

Reference:

1. Christensen et al. (2018): Exercise Training in Cancer Control and Treatment. In: *Comprehensive Physiology* 9 (1), S. 165–205.

Disclosure Statement: None

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Effects of Physical Activity on Sexual Dysfunction in Urooncological Patients – A Systematic Review

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Purpose: Many therapies performed as part of cancer treatment cause sexual dysfunction as a side effect, which can occur, for example, as impotence (up to 57%) and impaired sexual desire (up to 78%). Data show that a higher activity level in urooncological cancer patients is associated with better sexual health. This systematic review aimed at demonstrating the efficacy of exercise interventions for sexual dysfunction in urooncological patients.
Methods: A systematic data search was performed in PubMed in May 2019. In addition, the reference lists of individual publications were screened. The review was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.
Results: The current status of the paper may change until the Congress in February 2020. The systematic review currently includes 24 studies (16 RCTs, 1 non-RCT, 4 single-arm trials, 1 interview, 1 case report, 1 case series) involving approximately 1605 cancer patients. The studies involved prostate cancer (20), endometrial cancer (1), cervical cancer (1), gynaecological cancer (1), gynaecological and other cancers (1). The exercise interventions were performed individually or in combination with other interventions such as electrostimulation, nutrition or cognitive training. For prostate cancer, erectile and sexual function, potency, and libido improve (partly significantly) by performing pelvic floor muscle exercise (PFME), resistance and aerobic exercise, yoga and penile vibratory stimulation compared to control group. For women, PFME, Pilates, resistance and aerobic exercise show (partly significantly) positive effects on sexual activity and sexual function.
Conclusions: The first set of data shows positive effects of exercise interventions on urooncological patients. This requires further studies.

Reference:

with the main author

Disclosure Statement: There are no conflicts of interest.

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Patient Information, Communication and Competence Empowerment in Oncology (PIKKO) – A Supportive Care Intervention for Oncological Patients

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Purpose: In German healthcare, cancer patients are faced with confusing care structures and an inadequate integration of psychosocial and informative support services. For this reason, a new care concept, called PIKKO, is tested in the Saarland.

PIKKO is a collaborative project which is funded by the Innovation Fund. Consortium partners are German Cancer Society, Cancer Society of the Saarland, University Hospital Jena, IKK Südwest, Techniker Krankenkasse (TK), and Knappschaft.

Methods: Core elements of PIKKO are patient navigators, which accompany cancer patients on their way through their therapy. In addition, patients can access quality-assured information at any time via an exclusively created oncological knowledge database and can take advantage of specialized psychosocial counselling services.

All cancer types were included. Patients were either assigned to a control group (usual care) or intervention group (usual care + PIKKO). We used patient surveys to evaluate all patient related outcomes. Health care costs were analyzed with data from participating statutory health insurances.

Results: Main goal is to empower patients to deal with their disease in a well-informed and autonomous manner. In measurable terms, PIKKO should lead to a better quality of life, self-efficacy, health literacy and satisfaction with healthcare. At the same time there should be a reduction of psychological stress and costs of care.

Overall 15 patient navigators were deployed. Recruitment of patients for the control group is completed. The intervention group is recruiting until March 2020.

Conclusions: PIKKO is intended to become a well-established and benefit assessed program which improves care of all cancer patients in Germany.

Disclosure Statement: No competing interests.

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Safety and Effectiveness of Sensor-Controlled Scalp Cooling to Prevent Chemotherapy-Induced Alopecia in Patients with Ovarian and Other Female Genital Tract Cancers

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Purpose: In prospective clinical trials, sensor-controlled scalp cooling (SCSC) has been found to effectively reduce the risk of CIA in patients (pts) exposed to Ctx for early breast cancer. However, data on SCSC in pts with female genital tract cancer are largely lacking.

Methods: 44 pts with various female genital tract cancers who underwent SCSC alongside to CIA-inducing Ctx were included. 35 pts had epithelial ovarian and related carcinomas (79.5%), the remainder (20.5%) had various other malignancies, mainly cervical cancer. 18 pts (40.9%) were treated in a curative intent, 26 pts (59.1%) received palliative Ctx. 24 pts (54.5%) had been previously exposed to Ctx. Pts were subjected to SCSC during each Ctx cycle. CIA was quantified according to the Dean score (DS) 3 wks after the last Ctx cycle. Data were analyzed regarding feasibility indicated by the SCSC completion rate, quality of hair preservation (success: DS 0-2, failure: DS 3-4), reasons of SCSC discontinuation, and safety.

Results: 31 pts (70.5%) completed SCSC. The reasons for discontinuation were CIA in 10 (22.7%) and adverse effects in only 3 (6.8%) pts. All side effects, which did not exceed CTCAE grade 2, quickly resolved after cessation of SCSC. 24 pts (54.5%) experienced complete (DS 0) and 8 pts (18.2%) had incomplete hair preservation (DS 1-2). Three pts had DS 3 (6.8%), and further 9 pts (20.5%) had DS 4. Thus, the overall success rate of SCSC was 72.7%.

Conclusions: SCSC is safe and active in order to prevent CIA in pts with female tract malignancies. Our results are particularly impressive, since this study represent a more intensively pretreated population as enclosed in most breast cancer studies.

Disclosure Statement: All authors declare that no conflicts of interest have to be claimed.

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Feasibility and Satisfaction of Young Cancer Survivors Participating in Preventive Interventions. A Subgroup Analysis of the Care for CAYA Program (CFC-P)

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Purpose: Children, Adolescents and Young Adult Cancer Survivors (CAYA) are at in- creased risk for treatment- or disease-related late and long-term sequelae. Follow up of large cohorts provided associations between e.g. physical activity and cardiovascular morbidity. Despite these data, the feasibility, adherence and efficacy of specific interventions e.g. for lifestyle modification in this patient group is unclear.

Methods: The CfC-P comprehensively assesses potential future problems and offers dedicated preventive interventions in nutritional behavior, physical activity and psycho-oncology (five individual coaching sessions). CfC-P runs in 14 centers in Germany and is supported by a research grant from the Federal Joint Committee. Overall 1500 CAYA survivors are planned to be included. Measures include questionnaires at baseline

(T1) and follow-ups after 16 (T2) and 52 weeks (T3). The patient reported outcome measures for *satisfaction* was derived from the ZUF-8 questionnaire. This preliminary analysis provides patient reported data at T2 for the subgroup of patients in Hamburg.
Results: So far about 500 survivors have been recruited in the CfC-P since 12/2017. 127 CAYAs (57.5% female (n = 73)) of all cancer entities (28.2% lymphoma, 26.6% carcinoma, 21.8% leukemia, 12.9% sarcoma, 10.5% other) from Hamburg were included in this analysis. Mean age was 25.9 ± 6.3 years. About half of the included patients (59 of 127) already completed the T2-questionnaire. ZUF-8 questionnaire imply that 90.8% of all participants rate the intervention with a high or excellent quality and 90.6% are mostly satisfied or satisfied with the program. Updated data on satisfaction and adherence will be presented at the meeting.
Conclusions: The interventions within the CfC-P are feasible and participants report a high degree of satisfaction. Further analyses are required to confirm these preliminary results.

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Health Problems and Quality of Life of Young Cancer Survivors in the Comprehensive Care for CAYA Program

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Purpose: Children, Adolescents and Young Adults Cancer Survivors (CAYA) are at in- creased risk for treatment- or disease-related late and long-term sequelae. Assessing the individual health problems, quality of life and unmet needs in regular intervals and determin- ing potential preventive interventions is of utmost importance to improve long-term outcomes in this particular vulnerable population.
Methods: The Federal Joint Committee funded CfC-P comprehensively assesses potential future problems and offers need based preventive interventions (nutritional behavior, physi- cal activity and psycho-oncology). Comprehensive questionnaires compiled of different vali- dated questionnaires are conducted every 12 months in the CfC-P. The patient reported out- come measures for *health* was the EQ5D-L questionnaire, for self reported *health problems* the NCCN Distress Thermometer and Problem List, for *need for support* the SCNS-TF-9, and for *quality of life* (QoL) the EORTC QLQ-C30. This preliminary analysis provides patient re- ported data for the subgroup of patients in Hamburg and Lübeck at T1.
Results: 172 CAYAs (59.9% female (n = 103); n = 127 in Hamburg, n = 45 in Lübeck) from the CfC-P were included in this analysis. They are of all cancer entities (29.6% lymphoma, 21.9% carcinoma, 21.9% leukemia, 12.4% sarcoma, 14.2% other). Mean age was 25.7 ± 6.9 years. All participants completed T1-questionnaire. 21.5% reported not or slight problems regarding anxiety and depression, 20.9% reported no or slight pain or discomfort, 15.8% reported no or slight problems in usual activities, 8.2% reported no or slight mobility problems, 1.3% reported no or slight problems in self-care. The mean health status (EQ5-D- VAS) was 75.91 out of 100 (SD = 18.9). The most important health problems were worries (60%), fatigue (50.3%), pain (48.1%), fears (42.6%) and sleep (42.3%). Further data will be presented at the congress.
Conclusions: CAYAs have a large variety of health problems, unmet needs and QoL issues.

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Sceletal Muscle Hypertrophy in Cancer Patients and Survivors: A Meta Analysis

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Purpose: Depending on cancer site 14 to 80% of patients show significant loss of muscle mass (Sarcopenia), caused by physiological factors associated with the disease, its therapy and lifestyle changes[1]. Sarcopenia is known to have a negative impact on treatment toxicity, the patients' physical function[1] and their prognosis[2]. A promising approach to prevent this loss of muscle mass is the utilization of resistance training. A meta-analysis was conducted to verify this effect.
Methods: A systematic literature search was conducted in Pubmed, Cochrane Library, SportDiscus and CINAHL. Randomized controlled exercise trials where eligible if lean body mass or muscle mass were assessed. Primary outcome was post-test muscle mass. The model was adjusted for baseline group differences. Additionally, impact of supervision, therapy status, and training parameters were investigated. Model fit was evaluated via several information criteria.
Results: We included 31 studies into the primary analysis. Participants of the intervention group
showed a pooled increase in muscle mass of 0.83 kg (95%CI: 0.26, 1.39) compared to their controls. The effect was even larger when only supervised interventions were anaylsed (pooled mass increase of 1.20kg (0.17, 2.23)). After adjusting for supervision the main effect was almost vanished (0.25; 95%CI: -0,43, 0.92). Other predictors were lacked explanatory power.
Conclusions: Resistance training can help cancer patients and survivors to fight sarcopenia. However, analysis revealed that interventions need to be supervised in order to gain significant effects on muscle mass.

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Disclosure Statement: The authors have no conflicts of interest that relate to this abstract.

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Safety and Feasibility of Paravertebral Muscle Training in Patients with Unstable Spinal Metastases Undergoing Palliative Radiotherapy

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Purpose: Cancer patients with unstable spinal metastases have so far been excluded from exercise due to fear of fractures. Because a previous study in patients with stable spinal metastases found positive training effects (1), safety and feasibility of paravertebral muscle training was investigated in patients with unstable spinal metastases in an exploratory RCT (2).
Methods: Sixty cancer patients with spinal metastases (Taneichi score ≥D) scheduled for radiotherapy were randomized to an intervention group (INT, n=27 starters) or a control group (CON, n=29 starters). INT underwent isometric paravertebral muscle training daily during 10±2 days of radiotherapy and continued home-based on 3 days/week for 3 months. CON received muscle relaxation. Adverse events and adherence (primary endpoints), strength, pain and QoL (secondary endpoints) were assessed.
Results: There were no training-related adverse events. During radiotherapy, 67% of patients in INT and 55% of patients in CON attended ≥80% of the planned training sessions. Plank position holding time (strength) increased by 24±28 s in INT and dropped by 2±34 s in CON by the end of radiotherapy (p=0.01). During home-based training, 64% of patients performed ≥80% of the planned training sessions. There were no differences between groups for pain or QoL (p>0.05).
Conclusions: Isometric training of the paravertebral muscles is safe and in about 2/3 of cancer patients with unstable spinal metastases feasible. Now, larger studies powered for clinical endpoints should be conducted and the training program can be recommended to patients interested in physical training.

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Disclosure Statement: No conflict of interest.

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Treating CIPN with Complementary Nursing Procedures – Recommendations Developed with a Process of Consensus Finding and a Systematic Literature Review

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Purpose: Chemotherapy-induced peripheral neuropathy (CIPN) is a common symptom in cancer patients with prevalence rates ranging up to 85%. Symptom management strategies are highly relevant, because CIPN influences patients' quality of life, and prevails even after completion of primary treatment. The aim of the current project was to make recommendations for preventing or treating CIPN with non-pharmacological complementary nursing treatments.
Methods: The mixed methods approach included, first, a structured expert consensus process (workshop and further written rounds) for discussing and presenting nursing applications for CIPN. Each application was evaluated regarding 5 essential domains: safety, clinical expertise, effort of training, practical feasibility, research evidence. Then a systematic literature review was conducted within the databases MEDLINE, Cochrane Central, CINAHL, PsycINFO, and PEDro.
Results: The expert panel consisted of 16 participants with a naturopathic background with experience in cancer treatment and care, representing 6 different institutions. In total, 6 interventions were discussed and agreed upon, i.a., flaxseed bath or tactile stimulation strategies (e.g., beeswax dispersing, rap bath), for preventing CIPN. Overall 14 interventions were discussed and consented for treating CIPN, i.a., embrocations with Aconit or Arnica oil. All interventions were judged as safe and very feasible in daily patient care. The extent of the clinical expertise has been consented by evaluating the perceived effect of the mean of all treated patients, represented on a scale from 0=no effect until 5=maximum effect. In total, 9 interventions have been consented as ≥3. The literature review confirmed the effects only for a few of these interventions, as the research evidence is rather scarce in this supportive care area.
Conclusions: Complementary nursing applications might have the potential to prevent or treat CIPN in patients affected by cancer. More research, clarification, and education in this field is highly warranted.

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Social Service Counseling in German Breast Cancer Centers: What does Account for Differences in the Utilization?

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Purpose: Cancer patients often face enormous economic and social challenges. For this reason, it is compulsory for cancer centers certified by the German Cancer Society to offer social service counseling (SSC) to every patient. It turns out, however, that the utilization of SSC varies between breast cancer centers. This analysis addresses the question to what extent SSC rates vary across German breast cancer centers and whether patient characteristics account for these differences.
Methods: A multilevel analysis has been performed including 16,217 breast cancer patients nested in 13 German certified breast cancer centers. Data were collected within the project "OncoBox Research" between 2014 and 2019. Data analysis was performed with STATA 15.
Results: The intra-class correlation (ICC) for the null model (ICC=0.31) indicates that 31% of the utilization of SSC depends on the center. Patients older than 84 years use SSC significantly to a lesser degree than patients in the reference group (45-64 years), patients between 25- and 44-years old use SSC marginally to a lesser degree than patients in the reference group; no significant effects were found for other age groups. Metastasized patients use SSC to a higher extent than patients without metastases. Patients receiving surgery with a recommendation for chemotherapy utilize SSC to a higher degree than patients receiving surgery without recommendation for chemotherapy (reference group). Patients that did not undergo surgery utilize SSC to a lesser degree than patients receiving surgery without recommendation for chemotherapy. SSC utilization is higher the later the patients were diagnosed between 2014 and 2019.
Conclusions: The analysis confirms that utilization of SSC varies between breast cancer centers. Disease severity is associated with higher use of SSC. Above, age and therapy type are predictors for SSC utilization. Further subgroup analyses regarding therapy types will be available at the congress. Cohort effects indicate a better adaption of certification requirements over time in the centers.

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Demand for Integrative Medicine Among Women with Breast and Gynecological Cancer - A Multicenter Cross-Sectional Study in South and North Germany

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Purpose: The aim of this multicenter cross-sectional study is to analyze a cohort of breast cancer (BC) and gynecological cancer (GC) patients with regard to their interest in, perspectives on and demand for integrative therapeutic health approaches including integrative therapies.
Methods: Cancer patients with the diagnosis of BC or any other GC were surveyed at their first attendance of a specialized integrative outpatient clinic at two university medical centers in Germany. Data were collected through a validated standardized questionnaire. Treatment goals regarding integrative medicine (IM) were evaluated and differences between BC- and Ovarian cancer (OC) patients were elucidated.
Results: A total of 340 patients entered into the study. In total, 95.3% patients claimed to be interested in IM. Interest in IM correlated with older age, recent chemotherapy, higher education and advanced disease at time of enrolment without reaching statistical significance. A total of 89.8% in the BCG and 88.9.1% in the OCG used any integrative method at time of enrolment. The methods mostly used were exercise therapy and vitamin supplementation. The major short-term goal of the BCG was reduction of side effects of the conventional therapy, the major long-term goal slowing of tumor progression. In the OCG major short- and long-term goals were slowing tumor progression and prolonging survival time. When analyzing side effects, patients in the OCG are more impaired than those in the BCG, reaching statistical significance in the category pain (p=0.001), obstipation (<0.001), and depressive symptoms (p=0.005).
Conclusions: Our data demonstrates a high overall interest and frequent use of IM in BC and OC patients. This supports a strong demand of both patient groups for specialized counseling in IM and implementation of integrative treatments concomitant to conventional oncological treatment regimes. Primary tumor site, cancer diagnosis and side effects have a relevant impact on patients` perception and opinions about IM.

Disclosure Statement: No conflict of interest.

Surgical Oncology

Poster

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Resection of the Primary Tumors Prolonged the Overall and Progression Free Survival in Patients with Neuroendocrine Neoplasms Stage IV Treated by Peptide Radionuclide Therapy (PRRT)

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Purpose: To evaluate the benefit of a primary tumor (PT) resection after a treatment with peptide radionuclide therapy (PRRT) in patients with a metastasized neuroendocrine neoplasms stage IV.
Methods: Retrospectivly, we analyzed prospective data of 889 patients with advanced NEN (G1-3) in stage IV treated with PRRT (at least 1 cycle). PT was removed in 486 / 889 patients (group 1) and group 2 enfolded 403 / 889 patients without a PT resection before PRRT. Progression-free survival (PFS) and overall-survival (OS) was determined by 68Ga-SSTR-PET/CT applying RECIST and EORTC.
Results: The majority of patients had their primary in pancreas (n = 335) and small intestine (n = 284). Group 1 and 2 were treated with a mean of 4 cycles of PRRT (p = 0.835) with a mean cumulative radioactivity of 21.6 ± 11.7 and 22.2 ± 11.2 GBq (p = 0.407). Median OS was 134.0 (CI: 118 – 147 group 1) vs. 67.0 months (CI: 60 – 80 group 2; HR 2.79; p < 0.001). Median PFS was 18.0 (CI: 15 – 20 group 1) vs. 14.0 months (CI: 15 – 18 group 2; HR 1.21; p = 0.012).
Conclusions: Prior to PRRT PT resection in pancreatic and small intestine neuroendocrine neoplasms stage IV resulted in a prolonged PFS and OS.

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Disclosure Statement: Kaemmerer received travel support by the companies Ipsen, Pfizer, Novartis. Lecture fee: company Ipsen.

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Laparoscopic Salvage Resection for Patients with Disease Progression After Transarterial Chemoembolization: A New Treatment Algorithm in Primary Liver Cancer?

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Purpose: Primary liver cancer patients with disease progression after transarterial chemoemboliztion (TACE) have traditionally been considered candidates for palliative systemic treatment or best supportive care only. We herein report a clinical series of patients with progressive disease following TACE who underwent minimally-invasive salvage hepatic resection (HR) based on multidisciplinary board decision.
Methods: A retrospective review of patients who underwent salvage HR following non-responding TACE between 2018 and 2019 was performed. Clinicopathological outcomes were collected and presented as medians and ranges.
Results: A total of seven patients (five males, two females) received a median of 4 (1-5) TACE treatments with a median dose of 55mg (15-90mg) epirubicin. Laparoscopic HR was performed at a median of 55 days (14-147 days) after the last TACE session. Conversion to a mini laparotomy was required in 1 patient. Apart from a superficial surgical site infection in 1 patient no further postoperative complications were observed. Histopathological examination revealed cholangiocarcinoma (CCC) on final diagnosis in 2 patients. The R0 resection rate was 86%. Median postoperative length of hospital stay was 5 days (4-12 days). After a median follow-up of 60 days (14-125 days) no patient had recurrent disease.
Conclusions: Laparoscopic HR is safe and enables salvage treatment in patients with primary liver tumors and disease progression after TACE. Further studies are needed to evaluate the long-term outcomes of this novel treatment approach.

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Disclosure Statement: None of the authors have any conflicts or financial support to disclose.

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Altered Diversity and Composition of the Microbiome in Patients with Primary Untreated Colorectal Cancer

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Purpose: Recently, the gut microbiome has been associated with tumor development and progression and several authors have tried to link certain bacterial species to the colorectal cancer. The aim of the EMA-CRC study (Erlanger microbiome analysis colorectal cancer) is to characterize the microbiome profile of matched stool, tumor and mucosa samples from the proximal and distal resection margin. Furthermore we want to assess the effect of surgery and neoadjuvant therapy (e.g. chemo/ radiochemotherapy) on the gut microbiome.
Methods: Since 12/2018 we included 80 patients with previously untreated CRC in the study. Microbiota profiles were characterized by amplification of the V3/V4 region of the 16SrRNA gene and deep sequencing using the Illumina MiSeq platform. Stool samples were collected preoperatively, or prior to the beginning of neoadjuvant therapy, 4 weeks after ending of neoadjuvant therapy and postoperative. Intraoperatively, tumor tissue samples and mucosa samples from healthy regions were obtained.
Results: To date (study still recruiting), 67 stool samples were analysed. For colon cancer alpha and beta diversity of the stool samples were significantly different compared preoperative versus postoperative (for rectal cancer similar results were observed). Compared with preoperative samples, the postoperatively collected samples exhibited a significant increase of potentially pathogenic bacteria such as Escherichia Shigella, Veillonella, Clostridia and interestingly Fusobacterium. The butyrate producing bacteria Alistipes was identified in the preoperative stool samples.
Conclusions: Surgery exert an effect on the gut microbiome of CRC patients. Due to the potentially modifiable nature of gut bacteria a better understanding of the microbiome in colorectal cancer may lead to a microbiota based intervention (e.g. probiotics, prebiotics or antibiotics) during pre/postoperative management.

Disclosure Statement: No disclosures.

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Early Onset Colorectal Liver Metastases – The More Aggressive Disease?

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Purpose: Patients with early onset colorectal cancer (CRC) are well known to show different demographic, pathologic and clinical patterns compared to patients with late onset disease (LOD) 1, 2. However, colorectal liver metastases (CRLM) of patients with early onset disease (EOD) are not well examined.
Methods: Patients who underwent resection for colorectal liver metastases at the University Medical Center between 2015 and 2018 were included and evaluated regarding short and long term outcome. Patients who were diagnosed with CRC at the age of 45 or younger were defined as early onset.
Results: In total, 194 patients could be identified with EOD being present in 21 patients (11%). Patients with EOD were more often female compared to patients with LOD (p=0.005). While histopathologic features and mutation status (KRAS, BRAF, MSI) were comparable between the two groups, there was a trend for a more aggressive surgical strategy in patients with EOD (simultaneous resection of extrahepatic disease/HIPEC p=0.058; ALPPS procedure p=0.098). Although the proportion of patients who received systemic treatment (neoadjuvant p=0.703; adjuvant=0.919) was similar between the groups, EGF-R antibodies combined with neoadjuvant chemotherapy were more commonly used in the group of patients with EOD (p=0.05). Recurrence-free survival (RFS; p=0.611), liver-specific RFS and overall survival did not differ between patients with EOD and LOD.
Conclusions: Although patients with EOD may require a more aggressive surgical and oncological treatment, survival was comparable between patients with EOD and LOD.

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Disclosure Statement: None of the authors have anything to disclose.

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Associated Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) for Cholangiocarcinoma. Is the Risk Worth Taking? Single Centre Experience with 21 Right Trisectionectomies and Long Term Oncological Results

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Purpose: Bile duct cancer (CCA) remains a major challenge among liver tumors and surgery remains the only curative option, whereas a radical resection is possible, with a 1, 3 and 5 years-survival for iCCA of 80-86%, 50-60% and 15-40% and for phCCA of 70-80%, 27-42% and 13-40%. ALPPS could expand the rection possibilities also in patients with a small future liver remant. However, due to the high morbidity and mortality CCA is often considered a relative contraindication to ALPPS. The purpose of this study is to analyze the long-term outcome of patients that underwent ALPPS for cholangiocarcinoma.
Methods: We retrospectively analyzed our single center experience on the use of ALPPS for Cholangiocarcinoma focusing on postoperative outcome, patient survival and tumor recurrence.
Results: Between November 2010 and January 2019 we performed 53 ALPPS, of them 21 ALPPS for suspected cholangiocarcinoma (10 perihilar (phCCA) and 11 intrahepatic (iCCA)) with a feasibility of 100%. Median age was 70,3 and 68,3 years, respectively. BDA was performed in all phCCA and 8 iCCA. A R0 status was reached in 15 patients (6 phCCA, 9 iCCA). Severe Morbidity (≥IIIb according Dindo-Clavien) was 60% for phCCA and 45% for iCCA. The postoperative mortality rate was 20% for phCCA and 18% for iCCA. Overall mortality after recurrence was observed in 1 patient with phCCA (12,5%) and 4 patients with iCCA (44%). A tumor recurrence was observed in 1 patient with phCCA (12,5%) and 7 patients with iCCA (78%). Median disease free survival time was 29,5 months for the phCCA and 3,9 months (1-20,5) for iCCA. 1-, 3- and 5- year cumulative survival were respectively 80%, 80% and 60% for phCCA, 64%, 53% and 40% for iCCA.
Conclusions: Despite a high morbidity, with a precise patient selection mortality can be avoided and ALPPS can be used for cholangiocarcinoma, particularly in phCCA, to expand the pool of resectable patients, that otherwise have no therapeutical possibility and poor outcome.

Disclosure Statement: I have nothing to disclose.

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Robotic-Assisted Resection of Primary Hepatic Tumours and Hepatic Metastasis Using Isocyanine Green

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Purpose: Isocyanine green (ICG) is a fluorescent dye, which accumulates in degenerated hepatic cells. ICG-accumulation becomes visible using near infrared light and may help to differentiate degenerated from normal tissue. This study aimed to test the feasibility of preoperative iv-ICG-application for different types of tumours and real-time visualisation during robotic assisted primary and metastatic liver resections.
Methods: Patients who were planned for a robotic assisted resection of hepatic tumours or metastasis received 25 mg iv-ICG (Diagnostic Green GmbH, Germany) the evening before surgery. All procedures were performed using the DaVinci®-Xi robotic system with the included near infrared light FireFlyTM®.
Results: Between February and August 2019, 13 consecutive patients were included. Nine patients presented with hepatic metastases of mamma, colon, choroid coat and esophageal carcinomas. ICG-accumulation helped to locate metastases more precisely and perform tissue sparing resections usingDaVinci®-Xi in most cases. Interestingly, ICG accumulated in the metastasis of an esophageal carcinoma which was hence resected. Interestingly, there was no vital tumour tissue in the pathological analysis. Metastases of a choroid coat melanoma only showed ICG-accumulation halo-like at the outer rim of the metastases. Four patients had primary hepatic tumours. In patients suffering from liver cirrhosis, ICG accumulated ubiquitously in the cirrhotic tissue and did not help to differentiate tumour from normal liver tissue.
Conclusions: Preoperative iv-ICG-application can help to perform DaVinci®-assisted resection of primary and metastatic hepatic lesions. However, the performing surgeon should not only rely on non-quantitative ICG-colouring as cirrhotic tissue and other entities showed too much ICG-uptake. Preoperative imaging and intraoperative ultrasound are still mandatory for pre- and intraoperative planning. At the moment, ICG serves as an additional tool. With future improvements of dyes and devices more tailored approaches may be possible.

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Early Onset Colorectal Cancer with Liver Metastases – Low Incidence of High-Risk Features but Early Recurrence

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Purpose: The incidence of colorectal cancer (CRC) is increasing among younger patients 1,2. However, little is known about features of colorectal liver metastases (CRLM) in patients with early onset disease.
Methods: Patients who were diagnosed with colorectal cancer at the age of 45 or younger and underwent resection of CRLM at the University Medical Center Freiburg between 2008 and 2018 were included and evaluated regarding short and long term outcomes.
Results: Among 578 patients undergoing liver resection for CRLM, 44 (7.6%) were identified with early onset disease. This proportion increased over time (2008-2011: 5.2%, 2012-2014: 7.1%, 2015-2018: 10.8%). In 89% CRC was of sporadic origin, only 3 patients were diagnosed with FAP and 1 patient had a chronic inflammatory bowel disease. Although high-risk mutations such as KRAS and BRAF occurred in only 25% and 5% and none of the patients had a microsatellite instable tumor, RFS was poor (3-year RFS: 18.4%) with only 46% and 43% of patients having been systemically treated with neoadjuvant or adjuvant chemotherapy. Liver-specific RFS was 29.3% and OS 58.4% after 3 years.
Conclusions: Despite few high-risk characteristics among patients with CRLM and early onset disease, RFS is poor. This might favor a more aggressive strategy of systemic treatment in these patients.

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Disclosure Statement: None of the authors have anything to disclose.

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Long-Term Local Tumor Control of Kypho-IORT Treated Spinal Metastases

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Purpose: The Kypho-IORT is an established method for local therapy of vertebral metastases consisting of local irradiation and cement augmentation and stabilization of the vertebral body. The technical and procedural safety [1] and in a phase 1/2 study the medium-term local tumor control has been demonstrated [2]. The long-term tumor control is unclear so far.
Methods: A single-center Kypho-IORT-collective were contacted and an interview-follow-up was carried out. The last medical imaging (CT and/or MRI) were evaluated. External follow-up imaging was acquired. A long-term follow-up could be created.

This is a retrospective, non-comparative cohort study.

Results: A complete data set was obtained in 100/104 treated patients (n=27 alive, n=73 deceased). 143 Kypho-IORT procedures were performed in 104 pat. Longest follow-up period was 9 years.

A total of 10 local recurrences (6.9%, n=10/143) occurred; A Kaplan-Meier calc. was performed. A local relapse-free survival of 93% at 12 m and of 80% at 5 y. The average overall survival is 2.2 years.

Entities consisted of 49% breast, 14% prostate, 15% bronchial, 8% GI tumors and 15% other.

Conclusions: This study shows the long-term therapeutic effect of Kypho-IORT, comparable data from other centers do not exist.

The excellent medium-term local tumor control in the phase 1/2 study was confirmed by long-term course. Compared to other interventions (SBRT), Kypho-IORT appears at least equal [3].

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Disclosure Statement: The authors received financial support for establishing the method and for teaching the method in specimen courses. Financial travel support for congresses was given.

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Measuring the Integration of Radiotherapy Plus Surgery for Resectable Hepatocellular Carcinoma: A Pilot Study from National Cancer Center of China

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Purpose: To assess oncologic outcomes and liver reserve condition after a combined approach of neoadjuvant radiotherapy followed by surgery.
Methods: A phase 2, single-arm trial, with patient accrual from September 1, 2016, to August 31, 2018 (median follow-up, 16 months), was performed at the national cancer center of China. Patients 18 years or older with high recurrence risk and good performance status, with adequate liver reserve to undergo surgical resection, were studied. And patients underwent neoadjuvant radiotherapy (IMRT or VMAT) followed by surgery no more than 15 weeks later. Main outcomes focused on the recurrence of HCC and the liver reserve condition.
Results: So far, twenty male patients (mean [SD] age, 55.13 [8.453] age) were enrolled. 16 patients underwent a combined approach of neoadjuvant radiotherapy followed by surgery and were evaluable for the primary end point. The rates of local lesion necrosis, well response, $MVI^{negative}$ after radiotherapy are 68.75%, 68.75%, 62.5% respectively. The 30- and 90-day postoperative mortality rates were both 0%. Surgical complications rate is 12.5%, however without severe complications as well as liver failure. Recurrence accounts for 18.75% of the patients. And progression free survival was observed as mean period of 13.5 months (quartile 10-19 months).
Conclusions: The combined approach holds a security for patients with resectable HCC and there was no perioperative mortality, no influence of neoadjuvant radiotherapy on liver reserve. Further studies are needed to evaluate this combined approach compared with surgical resection alone.

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Disclosure Statement: This study received supports from the funds: LC2016A07; Beijing Hope Run Special Fund of Cancer Foundation of China.

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Surgical Treatment of Rectal Cancer Patients Aged 80 Years and Older - A German Nationwide Analysis Comparing Short- and Long-Term Survival After Laparoscopic and Open Tumor Resection

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Purpose: Minimally invasive removal of rectal tumors has proven to be a safe alternative to the open approach. Despite increased use of laparoscopy, its eligibility for patients aged 80 years and older requires further exploration.
Methods: This study compares perioperative mortality and 5-year overall, disease-free, and relative survival after laparoscopic and open surgery in rectal cancer patients aged 80 years and older. Data derive from 30 German regional cancer registries covering approximately one quarter of the entire German population. All primary nonmetastatic rectal adenocarcinoma cases with surgery between 2005 and 2014 were eligible for inclusion. To compare survival rates, Kaplan-Meier analysis, a relative survival model, and multivariable Cox regression were applied; a sensitivity analysis assessed bias by exclusion.
Results: 1,532 patients were included, of whom 17.1% underwent laparoscopic procedures. 30 days after surgery, 2.7% of the laparoscopy patients had died compared to 7.0% in the open surgery group. The multivariable analysis confirmed that minimally invasive procedures are followed by a lower 30-day postoperative mortality risk (odds ratio, OR, 0.352; 95% confidence interval, CI, 0.161e0.771; p =0.009). With a 5-year disease-free survival rate of 52.0 vs. 47.6% (p = 0.557), only a nonsignificant long-term advantage of the minimally invasive approach was observed.
Conclusions: Given the results of this study, older rectal cancer patients are likely to benefit from the laparoscopic approach in the short term, while there are no disadvantages in terms of long-term survival. Therefore, laparoscopy should be considered as standard procedure for patients aged 80 and older as well.

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Neoadjuvant Chemotherapy with Gemcitabine Plus Cisplatin Followed by Radical Liver Resection Versus Immediate Radical Liver Resection Alone with or Without Adjuvant Chemotherapy in Incidentally Detected Gallbladder Carcinoma After Simple Cholecystectomy or in Front of Radical Resection of BTC (ICC/ECC) – A Phase III Study Utilizing The German Registry of Incidental Gallbladder Carcinoma Platform (GR) – The AIO/ CALGP/ ACO- Gain-Trial –

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Purpose: Currently, complete surgical resection represents the only potentially curative treatment option for Biliary Tract Cancer (BTC) including Gallbladder Cancer (GBC). Even after curative resection, 5-year OS is only 20–40%. Gallbladder carcinoma is relatively rare, but still the fifth most common neoplasm of the digestive tract and even the most frequent cancer of the biliary system. Gallbladder carcinoma is suspected preoperatively in only 30% of all pts, while the majority of cases are discovered incidentally by the pathologist after cholecystectomy for a benign indication. For improving curative rates in BTC and GBC, early systemic therapy combined with radical resection seems to be a promising approach. The earliest moment to apply chemotherapy would be in front of radical surgery. The encouraging results of neoadjuvant/perioperative concepts in other malignancies provide an additional rationale to use this treatment in the early phase of GBC management and even ICC/ECC. Especially because data regarding pure adjuvant chemotherapy in BTC`s are conflicting.
Methods: This is a multicenter, randomized, controlled, open-label phase III study including pts with incidentally discovered GBCs after simple cholecystectomy in front of radical liver resection and pts with resectable/ borderline resectable cholangiocarcinomas (ICC/ ECC) scheduled to receive perioperative chemotherapy (Gemcitabine + Cisplatin 3 cycles pre- and post-surgery) or surgery alone followed by a therapy of investigator's choice. Primary endpoint is OS; secondary endpoints are PFS, R0-resection rate, toxicity, perioperative morbidity, mortality and QoL. A total of N=333 patients with GBC or BTC will be included. Recruitment has started in August 2019. ClinicalTrials.gov ID: NCT03673072; EudraCT number: 2017-004444-38

Disclosure Statement: No relevant disclosures.

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The Intratumoral and Intestinal Microbiome in Pancreatic Cancer

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Purpose: The intestinal and even intratumoral microbiome is just beginning to be recognized as an important player in carcinogenesis. Recently, it has been shown that modulation of the intratumoral pancreatic microbiome with antibiotics can alter the response to chemotherapy and bacterial dysbiosis influences PDA progression. Therefore, identification of microbiota within the tumor and in the adjacent compartments might prove useful for future therapy.
Methods: Since 1/2019 we intraoperatively obtained tissue and fluid samples from 30 patients with previously untreated pancreatic cancer. Microbiota profiles were characterized by amplification of the V3/V4 region of the 16SrRNA gene followed by deep sequencing and biostatistical analysis.
Results: Characteristic signatures for intratumoral and duodenal as well as bile samples were obtained. The intraindividual comparison showed only a partial overlap of the microbiota from these three compartments, suggesting an enrichment or immune evasion of specific microbiota in the tumor tissue. Cluster tree analysis based on the relative abundance of OTUs revealed no significant segregation of the bacterial microbiota structures from pancreatic cancer patients. Some bacterial taxa were differentiated between the pancreatic cancer patients at the taxonomy level of genus or higher such as Acinetobacter, Oceanobacillus, Rahnella, Delftia, and Sphingobium.
Conclusions: Microbial dysbiosis can drive PDAC progression by promoting immune tolerance and targeting the microbiome can reverse this process. We found that PDA is associated with a distinct stage- specific gut and pancreatic microbiome that could drive disease progression by inducing intratumoral immune suppression. Conversely, targeting the microbiome could protected against PDA and enhanced antitumor immunity and susceptibility to immunotherapy. Due to the potentially modifiable nature of gut bacteria a better understanding of the microbiome in pancreatic cancer may lead to a microbiota based intervention during postoperative clinical management.

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Nephron-Sparing Surgery in Solitary Kidney Tumors

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Purpose: To assess the oncological and long term functional results of nephron sparing surgery in patients (pts) with solitary kidney tumors.
Methods: 82 pts with solitary kidney tumor who had undergone partial nephrectomy in the National Medical Research Center of Radiology were analyzed. The mean age was 60.3 (29-77) years. Ratio of men to women was 2.4:1. The reasons for the absence of a contralateral kidney were primary multiple metachronous renal cell cancer in 69 pts (84.3%), renal hypoplasia - 7 (8.5%) pts, horseshoe kidney - 2 (2.4%) pts, hydronephrosis - 1 (1-2%) pts, urolithiasis -1 (1.2%) pts, pyelonephritis -1 (1.2%) pts, polycystic kidney-1 (1.2%) pts. Median sum RENAL score was 6 (4-12). Median preoperative glomerular filtration rate (GFR) was 56 (31-91) ml/min/1.73m2. Median follow up time was 54 (6-147) months.
Results: Open partial nephrectomy was performed 71 (86.6%) pts and laparoscopic partial nephrectomy - 10 (12.2%), and radiofrequency ablation - 1 (1.2%) pts. Median postoperative GFR was 50.6 (24.6-98) ml/min/1.73m2. Complication rate was 8.5%. Acute reduction in renal function with immediate hemodialysis was required in 2 (2.4%) pts. Clear cell renal cell carcinoma (RCC) was diagnosed in 69 (84.4%) pts, papillary RCC types in 5 (6%) pts, chromophobe RCC in 4 (4.8%), mixed types - in 1 (1.2%), angiomyolipoma in 1 (1.2%) pts, oncocytoma in 2 (2.4%) pts. 5-year progression free survival was 57.5% and overall survival was 86.4%, cancer-specific survival - 87.8%. Local recurrence was detected in 6 (7.3%) pts and distant metastases in 17 (20.7%) pts. During follow up period 8 (9.7%) pts were died and 6 (7.3%) from RCC progression. Statistically significant correlation was revealed between pT stage (R = 0.33), presence of sarcomatoid component (R = 0.28) and necrosis in tumor (R = 0.25) and Fuhrman grade (R = 0.43) and probability of disease progression ($p < 0.05$).
Conclusions: Partial nephrectomy of single kidney is an effective method of treatment of RCC with good long-term functional and oncological results.

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Surgery in Breast Cancer Liver Metastases - Essential Part of a Multimodal Treatment?

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Purpose: About 10% of breast cancer patients present with metastatic disease at diagnosis, about 30% of patients will develop metastases at a later time. In about half of these, metastatic spread occurs more than five years after initial diagnosis, with Breast Cancer Liver Metastases (BCLM) being the third most frequent site of metastatic spread (1). Usually, chemotherapy and hormonal therapy are used as palliative treatment for metastatic disease and patients are seldom considered for surgery.
Methods: We analyzed the outcome of 27 patients undergoing liver resection for BCLM between 1999 and 2018 at the Dpt. of Surgery, University of Freiburg, using retrospective data. Survival analysis was performed in SPSS.
Results: Median age at initial diagnosis was 48 (33-75). 23 patients (85%) developed metachronous metastases with median time between initial diagnosis and development of metastases of 5 yrs. (1-25 yrs.). 8 patients (28.6%) also had extrahepatic disease at the time of BCLM diagnosis (osseus, pulmonal, cerebral). 77,8% of patients received a systemic treatment (chemotherapy, antibodies, antihormonal therapy) at least 3 months prior to surgery. Four patients (14%) showed disseminated disease intraoperatively and no resection was performed.

Perioperative morbidity was low, with one Clavien-Dindo Grade IV (3,6%) and two Grade III (7.1%) complications. No perioperative mortality occurred.
Median overall survival was 38 months, 5-yr OS 34.4% and 3-yr OS 59%. Survival in the group of patients with R0/R1 resection was significantly higher (p=0,015) than in the group of patients with exploratory laparotomy/ R2 resection.
Conclusions: Lacking randomized controlled trials proving the benefit, surgical resection of BCLM is controversially discussed. Our small patient collective covered 20 years with varying systemic treatment and different surgical approaches - still, our results show an acceptable long-term survival, low morbidity and no mortality. Surgery for BCLM might be offered to patients as part of multimodal therapy concepts.

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Structural Analyses in Cell Junction Proteins after Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy

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Purpose: Extended liver resections are frequently required for R0 resection margins in patients suffering from liver tumors. One surgical technique to achieve a sufficiently functional liver volume is “Associating Liver Partition and Portal vein ligation for Staged hepatectomy (ALPPS). It is, however, rarely investigated and highly controversial, whether hypertrophy of the liver remnant increases functional liver parenchyma. The study group characterized the liver parenchyma in different stages of the ALPPS procedure. We focused on the integrity of cell-cell contacts, which we have shown to correlate to liver function (Hempel et al. Cell Mol Life Sci. 2015).
Methods: The structural integrity of liver parenchyma was analyzed by immunohistochemical detection of cell junction proteins ZO-1 and E-cadherin. Apoptosis was evaluated by detection of activated Caspase 3. In addition, (AST, ALT, bilirubin, µGT, INR, albumin) were analyzed until the patients´ discharge.
Results: In all patients, transaminases peaked after the first and the second surgical step of ALLPS. ZO-1 and E-cadherin was hardly detectable at cell junctions in the ligated liver lobe indicating structural impairment. In contrast, ZO-1 and E-cadherin were expressed physiologically at the surface of hepatocytes in the hypertrophied liver remnant. In 1 patient, nearly no ZO-1 and E-cadherin was expressed in the liver remnant indicating functional impairment. Apoptotic events were observed in both the ligated liver lobe and in the hypertrophied remnant. Whereas in the ligated liver lobe Caspase 3 was detected in non-parenchymal cells, it was more prominent in hepatocytes of the liver remnant.
Conclusions: Physiological ZO-1 and E-cadherin expression in the hypertrophied liver tissue was detected in most patients, indicating structural and bona fide functional integrity. Non-physiological expression in 1 patient might correlate with loss of function. This, however, needs confirmation by deeper functional analyses, e.g., by detection of plasma proteins and metabolic enzymes in the remnant liver tissue.

Translational Oncology

Best-of-Abstracts-Vorträge

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Mek Inhibitors Activate WNT Signalling and Induce Stem Cell Plasticity in Colorectal Cancer

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Purpose: In colorectal cancer (CRC), aberrant Wnt signaling is essential for tumorigenesis and maintenance of cancer stem cells. However, how other oncogenic pathways converge on Wnt signaling to modulate stem cell homeostasis in CRC currently remains poorly understood.
Methods: We performed large-scale compound screens to identify novel pharmacological modulators of Wnt signaling in CRC cell lines. Cellular activity of the Wnt pathway was measured using target gene expression und Wnt reporters. The effect of candidate compounds was validated in mouse models and different murine and human CRC organoid lines. The effect of combination drug treatment was determined using a novel CRC organoid derived xenograft model.
Results: The compound screens identified MEK inhibitors as potent activators of Wnt/beta-catenin signaling in CRC. Targeting MEK increases Wnt activity in different CRC cell lines and murine intestine in vivo. Truncating mutations of APC generated by CRISPR/Cas9 strongly synergized with MEK inhibitors in enhancing Wnt response in isogenic CRC cell lines and murine colon organoid models. Mechanistically, we demonstrate that MEK inhibition induces a rapid downregulation of AXIN1. Using patient-derived CRC organoids, we show that MEK inhibition leads to increased Wnt activity, elevated LGR5 levels and enrichment of gene signatures associated with stemness and cancer relapse. Furthermore, co-treatment of MEK and Wnt inhibitors efficiently reduce tumor growth in vitro and in vivo.
Conclusions: Our study demonstrates that clinically used MEK inhibitors inadvertently induce Wnt signaling and stem cell plasticity, revealing an unknown side effect of RAS pathway inhibition.

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Disclosure Statement: No conflict of interest.

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NGS-Based Mutation Analysis of BRCA1-Associated Triple-Negative Breast Cancers

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Purpose: Despite their common receptor status, triple-negative breast cancer (TNBC) is increasingly presenting as genetically diverse disease. About 15 % of TNBCs are associated with a *BRCA1* germline mutation. Aim of this study is to identify genes involved in tumor development and progression and to further characterize *BRCA1*-associated TNBCs by NGS-based mutation analysis.
Methods: Macrodissected FFPE tissues were analysed with two NGS multigene panels: QiaSeq Human Breast Cancer panel (Qiagen) and TST170 gene panel (Illumina). By additional RNA analysis, TST170 not only detects small DNA changes, but also amplifications as well as splice and fusion variants.
Results: TNBC tissue samples were available for 56 of 113 *BRCA1* mutation carriers identified in our breast and ovarian cancer center. Of 104 tissues received, 65 were processed. In 61 of these, tumor cell content (>30 %) was adequate. In 86 % (48/56), isolated DNA was sufficiently intact and amplifiable, as determined by qPCR. In 20 of 21 tumor samples currently analysed, the respective *BRCA1* germline mutation was detected, with variant frequencies indicating loss of heterozygosity. Preliminary data analysis revealed 37 SNVs /InDels rated as pathogenic. In addition to single events in different genes, we observed frequent mutations in *KMT2C* (11/11) and *TP53* (17/21). For mutations in genes shared by both panels, variant allele frequencies were similar. The TST170 panel further detected four gene fusion events (*BRCA1-STAT3, FGFR1-HFM1, NOTCH1-CPA6, TACC3-FGFR2*) and an *EGFR* splice variant.
Conclusions: In combination, both multigene panels enable the detection of a broad spectrum of diverse variant types in different genes. This could help identifying mutations with prognostic or predictive relevance in *BRCA1*-associated TNBCs.

Poster

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Reprograming of Innate Immunity by Tumor-Derived R-2-Hydroxyglutarate

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Purpose: Isocitrate dehydrogenase 1 (IDH1)-mutant tumors form biologically distinct subgroups in acute myeloid leukemia and low-grade gliomas. Mutations in the tumor-defining enzyme IDH1 result in the increased production of R-2-hydroxyglutarate (R-2-HG) and constitute a distinct, metabolically skewed biological entity. These tumors are associated with less abundant and phenotypically altered immune cell infiltrates compared to IDH1 wild-type tumors. Despite recent advancements, the

mechanisms shaping the immune microenvironment of IDH1-mutated tumors remain elusive.
Methods & Results: We could show that IDH1-mutated gliomas subdue their innate immune microenvironment by prompting a multifaceted re**programming** of myeloid cell metabolism. Integrated single-cell transcriptomic and proteomic analyses of human control and glioblastoma samples identified myeloid cell subsets with distinct fates in IDH1-mutated glioma that diverge from canonical trajectories of antigen-presenting cells. Paracrine tumor-derived R-2-HG, when transported into macrophages, induced an immunosuppressive state through dysregulated tryptophan metabolism and subsequent activation of the aryl hydrocarbon receptor (AHR), resulting in increased production of IL-10 and TGF-β, down-regulation of MHC-II expression, and consequent suppression of T cell activity. We demonstrate that effective immunotherapy in the context of mutant IDH1 requires normalization of this AHR-mediated phenotype.
Conclusions: These findings argue for the development of new immunotherapy concepts that recognize the cell-specific immunomodulatory effects of IDH1-mutated tumors; and could prove vital defining the relevant entities targeted by small molecule AHR inhibitors currently undergoing preclinical development.

Reference:
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Disclosure Statement: I have no financial relationships to disclose.

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Oncogenic Potential of Rare Mutations in RRAS2

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Purpose: The small GTPase RRAS2 is affected by low-frequency mutations in codons 23 and 72 in cancers of different tissue origin, including germ cell tumors. The contribution of these rare mutations to oncogenesis is unknown. The aim of this project is to understand the biology and oncogenic effects of RRAS2 mutations and to identify mutant RRAS2-specific vulnerabilities for therapeutic exploitation.
Methods: We engineered isogenic cell lines by lentiviral cDNA transfer of RRAS2 variants into immortalized human breast cells (MCF10A) and murine yolk sac cells (C166). These isogenic cell lines were phenotypically characterized by colony formation, proliferation, and soft agar assays. Genes and pathways responsive to mutant RRAS2 expression were investigated by western blot and RNA sequencing. Furthermore, we used a transgenic mouse model with global expression of mutant RRAS2 to study oncogenic effects *in vivo*.
Results: RRAS2 mutations in codons 23 and 72 strongly induced anchorage-independent growth in MCF10A and C166 cells and EGF-independent growth of MCF10A cells in colony formation assays. No significant proliferation changes were observed in either cell line when cultured in complete growth medium. Transcriptional profiling of RRAS2-mutant MCF10A cells revealed several deregulated pathways associated with cancer, most prevalently activation of the MAPK and PI3K pathways and induction of genes involved in epithelial-to-mesenchymal transition. Correspondingly, mutant RRAS2 increased phosphorylation of Erk1/2 and Akt in C166 cells. *In vivo*, global expression of mutant RRAS2 resulted in highly aggressive pancreatic ductal adenocarcinoma and preneoplastic lesions in the lung after two weeks.
Conclusions: We identified strong oncogenic effects of RRAS2 mutations *in vivo* and *in vitro* in cells from different tissue origin that correspond to primary tumor samples, reinforcing the importance of rare mutations as cancer drivers. These findings might open up opportunities for new therapeutic approaches.

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B Cells Sustain Inflammation and Predict Response to Immune Checkpoint Blockade in Human Melanoma

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Purpose: Tumor inflammation predicts response to immune checkpoint blockade in human melanoma. Established mechanisms of therapy response center on anti-tumor T cell responses. Here we show that tumor-associated B cells (TAB) are vital to tumor inflammation.
Methods: We used whole RNA-seq and (phospho)proteomics data from human peripheral blood- and tumor-derived B cells, whole and single cell (sc) RNA-seq and multiplex immunostaining data from human melanomas and a surrogate in vitro assay of T cell activation.
Results: In human melanoma, TAB are located at the invasive tumor-stroma margin arguing for a preferentially cell contact-independent communication with tumor cells. We therefore exposed *in vitro* peripheral blood- and melanoma-derived B cells to the secretome from autologous melanoma cells. In proteomics and RNA-seq data, we observed induction of pro- and anti-inflammatory factors and differentiation towards a *plasmablast-like* phenotype. We could find this B cell phenotype as a distinct B cell cluster in public scRNA-seq data as well as by 7 color multiplex immunostaining of human melanomas (1).

Depletion of TAB by anti-CD20 immunotherapy of metastatic melanoma patients led to a pronounced decrease in tumor inflammation signatures and $CD8^+$ T cell numbers, in line with scRNA-seq data on expression of T cell chemoattractants CCL3,4,5 in plasmablast-like TAB.

Interestingly, the frequency of plasmablast-like TAB in pretherapy melanoma samples predicted response and survival to immune checkpoint blockade in two independent large-scale clinical (sc)RNA-seq datasets. Consistently, melanoma secretome-induced B cells significantly increased the activation of PD1-expressing Jurkat T cells by PD1 blockade *in vitro*.
Conclusions: Together, our data argue that tumor-associated B cells orchestrate and sustain tumor inflammation, recruit CD8+ T effector cells and may represent a predictor for response and survival to immune checkpoint blockade in human melanoma.

Reference:
1. doi.org/10.1101/478735

Disclosure Statement: Supported by the FWF-Austrian Science Fund.

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Evaluation of the Transsectoral Cooperation and Educational Program of the Cologne Department of the German Consortium for Hereditary Breast and Ovarian Cancer (GC-HBOC) for Certified Breast and Gynecological Cancer Centers

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Purpose: Relevant familial cancer history concerns about 30% of all patients with breast and ovarian cancer. Thus, genetic counseling of these patients and their families is an important topic. To meet the challenges of germline gene panel analyses and the clinical translation of the test results, we established a structured and standardized educational program (EP) for physicians of certified breast and gynecological cancer centers within a transsectoral cooperation (TC) in 2015. The EP covers curricula with written exams and a practical training.
Methods: To date we performed 24 curricula, which covered topics from identifying persons at risk over genetic counseling and interpretation of genetic test results to risk-adjusted preventive measures and targeted therapies. To evaluate these curricula, we used an in-house survey and a standardized survey of the Ärztekammer Nordrhein (AekNo). To evaluate the TC we performed a survey among 79 physicians.
Results: A total of 235 in-house survey results were evaluated. We inquired the structure and comprehensibility of the curricula (1.57; scale 1 to 6, analogue to German school grades), presence of all clinically relevant information (1.58), and relevance for daily clinical counseling (1.61). Similar results arise from the survey of the AekNo.

The TC was evaluated by 37 of 79 physicians. A total of ten items could be rated. 81% stated a very good or good organization of the program, flow of information (86%), clarity of genetic reports (86%), and 100% a very good quality of our cancer prevention and therapy concept (scale: very good, good, acceptable or insufficient).
Conclusions: Participants stated a high or very high satisfaction with our curricula and TC. It assists highly specialized clinicians in genetic counseling, in clinical management of patients at high risk (e.g. participation in evidence-based risk-adjusted prevention programs) and in acquiring clinical data in knowledge-generating medicine. The GC-HBOC and the German Cancer Society currently implement the EP nation-wide.

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Establishing an IT-Supported Molecular Tumor Board in the Routine Setting – A Report from the Cancer Center Heilbronn-Franken

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Purpose: The increasing practicality of genomic sequencing technology has led to its incorporation into routine clinical practice. To strengthen implementation of genomics-guided cancer therapies, a Molecular Tumor Board (MTB) and a supporting IT-frame work (VITU) have been implemented at the Cancer Center Heilbronn-Franken in 2017.
Methods: A team comprising oncologists, genetic counselors and basic scientists meets weekly to discuss each case reviewing clinical and scientific evidence in the context of the tumor entity. To assist physicians, an individual report summarizing genetic aberrations and ranked treating options is generated. External experts and resident oncologists are able to participate via web-based video conferencing, and a newly developed open-source IT tool (VITU) is used for process and data management.
Results: Since 2017 more than 160 cases have been evaluated in the MTB. In 50% of all cases a molecular stratified treatment based on tumor genetic profile was recommended, with 15% of patients subsequently treated with MTB-recommended personalized targeted agents, and for another 15% targeted agents serve as an option in case of future progression. Inclusion in a clinical trial was possible for 3% of all patients. Furthermore, a database has been established enabling management and analysis of genomic and clinical data and outcome to optimize clinical benefit.
Conclusion: Molecular characterization is feasible in the routine setting and provides new treatment options for a substantial portion of cancer patients. However, patient-centered interpreting of variants still remains a challenge and, therefore, the implementation of a interdisciplinary MTB is of central importance. Novel IT-supported decision support tools and data sharing efforts will be crucial to exploit the full potential of comprehensive molecular cancer diagnostics. The digitization of processes supports the collaboration of experts and the practicality of routine operations in the hospital.

Disclosure Statement: No conflict of interest was reported by the authors.

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Unraveling Intra-Tumor Heterogeneity in Colorectal Cancer Using Oncoproteomics in Patient-Derived Organoids

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Purpose: Intra-tumor heterogeneity (ITH) poses a major obstacle in cancer therapy. In colorectal cancer (CRC), mutations in the transforming growth factor-β (TGF-β) pathway, especially in SMAD4 gene, have been correlated with decreased overall survival and are suspected to modulate chemoresistance. We have previously shown that $SMAD4^{R361H}$ is associated with differential drug response towards EGFR, MEK and PI3K inhibitors. In the present study, we uncover the mechanistic role of $SMAD4^{R361H}$ using oncoproteomics in isogenic CRISPR-engineered $SMAD4^{R361H}$, CRC patient-derived organoids (PD3D®).
Methods: Here, we investigated multiple organoid cultures from a single CRC and its liver metastasis. Targeted amplicon sequencing identified the $SMAD4^{R361H}$ mutation in 2/5 subcultures. Using CRISPR-Cas9 approach, we introduced the $SMAD4^{R361H}$ into the wildtype organoids. Organoid cultures were subjected to a comparative drug screening and subsequent multiplex protein profiling analysis (DigiWest®) with a panel of >100 (phospho-)proteins on cancer-specific cellular pathways at various timepoints.
Results: $SMAD4^{R361H}$ organoids showed a differential response to EGFR and MEK inhibition compared to their SMAD4 wildtype counterparts. Protein profiling revealed different levels of Wnt pathway activation under treatment, while showing only minor differences upon MEK inhibition in the downstream signaling cascade. Early results point towards an initial cell cycle arrest for growth inhibition.
Conclusions: PD3Ds recapitulate the genetic and phenotypic heterogeneity of the donor tumor tissue. We show that $SMAD4^{R361H}$ contributes to the sensitivity towards trametinib in vitro. The combination of multisampling, characterization and CRISPR is not limited to studying the role of the R361H mutation. It has a broad range of applications in

understanding cancer biology, ITH, drug response and may help to improve therapy response prediction in cancer patients.

Disclosure Statement: There is nothing to disclose.

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A 'Beyond Genomics' Approach to Precision Oncology: A Multiplex Protein Profiling Platform for Tumor and Tumor Organoid Samples

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Purpose: Precision medicine's goal of achieving a better response rate by avoiding ineffective therapies has sparked new approaches, including the testing of patient-derived 3d (PD3Ds) tumor cultures for modeling individual patient response, and the use of various molecular pathology techniques for advanced tumor profiling. However, well-established genomics methodologies cannot directly assess cell-signaling activity within the tumor cells defined by the phosphorylation status of cellular signaling pathway networks.
Methods: Here we present the development of a robust protein profiling strategy utilizing the DigiWest immuno-assay platform, to obtain data on the activation status of key cellular signaling networks implicated in cancer, and on proteins targeted by FDA-approved drugs including a number of targeted cancer therapies for e.g. EGFR, HER2, PI3K, mTOR, ALK and AKT.
Results: We compiled a list of relevant pathway nodes and their phosphorylation sites that yield activity information on RAS/RAF/ERK, PI3K/AKT and mTOR signaling pathways. Based on this, we validated 242 total and phospho antibodies in a pre-set oncoproteomic DigiWest panel that yields information on the activity of these signaling networks from the receptor level down to transcription factors, apoptosis and proliferation. This oncoproteomic panel can be utilized for elucidating drug response in pre-clinical cell models, in PD3D organoid models or in clinical tumor samples. Exemplary, we show differential effects of PI3K kinase inhibitor copanlisib vs MEK inhibitor trametinib at various levels within their signaling networks. Also, we tested this panel in PD3D organoids that were subjected to screening against common targeted therapies.
Conclusions: While the initial results are promising, further work on evaluating how such an oncoproteomic panel profiling might contribute to the rationale for personalized therapy decisions is required.

Disclosure Statement: NMI TT Pharmaservices offers DigiWest protein profiling as a service.

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Preclinical Case Study: Patient-Derived Head and Neck Cancer Xenograft on Mice Humanized with Autologous and Allogene Immune Cells, A Model for Personalized Immuno-Oncology Research

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Purpose: Models for the preclinical evaluation of novel immune modulators for cancer treatment require engraftment of human tumor with a matching immune cell population. In this case study, we established a patient-derived xenograft (PDX) from a head and neck squamous cell cancer (HNSCC). In parallel patients blood samples were collected.

Mice with engrafted HNSCC PDX, were humanized with patients PBMC. By this we successfully generated a patient-specific human tumor-immune cell model in mice with 100% HLA-match. Model development included the comparison of PDX engraftment on mice with either HLA- or non HLA-matching PBMC's from different donors or on humanized mice generated by HSC transplantation.

Finally, we validated the model by comparing treatment effects with the checkpoint inhibitor Nivolumab.
Methods: The HNSCC PDX were transplanted on NOG mice. After tumor engraftment mice were randomized in 6 groups, receiving PBMCs i.v. either from the patient or from 5 well characterized donors. Furthermore NOG mice were humanized with HSC from 5 donors. Blood and tumor samples were analysed by FACS and IHC.
Results: In the autologous PBMC model, no interference with the proliferation of the PDX was seen. However, on mice humanized with donor PBMC's with a high HLA match, a stimulation of tumor proliferation was observed. Surprisingly, treatment with Nivolumab did not induce a significant tumor growth inhibition in the autologous model. On the mice humanized with PBMC and HSC from different donors, we observed a correlation of treatment effects with HLA match. Finally, infiltrating immune cells were detected in the tumors.
Conclusions: We developed a humanized immune-PDX model enabling appropriate preclinical translational research on tumor immune biology and the evaluation of new therapies and combinations, as well as the identification and validation of biomarkers for immune therapy. Furthermore, results showed a correlation between immune therapy effect and HLA matching in preclinical models.

Disclosure Statement: I'm a full-time employee at EPO GmbH.

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Phenotypic and Functional Characteristics of Preclinical Breast Cancer Models

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Purpose: Generation of patient-derived models for breast cancer is difficult and the success is often low compared to other histologies. With the goal to develop a resource for testing novel compounds and combinations for treatment of refractory breast cancer, we established patient-derived xenograft models (PDX) from tumors clinically unresponsive to at least anthracyclines, platins and taxanes. Here we report phenotypic characterization and drug testing data of our established breast cancer models.
Methods: Breast cancer tissue samples were engrafted on immunodeficient NOG mice. The tissues were obtained from patients with disease progression after chemotherapy with three to four drugs. The established PDX were characterized by immunohistochemistry and are currently undergoing exome and transcriptome sequencing. The PDX were tested for response to all standard chemotherapy agents. The drug testing included platins, taxanes, anthracyclines, 5-FU, everolimus, eribulin and depending on the subtype tamoxifen, olaparib, and a CDK4/6 Inhibitor.
Results: 50 breast cancer samples have been processed under rapid and stringent conditions. Currently eight models, six TNBC and two hormone receptor positive PDX, have been fully engrafted, phenotypically characterized and drug screened. The immunohistochemistry stainings for estrogen/progesterone/androgen/Her2 receptors, Ki-67, and CK5/6 of the original tumor and the PDX were comparable. All patients had shown

clinical resistance to platin, anthracyclines, and taxanes in the neoadjuvant or palliative setting. Concordant with the clinical resistance, the PDX models showed only limited or transient sensitivity to single agents.
Conclusions: With our stringent approach, we successfully generated 8 new breast cancer PDX models (16% take). The phenotype between patient tumors and PDX was consistent. The minor differences in responsiveness to chemotherapy may be due to differences in stromal factors. In summary, the PDX of refractory tumors are a versatile resource for preclinical studies of novel treatment approaches.

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Changes in the Number of Circulating Epithelial Tumor Cells (CETCS) During Radiotherapy (RT) In Patients with Breast Cancer

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Purpose: Circulating tumor cells represent the liquid component of solid tumors and are a surrogate marker for residual cancer burden. RT reduces not only local recurrence but also improves overall survival by preventing distant metastases, which indicates its influence on the remaining occult tumor. Detection of CETCs may monitor the therapeutic effect in breast cancer patients. There is limited data on the changes of CETC numbers during radiotherapy in patients after neoadjuvant chemotherapy.
Methods: CETCs were analyzed prior to (baseline), 3 and 6 weeks after the start of RT in 54 primary breast cancer patients in early and locally advanced stages after adjuvant or neoadjuvant chemotherapy. The number of CETCs was investigated using the maintrac method.
Results: Patients with triple negative breast cancer had statistically significantly more CETCs as compared to patients with luminal A and B subtypes. Furthermore, patients treated with adjuvant chemotherapy had statistically significantly less CETCs as compared to patients who received neoadjuvant chemotherapy (median 9 vs. 22, $p<0.05$). Interestingly, the number of CETCs was continuously reduced during RT in patients after neoadjuvant chemotherapy but not after adjuvant chemotherapy. The final median numbers (after RT) of CETCs were not significantly different between patients in the neoadjuvant and adjuvant setting.
Conclusions: Although the number of CETCs was higher in patients who had received neoadjuvant chemotherapy, radiotherapy reduced CETCs but the same was not observed in patients who had received adjuvant chemotherapy. The clinical impact of this result needs to be analyzed in the future.

Disclosure Statement: We declare that we have no conflict of interest.

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The CCC Munichlmu Molecular Tumor Board: Clinical and Molecular Characteristics of the First 450 Patients

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Purpose: To establish a precision oncology program at University of Munich, the Molecular Tumor Board (MTB) was implemented in 2016. Now the first comprehensive review of cases was done to assess the clinical implications and utility of the program.
Methods: Charts, mutational spectra and tumor board decisions of the first consecutive 450 cases were reviewed. Descriptive statistics were applied to describe relevant findings.
Results: Of the 450 patients originally referred for Next Generation Sequencing (NGS), 406 underwent molecular diagnostics. In most cases (n=332) genetic analyses were performed on tumor tissue, in 27 cases cerebral spinal fluid was used for NGS. In 28 patients the analysis was performed on liquid biopsies taken from peripheral blood, in 2 patients, liquid biopsies were taken from malignant ascites. In 337 patients, diagnostics were technically successful. Unsuccessful tests were mostly due to insufficient amount or low quality of the provided tissue. In 309 cases (75%), a molecular alteration was identified, which was potentially druggable in over 75% (n=204).
Conclusions: The MTB has experienced a rapid growth in case numbers. With a broad range of different malignant diseases analyzed, the program serves as a clinical tool for patients from a variety of departments within the University of Munich. Based on our initial results patients with certain tumor entities seem to benefit more from extended molecular diagnostics. Still, access to targeted treatments outside of clinical trials is a major obstacle in precision oncology.

Reference:
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Disclosure Statement: No relevant financial disclosures with regard to this abstract.

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Algorithm for Investigating Cell-Cell Communication in Malignant and Healthy Bone Marrow Using SCRNAseq Data

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Purpose: Intercellular communication plays an essential role in the proper functioning blood homeostasis in the bone marrow and its alteration might contribute to development and maintenance of malignant neoplasms. In our project, we aim at developing an algorithm to assess the cell-cell communication between distinct cell types using single-cell RNAseq data. While several algorithms have been published lately, their results are often hard to visualize and interpret.
Methods: In our algorithm, we use new visualization and classification tools based on multiplex networks and network clustering strategies. As an example, we apply our algorithm to a single cell RNAseq data set (van Galen et al., 2019) that is publicly available.
Results: We analyzed benign bone marrow samples as well as several AML patients with serial time-points available and different treatment modalities (intensive induction chemotherapy or acazitidine + venetoclax). By this we could identify new lines of intercellular communication that change during malignant transformation and can be reestablished by treatment of the AML. In addition, we were able to show how different treatment modalities impact on intercellular communication and which intercellular communication could be important for benign bone marrow function.
Conclusion: These findings will serve as a basis for further biological validation of the found communication lines *in vivo* and show how existing data sets can be used to establish new data driven hypothesis for a deeper understanding of hematopoietic neoplasms.

Reference:
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Disclosure Statement: No conflict of interests.

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Increased Activity of Poly-Adp Ribose Polymerase (PARP) in Peripheral Blood Lymphocytes Predicts Prostate Cancer Risk

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Purpose: Defects in Homologous Recombination (HR) as the most accurate pathway for DNA-double-strand-break (DSB) repair are found in various types of cancer. Dysfunction in HR can lead to an increase of other less precise DSB-repair mechanisms. This is associated with genomic instability. So inherited and somatic mutations in susceptibility genes like *BRCA1*, *BRCA2, PALB1, RAD51C* can be found in a high proportion of breast- and ovarian cancer, as well as prostate cancer patients. Defects in DSB-repair pathways are utilized as therapeutic option with drugs like platinum-derivates and PARP inhibitors in prostate cancer as well as in ovarian- and breast cancer patients. In previous case-control-studies we found mutagenic DSB-Repair in peripheral blood lymphocytes (PBLs) were associated with elevated risk for breast- and ovarian cancer, which could be indicative of genetic predisposition.
Methods: We performed a case-control study to determine DSB repair-functions in PBLs from 75 prostate cancer patients and 47 healthy controls using the GFP-based test system established for pathogenic breast and ovarian risk gene mutations. In parallel, we examined sensitivities to Carboplatin and PARP inhibitors as well as PARP activities.
Results: Regarding PARP-activities in PBLs we detected a significant increase of basal ($P = 0.001$) and activated ($P = 0.006$) PARP activity in cancer patients in comparison to controls. Additionally we found higher sensitivities of PBLs from prostate cancer patients to carboplatin ($P < 0.0001$) and significant decrease of SSA with increasing age in prostate cancer patients ($P = 0.004$). Comparing DSB-repair activities and PARP-inhibitor sensitivities between cancer patients and controls we did not find significant differences.
Conclusions: These findings demonstrates the potential of detecting PARP activities in PBLs as method to estimate prostate cancer susceptibility. Furthermore measurement of carboplatin-sensitivities and DSB-repair-activities might have the potential to further classify patients individually risk.

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Novel Patient-Derived Xenografts (PDX) from Peritoneal Metastasis of Colorectal Cancer (PmCRC) for Improved Prediction of Therapy Response

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Purpose: For patients with colorectal cancer (CRC) peritoneal metastasis (pm) represents a terminal tumor stage with limited therapeutic options. Appropriate patient-derived xenograft (PDX) models of this disease allow preclinical trials to evaluate predictive biomarker signatures for standard chemotherapeutics, but also to find novel therapeutic targets and treatment options. This approach of personalized oncology might increase therapeutic efficacy and overall survival of pmCRC patients.
Methods: For model establishment, surgical specimens were transplanted subcutaneously (s.c.) onto immunocompromized NSG mice and engrafted tumors were transferred to NMRI nu/nu mice for further passaging. Models were characterized by histopathology, immunohistochemistry and molecularly characterized by RNAseq and (phospho-) proteomics. Chemosensitivity of pmCRC models was evaluated on a panel of conventional chemotherapeutic and targeted drugs. Bioinformatics of molecular data of patient and patient-derived tissue was used to evaluate predictive signatures for single drug treatments, but also to retrace mechanisms for response or resistance of individual models.
Results: The drug testing revealed individual response patterns in PDX. Most interestingly, different drug response patterns were observed in models derived from mucinous vs. non-mucinous tumor tissue, but also originating from the omentum or peritoneum of the same patient. Differentially expressed genes of responding and non-responding models were determined for most of the applied standard chemotherapeutics, whereas idiosyncratic effects of individual therapy responses for targeted drugs could be molecularly retraced.
Conclusions: We successfully established a platform of preclinical models for pmCRC. Patient-derived models maintain basic characteristics such as the morphology of the patient tumor in early passages, reflect heterogeneous response rates, and can be used to evaluate novel predictive biomarker signatures and therapeutic targets for improved personalized precision oncology.

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A Metastatic MACC1-WNT/B-Catenin-S100A4 Axis Promotes Cancer Cell Motility in CRC

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Purpose: Colorectal Cancer (CRC) is a leading cause of death worldwide, mainly due to metastatic spread. Biomarkers allow identification of high risk patients and expose targetable vulnerabilities of CRC. Metastasis-Associated in Colon Cancer-1 (MACC1) predicts metachronous metastases and promotes cell motility and metastasis. Wnt/β-catenin signaling is commonly deregulated in CRC and its target genes such as the metastasis-associated gene S100A4 induce and cell motility and motility. In this study we expose a functional link between both prometastatic genes in CRC progression.
Methods: MACC1 and S100A4 expression were analyzed in CRC cohorts as well as in CRC cell lines. Following overexpression or CRISPR-mediated knockout of MACC1 Wnt signaling was assessed with TOPflash assays. S100A4 regulation was quantified with a promoter reporter assay and on mRNA and protein level. Cancer cell migration was examined in Boyden chambers. The MACC1-Wnt/β-catenin-S100A4 axis was intercepted with siRNA against β-catenin and Wnt inhibitors. Phosphorylation of β-catenin was assessed with DigiWest and Western blot.
Results: MACC1 enhances Wnt/β-catenin activity in CRC cells and upregulates S100A4 expression and S100A4 promotor activity. Knockdown of β-catenin and Wnt inhibitors revert the upregulation of S100A4. MACC1 overexpression increases transwell migration in S100A4-proficient CRC cells, but not in S100A4-knockout cells. Mechanistically, MACC1 stabilizes β-catenin post-transcriptionally through phosphorylation of serine 552. Further, the mRNA expression of MACC1 and S100A4 correlates positively in two independent CRC patient cohorts.
Conclusions: MACC1 upregulates S100A4 via Wnt/β-catenin signaling and drives CRC cell motility in a S100A4-dependent manner. S100A4 is the effector of MACC1-driven cell motility in CRC. Depletion of S100A4 with neutralizing antibodies and small-molecule inhibitors will be tested against MACC1-driven CRC.

Disclosure Statement: No conflict of interest to declare.

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Targeted Chemotherapy Using VLP and Hydrogel

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Purpose: Most effective chemotherapeutics show a number of side effects due to the fact, that they damage both, cancer cells and non-cancer cells. Therefore, there is an immense need for targeted therapy options. Virus like particles (VLPs) are a candidate delivery system for therapeutics. With the aid of VLPs we aimed to apply a non-targeted therapy (Oxaliplatin and Paclitaxel) in a targeted way. Furthermore, we investigated the usefulness of hydrogel techniques for a continuous application.
Methods: In this study, we treated five cell lines of different entities (SKBR-3, SW480, SW620, L3.6, PaTu-8988T) with Oxaliplatin and Paclitaxel in four groups: A) we added Oxaliplatin (250µM) or Paclitaxel (100µM) to the medium (as positive control). B) We added VLPs, which were dialyzed with Oxaliplatin or Paclitaxel overnight. C) We treated the cells with hydrogel containing Oxaliplatin or Paclitaxel respectively, and D) we treated the cells with hydrogel containing VLPs, which were dialyzed with Oxaliplatin or Paclitaxel overnight. We performed Cell titer Blue (CTB) for cell viability measurement after 7/14/21 days (n=3).
Results: CTB assays show a significant decrease of cell viability applying Paclitaxel containing VLPs (16% cell viability after 7 days in SKBR-3, 15% in SW480, 16% in SW620, 10% in L3.6 and 6% in Patu-8988T), whereas Oxaliplatin does not accumulate well in VLPs due to its molecular weight. Applying hydrogel shows a continuous effect even after 21 days.
Conclusions: Applying chemotherapy via VLPs offers an opportunity to minimize side effects and enhance the antitumor-effect. However, not all therapeutics can be accumulated in VLPs. The hydrogel technique offers a continuous application of chemotherapy with a high local efficiency. Both methods can be combined to achieve an effective and targeted therapy.

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Diagnostic Leukapheresis as a Liquid Biopsy to Collect Circulating Tumor Cells in Breast Cancer Patients – Clinical Safety

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Purpose: The prognostic relevance of CTCs has been shown for all settings of breast cancer. The low number of CTCs detected by established methods limits the possibility for further evaluation. Implementation of diagnostic leukapheresis (DLA) enables detection of CTCs at high frequency. The aim of this clinical study was to assess the safety of DLA in 39 patients with primary and metastatic breast cancer.
Methods: DLA was performed at least 1d before surgery or chemotherapy. Complete blood count as well as measuring blood pressure and heart rate was performed before and after DLA. CTCs in DLA products were enumerated using CellSearch.
Results: In 2/41 patients DLA could not be performed due to technical problems. 26 patients had non metastatic breast cancer. 13 patients were diagnosed with MBC. Severe adverse events resulting in interruption of apheresis were not observed. DLA did not interfere with the start of chemotherapy or surgery. Complete blood count before and after DLA showed statistic significant but clinically irrelevant decrease in numbers of leukocytes, thrombocytes, hemoglobin and the percentage of hematocrit. 11/21 DLA samples (52%) of patients with primary breast cancer contained CTCs (1 - 51). 11/13 DLA samples (85%) of patients with MBC contained CTCs (1 - 2913).
Conclusions: Establishing a routine DLA protocol we demonstrated that this procedure is clinically safe and can be implemented into the clinical workflow of breast cancer patient care.

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Repositioned Drugs for Targeted Therapy of Biomarker Driven Cancer Metastasis

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Purpose: Biomarkers are important tools to stratify patients for their cancer and metastasis risk. MACC1 and S100A4 are drivers and prognostic biomarker for cancer progression and metastasis in a large variety of solid tumor types, particularly colorectal cancer. Patients expressing both biomarkers have the worst prognosis. Therefore, we are aiming to target both biomarkers simultaneously.
Methods: We used two independent luciferase reporter based high throughput screenings (HTS) comprising over 34000 compounds of four different compound libraries. Similarly, the LOPAC library was screened for S100A4 inhibitors. Most promising compounds were characterized in vitro using qRT PCR, Western Blot, EMSA, cell viability and motility assays. For MACC1 possible drug–target docking was shown in silico. To analyze the dependence of MACC1 on post-translational modifications Mass spectrometry and mutant forms of MACC1 were used additionally. We demonstrated the in vivo drug effects by bioluminescence imaging of xenografted mice. Patient samples were analyzed by qRT PCR.
Results: Two independent HTS revealed a statin as most potent MACC1 transcriptional inhibitor. They remarkably inhibited MACC1 promoter activity and expression resulting in reduced cell motility. Statins impair the binding of the transcriptions factors c-Jun and Sp1 to the MACC1 promoter. In CRC-xenografted mice, it restricted MACC1 expression and liver metastasis. MACC1 gets phosphorylated by MEK1. The phosphorylation of MACC1 by MEK1 is necessary for the MACC1 induced phenotype. Niclosamide was identified as most potent inhibitor for S100A4 gene expression. It lowered cell motility in vitro and metastasis formation in vivo. Targeting both biomarkers synergistically reduced cellular motility and proliferation.
Conclusions: This is the first identification of inhibitor combinations restricting cancer progression and metastasis via the biomarkers MACC1 and S100A4. This drug repositioning might be of therapeutic value for CRC patients stratified for expression of both MACC1 and S100A4.

Other Topics

Best-of-Abstracts-Vorträge

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Durability of Response with Larotrectinib in Adult and Pediatric Patients with TRK Fusion Cancer

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Purpose: Genomic rearrangements involving *NTRK1/2/3* result in constitutively active TRK fusion proteins that are oncogenic drivers in multiple cancers. Larotrectinib is a selective TRK inhibitor approved for the treatment of any TRK fusion cancer based on a primary analysis in 55 pts from 3 clinical trials. We now report median duration of response (DOR) data in this primary cohort, and updated data in an expanded cohort of 159 total TRK fusion pts treated with larotrectinib, with 153 (55 primary + 98 supplemental) evaluable for efficacy.

Methods: Patients with TRK fusion cancer detected by local molecular profiling were treated with larotrectinib across 3 studies (NCT02122913, NCT02637687, NCT02576431). Disease status was assessed by using RECIST1.1. Data cut-off was 19 Feb 2019.

Results: In the primary cohort of 55 pts with a median follow-up of 26 mo, the median DOR in 44 pts with complete or partial responses was 35.2 mo (95% CI 21.2–NE), with 17 progression events and 27 responses ongoing (range 1.6 –44 mo). The median PFS in the primary cohort was 25.8 mo (95% CI 9.9–NE), with 27 pts having progressed. In the expanded combined dataset, the most common tumor types included soft tissue sarcoma (n=36), infantile fibrosarcoma (n=29), thyroid carcinoma (n=26), salivary gland carcinoma (n=21), and lung cancer (n=12). The median age was 43 yrs, ranging from <1 mo to 84 yrs; 33% <18 yrs. The overall ORR was 79% (95% CI 72–85), with complete responses in 16%. Adverse events were primarily grade 1-2, with 13% of pts having had a grade 3-4 event related to larotrectinib. Only one pt discontinued due to an AE related to larotrectinib.

Conclusions: These data confirm the tissue-agnostic efficacy and long durability of response in pts with TRK fusion cancer treated with larotrectinib. Larotrectinib continued to demonstrate a favorable long-term safety profile. Screening pts for *NTRK* gene fusions should be actively considered.

Disclosure Statements:
Serge Leyvraz reports personal fees from Immunocore, and Bayer outside the submitted work.
David M. Hyman reports Consulting or Advisory Role: Chugai Pharma, CytomX Therapeutics, Boehringer Ingelheim, AstraZeneca, Pfizer, Bayer, Genentech, and Research Funding: AstraZeneca, Puma Biotechnology, Loxo, Bayer, Travel, Accommodations, Expenses: Genentech, Chugai Pharma.
Cornelis M. van Tilburg reports Bayer: advisor, and Novartis: advisor.
Catherine M. Albert none.
Daniel S.W. Tan reports Consultancy: Novartis, Merck, Loxo, AstraZeneca, Roche, Pfizer, Travel: Pfizer, Boehringer Ingelheim, Roche, Honoraria: BMS, Takeda, Novartis, Roche, Pfizer, and Research funding: Novartis, GSK, AstraZeneca.
Birgit Geoerger none.
Anna F. Farago reports Research support - Bayer Healthcare, Loxo Oncology, Inc., Genentech, Roche, Bristol-Myers Squibb, AstraZeneca, AbbVie, PharmaMar, Merck, Ignyta, Amgen, Novartis, Consultant - Bayer Healthcare, Loxo Oncology, Inc., Genentech, Roche, Bristol-Myers Squibb, AstraZeneca, AbbVie, PharmaMar, Boehringer Ingelheim, and Honorarium – DAVA Oncology, Clinical Care Options, Medical Learning.
Theodore W. Laetsch reports Consultancy: Novartis, Bayer, Loxo, Lilly, and Research funding: Pfizer, Novartis, Bayer, Loxo, Abbvie, Amgen, Atara, Biotherapeutics, BMS, Lilly, Epizyme, GSK, Janssen, Jubilant Pharmaceuticals, Novella Clinical, Servier.
Shivaani Kummar reports Bayer: advisory board, honoraria, travel support.
François Doz reports BAYER: travel expenses, advisory board, and ROCHE: advisory board.
Ulrik Lassen reports Bayer advisory board.
Steven G. DuBois reports Loxo: consultancy and travel expenses, and Roche: travel expenses.
Ray McDermott reports Travel expenses: Janssen-Cilag, Pfizer, Honoraria: Bayer, Sanofi, Janssen, Astellas, BMS, MSD, Pfizer, Novartis, Clovis, and Research funding: Sanofi, Janssen, Bayer, Astellas.
Leo Mascarenhas reports Bayer: speaker bureau.
Jordan Berlin reports Research funding: PsiOxus, Bayer, EMD Serono, Symphogen, Roche/Genentech, Immunomed, Honoraria, Nestle, and Consulting/advisory, Rafeal, Seattle Genetics, EMD Serono, Bayer, eisai, Taiho, Armo,Gritstone, Astra Zeneca, Celgene, Erytech.
Erin R. Rudzinski wird nachgereicht.
Michael C. Cox was an employee of Loxo Oncology Inc.
Shivani Nanda is an employee of Bayer.
Barrett H. Childs is an employee of Bayer.
Alexander Drilon reports HONORARIA/ADVISORY BOARDS: Ignyta/Genentech/Roche, Loxo/Bayer/Lilly, Takeda/Ariad/Millenium, TP Therapeutics, AstraZeneca, Pfizer, Blueprint Medicines, Helsinn, Beigene, BergenBio, Hengrui Therapeutics, Exelixis, Tyra Biosciences, Verastem, MORE Health, ASSOCIATED RESEARCH PAID TO INSTITUTION: Pfizer, Exelixis, GlaxoSmithKlein, Teva, Taiho, PharmaMar, RESEARCH: Foundation Medicine, ROYALTIES: Wolters Kluwer, OTHER: Merck - Food/Beverage, Puma - Food/Beverage, and CME HONORARIA: Medscape, OncLive, PeerVoice, Physicians Education Resources, Targeted Oncology, Research to Practice.
David S. Hong reports Research/Grant Funding: AbbVie, Adaptimmune, Amgen, Astra-Zeneca, Bayer, BMS, Daiichi-Sankyo, Eisai, Fate Therapeutics, Genentech, Genmab, Ignyta, Infinity, Kite, Kyowa, Lilly, LOXO, Merck, MedImmune, Mirati, MiRNA, Molecular Templates, Mologen, NCI-CTEP, Novartis, Pfizer, Seattle Genetics, Takeda, Travel, Accommodations, Expenses: LOXO, MiRNA, ASCO, AACR, SITC, Genmab, Consulting or Advisory Role: Alpha Insights, Axiom, Adaptimmune, Baxter, Bayer, Genentech, GLG, Group H, Guidepoint Global, Infinity, Janssen, Merrimack, Medscape, Numab, Pfizer, Seattle Genetics, Takeda, Trieza Therapeutics, and Other ownership interests: Molecular Match (Advisor), OncoResponse (founder), Presagia Inc (Advisor).

Poster

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Prähabilitation VOR Onkochirurgischen Eingriffen

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Purpose: It has long been known that regular exercise protects against chronic diseases, reduces the overall risk of mortality, and has enormous potential for preventive medicine, especially with regard to the genesis of tumors..
Methods: Literature review.
Results: The purpose of the following article is to give an overview of the current status and preparation for major surgical operations.
Conclusions: Nutrition in the operative discipline makes sense. There are now appropriate guidelines.

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Assessment of Treatment Options for Operated Patients with Stage IIIA Non-Small Cell Lung Cancer (NSCLC) Based on Baden-Württemberg Clinical Cancer Registry Data

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Purpose: This analysis aimed at assessing whether cancer registry data can be used to show different treatment options of NSCLC stage IIIA patients in the state of BW.
Methods: The analysis is based on data from BW Cancer Registry on diagnoses from 2014 to 2016. The data included UICC stage IIIA NSCLC (ICD-10: C34) patients, based on cTNM (version 7 and 8), who received anatomic or atypical resection after being diagnosed. Neoadjuvant therapy was defined as a start of therapy within 7 to 14 weeks prior to resection, adjuvant therapy was characterized by a start of therapy within 60 days after surgery. The data consists of reports from hospitals in BW and is based on the ADT/GEKID-dataset.
Results: 1.038 stage IIIA NSCLC patients were included in the analysis. Of those, 453 received surgical tumor resection, whereof 79% were primary resections. Another 13% (n=59) of the operated patients received neoadjuvant therapy. Over time (year of diagnosis 2014 to 2016), the frequency of neoadjuvant therapy increased from 8% to 20% whereas the frequency of initially operated patients decreased from 84% in 2014 to 74% in 2016. From the primary resected patients, 39% were treated with adjuvant therapy.
Conclusions: First evaluations with data from BW Cancer Registry on the application of different oncological treatment strategies are feasible. The analysis of various treatment modalities in the clinical practice is particulary vital for heterogeneous groups of tumor patients such as stage IIIA NSCLC patients. With further improvement of data quality and timeliness of data in the upcoming years, advanced analyses – also to show the application of new therapy strategies – can be realized.

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Prevalence of Dietary Supplement Use in Patients with Cancer

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Purpose: The use of dietary supplements (DS) such as phytopharmaceuticals, trace elements and vitamins represents a rapidly growing market. It is often believed that DS from natural sources are harmless, non-toxic and health-supporting. However, use of DS is frequently not reported to doctors (1), although evidence regarding negative interactions between DS and cancer treatment is increasing (2). This survey investigated prevalence of DS use in patients with cancer.
Methods: We conducted a survey in 756 outpatients (aged 70.4±11.9) undergoing cancer treatment, using a self-administered questionnaire about frequency of intake, type of DS, changes in dietary habits, source of information and motivation for DS use.
Results: 49.3% of patients reported current intake of DS, with a higher frequency in women (53.7 vs. 44.9%, p<0.001). 39.4% started intake of DS and 47.2% changed their dietary habits upon cancer diagnosis. Patients listed oncologists (32.3%), GP´s (30.7%) and print media (29.9%) as source of information. Only 15.5% of patients received consultation by dietitians. Phytopharmaceuticals (15.2%), calcium (14.4%), vitamin B complex (13.1%) and multivitamin supplementation (11.5%) were the most frequently taken supplements. 28.3% of patients stated supporting the immune system as the main reason for taking DS.
Conclusions: Our data imply that a relevant proportion of patients take DS and change their nutritional habits after cancer diagnosis. Knowing about the potential interactions between DS and anti-cancer treatment, these results emphasize the need for assessment of DS, and phytopharmaceuticals in particular.

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Disclosure Statement: The authors declare no conflict of interest.

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Ultrasound Guided Biopsy of Lymph Nodes

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Purpose: Enlarged lymph nodes are often in malignant diseases, especially lymphoma. A reliable histology is the backbone to plan therapy. The gold standard to get a reliable histology particularly in lymphoma is the surgical excision. But a excision is invasive and need resources. Ultrasound is an easy and broadly available procedure also for a guided biopsy. Here we report about target regions, efficacy and rate of complications.
Methods: This is a retrospective analysis of ultrasound g. biopsies in our division. Device: Toshiba Aplio 400. According to localization we used a convex array transducer, with biopsy application or a linear array transducer, with "free hand" technique. We applied True-cut needles with a range from 14 to 18G. The b. were done under local anesthesia and aseptic conditions. From each localization we obtained three b. on average and a cytology. Complications were graded in three categories: 1 for minor up to 3 for severe c..
Results: 1276 biopsies in different organs, therefrom 402 (31%) are lymph nodes. Results of this lymph node b.: 45% carcinoma, 39% lymphoma, 14% non- malignant and 2% no reliable histo.. Lymphoma subdivision: 54% high malignant NHL, 42% low mal. NHL and 4% Hodgkin-L.
Locations: neck: 40,6%, groin 20%, axilla: 18%, abdomen: 11%, retroperitoneum: 6%, iliacal: 2%, mediastinum 1%, miscellaneous: 0,4%.
Reliable histology: 98%, no need of further interventions.
Complications: 3%. Mostly minor c. like short pain.

Conclusions: Our analysis shows that ultrasound g. biopsy achieved a reliable histology in 98% with no need of further interventions. Complications occurred in 3% (mostly minor c. like short pain). Thus we conclude that surgical excision is maybe not the gold standard for the first line and should be reserved for the cases of uncertain histology. Our result could be base for a prospective randomized study: surgical excision versus ultrasound guided biopsy in lymph nodes.

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Disclosure Statement: No conflict of interest.

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Shared Decision-Making in Cancer Care: Ongoing Process Evaluation of a Stepped Wedge Cluster Randomized Implementation Trial

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Purpose: Shared decision-making (SDM) is highly relevant in oncology, demanded by patients and prioritized by health policies. However, routine implementation continues to lag. Implementation science stresses the importance of a thorough process evaluation when conducting implementation studies. The aim of this study is to evaluate the process of a multicomponent implementation program designed to foster SDM in routine cancer care.
Methods: The stepped wedge implementation study is conducted in three cancer care departments. It consists of training and coaching of clinicians, patient activation, provision of information material and decision aids, revision of quality management documents, and reflection of current organization of tumor boards. We conducted a mixed methods process evaluation, including interviews with recipients, field notes, and documentation of actual delivery of implementation strategies in each clinic, giving insights into reach and fidelity of implementation.
Results: We concluded the second of three implementation phases. We trained 50% of eligible clinicians. Facilitators included leadership support and delivery of training during regular meeting slots. Barriers included staff shortage and competing demands. 44% of clinicians participated in individual coaching. Adaptations regarding dose and timing of delivery were necessary. Information and patient activation material were distributed in all parts of the clinics. Revision of quality management documents and reflection of tumor boards progressed, but its implementation took more time than expected. Results of process evaluation of the third and final implementation phase will be presented at the conference.
Conclusions: Process evaluation offers reliable insights into the realization of a complex SDM implementation program in cancer care. Although we were generally able to pursue the implementation strategies, adaptations to the study protocol were necessary. Outcome evaluation will reveal whether reach was sufficient to foster SDM implementation.

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Translation, Adaption and Psychometric Testing of the German Version of the Organizational Readiness for Implementing Change Measure (ORIC)

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Purpose: For the successful implementation of shared decision-making (SDM) in routine cancer care, organizational readiness for change might be a crucial factor. The 10-item measure Organizational Readiness for Implementing Change (ORIC) assesses change commitment and change efficacy from the healthcare professionals' (HCPs') perspective. The ORIC was not available in German yet. The aim of the study was to translate the ORIC into German, adapt it for the context of SDM, and assess its psychometric properties.
Methods: We translated the original English ORIC into German using a team translation protocol. The translated version was revised according to comprehensibility assessment via cognitive interviews with HCPs. For psychometric evaluation we used data from a SDM implementation study. Secondary analysis included analysis of acceptance (response rate), structural validity (exploratory factor analysis, confirmatory factor analysis), item characteristics (item difficulties, corrected item-total correlations, inter-item correlations), and reliability (Cronbach's α).
Results: We analyzed n=11 cognitive interviews and n=230 questionnaires. Translation and adaption of the ORIC was successful except for item 10, which showed low comprehensibility. Response rate was > 97%. Structural validity analysis provided a one factorial structure. Item difficulties ranged between 55.98 and 65.32, corrected item-total-correlation ranged between .66 and .74, inter-item correlations ranged between .43 and .72, and Cronbach's α was .93.
Conclusions: This study provides the first German ORIC, a brief and highly accepted measure with satisfying psychometric properties. To increase comprehensibility of the measure we suggest removing item 10. The German ORIC can be used to analyze organizational readiness for change as a precursor for implementation success in routine cancer care in German-speaking countries.

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Patient's Expertship Improves Medical Demand Research – A Cooperation with the German Federal Association of Throat Cancer Patients

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Purpose: Medical demand research has to integrate the view of the relevant patient groups. How is it possible to use the expert knowledge of patients for this questionnaire-research?
Methods: Two interview studies were started together with the German Federal Association of Throat Cancer Patients. We used a three step algorithm for developing the questionnaires: 1. Narrative interviews with 3-4 patients about the specific topic (project 1: Loss os smell after laryngectomy, project 2: interests in artificial intelligence). 2. Developing prototypes of questionnaire together with the interview patients , and 3. Pilot interviews with one self-help group and lingual adaption / correction of the questionnaires.
Results: The finalized questionnaires were distributed according the population data of German federal states via the (federal state) self-help groups. The questionnaire and the letter of introduction were sent along with a stamped addressed envelope for the return of the questionnaire. 198/293 patients answered in the medical project 1 (67.6%). The questionnaire about artifical integlligence was filled out by 151/293 patients (51.5%). Both representive data pools are used by medical staff as well as patient interest groups. Patient's answers for both questionnaires will be avaiable in detail at the congress.
Conclusions: Integration of patient's expertship improves the quality and acceptance of questionnaires in medical demand research..

Disclosure Statement: The authors disclose any conflict of interest.

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Undergraduate Medical Education in Radiation Oncology: A Student's Perspective

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Purpose: Radiation oncology is an integral part of the medical studies curriculum in Germany. However, the specialization is taught differently in medical schools. We aimed to provide a differentiated view about teaching methods used in German medical schools in order to give recommendations and actively integrate medical students into research and clinical practise.in the field of radiation oncology.
Methods: An online survey containing 10 questions was sent to 40 members of the German society of radiation oncology (DEGRO e.V.) students working group (Club100). A questionnaire of students who are not members of the working group but registered at the same university was included for each completed questionnaire (matched pair design).
Results: 18 questionnaires were completed by student members of "Club 100" (responsive rate: 45%) and analyzed for congruence to responses of the same university. All students were in the clinical part of their studies at the time of the survey. 36% of the respondents reported that radiation oncology was taught exclusively during the 3rd year of their study. 40% indicated that radiation oncology was taught over several semesters (5th – 10th). 100% of the students stated the subject was taught via classical lecture-style teaching. 20% of all respondents had to attend a compulsory clinical rotation during their study program. 100% of the lecturers were offering clinical electives in their department. 44% of the students stated the possibility of attending an optional course in radiation oncology, 60% of all respondents reported that the completion of a doctoral thesis in radiation oncology was actively promoted. 33% of the students indicated that the discipline was taught in an integrative manner during other courses.
Conclusions: Radiation oncology is taught in classic lecture-style teaching. Several medical schools integrate radiation oncology during other courses. Lecturers need to evaluate optimal knowledge transfer and practise-orientated training methods in order to actively involve medical students into the field of radiation oncology.

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Implementation of a Culture-Sensitive Training Course for Volunteering in Hospice Care

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Purpose: Hospice care aims the support of patients and their relatives in advanced state of illness and at the end of life. It is important to preserve their quality of life. Hospice care provides to support emotional, social, and spiritual needs independent of cultural/religious affiliation or ethnic origin. Volunteers are very important in hospice care. They work with patients and families, and also with caregivers and physicians. At University Hospital Essen patients from all over the world are medicated. Research shows a poor access to end-of-life care for ethnic minorities (Jansky, 2013).

The aim of this study is to learn more about the different and similar attitudes of volunteers taking our culture-sensive course, to establish a curriculum based culture-sensitive volunteer training and finally to reach better access to hospice care for more patients.
Methods: To recruid volunteers we started an advertisement in a newspaper. Furthermore, we used social media (Facebook, Instagram) to promote our project. To inform the potential volunteers we invited to information-meetings. After face-to-face interviews we included 12 volunteers. After completing training, we interviewed them, and they got a questionnaire to get more information about personal and spiritual meanings.
Results: The age oft the volunteers is between 30 – 60. Nearly 90% are women. Nationalites are german, turkish, slovak and polish. The access to hospice- and palliative care increases in ethnic minority families. The volunteers communicate with patients in native language. Information about the opportunities in hospice and palliative care could be provided better.
Conclusions: The culture-sensitive volunteer training allows a better access to hospice and palliative care for all people and a better communication between patients, families and caregivers.

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Development and Evaluation of a Patient Empowerment Intervention to Support Shared Decision-Making in Cancer Care

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Purpose: Many cancer patients want active engagement in treatment decision-making. Interventions like Ask 3 Questions (A3Q) encourage patients to ask questions during clinical encounters and strengthen their abilities to engage in decision-making processes. A3Q was developed in Australia and different versions of the A3Q intervention were used in implementation programs around the globe. So far, A3Q was not available in German. Aims of this study were to develop a German version of the intervention and to assess its feasibility and acceptance in German routine cancer care.
Methods: Different English versions of the A3Q intervention were translated into German following a team translation protocol. Comprehensibility and relevance were tested via cognitive interviews with n=10 cancer patients. Acceptance and feasibility were assessed in focus groups and interviews with cancer patients, physicians and nurses. Focus groups and interviews were analyzed using qualitative content analysis.
Results: In cognitive interviews, cancer patients of different age (49.0 years ± 11.27), gender (f=5, m=5), years with disease (4.8 years ± 3.55), and health literacy levels participated. Comparison and testing of different A3Q versions led to a revised version that was well understood and seen as relevant for cancer patients. We conducted focus groups and interviews with n=24 cancer patients of different cancer entities, n=17 nurses and n=7 physicians. A3Q was perceived as a helpful tool to encourage patients to ask more questions in clinical encounters. It was also seen as a guideline for physicians in supporting to remember to answer important questions. Barriers and facilitators of the use of A3Q in routine care will be presented at the conference.
Conclusions: This study provides a German version of the A3Q intervention. Preliminary results suggest that A3Q could be a helpful instrument to empower patients to play an active role in decision-making processes. Barriers and facilitators must be analyzed carefully to understand how to best implement the A3Q intervention in German routine care.

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How to Make Multidisciplinary Team Meetings in Cancer Care More Patient-Centered? Recommendations from a Narrative Review

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Purpose: Multidisciplinary team meetings (MDTMs, also called tumor boards) are considered best practice in cancer care. However, MDTMs

have been found to mostly discuss medical information and pay little attention to the patient's perspective and psychosocial situation. Hence, the current organization of MDTMs has been argued to not support patient centered-care (PCC) and shared decision-making (SDM) between physicians and patients. This review aimed to identify recommendations for MDTMs to become more patient-centered.
Methods: A narrative review of existing literature recommending strategies to foster interdisciplinary communication and patient-centeredness in MDTMs was conducted. Two researchers with ample experience in SDM research in cancer care including observational studies in MDTMs reviewed the literature. Extracted recommendations were discussed with clinical cooperation partners at a comprehensive cancer center in Germany.
Results: We extracted recommendations from 30 publications, which included original research and reviews as well as opinion pieces. This led to 13 recommendations regarding the following areas:

1) routine pathways and quality management standards (e.g., consistent denomination as MDTM recommendation instead of decision);
2) participants (e.g., discussion of a case only if at least one participant has met the patient);
3) information discussed during MDTMs (e.g., documentation of more than one possible treatment, if uncertainty exists during meeting);
4) tasks of the MDTM chair (e.g., communication and leadership training for MDTM chairs).

After discussion with clinical cooperation partners, changes in the setting emerged as a fifth area (e.g., u-shaped seating arrangement).
Conclusions: Since MDTMs in their current organization do not foster PCC and SDM, recommendations for changes towards more PCC and SDM in MDTMs were reviewed and consolidated. Those recommendations can be used to inform implementation effort to foster patient-centered MDTMs and SDM in cancer care.

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Implementation of an Interprofessional Counseling Program for Complementary and Integrative Health Care at CCCS in Baden-Wuerttemberg (CCC – Integrativ)

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Purpose: Up to 80% of all cancer patients want complementary and integrative health care approaches (CIH) be part of their treatment. Positive effects have been proven for some CIH procedures such as yoga, acupuncture and herbal drugs. However, risks are also associated with CIH procedures e.g. drug interactions. Within a clinical trial an interprofessional, evidence-based CIH counselling program will be established at four CCCs in Baden-Wuerttemberg.
Methods: Aim is to empower patients during the first 6 months after diagnosis and to advise them on chances and risks of CIH. Counselling is offered by interprofessional teams of specially trained doctors and nurses accompanied by intersectoral activities.Within a controlled, non-randomized implementation study 2,000 patients (n=500 per CCC) will be included in the intervention group and receive CIH counselling (min. 3 contacts within 3 months). Primary outcome is the PAM-13, a predictor of patient activation. PAM-13 and secondary outcomes (e.g. quality of life, self-efficacy, clinical parameters) will be measured at baseline (T1), after 3 months (T2) and 6 months follow-up (T3). Data collection of the control group (n=500) will start prior to the intervention using identical instruments for primary/secondary outcomes at T1, T2, T3. Health insurance data will be analyzed to evaluate the use of health care services. Process evaluation will be conducted to identify relevant barriers and enablers for later implementation.
Results: The study design will be presented.
Discussion: The results will provide relevant information for future comprehensive and evidence-based CIH roll-out.
Funded by the Innovationsfonds of the Federal Joint Committee 2019-2022.

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Titel Clone: Clinical Trials in Oncology in the New Era of OMICS, Big Data, and Modeling. A BMBF Funded Summer School of the Krukenberg Cancer Center Halle (KKH) in Systems Medicine

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Purpose: Innovative data in cancer biology and bioinformatics are revolutionizing the understanding of cancer and have profound implications on the design of clinical trials with novel ethical and legal challenges. BMBF funded Summer Schools could be a platform facilitating interdisciplinary knowledge transmission from research to healthcare.
Methods: CLONE (a five-days program) was planned to bring physicians and researchers from various disciplines in Systems Medicine together to illuminate personalized oncology. The proposal of the KKH was accepted within the BMBF e:Med Summer school grant in September 2018. Participants from Germany and abroad were competitively selected by a panel of experts based on submitted abstracts. The faculty included thirty-eight national and international experts in their fields.
Results: CLONE took place from 24-28 June 2019 in Halle (Saale). A total of 23 participants from five countries qualified. The following topics were discussed: Day 1: Stratified versus personalized cancer medicine; emerging developments in Omics and Big Data Analytics in Life Sciences. Day 2 (Omics): Genomics; Epigenetics; Proteomics. Day 3: (Big Data): Bioinformatics; Modeling and simulation; real world data including registries. Day 4: (Clinical Trials in the era of Big Data): Planning and designing a clinical trial; Preparing a trial; Science versus regulations. Day5 (Engaging and communicating with patients): Ethical and legal considerations; Patients perspectives. Three poster walks and four workshops in molecular pathology, proteomics, epidemiology and clinical trials were held. A daily evening program was offered.
Conclusions: BMBF funding allowed a scientific exchange across different disciplines relevant for cancer research and treatment. The need for collaborative programs to analyse the vast amount of research data and how to translate the results into prognostic biomarkers and tailored clinical studies with targeted therapies were emphasized.

Disclosure Statement: Summer School was funded by BMBF. All authors have nothing to declare.

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Cancer Drugs Affect the Interaction of Nanoparticles with an in Vitro Placenta Barrier

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Purpose: The incidence of cancer during pregnancy increases. In industrialized countries women delay pregnancy to older ages, where the overall risk of cancer occurrence is elevated. Superparamagnetic iron oxide nanoparticles (SPION) can serve as imaging contrast for magnetic resonance imaging for early cancer detection in pregnant women. No harmful potential for the developing fetus is expected. In this study we analyzed the influence of common cancer drugs on the behavior of SPIONs and a model blood-placenta barrier.
Methods: A tri-culture model was used in a Transwell setting: Human trophoblast representing placenta cells (BeWo) and pericytes (hPC-Pl) formed the cellular barrier and reporter cells (MCF7 for doxorubicin and paclitaxel and K-562 for imatinib) were place in the target compartment. The cells were exposed to 0.002 mg/ml doxorubicin, 0.006 mg/ml paclitaxel or 20 µM imatinib for 48h, and then 100 µg/cm² neutral starch-coated SPIONs were added for 24h. Barrier integrity was verified by trans-endothelial resistance (TEER), molecular permeability and immunfluorescence staining of tight junction protein ZO-1. The passage of the therapeutic agents was evaluated via determination of the reporter cells by flow cytometry (Annexin V APC/PI) or MTS assay. The distribution of SPIONs was evaluated by atomic absorption spectroscopy.
Results: Both, TEER and molecular permeability assay showed a negative influence of doxorubicin and paclitaxel on blood-placenta barrier integrity. No additional effects were observed by the presence of the neutral-charged SPIONs. Doxorubicin markedly reduced ZO-1 expression indicating loss of cell-cell contacts. Imatinib exhibited minor effects. Doxorubicin and paclitaxel reduced the proportion of vital MCF7 to 44.4% ± 0.7% and 49.1 ± 2.5%, whereas imatinib reduced vitality of K-562 to 40% ± 4%. In the presence of the chemotherapeutics 1.5-fold more SPION can pass the *in vitro* barrier, but do not alter vitality of reporter cells.
Conclusions: Therapeutic agents enable increased passage of SPIONs through an in vitro blood-placenta barrier.

Late-Breaking Abstracts

Breast Cancer

Poster

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Does Collagenase Treatment of Capsular Fibrosis Favor the Spread of Triple Negative Breast Cancer Cells?

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Purpose: CCH can be a valuable treatment option for capsular contracture after silicone based breast reconstruction. The aim of this project was to determine whether the treatment with the Collagenase bacterium histolyticum (CCH) could be hazardous for patients with Triple- negative-Breast-Cancer (TNBC) harboring residual tumor cells.
Methods: In order to determine the effect of CCH treatment on TNBC cells we used human MDA-MB-231 TNBC cells in various in-vitro assays including proliferation (MTT), cell cycle distribution (FACS) and apoptosis induction (FACS). In addition, MDA-MB-231 cells (1x10^6) transfected with Firefly-luciferase were used in a mouse model (NSG) to assess the possible spread of the tumor cells in response to CCH treatment. An orthotopic tumor was induced and monitored for 21 days using bioluminescence imaging and caliper measurements.
Results: In the in-vitro experiments a significant reduction of cell viability was observed, as indicated by a 20% reduced proliferation of cells in response to CCH treatment. This effect was caused by a slightly increased incidence of apoptotic cells as confirmed by FACS analysis. Regarding the cell cycle analysis, no significant changes were observed. In vivo, the CCH treatment at the dosage used caused no toxic side effects (skin perforation, bleeding). Most importantly, the monitoring of the tumor growth by bioluminescence imaging and caliper measurements indicated no signs of tumor spread in the treated animals.
Conclusions: CCH treatment shows no pro-metastatic effect on MDA-MB-231 tumors but rather appears to inhibit cell-proliferation. Thus, there is no indication of an increased risk for TNBC patients receiving CCH treatment.

References:

Disclosure Statement: This study was sponsored by Endo Pharmaceuticals inc.

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Predictors of Cardiorespiratory Fitness in Healthy and Cancer-Diseased Women with a Germline BRCA1/2 Mutation Participating in the Libre-1 Trial

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Purpose: *BRCA1/2* mutation carriers are at an increased risk of developing breast and ovarian cancer compared to non-carriers. Studies indicate that cardiorespiratory fitness is an age-independent predictor of

tumor-specific mortality in sporadic breast cancer survivors. The impact of the cardiorespiratory fitness on cancer prevention and prognosis in *BRCA1/2* mutation carriers is unknown. Therefore, the purpose of the study was to identify predictors of cardiorespiratory fitness (VO_{2peak}) in healthy and cancer-diseased *BRCA1/2* mutation carriers.
Methods: 68 healthy and cancer-diseased *BRCA1/2* germline mutation carriers were recruited for the LIBRE-1 trial from university hospitals (Cologne, Kiel and Munich) in Germany. At study entry they were examined using cardiopulmonary exercise testing, accelerometer assessments and a questionnaire survey about their physical activity levels during adolescence (age 10 - 19 years) and the socioeconomic status. Additionally, they received a psychological questionnaire according to the theory of planned behavior asking about their attitude, intention, normative and behavior towards physical activity. Multivariate logistic regression models were used to identify predictors of the women's age-adjusted VO_{2peak}.
Results: Of the 68 participants (median age 42 (IQR: 33 – 50) years), 46 (68%) were cancer survivors. The strongest predictor for a higher age-related VO_{2peak} in the regression model was a positive attitude towards physical activity (Odds Ratio (OR) = 3.0; 95% CI = 1.3 – 8.4; p = 0.021). Neither the cancer-disease status nor the physical activity level during adolescence had a significant influence on the VO_{2peak} of *BRCA1/2* mutation carriers in this analysis.
Conclusions: The attitude towards physical activity seems to play a role in the current VO_{2peak} status in healthy and cancer-diseased *BRCA1/2* mutation carriers. Physical activity during adolescence and the health and socioeconomic status do not influence VO_{2peak}.

Disclosure Statement: The study was funded by the Deutsche Krebshilfe. There is no conflict of interest.

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Impact – Implementing Patients' Competence in Oral Breast Cancer Therapy – A Randomized, Controlled Study of Standardized Patient Coaching Versus Patient Management According to Local Practice for Patients with HR Positive HER2 Negative Metastatic Breast Cancer Treated with Abemaciclib

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Purpose: Oral agents, like CDK4/6 inhibitors, provide an attractive approach for the treatment of metastatic breast cancer. However, this type of therapy requires a high level of self-management competence by the patient. The non-interventional study (NIS) IMPACT intends to evaluate the effectiveness of a standardized patient education and coaching for therapy management provided by specially trained oncology nurses regarding persistence rate, side effects management and unplanned therapy interruptions in outpatient oncology care for patients under Abemaciclib treatment.
Methods: 212 Patients with HR+, HER2- MBC who are treated with Abemaciclib according to clinical routine will be enrolled in approx. 30 sites. Patients will be randomized to standardized patient coaching (based on MOATT®) or patient management according to local practice, respectively. Follow up is documented for a maximum of 24 weeks.
Results: Data of 212 MBC patients regarding a potential effect of standardized patient coaching on the persistence rate after 24 weeks of Abemaciclib therapy will be presented. Quality of live data as well as data regarding patient reported self-efficacy, side-effects, health related stress and therapy related knowledge will be presented.
Conclusions: The effectiveness of standardized patient coaching is observed and analyzed in a real-world setting to understand its benefits for MBC patients under Abemaciclib treatment with regard to therapy adherence and patient self-management competence.

Disclosure: Manfred Welslau; Advisory Role: AMGEN, BMS, Celgene, GILEAD, HEXAL, Janssen, Lilly, medac, NOVARTIS, Roche, SANOFI Expert Testimony: Ja, BMS; Honorare: AMGEN, astellas, AstraZeneca, Celgene, GILEAD, HEXAL, Janssen, Lilly, NOVARTIS, Roche, SANOFI;

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Prognostic Impact of IGKC in Breast Cancer Patients Treated with Adjuvant Chemotherapy

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Background: In previous work we could demonstrate that the presence of IgKC positive tumor infiltrating plasma cells was associated with a better prognosis in node-negative breast cancer patients who didn't receive any adjuvant treatment after operation and irradiation. In the present study we evaluated the prognostic significance of IgKC in breast cancer patients who were treated with chemotherapy according to the CMF or FEC scheme in the adjuvant setting.
Methods: IgKC expression was immunohistochemically analyzed in 234 breast cancer patients who received after operation and irradiation an adjuvant chemotherapy according to the CMF or FEC scheme between 1993 and 2001 at the department of gynecology and obstetrics of the university hospital Mainz with a median follow up of 11 years. From the 234 immunohistochemical stained tumor slides 193 were suitable for evaluation: 78 of the CMF- und 115 of the FEC cohort. The prognostic impact of IgKC expression was evaluated by Kaplan Meier survival analyses as well as uni – and multivariate Cox-Regression. Immunohistochemically determined IgKC expression levels were compared to the corresponding mRNA values in 65 patients using Spearman correlation.
Results: Kaplan Meier analyses identified IgKC as a prognostic marker in regard to the MFS: higher IgKC expression was correlated with a better outcome (p=0.02 Log Rank). Results of univariate Cox Regression confirmed the prognostic impact of IgKC expression: patients with a strong IgKC expression had a longer MFS compared to the patients with a weak IgKC expression (HR1.931; p=0.025). Multivariate cox regression showed an independent prognostic significance of IgKC expression (HR 2.486, p=0.012). Immunohistochemically determined IgKC correlated significantly with IgKC mRNA expression (ρ = 0.304; p=0.014).
Conclusion: IgKC expression had independent prognostic impact in the analyzed cohort of 193 breast cancer patients who received adjuvant chemotherapy.

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A Companion App to Improve Quality of Life and Adherence to Adjuvant Treatment in Early Breast Cancer Patients

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Purpose: Mobile applications (apps) can support cancer patients regarding their needs. The use of apps can reduce symptom burden and increase adherence for cancer therapy. Non-adherence rates to endocrine therapy (ET) range from 31% to 73%[1]. Consequently these patients have a poorer prognosis due to recurrence, progression and cancer death.

Methods: In an interdisciplinary approach we developed "Meine Busenfreundin" as a companion app. The app provides breast cancer patients with an instrument to accompany, inform, motivate and support them from diagnosis up to follow up care. The patient enters some data concerning her disease and person and creates an individual "medical profile": based on these data she will receive personalized information and support. By autonomous use she gets a tool for a self-determined contribution to her therapy.
Results: In a pilot study with 30 patients, the app got evaluated and usability was verified and confirmed.
Conclusions: This to our knowledge the first companion app for breast cancer patients turned out to be acceptable and feasible in a pilot study. Additionally we set up a protocol for a randomized, prospective, multicenter clinical trial to search out whether the therapy-conducted loss of quality of life can be reduced by the use of the app. The burden of the therapy and its side effects often result in unauthorized discontinuation of the therapy by patients. This study shall furthermore find out, whether the use of the app can also reduce the discontinuation-rate and therefore increase adherence to ET and improve outcome.

Reference:
1. Murphy et al, Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. Breast Cancer Res Treat. 2012 Jul;134(2):459-78.

Disclosure Statement: Government funding for this project is granted by the Bavarian Ministry of Economic Affairs, Regional Development and Energy. The funding agency has no role in the design and conduct of the study. Kiechle, M. and Große Lackmann, K. are equity owners of Meine Busenfreundin GmbH.

Cancer Prevention

Vorträge

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Risk-Adapted Screening for Prostate Cancer in Young Men – First Results of the Probase Trial

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Background: Prostate cancer (PCa) is the most frequent cancer and second leading cause of cancer-related death in men. The German "Prostate Cancer Early Detection Study Based on a Baseline PSA Value in Young Men" (PROBASE) aims at improving the specificity of a PSA based screening while preserving the sensitivity to detect metastatic disease in a prospective randomized controlled setting.
Methods: Between February 2014 and December 2019, more than 46,500 participants will have been randomized at four study sites in Germany to an immediate (arm A) and a 5-years deferred (arm B) PSA baseline measurement at age 45. The combined primary endpoints are the non-inferiority of the sensitivity to detect metastasis at age 60 and the superiority in terms of specificity using a delayed start of screening at age 50.
Results: At the time of last data cut-off, 20,402 (89.16%), 2,141 (9.36%), and 340 (1.49%) of participants in arm A had initial PSA values of < 1.5 ng/ml, 1.5-2.99 ng/ml, and ≥ 3 ng/ml, respectively. Only 185 were confirmed with a PSA value $\geq$ 3ng/ml (0.81% high risk). Mean and median PSA values in arm A were 0.896 ng/ml and 0.740 ng/ml, respectively. Participants at high risk had mean and median PSA values of 5.26 ng/ml and 4.12 ng/ml, respectively. Biopsy was performed in 113 of 185 (61.1%) men at high risk, 108 (95.6%) of those had a prior mpMRI. Thus, biopsy was performed as MRI/ultrasound fusion biopsy with an additional systematic biopsy (at least 12 cores). All biopsies and PCa were confirmed by reference pathology. A digito-rectal examination (DRE) as part of the statutory early detection program in Germany was offered to participants in arm B and data will be provided from 6.523 participants.
Conclusion: A risk-adapted PSA-based screening strategy at young ages (45 years) must include a confirmatory PSA value. An updated analysis of the first screening round data will be performed after the end of recruitment with a data-cut off at December 31, 2019. These results will be presented.

Funding: Deutsche Krebshilfe, Bonn

Poster

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Role of Resident Gynecologists in the Care of Counselees with Family Cancer Burden - A Needs Analysis

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Purpose: Investigating the need for and interest in education on genetic tumor syndromes in gynecology among resident gynecologists.
Methods: An 11-question online survey was conducted from 09-11/2019 and addressed 563 registered gynecologists in Berlin and Brandenburg. The survey concentrated on the incidence and handling of patients with family cancer burden in gynecological practices. It focused on the knowledge of resident gynecologists on genetic risk assessment and identification of patients at risk and their referral to specialized tumor genetic clinics.
Results: 97 respondents (17,2%) completed the survey. Whereas, 87 gynecologists (89,7%) take family history on a regular basis, only 13

gynecologists (13,4%) dared to assess the risk of hereditary tumor burden. Furthermore, knowledge of inclusion criteria for specialized tumor care consultation was limited among the interviewed gynecologists. Therefore, only 37 gynecologists (38,1%) referred patients to specialized tumor genetic clinics correctly.
While 59 gynecologists (60,8%) see 1-3 patients per week with gynecologically relevant cancers in the family, others (37,1%) see 4-5 or more than 5 patients per week.
74 respondents (76,3%) agreed, that comprehensive knowledge about hereditary cancer risks could improve the care of their patients.
Finally, 89 gynecologists (91,8%) stated interest in further education on genetic tumor syndromes in gynecology and 86 gynecologists (88,7%) already registered for the planned training course.
Conclusions: This survey emphasizes the high relevance of genetic tumor syndromes in outpatient gynecological care. The self-assessments of gynecologists showed some uncertainties in risk assessment, inclusion criteria and the referral to specialized centers. In this context, we develop a training course based on blended learning that is tailored to the special needs of gynecologists in outpatient practices.

Central Nervous System Tumors

Poster

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Impact on Long-Term Survival of Pre-OP Frailty of Patients with Limited Brain Metastases

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Introduction: Brain metastasis represents a major complication of many oncological diseases with a significantly shorter overall survival. In view of the generally poor prognosis, clinical decision making between not harming the patient and potentially withholding a therapeutic option can sometimes be very challenging. Thus the aim of this study was to identify whether easily leviable scores may be potentially useful to predict survival in this setting.
Methods: Patients within our retrospective cohort (n=100, median age 63.6 years) had undergone brain surgery because of one or more brain metastases in our institution. This cohort includes 52 patients with NSCLC, 27 patients with breast cancer, 8 patients with colorectal carcinoma and 13 patients with kidney cancer. To categorize these, we used different score systems which were capable to evaluate the patient in relation to self-sufficiency, activity and self-determination as part of activities of daily living. The used scores were: ECOG-Status, Karnofsky-Index, Barthel-Index, ASA-Classification, Katz-Index. Pre-processing and analysis of the data was implemented using KNIME, while we used the R-plugin nodes to perform the final statistical tests with R.
Results: Our analysis reveals that most of the frailty scores we tested on our patient population are able to give a reliable prediction on the overall survival after brain metastasis surgery. The survival rates decrease significantly with a lower score in all tested score systems, except the ASA-Risk score. In particular, a Katz Index <6 was identified to have a significant correlation with a lower cause specific survival (CSS) (HR 3.33, 95%-CI [2.17-5.00]; p-Value = $9.6*10^{-9}$).
Conclusion: Pre-operative frailty status measurements by indices of daily living represent a powerful predictor for overall survival after resection of brain metastases. Especially the easy and fast applicable Katz-Score is a very helpful pre-operative tool to assess the pre-operative status, which could be additionally included in clinical decision making in daily practice.

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The Prognostic Role of H3K27 Trimethylation in Meningioma

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Purpose: The prognostic role of the histone methylation H3K27 in meningioma has been described recently. The H3K27 trimethylation status can be detected immunohistochemically and could therefore be integrated into the routine diagnostic workflow to provide prognostic information for the clinical management of meningioma patients. The aim of this study was to assess the prognostic value of H3K27 histone trimethylation in a large single center cohort of meningiomas with defined clinical subgroups.
Methods: We included 429 patients with complete clinical data and available tissue who underwent meningioma resection between April 2011 and December 2015 at the University Hospital Tübingen. We performed H3K27me3 immunohistochemical staining, which was evaluated by two independent investigators. Correlation with clinical parameters (WHO grade, brain invasion, Simpson grade, age, gender, progression free survival) was performed using univariate and multivariate cox regressions as well as Fisher's exact and Log-Rank test.
Results: At the time of abstract submission, a total of 429 meningiomas were analyzed with a female to male ratio of 3.2, mean age of 59 years (range 15.84 – 89.95) and mean follow-up at 31 months (range 1.76 – 95.72). Univariate analysis showed a significant negative prognostic impact of male gender (p=0.0236), WHO grade II/III (p=0.0057), Simpson grade >2 (p<.0001) and H3K27me3 loss (p=0.0007). In the multivariate analysis Simpson grade and H3K27me3 status remained independent prognostic factors for meningioma recurrence (p = 0.0001 and 0.0084, respectively). H3K27 trimethylation loss was more common in male patients explaining the loss of prognostic impact of gender after inclusion of the histone methylation status in the multivariate analysis.
Conclusions: Loss of the trimethylation of H3K27 is an independent prognostic factor and in line with prior studies. Further correlations with clinical subgroups will be presented. Our data could help to continue the discussions on the clinical utility of H3K27me3 staining in meningioma.

Conflict of interest: None.

Developmental Therapeutics: Cytotoxic Chemotherapy

Poster

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Anti-Tumor Activity of CT913 In Vitro and In Vivo

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Purpose: CT913 is an anti-tumoral compound with a novel chemical structure. CT913 was designed not only to be an effective compound against cancer but also to be well tolerated in humans.
Methods: Different human tumor cell lines were maintained in specific culture medium. The cells were incubated with CT913 in a time dependent manner. Cell cycle analysis and apoptosis were accessed by flow cytometry using propidium iodide (PI) and Annexin-V/PI. Proteins, such as p21, p53, phospho-p38 and phospho-Erk1/2, were detected by western blotting. Expression of phospho-Erk1/2 in the cells was confirmed by flow cytometry after PMA stimulation. For metabolism studies, RP-HPLC methods combining UV- and MS-spectroscopy were used. A benzidine induced breast cancer and a human melanoma xenograft mouse model were used for animal studies.
Results: CT913 is a novel broad-spectrum antitumor agent inducing apoptosis in different human tumor cells. In addition, one metabolite (M1) of CT913 was investigated. CT913 and M1 both induced apoptosis via cell cycle arrest in G1/S after up-regulation of p21 and p53 and increased DNA-Damage-Response (DDR) over a longer time period resulting in metabolic and genomic instability. CT913 was designed according to Reverse-Metabolic-Drug-Design (RMDD) rules to deliver a well-tolerated anticancer drug. CT913 demonstrated antitumor activity in human breast cancer and malignant melanoma animal models.
Conclusions: CT913 shows an unique efficacy profile, triggering a deleterious metabolic cascade by addressing different decisive targets, such as damaging tumor metabolism on DNA-level, simultaneously blocking a specific repair system, triggering genomic and metabolic instability, and production of aberrant proteins possibly appearing on the surface of tumor cells (epigenetic changes) allowing the natural host defense system to recognize and attack these transformed cells.

Disclosure Statement: Nothing to declare

Developmental Therapeutics: Immunotherapy/Cellular Therapy

Vorträge

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The B Cell Maturation Antigen (BCMA) Chimeric Antigen Receptor (CAR) T Cell Therapy Idecabtagene Vicleucel (Ide-Cel; Bb2121) in Relapsed and Refractory Multiple Myeloma (Rrmm): Outcomes from a Phase 1 Study Support the Phase 3 Karmma-3 Study Design to Compare IDE-Cel Versus Standard Triplet Regimens

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Purpose: Despite new treatment options for myeloma, poor overall survival has been reported in patients with RRMM after >3 prior therapies. The CRB-401 phase 1 study (NCT02658929) evaluated ide-cel, a BCMA CAR T-cell therapy, in RRMM patients who received ≥3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, or were refractory to both drug classes. The objective response rate was 85% (45% complete response rate) and median progression-free survival (PFS) was 11.8 months (95% CI, 6.2–17.8.[1] All 16 evaluable responding patients were minimal residual disease (MRD)-negative ($\leq 10^{-4}$ nucleated cells).[1] Ide-cel has been granted PRIME eligibility in RRMM by the European Medicines Agency. KarMMa, the phase 2 pivotal study (NCT03361748), has completed accrual (140 patients as of November 2018). Informed by these studies, KarMMa-3 (NCT03651128), a phase 3 multicenter randomized trial, is designed to confirm the efficacy and safety of ide-cel in earlier treatment lines.
Methods: KarMMa-3 compares the efficacy and safety of ide-cel to those of standard triplet regimens in RRMM. Eligible patients have received 2–4 prior regimens, including an immunomodulatory drug, proteasome inhibitor, or daratumumab, and are refractory to their last therapy. Patients will be randomized 2:1 to receive either ide-cel treatment ($150–450 \times 10^6$ CAR+ T cells) or a standard triplet regimen such as daratumumab, pomalidomide, and dexamethasone (DPd); daratumumab, bortezomib, and dexamethasone (DVd); or ixazomib, lenalidomide, and dexamethasone (IRd); at the investigator's discretion. The primary endpoint is PFS. Secondary endpoints include overall survival, safety, MRD-negative status, and health-related quality of life. Patient accrual is ongoing.
Conclusions: Data from CRB-401 in patients with RRMM who received ≥3 prior therapies support investigating ide-cel in earlier treatment lines, as planned in KarMMa-3.

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Initial Results from a Phase II Study (TACTI-002) in Metastatic Non-Small Cell Lung or Head and Neck Carcinoma Patients Receiving Eftilagimod Alpha (Soluble Lag-3 Protein) and Pembrolizumab

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Purpose: Eftilagimod alpha (efti) is a soluble LAG-3 protein that binds to a subset of MHC class II molecules to mediate antigen presenting cell (APC) activation and then CD8 T-cell activation. The stimulation of the

dendritic cell network and subsequent T cell recruitment with efti may lead to stronger anti-tumor responses than observed with pembrolizumab alone. Combining an APC activator with an immune checkpoint inhibitor aims to increase efficacy without additional toxicity. We hereby report initial results of a phase II trial (NCT03625323).
Methods: The study is based on a Simon's 2-stage design, with objective response rate (ORR) as primary endpoint. Secondary endpoints include progression free and overall survival, PK, PD and immunogenicity. During the 1st stage of the study, patients (pts) regardless of PD-L1 expression are recruited into: A: 1st line, PD-X naïve NSCLC; B: 2nd line, PD-X refractory NSCLC; C: 2nd line PD-X naive HNSCC. Additional pts (N2) will be recruited for each part if the pre-specified threshold for ORR is met. Up to 109 pts will be enrolled. Efti is administered as 30 mg subcutaneous injection every 2 weeks for 8 cycles and then every 3 weeks for 9 cycles. Pembrolizumab is administered at a standard dose (200 mg intravenous infusion every 3 weeks for up to 2 years). The study was approved by ethics committees and institutional review boards.
Results: Between Mar and Dec 2019, 42 pts were enrolled. The mean age was 66 years (range 48-84) and 74 % were male. The ECOG was 0 in 57 % and 1 in 43 % of the pts, respectively. The most common (≥ 10%) adverse events being cough (26 %), asthenia (21 %), decreased appetite (17 %), fatigue (17 %), diarrhea (14 %) and dyspnea (14 %). All pts of part A (n=17) are evaluable for efficacy. Seven pts (42 %) had a partial response and six (35 %) pts had stable disease according to iRECIST leading to an ORR of 42 %. 11 (65 %) pts are still under therapy and 10 (59 %) have reached the 6 months landmark.
Conclusions: Thirty (30) mg efti s.c. every 2 weeks in combination with pembrolizumab is safe and shows encouraging antitumor activity in all comer PD-L1 1st line NSCLC.

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Enhanced Recruitment and Immunosuppression-Shielding Enables T Cell Therapy in Solid Tumors

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Purpose: CAR T cell therapy is remarkably successful in patients with hematological malignancies, in some cases inducing durable remissions. However, it remains ineffective in solid tumors, due to limited access to the cancer site and the subsequent immunosuppression. Overcoming these limitations is critical to enable CAR T cell therapy translation into solid tumors. We propose that engineering CAR T cells with the C-C chemokine receptor 8 (CCR8) can improve migration towards solid tumor tissues. Further, simultaneous engineering with a dominant-negative TGF-β-receptor 2 (DNR) allows T cell proliferation despite TGF-β, a well-studied cytokine that suppresses T cell cytotoxic potential and proliferative capacity, that can be found in high amounts in certain solid tumors, such as pancreatic adenocarcinoma.
Methods: We used 6- to 10-week-old female mice from C57Bl/6 or NSG strains and experiments were performed in a blinded and randomized manner. The tumor cell lines used for this study were either Panc02, Panc02-CCL1, Panc02-OVA-EpCAM, or SUIT-2-MSLN-CCL1. Effects have been assessed through flow cytometry, multi-photon intra-vital microscopy and tumor size measurements.
Results: We observed improved functionality of our CCR8-DNR CAR T cells compared to the control conditions. *In vivo* we demonstrated the enhanced infiltration capacity conferred by CCR8 through intra-vital multi-photon microscopy. Pancreatic tumor challenge experiments showed, both for murine syngeneic and human xenograft models, significant reduction of tumor burden with improved survival rates. Lastly, analysis of a large sample of patients led to identification of genetic hallmarks that sustain the employment of this rationale not only to pancreatic tumors but also breast, colon and skin tumors.
Conclusion: Our results show that CCR8 and DNR can effectively be employed to render CAR T cell therapy effective in solid tumors.

Poster

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Medical Gas Plasma Technology – An Emerging Immunostimulatory Anticancer Agent

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Purpose: Therapy of skin cancer including malignant melanoma has made significant progress in the past years. However, a fraction of patients still does not benefit from therapy or acquires drug resistant cancers, motivating the need of new therapeutic avenues. Medical gas plasma technology is an emerging tool to reduce tumor growth in vitro and in vivo that mainly acts via local release of a plethora of reactive oxygen and nitrogen species.
Methods: Human and murine melanoma cells were treated in vitro with plasma technology. Cellular function and viability as well as immunogenic properties were characterized. In a syngeneic B16F10 melanoma model, tumors were exposed to either gas plasma or positive control imiquimod. The intratumoral immune infiltrate and splenic leukocytes were characterized by multicolor flow cytometry. Moreover, mice were vaccinated with plasma-treated melanoma cells and later re-challenged with viable melanoma cells to investigate the extent of immunoprotection via ROS-induced tumor cell death.
Results: Gas plasma induced cell death was observed in a pro-immunogenic fashion in vitro and in vivo. In mice, plasma-treated tumors as well as positive controls showed elevated levels of infiltrated leukocytes. Splenic immune cells re-stimulated with melanoma cells in vitro showed an enhanced activation. Moreover, 50% of animals were protected from melanoma growth in mice vaccinated with plasma-treated melanoma cells.
Conclusions: Medical gas plasma technology may serve as novel tool to target skin cancer in an immunogenic fashion.

Disclosure Statement: Nothing to disclose.

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RNA Editing as a tool to Improve Sensitivity to Immunotherapy

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Purpose: Immunotherapy had drastically improved success in treatment of cancers. But despite this remarkable clinical success many patients do not respond to immunotherapy, or develop therapeutic resistance. For this reason, the need for development of novel strategies that sensitize tumours to immunotherapy currently in use, is urgent.
Methods: Mutations within a tumour lead to a higher sensitivity to immunotherapy[1]. It is assumed that increased mutation correlates with an increase in neoepitope/antigen formation, and therefore increased sensitivity to T cell attack. Therefore, a method leading to increase neoepitope formation specifically in cancer cells would be optimal solution to sensitize tumours to immunotherapy. The RNA editing enzyme ADAR1 is highly expressed in many human tumours and can be re-targeted to

coding regions in a sequence-specific manner. The main goal here is to test whether ADAR1 re-targeting to coding regions will increase the level of tumour "neoantigenicity" and thus render the tumour sensitive to immune checkpoint blockade.
Results: All the available systems to induce RNA editing were evaluated in their efficiency to re-code, exogenously and endogenously expressed, transcripts. Differently from Cas13b based system[2], lambda-N-ADAR and SNAP-ADAR technologies[3,4] were able to induce editing in both contexts.
Conclusions: Our data show that RNA editing can be retargeted to re-code specific transcripts. These results disclose the possibility to use RNA editing to create "neo-epitopes" within cancer cells, sensitizing them to recognition and subsequent killing/clearance by T cells.

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Disclosure Statement: Re-targeted RNA editing can be used to generate "neo-epitopes" within cancer cells.

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Innovative Antibody Fragment-Based Targeted Constructs as Bispecific Treatment Option for Medulloblastoma

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Purpose: Medulloblastoma (MB), the most frequent malignant brain tumor in children shows overexpression of the EGF-receptor. Radio-and chemotherapy often results in severe long-term side effects in children. Therefore, targeted treatment options are urgently needed. Our innovative approach is to evaluate bispecific T-cell engagers (BiTEs) with already established EGFR-specific scFvs as targeted therapy for MB. The structure and specificity allows a BiTE to link a T cell to a tumour cell, stimulating T cell activation, tumour killing and cytokine production. Using BiTEs in MB, they must cross the Blood-Brain-Barrier (BBB). To evaluate the diffusion kinetics of BiTEs, we want to test them in a novel in vitro-BBB-model.
Methods: EGFR-overexpression in MB-cell lines, human and mouse MB-biopsies was tested in flow cytometry, immunohistochemistry or western blot. To obtain BiTEs the EGFR-specific scFvs were fused to a CD3-specific scFv joined by a flexible linker. The BiTEs were expressed in HEK-293T cells and purified using the His-Tag. Effector- and target-cell specificity was demonstrated via flow cytometry. To test the cytotoxicity apoptosis and flow cytometry based assays were used.
Results: Surface EGFR-overexpression was proven in mouse and human SHH-MB. BITEs show specific binding to effector and to EGFR-expressing MB-cells. Human PBMCs were incubated with various concentrations of BiTES and activation was confirmed using anti-CD69 staining. The BiTEs demonstrate specific apoptotic effects in a 5:1 effector to target cell ratio.
Conclusions: EGFR-specific BiTEs show first promising results in MB and will be tested in a BBB-model. The latter will be composed of human inducible pluripotent stem cells and MB cells in the basolateral compartment. Having a functional cloning/expression system available, the target-scFv can be exchange by novel antigens to obtain new immunotherapeutic options.

Disclosure Statement: The authors disclose no conflict of interest.

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Safety and Efficacy Results From Transcend NHL 001, a Multicenter Phase 1 Study of Lisocabtagene Maraleucel (Liso-Cel) In Relapsed/Refractory (R/R) Large B-Cell Lymphoma (LBCL)

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Purpose: To evaluate the safety, antitumor activity, and PK of liso-cel in R/R LBCL (NCT02631044).
Methods: Patients (pts) aged ≥18 y had R/R DLBCL not otherwise specified, HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements, PMBCL, or FL grade 3B after ≥2 lines of therapy, and ECOG PS of 0–2. Pts with mild/moderate organ dysfunction and secondary CNS lymphoma were eligible. Bridging therapy was allowed. Liso-cel was given at 50×10^6 (dose level [DL]1), 100×10^6 (DL2), or 150×10^6 (DL3) viable CAR+ T cells. Primary end points were treatment-emergent adverse events (TEAEs) and ORR. Secondary end points were CR rate, duration of response (DOR), progression-free survival (PFS), and overall survival (OS).
Results: Of 344 pts leukapheresed, 269 received liso-cel (DL1, n = 51; DL2, n = 177; DL3, n = 41). Median age was 63 y (range, 18–86 y; ≥65 y, 42%; ≥75 y, 10%). 26% of pts had ≥4 lines of prior therapy (median, 3; range, 1–8), 67% were chemorefractory, 44% had never achieved CR, and 59% had bridging therapy. 25 pts received liso-cel as outpatients. Outcomes were similar across DLs, so data were pooled. 79% of pts had grade ≥3 TEAEs, mostly cytopenias. 47% of pts had CRS and/or NEs, with late onset (median, 5 and 9 days, respectively). Grade ≥3 CRS (2%) and NE (10%) incidence was low. Four grade 5 liso-cel–related TEAEs occurred. Safety was similar among pt subgroups. All primary and secondary efficacy end points were met. Of 256 efficacy-evaluable pts, ORR was 73% (95% CI, 67–78); CR rate was 53% (95% CI, 47–59). Responses were similar across pt subgroups. Median DOR was not reached (NR; 95% CI, 8.6-NR) with 12.0 mo of median follow-up; median DOR for pts in CR was NR (95% CI, NR-NR). Median PFS was 6.8 mo (95% CI, 3.3–14.1). Median OS was 21.1 mo (95% CI, 13.3-NR).
Conclusions: Liso-cel showed durable clinical activity with a favorable safety profile across R/R LBCL histologic subgroups and in pts with poor prognosis, including chemotherapy refractory, older age, comorbidities, and high tumor burden. Incidence of severe CRS and NEs was low, with late onset, allowing for outpatient administration.

Developmental Therapeutics: Molecular Therapeutics

Poster

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Efficiency and Toxicity of Lenvatinib in Advanced HCC in Later Treatment Lines

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Purpose: Until 2018 sorafenib was the only first-line systemic treatment option for advanced hepatocellular carcinoma (HCC). Ten years later a new agent, called lenvatinib, showed equal efficiency in comparison to sorafenib. Currently sorafenib and lenvatinib are options for first line treatment with regorafenib, cabozantinib and ramucirumab (if alpha fetoprotein > 400 ng / ml) as second-line treatment choices. Yet, it has so not demonstrated, if lenvatinib is an option for a treatment line beyond the second.
Methods: In this study, we selected 5 patients with advanced HCC from our hospital, who had been treated with local ablative procedures as well as at least three different systemic therapies before receiving lenvatinib. Retrospective analysis was performed to investigate clinical and radiolic response rates as well as side effects.
Results: 3/5 patients achieved regression in third and fourth treatment lines. One patient showed stable disease, and only one of these five patients showed a mixed response. The toxicity profile was heterogeneous. One patient developed a mild hand-foot syndrome. Another one evolved hypertension. One patient developed proteinuria leading to stop treatment. Developing psychiatric disorder, which ws possibly associated with lenvatinib could be seen in one patient. Response was independent of the underlying cause of HCC.
Conclusions: Lenvatinib is a promising agent for treating advanced HCC in later treatment lines and revealed a tolerable toxicity profile.

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Disclosure Statement: AEK: Speaker fee from Eisai

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The Effect of the Triazene Compound CT913 on Ovarian Cancer Cells in Vitro and its Interaction with PARP-Inhibitors

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Purpose: The identification of innovative therapeutic strategies for ovarian cancer, extending the therapeutic spectrum of PARP-inhibition (PARPi) beyond HR-deficiency, is of high clinical interest. In this regard, the combination of PARPi with either biological anti-cancer agents or chemotherapy is a promising strategy for defining new therapeutic standards. Here, we analysed the therapeutic effect of novel triazene derivatives, including the drug CT913 and its metabolite CT913-M1 on ovarian cancer cells and describe their interaction with PARPi.
Methods: *In vitro* assays for drug characterization were applied in a panel of six ovarian cancer cell lines.
Results: CT913 treatment conferred a dose-dependent reduction of cell viability in a set of platinum-sensitive and platinum-resistant ovarian cancer cell lines with an IC_{50} in the micro- to almost millimolar range (107-940µM), whereas its metabolite CT913-M1 was about 10-fold more potent with an IC_{50} of 17-93µM. Platinum-resistant Res2-Igrov-1 cells were more sensitive so CT913-M1 treatment than parental platinum-sensitive Igrov-1 cells. However, in a combined treatment with cisplatin (CP), neither CT913 nor CT913-M1 increased the cytotoxic effect of CP. CT913 and CT913-M1 alone were more effective in BRCA1-deficient compared to isogenic BRCA1-proficient ovarian cancer cells, indicating that homologues recombination repair may contribute to its mechanism of action. As our key finding, we showed that CT913 sensitized for Olaparib treatment, independently of BRCA-1 status.
Conclusion: This is the first study, suggesting the triazene drug class CT913 as potential combination candidate for extending the therapeutic spectrum and window of PARPi.

Disclosure Statement: The authors declare that no conflict of interest exists.

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Updated Efficacy and Safety of Entrectinib in Patients (PTS) with NTRK Fusion-Positive (NTRK +) Tumors: Integrated Analysis of STARTRK-2, STARTRK-1, and ALKA-372-001

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Purpose: Entrectinib is a systemic and CNS-active, potent inhibitor of TRKA/B/C and ROS1. Primary data from integrated efficacy and safety analyses (6 mo follow-up) from clinical trials have shown that entrectinib is a promising option for pts with *NTRK*+ solid tumors; blinded independent central review (BICR) objective response rate (ORR) was 57.4% (95% CI 43.2–70.8). We show longer follow-up data from this integrated analysis.
Methods: Pts with locally advanced/metastatic *NTRK*+ solid tumors confirmed by nucleic acid-based methods and enrolled in global (>150 sites, 15 countries) Phase 1/2 entrectinib trials (ALKA [EudraCT 2012-000148-88], STARTRK-1 [NCT02097810], STARTRK-2 [NCT02568267]) were included. Tumors were assessed after 4 wks (Cycle 1) then every 8 wks. Scans underwent BICR using RECIST v1.1. Primary endpoints were ORR and duration of response (DOR) by BICR. Secondary endpoints included overall survival (OS); ORR and DOR in pts with and without baseline CNS disease; intracranial (IC) ORR and DOR in pts with baseline CNS disease; safety.

Results: There were 54 adults in the efficacy-evaluable population with advanced/metastatic *NTRK*+ solid tumors, including pts with baseline CNS metastases. As of Oct 30, 2018 (additional 5 mo follow-up), BICR ORR was 59.3% (95% CI 45.0–72.4); complete responses n=4 (7.4%). Median BICR DOR was 12.9 mo (95% CI 7.9–NE) and median OS was 23.9 mo (95% CI 16.8–NE). Per baseline CNS status, BICR ORR was 58.3% (95% CI 27.7–84.8) and 59.5% (95% CI 43.3–74.4) and median DOR was NE (95% CI 4.2–NE) and 12.9 mo (95% CI 7.9–NE) for pts with (n=12) and without (n=42) CNS disease, respectively. IC ORR was 54.5% (95% CI 23.4–83.3) and median IC DOR by BICR was NE (95% CI 6.7–NE). Entrectinib was well tolerated with a safety profile consistent with previously reports; there were no new or unexpected safety findings.
Conclusions: In line with the primary data, these results at an additional 5 mo of follow-up show that entrectinib induced clinically meaningful, durable systemic and intracranial responses in pts with *NTRK*+ solid tumors.

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Genomic Landscape of Entrectinib Resistance from Circulating Tumor DNA (CTDNA) Analysis in STARTRK-2

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Purpose: Entrectinib is a small molecule inhibitor of ROS1 and TRKA/B/C with deep and durable responses in *ROS1* fusion-positive NSCLC (*ROS1*+) and *NTRK1,2,3* fusion-positive solid tumors (*NTRK*+). Despite clinically meaningful activity, progression on entrectinib eventually occurs. Understanding the mechanisms of resistance could inform subsequent new personalized therapeutic options in these patients (pts).
Methods: Blood samples were collected at baseline and at time of progression from most pts in the *NTRK*+ and *ROS1*+ populations enrolled in STARTRK-2 (NCT02568267). These were tested using the Foundation Medicine FoundationOne Liquid NGS-based test that assesses base substitutions, indels and rearrangements from 324 genes (including *ROS1* and *NTRK1,2,3*), as well as copy number alterations from select genes using ctDNA extracted from the plasma of pts from pre-treatment and following progression on entrectinib.
Results: Of the 54 pts with *NTRK*+ tumors, 29 had paired samples at baseline and progression at data cut-off. 10 pts (35%) had a detectable NTRK solvent front mutation at disease progression (NTRK1: n=5; NTRK3: n=5); not detected in the pre-treatment sample. *BRAF* V600E and *KRAS* G12D mutations were detected at progression from a pancreatic cancer pt who had a partial response. Of the 53 pts with *ROS1*+ NSCLC, 18 had paired samples at baseline and progression at data cut-off. 4 CD74-ROS1 and 1 SLC34A2-ROS1 pts showed the emergence of an acquired ROS1 resistance mutation (G2032R and F2004C/I) at disease progression (28%); both not present pre-treatment. 1 *NRAS* Q61K mutation was detected at the end of treatment collection sample from a pt who had a partial response.
Conclusions: From blood analysis, acquired resistance mutations were detected in 35% of *NTRK*+ solid tumor and 28% of the *ROS1*+ NSCLC cohorts, all of which were mutations in the kinase domain of the oncogenic driver. 1 additional pt from each cohort showed the emergence of a mutation in an oncogene within the MAPK pathway. Resistance to entrectinib can occur by multiple mechanisms; this should be studied in larger cohorts.

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A Final Report of the Phase I/IB Study of the Smoothened/Hedgehog Pathway inhibitor Sonidegib Combined with Azacitidine in Relapsed or Refractory AML and MDS Patients

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Background: Despite the remarkable improved response rates and new standard combining the BCL-2 inhibitor Venetoclax with hypomethylating agents (HMAs) or Low-dose AraC (LDAC) in newly diagnosed elderly AML patients, the outcome of HMA and Venetoclax relapsed or refractory (R/R) AML and MDS patients remains dismal. We identified inhibition of Hedgehog pathway (HP) genes as a potential rational combination to overcome a priori and acquired HMA resistance. The smoothened (SMO)/ hedeghog pathway inhibitor glasdegib has recently been approved with LDAC in newly diagnosed AML and glasdegib with HMA in upfront treatment has shown activity. To date there is no study combining a SMO inhibitor in R/R AML and MDS. Here we report the final results of the first study combining the SMO inhibitor Sonidegib (SON, LDE225) in combination with Azacitidine (AZA) in 35 patients with R/R AML or MDS.
Results: In a Ph1 (3+3) dose escalation and Ph1B (expansion cohort) study 10 and 25 pts respectively were treated both arms. DLTs occurred at 400mg SON consisting of COP elevation and the MTD of the SONAZA combination was determined at 200mg SON daily and AZA 75mg/m2 for 7 days each cycle every 28 days at which level 1 pt had grade 3 vomiting (possibly related) and a 2nd pt had grade 3 fatigue (probably related).
Of 28 pts evaluated at the MTD dose level of 200 mg 2 pts had a CR and MLFS, however 20 pts had no progression, only 2 pts progressed and 4 pts could not be assessed. At a median follow up of 8.7 ms, the overall survival (OS) in the AML cohort was 7.6 ms with most of the pts having failed prior HMA based treatment and/ or cytotoxic chemotherapy. The 6 ms OS was 50%. More remarkable, 1/3 of patients had a long response ranging from 7-24 ms, despite having failed prior HMA.
Biomarker analysis of long-vs short responders is ongoing to identify pts at chance of durable responses and will be presented at the meeting.
Conclusion: Combined SMO and HMA treatment in R/R AML and MDS shows encouraging responses and biomarker stratification will help to identify pts for a personalized medicine approach in hematology.

Epidemiology

Poster

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The Direct Effect of Social Disparity on Head and Neck Cancer Survival: Preliminary Results

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Purpose: Despite recent clinical improvements of cancer treatment in Germany, a marked difference in cancer survival based on socio-economic factors persists[1]. We aim to quantify the direct effect of socioeconomic inequality on head and neck cancer survival, on the district-level, independent of modifiable external factors.
Methods: Patients diagnosed with head and neck cancer in1998-2014 from 10 German cancer registries (covering 32 million residents) were included in our analysis. The Socioeconomic position of the patients was determined using the German Index of Socioeconomic Deprivation (GISD) assigned to German districts. The 5-year age-standardized relative survival was calculated and stratified based on GISD quintiles. We used mediation analysis to differentiate between total effect of social inequality and the amount meditated through treatment, stage at diagnosis, or number of hospital beds available at the respective district.
Results: The majority of the head and neck cancer patients lived in the most deprived districts compared to the least deprived districts (11,203 vs 7,791). Although the mean age at diagnosis was lower in the deprived districts, less patients were alive at the end of follow-up (40.1% vs. 53.4%). 80.0% of patients in the least deprived districts received radiotherapy treatment compared to 61.1% of patients in the most deprived districts. The 5-year age-standardized relative survival of patients living in the most deprived districts compared to those living in the least deprived districts was 60.0% vs 53.3% respectively.
Conclusions: Our preliminary results showed differences in survival with respect to socioeconomic position. Our descriptive analysis also suggests a notable inequality when it comes to treatment received.

Reference:

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Gastrointestinal (Colorectal) Cancer

Vorträge

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Lefitolimod vs Standard of Care (SOC) for Patients with Metastatic Colorectal Cancer (mCRC) Responding to First-Line Therapy: Results from IMPALA Trial

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Purpose: The TLR9 agonist lefitolimod broadly activates the innate and adaptive immune system. Lefitolimod was evaluated in this phase 3 trial as switch maintenance treatment in patients with mCRC who have responded to first- line therapy.
Methods: The international, multicenter, open-label phase 3 IMPALA trial was conducted including the AIO, TTD and GERCOR cooperative groups. The study recruited 549 patients across 8 European countries including 191 patients from German sites. Patients with an objective response to first-line induction therapy (5FU/FA or CAPE, plus OX or IRI, alone or plus antiVEGF or antiEGFR) were randomized to receive either lefitolimod monotherapy (experimental arm) or local SOC (control arm). After first progression, patients started re-induction therapy, with those in the experimental arm continuing lefitolimod on top.
Results: Demographics and baseline characteristics were well balanced between the study arms. Median duration of follow up was 35 months. The primary endpoint overall survival (OS) was not met: median OS was 22.0 in the lefitolimod and 21.9 months in the control group (p=0.2765; HR=1.12; 95% CI 0.91 - 1.38). Progression free survival, event-free rates, pre-defined sub-group analyses including molecular and immunological parameters for OS did also not indicate a benefit. In comparison with the control arm treatment with lefitolimod was generally well tolerated. Grade 3, 4 and 5 toxicities rates were 6.3, 1.9 and 0%, respectively and no new safety signals or autoimmune events were identified while immune activation was confirmed in peripheral blood.
Conclusions: Lefitolimod did not show superiority to SOC as a single agent maintenance treatment in patients with mCRC. Limited add-on toxicity confirmed the favorable safety and tolerability profile of lefitolimod. Hence, and given its mode of action, lefitolimod will be evaluated in combination with other anti-cancer immunotherapies.

Reference:

1. Clinical trial identification NCT02077868

Disclosure Statement: The IMPALA study was sponsored by Mologen AG

Poster

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Role of Intensified Radiochemotherapy for Older Patients with Locally Advanced Rectal Cancer

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Purpose: The benefit of adjuvant/neoadjuvant chemotherapy in combination with radiation for rectal cancer with regard to survival is negligible, especially for older patients (pts). 5-fluorouracil (5-FU) alone or in combination with folinic acid (FA), oral capecitabine or an intensified therapy using oxaliplatin are presently used. The aim of the present retrospective evaluation was to compare the oncologic outcome of rectal cancer pts with regard to adjuvant treatment and age.
Methods: Data of pts from the randomized phase-III FOGT-2 trial (1) were updated and analyzed with regard to age, under 70 years termed younger versus ≥ 70 years termed older.
Results: Out of the 796 pts included 140 were older (17.6%). Overall 257 pts displayed toxicity grade III/IV (32.3%), 217 (33.1%) occurred in younger and 40 (28.6%) in older pts, respectively. Modulated treatment increase toxicity in younger and older pts. 5-FU alone resulted in younger and older pts in 35.2% (82/233) and 40.8% (20/49), respectively, in discontinuation of treatment, while modulated 5-FU had this effect in 36.9% (156/423) and 44.0% (40/91), respectively. 8-year overall survival (8-y OS) was 50.7% (95% CI: 43.1-57.8; n=282) for 5-FU alone and 52.3% (46.5-57.9; n=514) for modulated 5-FU, respectively. 8-y OS was 52.8% (95% CI: 44.8-60.2; n=233) for 5-FU alone and 55.9% (49.6-61.8; n=423) for modulated 5-FU, respectively, in younger pts. Interestingly 8-y OS for older pts was 41.4% (95% CI: 22.2-59.6; n=49) for 5-FU alone, but only 33.6% (18.3-49.7; n=91) for modulated 5-FU.
Conclusions: In pts with rectal cancer under the age of 70 5-FU modulation also in combination with radiation seems to increase the benefit in analogy to adjuvant treatment of colon cancer. Modulation of 5-FU in combination with radiation seems to rather decrease outcome in pts ≥ 70 years and therefore should be avoided.

Reference:

1. Kornmann M et al. Br J Cancer 2010;103:1163-72.

Disclosure Statement: No conflicts of interest.

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Drivers of Secondary Resistance to Anti-Egfr Therapy in Metastatic Colorectal Cancer

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Purpose: Secondary Resistance (SR) evolves in virtually all metastatic colorectal cancers (mCRC) treated with anti-EGFR targeting drugs such as Cetuximab (Cmab). Yet, SR patient-derived xenograft (pdx) models are largely lacking. Here, we established eight SR pdx models through chronic Cmab treatment of drug-sensitive mCRC pdx. All pdx models were initially wild-type for *KRAS, NRAS, PI3K* and *BRAF* genes. Global gene expression analyses identified widespread transcriptional reprograming with many genes. Among the highly dysregulated genes, fibroblast growth factors *FGF13, FGF19, FGF20*, and insulin-like growth factor *IGF2* stood out as potential drivers of SR through upregulation of RTK signaling.
Methods: Functional molecular analyses of these factors were performed using lentiviral vector mediating gene transduction. Cell viability, proliferation assays and western blot (WB) analyses were applied to assess the molecular functionality of FGFs and IGF2-ligands *in vitro*. Finally, transgenic cell lines were injected into nude mice to test their therapeutic response towards Cmab treatment.
Results: Stable lentiviral overexpression of *FGF13* and *IGF2* in drug-sensitive cell lines and pdx models triggered SR both *in vitro* and *in vivo*. WB analyses showed that FGF13 and IGF2 overexpression induced phosphorylation of pAKT, pS6, and pERK. Conversely, knockdown of FGF13 and IGF2 in a cell line with high endogenous IGF2 expression improved Cmab sensitivity. Lastly, when subjecting a Cmab SR pdx model with high endogenous overexpression of FGF13 and FGF19 to a Pan-FGF inhibitor (LY2874455), we observed a conversion of the SR into partial response.
Conclusions: Taken together, these results support a role of IGF2 and FGFs as candidate proteins conferring SR in an autocrine fashion in the setting of *KRAS* wild-type mCRC under chronic anti-EGFR treatment. Importantly, these results also suggest that potential combination therapies of Cmab and an IGF2 or FGF inhibitor could prevent establishment of SR and offer new treatment opportunities for patients with SR mCRC.

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Noninferiority on Overall Survival of Every-2-Weeks vs Weekly Schedule of Cetuximab for First-Line Treatment of RAS Wild-Type Metastatic Colorectal Cancer

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Purpose: Cetuximab (CET) in combination with chemotherapy (CT) is approved for a once-weekly (q1w) schedule at an initial dose of 400 mg/m², followed by weekly doses of 250 mg/m², in patients with *RAS* wild-type (wt) metastatic colorectal cancer (mCRC). In clinical practice, an off-label schedule of CET 500 mg/m² every-2-weeks (q2w) is used. This pooled analysis of patient-level data (PLD) aimed to test the noninferiority of the q2w vs q1w schedule on overall survival (OS).
Methods: All post-authorization studies with PLD available to marketing authorization holder, in patients with *RAS* wt mCRC who received 1st-line treatment with CET q1w or q2w in combination with CT from 2007 to 2018 were included: 2 non-interventional studies (NIS) and 3 clinical trials. Patients were categorized as q1w or q2w according to CET schedule planned at initiation. OS was assessed from CET initiation until all-cause death and censored at last date known to be alive. Noninferiority of the q2w vs q1w schedule was tested with a hazard ratio (HR) margin of 1.25 using a Cox proportional hazards regression model. Differences in baseline characteristics were accounted for with inverse probability of treatment weighting (IPTW) based on a propensity score.
Results: 763 and 554 patients were included in the q1w and q2w groups, respectively. Median (Q1-Q3) age in years was 66 (57-73) for q1w and 60 (53-69) for q2w. Liver-limited disease concerned 42.6% of patients for q1w and 37.9% for q2w. A baseline ECOG Performance Status of 0-1 was reported in 81.8% of q1w and 90.6% of q2w patients. FOLFIRI was most frequently used in combination with q1w (49.4%) and FOLFOX with q2w

(59.2%). HRs for OS were in favor of q2w: 0.83 (95% CI, 0.71-0.96) and 0.73 (95% CI, 0.61-0.88) when restricted to NIS. Progression-free survival and response rate support OS results.

Conclusions: This pooled analysis confirmed the noninferiority of CET q2w vs q1w. Results suggest an improved OS with the q2w schedule.

Disclosure Statement: Previously presented at ESMO 2019, FPN 584P, Kasper et al. Reused with permission. Wording adapted to match word count.

Gastrointestinal (Noncolorectal) Cancer

Vorträge

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Atezolizumab (ATEZO) + Bevacizumab (BEV) vs Sorafenib (SOR) in Patients (PTS) with Unresectable Hepatocellular Carcinoma (HCC): Phase 3 Results from Imbrave150

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Purpose: Ph 1b data has shown promising efficacy and safety for Atezo + Bev in unresectable HCC pts who have not received prior systemic therapy. We report the primary analysis data from the Ph 3 IMbrave150 trial comparing Atezo + Bev vs Sor in this patient population.
Methods: IMbrave150 (NCT03434379) enrolled systemic treatment (tx)-naïve pts with unresectable HCC. Pts were randomised 2:1 to receive either Atezo 1200 mg IV q3w + Bev 15 mg/kg IV q3w or Sor 400 mg BID until unacceptable toxicity or loss of clinical benefit per investigator. Coprimary endpoints were OS and PFS by independent review facility (IRF) assessed RECIST 1.1. The key secondary endpoints IRF-ORR per RECIST 1.1 and IRF ORR per HCC mRECIST were also part of the study statistical hierarchy.
Results: The ITT population included 336 pts randomised to Atezo + Bev and 165 randomised to Sor. Baseline demographics were well balanced. With a median follow up of 8.6 mo, median OS was not estimable (Atezo+Bev) vs 13.2 months (Sor). Median PFS was 6.8 months (95% CI, 5.7, 8.3) in Atezo + Bev vs 4.3 months (4.0, 5.6) in Sor. OS HR was 0.58 (0.42, 0.79; $P = 0.0006$) and PFS HR was 0.59 (0.47, 0.76; $P < 0.0001$) for Atezo + Bev vs Sor. ORR was 27% vs 12% ($P < 0.0001$) per IRF RECIST and 33% vs 13% ($P < 0.0001$) per IRF HCC mRECIST for Atezo + Bev vs Sor, respectively. Results were consistent across clinical subgroups. Atezo + Bev delayed deterioration of quality of life vs Sor. Median tx duration was 7.4 mo for Atezo, 6.9 for Bev and 2.8 for Sor. Gr 3-4 AEs occurred in 57% of pts receiving Atezo + Bev and 55% of pts receiving Sor. Gr 5 AEs were seen in 5% and 6% of pts, respectively.
Conclusion: IMbrave150 demonstrated statistically significant and clinically meaningful improvement in both OS and PFS for Atezo + Bev vs Sor in pts with unresectable HCC who have not received prior systemic therapy. The safety of Atezo + Bev is consistent with the known safety profile of each agent, and no new safety signals were identified. Atezo + Bev has the potential to be a practice changing tx in HCC.
Presented at ESMO Asia 2019, LBA #3, Cheng et al. Reused with permission

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Fight-202: A Phase 2 Study of Pemigatinib in Patients (PTS) with Previously Treated Locally Advanced or Metastatic Cholangiocarcinoma (CCA)

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Purpose: Fibroblast growth factor receptor (FGFR) 2 alterations are implicated in CCA. We present data from a phase 2, open label, single arm study of pemigatinib, a potent, selective, oral FGFR1–3 inhibitor, in pts with previously treated locally advanced or metastatic CCA (NCT02924376).
Methods: Eligible adults had progressed after ≥1 prior treatment and had documented *FGF/FGFR* status. Pts assigned to cohorts A (*FGFR2* rear-

rangements/fusions), B (other *FGF/FGFR* alterations), or C (no *FGF/FGFR* alterations) received oral pemigatinib 13.5 mg QD (21-d cycle; 2 wks on, 1 wk off) until disease progression/unacceptable toxicity. Primary endpoint was centrally confirmed objective response rate (ORR; cohort A); secondary endpoints were ORR (cohorts B, A+B, and C); duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS); safety.
Results: At data cutoff (Mar 22, 2019), 146 pts were enrolled (cohort A, n=107; B, n=20; C, n=18; 1 pt undetermined). Median (range) age was 59 (26–78) y; 61% and 39% had 1 and ≥2 prior therapies. Fewer pts discontinued therapy in cohort A (71%) vs B and C (each 100%), most for progressive disease (cohort A, 53%, B, 75%, C, 67%). ORR in cohort A was 35.5% (95% CI, 26.5%–45.4%), with 3 complete responses; median (m) DOR was 7.5 (95% CI, 5.7–14.5) months (mo), DCR was 82% (95% CI, 74%–89%), mPFS and mOS were 6.9 (95% CI, 6.2–9.6) and 21.1 (14.8–not reached) mo (OS not mature at cutoff). In cohorts B and C, no patient achieved a response. Overall, most common adverse events (AEs) were hyperphosphatemia (60%; grade ≥3, 0%), alopecia (49%; 0%), diarrhea (47%; 3%), fatigue (42%; 5%), nail toxicities (42%; 2%), and dysgeusia (40%; 0%). Hyperphosphatemia was managed with diet modifications, phosphate binders, if needed; diuretics or dose reductions/interruptions. Discontinuation, dose reduction and interruption due to AEs occurred in 9%, 14% and 42% of pts, respectively.
Conclusions: These data support pemigatinib as a potential treatment option for previously treated pts with CCA harboring FGFR2 gene rearrangements/fusions.

Poster

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Characterization of the Immune Infiltrate and its Prognostic Value in Highly Proliferative Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NEN)

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Purpose: The tumor immune microenvironment plays a critical role for the response to "immune checkpoint blockade" in several cancer types. We aimed to characterize the immune infiltrate of highly proliferative GEP-NEN in order to explore the potential role of immunotherapeutic approaches in this fatal disease.
Methods: We analyzed formalin-fixed paraffin-embedded (FFPE) samples from 37 patients diagnosed with highly proliferative GEP-NEN (G3; Ki-67>20%). Samples were immunohistochemically stained for the checkpoint molecules PD-L1 and PD-1, and the immune markers CD8 and CD206. PD-L1 positivity was defined as a CPS ≥1. PD-1 was quantified as the percentage of positive immune cells. CD206 and CD8 were quantified using Definies Software®. For PD-1, CD206 and CD8 the median levels served as cutoff. Marker expression was correlated with overall survival (OS) using the log-rank (Mantel-Cox) test. Multiplex immunofluorescence (IF) staining illustrated the spatial interaction of PD-L1, PD-1 and CD8.
Results: PD-L1 was significantly associated with improved median OS: 15.6 months (mth) (CI 95%: 7.0; 24.2) vs 9.3 mth (CI 95%: 3.7; 15) (p=0.028). CD206, CD8 and PD-1 alone had no significant impact on OS. Co-expression of PD-L1 and high PD-1 was associated with a median OS of 19.1 mth (CI 95%: 9.4; 28.7) vs 9.3 mth (CI 95%: 3.4; 15.2) (p=0.009). Patients with triple positive tumors (PD-L1, high PD-1, high CD8) showed the longest median OS of 20.6 mth (CI 95%: 15.1; 26.1) vs 10 mth (CI 95%: 5.4; 14.6) (p=0.002). IF illustrated the co-expression of PD-1 and CD8 on cytotoxic T cells and a strong interaction between $PD1^{+}CD8^{+}$ lymphocytes and PD-L1 on immune and tumor cells.
Conclusions: PD-1/PD-L1 co-expression had a stronger prognostic value than $CD8^{+}$ T cell infiltrate alone, but simultaneous expression of these three markers showed strongest prognostic relevance. Our data support clinical studies of immunotherapy in highly proliferative GEP-NEN.

Disclosure Statement: The authors declare no conflict of interest.

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Maintenance Therapy with FOLFIRI after FOLFIRINOX for Advanced Pancreatic Ductal Adenocarcinoma: A Retrospective Single Center Analysis

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Purpose: Patients with pancreatic ductal adenocarcinoma (PDA) receiving FOLFIRINOX often develop oxaliplatin-induced polyneuropathy, which limits the continuation of this therapy. We evaluated the efficacy and safety of FOLFIRI maintenance treatment after FOLFIRINOX induction in a retrospective single center study.
Methods: Patients with advanced PDA treated with FOLFIRI as maintenance therapy after achieving disease control under FOLFIRINOX according to the local operating procedure between 2011 and 2016 were identified. Medical records of this group were evaluated retrospectively.
Results: Overall, 22 patients with PDA were treated with FOLFIRI (mean age 59 years, 55 % female, 45 % male). Before receiving FOLFIRI all patients were treated with FOLFIRINOX for a median of 4 months. The median progression free survival (PFS) under FOLFIRI maintenance therapy was 8 months. Side effects grade 3 - 4 (CTCAE v4.0) were observed in 18 % of patients receiving FOLFIRI. Considering together FOLFIRINOX induction and subsequent FOLFIRI maintenance therapy, the median PFS was 11 months. The median overall survival (OS) from the beginning of palliative treatment was estimated at 46 months.
Conclusions: In the selected group of PDA patients achieving disease control with FOLFIRINOX, FOLFIRI maintenance therapy was feasible, safe and effective, with some patients achieving long-term disease stabilization.

Disclosure Statement: M.V. has served as a speaker, a consultant or an advisory board member for Lilly, Bristol-Myers Squibb, MSD, Merck Serono, Bayer vital, Amgen, Nordic Pharma, Ipsen and Celgene. P.M. has served as a speaker for Abbott Laboratories, Allergan, Alfasigma, Bayer, Biocodex, AstraZeneca, Falk Pharma and Takeda. A.C. and C.F. have nothing to declare.

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Top Ten Research Priorities for the Treatment of Pancreatic Cancer - Results of the Priority Setting Partnership Pancreatic Cancer Treatment

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Purpose: Pancreatic cancer (PC) is the fourth leading cause of cancer deaths in Europe [1]. Research is thus urgently needed. However, a mismatch exists between research questions considered important by researchers hand and those important to patients, carers, and health-care professionals[2]. In order to address this shortcoming a Priority Setting Partnerships (PSPs) brings patients, carers and clinicians together to identify and prioritise unanswered questions that they agree are the most important.
Methods: A steering group consisting of an equal number of patients and health-care professionals was established to decide on all aspects of the PSP jointly. A modified nominal group method established by the James Lind Alliance was used to involve patients, carers, members of patient support groups, and health-care professionals. Between 2017-2019 open research questions were identified and prioritized in two national-wide surveys. Final prioritization of the remaining research questions was done in a face-to-face consensus conference.
Results: In the first survey from August to November 2017, >500 research questions were obtained (52.1% patients). More uncertainties were added after screening current guidelines. After removal of duplicates and out of scope questions, suggestions were collated to indicative questions and verified as unanswered in the research literature. The remaining uncertainties were listed in the second survey for interim prioritization accomplished from June to September 2019 (50.7% patients) to rank the top ten research priority questions. From the 21 questions that received the most representative votes, ten research priorities were agreed upon. The final top 10 research questions will be presented at the Krebskongress 2020.
Conclusions: The identified top ten priorities for PC treatment provide an important basis future researcher and funding bodies.

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Disclosure Statement: The authors report not conflicts of interest.

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Obesity and Pancreatic Ductal Adenocarcinoma (PDAC): A Matched-Pair Survival Analysis

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Purpose: Incidence of morbid obesity is increasing in western world. Epidemiological data show that obesity has an impact on overall survival (OS) of many tumors and postoperative complication rates[1,2]. This study evaluates the influence of obesity on OS in patients with PDAC.
Methods: From a prospective database, we retrospectively evaluated all patients who underwent pancreatic resection for PDAC (1997-2018). Matched pairs (1:1) were generated according to the following predefined match criteria: age, gender and ASA. Only full matches were accepted. Primary endpoint was the OS difference of patients with and without obesity. Obesity was defined according to the WHO criteria as BMI > 30 kg/m^2. Secondary endpoints were intra- and postoperative outcomes, pathological characteristics and adjuvant chemotherapy. Survival analysis was done by using Kaplan-Meier and uni- and multivariate analysis were performed for comparison between groups.
Results: Out of 553 patients a total of 76 fully matched pairs were generated. Obese patients had a mean BMI-level of 33 compared to 25 kg/m^2 in patients without obesity. All patients had ASA-status ≤III. Patients with obesity had a higher frequency of diabetes m. (49% vs. 30%, p=0.031) and Clavien-Dindo grade >III was slightly higher (14% vs. 9%, p=0.182). 90-day mortality rates were similar in both groups. 39 obese patients (57%) received adjuvant chemotherapy compared to 30 (46%) (p=0.226). The median OS was 19 months (12-29) in patients with and 21 months (12-26) without obesity (P=0.99).
Conclusions: We could not observe an influence of obesity on OS and postoperative complications in patients with PDAC. Therefore, pancreatic surgery should not be withheld for obese patients.

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Disclosure Statement: -

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Prognostic Value of Systemic Inflammatory Response Markers in Highly Proliferative Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NEN)

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Purpose: Chronic inflammation plays a critical role in the development and progression of cancer (1). Systemic inflammatory response (SIR) markers can be routinely assessed in clinical settings and are associated with survival in several cancer entities (2). In this study, we evaluated the prognostic value of pretreatment SIR markers in highly proliferative gastroenteropancreatic neuroendocrine neoplasms (GEP-NEN).
Methods: We established a database of 82 patients with highly proliferative GEP-NEN (G3; Ki-67>20%). SIR markers were retrospectively assessed before start of any treatment (resection, radiation or chemotherapy). Absolute blood cell count was applied. Cutoff values were set as the median of each marker. SIR markers such as the differential blood count, CRP, neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR) were correlated with overall survival (OS) using the log-rank (Mantel-Cox) test and Cox proportional hazard models.
Results: Median OS of the full cohort was 11 months (CI 95%: 9.7; 12.3 month). High blood lymphocyte counts were significantly associated with better OS: 13.1 vs 9.5 month (HR 0.58; CI 95%: 0.36; 0.95; p=0.03). The median OS for patients with high NLR was 9.5 vs 13.1 months (HR 1.69; CI 95%: 1.04; 2.75; p=0.035), for high LMR: 14 vs 7.4 months (HR 0.49; CI 95%: 0.3; 0.8; p=0.004), for high PLR: 10 vs. 14 months (HR 1.67; CI 95%: 1.02; 2.73; p=0.04) and for high CRP: 7.6 vs 14.2 months (HR 1.85; CI 95%: 1.14; 3.01; p=0.013).
Conclusions: Our data suggest a strong prognostic value of pretreatment SIR biomarkers in highly proliferative GEP-NEN. Especially the absolute

lymphocyte count could serve as a stratification factor for further treatment studies in this disease.

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Disclosure Statement: The authors declare no conflict of interest.

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Investigating the Impact of Extrahepatic Metastasis in Patients with HCC: Does Location Matter?

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Purpose: Extrahepatic metastatic disease (EMD) in patients with hepatocellular carcinoma (HCC) leads to classification into advanced stage in which systemic therapy is recommended. However, data on the prognostic impact of EMD is rare, especially when taking into account the exact location. Therefore, aim of this study was to determine the prognostic impact of EMD in general and according to different EMD sites using a longitudinal approach.
Methods: As the work-up is still ongoing, so far 741 patients with HCC treated between 01/2005-01/2019 were extracted from the clinical registry of our tertiary referral center to reevaluate the impact of EMD. All cross sectional imaging studies were re-reviewed by a board certified radiologist specialized in HCC-imaging to determine date and location of EMD development. Locations were classified into 6 categories: lymph nodes, peritoneum, lung, bone, adrenal gland, brain, and others. Furthermore, the status of macrovascular invasion (MVI) was determined.
Results: Of the 741 patients, 41 patients could not be evaluated due to concurrent malignant disease. Overall, 153/700 patients developed EMD: 73 (47.8%) patients presented with EMD synchronous to initial HCC diagnosis, 80 (52.2%) patients had metachronous EMD. Median OS after initial diagnosis was 15.8 months without and 10.9 months with EMD ($p<0.001$). The most common metastatic sites were: lymph node (n=79), lung (n=78), bone (n=37), peritoneum (n=30), adrenal gland (n=23), and others (n=13). Residual median OS after detection of lymph node, lung, bone, peritoneal, adrenal, brain, and other metastases was 5.6, 5.1, 3.4, 4.3, 5.8, and 5.6 months respectively ($p>0.05$). Incidence of MVI in patients with EMD was higher than in patients without EMD ($p<0.001$).
Conclusions: EMD had a significant impact on OS. However, there was no discernible difference in OS between metastatic sites. Therefore, under systemic treatment, the exact site is rather of secondary importance for OS. As EMD showed strong correlation with MVI, diagnosis of MVI should prompt additional imaging.

Disclosures: None

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Optineurin Knockdown Reverses Cell Cycle Changes Induced by Cisplatin in BRCA1 Mutated and Wild Type Pancreatic Cancer Cells

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Purpose: BRCA mutations have been associated with increased sensitivity to cisplatin in ovarian and breast cancers. Autophagy plays a role in acquired chemotherapeutic resistance. Pancreatic ductal adenocarcinoma (PDAC) shows high levels of basal autophagy and PDAC cell lines can harbor BRCA mutations. In the present work, the effect of cisplatin was investigated in Capan1 cells, which harbor a BRCA2 mutation and in Miapaca cells, which are BRCA wild type; this treatment was combined with knockdown of the autophagy receptor optineurin (OPTN) for obtaining improved therapeutic outcome.
Methods: Proliferation was tested in Miapaca (BRCA2 wild type) and Capan1 (BRCA2 mutated) cells by MTT-assay after exposure to cisplatin. OPTN was knocked down by specific siRNA (30 pM). After 48 h, the effect on mRNA and protein expression levels was determined by qRT-PCR and Western blot. The influence on cell cycle distribution was followed by FACS. Western blot was used to assess protein levels of p-P53, and p-Chk 2.
Results: Capan1 cells were by 2 orders of magnitude more sensitive to cisplatin than Miapaca cells (IC50 Capan: 0.06 µM compared to 6 µM in Miapaca cells at 72 h). In Miapaca cells, cisplatin reduced the percentage of G1 phase cells by 56% and increased that of S-phase cells by 66%. In Capan 1 cells, it reduced the G1 fraction by 41% and increased the S fraction by 48%. Interestingly, these effects were almost normalized when cisplatin was combined with knockdown of OPTN. A significant increase was observed in both cell lines in the expression of p-Chk 1, and p-P53.
Conclusions: Cisplatin showed a higher sensitivity in the PDAC cell line containing a BRCA mutation. Knockdown of OPTN lead to normalizing the effect of cisplatin on cell cycle in both cell lines.

Genito-urinary Cancer, including Prostate Cancer

Poster

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Sarcopenia Assessments as Predictors of Overall Survival in Patients with Metastatic Renal Cell Carcinoma

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Purpose: Sarcopenia can be an important prognostic marker in tumor patients receiving systemic therapy. However, measurement methods and threshold values are not uniformly defined. The aim of this study is therefore to determine the prognostic value of different sarcopenia indices in patients with metastatic renal cell carcinoma treated with TKI.
Methods: In 93 patients who received TKI therapy for metastatic renal cell carcinoma, sarcopenia indices were determined based on CT imaging before the start of therapy. Clinical progression parameters were recorded prospectively. The correlation of sarcopenia parameters with overall survival was investigated as univariate and multivariate correlations, taking into account the MSKCC score.
Results: The mean age at inclusion was 65.8 years (21-86). Median survival was 12.3 months. The total muscle cross-section at LWK-3 level was 112.9 cm^2 in women and 159.0 cm^2 in men.
As the definitions of sarcopenia differ considerably, 23-55% of the patients were classified as having sarcopenia. In univariate and multivariate analysis, indices based on total muscle area and indices based on psoas muscle are significantly associated with overall survival.
Conclusions: The determination of sarcopenia indices using routine CT imaging can contribute to the prognosis estimation of patients under TKI therapy with metastatic renal cell carcinoma. Indices based on the exact determination of skeletal muscle area or psoas muscle area at LWK-3 are independent prognostic markers.

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A Phase III Study Testing the Role of Proactive Coaching on Patient Reported Outcome in Advanced or Metastatic Renal Cell Carcinoma Treated with Sunitinib or a Combination of Axitinib + Checkpoint Inhibitor (CPI) in First Line Therapy (Prepare)

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Purpose: PREPARE is an ongoing phase III clinical study that tests if structured pre-emptive therapy management during sunitinib treatment improves clinical outcome. Since the conception of the PREPARE study, new mRCC treatment strategies using immune checkpoint inhibitors (CPI) have emerged. Promising approaches include the combination of CPIs with tyrosine kinase inhibitors (TKI) such as the recently approved combinations of axitinib + avelumab or pembrolizmab. Therapy management in PREPARE aims to raise awareness, educate patients and implement preventive measures in routine practice. This principle is also very relevant to the novel combinations and an adaptation of the procedures within PREPARE will allow for the enrollment of patients treated with axitinib + CPI.
It is hypothesized that this approach of proactive coaching of mRCC patients receiving 1st-line sunitinib or a combination of axitinib + CPI will improve patients health-related quality of life and may improve patient adherence to treatment and ultimately clinical outcome.
Methods: 430 patients will be randomized 1:1 between concomitant coaching and standard of care. Nurses are trained in proactive Adverse Drug Reaction (ADR) management in order to act as coaches and as such collaborate closely with the investigators. Coaching aims at patient education on ADRs, preventive measures, self-care and remedies, including management of fatigue, diarrhea, stomatitis, skin toxicities and hypertension. Quality of life will be assessed as primary endpoint using FKSI-15. Secondary outcome measures include ORR, progression-free survival, overall survival, treatment duration and ADRs.
Results: Initiation of study sites started in January 2017 and is ongoing. As of January 2020, 24 study sites have been initiated and 40 patients randomized. Results will be published after finalization of study.
Conclusions: PREPARE will shed further light on the value of proactive management of TKI side effects as well as TKI-CPI combinations.
ClinicalTrials.gov Identifier: NCT03013946
EudraCT No.: 2016-000399-28

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Molecular Tumor Board for Metastatic Prostate Cancer in Routine Clinical Practice

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Purpose: Molecular stratification for targeted tumor therapy in metastatic prostate cancer (PC) is not routinely implemented. Previous studies found that PC cells frequently harbor aberrant cellular signaling pathways associated with treatment response [1-3]. Here we present the data obtained from PC patients analyzed by the Molecular Tumor Board (MTB) Technical University of Munich as a framework classifying genomic alterations for cancer precision medicine in routine practice.
Methods: Key MTB inclusion criteria were confirmed metastatic PC with one of the following items: patient age < 60 years, unusual metastasis pattern, aggressive course of disease or last line tumor therapy. Fresh tumor/metastasis biopsy material was processed. The Oncomine Comprehensive Assay using next-generation sequencing was used to detect relevant single-nucleotide variants, copy number variations, gene fusions and indels. Microsatellite instability (MSI) and PDL-1 status was assessed by immunohistochemistry. Process maps for MTB screening, inclusion, treatment and follow-up were designed. A license for a secure web-based software platform created to support data capture for research was obtained and a unique electronic case report form was designed [4].
Results: The routine MTB procedure was initiated in November 2019 and a total of 17 PC patients were already included within two months: 10/17 (59%) patients showed clinically actionable mutations targeting predominantly the PI3K/Akt/mTOR. 6/17 (35%) patients had mutations in

DNA-repair pathways and were eligible for PARP-inhibitor therapy. 1/17 (6%) positive PDL-1 status but no MSI were detected.
Conclusions: The initiation of advanced clinically integrative genomics in metastatic PC is an important step to enhance the personalized cancer therapy in routine practice.

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Disclosure Statement: The authors declare no conflict of interest and have nothing to disclose.

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Depth of Response (DEPOR) Analysis and Correlation with Clinical Outcomes from JAVELIN Renal 101

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Purpose: The phase 3 JAVELIN Renal 101 trial (NCT02684006) demonstrated significantly improved progression-free survival (PFS) in patients (pts) with advanced renal cell carcinoma (aRCC) treated with avelumab + axitinib (A+Ax) vs sunitinib (S) (HR, 0.69; 95% CI, 0.56, 0.84; P<0.001).[1] We report on the correlation of PFS with DepOR at early imaging timepoints.[2]
Methods: Data from all pts were analyzed based on blinded independent central review per RECIST 1.1. Tumor shrinkage or growth was categorized by best % change in target lesions on imaging obtained up to 13 wk. The landmark analysis included pts without progressive disease and who had not died at or prior to 13 wk after randomization. PFS was analyzed for each category. A Cox multivariate landmark analysis was conducted for PFS in the A+Ax arm with DepOR as a continuous variable.
Results: Results are reported based on the first interim analysis, with a minimum follow-up of 6.0 mo. Within shrinkage categories ≥0 – <30%, ≥30 – <60%, and ≥60%, median PFS (95% CI) in the A+Ax arm was 16.6 mo (13.8, not estimable [NE]), NE (13.3, NE), and NE (NE) vs 16.7 mo (11.1, NE), 13.9 mo (9.1, NE), and NE (6.2, NE) in the S arm, respectively. The 12-mo PFS rates (95% CI) in the A+Ax arm were 63.2% (52.5, 72.2), 68.4% (58.9, 76.1), and 85.2% (60.2, 95.1) vs 57.0% (47.6, 65.3), 60.3% (39.9, 75.7), and 66.7% (28.2, 87.8) in the S arm, respectively. In the tumor growth category >0 – <20%, median PFS in the A+Ax arm was 5.7 mo (4.2, NE) vs 9.5 mo (5.6, 17.3) in the S arm; the 12-mo PFS rate (95% CI) was 27.0% (7.6, 51.3) vs 42.0% (18.8, 63.7). After adjusting for prognostic covariates, Cox multivariate analyses showed a meaningful association between DepOR and PFS in the A+Ax arm, consistent with the results in each shrinkage category.
Discussion: Greater tumor shrinkage at early imaging timepoints was associated with longer PFS in JAVELIN Renal 101.
Conclusions: DepOR could be a predictor of clinical outcomes in pts with aRCC.

References:
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2. Prior submission: ASCO-GU 2020 (#286971).

Funding: Pfizer and Merck KGaA, Darmstadt, Germany

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Race IT-Preoperative Radiation Therapy Before Radical Cystectomy Combined with Immunotherapy in Locally Advanced Urothelial Carcinoma of the Bladder

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Purpose: Patients with locally advanced bladder cancer have a poor prognosis despite radical surgical therapy.[1] Anti-PD1/PDL1-based immunotherapies have shown activity in metastatic urothelial cancer. Preliminary data on neoadjuvant immunotherapy in muscle invasive bladder cancer demonstrated high antitumor activity. Early data suggest a synergistic effect of radiation and immunotherapy. Therefore we designed a trial to evaluate feasibility, safety and efficacy of neoadjuvant radio-immunotherapy before radical cystectomy in this cohort.
Methods: In this prospective, multicenter, phase II IIT- trial, patients (n=33) are treated with Nivolumab 240 mg q2w for 4 cycles with simultaneous radiotherapy of the pelvis with 50.4 Gy. After the treatment phase a radical cystectomy is performed with a postoperative follow-up phase. Main inclusion criteria are locally advanced (cT3/4 cN0/N+ cM0) urothelial bladder cancer in patients, who are unfit for neoadjuvant cisplatin-based chemotherapy or refuse neoadjuvant chemotherapy. Main exclusion criteria are metastatic disease, prior chemotherapy and pelvic radiation.
Results: Since February 2019 11 patients were enrolled. A planned interims analysis regarding safety was performed with positive result.
Conclusions: After an inclusion of a third of the study population and a planned interim analysis for safety, further patient recruitment will continue in January 2020.
Clinical trial information: NCT03529890

Reference:
1. Hautmann, R.E., et al., J Urol, 2006. **176**(2): p. 486-92.

Disclosure Statement: SCS received travel grants from Astellas, Janssen-Cilag, Novartis and Bristol-Myers Squibb (BMS). MR received consultancy honoraria from

Bayer, BMS, Ipsen Pharma, Janssen Cilag, MSD, Novartis, Pierre Fabre, Pfizer and Roche and JEG from Bayer, BMS, MSD, Novartis, Pierre Fabre, Pfizer and Roche.

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A Randomized Phase II Study of Nivolumab Plus Ipilimumab Versus Standard of Care in Previously Untreated and Advanced Non-Clear Cell Renal Cell Carcinoma (Suniforecast)

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Purpose: Non-clear cell renal cell carcinomas (nccRCC) are heterogeneous tumors accounting for approximately 25% of RCC patients (pts). Since most clinical trials focus on clear-cell RCC (ccRCC), data on treatment strategies for nccRCC are limited. The combination of Nivolumab and Ipilimumab has recently been approved for treatment in RCC showing a significant improvement in overall survival (OS), progression free survival (PFS) and overall response (ORR) in intermediate and high-risk pts. compared to sunitinib. Currently retrospective analyses have also shown promising results for this combination in nccRCC patients.
Methods: In this prospective randomized phase-II multicenter trial pts with advanced or metastatic nccRCC with no prior systemic therapy are eligible. Other key inclusion criteria are: available tumor tissue, Karnofsky >70% and measurable disease per RECIST 1.1. All diagnoses are reviewed by a central pathologist. The study plans to randomize ~306 pts stratified for papillary or non-papillary histology and by the International Metastatic RCC Database Consortium (IMDC) risk score. Pts will be randomized 1:1 to either i) Nivolumab 3mg/kg intravenously (IV) plus Ipilimumab 1mg/kg IV every 3 weeks for 4 doses followed by Nivolumab fixed dose 240mg IV every 2 weeks or ii) standard of care according to the approved schedule. Treatment will be discontinued in case of unacceptable toxicity or withdrawal of informed consent. Pts may continue treatment beyond progression, if clinical benefit is achieved and treatment is well tolerated. Primary endpoint is the OS rate at 12 months. Secondary endpoints include OS rate at 6 and 18 months, median OS, PFS, ORR and quality of life. The trial is in progress and 111 pts have been randomized so far. Clinical trial identification NCT03075423

Geriatric Oncology

Poster

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Immunoncology in Elderly Patients is Safe and Even Successful

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Introduction: Immunoncology has became the fourth component in tumour treatment and shows often remarkable results in many tumour entities (lung cancer, melanoma, head and neck tumours, renal and urothelium carcinoma, SCC of the skin). Side effects of immunoncology are quiet different to chemotherapy, but we learned to manage these side effects.
Method: We report of 24 patients (male: 19; female: 5) aged over 70 years (range 70 – 92 years), who entered our hospital between 10/2016 and 09/2019 for treatment of their recurrent solid tumours by immunoncology.

Patients diagnosis:
- NSCLC: 8 (3 × 2nd. Line; 5 × 3rd. Line)
- Urothelium: 5 (5 × 2nd. Line)
- Melanoma 4 (all metastatic 1st. Line)
- H&N 4 (1 × 2nd. Line; 3 × 3rd. Line)
- PE- Ca Skin 2 (both 2nd. Line)
- M. Hodgkin 1 (4th. Line)

Results: We saw a very good benefit especially in head and neck tumours: One patient achived in 3rd. Line a CR more for then 18 months (on going).
3/4 with head and neck have an on going PR for 12, 14 and 17 months.
2/8 whith NSCLC responded in 3rd. Line for more then 30 months at an age of 81 and 88 years.
One patient with SCC oft he skin is on going with a VGPR for 35 months at the age of 89 years.
In totally we saw : 1/24 CR, 3/24 VGPR, 10/24 PR, 5/24 SD, 5/24 PD.
Side effects were rare. One male patient developed a diabetes and was treatet in a hospitaly successfully.
Immunoncology therapie was given always in out patients setting.
Conclusion: Immunoncology therapy is well proven in many tumour entities and may become a leading role in first line treatment scedules.
There could be a chance of long time surviving for some patients.
Further studies are needed.

Gynecological Cancer

Poster

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Counseling for Hereditary Breast and Ovarian Cancer at Charité - Characteristics of the Counselees

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Purpose: About 5-10% of all breast cancers and 15-20% of all ovarian cancers are due to pathogenic mutations in different risk genes. As one of 20 centers in Germany, the Center of Hereditary Breast and Ovarian Cancer at Charité offers genetic counseling. Extensive data of the collective was now evaluated for the first time. The aim of this study was to ease the preparation for counseling and gather information for more individualized counseling.
Methods: Data from 2531 counselees at the Charité -Centre of 2016 and 2017 were retrospectively evaluated. Special emphasis was laid on sociodemographic data, results of genetic testing and mutation frequencies.
Results: 2531 counselees were almost exclusively female (n = 2493; 98.5%), 42.9 years old on average and came to the center for the first time (n = 2198; 86.8%). 2287 (90.4%) counselees met the inclusion criteria. Of these, 863 (37.7%) were already diagnosed with breast or ovarian cancer. 1367 (59.8%) were genetically tested. Mutations were detected in 545 (39.9%) tested persons. Most mutations were detected in *BRCA1*, *BRCA2*, *CHEK2* and *ATM*. The highest mutation frequency was found among persons from families with both breast and ovarian cancer and in patients with TNBC. A significant correlation was found between mutation frequency in TNBC and age at first diagnosis.
Conclusions: In summary, these results provide a comprehensive overview of the care structure at the Charité -Center, enabling more individualized counseling and more focused preparation for the consultation.

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Disclosure Statement: No information provided.

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Infiltration of MDR1 Positive M2 Macrophages Leads to Worse Prognosis in Ovarian Cancer

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Purpose: MDR1 expression on tumor cells has been widely investigated in context of drug resistance. However, the role of MDR1 on the immune cell infiltrate of solid tumors is widely unknown. Aim of this study is to clarify the prognostic significance of a MDR1 positive immune cell infiltrate in epithelial ovarian cancer (EOC) and to identify the MDR1 positive leucocyte subpopulation.
Methods: MDR1 expression has been analyzed by immunohistochemistry in 156 EOC samples. In addition to MDR1 positive cancer cells, we detected a MDR1 positive leucocyte infiltrate, which was quantified, grouped by low infiltrate and high infiltrate, correlated with clinical and pathological data and compared in terms of OS. To identify the immune

cell subpopulation immunofluorescence co-staining for MDR1 and different immune cell markers was performed.
Results: A high number of immune cells infiltrating EOC samples of all subtypes was detected. Significant correlations of the leucocyte infiltrate with Her2 (cc=0.258, p=0.005) and TA-MUC1 (cc=0.202, p=0.022) expression of the tumor were found. A MDR1 positive leucocyte infiltrate leads to decreased OS (median OS 69.1 vs. 94.3 months, p=0.057) with long term effects that turn significant from 24 month up to 9 years (median OS 97.4 vs. 128.7 months, p=0.031). Especially in TA-MUC1 positive patients (median OS 53.8 vs. 92.6 months, p=0.021) the OS was significantly lower with a high MDR1 positive immune cell infiltrate. The subpopulation of M2 macrophages was identified by immunofluorescence co-staining, expressing MDR1, the M2 marker CD163, and the pan-macrophage marker CD68.
Conclusions: Infiltration with MDR1 positive M2 macrophages leads to poor prognosis in long term survival of EOC patients, especially in the TA-MUC1 positive subgroup. Further understanding of the interaction of M2 macrophages, MDR1 and TA-MUC1 is a key point to overcome drug resistance in ovarian cancer.

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A Comparison of Laparoscopic vs Open Procedure in Patients with Pelvic and Paraaortic Lymph Node Dissection for Intermediate and High-Risk Endometrial Cancer – A Retrospective Cohort Study on Overall and Recurrence Free Survival

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Purpose: The primary therapy for intermediate and high risk endometrial cancer includes pelvic and paraaortic lymph node evaluation. Laparoscopic surgery is an increasingly popular intervention due to decreased risk and better short term morbidity; however, a recent study casts doubt on the benefit of this approach in terms of oncological safety. In this cancer registry study, we sought to evaluate the benefit of laparoscopy and retrospectively compared overall survival, recurrence rates, and recurrence-free survival among patients with intermediate and high-risk endometrial cancer who underwent either laparoscopic or open surgery.
Methods: The study included 419 patients who are recorded in clinical cancer registries in Regensburg and Erlangen/Nuremberg from 2011 to 2017. We employed Kaplan-Meier-method, and univariable and multivariable Cox-regression in order to compare overall survival, recurrence rates, and recurrence free survival in 110 patients, who underwent laparoscopic, with 309 patients, who underwent open surgery. To address confounding bias, we also performed a propensity score matching (PSM) analysis including 357 patients (laparoscopy: n = 107; open surgery: n = 250).
Results: We found a benefit for laparoscopic over open surgery in patients with intermediate and high-risk endometrial cancer for overall survival in both univariable (p = 0.002; PSM: p = 0.016) and multivariable analysis (p = 0.019; PSM: p = 0.007). In contrast, there was no statistically significant difference between both patient groups regarding the cumulative recurrence rates. A univariable analysis identified a significant benefit for laparoscopy regarding recurrence free survival (p = 0.003; PSM: p = 0.029) but a multivariable analysis failed to confirm this finding (p = 0.108; PSM: p = 0.118).
Conclusions: Our study provides evidence that with regard to oncological safety laparoscopic systematic lymphadenectomy does not fare worse than open surgery in the treatment of endometrial cancer.

Disclosure Statement: The authors declare no conflict of interest.

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Familial Breast and Ovarian Cancer and the Role of Resident Gynecologists

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Purpose: 5-10% of all mamma carcinomas and 10-15% of all ovarian carcinomas result from genetic mutations[1]. As resident gynecologists (RGs) know their patients' family history, they can help to significantly improve early detection of patients at risk for familial breast/ovarian cancer and inform them about possible next steps such as specialized genetic counseling. The aim of this study was to examine how BRCA patients experience the interaction with their RG regarding the topic of genetic counseling and testing.
Methods: We conducted a semi-structured focus group interview with BRCA mutation carriers (n = 9) and assessed the material according to source and timing of referral to genetic counseling as well as women's associated impressions.
Results: RGs played a minor role in BRCA patients' course of genetic counseling and testing: None of the participants had been referred to genetic counseling by her RG. Only one woman was tested *before*, all other women *after* the onset of a cancer, often in spite of a family history of gynecological cancer. Several women expressed that they felt "deprived of treatment options" since they had not been referred to genetic counseling earlier.
Conclusions: The experiences of nine women with BRCA indicate that the topic of genetic counseling and testing is hardly covered in the RG-patient interaction. This leaves unexploited potential for the early detection of patients at risk for familial breast/ovarian cancer. If RGs identify patients at risk at an early stage and refer them to specialized genetic counseling centers, they can help to improve the care of women at risk for familial breast/ovarian cancer. Moreover, they foster patient empowerment by offering them an enlarged scope of action and better informed decision-making. To help facilitate the early detection of these women at risk, we currently design a specialized training to convey the necessary skills and knowledge to RGs.

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Cytokeratin 7 Expression as Prognostic Marker in Squamous Cell Carcinoma of the Vulva

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Purpose: Patients with squamous cell carcinoma of the vulva (SCCV) have different survival rates even within a tumor stage and nodal status. In other tumor entities, Cytokeratin 7 (CK7) was identified as a prognostic marker. The purpose of the study was to investigate the prognostic value of CK7 expression in patients with SCCV.
Methods: 110 Patients treated between 2002-2017 at the University hospital in Bonn were enrolled in the trial after ethical agreement Tissue microarray (TMA) of 110 Specimen of SCCV of patients staged FIGO I-IV were evaluated with CK7 monoclonal antibodies using Four-Score technique, based on the intensity of cell staining. Kaplan-Meier, Chi-square and Log-rank analysis were performed to characterize the prognostic impact of CK7 expression in SCCV patients.
Results: CK7 expression was present in 7 out of 110 specimen only (6.3%). Median Progression Free Survival was 24 months, 1 out of 36 recurrences was CK7 positive. Median Overall Survival (OS) in patients with CK7 expression was 47 months (95% CI 20-73 months) in comparison with 97 months (95% CI 84-111 months) in patients with negative CK7 expression, albeit no significance could be shown (p=0.174). CK7 expression did not correlate with tumor stage, grading, nodal status, metastasis, vascular, or lymphatic invasion.
Conclusion: Median survival was not statistically different in patients with CK7 expression in SCCV although OS differed by 50 months. Failure to reach significance was likely caused by the low prevalence of CK7 positive tissue in our study. Expression of CK7 in SCCV therefore remains a promising prognostic marker and warrants further investigation in a larger cohort.

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Study Protocol of the German Multicentre Study "Evaluation of a Decision Coaching Program for Structured Decision Support of Preference Sensitive Decisions within the Context of Risk-Adapted Prevention for BRCA1/2 (Breast Cancer) Gene Carriers" (EDCP-BRCA)

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Background: Female BRCA mutation carriers have an increased lifetime risk for breast and ovarian cancer compared to the general population. Women who carry this mutation have several options to deal with their cancer risk, such as risk-reducing surgeries or intensified breast cancer screening. Previous research has shown that preferences in this scenario are highly dependent on affected women's personalities and value-systems. To support these women in the decision-making process, a structured decision support consisting of a decision coaching combined with a decision aid might be helpful.
Methods: A randomized controlled trial will be conducted in order to compare usual care with a structured decision support alongside usual care. The decision support program entails a nurse-led decision coaching as well as an evidence-based patient decision aid. Nurses are qualified by a four day training in informed decision-making and decision coaching. Six centers for Familial Breast and Ovarian Cancer in Germany will be included in the study, with a planned sample size of 398 women.
The primary outcome is the congruence between the preferred and the actual played role in the decision-making process as measured by the Control Preferences Scale. It is hypothesized that the structured decision support will enable women to play the preferred role in the decision-making process. Secondary outcomes include the knowledge and attitudes about preventive options, decisional conflict, depression and anxiety, coping self-efficacy, impact of event, and self-concept. A process evaluation will accompany the study.

Discussion: The EDCP-BRCA study is the first study to implement and evaluate a decision coaching combined with a decision aid for healthy BRCA mutation carriers worldwide.

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Epigenetic Signature as a Prognostic Marker for High Grade Cervical Neoplasia

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Objectives: Patients with a persisting hrHPV infection, in particular HPV16, have an increased risk for developing high grade cervical intraepithelial neoplasias (CIN). Nevertheless, most hrHPV infections are cleared by the immune system. Clinically validated molecular biomarkers indicative for the development of CIN are still lacking. However, there is growing evidence that DNA hypermethylation of host DNA may indeed have prognostic potential.
Methods: In a retrospective, longitudinal study cervical scrapes from 119 patients with the final histopathology diagnosis CIN3, for whom at least one sample prior to histopathological diagnosis was available, were analyzed for methylation of CpG islands in the gene regions ASTN1, DLX1, ITGA4, RXFP3, SOX17 and ZNF671. The methylation status of these markers, that comprise the cervical cancer diagnostic test GynTect®, was determined using methylation-specific PCR and was correlated to histopathology, HPV prevalence and cytology findings.
Results: Detection of at least two of the six markers was obtained before histopathological diagnosis CIN3 in 62% of the 119 cases. Twenty % of cases were methylation positive 18 months prior to histopathological confirmation of CIN3. In a control group comprising 733 patient samples with Pap I findings, the GynTect® detection rate was only 3.4%.
Conclusions: The results of this study underscore the prognostic value of the six methylation markers for severe cervical dysplasia. We are currently conducting a prospective trial "GynTect-PRO" which aims to confirm the prognostic value of the GynTect® methylation markers in patients with CIN2/3 aged ≤ 24 years who are undergoing watchful waiting for up to 2 years.

Head and Neck Cancer

Vorträge

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Comprehensive Genomic and Transcriptomic Analysis of Primary and Recurrent Head and Neck Cancers

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Purpose: Head and neck squamous cell carcinomas (HNSCCs) are a group of heterogeneous diseases arising from the epithelial cells of oral cavity, pharynx, larynx, nasal cavity and salivary glands. Major risk factors are smoking, excessive alcohol use and human papillomavirus (HPV) infection. Despite aggressive treatment, up to 50% of the patients relapse within three years and have very poor prognoses. In this study, we investigated how the genetic landscape and the patterns of gene expression change during tumor evolution, upon recurrence and after treatment. This information can improve our understanding of tumor progression and help in predicting it, also in connection to patient history.
Methods: We sequenced whole exome and transcriptome of matched primary and recurrent tumor samples from nine patients, with different treatment and patient histories. These data were used to call somatic Single Nucleotide Variants (sSNVs), perform a differential expression analysis and quantify immune cell infiltration in the tumor.
Results: The analysis of sSNVs showed that tumor mutational burden varies considerably across patients, but is generally higher in recurrent samples than in primary tumors: part of the mutation profile is shared, but in the majority of the patients recurrent samples acquire additional sSNVs. A differential gene expression analysis highlighted ca. 250 genes that are consistently up- or down-regulated in the recurrent samples compared to the primary tumor, in spite of the diverse patient histories. Immune cell infiltration in the tumor is overall higher in primary than in recurrent samples, although heterogeneity across patients is substantial in this regard, too.
Conclusions: Altogether, these results highlight the complexity and the important differences occurring in the genomic and transcriptomic landscape of HNSCC samples, and support the administration of individualized immunotherapy treatments to patients affected by this cancer entity.

Disclosure Statement: Valesca Bukur and Christian Albrecht: paid consultants/part-time employees of BioNTech SE.
Ugur Sahin: co-founder and shareholder of TRON, co-founder and CEO of BioNTech SE.
Anthony Kong: received fees for consulting, advisory, speaker's roles and/or research funding from PUMA BioTechnology, AstraZeneca, Merck, MSD, Bristol-Myers Squibb, Avvinity Therapeutics.
Hisham Mehanna: personal financial interests with AstraZeneca, MSD, GSK, Sanofi Pasteur, Merck, Warwickshire Head Neck Clinic Ltd; institutional financial interests with AstraZeneca, GSK PLC, Sanofi Pasteur, MSD, GSK Biologicals, Silence Therapeutics; leadership roles: Chief of Liteform Trial Steering Committee, Chair of NIMRAD Trial Steering Committee, President of the British Association of Head Neck Oncologists, Trial Steering Group member of the MRC CTU Cancer Trials Steering Committee, Council member of the International Association of Oral Oncology, Director of the Institute for Head Neck Studies and Education, Secretary of the Head Neck Cancer InterGroup.
All other authors have no conflict of interest.

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Tpextreme Randomized Trial: TPEX Versus Extreme Regimen in 1st Line Recurrent/Metastatic Head & Neck Squamous Cell Carcinoma (R/M HNSCC), Updated Analysis

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A joint trial of the GORTEC (France), AIO-Studien-gGmbH (Germany), TTCC (Spain)

In collaboration with GETTEC-GERCOR and with H&N UNICANCER group (France)

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Purpose: After promising results from the GORTEC TPEx phase II trial, the role of taxane instead of 5FU in 1st-line R/M HNSCC chemotherapy (CT) remained to be confirmed by comparing TPEx to the reference EXTREME regimen.
Methods: Randomized (1:1), open-label trial. Main inclusion criteria were R/M HNSCC not suitable for locoregional treatment, age 18-70 years, PS <2, creatinine clearance >60ml/min, prior cisplatin <300 mg/m^2. Reference EXTREME regimen (arm A: 6 cycles every 3 weeks (Q3W) of 5FU–cisplatin-cetuximab (cetux) followed by weekly cetux maintenance) was compared to TPEx regimen (arm B: 4 cycles Q3W of docetaxel 75mg/m^2–cisplatin 75mg/m^2- cetux 250mg/m^2 with mandatory G-CSF support followed by every 2W cetux 500mg/m^2 maintenance). The primary endpoint was Overall Survival (OS).
Results: 539 pts were enrolled in 37 mo. Median age was 60 years, 93% were smokers, 40% had oropharyngeal tumor (p16 or HPV DNA positive in 28%). In arm A, 44% of pts received all CT cycles vs 72% in arm B. Delays in administration were more frequent in arm A (27% vs 10%). Cisplatin was more frequently switched to carboplatin in arm A (34% vs 9%). Toxicity was lower in arm B: 34% pts had grade ≥4 adverse events during CT in arm B vs 50% in arm A (p<0.001). Less pts in arm A started maintenance than in arm B (53% vs 73%). At time of analysis, the median follow-up duration was >30 mo and 406 pts had died. OS was not significantly different between arms: HR=0.87 (95%CI: 0.71-1.05), p=0.15. Median OS was 13.4 mo in arm A vs 14.5 in arm B. ~~2-year OS rate was 21.0% in arm A vs 28.6% in arm B.~~ Median PFS was 6.1 mo in arm A vs 6.0 in arm B.
Conclusions: This large randomized trial confirmed the encouraging survival results of the TPEx regimen observed in the first phase II. Despite lack of significant OS increase, taxane based TPEx regimen appears to be a new option in 1st line R/M HNSSCC, with a shorter time on CT and significantly lower toxicity than the EXTREME regimen.

Reference:
1. J. Guigay et al, J Clin Oncol 37, 2019 (suppl; abstr 6002)

Funding source: Grant from Merck Serono.

Poster

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Prognostic Significance of CD8-Based Immune Status Inflamed, Immune-Excluded and Immune Desert in Head and Neck Tumors can be Further Subdivided by Regulatory T Cells

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Purpose: It has been postulated that there are tumors with very low infiltration of inflammatory cells, i.e. immune deserts, with immune response limited to the stroma, i.e. immune excluded and the inflamed tumors with many inflammatory cells intraepithelially. We studied the prognostic significance of CD8, classified according to immune desert, immune exclusion and inflammation, as well as the influence of regulatory T cells, in tissue sections of 284 HNSSC patients.
Methods: Cytotoxic T cells (CD8+) and regulatory T cells (FoxP3+) were determined separately in the stromal and intraepithelial compartment by double staining in 284 tissue samples using image analysis software.
Results: The division of the tissues into desert (<34 cells per mm²; FoxP3 17.3 stromal, 0.0 intraepithelial), excluded (<334 cells intraepithelial; 190.6 / 46.3) and inflamed (>334 cells intraepithelial; 382.3 / 132.4). In overall survival (Kaplan Meier) the desert group had a median survival of 41 months, excluded 57 m and inflamed the best survival with 81 m. In addition, the importance of FoxP3+ cells in the three groups was analyzed. In the desert group, stromal FoxP3 had no significance. In the excluded group low intraepithelial FoxP3 with 76 m v. 37 m was associated with clearly better survival. In contrast, high stromal FoxP3 was favorable (94 m v. 44 m) for survival. In Inflamed high FoxP3 were favorable, stromal with >96 m v. 77 m and intraepithelial with >96 m v. 72 m.
Conclusions: In the desert and excluded group, the few cytotoxic cells (low CD8) were immunosuppressed by high regulatory T cells, leading to an unfavorable prognosis. In the inflamed group, the importance of regulatory T cells is reversed and a high number leads to a more favorable prognosis. This could be interpreted as the suppression of inflammation and thus the reduction of inflammatory mediators and tumor growth-promoting properties. Although the three groups already differ significantly in their prognosis, their importance can be further differentiated by the regulatory T cells.

Disclosure: The authors declare no conflict of interest.

Immunotherapy Side Effects

Poster

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Serio - Side Effect Registry in Immuno-Oncology

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Purpose: In an era where immunotherapies have become standard for oncological therapy of a variety of tumor entities, adequate management of side effects is essential. However, little is known about rare, severe or complex immune-related adverse events (irAE). Thus, these cases have to be analyzed together to gain further understanding of risk factors, occurrence, optimal treatment and outcome of these side effects.
Methods: SERIO is an international side effect registry for rare, severe and/or treatment-refractory side effects induced by immune checkpoint blockade, i.e. CTLA4- and PD1/PD-L1 inhibitors or other immunotherapies. The patients´ medical history, symptoms, diagnostic findings and management of the side effects as well as the outcome are documented.
Results: Until now, more than 1,000 cases of rare, severe, complex or treatment-refractory side effects induced by nivolumab, pembrolizumab, atezolizumab, cemiplimab or ipilimumab have been assessed. From these analyses, recommendations, pathogenetic studies and several publications have been developed from it, also in special patient cohorts. In cooperation with the Paul-Ehrlich-Institute the registry is currently being developed for online use.
Conclusions: The SERIO registry will increase knowledge on rare and severe side effects induced by immunotherapy. Shared experiences will enable better management of side effects and better patient information with regard to outcome of side effects thus reducing patient morbidity and mortality. Eventually, it will enable to better understand pathogenesis and prediction of irAEs.

Lung Cancer

Vorträge

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Updated Results from the Phase 3 ALTA-1L Trial of Brigatinib (BRG) vs. Crizotinib (CRZ) in ALK Inhibitor-Naive Advanced ALK + NSCLC

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Purpose: We report results of the ALTA-1L trial (NCT02737501) from the second interim analysis, planned at 75% of 198 expected events.
Methods: Patients (pts) with ALK inhibitor–naive advanced ALK+ NSCLC and ECOG PS 0–2 were enrolled and stratified by baseline (BL) brain metastases and prior chemotherapy. One prior chemotherapy for advanced NSCLC and asymptomatic CNS metastases were allowed. All pts had brain MRI at each tumor assessment. Pts were randomized 1:1 to BRG 180 mg QD (with 7-day lead-in at 90 mg) or CRZ 250 mg BID. Pts in the CRZ arm were offered BRG at progression. Primary endpoint: BIRC-assessed PFS (RECIST v1.1). Secondary endpoints included confirmed ORR, confirmed iORR, iPFS by BIRC, OS, and safety.
Results: 275 pts were randomized (BRG/CRZ, n=137/138); median age 58/60 y. 26%/27% received prior chemotherapy; 29%/30% had BL brain metastases. As of 28 Jun 2019, median follow-up was BRG/CRZ: 24.9/15.2 mo, with 150 (63/87) PFS events. HR of BIRC-assessed PFS was 0.49 (95% CI 0.35–0.68, log-rank P<0.0001); BRG mPFS (95% CI) was 24.0 mo (18.5–NR) vs CRZ 11.0 mo (9.2–12.9). Investigator-assessed PFS HR was 0.43 (0.31–0.61, log-rank P<0.0001); median 29.4 vs 9.2 mo. Confirmed ORR for BRG was 74% (66–81) vs CRZ 62% (53–70); median DoR was NR (19–NR) vs CRZ 14 mo (9–21). OS was immature (total events: 33/37, BRG/CRZ). In pts with BL brain metastases, BIRC-assessed PFS HR (BRG/CRZ, n=40/41, per investigator) was 0.25 (0.14–0.46) and iPFS HR (n=47/49, by BIRC) was 0.31 (0.17–0.56); log-rank P<0.0001 for both. In pts without BL brain metastases (n=97/97), PFS HR was 0.65 (0.44–0.97, log-rank P<0.0298). In pts with measurable iCNS disease (BRG/CRZ, n=18/23), confirmed iORR was BRG 78% (52–94) vs CRZ 26% (10–48); P=0.0014; median iDoR NR (6–NR) vs 9 mo (4–9). Most common TEAEs grade ≥3: BRG: increased CPK (24.3%) and lipase (14.0%), hypertension (11.8%); CRZ: increased ALT (10.2%), AST (6.6%), and lipase (6.6%). Any grade ILD/pneumonitis (BRG/CRZ): 5.1%/2.2%; discontinuations due to AE: 12.5%/8.8%.
Conclusions: BRG showed durable PFS superiority vs CRZ in ALK inhibitor–naive ALK+ NSCLC.

Study funder: ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

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Impower110: Interim OS Analysis of a Phase III Study Of Atezolizumab (ATEZO) vs Platinum-Based Chemotherapy (Chemo) as 1L Treatment (TX) in PD-L1–Selected NSCLC

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Background: PD-L1/PD-1–inhibitors (CPI) as monotherapy (mono) or combined with doublet chemo (± bevacizumab) are 1L tx options in metastatic NSCLC, with choice of agent(s) determined by PD-L1 expression. For patients (pts) ineligible for combination therapy, CPI mono remains an attractive tx choice. IMpower110 evaluated atezo as 1L tx in PD-L1–selected pts.
Methods: IMpower110 (NCT02409342) enrolled 572 chemo-naive pts with stage IV nonsquamous [nsq] or squamous [sq] NSCLC, PD-L1 expression ≥ 1% on tumour- (TC) or tumour-infiltrating immune cells (IC), measurable disease by RECIST 1.1 and ECOG PS 0-1. PD-L1 expression was centrally evaluated (VENTANA SP142 IHC assay) and classified as TC/IC3 (TC ≥ 50% or IC ≥ 10% PD-L1+), as TC/IC2-3 (TC ≥ 5% or IC ≥ 5% PD-L1+) or TC/IC1-3 (TC ≥ 1% or IC ≥ 1% PD-L1+). Pts were randomized 1:1 to receive atezo 1200 mg IV q3w (Arm A) or platinum-based chemo (Arm B; 4 or 6 21-day cycles). Arm B nsq pts received cisplatin (cis) 75 mg/m^2 or carboplatin (carbo) AUC 6 + pemetrexed 500 mg/m^2 IV q3w; Arm B sq pts received cis 75 mg/m^2 + gemcitabine (gem) 1250 mg/m^2 or carbo AUC 5 + gem 1000 mg/m^2 IV q3w. The primary endpoint of OS is tested hierarchically in wild-type (WT; *EGFR/ALK* negative) pts (TC/IC3 then TC/IC2-3 then TC/IC1-3).
Results: The 3 primary efficacy populations included 554 TC1-3 or IC1-3-WT pts, 328 TC2-3 or IC2-3-WT pts, and 205 TC3 or IC3-WT pts. Within the TC3 or IC3-WT population, atezo improved median OS by 7.1 mo (HR 0.595; *P* = 0.0106) vs chemo (median follow-up 15.7 mo). Median OS-gain in the TC2-3 or IC2-3-WT group after atezo was 3.3. mo (HR 0.717; P = 0.0416) but not significant in the entire population. The safety population comprised 549 pts. Treatment-related/grade 3-4 AEs occurred in 60.5%/12.9% (Arm A) or 85.2%/44.1% (Arm B), respectively.

Conclusions: At this interim analysis, IMpower110 met the primary OS endpoint with statistically significant and clinically meaningful improvement in the TC3 or IC3-WT population. The safety profile favored Arm A with no new or unexpected safety signals seen.
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Impower133: Updated Overall Survival (OS) Analysis of First-Line (1L) Atezolizumab (ATEZO) + Carboplatin + Etoposide in Extensive-Stage SCLC (ES-SCLC)

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Background: IMpower133 (NCT02763579), a global Phase I/III, double-blind, randomized, placebo-controlled trial, showed that adding atezo (anti–PD-L1) to 1L carboplatin + etoposide for ES-SCLC led to a statistically and clinically significant improvement in OS and progression-free survival (PFS) vs carboplatin + etoposide alone. This combination was US FDA–approved in March 2019. Here we present an exploratory updated OS analysis of IMpower133.
Methods: Patients (pts) without prior systemic tx for ES-SCLC were enrolled. PD-L1 testing was not required for enrolment eligibility, but tissue was collected when possible. Pts were randomised 1:1 to receive four 21-day cycles of carboplatin (AUC 5 mg•mL/min IV, Day 1) + etoposide (100 mg/m^2 IV, Days 1-3) with either atezo (1200 mg IV, Day 1) or placebo (PBO), then maintenance therapy with atezo or PBO until intolerable toxicity or progression. Pts meeting predefined criteria could receive tx beyond progression. Coprimary endpoints were OS and investigator-assessed PFS. OS interim and final analyses were planned for ≈ 240 and ≈ 306 OS events, respectively. Since OS was statistically significant at the interim analysis, an exploratory updated OS analysis was conducted, and exploratory biomarker analyses are in progress.
Results: 201 pts were randomized to the atezo group and 202 to the PBO group. At this updated analysis, 302 OS events had been observed. Median follow-up was 22.9 mo. Median OS remained 12.3 mo in the atezo group and 10.3 mo in the PBO group (HR, 0.76 [95% CI: 0.60, 0.95]; descriptive $P = 0.0154$). Cumulative survival rates at 6, 12 and 18 mo were 86%, 52% and 34% in the atezo group, and 83%, 39% and 21% in the PBO group, respectively. Other efficacy analyses, including by PD-L1 status, will be presented.
Conclusion: The addition of atezo to carboplatin and etoposide continued to provide improvement in OS for 1L ES-SCLC. These results further support this regimen as the new standard of care for untreated ES-SCLC.
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Nivolumab (N) + Low-Dose Ipilimumab (I) vs Platinum-Doublet Chemotherapy (Chemo) as First-Line (1L) Treatment (tx) for Advanced Non-Small Cell Lung Cancer (NSCLC): Checkmate 227 Part 1 Final Analysis

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Purpose: Part 1 of CheckMate 227 (NCT02477826), a phase 3 study in 1L NSCLC, previously met one of its dual primary endpoints, progression-free survival (PFS) with N+I vs chemo in patients (pts) with tumor mutational burden ≥ 10 mut/Mb. We report the primary endpoint of overall survival (OS) for N+I vs chemo in pts with tumor PD-L1 ≥ 1%.
Methods: Pts were chemo-naive, with stage IV or recurrent NSCLC without *EGFR* or known *ALK* alterations, ECOG PS 0–1. Pts with PD-L1 ≥ 1% were randomized 1:1:1 to N 3 mg/kg Q2W + I 1 mg/kg Q6W (n = 396), N 240 mg Q2W (n = 396), or histology-based chemo (n = 397); pts with PD-L1 < 1% were randomized 1:1:1 to N 3 mg/kg Q2W + I 1 mg/kg Q6W (n = 187), N 360 mg Q3W + chemo (n = 177), or chemo (n = 186). Pts were stratified by histology and treated until progression, unacceptable toxicity, or for 2 y of immunotherapy.
Results: Baseline characteristics were balanced across tx arms. Minimum follow-up for OS was 29.3 mo. For pts with PD-L1 ≥ 1%, median OS (95% CI) was 17.1 mo (15.0–20.1) with N+I vs 14.9 mo (12.7–16.7) with chemo (HR 0.79, 97.72% CI 0.65–0.96; $P = 0.007$). HR for PFS was 0.82 (95% CI 0.69–0.97), objective response rate was 35.9% (N+I) vs 30.0% (chemo), and median duration of response was 23.2 mo vs 6.2 mo. In pts with PD-L1 < 1%, median OS was 17.2 mo with N+I and 12.2 mo with chemo (HR 0.62, 95% CI 0.48–0.78) and in all randomized pts, 17.1 mo and 13.9 mo (HR 0.73, 95% CI 0.64–0.84). N+I showed enhanced efficacy vs N in PD-L1 ≥ 1% and vs N+chemo in PD-L1 < 1%. Grade 3–4 tx-related adverse event rates in all randomized pts were 33% (N+I), 19% (N), and 36% (chemo).
Conclusions: CheckMate 227 met its primary endpoint of significantly improved OS with N+I vs chemo in 1L advanced NSCLC with PD-L1 ≥ 1%. OS was also improved with N+I in PD-L1 < 1% and in all randomized

pts. Safety was consistent with prior reports in NSCLC. N+I may represent a new chemo-free tx option for 1L advanced NSCLC.

Disclosure Statement:
Funding: BMS
Previously presented at ESMO 2019, FPN LBA4_PR, Peters et al. Reused from: *Ann Oncol* 2019; 30 (Suppl_5): v193-v194, doi:10.1093/annonc/mdz394.075, by permission of Oxford University Press on behalf of ESMO.

Poster

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Stage IV Lung Cancer - Cost-Effectiveness of the Real-World Administration of Chemotherapy and Add-on Viscum Album L. Compared to Chemotherapy Alone

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Purpose: Improved overall survival (OS) has been observed in late stage cancer patients receiving add-on *Viscum album* L. treatment [1, 2]. The objective of the present study was the cost-effectiveness analysis (CEA) for chemotherapy plus add-on *Viscum album* L (V) compared to chemotherapy alone (C) in patients with stage IV lung cancer.
Methods: A real-world study was conducted (DRKS00013335). Patients with stage IV lung cancer received C or V treatment in a certified German Cancer Centre. Cost analyses and CEA (hospital's perspective) were performed.
Results: 118 patients (C: n=86, V: n=32) were included (mean age 63.8 y, 55% male). Adjusted hospital's mean costs were €16,288.98 for C (over an adjusted mean OS time of 13.4m) and €17,992.26 for V (over an adjusted mean OS time of 19.1m), respectively. Hospital's savings of €273.60 per mean month OS in the V-group were observed compared to C. The costs per additionally gained OS year with the V-treatment compared to C were €3,585.84 (ICER).
Conclusions: The stationary costs per mean OS month were lower for the combinational V- compared to the C-treatment alone. Further prospective and randomized studies are mandatory.

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1. Tröger W et al. European Journal of Cancer, 2013
2. Schad F et al. PLoS One, 2018.

Disclosure: Grants from Helixor Heilmittel GmbH (FS). Administrative board Weleda AG (HM). No competing interests (AT, TR, PVT).

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Efficacy of Docetaxel/Ramucirumab as Palliative Third-Line Therapy Immediately after Second-Line Immune-Checkpoint Inhibitor (ICI) Treatment in Patients with Non-Small Cell Lung Cancer (NSCLC) UICC Stage IV

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Background: Antiangiogenic agents have shown to stimulate the immune system and cause synergistic effects in combination with chemotherapy. This effect might be even stronger after immune-checkpoint-inhibitor (ICI) therapy. Therefore, we conducted a retrospective analysis to evaluate the efficacy of ramucirumab plus docetaxel (ram+doce) as 3rd line treatment after failure of platinum-based combination and ICI in patients with NSCLC stage UICC IV in 1st and 2nd line, respectively.
Methods: 67 patients with non-small cell lung cancer (NSCLC), starting their palliative 1st line treatment between 3/13 and 9/18 could be collected from nine German high-volume Thoracic Oncology Centers. All patients were treated by the same kind of 1st and 2nd line therapy and received at least one cycle of 3rd line therapy with ram+doce. The numbers of cycles, response rate, PFS to 3rd line treatment and OS were investigated after a positive IRB vote.
Results: The median age of patients was 62 (range: 42-82) years with 69% of the patients being male. The histology was adenocarcinoma, squamous cell carcinoma and other in 58%, 36% and 6%, respectively. Due to 3rd line, the mean number of ramucirumab cycles was 6.5 (95%CI: 5.3-7.7) with a mean number of 3.5 cycles given as a combination treatment. The ORR to ram+doce was 36% and DCR of 69%. More patients received a response to 3rd line as to 2nd line with 11% having a response to both lines. mPFS was 6.8 months (95%CI:4.6-9.0) with a DOR of 10.2 months (95%CI: 9.3-11.1). The mOS from starting with 3rd line therapy was 11 months (95%CI: 7.1-14.9). With 17 patients (25%) receiving further treatment in 4th line the mOS was 29 months (95%CI: 25.4-32.8). Concerning histology, there was no difference between adenocarcinoma and squamous cell carcinoma for the PFS results. Additionally, no new AE were reported.
Conclusions: Ram+doce showed encouraging effectivity in 3rd line therapy immediately after failure of 2nd line ICI and can be used irrespectively of NSCLC histology. Effectivity after ICI plus chemotherapy in 2nd line treatment is actually analyzed in a separate cohort.

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Entrectinib in Locally Advanced / Metastatic ROS1 and NTRK Fusion-Positive (NTRK+) Non-Small Cell Lung Cancer (NSCLC): Updated Integrated Analysis of STARTRK-2, STARTRK-1 and ALKA-372-001

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Purpose: Entrectinib is a systemic and central nervous system (CNS)-active potent inhibitor of ROS1 and TRKA/B/C. Primary data showed that entrectinib was tolerable and achieved high objective response rates (ORR) in patients (pts) with *ROS1*-positive (*ROS1*+), ROS1 inhibitor-naïve NSCLC, and in pts with NTRK+ NSCLC, including pts with baseline CNS disease. We present data from an additional 5 mo follow-up.
Methods: Pts with locally advanced/metastatic *ROS1*+ or *NTRK*+ tumors (with or without baseline CNS disease) confirmed by nucleic acid-based methods, enrolled in global Phase 1/2 entrectinib trials (ALKA-372-001 [EudraCT 2012-000148-88], STARTRK-1 [NCT02097810], STARTRK-2 [NCT02568267]) were included. Disease burden was assessed per blinded independent central review (BICR) using RECIST v1.1, after 4 wks (Cycle 1), then every 8 wks. Primary endpoints were ORR and duration of response (DOR) by BICR. Secondary endpoints included ORR and DOR in pts with or without baseline CNS disease, and safety. Intracranial (IC) ORR and DOR were evaluated in pts with baseline CNS disease.
Results: There were 53 efficacy-evaluable pts with treatment-naïve, *ROS1*+ NSCLC and 10 pts with *NTRK*+ NSCLC. As of Oct 30, 2018 (additional 5 mo follow-up), BICR ORR: *ROS1*+ 79.2% (95% CI 65.9–89.2) and *NTRK*+ 70.0% (95% CI 34.75–93.33) with complete responses in 5 (9.4%) pts and 1 (10.0%) pt, respectively. In ROS1+ NSCLC, median DOR: 24.6 mo (95% CI 12.6–34.8); in pts with and without baseline CNS disease, ORR was 73.9% (95% CI 51.6–89.8) and 83.3% (95% CI 65.3–94.4); IC ORR was 55.0% (95% CI 31.5–76.9); and median IC DOR was 12.9 mo (95% CI 5.6–not estimable). Additional efficacy for *NTRK*+ NSCLC pts will be presented. Entrectinib was well tolerated, with a safety profile consistent with that previously reported; there were no new or unexpected safety findings.
Conclusions: In line with the primary data, in pts with *ROS1*+ and *NTRK*+ NSCLC, after an additional 5 mo follow-up, entrectinib was well tolerated, and showed clinically meaningful, durable systemic and intracranial responses.

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Entrectinib in Patients with NTRK Fusion-Positive Solid Tumors or ROS1-Positive NSCLC with CNS Metastases

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Purpose: Entrectinib potently inhibits kinases encoded by *NTRK* and *ROS1* genes. It achieves therapeutic levels in the CNS with antitumor activity in intracranial tumor models. We report an integrated analysis data (May 31, 2018 data cut-off) from three Phase 1/2 entrectinib trials (ALKA-372-001 [EudraCT 2012-000148-88]; STARTRK-1 [NCT02097810]; STARTRK-2 [NCT02568267]) for a large cohort of adult patients.
Methods: Patients had locally advanced/metastatic *NTRK*+ solid tumors or *ROS1*+ NSCLC confirmed by nucleic acid-based assays. Baseline CNS metastases were identified by CT/MRI. Tumor assessments were performed at baseline, week 4, and then every 8 weeks by BICR (RECIST v1.1). Primary endpoints were overall response rate and duration of response. Secondary endpoints included progression-free survival, overall survival, intracranial efficacy in patients with CNS metastases, and safety.
Results: Most patients were treated first-line or after one line of prior therapy. CNS lesions at baseline were observed in 22.2% of *NTRK*+ solid tumors (n=54; 18% NSCLC) and 43.4% of *ROS1*+ NSCLC (n=53), with 58.3% and 65.2% of these having received prior radiotherapy. Intracranial ORR was 54.5 (95% CI 23.4–83.3) for *NTRK*+ and 55.0 (31.5–76.9) for *ROS1*+ NSCLC. Durability of treatment effect and potential delayed progression in the CNS was observed; Time to CNS progression was 17.0 months (95% CI 14.3–NE) for *NTRK*+ solid tumor patients and NE (95% CI 15.1–NE) for *ROS1*+ NSCLC. Median duration of response was NE (5.0–NE) and 12.9 (5.6–NE) for *NTRK*+ and *ROS1*+ NSCLC, respectively. In the subset of patients with *NTRK*+ NSCLC (n=10), 6 patients had CNS metastases at baseline (by BICR); IC-ORR was 66.7% (4/6), 2 CR; IC-DOR was NE. In both the *NTRK*+ and *ROS1*+ populations, entrectinib was tolerable with a manageable safety profile; most treatment-related AEs were grade 1–2.
Conclusions: Entrectinib induced clinically meaningful durable responses in patients with *NTRK*+ solid tumors or *ROS1*+ NSCLC with CNS disease at baseline.

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Nivolumab (NIVO) Plus Low-Dose Ipilimumab (IPI) as First-Line (1L) Treatment (tx) of Advanced Nsclc: Overall Survival (Os) Analysis of Checkmate 817

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Purpose: NIVO + IPI showed improved OS vs chemotherapy as 1L tx for advanced NSCLC with tumor programmed death ligand 1 (PD-L1) ≥ 1% and < 1% in CheckMate 227. CheckMate 817 (NCT02869789) is a multi-cohort, single arm, phase 3b study evaluating flat-dose NIVO + weight-based low-dose IPI in advanced NSCLC. Preliminary safety and efficacy results were previously reported for cohorts A and A1. We present additional safety data and OS in these cohorts.
Methods: Patients (pts) with previously untreated stage IV or recurrent NSCLC, and no known sensitizing *EGFR* or *ALK* alterations, were eligible regardless of PD-L1 expression. Cohort A (n = 391) had ECOG performance status (PS) 0–1; cohort A1 (special populations; n = 198) had ECOG PS 2 or a specified comorbidity (asymptomatic untreated brain metastases, hepatic or renal impairment, or HIV). Pts were treated with NIVO 240 mg Q2W + low-dose IPI 1 mg/kg Q6W for 2 y or until disease progression/unacceptable toxicity. Safety in cohort A was the primary endpoint; efficacy endpoints were secondary/exploratory; A1 safety and efficacy analyses were exploratory.
Results: Baseline characteristics, except ECOG PS and comorbidities, were similar between cohorts. With minimum follow-up of 21 mo (A) and 14 mo (A1), median OS was 17.0 mo and 9.9 mo, respectively. At 1 y, 60% (A) and 47% (A1) of pts were alive. OS by PD-L1 expression and tumor mutational burden levels will be presented. The safety profile (type and rate of treatment-related adverse events [TRAEs]) was consistent between the cohorts. The range of median time to onset of select TRAEs was 2–26 wk (A) and 2–21 wk (A1). Most select TRAEs had resolved (40%–100%).
Conclusions: The select TRAE profile of NIVO + low-dose IPI was similar between cohorts A and A1. Durable OS outcomes were observed with 1L NIVO + IPI in pts with advanced NSCLC (cohort A) and were comparable with CheckMate 227; although as expected, comorbidities and/or poor PS impacted outcomes in cohort A1.

Disclosure Statement:
Funding: BMS
Previously presented at ESMO I-O 2019, FPN 92O, *Barlesi* et al. Reused with permission.

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Final Progression-Free Survival (PFS), Updated Overall Survival (OS), And Safety Data from the Global, Randomized, Phase 3 Alex Study of Alectinib (ALC) Versus Crizotinib (CRZ) in Untreated Advanced ALK+ Non-Small Cell Lung Cancer (NSCLC)

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Purpose: To report mature PFS, updated OS, and safety from the ALEX study (NCT02075840) after a further 12 months (m) of follow-up (FU; cutoff: 30/11/18).
Methods: Pts had stage IIIB/IV *ALK*+ NSCLC (central IHC), ECOG PS 0–2, and no prior systemic therapy for advanced NSCLC. Asymptomatic CNS mets were allowed. Pts were randomized 1:1 to bid ALC 600 mg (n=152) or CRZ 250 mg (n=151). Primary endpoint: investigator-assessed PFS (INV-PFS; RECIST v1.1), with q8w CNS imaging in all pts.
Results: Mature median INV-PFS: 34.8 m (95% CI 17.7–NR) ALC v 10.9 m (95% CI 9.1–12.9) CRZ (ITT stratified HR 0.43, 95% CI 0.32–0.58; p<0.0001); events: 53.3% ALC v 80.8% CRZ. Median FU: 37.8 m ALC v 23.0 m CRZ. Median INV-PFS was longer with ALC v CRZ in pts with baseline (BL) CNS mets (25.4 m v 7.4 m, HR 0.37, 95% CI 0.23–0.58) and in those without (38.6 m v 14.8 m, HR 0.46, 95% CI 0.31–0.68). PFS event-free rate was higher with ALC v CRZ regardless of BL CNS mets. % PFS event-free rates (95% CI; ALC v CRZ): 1 year: 67.8 (60.3–75.3) v 48.0 (39.7–56.2); CNS mets: 58.5 v 32.5; no CNS mets: 74.5 v 57.2; 2 years: 56.6 (48.6–64.6) vs 24.8 (17.6–32.1), CNS mets: 52.0 v 6.3; no CNS mets: 59.8 v 35.7; 3 years: 46.4 (38.2–54.5) v 13.5 (7.7–19.3); CNS mets: 40.5 v 2.1; no CNS mets: 50.6 v 20.2; 4 years: 43.7 (35.4–51.9) v not estimable (NE); CNS mets: 38.0 v NE; no CNS mets: 47.6 v NE. OS data remain immature (ALC events: 32%; stratified HR 0.69, 95% CI 0.47–1.02). OS in pts with BL CNS mets, HR 0.60 (95% CI 0.34–1.05) and in pts without BL CNS mets, HR 0.77 (95% CI 0.45–1.32). % OS event-free rates (ALC v CRZ): 1 year: 84.3 (78.4–90.2) v 82.5 (76.1–88.9); 2 years: 72.5 (65.1–79.9) v 65.1 (56.7–73.4); 3 years: 66.9 (59.0–74.8) v 56.7 (47.8–65.6); 4 years: 64.5 (55.6–73.4) v 52.2 (42.6–61.8).
Considering the longer median treatment duration with ALC v CRZ (27.7 m v 10.8 m), the safety profile for ALC remains favorable; fewer ALC-treated pts experienced grade 3–5 adverse events (48.7% v 55.0%).
Conclusions: This final updated PFS analysis confirms the superior efficacy and favorable tolerability of ALC v CRZ in pts with untreated *ALK*+ NSCLC. OS data remain immature.

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Characterization of Lung Cancer Cell Lines by Single Cell Analysis

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Purpose: Lung cancer is the most common and most deadly form of cancer with a prevalence of 11.6% and 1.7 million cancer related deaths worldwide [1]. Primary tumors consist of millions of cells which show distinct morphological and phenotypical differences. These differences are even more evident between cells related to the primary tumor and cells related to metastasis. Tumor heterogeneity is highly associated with acquired drug resistance. The elucidation of cell-to-cell heterogeneity is a major challenge but will be helpful to improve personalized therapy. To face this challenge, we intent to use single cell analysis to better understand tumor heterogeneity and thus improve cancer diagnosis and treatment design.
Materials and methods: The lung cell lines A549 and 103H were used for single cell analysis. The cell line A549 represents adenocarcinoma and 103H large cell lung carcinoma. Both were cultivated and prepared to isolate single cells with the CellCelector™. After cell lysis DNA and mRNA were prepared simultaneously [2].The quality of prepared DNA and mRNA was validated using selected DNA-sequences or housekeeping-genes. KRAS mutation analysis (34G>A) was performed by pyrosequencing. Expression levels of BIRC5 and STK11 were determined by qPCR.
Results: 64 A549 single cells and 56 103H single cells were isolated, as well as 56 single leukocytes for control. Pyrosequencing revealed that 47% of A549 single cells exhibit the homozygous KRAS mutation (34G>A), whereas no 103H cell or leukocyte showed neither homozygous nor heterozygous mutations. Regarding the expression of BIRC5 A549 and 103H showed a robust expression, whereas leukocytes expression levels were below detection limit. In contrast, the expression level of STK11 was comparable in all cell types tested.
Conclusion: The detection of KRAS mutation 34G>A in single cells confirms the potential of this approach to screen for genomic alterations in rare cells, e.g. circulating tumor cells, as well as for expression patterns.

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Tumor PD-L1 Expression in Stage III NSCLC: Initial Biomarker Results from the German Intergroup Lung Trial (GILT-CTRT)

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Purpose: PD-L1 expression may predict benefit from PD-L1 inhibition following radiochemotherapie (RTCT). The multicenter German Intergroup Lung Trial (GILT) randomised patients with inoperabel stage III NSCLC to RTCT with or without consolidation chemotherapy. We analysed immune markers in biopsies from the GILT trial, investigating the prognostic role of PD-L1 and tumor infiltrating lymphocytes (TiL) in this setting.
Methods: We retrospectively collected biopsies from patients treated in the GILT trial. PD-L1 expression was analysed using the Ventana SP263 assay. The primary endpoint of these analyses was PFS following RTCT in patients with PDL-1 positive (IHC ≥ 1% PDL-1) vs. PDL-1 negative (IHC<1% PDL-1) NSCLC. Secondary endpoints explored additional PD-L1 cut-offs, TiLs (score and pattern), driver mutations, and the markers CD3 and FOXP3. Here we present results of PD-L1 expression scores.
Results: 279 patients were included in the GILT study; biopsies were available from 95 patients. Those with available samples were similar to the whole study population in age, gender, histology and stage. PD-L1 scores from 61 samples were available for this initial analysis: 22 samples showed no PD-L1 expression and 39 showed expression in ≥ 1% of tumor cells. There was no PFS-difference in PD-L1 0 vs. PD-L1 ≥ 1% subgroups. An exploratory cut-off of 20% PD-L1 expression showed a slight trend to improved PFS with PD-L1 ≥ 20%.
Conclusions: In biopsies from the large, randomised GILT study, PD-L1 did not correlate significantly with PFS following RTCT. Further analyses to explore the effect of TiLs, mutations and other immune cell populations are planed.

Disclosure Statement: IIT funding from AstraZeneca

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First Description of an Unknown Anaplastic Lymphoma Kinase (ALK) Exon 23 Mutation Following Treatment with Alectinib in a Patient with Metastatic Non-Small Cell Lung Cancer (NSCLC)

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Purpose: Rearrangements of the *ALK* gene are harbored in 3 to 5% of NSCLC patients. The presence of genetic driver mutations enables the use of targeted therapies with tyrosine kinase inhibitors (TKIs). Following TKI therapy disease progression can occur due to new resistance mutations. Against this background, molecular genetic testing using tissue or liquid biopsy is increasingly used. However, knowledge of second line TKI effectiveness on resistance mutations has only been gained from in vitro data and the actual effect on tumor growth therefore remains unclear. Here we present our case report of a rare resistance mutation following treatment with Alectinib.
Methods: To highlight molecular testing using next generation sequencing (NGS) and to describe an unknown *ALK*-mutation we present a case report with clinical, radiological and molecular genetic data.
Results: Following detection of chromosome 2p23 *ALK* translocation, a 65-year old patient with metastatic NSCLC was successfully treated with Alectinib over a period of 20 months. Due to hepatic disease progression tissue sampling was subsequently performed. Using NGS the p.A1200_G1201delinsW mutation in exon 23 of the *ALK*-gene was detected in both liquid and tissue biopsy. This mutation is in close proximity to the well-known G1202R mutation and has not been described so far in literature. Therapy with the second generation ALK-inhibitor Brigatinib was started, interestingly leading to complete resolve of B-symptoms and to a radiologically proven stable disease.
Conclusions: Disease progression after first line TKI therapy entails the need for renewed tumor tissue sampling with genetic testing. Of interest, detection of the p.A1200_G1201delinsW mutation in exon 23 of the *ALK*-gene has not yet been described. Treatment with the next generation *ALK*-inhibitor Brigatinib may be a potential treatment option when this mutation is detected. Therefore, after first line TKI therapy, further ALK inhibition should also be considered, even if unknown resistance mutations occur.

References:

Disclosure Statement: Nothing to declare

Lymphoma and Plasma Cell Disorders

Vorträge

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Magnify: A Phase IIIB Trial Shows Promising Efficacy in the Treatment of Relapsed/Refractory, Indolent Non-Hodgkin Lymphoma Patients with Lenalidomide in Combination with Rituximab (R^2)

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Purpose: Standard treatment is lacking in relapsed/refractory (R/R) indolent NHL (iNHL), as indicated by a median PFS of <1 y with PI3K inhibitors. Recently, the immunomodulatory agent lenalidomide (L) reported enhanced activity with rituximab (R) as combination R^2, with a median PFS of 39.4 mo in R/R iNHL patients (pts; AUGMENT: Leonard et al. *J Clin Oncol*; 2019.).
Methods: The global, multicenter, non-registrational, randomized phase IIIb MAGNIFY trial was designed to determine the optimal duration of R^2 in pts with R/R FL gr 1-3a and MZL (NCT01996865). R^2 treatment is 12 cycles of L (20 mg/d, d1-21/28) + R (375 mg/m^2/wk cycle 1 and every 8 wk for cycles 3+) followed by 1:1 randomization in patients with stable disease or better to continue with R^2 vs R maintenance. The interim primary endpoint was overall response rate (ORR) by 1999 IWG criteria with induction R^2 in treated, efficacy-evaluable pts with baseline/post-baseline assessments.
Results: At a median 16.7-mo follow-up (range, 0.39-48.8), 370 pts (295 [80%] FL gr 1-3a; 75 [20%] MZL) were enrolled with a median age of 66 y, 83% stage III/IV disease, and a median of 2 prior therapies (range, 1-11; 95% prior R-containing). Efficacy-evaluable pts showed a 73% ORR and 45% CR. Median TTR was 2.7 mo, median DOR was 36.8 mo, and median PFS was 36.0 mo (overall) and 18.1 mo (rituximab-refractory). The most common all-grade AEs were 48% fatigue, 40% neutropenia, 35% diarrhea, 30% nausea, and 29% constipation. Grade 3/4 neutropenia was 34%; all other grade 3/4 AEs were <6%. These results are corroborated by the AUGMENT trial, in which a total of 358 pts with R/R FL gr 1-3a and MZL were randomized to R^2 (n=178) vs placebo/rituximab (n=180), where PFS was significantly improved for R^2 with a HR of 0.46 (95% CI, 0.34-0.62; P<0.001) and median PFS of 39.4 mo (95% CI, 22.9 mo-NR) vs 14.1 mo (95% CI, 11.4-16.7), respectively.
Conclusions: L improves the efficacy of R, as shown by a clinically active (with a high CR rate) and well tolerated R^2 therapy in pts with recurrent indolent lymphoma, including those refractory to rituximab.

Pediatric Cancer

Poster

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Associated Factors to Reduced Physical Activity in Long-Term Childhood Cancer Survivors in Germany

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Purpose: Based on the "Cardiac and vascular late sequelae in long-term survivors of childhood cancer (CVSS)-study", the physical activity (PA) level in German childhood cancer survivors (CCS) was evaluated in relation to tumor entity and compared to the general population.
Methods: In this cross-sectional study, 1002 CCS diagnosed with neoplasia prior to 15 years of age between 1980 and 1990 were recruited. Level of PA was determined by questionnaire. An activity score (AS) was then calculated based on reported intensity and time of PA and compared to the population-based Gutenberg Health Study (GHS) cohort. Participants were 23 to 50 years old.
Results: In total, physical activity questionnaire data was available from 951 CCS and compared to data from 5497 GHS participants. After adjusting for sex and age, results from multiple linear regression model revealed that AS was 24% lower in CCS than in GHS participants (-0.24 (95% CI -0.32 to -0.15); p<0.0001). With regard to tumor entity, AS was lower in CCS from leukemia (-0.18 (95% CI -0.29 to -0.072; p=0.0012), central nervous system tumor (-0.39 (95% CI -0.57 to -0.20), p=0.0001), renal tumor (-0.27 (95% CI -0.50 to -0.043); p=0.020), soft tissue sarcoma (-0.34 (95% CI -0.58 to -0.10); p=0.0052) and malignant bone tumor (-0.54 (95% CI -0.81 to -0.26); p=0.00014) compared to GHS participants. However, in CCS from lymphoma, neuroblastoma and germ cell tumor, there was no significant difference in AS compared to GHS participants. Furthermore, no association of AS was found in relation to chemotherapy, radiotherapy, recurrence rate and age at diagnosis among CCS.
Conclusions: In the present study, reduced PA level in German CCS was associated to tumor entity. Based on these findings, future investigations should explore potential benefits of adapted exercise programs on PA behavior and associated physical and mental wellbeing.

Reference:
1. PMID: 10993420; PMID: 29534171

Disclosure Statement: Nothing to disclose
The abstract was also submitted for the 8th Annual Meeting of Exercise is Medicine in Europe, September 20-21, 2019, Amsterdam

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Mental Health and Health-Related Quality of Life in Young Survivors of Early Childhood Cancer. Results of the Prospective Cohort Study IKIDS-OEVA

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Purpose: Long-term survivors of childhood cancer are at increased risk for sequelae as poor mental health (MH) or health-related quality of life (HrQoL). We aimed to evaluate early adverse effects on MH and HrQoL in preschool survivors of early childhood cancer.
Methods: A nationwide prospective cohort study was performed. Children aged 5 or 6 years with an oncological disease at preschool age (OEVA, excluding brain tumors) and completed cancer treatments were identified in the German Childhood Cancer Registry and approached. The comparison group were children of the same age without oncological disease who participated in the prospective population-based health survey ikidS. In both groups, children with expected delayed school enrollment were excluded. MH problems and HrQoL were assessed by parental versions of the Strengths and Difficulties (SDQ) and the KINDL questionnaires, respectively. Children with other chronic health conditions were identified by the Children with Special Health Care Needs screener. The associations between OEVA and MH problems as well as HrQoL were analyzed by linear regression adjusted for potential confounders.
Results: Of 382 children with OEVA contacted, 145 were enrolled, and 124 analyzed (48% boys, mean age at diagnosis 2.4 y). Compared to children without OEVA (3683 contacted, 2003 enrolled, 1422 analyzed), children with OEVA had more MH problems (13% vs. 3%) and slightly poorer HrQoL (median 78.7 vs. 80.2 points). In the adjusted analysis, children with OEVA had higher SDQ scores (adjusted mean difference 2.2, 95%CI [1.3; 3.0]; P<0.001) and lower KINDL scores (adjusted mean difference -2.4, 95%CI [-3.7; -1.1]; P<0.001) compared to children who had neither OEVA nor a special health care need.
Conclusions: Childhood cancer survivors at preschool age may be at increased risk of MH problems and poorer HrQoL. This could have an impact on subsequent educational attainment. Follow-up health care for OEVA survivors should include early screening for MH problems and other HrQoL deficits.

References:
1. PMID:29584786.

Disclosures: No conflict of interest.

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Sports Therapy in Pediatric Oncology at the Children's Hospital Munich Schwabing – Results after 3,5 Years of Interdisciplinary Collaboration

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Purpose: Treatment of childhood cancer is associated with physical inactivity, a reduced quality of life and motor performance. Therefore, sports interventions over all phases of treatment might be a supportive therapy option to improve the patients' physical and mental well-being.[1]
Methods: The approach of accompanying sports therapy was implemented by a feasibility study at our department. Aiming at a holistic model we promote physical activity from diagnosis to aftercare during in- and outpatient treatment among children from 2 years. Accomplishing the objectives sport scientists work closely together in an interdisciplinary team. Furthermore, continuity is ensured supporting the process of reintegration into sports structures among childhood cancer survivors.
Results: Since sports therapy was established in June 2016, 177 patients (9.0±4.5 yrs, 62% ♂) with different cancer entities participated in a daily sports program. Two part-time sports scientists provided 1776 exercise sessions (57.5% inpatient) with mean duration of 28.4±15.9min. Training content and intensity were specifically adjusted regarding age, interests and individual exercise capacity. Various sports groups and outdoor camps are completing our offers in the aftercare.[2]
Conclusions: Continuous sports promotion over all phases of treatment increases physical activity and supports the maintenance of mobility and autonomy. In order to develop a long-term active lifestyle and reduce possible disease- and therapy-related late effects the patients have to be sustainable encouraged after diagnosis. Further multi-center research projects will be essential to investigate the effects of physical exercise during pediatric cancer treatment with the intension of establishing sports therapy as part of standard care.

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2. Abstracts from the 51st Congress of the SIOP Lyon, 2019. Pediatric blood & cancer 66 Suppl 4, e27989.

1048

T Cell Receptor Based Immunotherapy in Immune Inert Pediatric Malignancy: Addressing the Challenge of Early Metastasis and Low Immunogenicity

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P: Most pediatric malignancies, in particular Ewing sarcoma (EwS) are characterized by low mutational load, low immunogenicity, and early metastasis. Ideally, targeted therapies address gene products required for metastasis. We completed *in vivo* functional analyses for metastasis of 9/37 genes that we had shown to be overexpressed in EwS (*Staege at al. Cancer Res. 2004*) and generated HLA class I restricted cytotoxic T cells against these gene products.
M: All targets were involved in fetal development and 8/9 demonstrated functional relevance for metastasis. Allorecognition repertoire-derived T Cell Receptors (TCRs) against 8/9 targets were cloned and sequenced; one target (DKK2) was non-immunogenic. 7/8 TCRs were cross reactive, caused fratricide or clonal TCR expansion failed. In the tumor microenvironment we found an immunosuppressive transcriptomic signature. Amongst these most selectively expressed and metastasis sustaining targets, chondromodulin-I (CHM1) was addressable by a non-cross reactive TCR. CHM1 is a direct downstream target of the oncogenic driver EWS-FLI1.
We clinically assessed HLAA* 02:01/CHM1-specific TCR transgenic $CD8^+$ T cells against EwS. Four refractory HLA-A2+ EwS patients (pts) were treated with $CHM1^{319}$-specific TCR-CDR3 transgenic T cells. Pt derived cell lines (PDCL) were established in all cases. Pts received up to

10^7/kg TCR transgenic CD8+ T cells. All pts were treated with the same TCR-CDR3 recognition-sequence for CHM1.
R: All PDCLs displayed persistent HLA-A2 expression. Transgenic T cells showed specific *in vitro* lysis of all PDCLs. Pt #1 #3 and #4 showed delayed progression, whereas pt #2, while having bone marrow (BM) involvement and accessible multifocal disease, showed partial metastatic regression associated with T cell homing to involved lesions.
C: $CHM1^{319}$-TCR transgenic T cells may home to affected BM & may cause partial remission. CHM1-TCR transgenic T cells address a persistently expressed target required for metastasis, suggesting lack of immunoediting selection pressure. They proliferate *in vivo* without causing GvHD.

Palliative Care

Poster

1051

Symptom Burden of Cancer Patients Ad Admission to a Palliative Care Unit: Cancer-Related Fatigue is Predominant

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Introduction: Cancer-related fatigue (CRF) is frequent in advanced stage cancer patients with an enormous impact on quality of life. In this survey we investigated the symptom burden of in-patient palliative care patients at the time of admission to our palliative care unit focussing on CRF.
Methods: Starting July 1st 2019, we questioned all cancer patients (pts.) during the admission process to our palliative care unit about the 3 most troublesome symptoms. Besides demographic data, we captured tumor type, ECOG performance status (PS) and application of any tumor therapy (chemotherapy, antibody or targeted therapy, radiotherapy) in the last 6 month prior to admission. A special interest was set on the existence and severity of CRF using the brief fatigue inventory (BFI), available and validated in german language.
Results: 105 tumor patients (51 women, 54 men, median age 70.8 years, mean ECOG PS 3.5) with 26 different malignancies were eligible. The 3 most frequent tumor types were lung cancer (23 pts., 21.9%), breast cancer (11 pts., 11.5%) and pancreatic cancer (13 pts., 12.4%). The most frequently reported tumor symptoms were fatigue (78%), pain (54%), cachexia/anorexia (39%), psychologic symptoms (29%), dyspnea (22%), neurologic symptoms (22%), nausea/vomiting (17%) and constipation (10%). 73 patients (69.5%) were able and willing to complete the BFI, mean BFI Score was 6.4. 7 pts. (9.5%) had mild fatigue (BFI score < 4), 35 pts. (47.9) had moderate (BFI score ≥ 4 and < 7) and 31 pts. (42.5%) had severe fatigue (BFI Score > 7). Fatigue was most prevalent in breast cancer pts. (91%, mean BFI score 6.3), similarly high in patients with lung (78%, mean BFI score 6.7) and pancreatic cancer (75%, mean BFI score 5.4).
34.9% of the patients received any tumor therapy in the last 6 weeks prior to admission. 82.8% of those pts. reported fatigue with a mean BFI score of 7.0, comparing to 70.4% and a mean BFI score of 6.4 in the 65.1% of pts. with no recent tumor therapy.
Conclusions: CRF is by far the predominant symptom of cancer patients and mostly the main cause for admission to our palliative care unit.

Psychooncology

Poster

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Development and Validation of the Readiness for End-of-Life Conversations (REOLC) Scale

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Purpose: Being treated with respect and asked for wishes at the end of life (EOL) is often defined as key factor of a "good death". However, people tend to avoid preparations for death until they are unexpectedly confronted. Then stress, anxiety, isolation and depression are experienced and wishes not known. In order to reduce barriers of preparedness and provide interventions to further increase readiness, people in different stages of readiness need to be identified and intervention effects need to be measured correctly. The present study focused on development and validation of a questionnaire to assess peoples' readiness to engage in EOL conversations [1].
Methods: Thirteen Items that have been answered by a healthy control sample (N = 213) were analyzed using exploratory factor analysis. Items were excluded based on insufficient contributions to factor loadings, internal consistency and theoretical value to the scale.
Results: Two factors were extracted. Readiness (8 items) explained 73% of variance with factor loadings ranging from $\lambda_1 = 0.50 - 0.80$ (Cronbach's $\alpha = .87$). Acknowledgment of values (3 items) explained 27% of variance with factor loadings ranging from $\lambda_2 = 0.53 - 0.76$ (Cronbach's $\alpha = .61$).
Conclusions: Preliminary results indicate that readiness to engage in discussion about EOL and assessment of values explain healthy peoples' readiness and can be used to identify the extent of readiness and changes after interventions. As a next step the questionnaire is currently validated in a sample of cancer patients.

Reference:

1. Abba, Katharine; Byrne, Paula; Horton, Siobhan; Lloyd-Williams, Mari (2013): Interventions to encourage discussion of end-of-life preferences between members of the general population and the people closest to them - a systematic literature review. In: *BMC palliative care* 12 (1), S. 40. DOI: 10.1186/1472-684X-12-40.

Disclosure Statement: In preparation

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Fostering Communicative Competence and Performance of Physicians (KPAP Study Protocol) – Multimodal Assessment of Long Term Effects of a Communication Trainings Programme (Funded by German Cancer Aid)

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Purpose: Communication trainings improve communication skills of health care professionals in oncology. Only sparse data exists regarding long-term effects of communication trainings for physicians. The aim of this project is to investigate in a multimodal approach self-assessment of the physicians and external assessment of these physicians by experts and trained patient raters three years after a communication skills training (CST).
Methods: Until now, nearly 170 physicians have participated in the training program "Kommunikative Kompetenz" of the University Hospital of Cologne based on the KoMPASS project. Self-reported questionnaires (empathy, burnout, self-confidence etc) are filled in at baseline and at the end of the 2.5 days CST (t0 and t1), at the 6 hours refresher session at least three months later (t2) and, as part of the funded study, at least three years later (t3).
Delivering bad news with standardized simulation patients and participants were videotaped at t0 and t2 and in a subsample (n=60) at t3. Patient raters and expert raters will assess the videos using the AGBS as primary outcome (breaking bad news) and the ComOnRating Scale (communication skills in oncology). Experts will assess these videos regarding RIAS, patients by using the perceived empathy scale CARE.
Results: The study protocol will be presented.
Conclusions: This multimodal assessment may allow to proof the sustainability of the CST program and to detect differences and similarities of the three assessment perspectives.

Reference:

1. Vitinius F ….. Keller M. [KoMPASS--design, implementation and experiences concerning a structured communication skills training for physicians dealing with oncology]. PPmP 2013

Disclosure Statement: Funding by DFG, BMBF, Innovationsfonds and DKH, fees for CSTs.

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Anxiety and Depression Predict Decisional Conflict in Shared Decision Making

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Purpose: Receiving or anticipating a serious diagnosis like cancer can be a profound experience and often results in negative emotional responses. Such negative affect may influence how conflicted patients feel about treatment choices. This poses a potential barrier to shared decision making (SDM). Yet, affect is typically not systematically assessed in medical consultation. Thus, we examined whether patients report anxiety and depression prior to a urological consultation and if emotional distress predicts decisional conflict after SDM.
Methods: We recruited a large sample of urological out-patients ($N = 227$) with a range of different diagnoses (*40%* uro-oncological) at a university hospital. Prior to a medical consultation, patients filled in a set of validated questionnaires including socio-demographic characteristics and the Hospital Anxiety and Depression Scale. After the consultation, patients completed the Decisional Conflict Scale. We calculated the prevalence of anxiety and depression in our sample and conducted regression analysis to examine if emotional distress before the consultation predicts decisional conflict after.
Results: Overall, there was a broad range of anxiety and depression scores, with 24% of patients reaching values at or above cut-off for clinically relevant emotional distress. There were no significant differences in emotional distress between patients with an oncological and non-oncological diagnosis. Although only few patients reported high levels of decisional conflict, emotional distress significantly predicted a higher degree of decisional conflict which accounted for 10% of variance.
Conclusions: Negative emotions were often reported prior to clinical decision-making in urological patients, independent of diagnosis. Most importantly, anxiety and depression predicted more decisional conflict after a medical consultation. Thus, emotional distress should be systematically assessed and addressed in clinical consultations to improve the outcome of SDM and to help identify patients who may benefit from additional support.

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Patients' Attitudes and Beliefs can be a Barrier to Shared Decision Making

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Purpose: In oncology, patients are confronted with complex treatment-decisions. Discrete treatment options may be equally effective and supported by medical evidence while they may differ in their impact on a specific patient's life. Therefore, options are ideally selected with active involvement of the patient; a process called shared decision making (SDM). While many structural aspects are known to influence whether SDM is put into practice, a patient's individual characteristics may also be relevant. The primary goal of this study is, to investigate the effect of patients' attitudes and beliefs on their willingness to take a more active role.
Methods: The Patients' Attitudes and Beliefs Scale (PABS) was translated and backtranslated independently. We recruited a patient sample ($N = 225$) at a university hospital, as part of an ongoing study. Patients were between 19 and 85 years old and had a wide range of diagnoses (43.6% uro-oncological). In addition to the PABS-D, patients' preference for participation was assessed with the Autonomy Preference Index (API). Preliminary analyses were based on multiple linear regression.
Results: First, we replicated the association of participation preference and sociodemographic factors. Second, Patients' positive and negative attitudes were a strong predictor of their participation preference and their intention to participate in the decision. Third, when we control for these attitudes and beliefs, the influence of sociodemographic factors is reduced. Lastly, psychometric properties of the translated PABS-D are promising.
Conclusions: Negative attitudes and beliefs limit patients in their intention to participate in SDM independent of the well-established influence of sociodemographic factors. Importantly, in contrast to sociodemographic factors, attitudes and beliefs may be targets for interventions such as supplying patients with individualized information. Thus, future efforts to implement SDM may benefit from systematically assessing attitudes and beliefs.

Radiation

Poster

1050

Development of Admission to Radiotherapy Departments in Germany: A Population-Based Study of DRG Data

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Purpose: With the increasing complexity of oncological therapy, the amount of inpatient admission to radiotherapy departments might have changed. In this study, we aim to quantify the proportion of inpatients receiving radiotherapy in radiation oncology units and respective developments since 2008.
Method: The analysis is founded on data of all hospitalized cases in Germany based on Diagnosis-Related Group Statistics (G-DRG Statistics, delivered by the Research Data Centres of the Federal Statistical Office and the Statistical Offices of the federal states[1]).
The data set includes information on the main diagnosis and the procedures that were performed during the hospitalization and are relevant for claims of reimbursement. We used linear regression models to analyse temporal trends.
The considered data encompass the period from 2008 to 2014 and are presented in a monthly pattern (smallest available time unit).
Results: Starting in 2008, 48.9% of a cases received their treatment solely in a radiation oncology unit. This figure decreased to 45.0% in 2014. We found a steplike decrease between December 2011 and January 2012 amounting to 4.3% (absolute case numbers of 685.3; 95% CI: 480.0-890.6). For cases not treated in radiotherapy departments numbers remained virtually constant. Fractions received in radiotherapy departments decreased slightly by 34.4 (95% CI: 12.4-56.3) fraction per month. The total duration spent in radiotherapy units decreased by 76.5 (95% CI: 41.9-111.0) days per month starting from a total of 64,842 days in January 2005 to 45,003 days in 2014.
Conclusion: Our data give evidence to the notion that radiotherapy remains a discipline with an important inpatient component. As treatment become more complex and patients become older, radiotherapy clinics could sustain a steady number of case numbers.

Reference:

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Disclosure Statement: There is no conflict of interest

Rehabilitation and Long-term Burden in Social Medicine (Survivors)

Poster

969

Potency After Nervesparing Prostatectomy and Results 4 Years Postoperatively, a Retrospective Comparison of Three Surgical Methods

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Purpose: Radical prostatectomy is a standard procedure for the treatment of prostate cancer. The surgery can be performed differently, established are open, laparoscopic and robotic surgical procedures. It is increasingly trying to perform the operation nerve sparing. This can be done on one side or on both sides. The aim is to record with which OP method a nerve sparing is most often to achieve and to determine the rate of spontaneous erections postoperatively.
Methods: In May 2019, a standardized written survey of the patients who had a rehabilitation after radical prostatectomyctomy or after curative radiation in the period 2015-2016in the Müritz-Klinik. The patients were interviewed regarding a nerve-sparing surgical procedure, the possibility of getting a sufficient erection for sexual intercourse, and the remedies that may be used.
Results: From 716 patients, 409 patients responded, 337 of whom were operated in 2015. This corresponds to a rate of 82.40%. 152 patients (45.10%) used nerve sparing procedures. Particularly often, the robot-assisted surgeries were nerve-sparing (71.19%) and the laparoscope. (37.70%) and the open (40.09%) surgeries were significantly less. Averaged over all three surgical methods, 23.68% of the nervously operated reported to be able to have sexual intercourse again without any aids. Broken down, this can significantly more lap. (30.43%) and roboterass. (28.57%) as open operated (19.54). The most commonly used adjuncts are the use of PDE-5 inhibitors and the penis pump.
Conclusions: Sexuality is an important factor in human quality of life. As early as 2015, 45.10% of surgeries were carried out nervesparing. Only a little more than every 5th patient gets a sufficient erection for sexual intercourse, despite the fact that the nerve is protected. Minimally invasive surgical techniques are an advantage here. In the course of optimizing the surgical methods seems to further improve the postop. erectile function possible.

Disclosure Statement: No

1010

Relationship between Nerve-Sparing Prostatectomy and Continence a Retrospective Survey

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Purpose: Radical prostatectomy is a standard procedure for the treatment of prostate cancer. The operation can be carried out in different ways, open, laparoscopic and robotic surgical procedures have been established. Attempts are increasingly being made to carry out the operation in a manner that is to preserve the dorsolateral vascular nerve bundle. This can be done on one or both sides. A connection between continence and nerve-sparing is reported. The aim of our survey was to find out whether the effect would continue for four years postoperatively.
Methods: There was a standardized written survey in May 2019 of patients who received inpatient rehabilitation at the Müritz Clinic after radical prostatoviculectomy or after curative radiation in the period 2015-2016. The survey was carried out with regard to a nerve-holding operation and the current continence status.
Results: Out of 716 letters, 409 responded. 337 of these were operated on in 2015, which corresponds to a rate of 82.40%. In 152 patients (45.10%) nerve-sparing procedures were used. Especially often the robotic operations are nerve-saving (71.19%), lap (37.70%) and open (40.09%) operatios were significantly less.

With all surgical methods it can be seen that patients with nerve sparing are four years postoperatively more continent (60.53%) than patients without (45.41%). Broken down according to the surgical methods, the following constellation shows that 47.48% of the openly operated patients with nerve-sparng are continent. 44.62% without. In laparoscopic prostatectomised patients with nerve-sparing, 60.87% are continent, without nerve-sparing 42.11%. Among the robotically operated, 66.67% are continent with nerve-sparing, 58.82% without.

Conclusions: Long-term observation shows a positive effect of nerve-sparing surgery on continence. This is particularly pronounced in our lap patient population. In contrast, the difference is not significant for open surgery.

Sarcoma

Poster

990

Ewing Sarcoma of the Kidney in a 23-Year Old Female: An Interdisciplinary Workup of an Uncommon Entity

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Purpose: Ewing sarcoma predominantly occurs in the bones such as pelvis, femur, humerus but, however, it can occur anywhere in the body. It usually affects teenagers and younger adults. Primary Ewing sarcoma of the kidney is a rare type of malignant tumor and its preoperative discrimination from benign renal masses as well as renal cell carcinomas is difficult.

Methods: We present a case of a 23-year-old woman with pre-, intra- and postoperative imaging and review the literature for this kind of malignancy.

Results: Our female patient presented with unspecific symptoms such as generally feeling unwell and fatigue over a period of 4 months. Physical examination, urinalysis and serum biochemistry via general physician remained without pathological findings. An ultrasound of the abdomen showed a suspicious mass of the left kidney measuring 4 x 4 cm. Subsequent evaluation with MRI confirmed a solid tumor at the lower pole of the left kidney which appeared malignant. Therefore, a partial nephrectomy through a lumbar incision was performed. The treatment was well tolerated and no relevant complications occurred. Histopathological examination revealed an extra osseous Ewing sarcoma of the kidney (pT1, L0, V0, Pn0, G3, R0). FDG-PET-CT and cerebral MRI ruled out distant metastases (cN0, cM0). Adjuvant multidrug chemotherapy (6 courses VIDE (vincristine, ifosfamide, doxorubicin, etoposide) and a close follow-up was recommended by the multidisciplinary tumorboard. Before chemotherapy started patient went for oocytes cryopreservation.

Conclusions: This case demonstrates that even patients with non-specific symptoms should undergo careful physical examination including imaging e. g. ultrasound. However, tumor entity often remains unclear despite imaging and surgery is required even in younger patients. Rare malignancies as primary Ewing sarcoma of the kidney require close interdisciplinary cooperation between urologists, radiologists, oncologists and pathologists.

Skin Cancer, including Melanoma

Poster

1038

Variant Effects of Ingenol Mebutate on Apoptosis Regulation in Cutaneous T-Cell Lymphoma Cells

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Purpose: Ingenol mebutate (PEP005, Picato®) has been described to display proapoptotic activity in neoplastic lymphocytes *in vitro*. While a clinical study suggested that topical treatment may be beneficial for CTCL patients (Ref 1), its mode of action remained elusive. For apoptosis regulation in CTCL cells, the extrinsic caspase cascade and reactive oxygen species (ROS) are of particular importance (Ref 2). Here, the effects of ingenol mebutate were investigated in CTCL cell lines.

Methods: CTCL cell lines: HH, HuT-78, MyLa and SeAx. Apoptosis: cell cycle analysis after propidium iodide staining; cell viability: calcein staining and flow cytometry; cell proliferation: WST-1 assay. Mitochondrial membrane potential and ROS: flow cytometry after staining with $TMRM^+$ and H_2DCF-DA, respectively. Western blotting for caspase-3, caspase-8 and cFLIP (Flice-inhibitory protein).

Results: CTCL cell lines revealed highly different responses to ingenol mebutate. While HuT-78 and HH showed high and moderate sensitivity, respectively, MyLa and SeAx appeared as resistant. Ingenol mebutate resulted in loss of mitochondrial membrane potential in HuT-78 as well as in enhanced ROS in HH and HUT-78. Inhibition of ROS in HH by the antioxidant α-tocopherol resulted in suppressed apoptosis. Finally, proapoptotic caspases 3 and 8 were activated in HH and HuT-78, as well as c-FLIP was downregulated in HH. The apoptosis inhibitor c-FLIP was also stronger expressed in resistant cell lines MyLa and SeAx.

Conclusions: Ingenol mebutate may be considered as strategy for treatment of some CTCL patients, while others may not profit from this therapy. Thus, reliable markers for responsiveness are needed. Its mode of action in CTCL cells is related to caspase activation and ROS production.

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Disclosure Statement: No conflict of interest

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Microrna-Mediated MCL-1 Silencing in Melanoma Cells Enhances the Pro-Apoptotic Potential of BRAF and ERK 1/2 Pathway Inhibitors

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Purpose: BRAF and MEK Inhibitors have revolutionized standard care of melanoma patients. However, despite clear clinical benefits, emergence of drug resistance is limiting their success. Mcl-1 is a potent antiapoptotic protein and highly amplified in human cancer including melanoma. Current data showed that extensive expression of Mcl-1 in melanoma is associated with tumor progression, and resistance to BRAF inhibition. Aim of this study is to assess the effects of Mcl-1 inhibition in combination with BRAF and ERK inhibitors.
Methods: Mcl-1 was inhibited via miR-193b-3p and miR-339-3p as well as by the selective inhibitor S63845. Mcl-1 expression, ERK and caspase activation was defined by Western blot analysis. Cell viability, apoptosis induction, mitochondrial membrane potential as well as Bax and Bak activation were determined by flow cytometry, cell proliferation by WST-1 assay.
Results: We show high efficiency of the BRAF inhibitor Vemurafenib in combination with the Mcl-1 inhibitor S63845, driving a high apoptosis via Bax and/or Bak activation. Furthermore, we develop miRNA-based strategies for Mcl-1 targeting using miR-193b-3p and miR-339-3p. Comparable to Mcl-1 inhibitor, miR-193-3p in combination with Vemurafenib resulted in strong apoptosis induction (up to 80%). Also, the combination of S63845 with the ERK inhibitor SCH772984 strongly enhances the proapoptotic efficacy in BRAF-wt melanoma cells.
Conclusions: Targeting Mcl-1 in combination with MAPK pathway inhibitors in melanoma could improve the therapeutic index and patient´s outcomes. In addition to pharmacological inhibition, miR-193b-3p might represent a useful genetic approach for efficient Mcl-1 targeting.

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Disclosure Statement: No conflict of interest

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Mutual Enhancement of Apoptosis in Cell Lines of Cutaneous Squamous Cell Carcinoma by Combination of Celecoxib and Death Ligands

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Purpose: Actinic keratosis (AK) shows strongly increasing prevalence in fair-skinned populations worldwide and may proceed into cutaneous squamous cell carcinoma (cSCC). Important risk factors are UV irradiation and immunosuppression. Nonsteroidal anti-inflammatory drugs (NSAIDs), as diclofenac and celecoxib, are considered and are partly approved for treatment. While synergistic effects of celecoxib and immune modulators as anti-PD1 or anti-PDL1 have not been reported so far, this seems to play role in the mode of action of other NSAIDs.
Methods: Cutaneous SCC cell lines: SCL-I, SCL-II. SCC-12, SCC-13. Apoptosis: cell cycle analysis after propidium iodide staining; cell viability: calcein staining and flow cytometry; cell proliferation: WST-1 assay. Mitochondrial membrane potential and ROS: flow cytometry after staining with $TMRM^+$ and H_2DCF-DA, respectively.
Results: Celecoxib resulted in significant, dose-dependent antiproliferative effects in four cSCC cell lines, accompanied by strongly enhanced intracellular ROS levels. However, moderate concentrations (25 µM, 50 µM) did not efficiently affect apoptosis or cell viability, which are fundamental for anticancer treatment. As highly effective appeared the combination of celecoxib with death ligands (CD95/Fas ligand, TRAIL), which resulted in up to 60% apoptosis and almost complete loss of cell viability. This was accompanied by loss of mitochondrial membrane potential. Western blotting revealed downregulation of the antiapoptotic Bcl-2 protein Mcl-1 and of the caspase-3 antagonist XIAP (chromosome X-linked inhibitor of apoptosis protein).
Conclusions: As CD95L and TRAIL are also produced by the immune system, these findings suggest that celecoxib can enhance the antitumor effects of the immune system This may also explain the efficiency of combinations with checkpoint inhibitors (anti-PD1), recently approved for treatment of cSCC.

Disclosure Statement: No conflict of interest.

Supportive Care

Poster

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Benefits from Exercise Training in Pediatric Oncology: Results from the Randomized Controlled Mucki-Trial

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Purpose: Disease- and treatment-related reductions of muscular and aerobic performance have been observed in childhood cancer patients. In adult cancer patients, specific exercise training revealed positive effects on muscular and aerobic capacity which were associated with benefits on fatigue and quality of life. Within the "Effects of Combined Resistance and Endurance Training in Pediatric Cancer Patients During Intensive Treatment Phase (MUCKI)-trial" training effects on muscular and walking performance were evaluated.
Methods: In this stratified randomized controlled trial, childhood cancer patients aged between 4 and 18 years were enrolled during intensive cancer treatment phase (ICT). Individuals within the exercise group (EG) participated in supervised exercise training. Training was focused on child adapted playful, moderate intense resistance and endurance exercises and took place 3 to 5 times weekly over a period of 6 to 8 weeks. Individuals of the control group (CG) received usual care. Pre- and post-intervention handheld dynamometry testing for knee flexor strength and six minute-walk test were performed.
Results: In total 16 patients in the EG and 17 in the CG completed the study. Group-time-interactions on muscular and walking performance were evaluated by analysis of covariance adjusting for baseline values and stratification factors. Subsequent results revealed favoring effects for EG in knee flexor strength ($F(1,20) = 5.733$; $p = 0.027$; $\eta^2_p = 0.223$) and walking performance ($F(1,25) = 4.270$; $p = 0.049$; $\eta^2_p = 0.146$). Compliance to the training was rated very good to good, no severe adverse events occurred.

Conclusions: The present results provide further evidence for beneficial effects from adapted exercise programs in childhood cancer patients suffering from different tumor entities. Adapted pediatric exercise programs are getting attention only recently. In this context, the present findings support further elaboration and implementation of adapted exercise offers in pediatric oncology.
Abstract also submitted 2019: SIOP, EIM, UCT Sc. Day Mainz, DVS

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Pilot Case-Series: Can Short-Term WB-EMS be Effective in Cancer Patients?

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Purpose: The loss of body weight, muscle mass and function is a severe but common burden in cancer patients. Innovative exercise methods, such as whole-body electromyostimulation (WB-EMS) seem to be a potent and safe alternative to conventional exercise types to maintain or improve body mass and function. Due to its time-saving nature and low-threshold even for non-exercising patients, the question arises if WB-EMS also could be applied effectively in a short duration such as two weeks.
Methods: This pilot case-series included 13 cancer patients with diverse entities, disease stages and phases of treatment, which were exercised with supervised WB-EMS four times within two weeks. Physical functioning and self-reported outcomes as quality of life, fatigue and depression were assessed before and after the exercise period. Also, the patient's subjective body perception was documented prior and post every exercise session.
Results: All 13 patients were able to perform the four WB-EMS sessions. No adverse events occurred. Within the descriptive statistics, the patients showed improved muscle strength and maintained or improved their cardiovascular performance. WB-EMS exercise also seems to be beneficial in depression and anxiety scores and global quality of life. Nevertheless, the exercise showed some negative impacts on the patient's fatigue and some symptom domains, such as diarrhea or overall pain. The patient's subjective body perception following a WB-EMS session was increased in all four sessions and additionally showed reductions in domains of temporarily pain and discomfort.
Conclusions: WB-EMS seems to be a safe and feasible exercise method for cancer patients. Although exercise duration was relatively short, the findings suggest a positive impact on physical performance and patient-reported outcomes, indicating a potential use of WB-EMS in short time-frames, such as pre-surgery or pre-chemotherapy. However, this exercise method seems to be at risk of exacerbating the patient's fatigue, what should be monitored with caution and addressed in future trials.

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Using a New Controlled Thermotherapy (Hilotherapy®) During Chemotherapy Prevents Chemotherapy Induced Polyneuropathy

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Introduction: Chemotherapy-induced peripheral neuropathy (CIPN) is an adverse effect of many commonly used chemotherapeutic agents, especially taxane-based regimen (Paclitaxel, nab-Paclitaxel, Docetaxel). CIPN reduces patients health-related quality of life for years and often results in dose delay, dose reduction or treatment discontinuation. The prophylactic use of controlled thermotherapy (Hilotherapy®) prevents CIPN.
Method: 172 breast cancer patients used the prophylactic Hilotherapy®, a new method of physical thermotherapy device, equiped with hand and foot cuffs to allow a constant cooling.
Continous cooling of hands and feet was performed 30 minutes before to 60 minutes after completing drug infusion with a temperature of 10-12°C. CIPN symptoms were evaluated after each cytotoxic cycle using common terminology criteria for adverse events (CTCAE).
Sustainability of the impact was assessed by long-term datas (every 3 months).
130 patients used the prophylactic Hilotherapy® for each cytotoxic treatment (Group 1: primary Prophylactic Hilotherapy® - pPHT).
Results: From 130 patients using pPHT, 121 patients (93%) developed none or mild symptoms of CIPN (grade 0-1). 8 patients (6,1%) reported grade 2, 1 patient grade 3 (0,8%) toxicity.
The symptoms of CIPN were reversible. 4 months after chemotherapy, 98% of the patients had no CIPN > grade 1, 2 patients (2%) suffered intermittent toxicity grade 2.
Without using pPHT 50% of the patients developed grade 3 and 2 CIPN. The sustainability of the impact was assessed by long-term datas (Follow Up patient contact every 3 months).
Conclusions: Prophylactic Hilotherapy prevented limiting CIPN Symptoms (> grade 1) in 93% of patients. 4 months after chemotherapy treatment, 98% of the patients were without any limiting symptoms (grade ≤ 1). No dose modifications or treatment interruptions had been necessary. Without pPHT 50 % of the patients developed CIPN (grade 2-3).
Datas will be updated.

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Predictors of Postural Control in Cancer Patients Undergoing Neurotoxic Chemotherapy

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Purpose: Postural control (PC) in cancer patients deteriorates during neurotoxic chemotherapy (NTX), which may be due to altered proprioception. However, clinically diagnosed nerve damage showed only moderate correlations with PC [1]. Thus, other predictors might exist that influence the change in PC during NTX.
Methods: Fifty-four cancer patients participated in this longitudinal study (age 54 ± 11 years). PC in semitandem stance with eyes closed (force plate: center of pressure data), CIPN symptoms (EORTC QLQ-CIPN20), nerve conduction studies (NCS: motor (CMAP) and sensory action potentials (SNAP)), quadriceps maximal voluntary contraction (MVC), and physical activity (PA) were assessed before (t0) as well as 3 weeks (t1) and six months after completion of NTX (t2). Time differences in PC, CIPN and NCS were determined by dependent t-tests (Bonferroni corrected). The influence of CMAP, SNAP, PA and change in MVC (Δt0-t1) on the change in PC during NTX (Δt0-t1) was analyzed by multiple linear regression adjusted for age and BMI.
Results: PC, CIPN symptoms and NCS significantly deteriorated during NTX (t0-t1: $p < .01$). Six months after NTX, patients recovered from postural instabilities (t0-t2: $p = .77$), whereas CIPN symptoms and NCS were still worse compared to t0 ($p < .01$). The regression model showed that low baseline CMAP ($\beta = -47.7$; $p < .01$) and high SNAP ($\beta = 25.6$; $p = .01$) predicted greater loss of PC.
Conclusions: Unexpectedly, good sensory nerve function at baseline predicted a greater loss of PC during NTX. It can be assumed that disturbed peripheral sensory information may lead to adaptation processes (neuronal plasticity). Therefore, patients with poorer sensory nerve function at baseline may have been less affected by further deterioration of somatosensory feedback as they had already adapted to these impairments. This hypothesis is supported by follow-up data: Although CIPN symptoms and CVS were still worse compared to baseline, PC recovered.

Disclosure Statement: No conflict of interests.

Reference:
1. Müller et al. (2019). Gait Posture (*submitted*)

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Analysis of the Current Status of Exercise Therapy for Oncological Patients: A Cross-Sectional Survey Among Resident Oncologists and Physiotherapists in an Out-Patient Setting

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Purpose: The goal of the cross-sectional study conducted in July/ August 2018 in Germany for the first time simultaneously among resident oncologists and physiotherapists to identify the benefit of special exercise therapy for oncological patients was to determine the current state of knowledge of both professions and relevant information for out-patient oncological care. The analysis was motivated by an obvious discrepancy: While more and more studies are providing evidence of the positive effects of special exercise therapy, the care structures have not yet been designed in such a way that quality-assured exercise programs for oncology patients are offered across the board.
Methods: The collected data, which were generated by a written survey conducted by the Center for Integrated Oncology (CIO), were evaluated using descriptive statistical methods. 300 questionnaires were distributed to both service providers, selected by stratified random sampling. The response rate was 21% for oncologists (N=63) and 29% for physiotherapists (N=88).
Results: The majority of both professions attribute a high value and benefit to special exercise therapy and seem to be informed and educated about the proven positive effects in the major cancer diseases. Larger differences, among others, were found in the fatigue topic. While almost all oncologists (95,2%, *n*=50) were aware that exercise therapy is the most effective method for reducing fatigue, this was not true to a comparable extent for physiotherapists (58%, *n*=51). The majority of oncologists (98,4%, n=62) often recommend a physically active everyday life to their patients and see an average need of four patients per day for a special exercise therapy (*n*=55). The results also provided indications of current barriers to the expansion of exercise therapy programs.
Conclusions: The results not only inform current discourses about the goal of a nationwide, guideline-based and quality-assured care structure in Germany, they also indicate a need for improvement in the expansion necessary network of oncologists and physiotherapists.

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Influence of Target-Oriented Exercise Therapy on the Fatigue Syndrome and Strength Capacity in Cancer Patients

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Purpose: CRF is the most common side effect of medical treatment in cancer patients. The efficacy of exercise on cancer induced side effects like psychological distress is scientifically proven. The impacts vary from enhanced physical performance to an increased patient compliance and an improved prognosis of the disease. The present study aimed to determine the coherence between the increase in strength and psychological distress.
Methods: To examine this coherence, a pre-test and post-test was conducted with the use of machine-supported, supervised training. The presence of the CRF was evaluated through two assessments (MFI, VAS) whereas the burden of anxiety and depression was self-reported with HADS. The study design divides participating patients into five groups with different workout intensities. Two groups performed an endurance training and two groups performed a strength training. Group 5 experiences the standard care. 33 aftercare patients participated in the study.
Results: The present study shows a high impact of physical exercise on reducing cancer-related fatigue. Regardless of the intervention group, 73.03% of the participants benefited from the activity. Concerning the different groups, the high-intensity groups showed positive results. Especially the strength-HIT group needs to be emphasized with every patient in the group increasing strength whilst reducing the MFI-score, hence reducing fatigue. The study population shows a highly significant reduction in MFI-scores.
Conclusions: This result shows the need of initiating interdisciplinary treatment concepts in order to improve functional health for patients. Further studies need to prove the sustainable effects of indication-specific exercise programs, together with verifying the dose-response relationship. Studies should aim to individualize exercise therapy with respect to severity of the fatigue-symptoms, personal preferences or resources.

Disclosure Statement: I declare that we have no relevant or material financial interests that relate to the research described in this paper.

Oncology Research and Treatment

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