Gemeinschaftsklinikum Mittelrhein
Kemperhof

San Antonio 2021
Frühes Mammakarzinom

Neues zur Neo- / Adjuvanten Therapie

A. Franzen
Frauenklinik, Brustzentrum

Themenübersicht

Gemeinschaftsklinikum Mittelrhein

- Checkpoint Inhibition bei Triple Neg. Ma-Ca (TNBC) NEOadjuvant – *Keynote-522*

- CDK4/6 Inhibitor adjuvant geben ? – *Pallas*
- Metformin zur Verminderung des Rezidivrisikos ? - *CCTGMA.32*
- AI vs. TAM und Ovarielle Suppression in der Prämenopause – *EBCTCG* – Metaanalyse und Update *SOFT / TEXT* Studie
- Anthracyclinfreie Chemotherapie sinnvoll ?
  EBCTCG- Metaanalyse

GS1-01

Gemeinschaftsklinikum Mittelrhein

San Antonio Breast Cancer Symposium®, December 7-10, 2021

KEYNOTE-522 Study of Neoadjuvant Pembrolizumab + Chemotherapy vs Placebo + Chemotherapy, Followed by Adjuvant Pembrolizumab vs Placebo for Early-Stage TNBC: Event-Free Survival Sensitivity and Subgroup Analyses

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GS1-01 Keynote-522 Studie
Triple Neg. Ma-Ca
Hintergrund

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- **Pembrolizumab: zeigte Antitumoraktivität u. Sicherheit / bei met. TNBC und in Neo-Adjuvanzstudien zusammen mit Chemotherapie (Keynote-173, I-Spy2)**

- **Erste Phase III Studie zum Vgl. Pembro.+Chemo vs. Pembro + Placebo NEO-adjuvant → OP → Pembro. Vs. Placebo Adjuvant**

- **Primäre Analyse zeigte für Pembro. Kombination:**

→ Neoadjuvant: signifikant höhere pCR

→ Neoadj . + Adj. : signif. Verbesserung des EFS

- **Seither FDA Zulassung**

- **Jetzt: Neue Sensitivitäts u. Subgruppenanalysen zum EFS**

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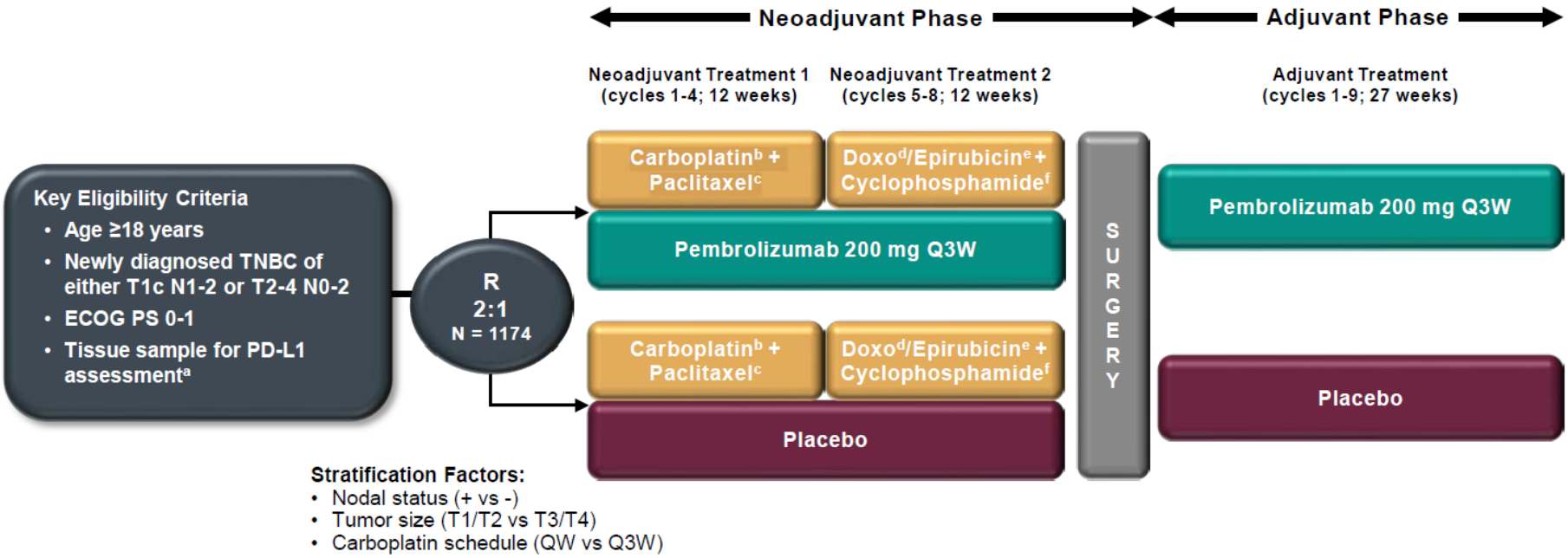
KEYNOTE-522 Study Design (NCT03036488)



Stratification Factors:
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW.
[c]Paclitaxel dose was 80 mg/m² QW.
[d]Doxorubicin dose was 60 mg/m² Q3W.
[e]Epirubicin dose was 90 mg/m² Q3W.
[f]Cyclophosphamide dose was 600 mg/m² Q3W.

Study Endpoints

- Primary Endpoints
  - pCR (ypT0/Tis ypN0) assessed by local pathologist in ITT population[a]
  - EFS assessed by investigator in ITT population[a]
- Secondary Endpoints
  - pCR by alternative definitions (ypT0 ypN0 and ypT0/Tis)[a]
  - OS[b]
  - pCR[a], EFS[a] and OS[b] in the PD-L1–positive population[c]
  - Safety in all treated patients
- Exploratory Analyses
  - EFS sensitivity analyses
  - EFS in patient subgroups

Prespecified sensitivity and subgroup analyses were performed to assess the robustness and consistency of the primary EFS result

[a]Primary pCR and EFS analyses presented previously. [b]To be presented later. [c]PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of viable tumor cells x 100); PD-L1–positive = CPS ≥1.

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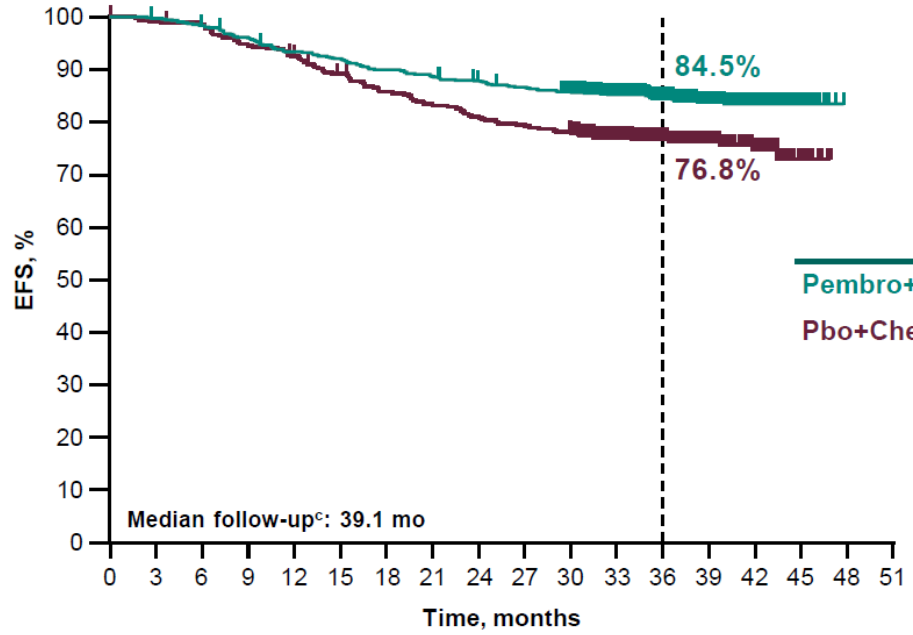
Primary EFS Analysis



	Events	HR (95% CI)	*P*-value
Pembro+Chemo/Pembro	15.7%	0.63[a] (0.48-0.82)	0.00031[b]
Pbo+Chemo/Pbo	23.8%		

No. at risk

784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [b]Prespecified *P*-value boundary of 0.00517 reached at this analysis. [c]Defined as the time from randomization to the data cutoff date of March 23, 2021.

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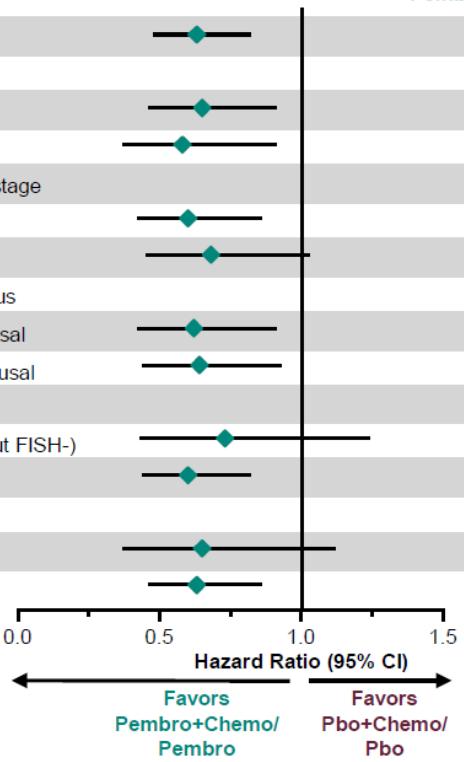
EFS Subgroup Analyses

EFS Analyses	No. of events/no. of patients (%) Pembro+Chemo/Pembro	Pbo+Chemo/Pbo	Hazard Ratio (95% CI)
Primary analysis	123/784 (15.7)	93/390 (23.8)	0.63 (0.48 to 0.82)
Nodal status			
Positive	80/408 (19.6)	57/196 (29.1)	0.65 (0.46 to 0.91)
Negative	43/376 (11.4)	36/194 (18.6)	0.58 (0.37 to 0.91)
Overall disease stage			
Stage II	65/590 (11.7)	54/291 (18.6)	0.60 (0.42 to 0.86)
Stage III	54/194 (27.8)	39/98 (39.8)	0.68 (0.45 to 1.03)
Menopausal status			
Pre-menopausal	60/438 (13.7)	47/221 (21.3)	0.62 (0.42 to 0.91)
Post-menopausal	63/345 (18.3)	46/169 (27.2)	0.64 (0.44 to 0.93)
HER2 status			
2+ by IHC (but FISH-)	32/188 (17.0)	24/104 (23.1)	0.73 (0.43 to 1.24)
0-1+ by IHC	91/595 (15.3)	69/286 (24.1)	0.60 (0.44 to 0.82)
LDH			
>ULN	29/149 (19.5)	23/80 (28.8)	0.65 (0.37 to 1.12)
≤ULN	93/631 (14.7)	69/309 (22.3)	0.63 (0.46 to 0.86)



Primary analysis based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors; subgroup analyses based on unstratified Cox mod
Data cutoff date: March 23, 2021.

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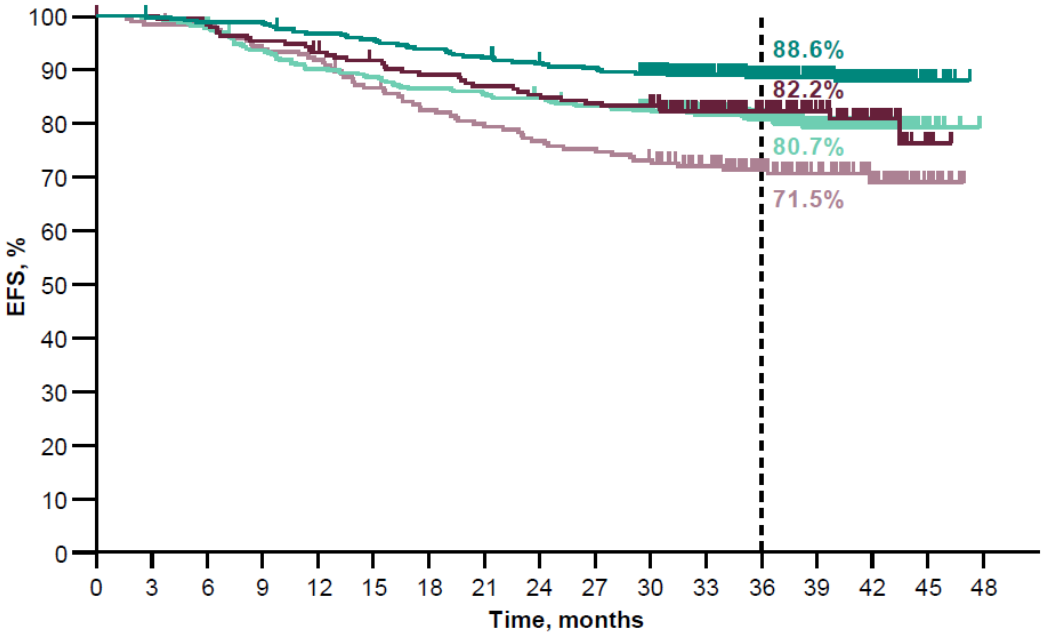
EFS by Nodal Status

Node Negative	Events	HR (95% CI)
Pembro+Chemo/Pembro	11.4%	0.58 (0.37-0.91)
Pbo+Chemo/Pbo	18.6%	

Node Positive	Events	HR (95% CI)
Pembro+Chemo/Pembro	19.6%	0.65 (0.46-0.91)
Pbo+Chemo/Pbo	29.1%	



No. at risk																
Pembro+Chemo/Pembro, Node Negative	376	374	371	371	362	358	351	345	338	335	322	272	212	151	81	16	0
Pbo+Chemo/Pbo, Node Negative	194	193	190	184	179	174	169	165	162	159	157	131	101	71	39	7	0
Pembro+Chemo/Pembro, Node Positive	408	407	398	380	366	360	351	347	343	336	330	279	221	152	84	12	0
Pbo+Chemo/Pbo, Node Positive	196	193	192	184	179	168	159	154	148	145	140	119	94	69	44	10	0

Data cutoff date: March 23, 2021.

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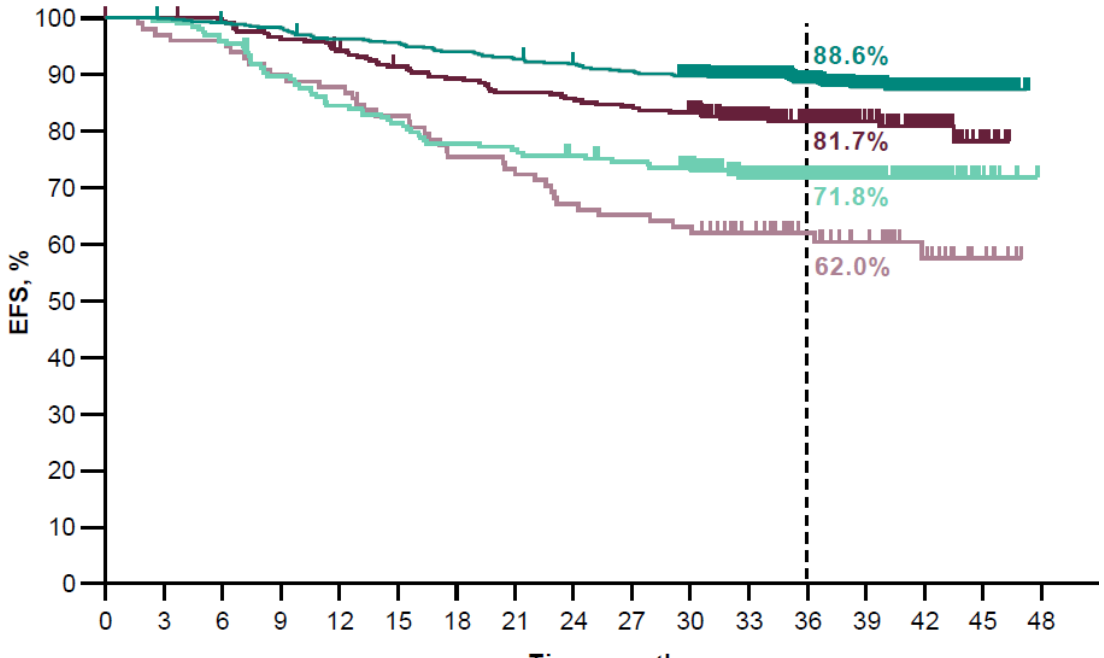
EFS by Overall Disease Stage

Stage II	Events	HR (95% CI)
Pembro+Chemo/Pembro	11.7%	0.60 (0.42-0.86)
Pbo+Chemo/Pbo	18.6%	

Stage III	Events	HR (95% CI)
Pembro+Chemo/Pembro	27.8%	0.68 (0.45-1.03)
Pbo+Chemo/Pbo	39.8%	



No. at risk																
Pembro+Chemo/Pembro, Stage II	590	588	583	578	565	561	552	544	536	529	515	434	345	243	126	20	0
Pbo+Chemo/Pbo, Stage II	291	290	287	279	271	261	255	248	245	241	236	197	156	109	63	12	0
Pembro+Chemo/Pembro, Stage III	194	193	186	173	163	157	150	148	145	142	137	117	88	60	39	8	0
Pbo+Chemo/Pbo, Stage III	98	95	94	88	86	80	73	71	65	63	61	53	39	31	20	5	0

Data cutoff date: March 23, 2021.

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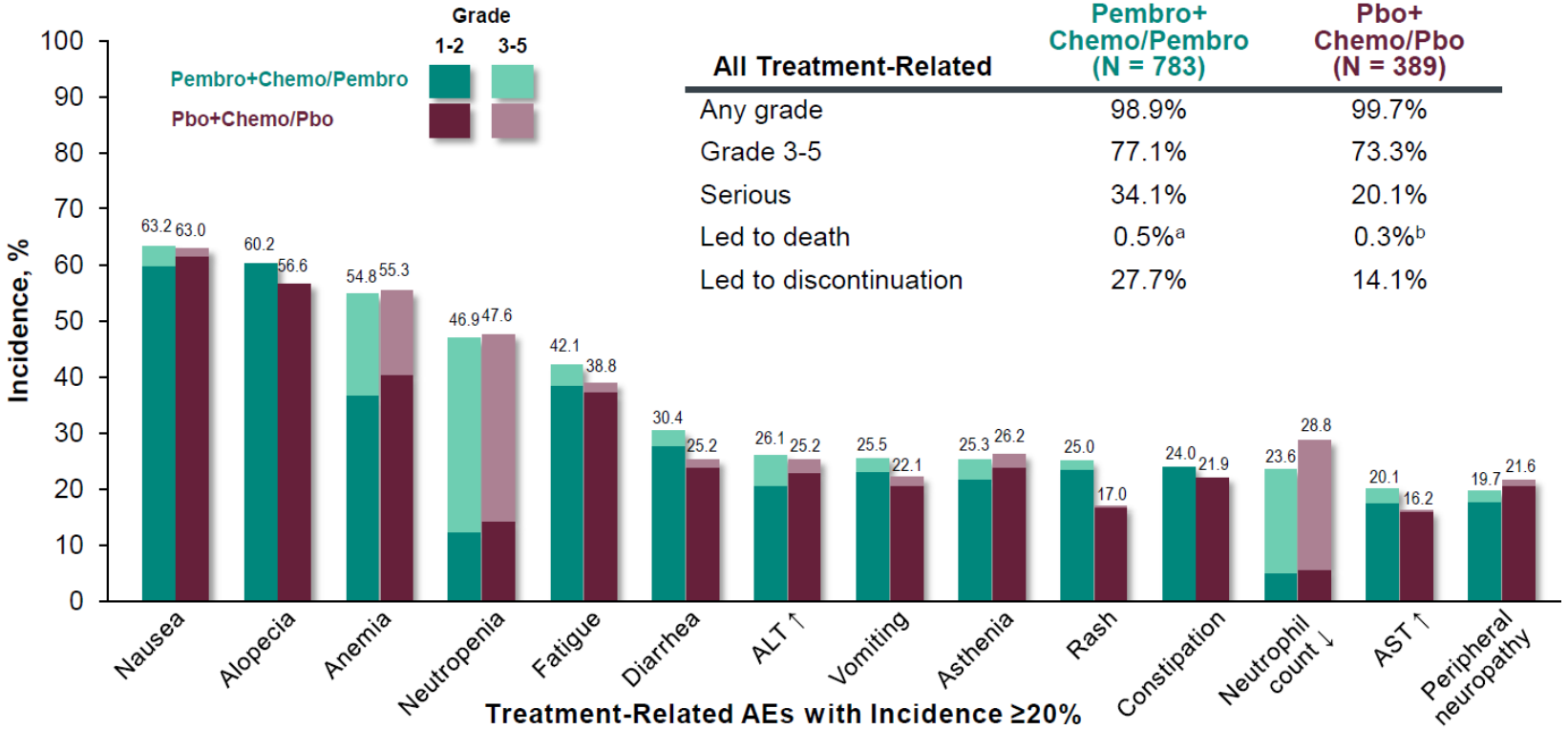
Treatment-Related AEs in Combined Phases



All Treatment-Related	Pembro+ Chemo/Pembro (N = 783)	Pbo+ Chemo/Pbo (N = 389)
Any grade	98.9%	99.7%
Grade 3-5	77.1%	73.3%
Serious	34.1%	20.1%
Led to death	0.5%[a]	0.3%[b]
Led to discontinuation	27.7%	14.1%

[a]1 patient from sepsis and multiple organ dysfunction syndrome; 1 patient from pneumonitis; 1 patient from pulmonary embolism; 1 patient from autoimmune encephalitis. [b]1 patient from septic shock. Data cutoff date: March 23, 2021.

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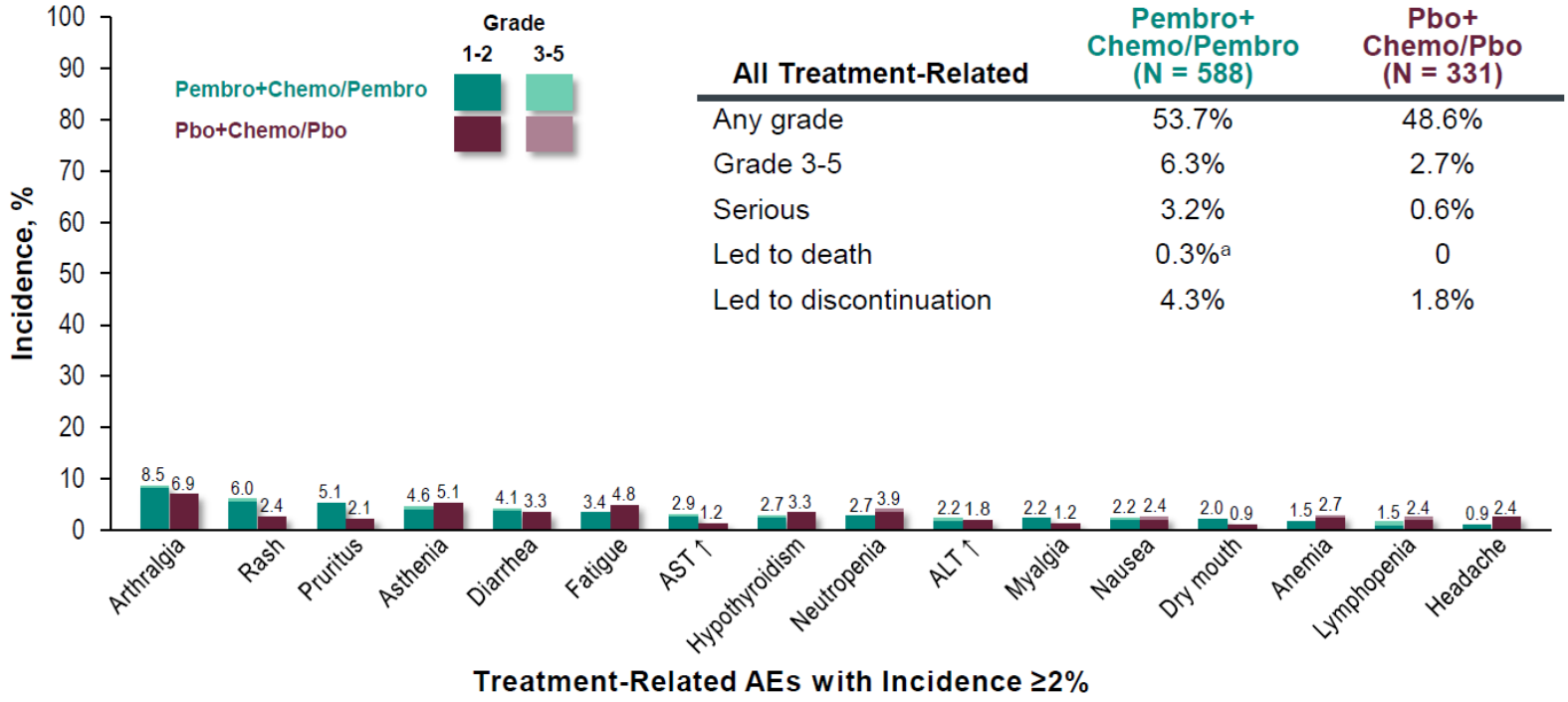
Treatment-Related AEs in Adjuvant Phase



All Treatment-Related	Pembro+ Chemo/Pembro (N = 588)	Pbo+ Chemo/Pbo (N = 331)
Any grade	53.7%	48.6%
Grade 3-5	6.3%	2.7%
Serious	3.2%	0.6%
Led to death	0.3%[a]	0
Led to discontinuation	4.3%	1.8%

Treatment-Related AEs with Incidence ≥2%

[a]1 patient from pulmonary embolism and 1 patient from autoimmune encephalitis. Data cutoff date: March 23, 2021.

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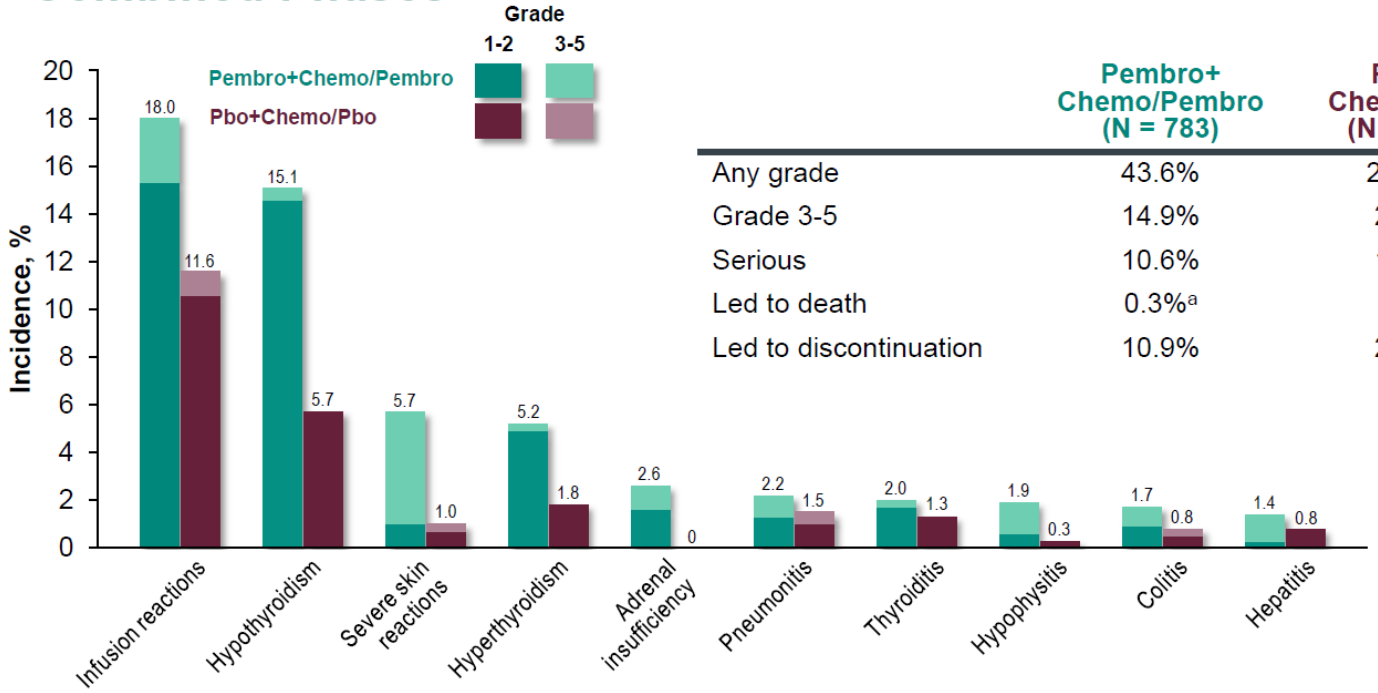
Immune-Mediated AEs and Infusion Reactions in Combined Phases



	Pembro+ Chemo/Pembro (N = 783)	Pbo+ Chemo/Pbo (N = 389)
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%
Serious	10.6%	1.3%
Led to death	0.3%[a]	0
Led to discontinuation	10.9%	2.6%

Immune-Mediated AEs and Infusion Reactions with Incidence ≥10 Patients

[a]1 patient from pneumonitis and 1 patient from autoimmune encephalitis. Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed. Data cutoff date: March 23, 2021.

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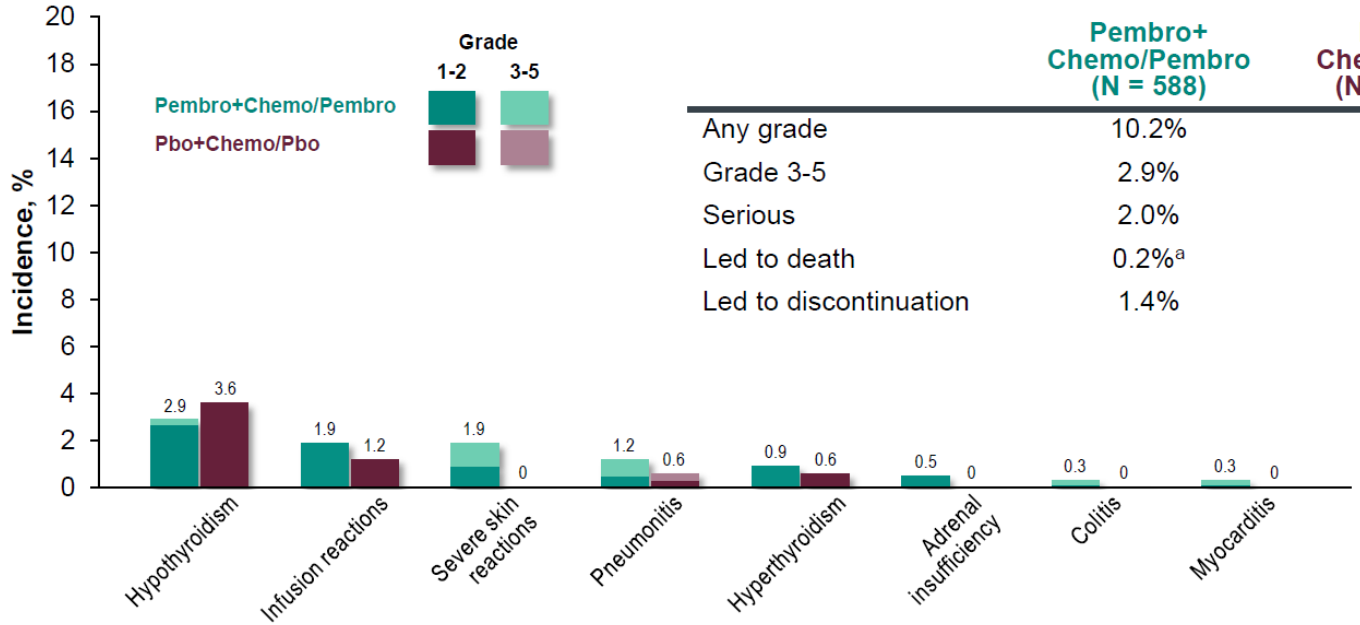
Immune-Mediated AEs and Infusion Reactions in Adjuvant Phase



	Pembro+ Chemo/Pembro (N = 588)	Pbo+ Chemo/Pbo (N = 331)
Any grade	10.2%	6.0%
Grade 3-5	2.9%	0.3%
Serious	2.0%	0.3%
Led to death	0.2%[a]	0
Led to discontinuation	1.4%	0.3%

Immune-Mediated AEs and Infusion Reactions with Incidence ≥2 Patients

[a]1 patient from autoimmune encephalitis. Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed. Data cutoff date: March 23, 2021.

Fazit :
Keynote-522

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- **Statististisch signifikante u. klinisch relevante Verbesserung der Lebenserwartung (EFS) für Pembrolizumab + CHT**
- **Der Behandlungsvorteil zeigt sich stabil über breite Subgruppen für das frühe , unbehandelte TNBC**
- **Keine neuen Sicherheitsbedenken / Nebenw.**
-
- **Erwarteter neuer Standard**

GS1-07
Pallas Studie

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San Antonio Breast Cancer Symposium®, December 7-10, 2021

Adjuvant palbociclib in HR+/HER2- early breast cancer: Final protocol-planned analysis results from 5,761 patients in the randomized phase III PALLAS trial

Michael Gnant MD FACS FEBShon

Michael Gnant, Amylou Dueck, Sophie Frantal, Miguel Martin, Hal Burstein, Richard Greil, Peter Fox, Antonio Wolff, Arlene Chan, Eric Winer, Christian Singer, Kathy Miller, Marco Colleoni, Michelle Naugthon, Gabor Rubovsky, Judith Bliss, Ingrid Mayer, Guenther G. Steger, Zbigniew Nowecki, Olwen Hahn, Norman Wolmark, Hope Rugo, Georg Pfeiler, Hannes Fohler, Otto Metzger, Céline Schurmans, Kathy Puyana Theall, Dongrui Ray Lu, Kathleen Tenner, Christian Fesl, Angela DeMichele*, Erica L Mayer*, on behalf of the PALLAS groups and investigators

PALLAS ABCSG 42 / AFT-05 / BIG 14-03 | Sponsored by AFT and ABCSG, in cooperation with PrECOG, BIG, GBG, NSABP, and supported by Pfizer.

GS1-07 – Pallas Studie
HR + / Her 2 -
Hintergrund

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- CDK4/6 Inhibitoren : Standardtherapie in met. Situation (+ AI)
- Nachgewiesene Effekte auf die Überlebensdaten (PFS/OS)
- Gute Verträglichkeit

- Laufende andere große Studien zum Einsatz beim frühen Brustkrebs

- Hier :
- Finale Analyse der Überlebensdaten für Palbociclib + AHT vs. AHT alleine in der adjuvanten Situation

- PALbociclib Collaborative Adjuvant Study – „PALLAS“

PALLAS: Phase III Study of Adjuvant Palbociclib

Eligibility:
- Stage II-III HR+/HER2-
- Completion of prior surgery, +/- chemo, RT
- Within 12 mo of diagnosis, within 6 mo of starting adjuvant ET
- FFPE tumor block submitted and received at biorepository

N=5,600

Ki67 assessment was not mandated

Stratification:
- **Stage** (IIA vs IIB/III)
- **Chemotherapy** (yes vs no)
- **Age** (≤50 vs >50)
- **Geographic region** (US vs Europe vs Other)

RANDOMIZE 1:1

Arm A
Palbociclib x 2 years
(125 mg qd, 3 wks on/1 wk off)
+
Endocrine Treatment*

Arm B
Endocrine Treatment*

** Aromatase inhibitor or tamoxifen, +/- LHRH agonist (Duration: at least 5 years)*

Open Label

Primary Endpoint: Invasive Disease-Free Survival (iDFS)

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PALLAS Patient Characteristics

- **5,761 patients** randomized (ITT)
- Majority: higher stage disease (82% IIB/III), prior chemotherapy (83%)
- Median age: 52 years (IQR 45-61)
- Clinical „high risk“: 59%

Variable	Palbociclib + ET (N=2,884)	ET (N=2,877)
Stage		
I/IIA	513 (17·8%)	519 (18·0%)
IIB/III	2370 (82·2%)	2358 (82·0%)
T-Stage		
T0/T1/Tis/TX	558 (19·3%)	501 (17·4%)
T2	1603 (55·6%)	1636 (56·9%)
T3/T4	722 (25·0%)	740 (25·7%)
N-Stage		
N0	365 (12·7%)	385 (13·4%)
N1	1431 (49·6%)	1411 (49·0%)
N2	700 (24·3%)	709 (24·6%)
N3	386 (13·4%)	372 (12·9%)
Histologic Grade		
G1/G2	1926 (66·8%)	1971 (68·5%)
G3	836 (29·0%)	769 (26·7%)
Prior Chemotherapy	2384 (82·7%)	2370 (82·4%)
Menopausal Status		
Postmenopausal	1562 (54·2%)	1534 (53·3%)
Pre/Perimenopausal	1303 (45·2%)	1323 (46·0%)
Gender		
Female	2867 (99·4%)	2858 (99·3%)
Male	17 (0·6%)	19 (0·7%)
Clinical Risk		
High risk	1711 (59·3%)	1673 (58·2)
Low risk	1171 (40·6)	1204 (41·8)

PALLAS
ABCSG 42 / AFT-05 / BIG 14-03

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ABCSG ALLIANCE FOUNDATION TRIALS, LLC BIG Pfizer Oncology

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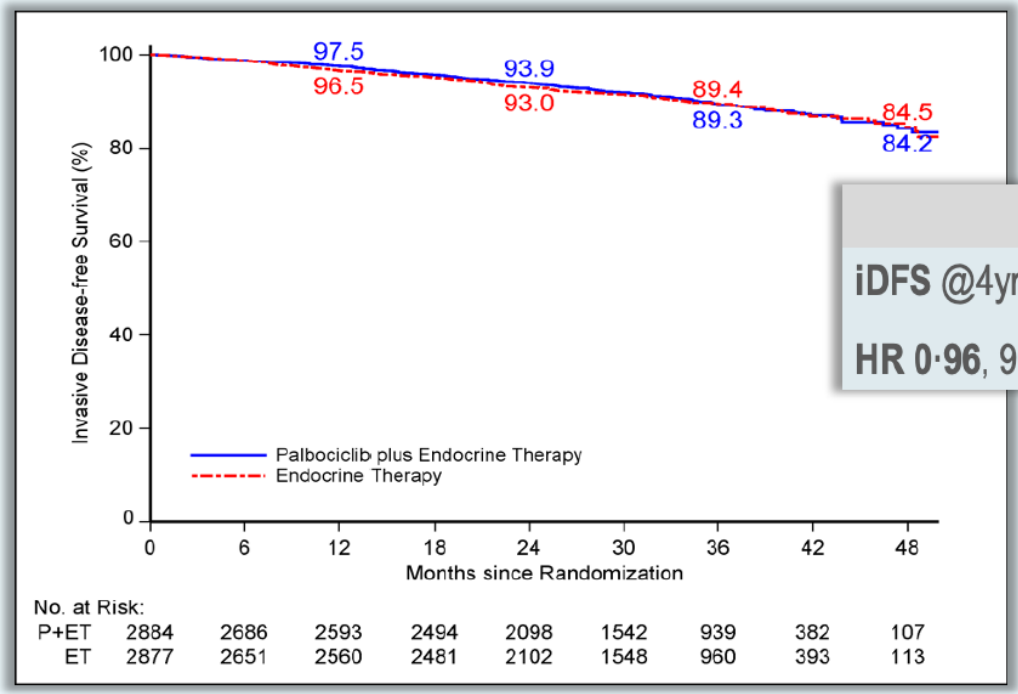
PALLAS: Primary Endpoint iDFS



	Palbociclib + ET	ET alone
iDFS @4yrs	84.2%	84.5%

HR 0·96, 95% CI 0·81-1·14; log-rank p = 0·65

253 vs 263 iDFS events, no difference in event categories (distant recurrences, second primaries, local, regional, contralateral, deaths without recurrence)

Efficacy population:
Intent-to-treat (ITT) principle, with patients withdrawing consent for all data excluded

At a median follow-up of 31 months, **no significant difference in 4-year iDFS** was observed

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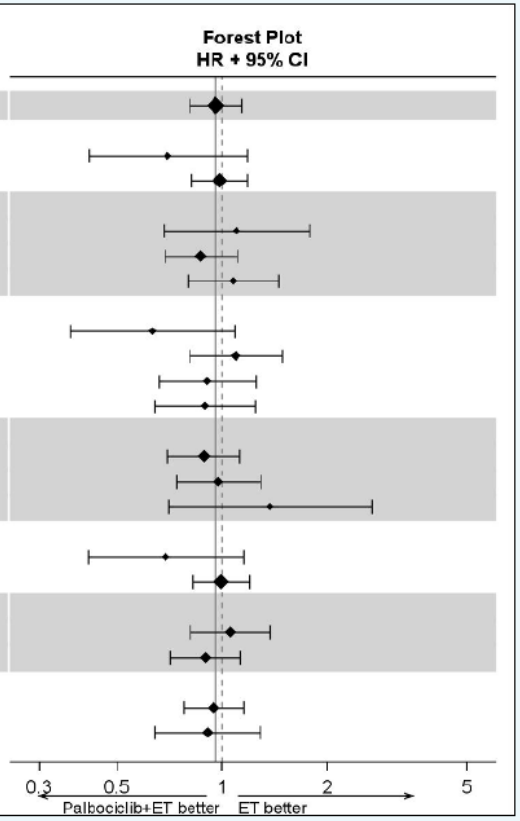
PALLAS: iDFS in Subgroups

Subgroup	Palbociclib+ET Events / N	ET Events / N	HR (95% CI)
All patients	253 / 2884	263 / 2877	0.96 (0.81 - 1.14)
Anatomic Staging			
I/IIA	23 / 513	36 / 519	0.70 (0.41 - 1.18)
IIB/III	230 / 2370	227 / 2358	0.98 (0.82 - 1.18)
T-Stage			
T0/T1/Tis/TX	36 / 558	31 / 501	1.10 (0.68 - 1.78)
T2	127 / 1603	149 / 1636	0.87 (0.69 - 1.10)
T3/T4	90 / 722	83 / 740	1.07 (0.80 - 1.45)
N-Stage			
N0	21 / 365	36 / 385	0.63 (0.37 - 1.08)
N1	86 / 1431	80 / 1411	1.09 (0.81 - 1.48)
N2	73 / 700	78 / 709	0.91 (0.66 - 1.25)
N3	73 / 386	69 / 372	0.89 (0.64 - 1.24)
Grading			
G1/G2	129 / 1926	150 / 1971	0.89 (0.70 - 1.12)
G3	105 / 836	97 / 769	0.98 (0.74 - 1.29)
GX	19 / 122	16 / 137	1.37 (0.71 - 2.67)
Neo/adjuvant Chemotherapy			
No	24 / 499	37 / 507	0.69 (0.41 - 1.15)
Yes	229 / 2384	226 / 2370	0.99 (0.83 - 1.20)
Age group			
<=50	116 / 1310	109 / 1304	1.05 (0.81 - 1.37)
>50	137 / 1573	154 / 1573	0.90 (0.71 - 1.13)
Clinical Risk			
high risk	194 / 1711	193 / 1673	0.95 (0.77 - 1.15)
low risk	59 / 1171	70 / 1204	0.91 (0.64 - 1.28)



PALLAS: Safety and Side Effects

- **No new safety signals** for palbociclib treatment
- SAEs: 369 (13.0%) palbociclib and ET
  229 (7.9%) ET alone
- None of the 176 deaths in the trial was related to study treatment

Adverse Events, incidence ≥ 15%

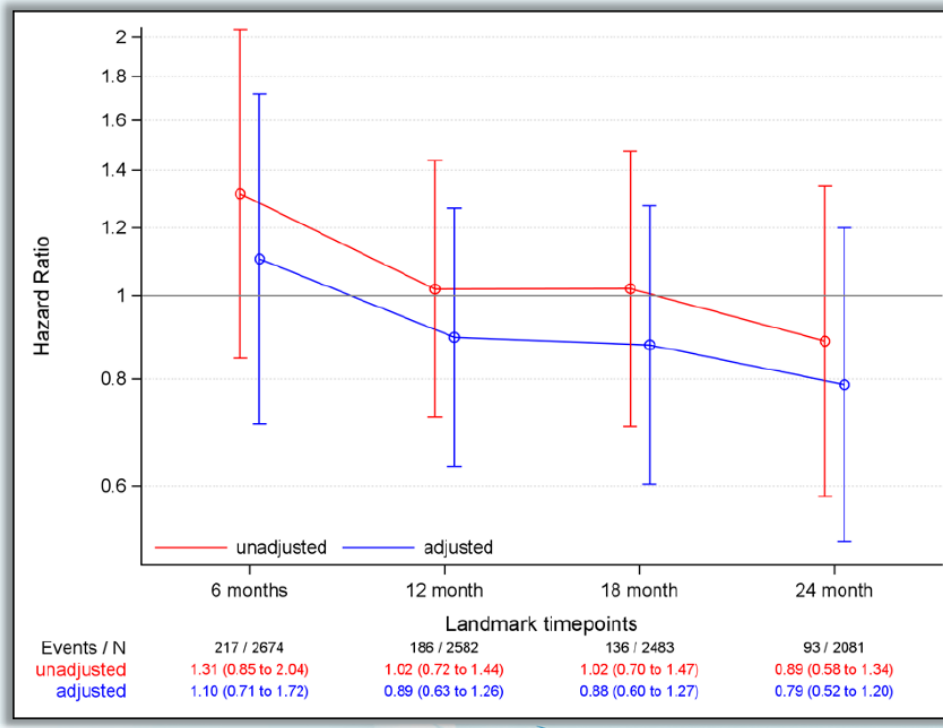
Adverse Event	Palbociclib + ET (N=2,841)			ET (N=2,902)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Any adverse event	2826 (99·5%)	1917 (67.5)	163 (5.7)	2604 (89·7%)	417 (14.4)	24 (0.8)
Neutropenia	2371 (83·5%)	1635 (57.6)	124 (4.4)	144 (5·0%)	11 (0.4)	0
Leukopenia	1566 (55·1%)	850 (29.9)	14 (0.5)	219 (7·5%)	3 (0.1)	0
Fatigue	1164 (41·0%)	60 (2.1)	0	560 (19·3%)	10 (0.3)	0
Arthralgia	1087 (38·3%)	32 (1.1)	0	1305 (45·0%)	35 (1.2)	0
Upper respiratory tract infection	839 (29·5%)	32 (1.1)	0	481 (16·6%)	4 (0.1)	0
Hot flush	704 (24·8%)	7 (0.2)	0	849 (29·3%)	7 (0.2)	0
Anaemia	669 (23·5%)	14 (0.5)	0	159 (5·5%)	4 (0.1)	0
Thrombocytopenia	619 (21·8%)	24 (0.8)	1 (0.0)	50 (1·7%)	1 (0.0)	0
Nausea	552 (19·4%)	7 (0.2)	0	242 (8·3%)	4 (0.1)	0
Alopecia	511 (18·0%)	0	0	149 (5·1%)	0	0
Diarrhoea	475 (16·7%)	21 (0.7)	0	150 (5·2%)	5 (0.2)	0
Headache	446 (15·7%)	8 (0.3)	0	338 (11·6%)	7 (0.2)	0

Safety population: Patients who initiated palbociclib vs. patients who initiated ET only

PALLAS: Treatment Exposure / Discontinuation

- Rates of palbociclib discontinuation were closely monitored
- Early discontinuation of palbociclib (competing risk analysis)
  - @6 months: 17.9%
  - @12 months: 30.2%
  - @18 months: 38.3%
  - @24 months: 44·9%
- Final analysis data confirm earlier result that **longer palbociclib duration** or **>70% dose intensity** **did not** markedly **improve iDFS**

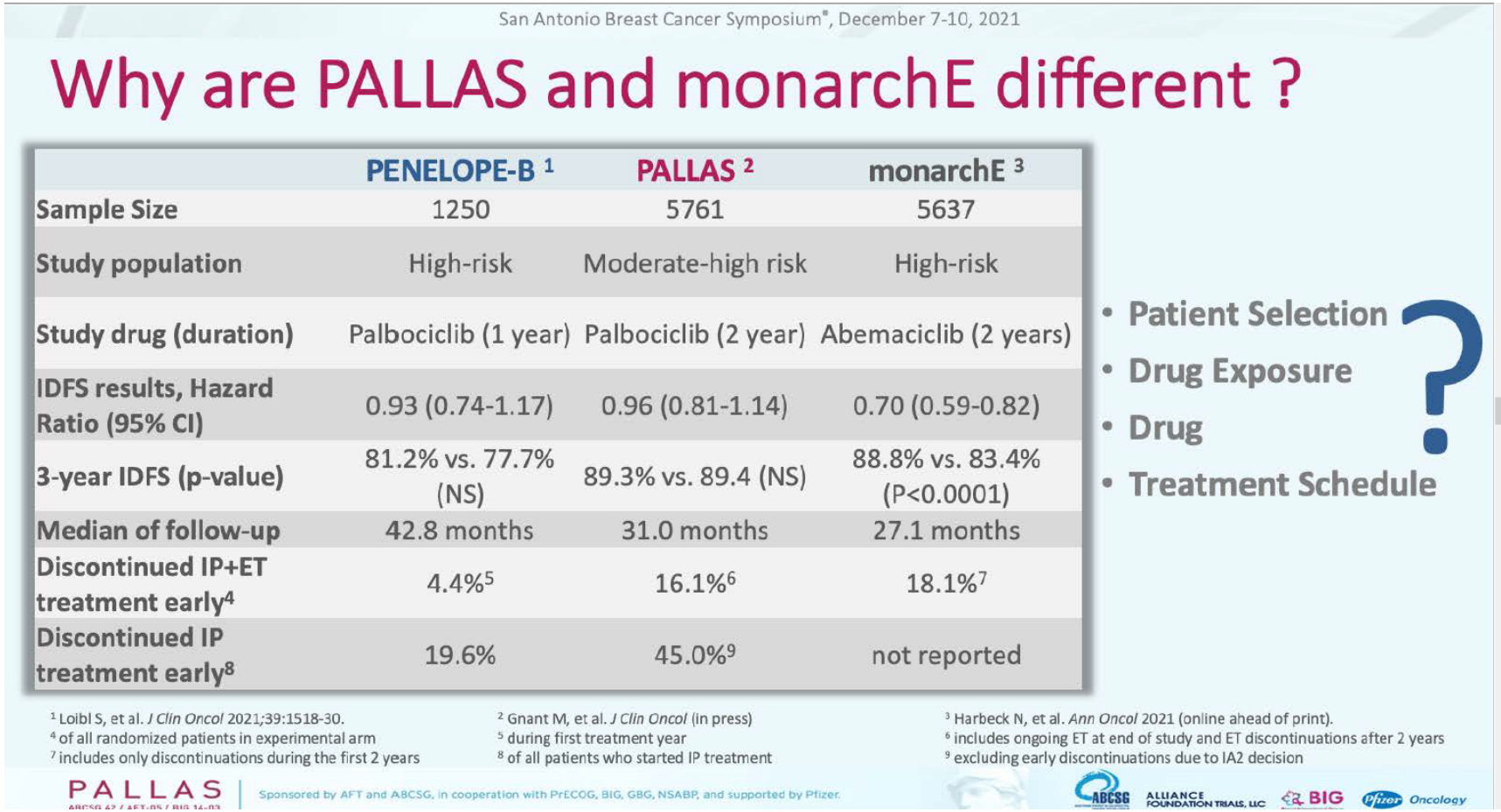
(Mayer EL et al, under revision)



PALLAS ABCSG 42 / AFT-05 / BIG 14-03 | Sponsored by AFT and ABCSG, in cooperation with PrECOG, BIG, GBG, NSABP, and supported by Pfizer.

Diskussion im Kontext anderer Studien - vgl SABCS 2020, hier

Gemeinschaftsklinikum Mittelrhein



	PENELOPE-B [1]	PALLAS [2]	monarchE [3]
Sample Size	1250	5761	5637
Study population	High-risk	Moderate-high risk	High-risk
Study drug (duration)	Palbociclib (1 year)	Palbociclib (2 year)	Abemaciclib (2 years)
IDFS results, Hazard Ratio (95% CI)	0.93 (0.74-1.17)	0.96 (0.81-1.14)	0.70 (0.59-0.82)
3-year IDFS (p-value)	81.2% vs. 77.7% (NS)	89.3% vs. 89.4 (NS)	88.8% vs. 83.4% (P<0.0001)
Median of follow-up	42.8 months	31.0 months	27.1 months
Discontinued IP+ET treatment early[4]	4.4%[5]	16.1%[6]	18.1%[7]
Discontinued IP treatment early[8]	19.6%	45.0%[9]	not reported

[1] Loibl S, et al. *J Clin Oncol* 2021;39:1518-30.
[2] Gnant M, et al. *J Clin Oncol* (in press)
[3] Harbeck N, et al. *Ann Oncol* 2021 (online ahead of print).
[4] of all randomized patients in experimental arm
[5] during first treatment year
[6] includes ongoing ET at end of study and ET discontinuations after 2 years
[7] includes only discontinuations during the first 2 years
[8] of all patients who started IP treatment
[9] excluding early discontinuations due to IA2 decision

GBG-Penelope: Post-Neoadj : negativ
monarchE: Adj. : positiv
Weitere Biomarkerstudien geplant : „Trans-PALLAS Projekt“

Fazit:
Pallas Studie

Gemeinschaftsklinikum Mittelrhein

- **Kein Vorteil für die Hinzunahme von Palbociclib zur AHT in der adjuvanten Situation**

GS1-08
„Metformin“ Studie

Gemeinschaftsklinikum Mittelrhein

Canadian Cancer Trials Group

CCTG MA.32

A Phase III Randomized Trial of the Effect of Metformin versus Placebo on Recurrence and Survival in Early-Stage Breast Cancer

CCTG Study Chair: Pamela Goodwin

CCTG Senior Investigator: Wendy Parulekar

CCTG Senior Biostatistician: Bingshu Chen

CCTG Study Coordinator: Paul Stos

Correlative Chair: Vuk Stambolic

Trial Committee Members: Karen Gelmon, Kathleen Pritchard, Timothy Whelan, Lois Shepherd, Jennifer Ligibel, Dawn Hershman, Ingrid Mayer, Timothy Hobday, Priya Rastogi, Dan Rea, Alastair Thompson, Judith Bliss, Manuela Rabaglio

Fatigue Substudy: Patti Ganz Mammographic Density Substudy: Marie Wood

GS1-08
„Metformin“ Studie
Hintergrund

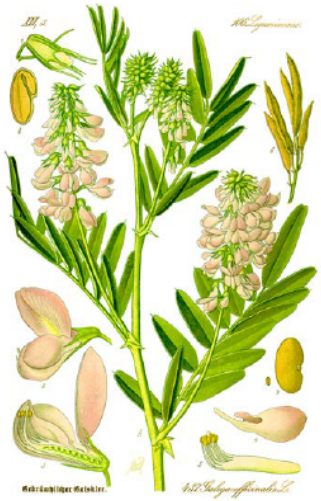
Gemeinschaftsklinikum Mittelrhein

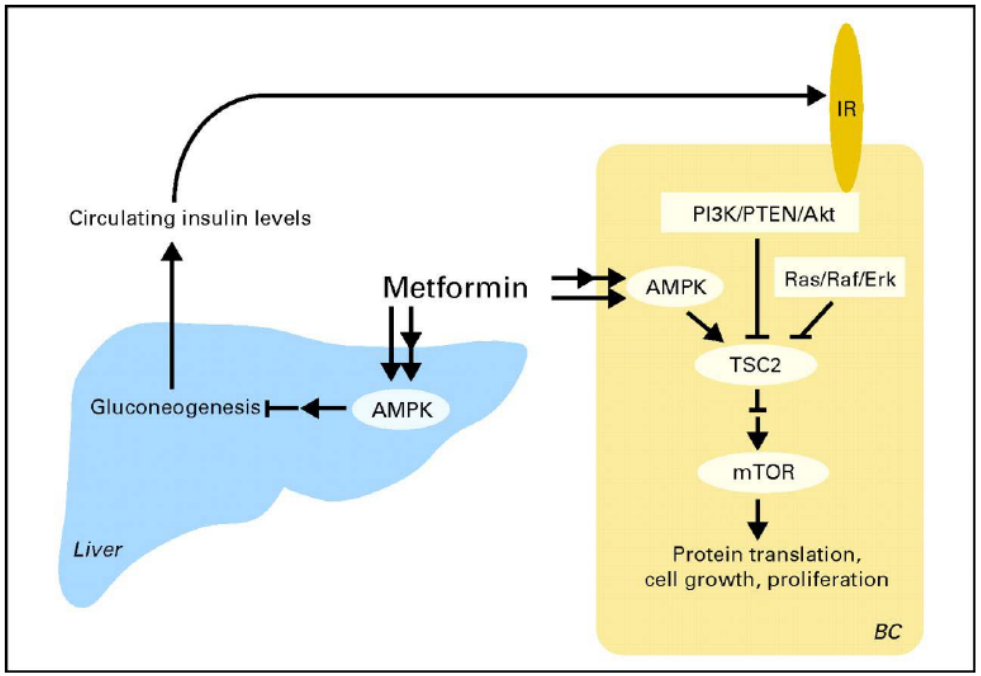
- **Übergewicht und hohe Insulinspiegel haben bekannte negative Effekte auf die Prognose beim Brustkrebs**

- **Metformin:**
  Senkt Insulinspiegel und fördert Gewichtsreduktion
  präklinische Studien mit Anti-Krebs Effekten : Ki67 Red., Tumorzellwachstum Red.

- **Hier:**
  Phase III Studie zum Einsatz in der adjuvanten Situation

Metformin As A Potential Anti-Cancer Agent





Adapted from Goodwin P J et al. J Clin Oncol 2009; 27:3271-3273

MA.32 Objectives

Primary objective:

To compare **invasive disease-free survival (IDFS)** between subjects treated with metformin (850 mg po bid for 5 years) versus placebo (bid for 5 years) in addition to standard breast cancer therapy

IDFS events: breast cancer recurrence (locoregional, distant), new primary cancer (breast, non-breast), death (any cause)

Secondary objective(s):

To analyze the effect of metformin vs placebo on:

- other BC outcomes (OS, DDFS, BCFI, BCSM, contralateral breast cancer)
- new diagnosis of diabetes mellitus or cardiovascular hospitalization/death
- adverse events ≥ grade 3
- BMI and circulating metabolic factors
- First 888 subjects: HRQOL (EORTC QLQ-C30), trial specific symptom checklist; diet, PA

Correlative Analyses – fasting blood (baseline, 6 and 60 months), tissue (cancer, normal breast)

Gemeinschaftsklinikum Mittelrhein

San Antonio Breast Cancer Symposium®, December 7-10, 2021

MA.32 Study Design

Population:
- 18-74 years of age
- Invasive BC dx within 1 year, excised with negative margins
- T1c-T3,N0-3,M0 (if T1cN0 ≥ 1 of: high grade/Ki67/Oncotype RS, ER/PgR -ve, HER2 +ve)
- Standard BC therapy
- Not diabetic, FBS ≤ 7 mmol/L= 126 mg/dl
- Adequate heart, liver, kidney fn
- ≤ 3 ETOH drinks/day, no hx lactic acidosis

Randomize 1: 1

Stratified for:
ER/PgR pos (≥1%) vs neg
BMI ≤ 30 vs > 30 kg/m^2
HER2 pos vs neg
Chemo – any vs none

Metformin 850 mg bid X 5 years (4 week ramp up of 850 mg daily)

Placebo one caplet bid X 5 years (4 week ramp up of one daily)

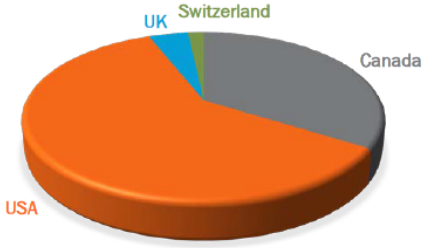
Follow-up
Recurrence
New Primary
Death

Fasting Blood – Baseline, 6 months, 60 months
Tumor and normal breast tissue (surgical specimen)
First 888: HRQOL, Symptoms, Diet, PA

PARTICIPATING GROUPS:

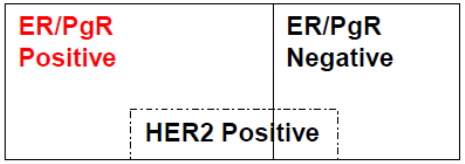
CCTG (co-ordinating)
ALLIANCE
ECOG/AKRIN
NRG
SWOG
CRUK
IBCSG

INTERNATIONAL ENROLMENT



Canadian Cancer Trials Group

1. **Primary Analysis**: ER/PgR positive BC (regardless of HER2 status)
2. **Follow-up of the Futility Result**: ER/PgR negative BC (regardless of HER2 status)
3. **Exploratory Analysis**: HER2 positive BC (regardless of ER/PgR status)



Gemeinschaftsklinikum Mittelrhein

San Antonio Breast Cancer Symposium®, December 7-10, 2021

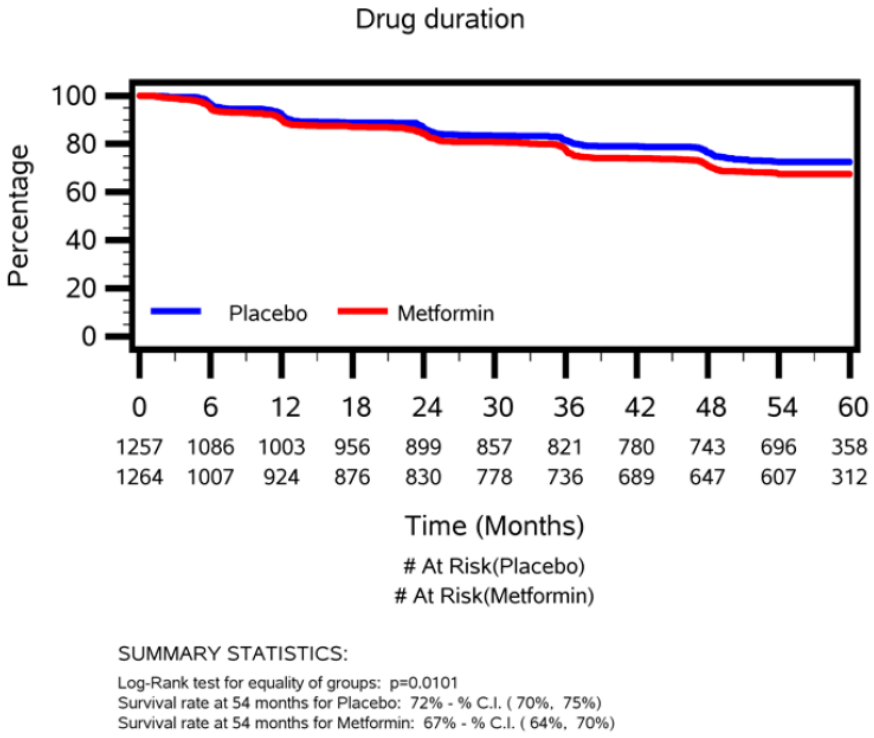
MA32 ER/PgR Positive Population n = 2553

	Metformin (n = 1268)	Placebo (n = 1265)
Age (years) - median (range)	52 (25-74)	53 (25-74)
BMI (kg/m^2) – mean (SD)	29.0 (6.8)	28.6 (6.1)
Postmenopausal	62.1%	60.2%
Race – White/Black/Asian/Other	92.1%/3.7%/2.4%/1.8%	91.2%/3.5%/2.6%/2.0%
ECOG PS - 0/1/2	80.9%/18.8%/0.3%	80.0%/19.8%/0.2%
T stage T1c	33.2%	32.4%
T2	52.5%	54.2%
T3	14.2% (0.1% T4)	13.4%
N stage N0	33.6%	32.9%
N1	33.8%	33.5%
N2	11.2%	10.8%
N3	4.7%	4.6%
Grade 1	12.9%	12.6%
2	44.9%	45.8%
3	41.7%	40.6%
HER 2 – Positive (97% received trastuzumab)	16.5%	17.4%
(Neo)Adjuvant Chemotherapy	84.9%	84.9%
Adjuvant Hormone Therapy	87.8%	87.8%
Adjuvant Radiation	73.8%	76.3%

Canadian Trials Group

Gemeinschaftsklinikum Mittelrhein

MA.32 Study Drug Compliance in ER/PgR Positive Subjects



SUMMARY STATISTICS:

Log-Rank test for equality of groups: p=0.0101
Survival rate at 54 months for Placebo: 72% - % C.I. (70%, 75%)
Survival rate at 54 months for Metformin: 67% - % C.I. (64%, 70%)

Canadian Cancer Trials Group

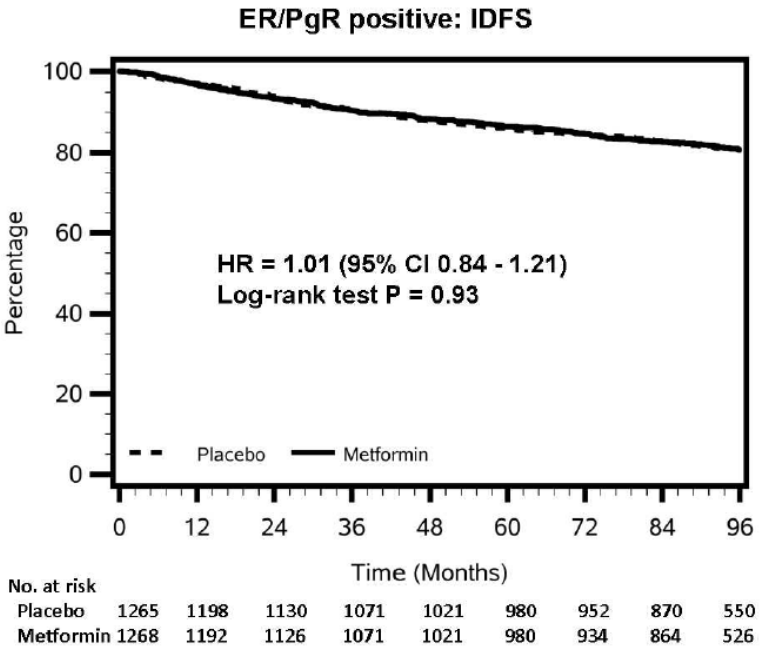
Gemeinschaftsklinikum Mittelrhein

San Antonio Breast Cancer Symposium®, December 7-10, 2021

MA.32: IDFS in ER/PgR Positive Subjects

75.6% of events were breast cancer related

	Metformin (n =1268)	Placebo (n = 1265)
Subjects with IDFS events	**234 (18.5%)**	**231 (18.3%)**
Distant recurrence	127 (10.0%)	129 (10.2%)
Local/regional recurrence	32 (2.5%)	39 (3.1%)
Contralateral invasive cancer	15 (1.2%)	9 (0.7%)
New primary cancer (non-breast)	49 (3.9%)	48 (3.8%)
Deaths		
Other primary malignancy	0 (0.0%)	1 (0.1%)
Cardiovascular disease	3 (0.2%)	1 (0.1%)
Other	8 (0.6%)	4 (0.4%)

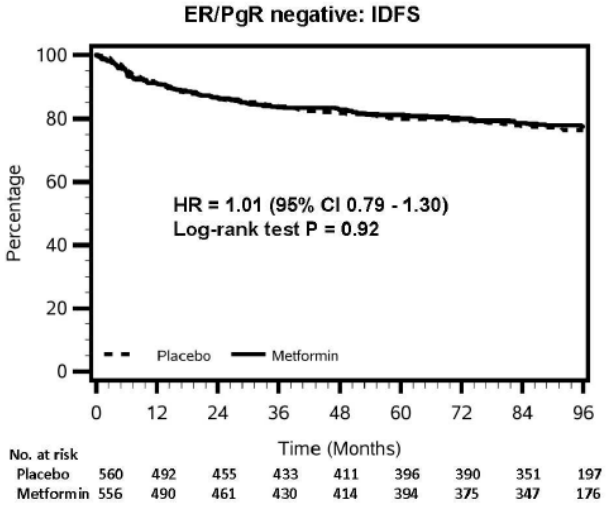


HR 1.01 (0.84-1.21), p = 0.93

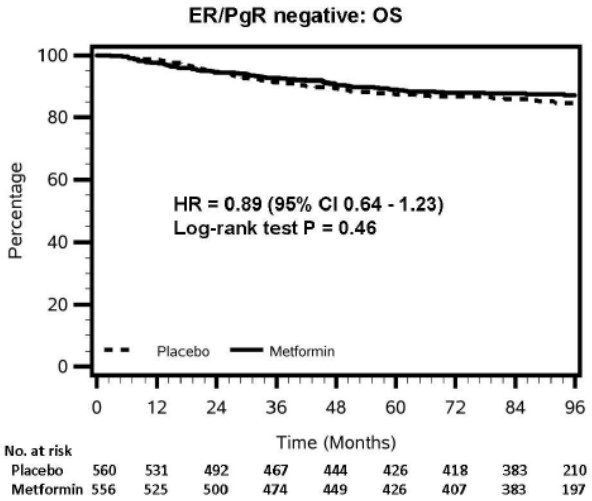
Canadian Cancer Trials Group

MA:32 ER/PgR Negative Breast Cancer (n = 1116)

- Futility was established at the second interim analysis with datalock at 29.5 months median follow-up after 172 IDFS events
- Study drug stopped at 36.7 months median exposure, blinding and follow-up continued
- At the current analysis there were 245 IDFS events with 96 months median follow-up



IDFS HR 1.01 (0.79-1.30), p = 0.92



OS HR 0.89 (0.64-1.23), p = 0.46

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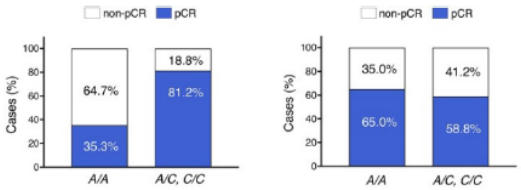
MA.32: HER2 Positive Breast Cancer

- **Exploratory analysis reflects**:
  - **Stratification** for HER2
  - Informed by results of a **24 week neoadjuvant study** (METTEN - Cuyas E Front Oncol 2019):
    - HER2 +ve BC treated with chemotherapy and trastuzumab ± metformin for 24 weeks
    - In those randomized to metformin, subjects with at least one C allele of a prespecified ATM associated **rs11212617 snp** (vs no C allele) experienced a significantly higher pCR than those with no C allele



Metformin Placebo

rs11212617 snp:

-Close to ATM gene with enhancer activity for ATM gene; associated with AMPK dependent and AMPK independent differential expression of thousand of genes (Luizon M et al PLOS 2016).

-Associated with metformin benefit on glucose control in diabetes

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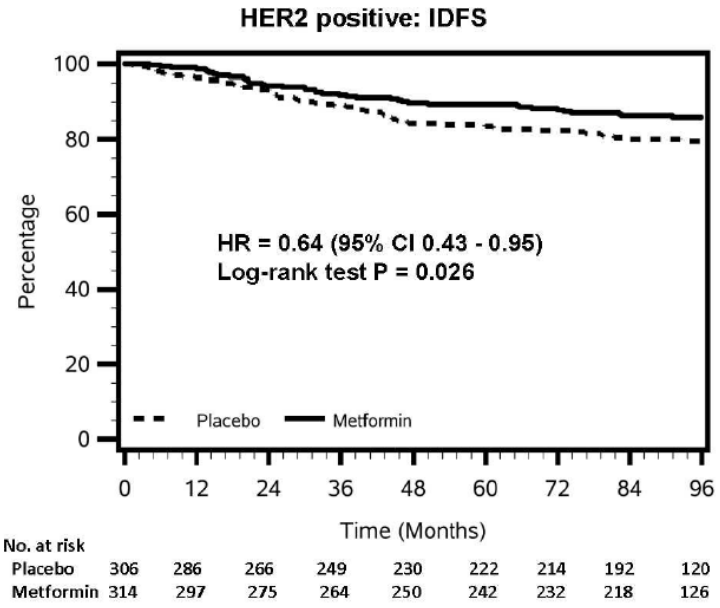
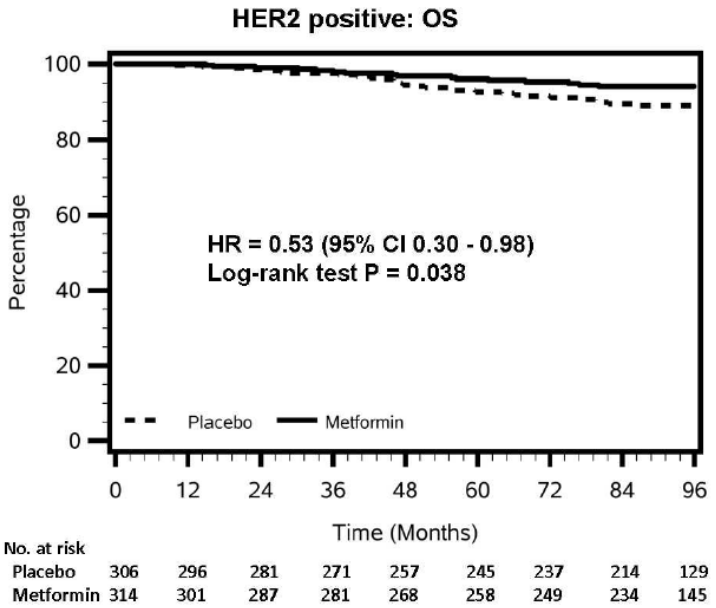
MA.32: ALL HER 2 + IDFS and OS (n = 620)





HR 0.64 (0.43- 0.95), p = 0.03

HR 0.53 (0.30- 0.98), p = 0.04

Canadian Cancer Trials Group

MA.32: Conclusions in HER2 Positive Subjects

Subjects with HER2+ BC (notably those with at least one "C" allele of the ATM associated rs 11212617 snp) experienced improved IDFS and OS with metformin, consistent with reported metformin effects on pCR in the neoadjuvant setting.

No p-value "spend" was allocated to this comparison; as a result, it requires replication in a prospective trial focusing on the HER2 positive population.

Fazit:
GS1-08: „Metformin“ Studie

Gemeinschaftsklinikum Mittelrhein

- **Keine Verbesserung von Überlebensdaten durch Metformin bei HR+ und HR – Brustkrebs**
- **Möglicher schwacher Vorteil beim HER2+ MaCa (Subtyp / Allel)**
- **Kein Einsatz empfohlen**
- **Gewichtsreduktion und körperliche Aktivität bleiben wichtig – nicht ersetzbar durch Metformin**

Gemeinschaftsklinikum Mittelrhein

San Antonio Breast Cancer Symposium®, December 7-10, 2021

Aromatase inhibitors versus tamoxifen in pre-menopausal women with ER+ early stage breast cancer treated with ovarian suppression: A patient level meta-analysis of 7,030 women in four randomised trials

Rosie Bradley, Jeremy Braybrooke, Richard Gray, Robert Hills, Zulian Liu, Hongchao Pan, Richard Peto, David Dodwell, Paul McGale, Carolyn Taylor, Jonas Bergh, Sandra Swain, Prudence A Francis, Michael Gnant, Francesco Perrone, Meredith M Regan, for the

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)

GS2-04
Metaanalyse, Oxford Studiengruppe
Hintergrund

Gemeinschaftsklinikum Mittelrhein

- **Tamoxifen reduziert die Brustkrebsmortalität beim ER+ nach 15 Jahren um ein Drittel (EBCTCG , Lancet 2011)**
- **In der Postmenopause sind AI noch effektiver (EBCTG, Lancet 2015)**
- **Prämenopausale Pat. können von ovarieller Suppression profitieren**
- **Hier:**
- **Profitieren prämenopausale Frauen von GnRH + AI gegenüber GnRH + Tamoxifen ?**

Methods

- Meta-analysis of individual patient data for 4 trials of pre-menopausal women with early stage breast cancer treated with OFS, randomised to AI or tamoxifen

- Primary outcomes were recurrence and cause specific mortality analysed by standard EBCTCG* methods

- $2p<0.05$ for primary outcomes
- $2p<0.01$ for subgroup analyses

*EBCTCG 1990

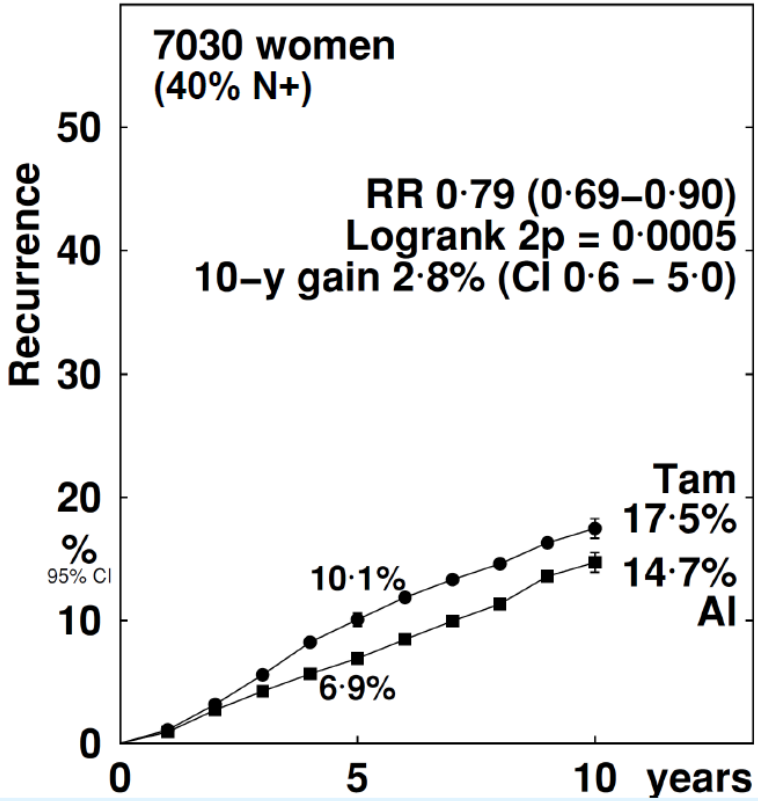
Trials

Trial	Year started	Comparison	N	Median FU
ABCSG 12	1999	Goserelin: (anastrozole vs tamoxifen) ± zoledronic acid x 3yrs	1694	8.0yrs
TEXT	2003	Triptorelin: (exemestane vs tamoxifen) x 5yrs	2635	9.1yrs
SOFT	2003	Triptorelin: (exemestane vs tamoxifen) x 5yrs	1998	7.9yrs
HOBOE	2004	Triptorelin: (letrozole vs tamoxifen) x 5yrs	703	5.3yrs
Total			7030	8.0yrs

Chemotherapy by trial

- ABCSG 12: only neo-adjuvant allowed (5%)
- TEXT: optional, concurrently with OFS (60%)
- SOFT: before randomisation but patient had to remain pre-menopausal after completion (54%)
- HOBOE: before randomisation (63%)

Recurrence



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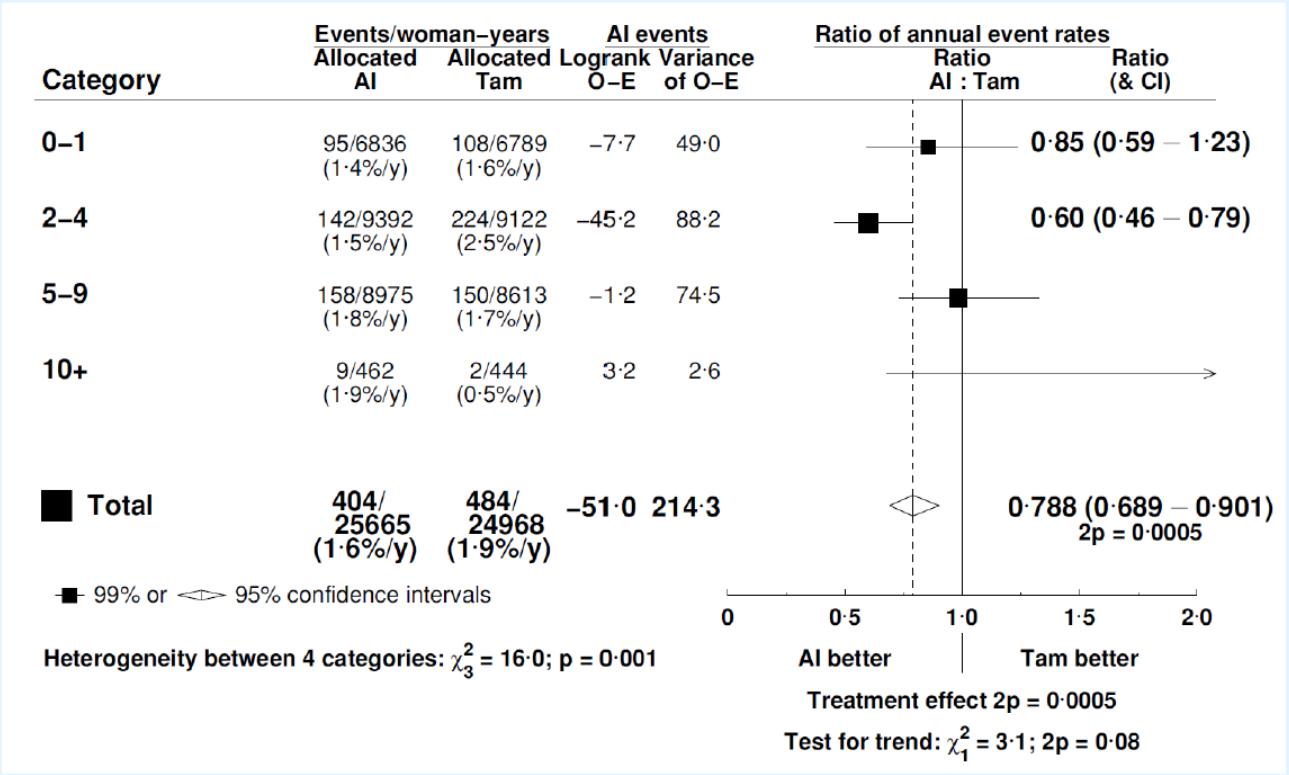
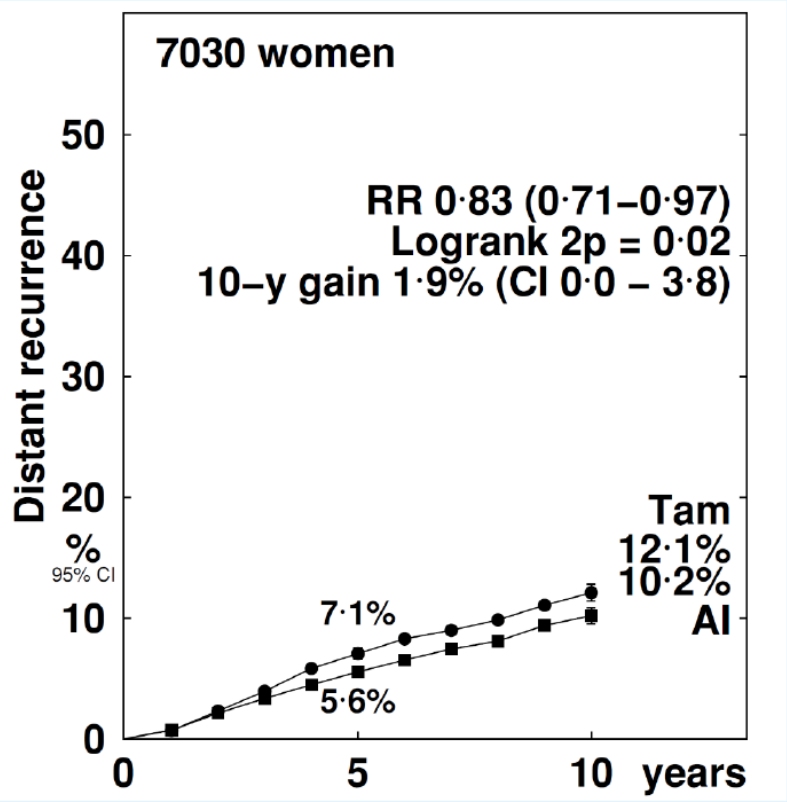
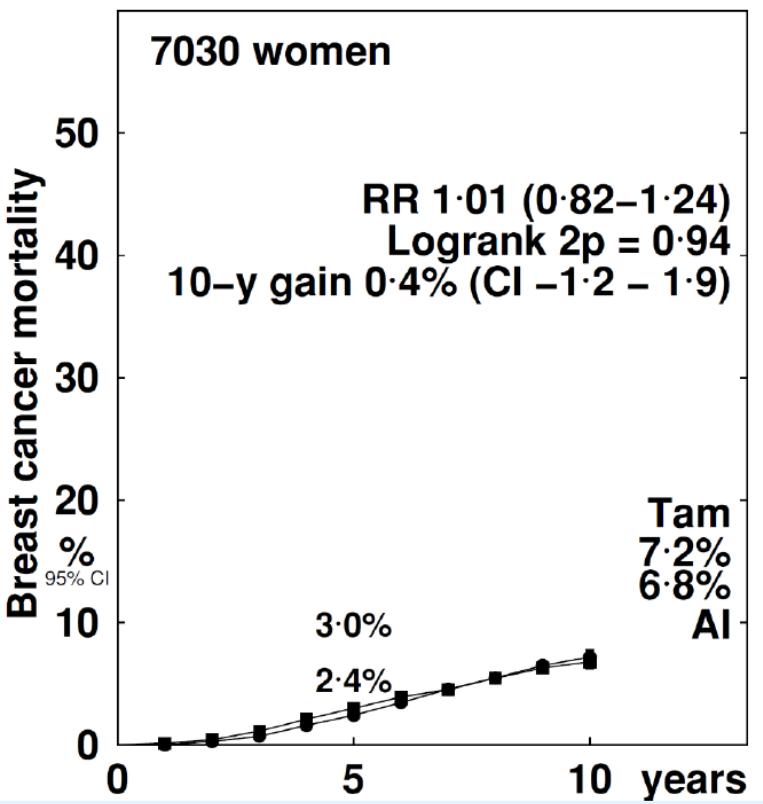
Recurrence by follow up period



Distant recurrence



BC mortality



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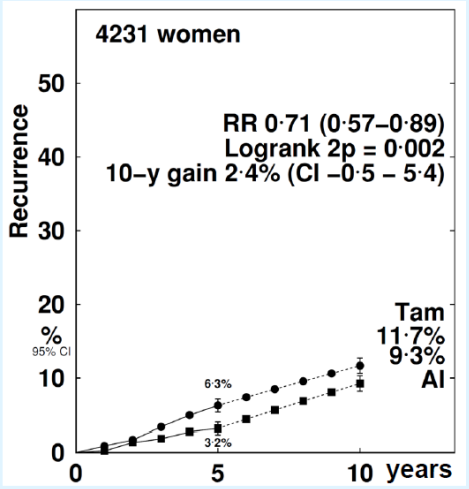
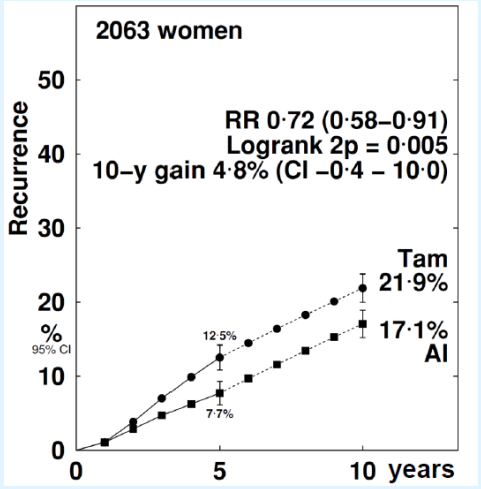
Recurrence by nodal status*

N0



N1-3

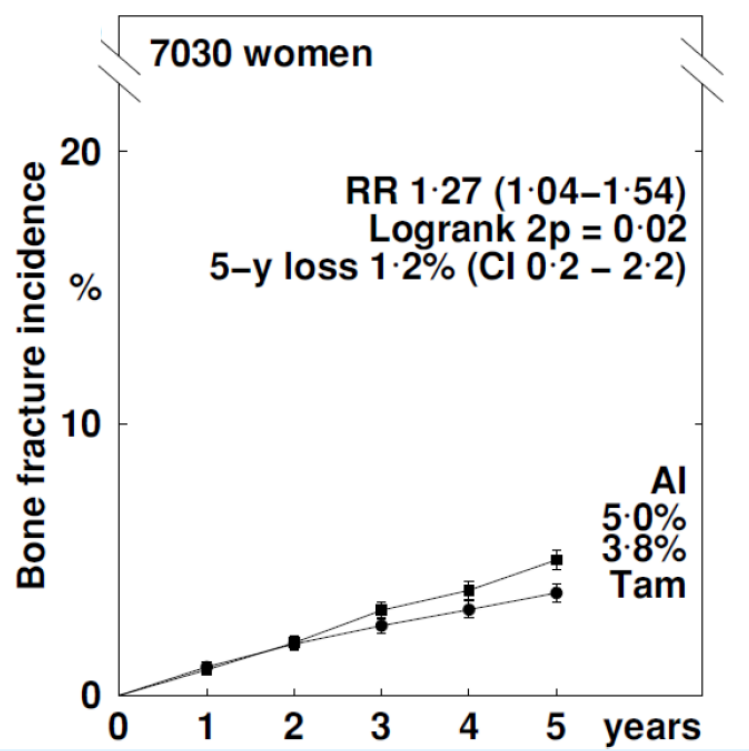


*Smoothed from 5 years

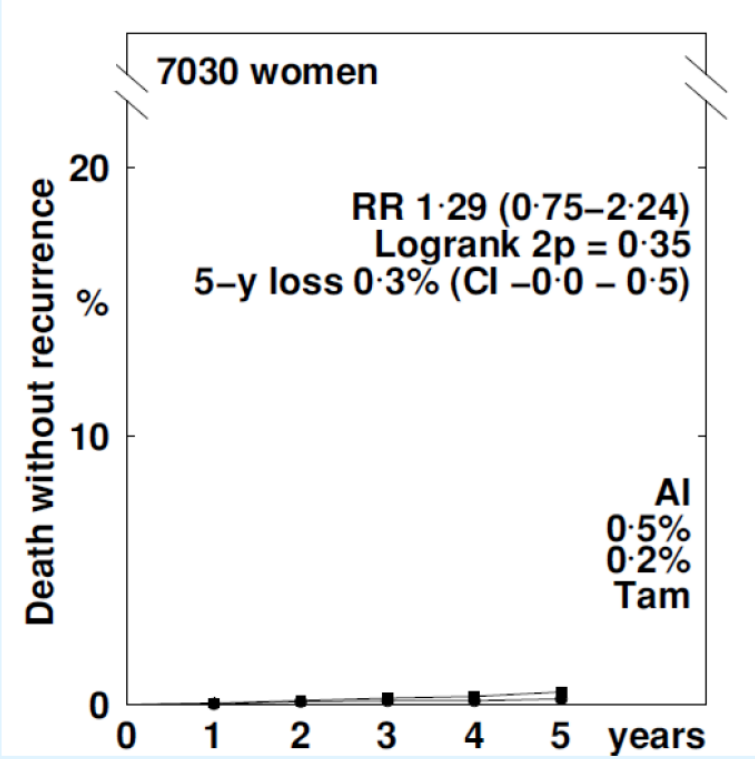
Gemeinschaftsklinikum Mittelrhein

San Antonio Breast Cancer Symposium®, December 7-10, 2021

Bone fractures



Non-breast cancer death



Fazit
GS2-04 Oxford Metaanalyse

Gemeinschaftsklinikum Mittelrhein

- GnRh + AI in der Prämenopause reduziert das Risiko eines Rezidivs gegenüber GnRH + Tamoxifen um ca. 21 %
- Kein Effekt auf Mortalität bislang (Follow up)
- Keine Zunahme der nicht brustkrebsabhängigen Todesfälle
- Mehr Frakturen in der AI Gruppe

GS2-05

Gemeinschaftsklinikum Mittelrhein

IBCSG International Breast Cancer Study Group

BIG Breast International Group

NCI National Clinical Trials Network
a National Cancer Institute program

Randomized comparisons of adjuvant exemestane + ovarian function suppression (OFS) vs tamoxifen + OFS vs tamoxifen in premenopausal women with HR+ early breast cancer: update of the TEXT and SOFT trials

Meredith M. Regan, BA Walley, GF Fleming, PA Francis, O Pagani,
I Láng, HL Gómez, C Tondini, HJ Burstein, MP Goetz, E Ciruelos, V Stearns, H Bonnefoi, S Martino,
CE Geyer Jr, C Chini, AM Minisini, S Spazzapan, T Ruhstaller, EP Winer, B Ruepp, M Bellet, A Bernardo,
MA Climent, B Bermejo, NE Davidson, JN Ingle, RE Coleman, B Müller, F Le Du, S Loibl,
M Colleoni, A Di Leo, S Loi, RD Gelber, AS Coates, A Goldhirsch
SOFT and TEXT Investigators

SABCS December 2021

GS2-05
Update SOFT / TEXT Studie
Hintergrund

Gemeinschaftsklinikum Mittelrhein

- Bisher bekannt aus früherer Analyse:
- Kombinierte SOFT / TEXT Analyse nach 9 Jahren Follow-UP:

- prämenopausal, frühes CA:

→ GnRH zusätzlich zu TAM: Reduktion Rezidivrisio + Tod

→ GnRH + EXE. vs. GnRh + TAM : weitere Reduktion des distanten ´ Rezidivs , aber nicht Tod

- Absoluter Benefit abhängig vom Basis - Risiko
- Niedrigrisiko –Tumoren mit TAM alleine ausreichend gut behandelt

- Heute vorgestellt :
- Spätrezidive sind typisch für HR + MaCa : daher Langzeitdaten wichtig

- Aktuelle Analyse nach 13 Jahren medianem Follow Up

Gemeinschaftsklinikum Mittelrhein

TEXT and SOFT Designs

Enrolled: Nov'03-Apr'11

- Premenopausal HR+
- ≤12 wks after surgery
- Planned OFS
- No planned chemo (N=1053) *OR* planned chemo (N=1607)

RANDOMIZE

TEXT (N=2672)

→ Tamoxifen+OFS x 5y

→ Exemestane+OFS x 5y

- Premenopausal HR+
- ≤12 wks after surgery
- No chemo (N=1419)

OR

- Remain premenopausal ≤8 mos after chemo (N=1628)

RANDOMIZE

SOFT (N=3066)

→ Tamoxifen x 5y

→ Tamoxifen+OFS x 5y

→ Exemestane+OFS x 5y

Median follow-up 12 years

1e: OFS Question

2e: E+OFS vs T

OFS=ovarian function suppression, by GnRH analogue triptorelin or oophorectomy

Tamoxifem and **EX**emestane **T**rial : **TEXT**
Suppression **O**f Ovarian **F**unction **T**rial : **SOFT**

TEXT and SOFT Designs

Enrolled: Nov'03-Apr'11

- Premenopausal HR+
- ≤12 wks after surgery
- Planned OFS
- No planned chemo (N=1053) *OR* planned chemo (N=1607)

RANDOMIZE

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- ≤12 wks after surgery
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OR

- Remain premenopausal ≤8 mos after chemo (N=1628)

RANDOMIZE

SOFT (N=3066)

→ Tamoxifen x 5y

→ Tamoxifen+OFS x 5y

→ Exemestane+OFS x 5y

AI Question (N=4690)

Tamoxifen+OFS x 5y

Exemestane+OFS x 5y

Median follow-up 13 years

OFS=ovarian function suppression, by GnRH analogue triptorelin or oophorectomy

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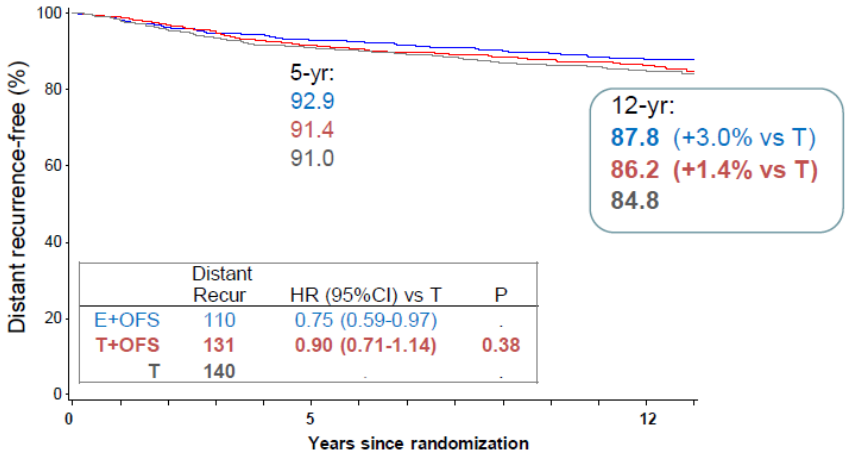
OFS Question: SOFT Overall Population

35% LN+; 12 years median follow-up

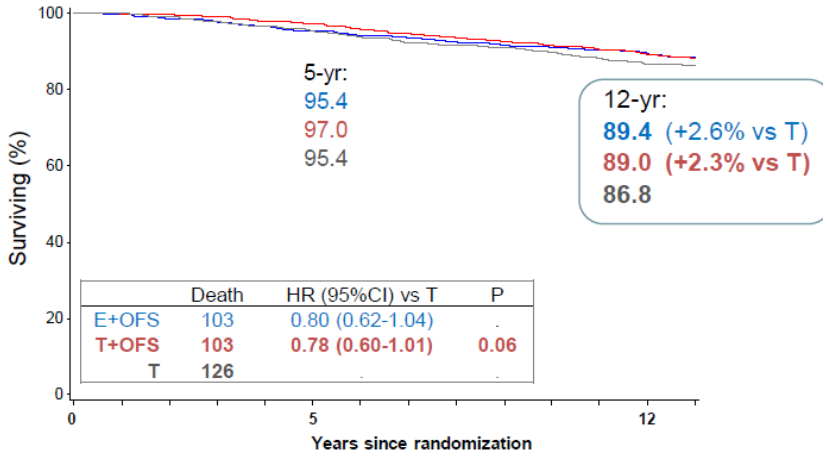
Distant Recurrence-free Interval



	Distant Recur	HR (95%CI) vs T	P
E+OFS	110	0.75 (0.59-0.97)	.
T+OFS	131	0.90 (0.71-1.14)	0.38
T	140	.	.

	0-5 years		>5 years	
	Recur	HR (95% CI) vs T	Recur	HR (95% CI) vs T
E+OFS:	68	0.76 (0.55-1.04)	42	0.74 (0.50-1.12)
T+OFS:	83	0.93 (0.69-1.25)	48	0.85 (0.58-1.26)
T:	87	.	53	.
At risk:	3047 pts	13787 pyfu	2521 pts	16343 pyfu

Overall Survival



	Death	HR (95%CI) vs T	P
E+OFS	103	0.80 (0.62-1.04)	.
T+OFS	103	0.78 (0.60-1.01)	0.06
T	126	.	.

	0-5 years		>5 years	
	Deaths	HR (95% CI) vs T	Deaths	HR (95% CI) vs T
E+OFS:	45	1.00 (0.66-1.51)	58	0.70 (0.50-0.98)
T+OFS:	29	0.63 (0.40-1.01)	74	0.86 (0.63-1.18)
T:	45	.	81	.
At risk:	3047 pts	14524 pyfu	2745 pts	18383 pyfu

T+OFS vs T: absolute reductions in distant recurrence and death 1.4% and 2.3% at 12 years

E+OFS vs T: absolute reductions in distant recurrence and death 3.0% and 2.6% at 12 years

pyfu=person-years follow-up

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AI Question: SOFT+TEXT Overall Populations

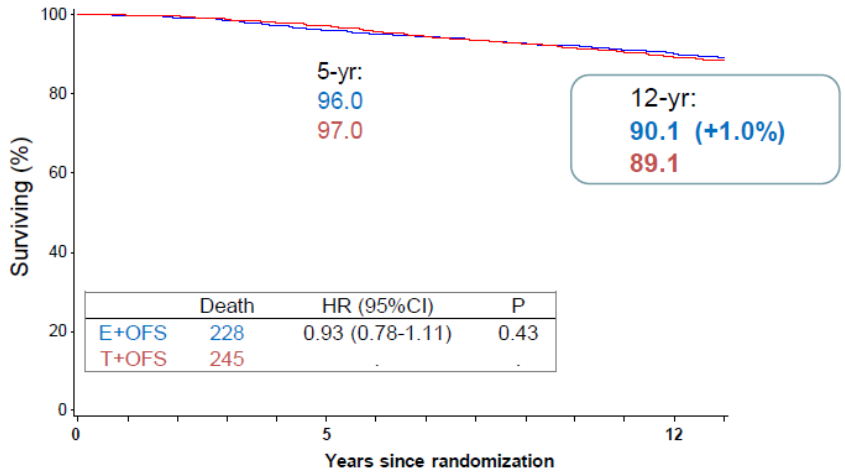
42% LN+; 13 years median follow-up

Distant Recurrence-free Interval

	Distant Recur	HR (95%CI)	P
E+OFS	249	0.83 (0.70-0.98)	0.03
T+OFS	295	.	.

	0-5 years		>5 years	
	Recur	HR (95% CI)	Recur	HR (95% CI)
E+OFS:	139	0.78 (0.63-0.98)	110	0.90 (0.70-1.17)
T+OFS:	175	.	120	.
.	.	.	.	.
At risk:	4690 pts	21535 pyfu	3947 pts	26891 pyfu

Overall Survival



	Death	HR (95%CI)	P
E+OFS	228	0.93 (0.78-1.11)	0.43
T+OFS	245	.	.

	0-5 years		>5 years	
	Deaths	HR (95% CI)	Deaths	HR (95% CI)
E+OFS:	91	1.34 (0.98-1.84)	137	0.77 (0.62-0.97)
T+OFS:	68	.	177	.
.	.	.	.	.
At risk:	4690 pts	22467 pyfu	4283 pts	30294 pyfu

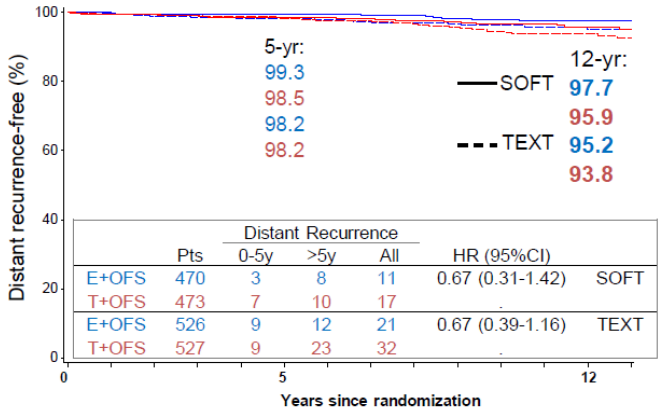
E+OFS vs T+OFS: absolute reduction in distant recurrence, 1.8% at 12 years
absolute reduction in death, 1.0% at 12 years

pyfu=person-years follow-up

SOFT+TEXT No Chemotherapy Cohorts

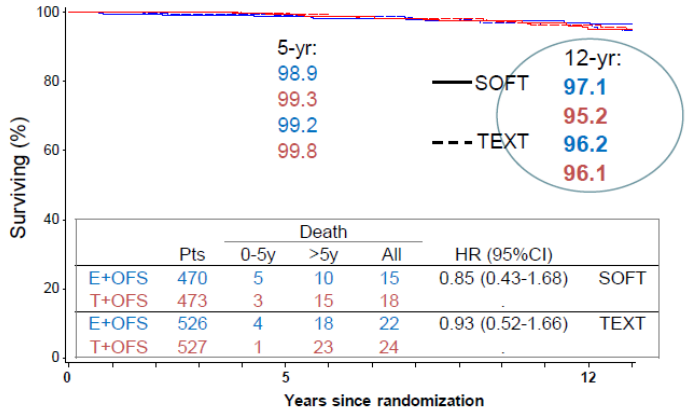
9% & 21% LN+; 13 years median follow-up

Distant Recurrence-free Interval



	Pts	Distant Recurrence 0-5y	>5y	All	HR (95%CI)	
E+OFS	470	3	8	11	0.67 (0.31-1.42)	SOFT
T+OFS	473	7	10	17	.	
E+OFS	526	9	12	21	0.67 (0.39-1.16)	TEXT
T+OFS	527	9	23	32	.	

Overall Survival



	Pts	Death 0-5y	>5y	All	HR (95%CI)	
E+OFS	470	5	10	15	0.85 (0.43-1.68)	SOFT
T+OFS	473	3	15	18	.	
E+OFS	526	4	18	22	0.93 (0.52-1.66)	TEXT
T+OFS	527	1	23	24	.	

>95% of women surviving at 12 years
70% deaths after a BC event

Numbers of deaths, relative to a BC event or 2nd (non-breast) cancer

SOFT	All Deaths	After BC Event	2nd Cancer	No Cancer	Unkn. Cancer
E+OFS	15	7	4	2	2
T+OFS	18	10	4	1	3
TEXT					
E+OFS	22	19	2	0	1
T+OFS	24	19	2	3	0

Unkn (unknown)=death with no information about breast or 2nd (non-breast) cancer event

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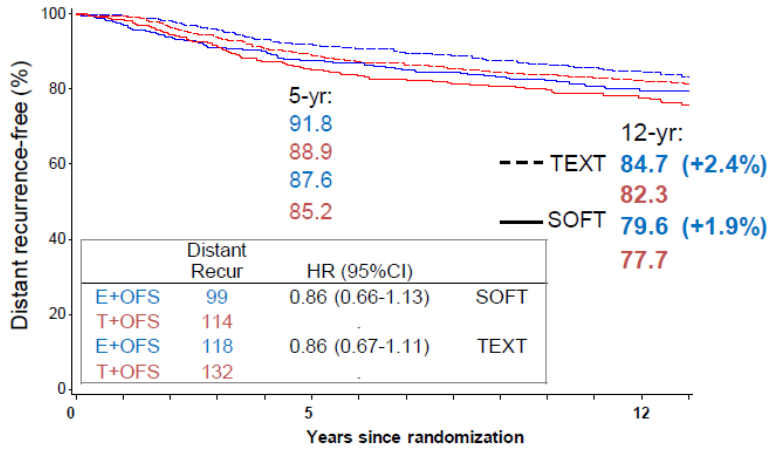
SOFT+TEXT Chemotherapy Cohorts

57% & 66% LN+; 13 years median follow-up

Distant Recurrence-free Interval



	Distant Recur	HR (95%CI)	
E+OFS	99	0.86 (0.66-1.13)	SOFT
T+OFS	114	.	
E+OFS	118	0.86 (0.67-1.11)	TEXT
T+OFS	132	.	

		0-5 years		>5 years	
		Recur	HR (95% CI)	Recur	HR (95% CI)
SOFT	E+OFS:	65	0.85 (0.61-1.19)	34	0.88 (0.56-1.41)
	T+OFS:	76	.	38	.
TEXT	E+OFS:	62	0.73 (0.52-1.01)	56	1.10 (0.75-1.61)
	T+OFS:	83	.	49	.
	At risk:	2694 pts	12086 pyfu	2166 pts	14702 pyfu

Overall Survival

	Death	HR (95%CI)	
E+OFS	88	1.06 (0.79-1.43)	SOFT
T+OFS	85	.	
E+OFS	103	0.85 (0.65-1.11)	TEXT
T+OFS	118	.	

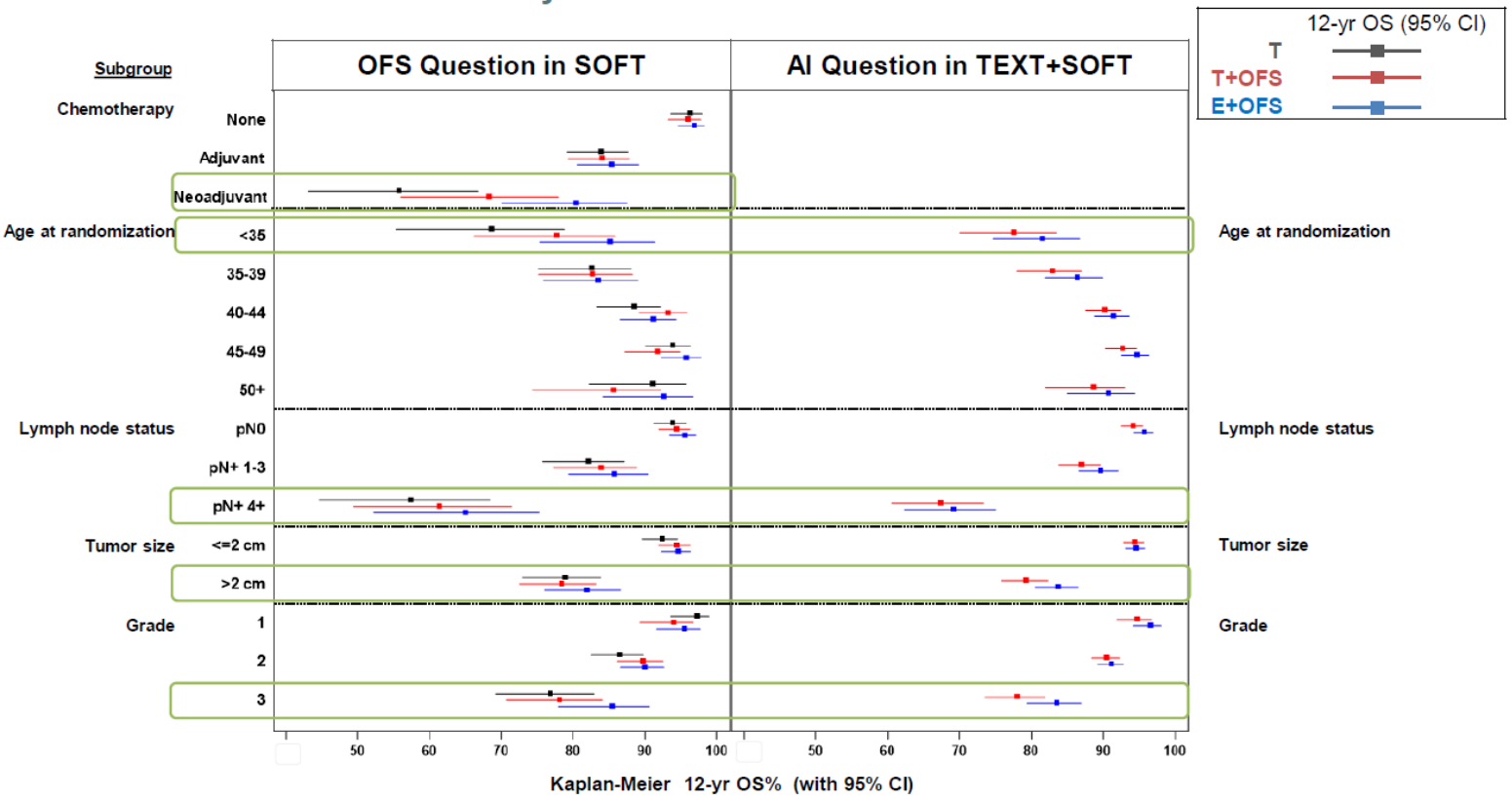
		0-5 years		>5 years	
		Deaths	HR (95% CI)	Deaths	HR (95% CI)
SOFT	E+OFS:	40	1.57 (0.96-2.57)	48	0.84 (0.57-1.22)
	T+OFS:	26	.	59	.
TEXT	E+OFS:	42	1.10 (0.71-1.70)	61	0.74 (0.53-1.03)
	T+OFS:	38	.	80	.
	At risk:	2694 pts	12774 pyfu	2395 pts	16928 pyfu

E+OFS vs T+OFS: reductions in distant recurrence 1.9% SOFT and 2.4% TEXT at 12 years overall survival, -0.7% SOFT and +2.6% TEXT at 12 years

pyfu=person-years follow-up

Overall Survival in Subgroups with HER2-negative Cancers

12-year Overall Survival



GS2-05
SOFT / TEXT Metaanalyse
Fazit

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- **Späte Metastasierung und Todesfälle bei prämen. HR + Karzinomen**

- **Bedeutsame rel. Risikoreduktion für Metastasierung und Tod durch GnRH + Tam vs Tam alleine : insbesondere bei hohem klinischen Risiko**
- **Niedrigrisiko-Pat (N-, keine CHT) : durch alle Therapien gut behandelt – dann hohe Überlebensraten**

- **Vorteil (Red. Fernmetastasen): GnRH + EXE vs GnRH + TAM im Risikokollektiv , insbes. nach Chemoth.**

  (vgl analog / konsistent zu AI vs Tam bei postmen. Pat.)

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Adjuvante endokrine Therapie bei prämenopausalen Patientinnen (Jahr 1–5)

	Oxford LoE	GR	AGO
▪ Tamoxifen 5 Jahre (niedriges Rezidivrisiko)	1a	A	++
▪ Tamoxifen + OFS 2-5 Jahre (höheres Rezidivrisiko)*	2b	C	++
▪ AI + OFS# über 5 Jahre (höheres Rezidivrisiko)*	1b	B	+
▪ GnRHa Monotherapie (Bei relevanten Kontraindikationen für Tam, gegenüber keiner Therapie)	1a	B	+

OFS: Ovarialfunktions-Suppression;

* Behandlung nur solange sie tolerabel ist und die Pat. eindeutig prämenopausal ist
Bei Z.n. Chemotherapie bei Wiedereintritt der Ovarialfunktion innerhalb von 24 Monaten
Die Applikation einer Chemotherapie war in den Studien ein Surrogatmarker für hohes Rezidivrisiko

\# AI NUR in Kombination mit OFS bei prämenopausalen Patientinnen

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San Antonio Breast Cancer Symposium®, December 7-10, 2021

Taxane with anthracycline versus taxane without anthracycline: a patient level meta-analysis

Jeremy Braybrooke, Rosie Bradley, Richard Gray, Robert Hills, Zulian Liu, Hongchao Pan, Richard Peto, Joanne Blum, Xiaosong Chen, Bent Ejlertsen, Wolfgang Janni, Ulrike Nitz, Dennis Slamon, Masakazu Toi, Toru Watanabe, Zhi-Ming Shao, Ke-Da Yu, Sandra Swain, Jonas Bergh, for the

Early Breast Cancer Trialists' Collaborative Group

GS2-06:
Metaanalyse: Taxane +/- Anthracycl.
Hintergrund:

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- Gabe von Taxan + Anthracyc. Chemotherapie vs. keine Chemoth. reduziert die Brustkrebssterblichkeit beim frühen Ca um ca. ein Drittel (EBCTCG , Lancet 2012)

- Bekannte NW :
  → Anthracyl. : Kardiovaskulär, Leukämie
  → Taxane :Neuropathie

- Zunehmende Anwendung von anthracyclinfreien Regimen

- Hier:
- Führt die Verwendung von Anthracyclinen zu einer höheren Effektivität ?

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Trial Comparisons

	Comparisons	No. people	No. Trials with data
(A)	6 x concurrent anth + docetaxel + cyclophosph. vs 6 x **SAME** dose docetaxel plus cyclophosph.	**2,469**	**3**
(B)	Sequential anthracycline / taxane vs **HIGHER** cumulative dose docetaxel plus cyclophosph.	**11,386**	**8**
(C)	Taxane plus anthracycline versus **HIGHER** cumulative dose taxane +/- capecitabine	**1,552**	**3**
(D)	Taxane plus anthracycline versus **HIGHER** cumulative dose taxane plus carboplatin	**2,796**	**2**
	Total	**18,203**	**16**

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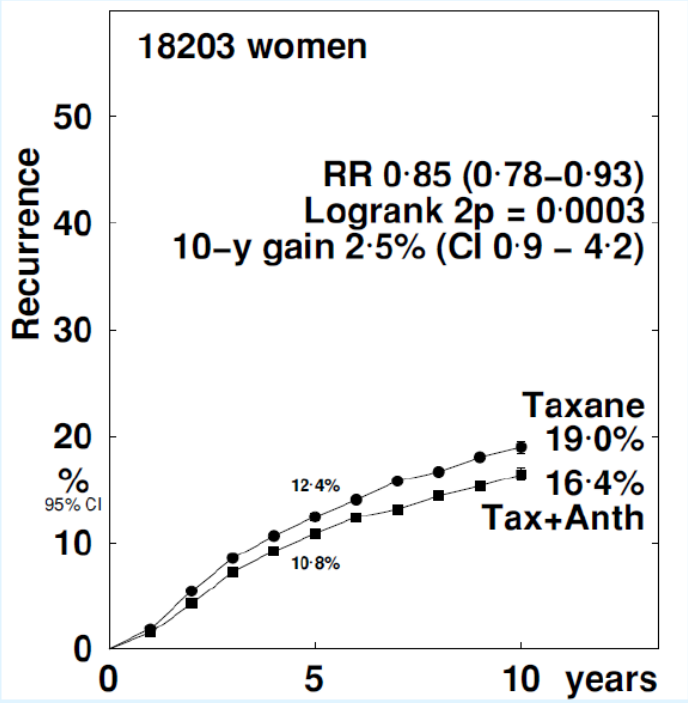
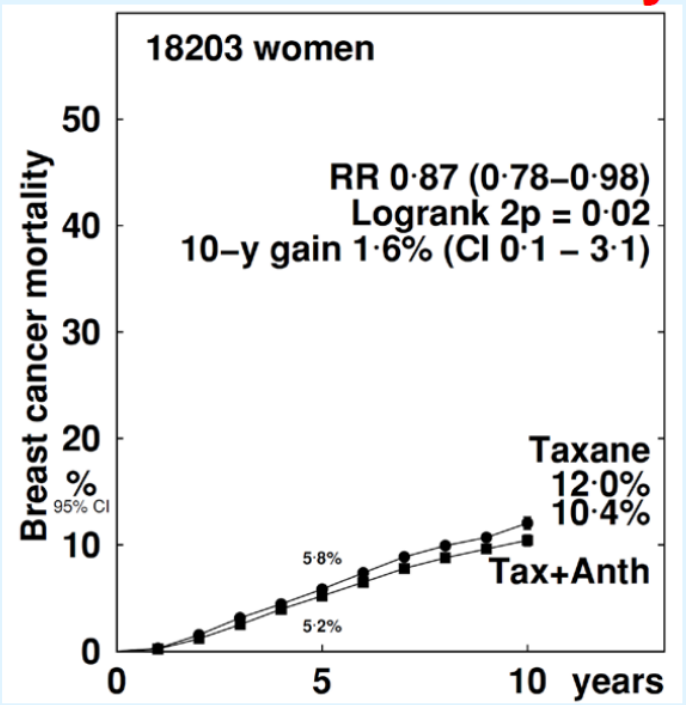
Combined analysis – all 16 trials (A – D)

Recurrence



Breast cancer mortality



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Taxane WITH Anthracycline Vs. Docetaxel plus Cyclophosphamide (A-B)

	Comparisons	Cumulative Anthracycline (mg/m^2)	Cumulative docetaxel (mg/m^2)
(A)	6 x <u>concurrent</u> anth + docetaxel + cyclophosph. vs 6 x **SAME** dose docetaxel plus cyclophosph.	**Doxorubicin ≈300**	**450 vs 450**
(B)	<u>Sequential</u> anthracycline / taxane vs **HIGHER** cumulative dose docetaxel plus cyclophosph.	**Epirubicin ≈300**	**≈300 vs 450**

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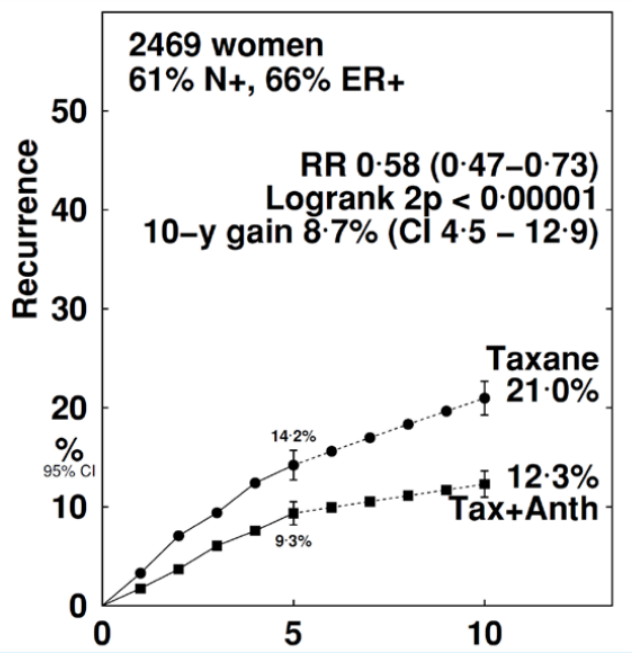
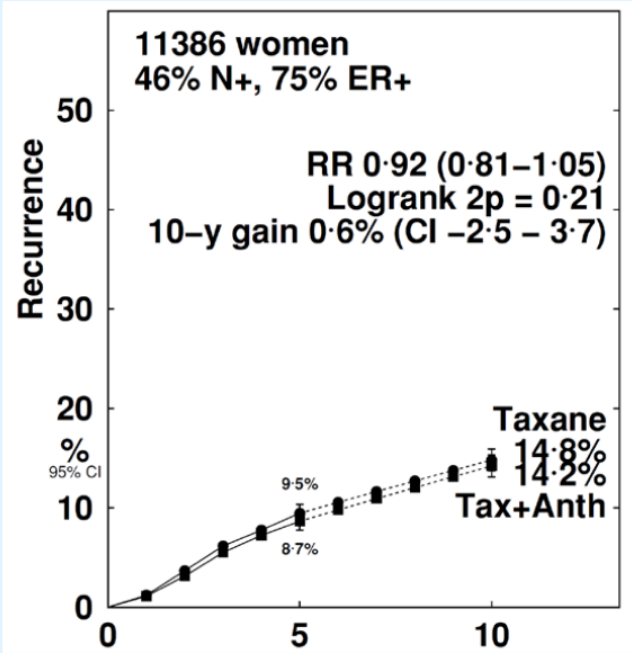
Comparison (A) versus (B)

Recurrence

(A) Concurrent



(B) Sequential



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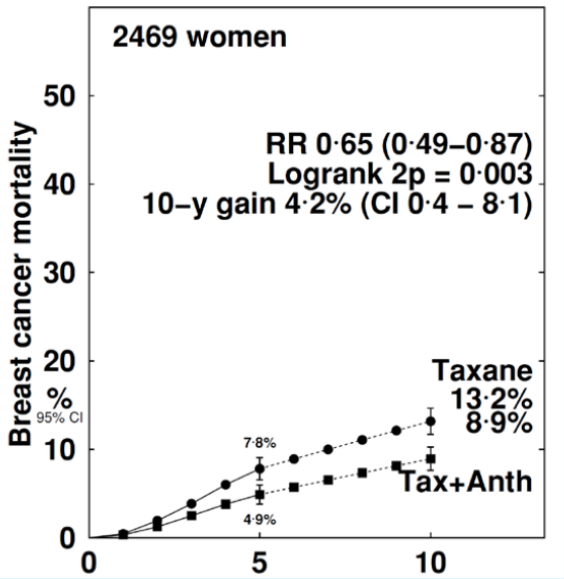
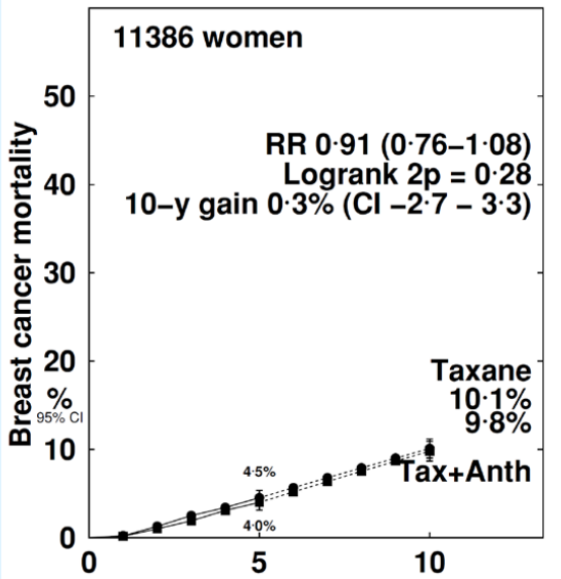
Comparison (A) versus (B)

Breast cancer mortality

(A) Concurrent



(B) Sequential



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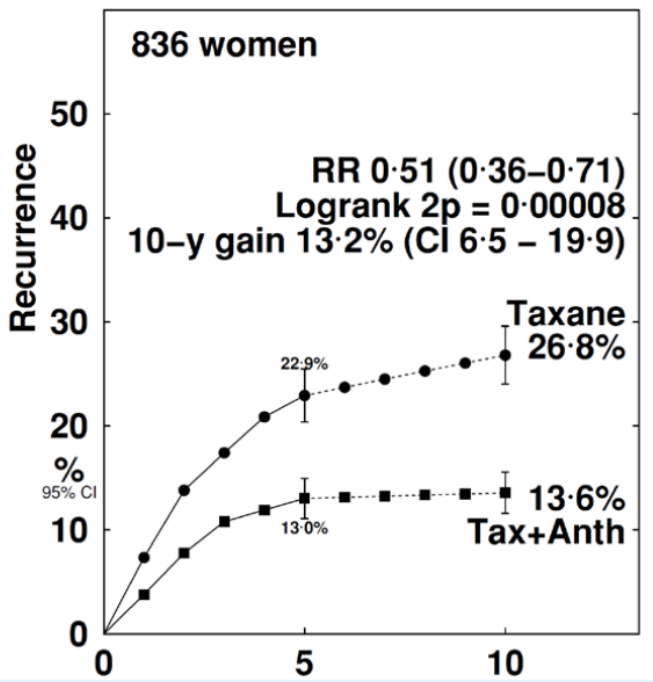
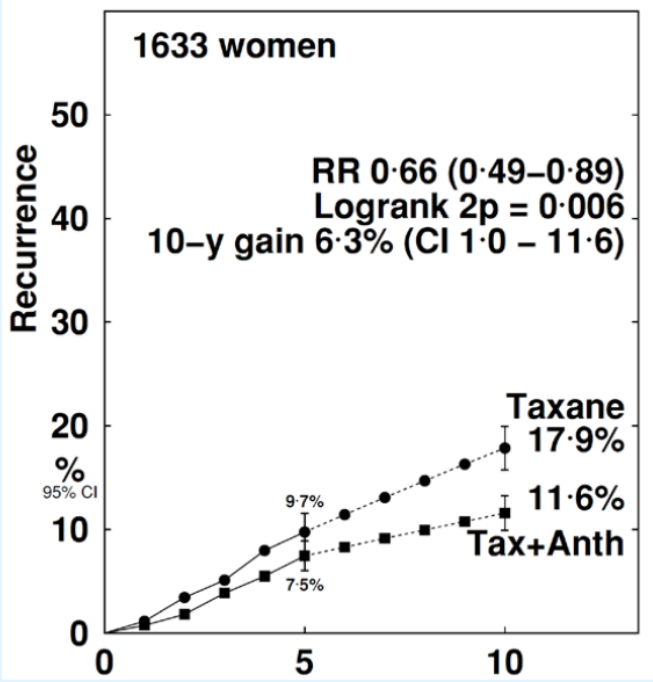
Comparison (A) – hormone receptor status

ER-negative



ER-positive



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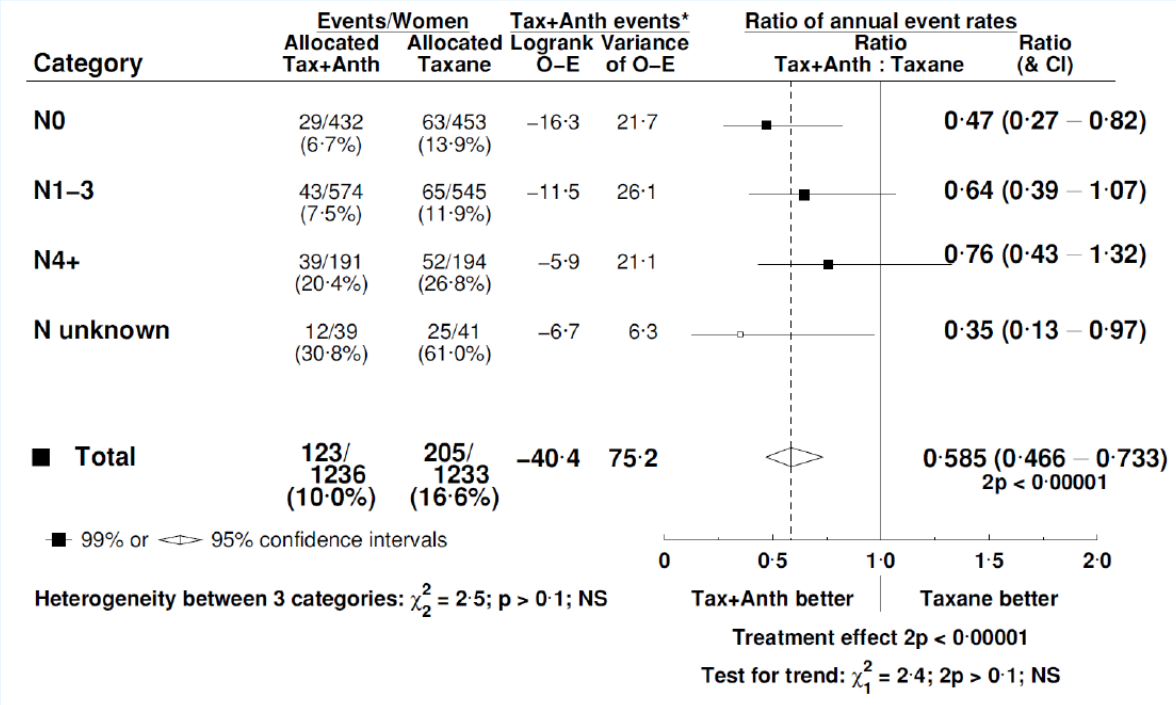
Comparison (A) – Nodal status



Toxicity and Quality of Life

- Combined analysis - no statistically significant difference in death without recurrence (RR 1.06 95%CI 0.83-1.37, p=0.63)
- No difference in deaths from cardio-vascular disease or leukaemia **but longer term follow up needed**
- Individual patient level data on quality of life and toxicity not available

GS2-06
Fazit

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- **15 % rel. Reduktion (2,5 % abs.) des Rezidivrisikos nach 10 Jahren für Kombination Anthracycline + Taxane vs. Taxane**

- **42 % rel. Reduktion bei gleichzeitigen Regimen bei gleicher Taxan Dosis in beiden Armen und einzigem Unterschied +/- Anthracyclin**
- **Wenig / kein Vorteil bei sequentieller Gabe Anthracyclinen und Taxanen vs. Taxan in höherer Dosis alleine**
- **Nicht abhängig vom ER Status oder Nodalstatus**

- **Dosisdichte Schemata und Her2 + Tumore wurden hier nicht geprüft**
- **Stellenwert nicht abschließend geklärt**
- **Sequentielles AT-Schema wahrscheinlich äqui-effektiv zu 6 x DC**

Gemeinschaftsklinikum Mittelrhein

Zusammenfassung – Take Home

- **Pembrolizumab + Platinhaltige CHT neoadjuvant → OP → Pembrolizumab als neuer Standard beim frühen High Risk TNBC (?) , Zulassung ? (Keynote-522) (Neue Fragen dadurch : Rolle Capecitabin (Create X) bzw Olaparib (Olympia) (bei BRCAmut) bei Non-pCR und POSTneoadjuvant ??)**

- **Keine Effektivität von Palbociclib adjuvant (Pallas)**
- **Keine Effektivität von Metformin adjuvant (CCTG MA.32)**

- **Verbesserung von Überlebensdaten durch OFS/GnRH bei prämenopausalen Pat. zusätzlich zu TAM oder AI und hohem Rezidivrisiko.**
  AI dabei etwas besser als TAM (jeweils + GnRH) , aber mehr NW bei keinem (EBCTCG) oder geringem (SOFT/TEXT) Vorteil im OS
  → individuelle Entscheidung : NW / Benefit / Verträglichkeit
  (EBCTG und TEXT/ SOFT Metaanalyse)

- **Anthracyclinfreie adj. Chemotherapie (DC) ist wahrscheinlich äqui-effektiv zu sequentieller AT Chemotherapie (EBCTG Metaanalyse)**

Danke für die Aufmerksamkeit

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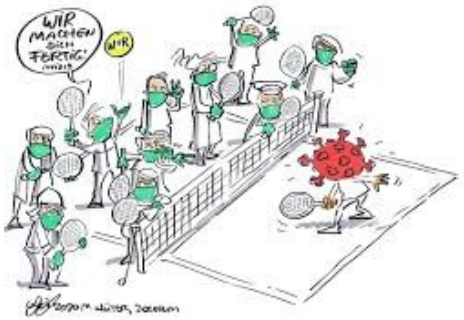

Santo Antonio