



SABCS 2021

Neue Wirkmechanismen und Medikamente

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Brustkrebs in Deutschland

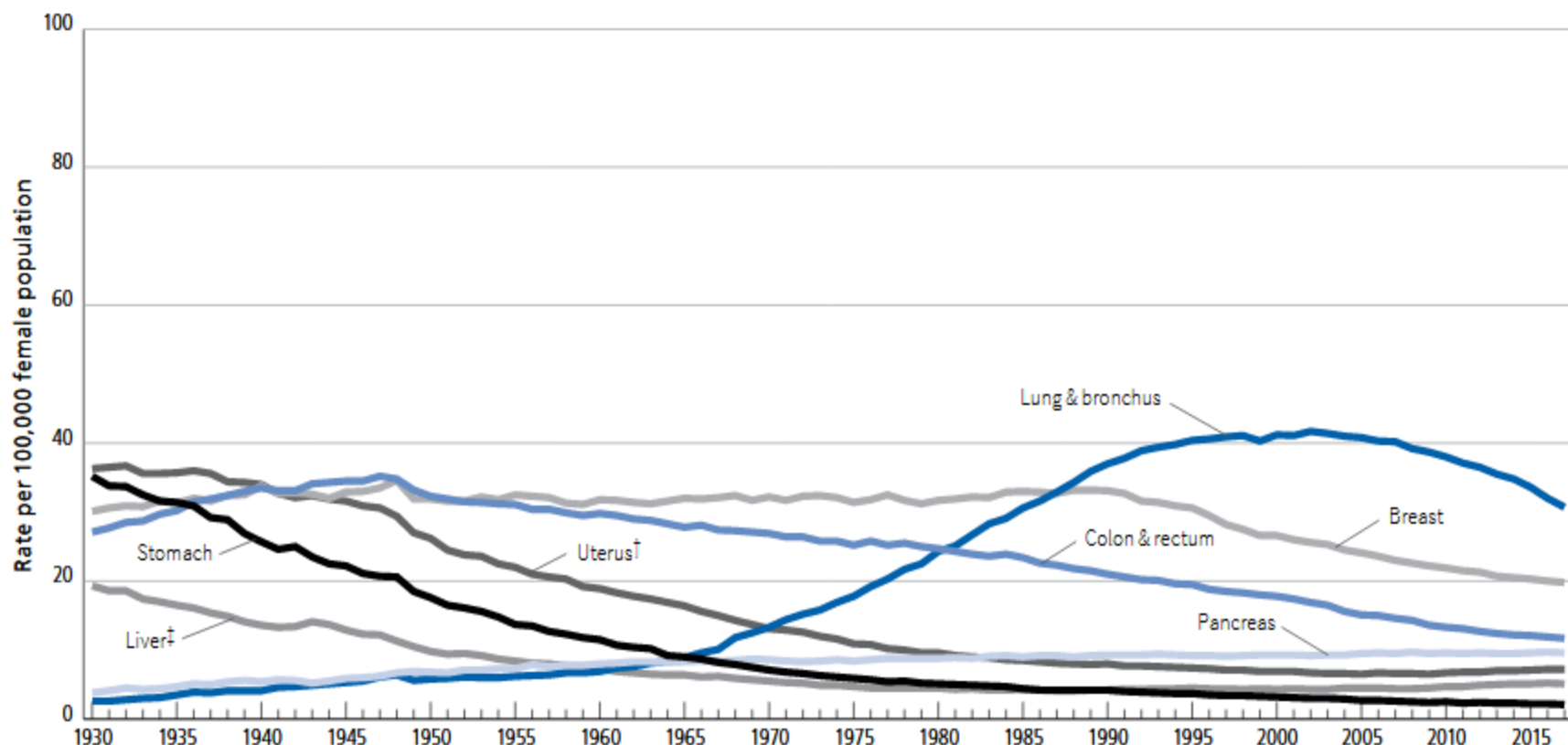


- Jede 8. Frau erkrankt an Brustkrebs**
- 69.900 Neuerkrankungen pro Jahr**
- 18.591 Todesfälle pro Jahr**
- Relatives Fünf-Jahres-Überleben nach UICC:**
 - Stadium I: 100%**
 - Stadium II: 95%**
 - Stadium III: 75%**
 - Stadium IV: 31%**

Quellen:

Robert Koch Institut: „Krebs in Deutschland 2017/2018“:

Figure 2. Trends in Age-adjusted Cancer Death Rates* by Site, Females, US, 1930-2017



*Per 100,000, age adjusted to the 2000 US standard population. Rates exclude deaths in Puerto Rico and other US territories. †Uterus refers to uterine cervix and uterine corpus combined. ‡The mortality rate for liver cancer is increasing.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung and bronchus, colon and rectum, and uterus are affected by these coding changes.

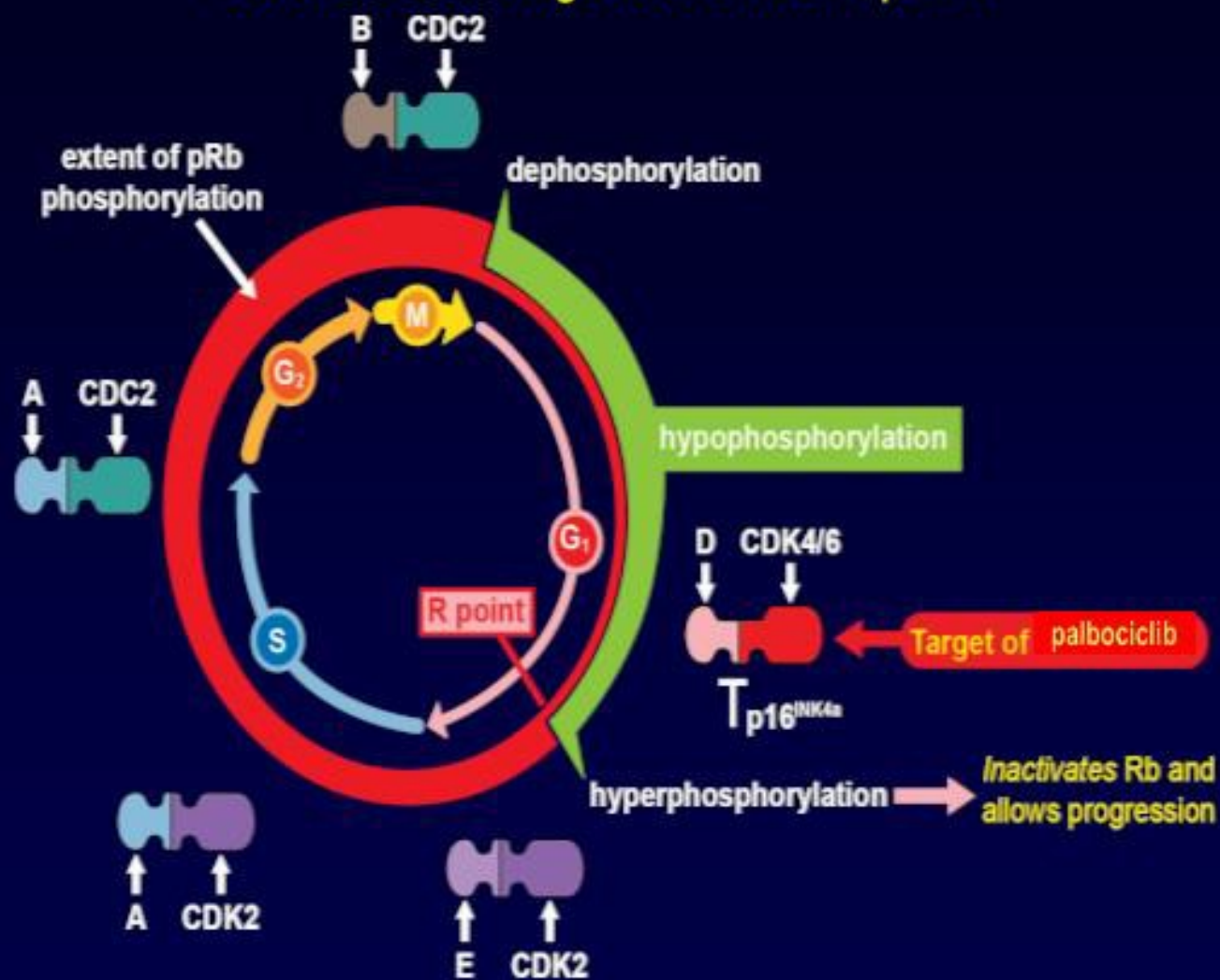
Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2017, National Center for Health Statistics, Centers for Disease Control and Prevention.

©2020, American Cancer Society, Inc., Surveillance Research

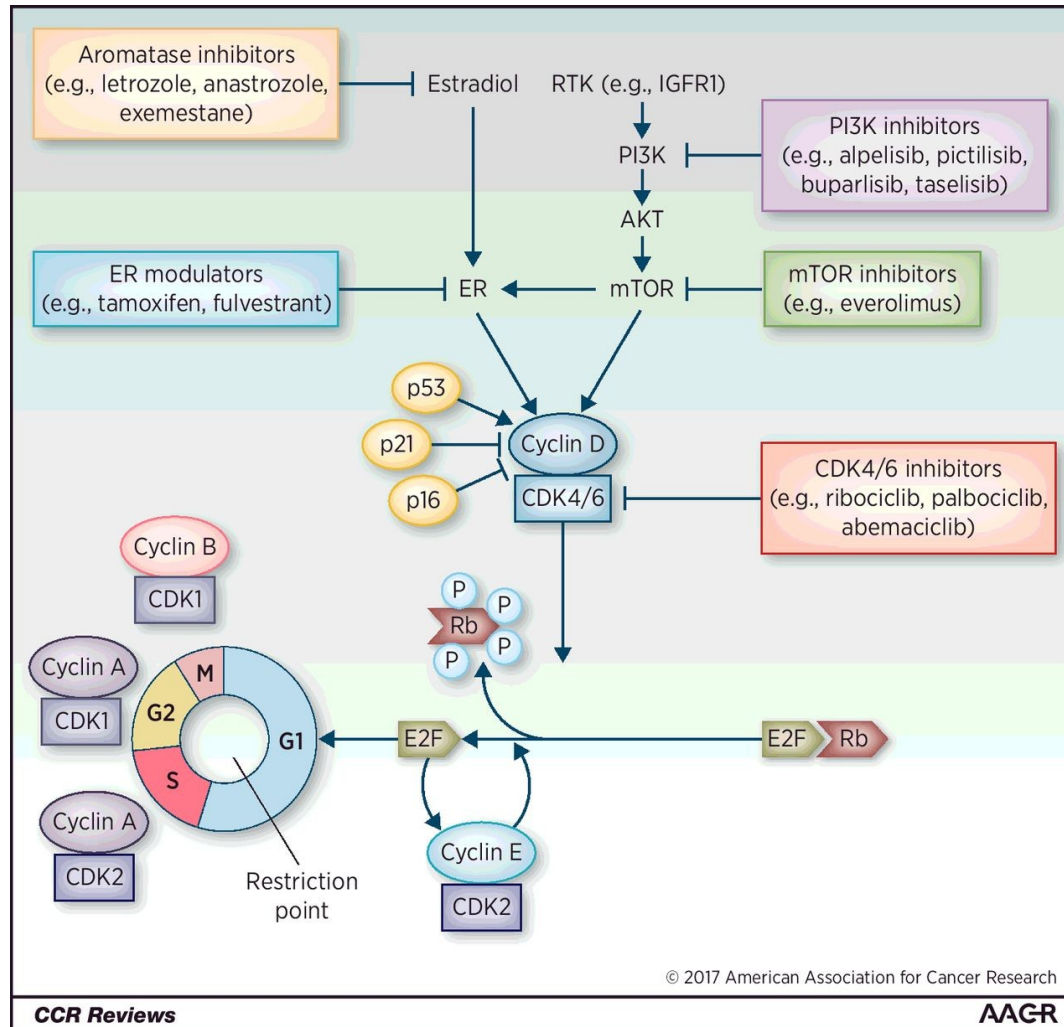
Wirkmechanismus neuer Medikamente:

- Cyclin-D4/6+D7-Kinase-Inhibitoren**
- Immunchekpunkt Blockade**
- PARP-Inhibitoren**
- PIK3CA-Inhibitoren**
- Orale SERDS**
- Anti-Trop2-Therapien**
- Anti-Her2-Therapien**

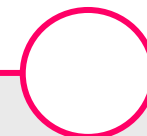
Rb as Master-Regulator of the R-point



The role of cyclin–CDK complexes and the cyclin D–CDK4/6–p16–Rb pathway in the cell cycle.



Debu Tripathy et al. Clin Cancer Res 2017;23:3251-3262

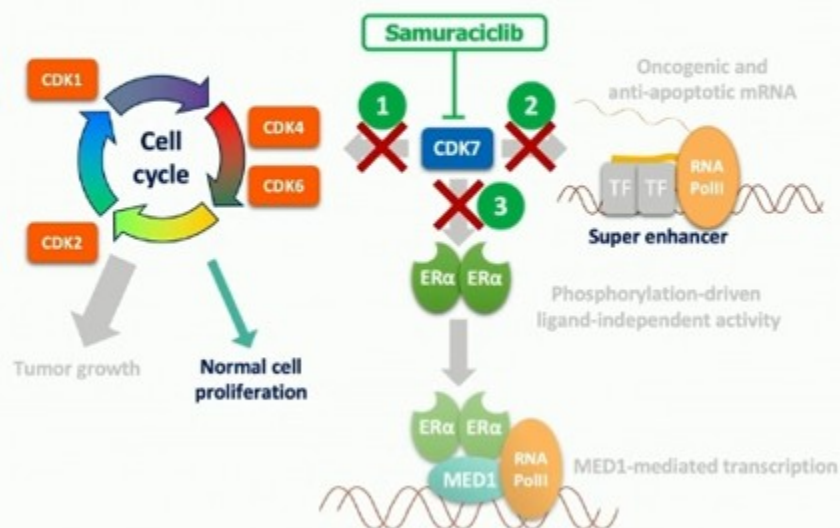


San Antonio Breast Cancer Symposium[®], December 7–10, 2021

The CDK7 inhibitor samuraciclib (CT7001)

- Once-daily, oral, small molecule, ATP-competitive, selective inhibitor of CDK7
- Synergistic with hormonal therapy in HR+ breast cancer xenograft models
- Blocks CDK7-mediated oncogenic effects

- 1 The cell cycle through phosphorylation of other CDKs
- 2 Transcription of oncogenic and anti-apoptotic genes
- 3 Signaling by and activation of hormone receptors (ER and AR)

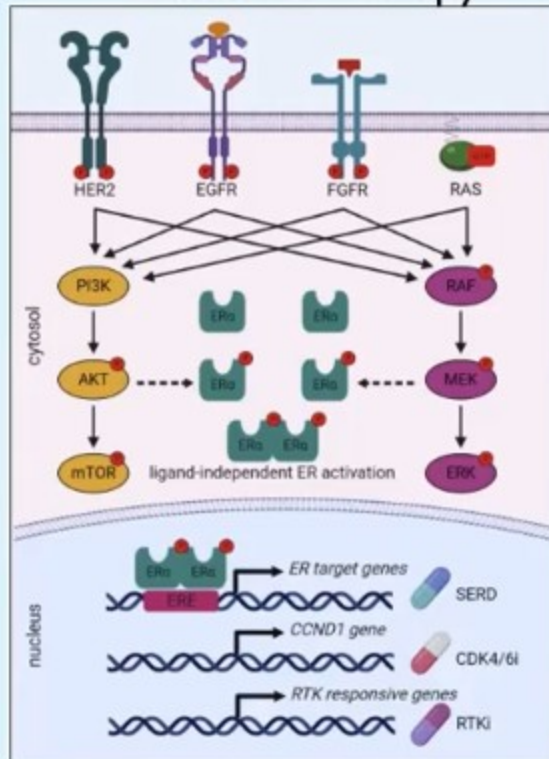


Patel H, et al. Mol Cancer Ther 2018;17:1156–66

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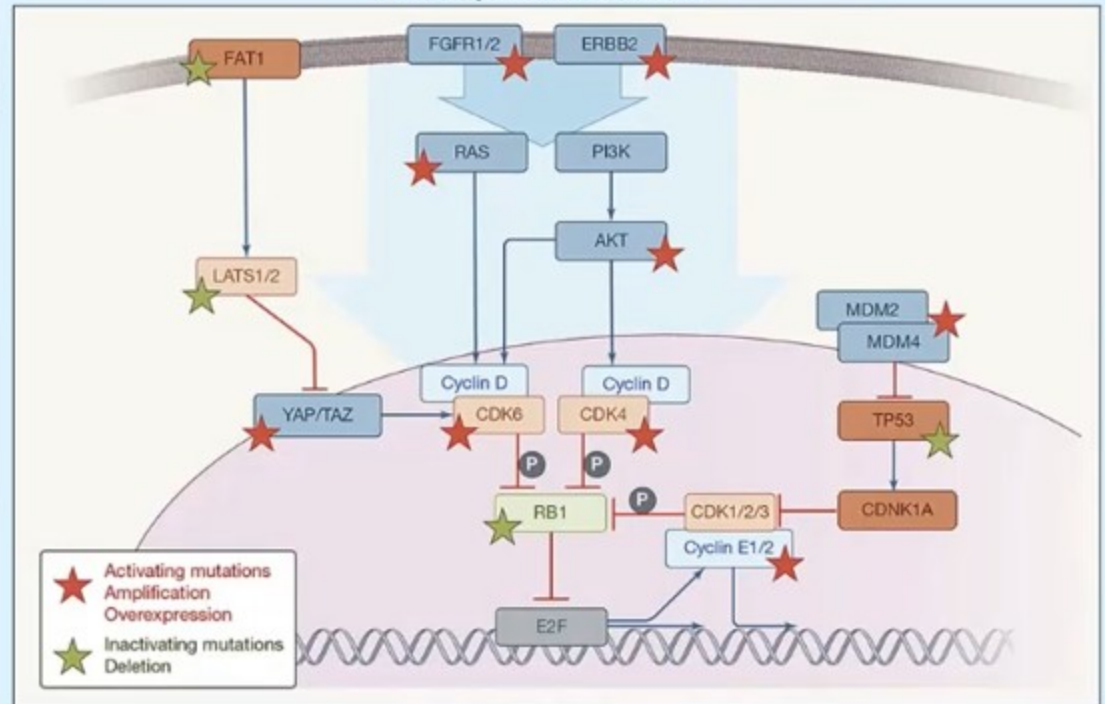
Multiple targets and routes to resistance

Endocrine Therapy



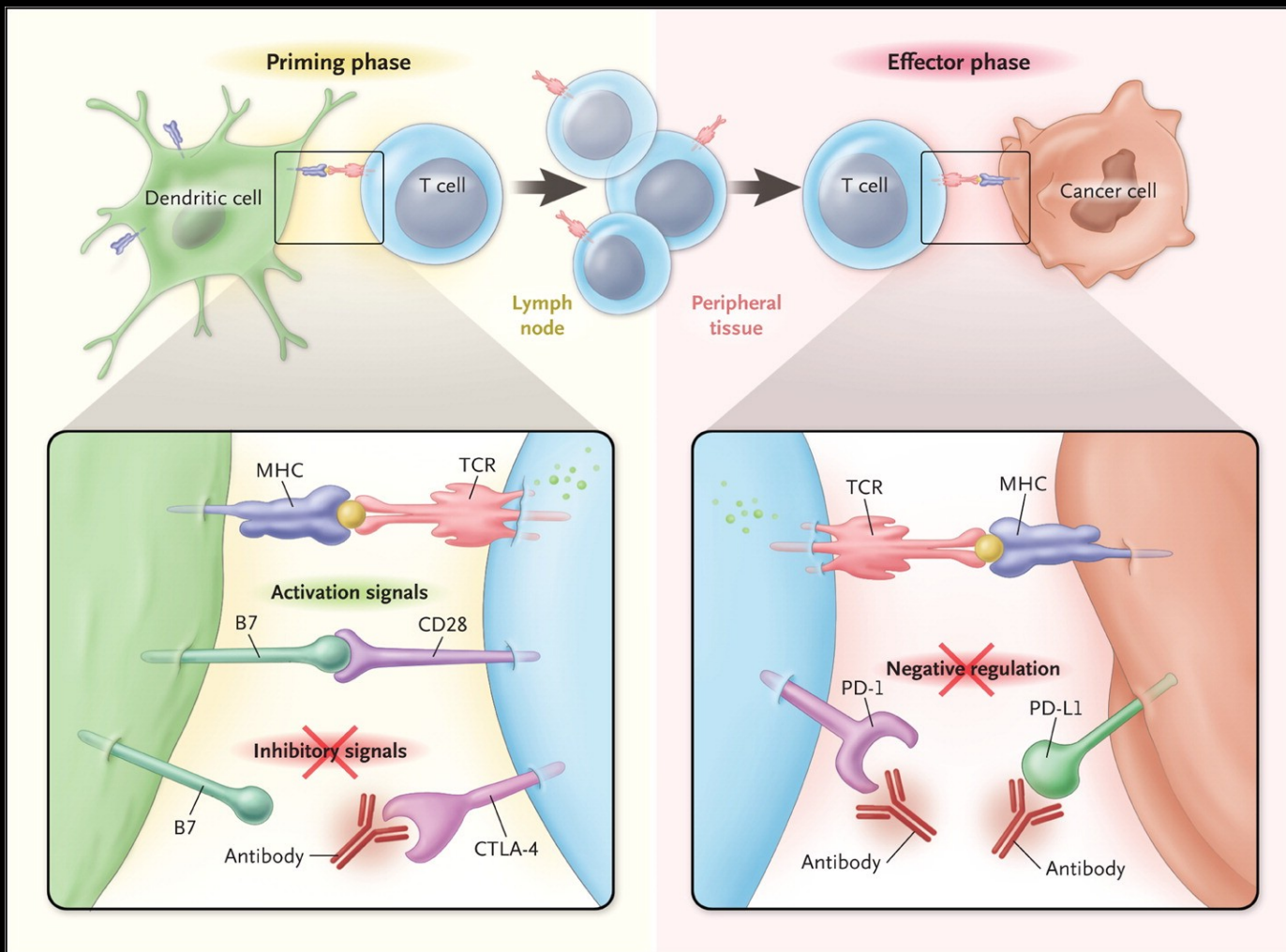
Hanker et al, Cancer Cell 2020

CDK4/6 inhibitors



Alvarez-Fernandez Cancer Cell 2020

Blockade of PD-1 or CTLA-4 Signaling in Tumor Immunotherapy.





Anti-PD1-Antikörper

-Nivolumab

Zulassung u.a. für: MetMelanom, MetNSCLC,
MetNiere, M.Hodgkin, MetUrothel

-Pembrolizumab

Zulassung u.a. für: MetMelanom, MetNSCLC
Triple-negatives MetMamma (Keynote 355)
Triple-negatives frühes Mamma-Ca (Keynote 522)

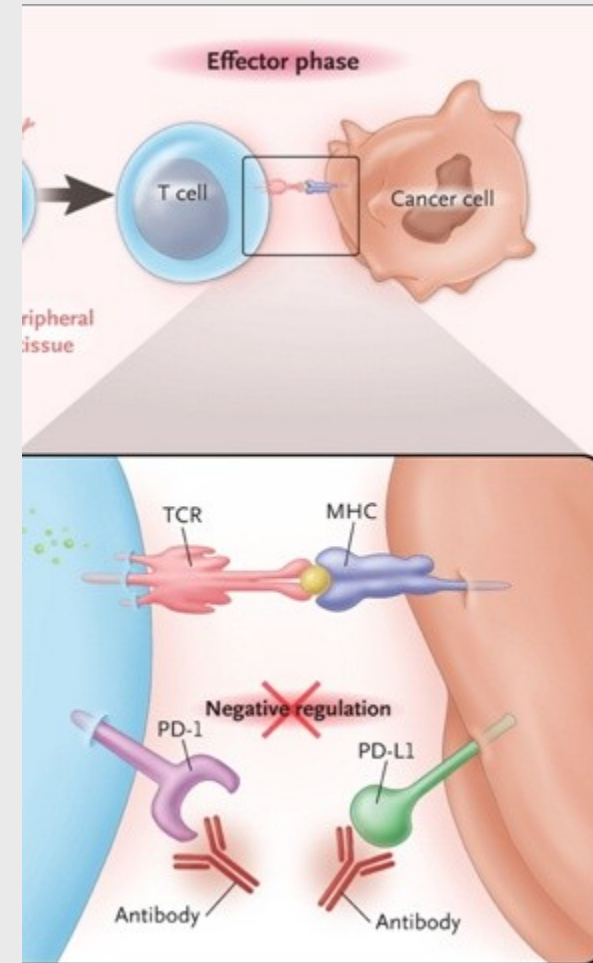
Anti-PD-L1-Antikörper

-Atezolizumab

Zulassung u.a. für: MetNSCLC, MetUrothel,
MetMamma (triple-negativ)

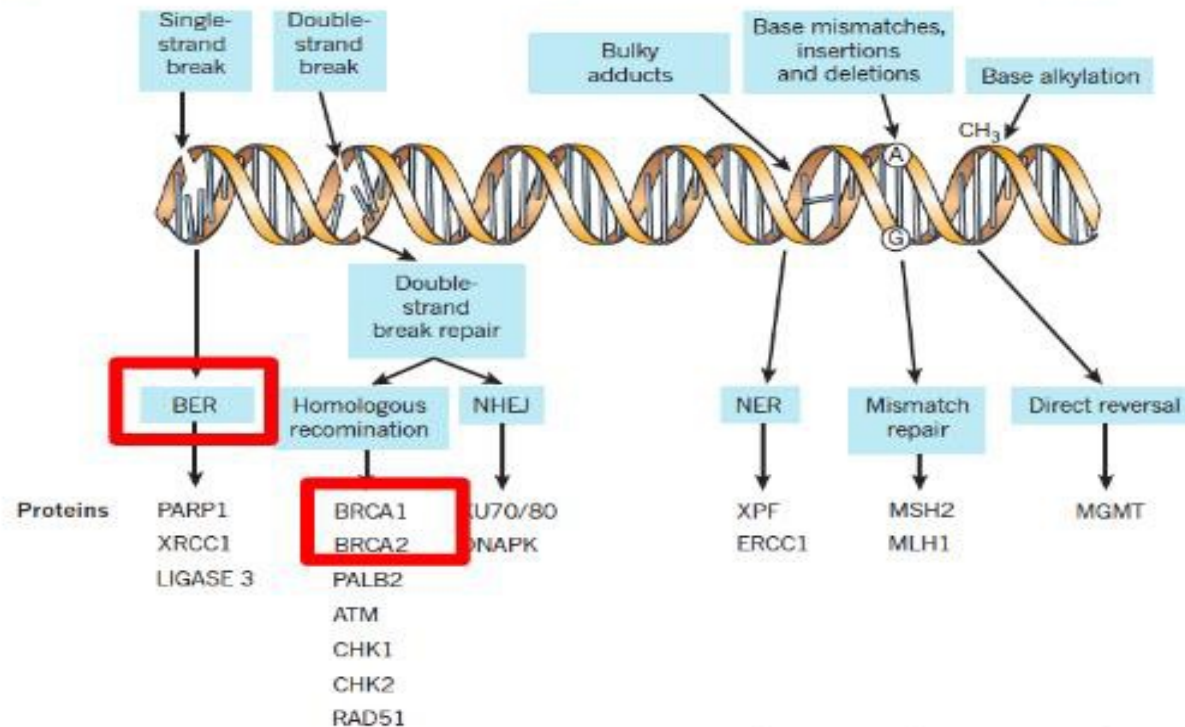
-Durvalumab

Zulassung u.a. für: NSCLC, Urothel



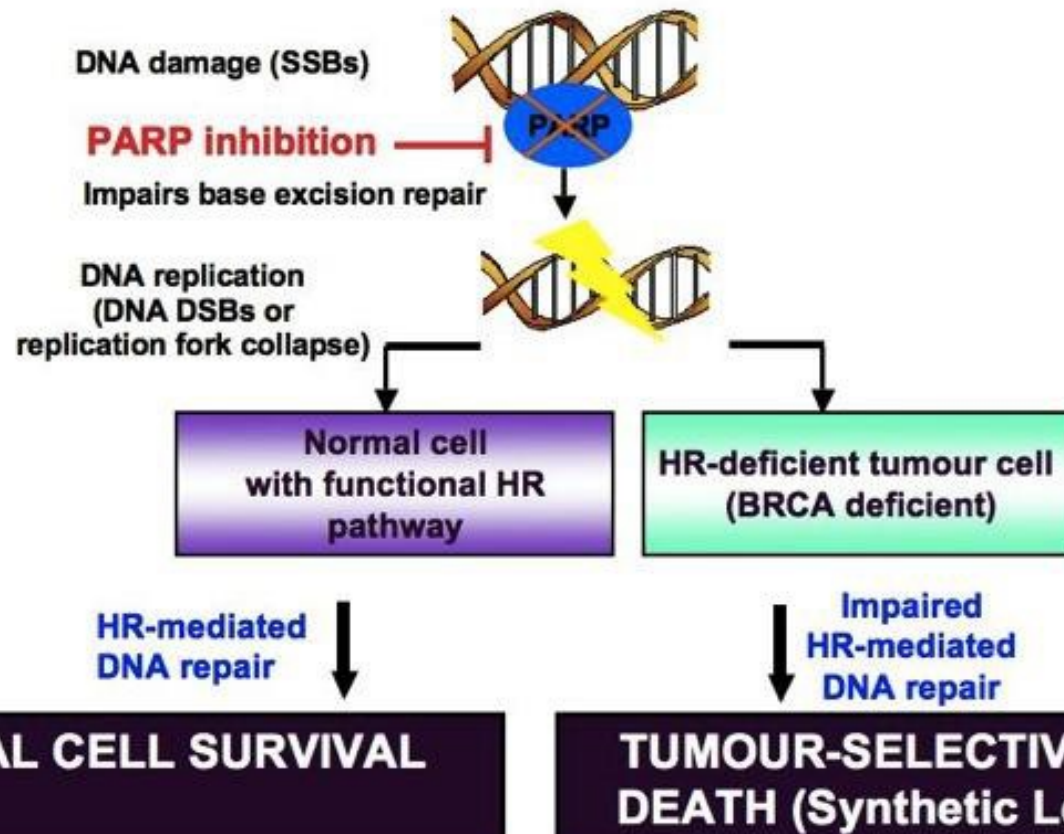
Poly-ADP-Ribose-Polymerase (PARP):

Multiple DNA Repair Pathways Deal with Distinct Types of DNA Damage



Lord & Ashworth: **The DNA damage response and cancer therapy.** Nature 2012

Synthetic Lethality Between PARP Inhibition and BRCA1/2 Mutation



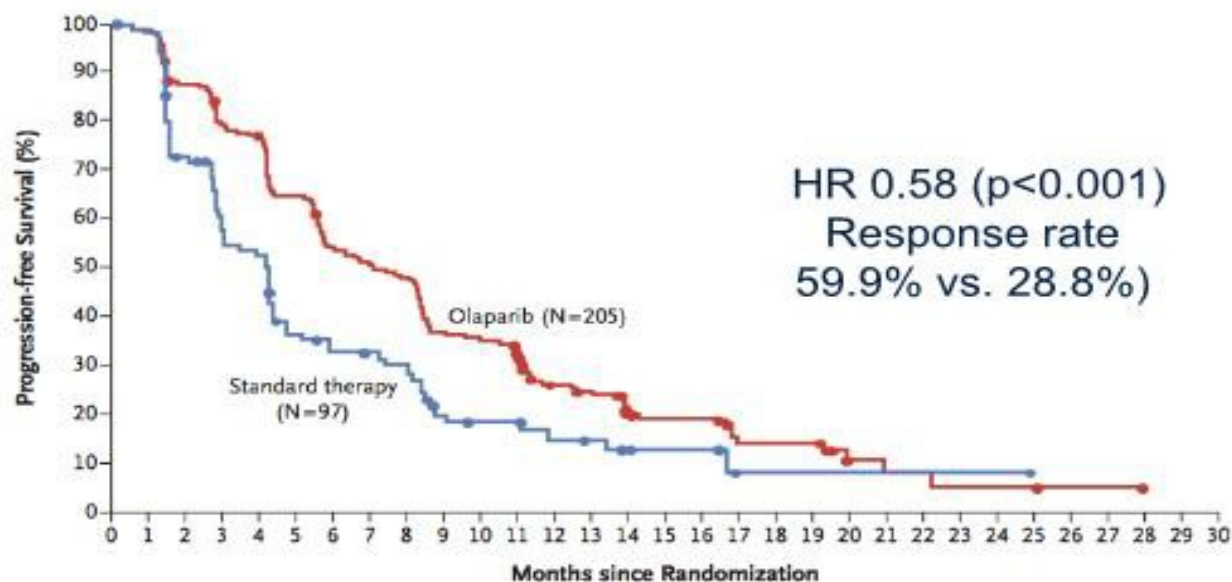
ORIGINAL ARTICLE

Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation

Mark Robson, M.D., Seock-Ah Im, M.D., Ph.D., Elzbieta Senkus, M.D., Ph.D., Binghe Xu, M.D., Ph.D., Susan M. Domchek, M.D., Norikazu Masuda, M.D., Ph.D., Suzette Delaloge, M.D., Wei Li, M.D., Nadine Tung, M.D., Anne Armstrong, M.D., Ph.D., Wenting Wu, Ph.D., Carsten Goessi, M.D., Sarah Runswick, Ph.D., and Pierfranco Conte, M.D.

August 2017

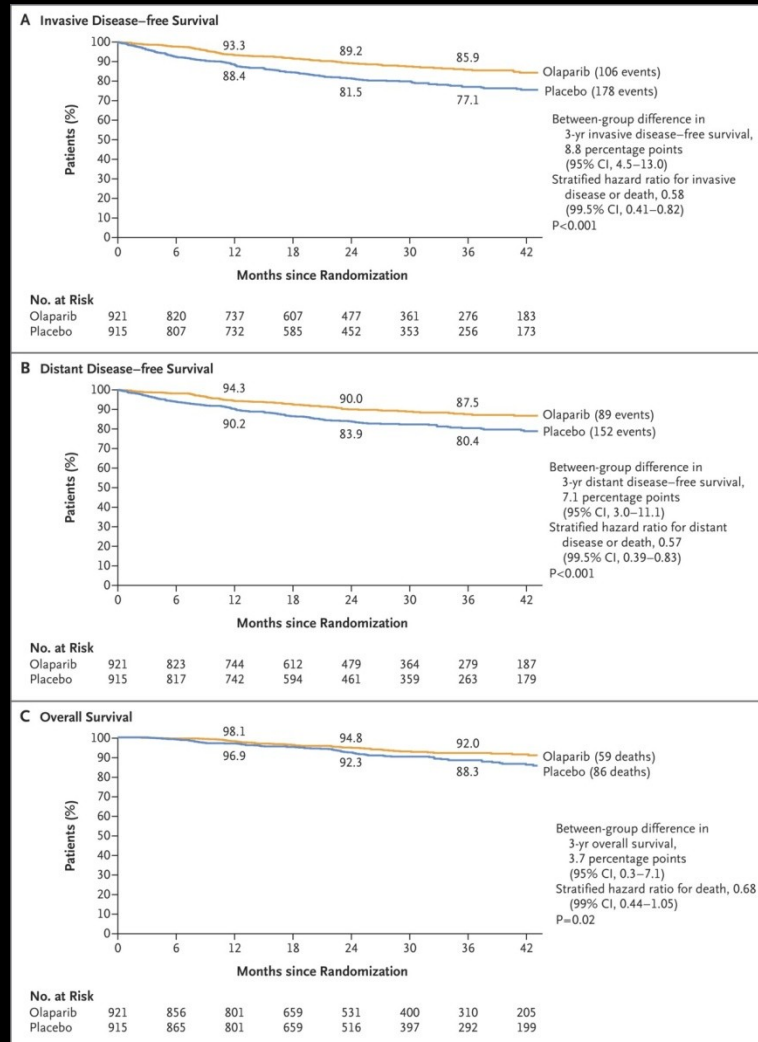
Efficacy of a PARP inhibitor in BRCA-mutant metastatic breast cancer



No. at Risk

Olaparib	205	201	177	159	154	129	107	100	94	73	69	61	40	36	23	21	21	11	11	11	4	3	3	2	2	1	1	1	0
Standard therapy	97	88	63	46	44	29	25	24	21	13	11	11	8	7	4	4	4	1	1	1	1	1	1	1	1	0	0	0	0

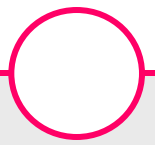
Kaplan–Meier Estimates of Survival.



Tutt ANJ et al. N Engl J Med 2021;384:2394-2405



The NEW ENGLAND
JOURNAL of MEDICINE



-PIK3CA-Inhibitoren

-Orale SERDS

-Anti-Trop2-Therapien

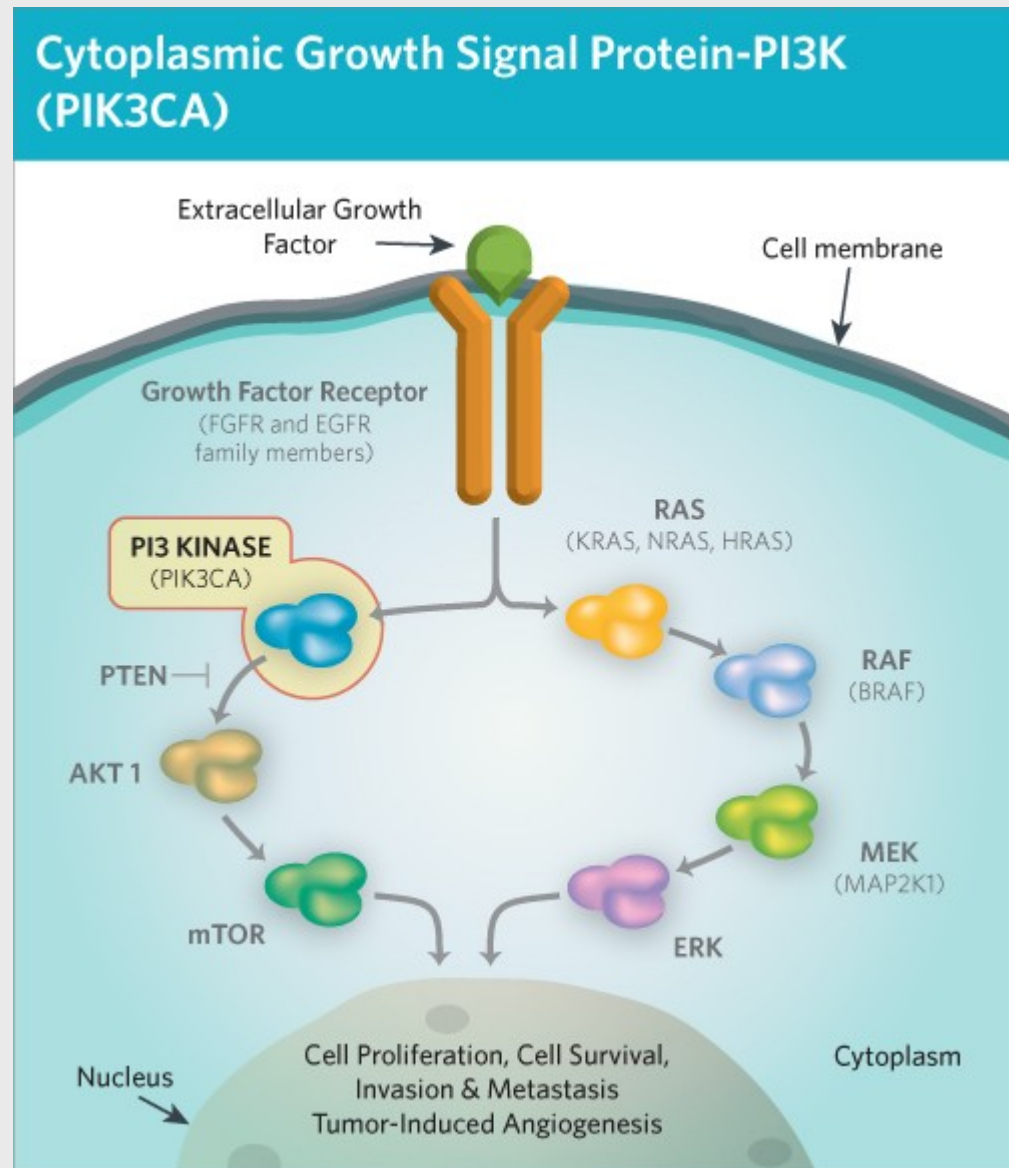
-Anti-Her2-Therapien

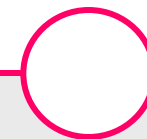
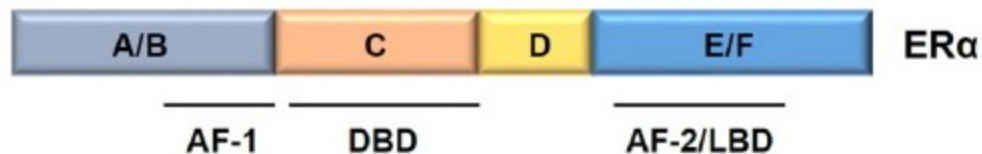
PIK3CA-Inhibitoren:

Die Phosphatidylinositol-4,5-bisphosphat-3-Kinase, katalytische Untereinheit alpha, auch p110 α -Protein genannt, ist eine katalytische PI-3-Kinase-Untereinheit der Klasse I. Das humane p110 α -Protein wird vom PIK3CA-Gen kodiert.

-Idelalisib (CLL)

-Alpelisib (Mammakarzinom)



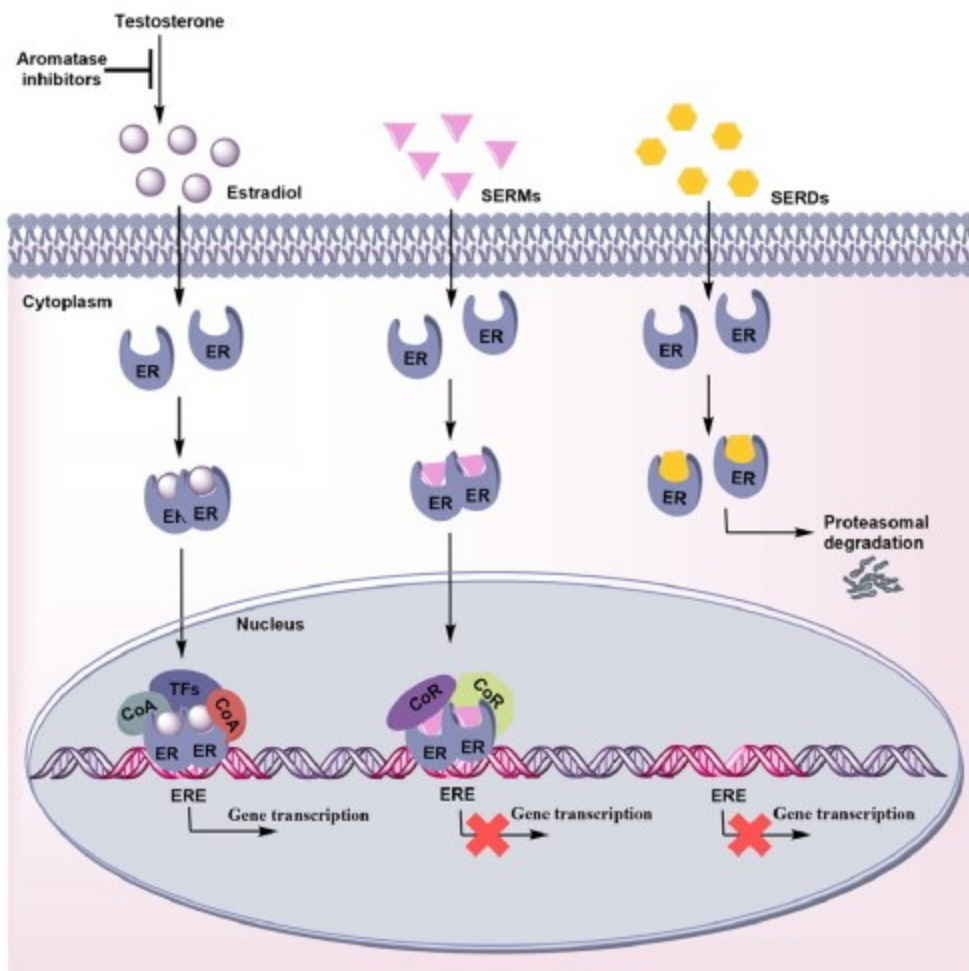


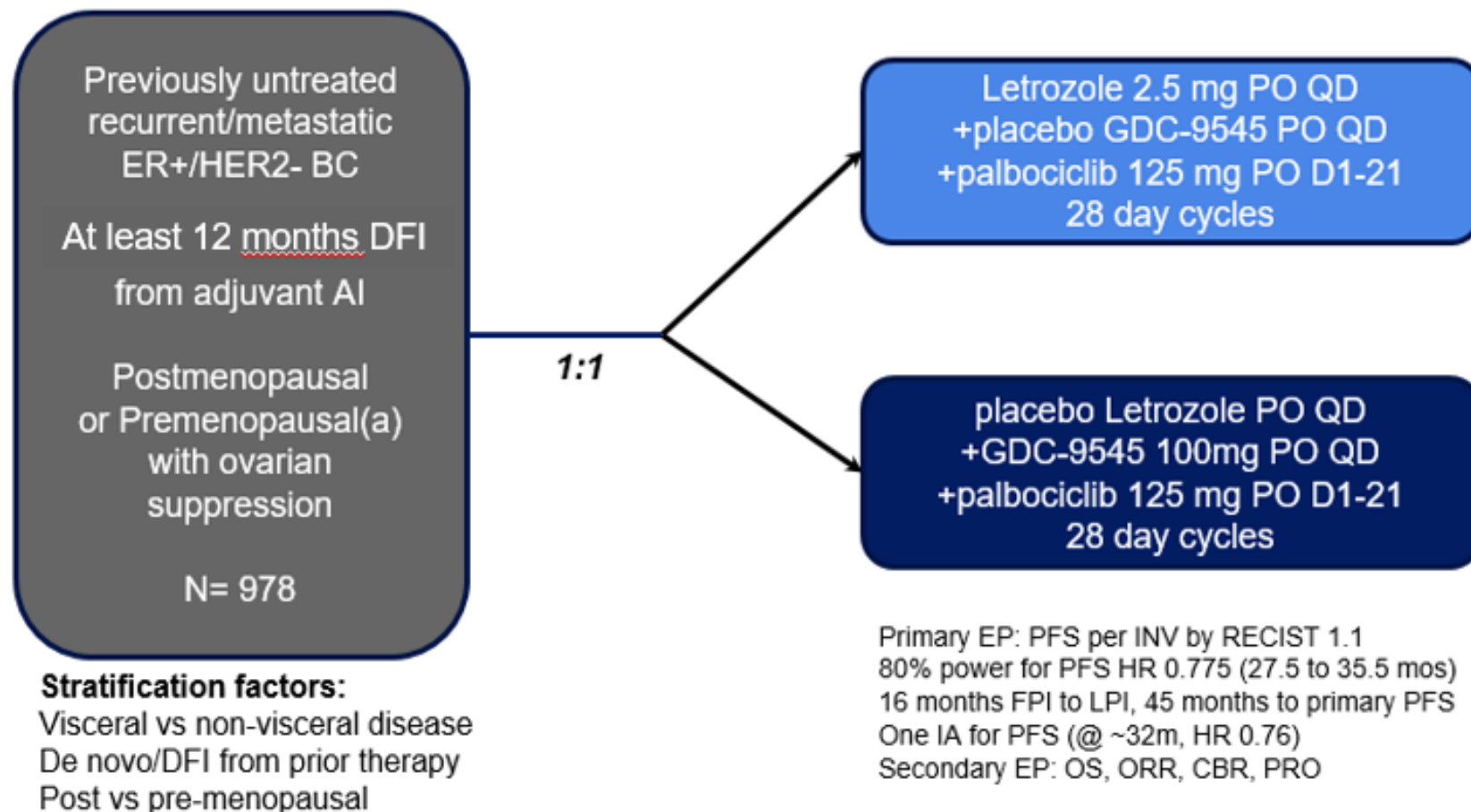
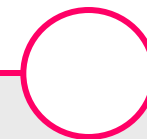
SERD

Selective Estrogen Receptor Degradator

zB GIREDESTRANT
GDC-9545 (oral)

B.





D = Day; ER+ = estrogen receptor-positive; HER2- = HER2-negative; PO = orally; QD = once a day.

^a Premenopausal patients in both arms will receive goserelin SC 3.6 mg on D1 of each cycle.



Anti-Trop-2-Therapien

TROPiCS-02: A Phase III study investigating sacituzumab govitecan in the treatment of HR+/HER2-metastatic breast cancer

Hope S Rugo , Aditya Bardia, Sara M Tolaney, Carlos Arteaga, Javier Cortes, Joohyuk Sohn, Frederik Marmé, Quan Hong, Rosemary J Delaney, Amir Hafeez, Fabrice André & Peter Schmid

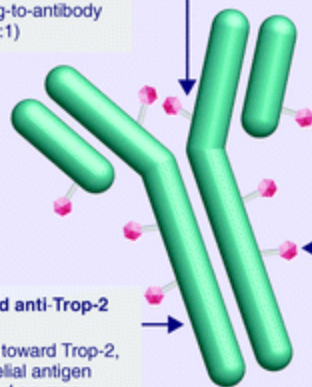
Rechteckiges Ausschneiden

Published Online: 30 Mar 2020 | <https://doi.org/10.2217/fon-2020-0163>

Anti-Trop-2-Therapie

Linker for SN-38

- Hydrolyzable linker for payload release
- High drug-to-antibody ratio (7.6:1)



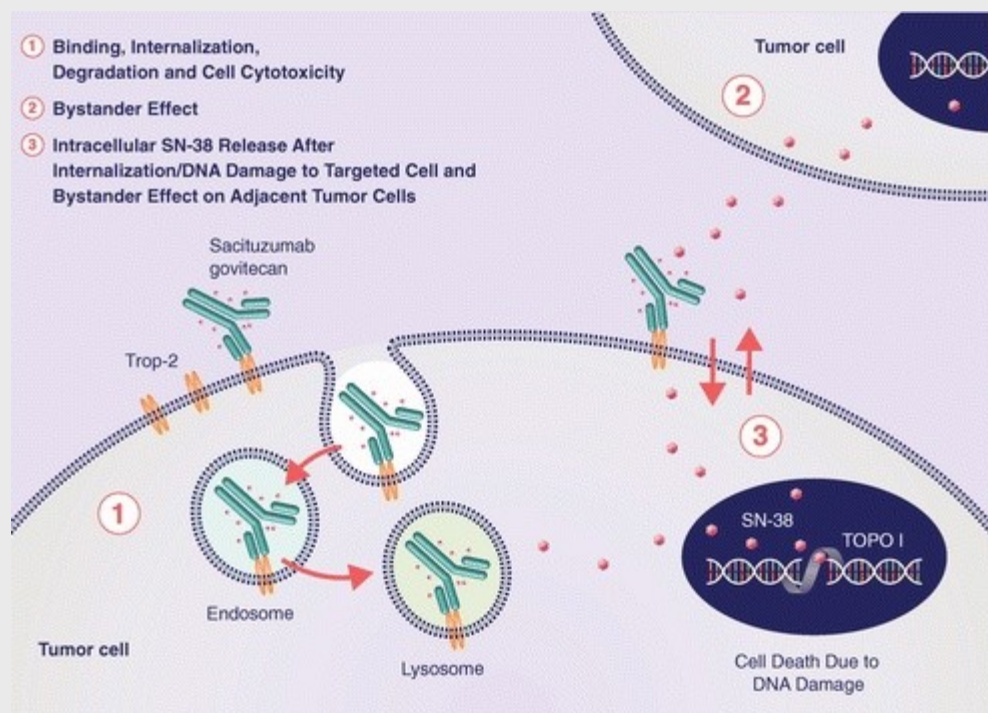
Humanized anti-Trop-2 antibody

- Directed toward Trop-2, an epithelial antigen expressed on many solid cancers

SN-38 payload

- Metabolite of Topo I inhibitor
- SN-38 more potent than parent compound, irinotecan

- 1 Binding, Internalization, Degradation and Cell Cytotoxicity
- 2 Bystander Effect
- 3 Intracellular SN-38 Release After Internalization/DNA Damage to Targeted Cell and Bystander Effect on Adjacent Tumor Cells



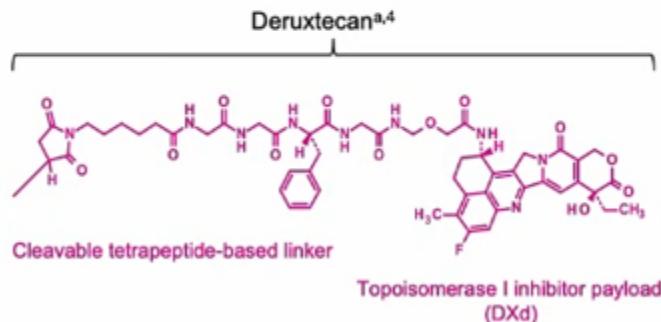
Trop-2 is a calcium signal transducer discovered to play a role in anchorage-independent cell growth, migration and invasion [12]. Trop-2 has been implicated in several intracellular signaling pathways, such as MAPK, Raf and NF- κ B, further contributing to tumor cell survival and progression [12,13]. Overexpressing Trop-2 has been found to be necessary and sufficient to stimulate tumor growth [13].

Datopotamab Deruxtecan (Dato-DXd) Was Designed With 7 Key Attributes

Dato-DXd is an ADC with 3 components^{1,2}:

- A humanized anti-TROP2 IgG1³ monoclonal antibody attached to:
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleavable linker

Humanized anti-TROP2
IgG1 mAb



Payload mechanism of action:
topoisomerase I inhibitor^{b,1}

High potency of payload^{b,2}

Optimized drug to antibody ratio ≈ 4 ^{b,c,1}

Payload with short systemic half-life^{b,c,2}

Stable linker-payload^{b,2}

Tumor-selective cleavable linker^{b,2}

Bystander antitumor effect^{b,2,5}

^a Image is for illustrative purposes only; actual drug positions may vary. ^b The clinical relevance of these features is under investigation. ^c Based on animal data.

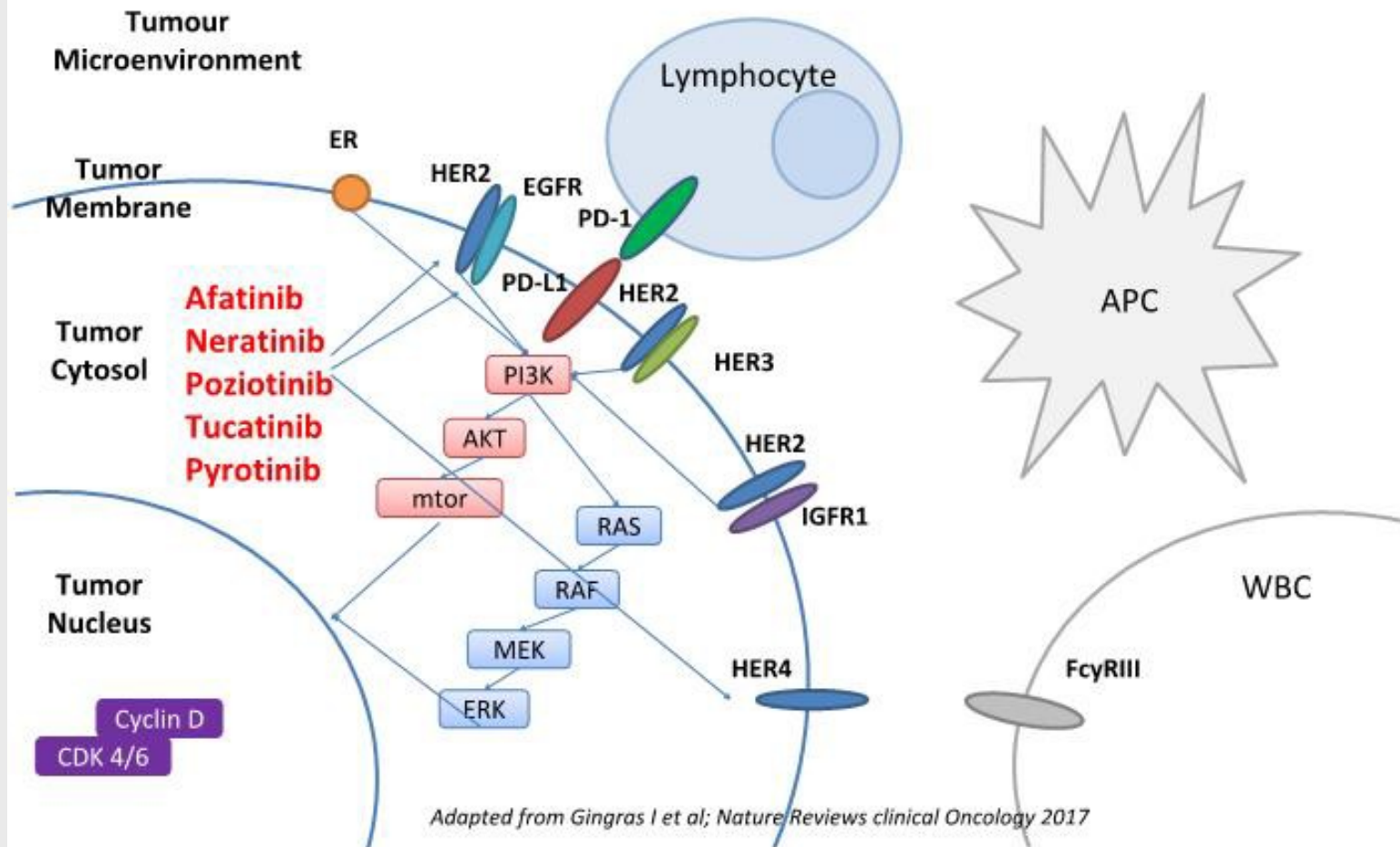
1. Okajima D, et al. AACR-NCI-EORTC 2019; [abstract C026]; 2. Nakada T, et al. *Chem Pharm Bull*. 2019;67(3):173-185; 3. Daiichi Sankyo Co. Ltd. DS-1062. Daiichi Sankyo.com. Accessed October 6, 2020. https://www.daiichisankyo.com/media_investors/investor_relations/ir_calendar/files/005438/DS-1062%20Seminar%20Slides_EN.pdf; 4. Krop I, et al. SABCS 2019; [abstract GS1-03]; 5. Ogitali Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

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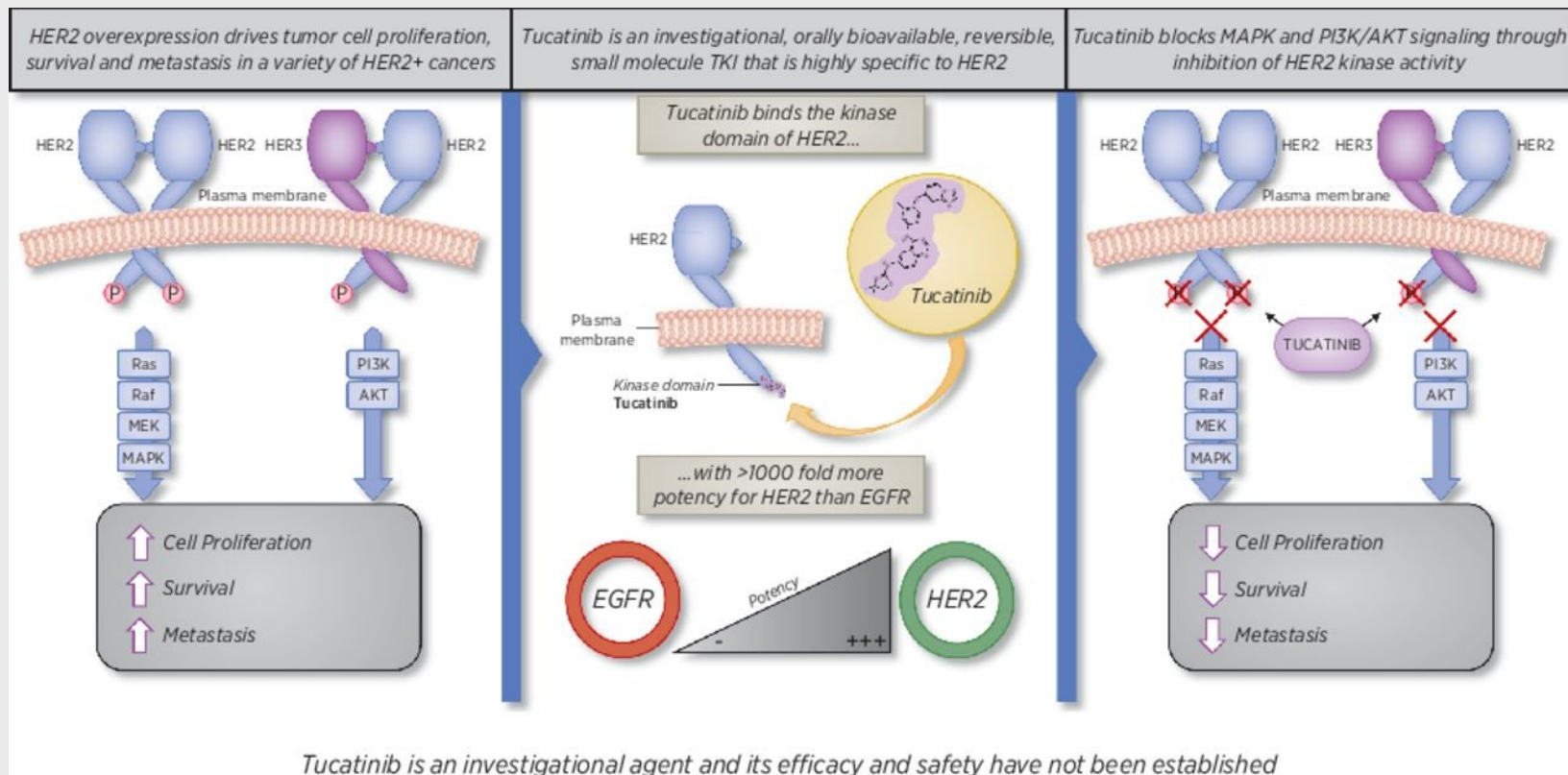
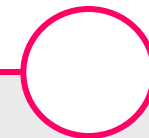


Anti-HER-Therapien

New Strategies : **New anti-HER TKIs**



NEUE ANTI-HER2-THERAPIEN: TUCATINIB



Anita Kulukian et al. Mol Cancer Ther 2020;19:976-987

Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer

Rashmi K. Murthy, M.D., Sherene Loi, M.D., Alicia Okines, M.D., Elisavet Paplomata, M.D., Erika Hamilton, M.D., Sara A. Hurvitz, M.D., Nancy U. Lin, M.D., Virginia Borges, M.D., Vandana Abramson, M.D., Carey Anders, M.D., Philippe L. Bedard, M.D., Mafalda Oliveira, M.D., [et al.](#)

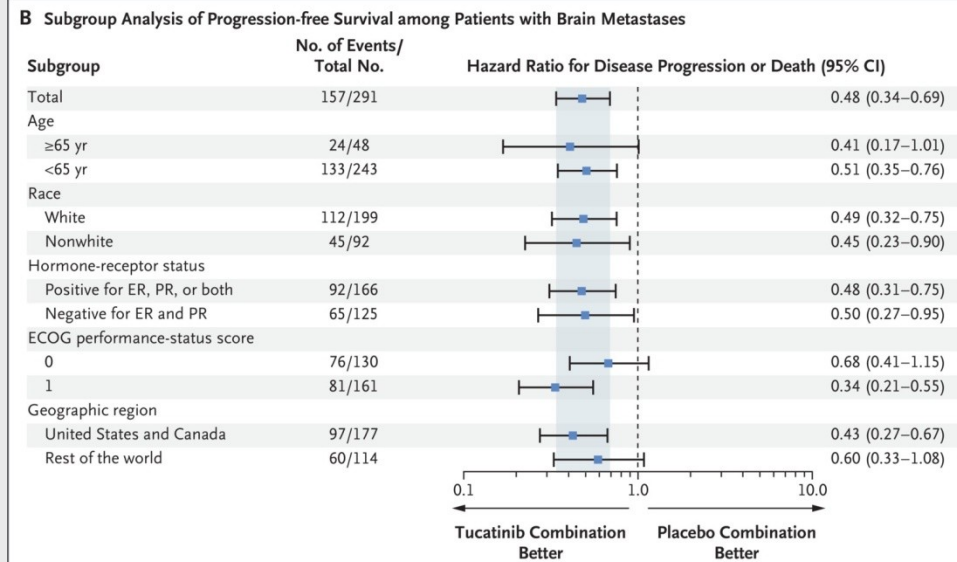
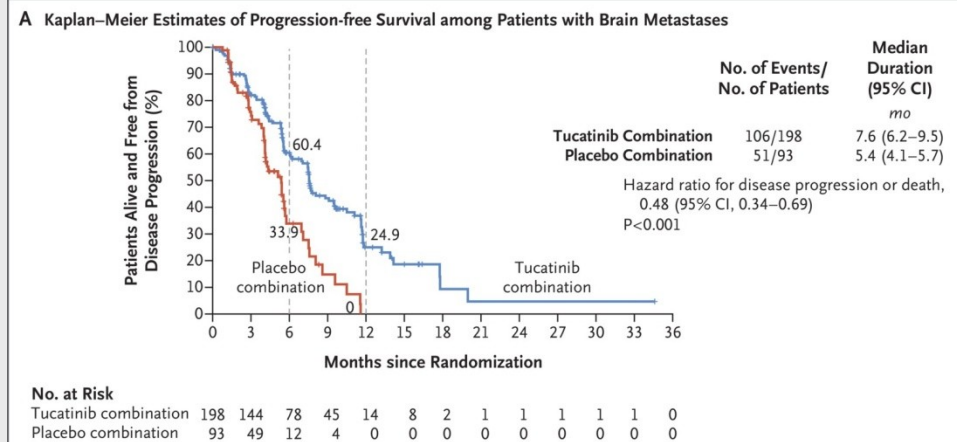
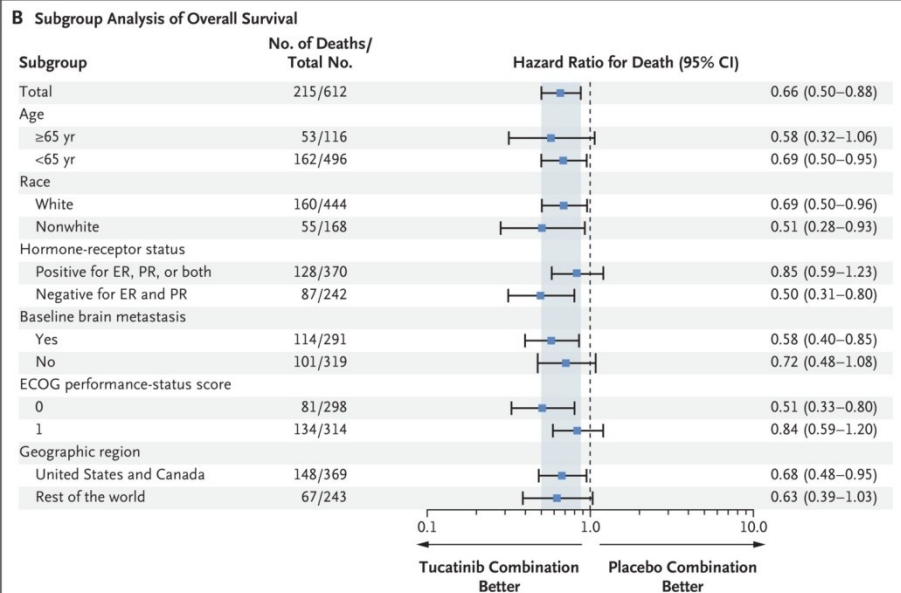
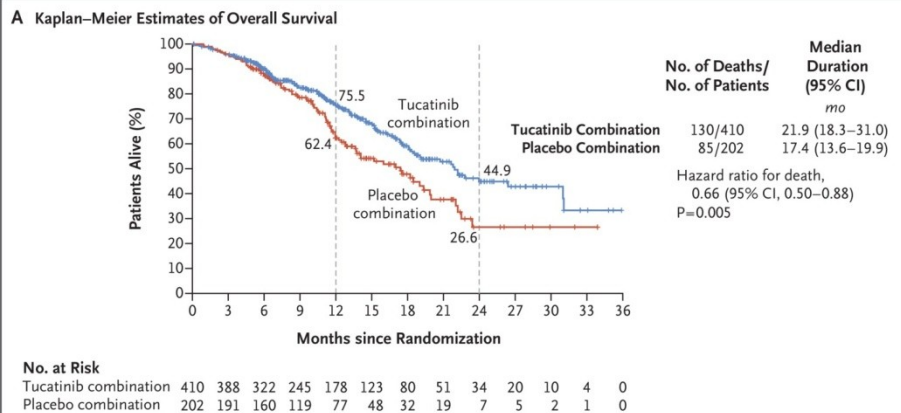
[Article](#) [Figures/Media](#)

[Metrics](#)

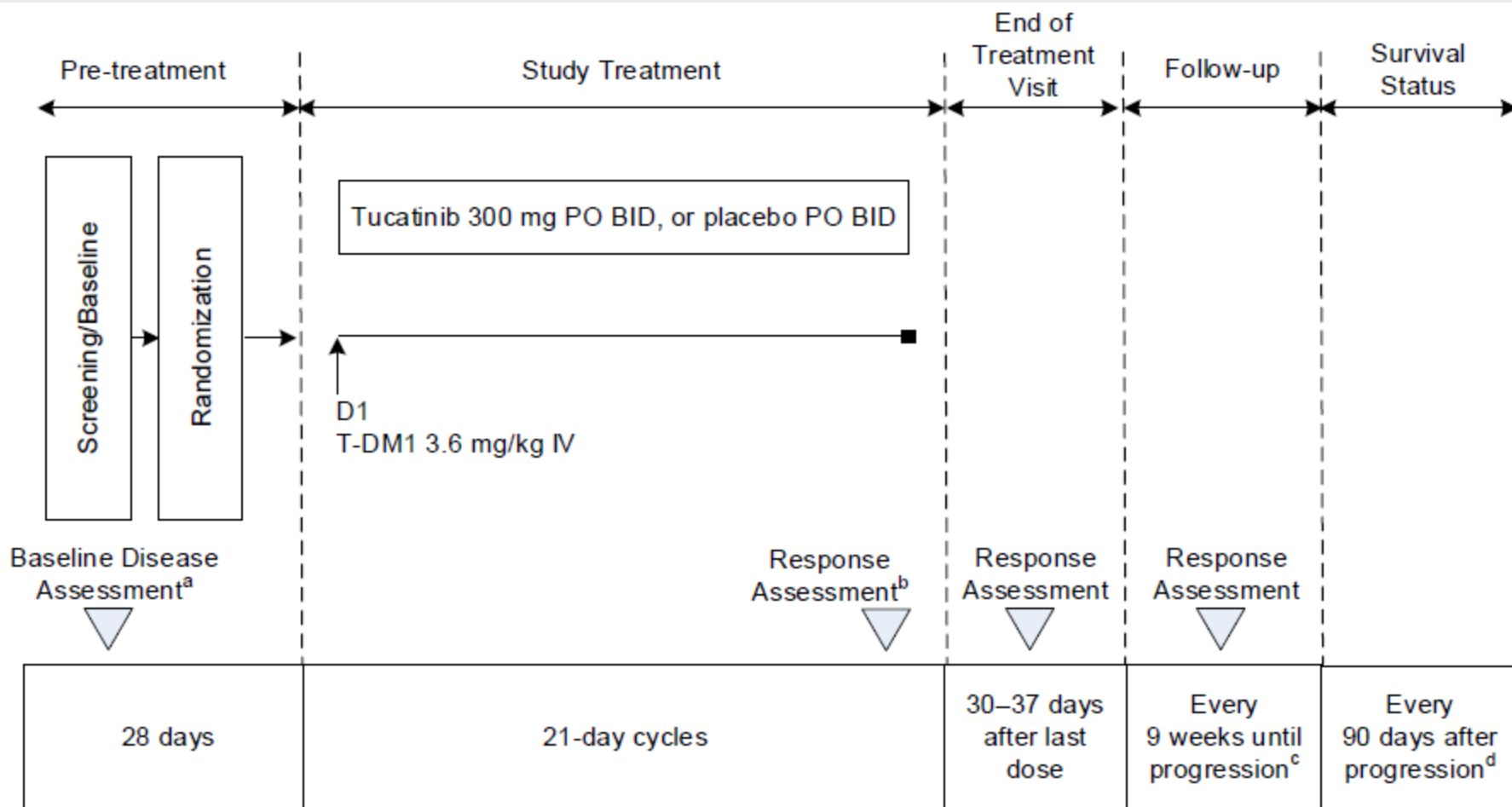
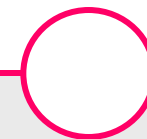
February 13, 2020

N Engl J Med 2020; 382:597-609

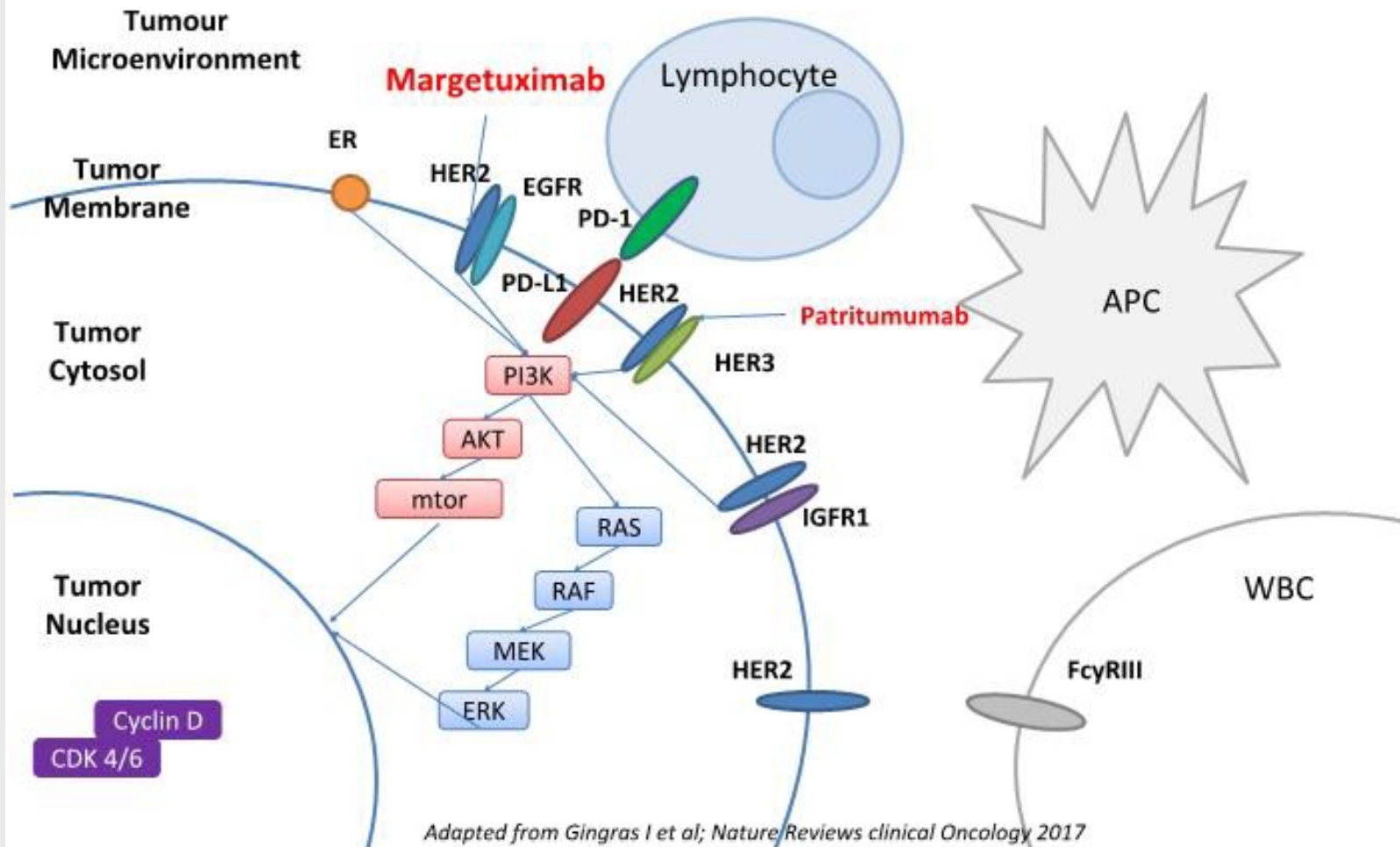
DOI: 10.1056/NEJMoa1914609



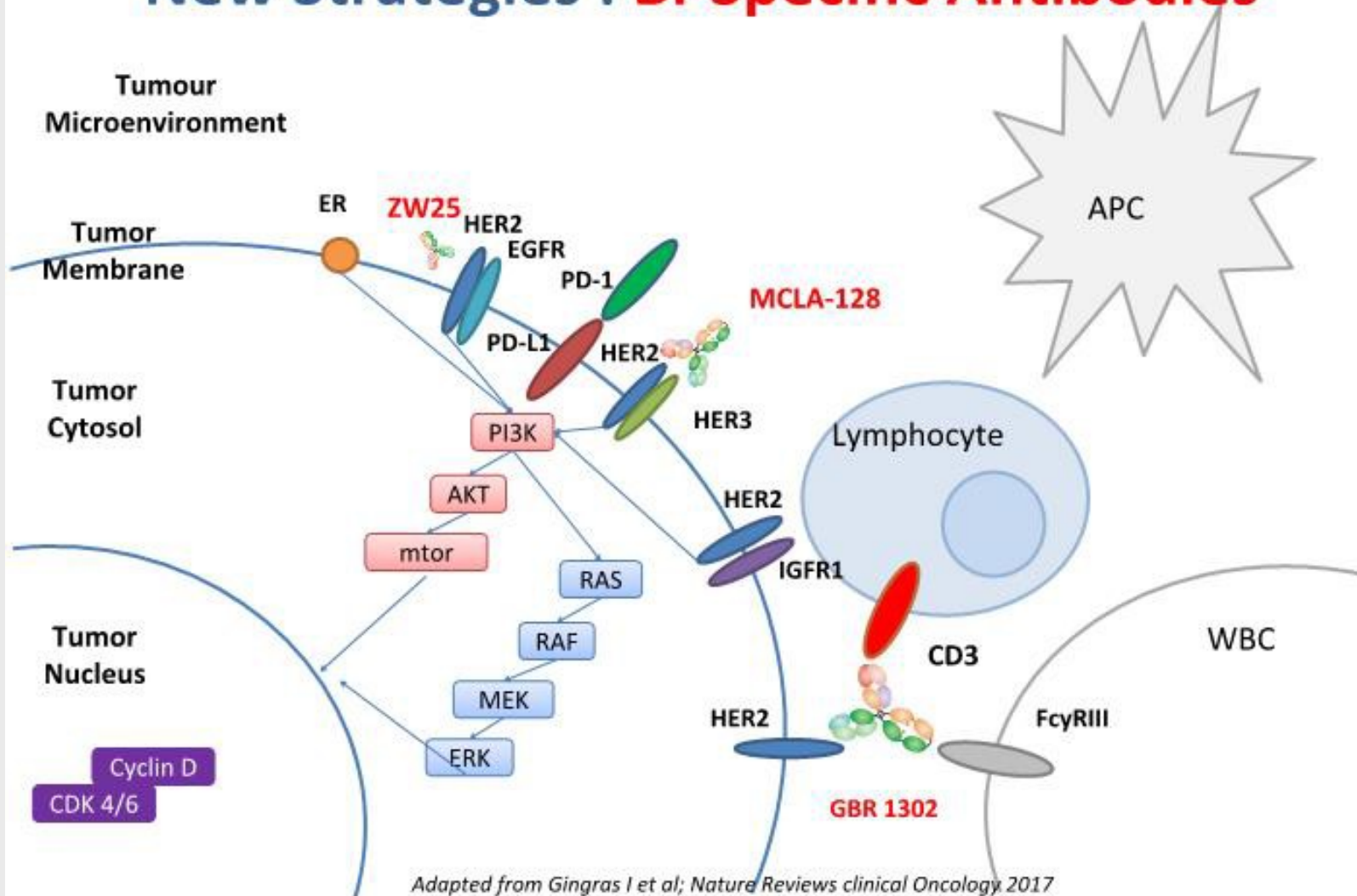
HER2CLIMB-02



New Strategies : New Anti-HER AntiBodies



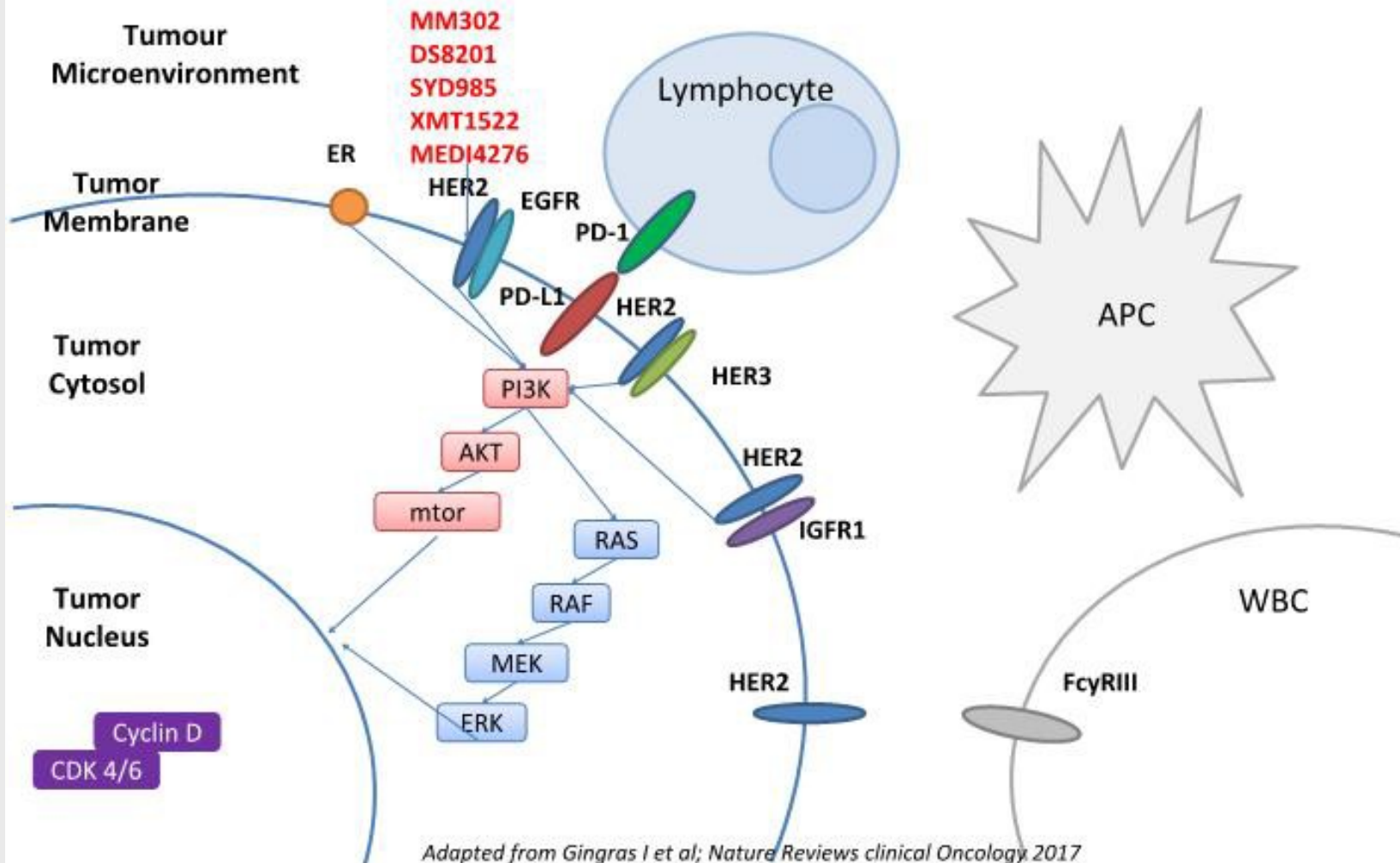
New Strategies : **Bi-Specific Antibodies**



Adapted from Gingras I et al; Nature Reviews clinical Oncology 2017

New Strategies

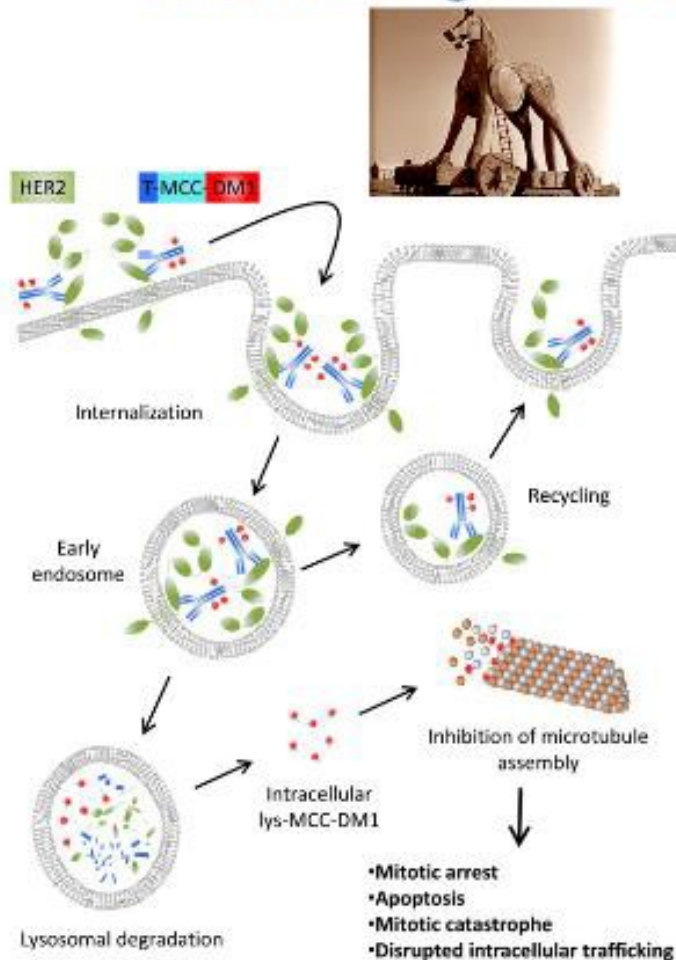
New Antibody Drug Conjugates



Adapted from Gingras I et al; Nature Reviews clinical Oncology 2017

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New Strategies : New Antibody Drug Conjugates



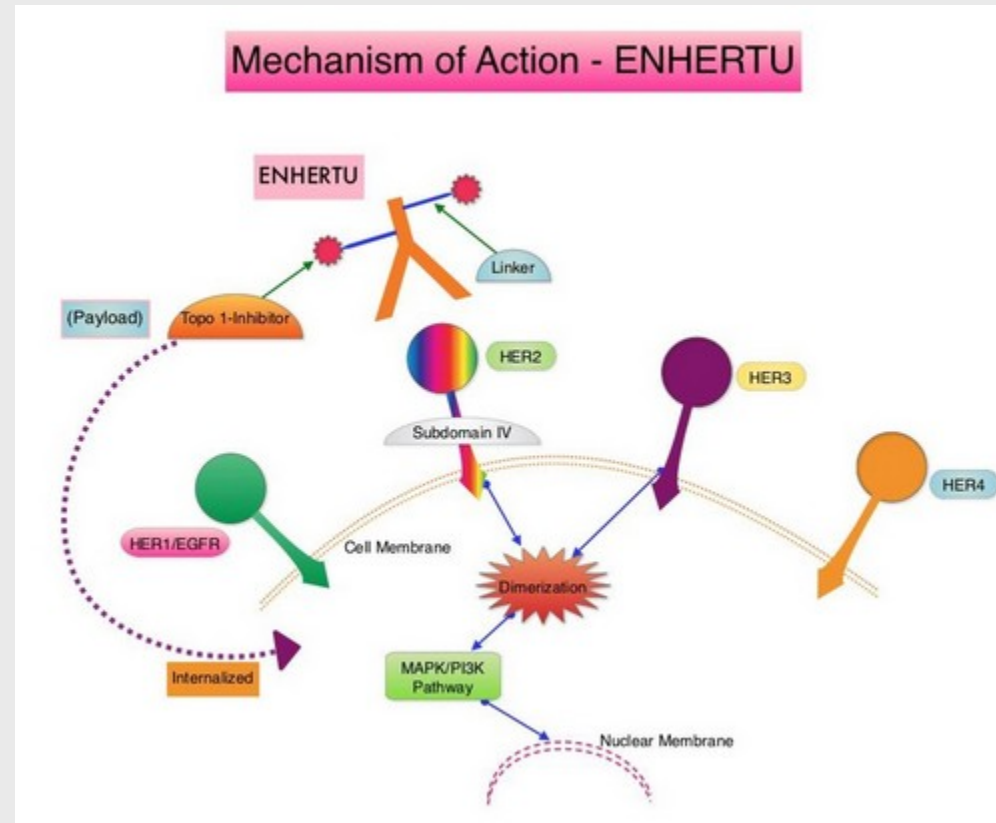
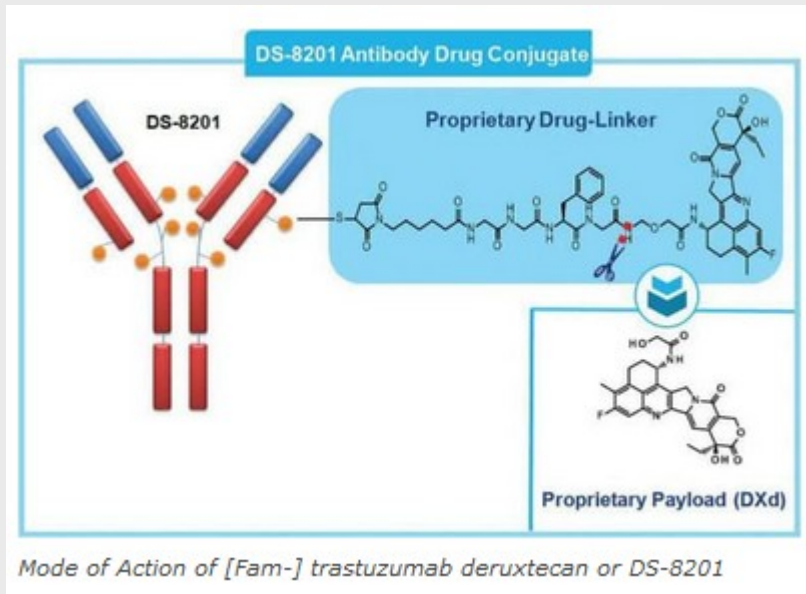
The success of T-DM1 has created a lot of excitement around ADCs

Drug Name	Antibody	Chemotherapy
MM - 302 ²	Humanized anti-HER2 antibody	Liposomal doxorubicin
DS - 8201a ³	Humanized anti-HER2 antibody	Exatecan
SYD- 0985 ⁴	Trastuzumab	Duocarmycin
XMT - 1522 ⁵	HT-19 (Humanized anti-HER2 antibody)	Auristatin
MEDI 4276 ⁶	Bispecific anti-HER2/HER2 antibody	Tubulysin

1. Barok M. *Breast Cancer Res.* 2014; 16(2): 209; 2. Espelin CW et al *Cancer Res* 2016 76(6):1517-27; 3. Ogitan Y et Al *Clin Cancer Res* 2016 22 (20) 5097-5108; 4. Dokter W. et al *Mol Cancer Ther* 2014;13(11):2618-29; 5. Bergstrom DA et al *AACR Abstract* 6716; 6. Li J et al *Abstract* 2970

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ANTI-HER2: Trastuzumab-Deruxtecan (ADC: Topoisomerase I-Inhibitor)



Funktion der Topoisomerase I in Eukaryoten:

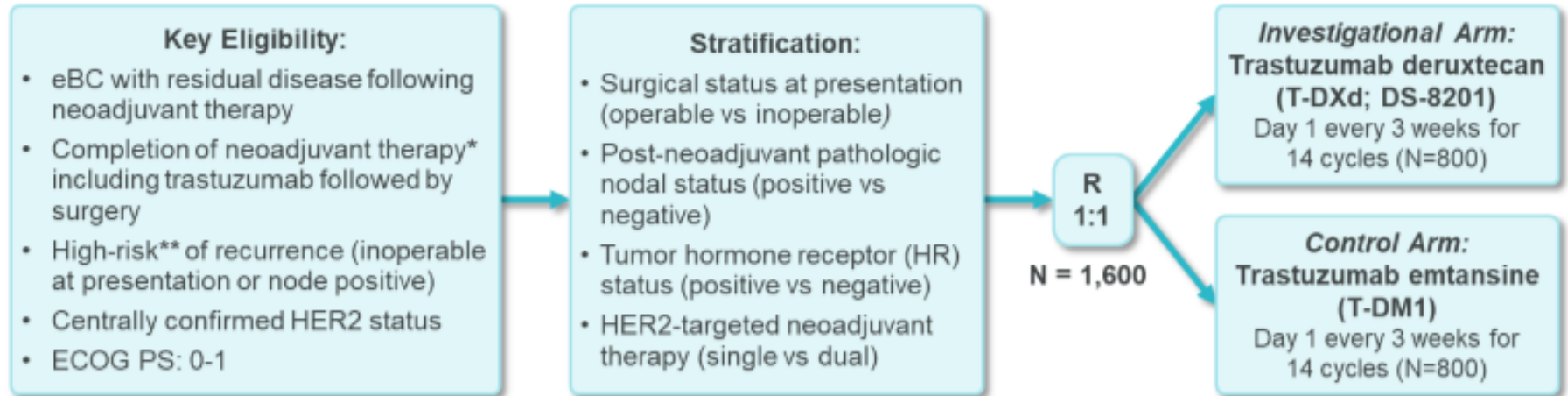
Die eukaryotische Topoisomerase I entspannt sowohl positiv als auch negativ superspiralisierte DNA. Sie bindet mittels **Hydroxygruppe** eines Tyrosinrestes an das 5'-Ende (Phosphatrest) des Strangbruchs und lässt die 3'-Segmente rotieren.

Durch die für die Vorgänge **Transkription** und **Replikation** notwendige Entspiralisierung der gerade abgelesenen DNA-Abschnitte kommt es in angrenzenden Bereichen der Helix automatisch zum **Positiven supercoiling**, einer zu starken Verwindung der DNA-Doppelhelix, die mit Torsionskräften einhergeht. Um den Torsionskräften entgegenzuwirken wird das positive supercoiling durch die eukaryotische Topoisomerase Typ I entspannt. Dabei verursacht die Topoisomerase Typ I einen Einzelstrangbruch ohne dabei ATP zu verbrauchen.^[2] Bei ihrem Abgang von der DNA verschließt sie den Bruch wieder. Anschließend entfernen die Topoisomerase I & IV die negative Abweichungen des Verwindungszustandes und stellen so den physiologischen Normalzustand wieder her.^[3]

DESTINY-Breast05

DS8201-A-U305 (DESTINY-Breast05) Study Design

Trastuzumab deruxtecan (T-DXd) vs. T-DM1 in high-risk HER2-positive early breast cancer patients with residual invasive disease following neoadjuvant therapy



***Neoadjuvant therapy** to include at least 16 weeks of total systemic treatment in the preoperative setting, including:

- At least 9 weeks of HER2-targeted therapy including **trastuzumab** (with or without pertuzumab) and,
- At least 9 weeks of **taxane** therapy

****High-risk definitions:**

- **Inoperable:** Inoperable breast cancer at presentation with residual invasive cancer in the breast or axillary nodes.
- **Node-positive:** Metastatic disease in axillary node(s) following neoadjuvant therapy irrespective of presence or absence of residual invasive cancer in the breast.

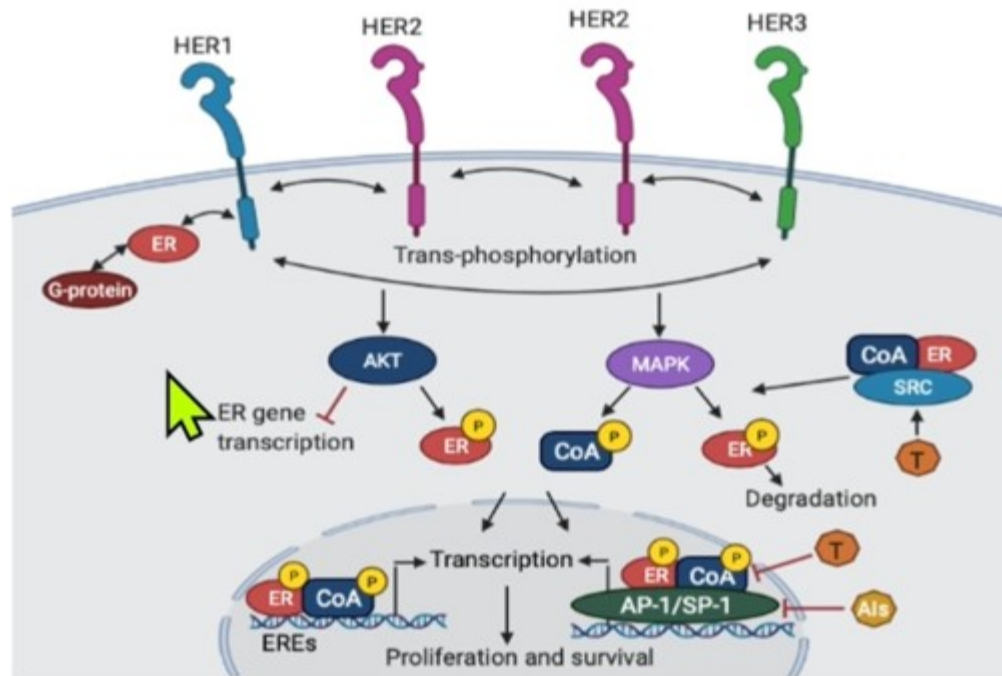
Additional Notes: Randomization within 12 weeks of surgery; adjuvant radiotherapy and/or endocrine therapy per protocol and local guidelines.

eBC=early breast cancer; ECOG PS=Eastern Cooperative Oncology Group performance status; HER2=Human epidermal growth factor receptor 2; PK=pharmacokinetics; R=randomization

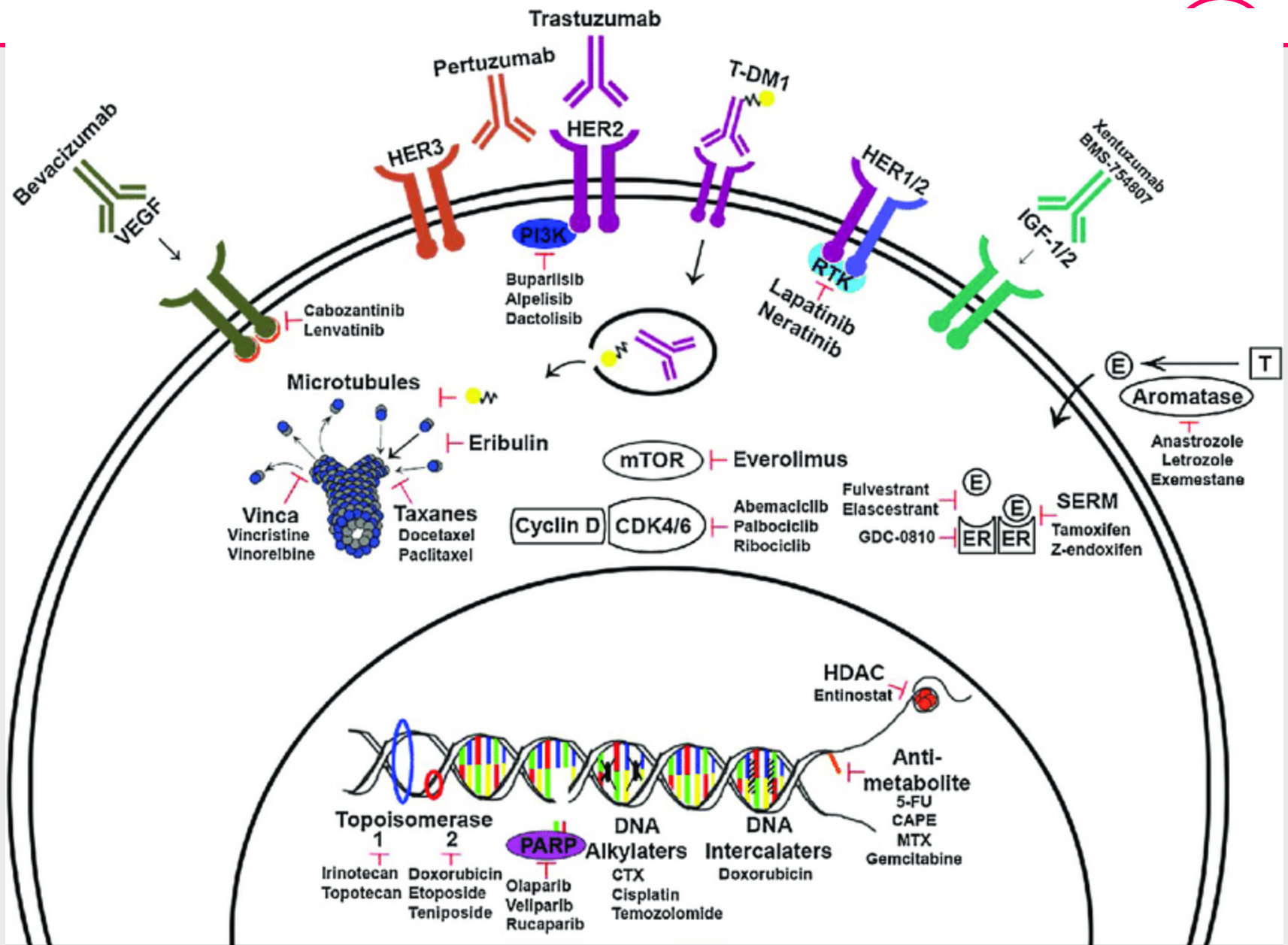
Endpoints:

- **Primary:**
 - IDFS (Invasive disease-free survival)
- **Secondary:**
 - DFS (Disease-free survival)
 - DRFI (Distant recurrence-free interval)
 - BMFI (Brain metastases-free interval)
 - OS (Overall survival)
 - Adverse events
- **Exploratory:**
 - PROs (Patient reported outcomes; QoL)
 - Biomarkers associated with efficacy/safety
 - PK associated with efficacy/safety

ER/HER2 molecular cross talk



Adapted from Giuliano M et al. Breast Care, 2013, PMID: 24415978



Zusammenfassung:



- Cyclin-D4/6-Kinase-Inhibitoren bei ER-positiven metastasierten Mammakarzinomen – Stellenwert in der adjuvanten Mammakarzinomtherapie wird klarer**
- CDK-7-Hemmung als neuer Therapieansatz**
- Immuncheckpoint Blockade hält Einzug in die Therapie des triple-negativen Mammakarzinomes**
- PARP-Inhibitoren etablieren sich bei metastasierten Mammakarzinomen mit BRCA1/2-Mutation**
- PIK3CA-Inhibitoren bei PIK3CA-Mutationen**
- Anti-Trop2-Therapien in der Metastasierung und Adjuvanz**
- Orale SERDS beim metastasierten Mammakarzinom**
- Neue Anti-Her2-Therapien sind am Horizont**