Aktueller Stand und zukünftige Herausforderungen der Immunonkologie beim frühen Mammakarzinom

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GBG GERMAN BREAST GROUP

21. Annual Scientific Meeting der German Breast Group
Frankfurt, 29. Februar – 1. März 2024

Conflicts of Interest

Research grants from:

Celgene, Roche

Honoraria from:

Amgen, AstraZeneca, Aurikamed, Bayer, Celgene, ClinSol, Clovis Oncology, coma UroGyn, Connectmedica, Daiichi Sankyo, Gilead, GSK, if-kongress, I-MED, iOMEDICO, Lilly, MCI Deutschland, med publico, Metaplan, MSD, Mylan, NanoString Technologies, Novartis, onkowissen.de, Pfizer, Pierre Fabre, promedicis, Roche, Seagen, streamedup, Tesaro

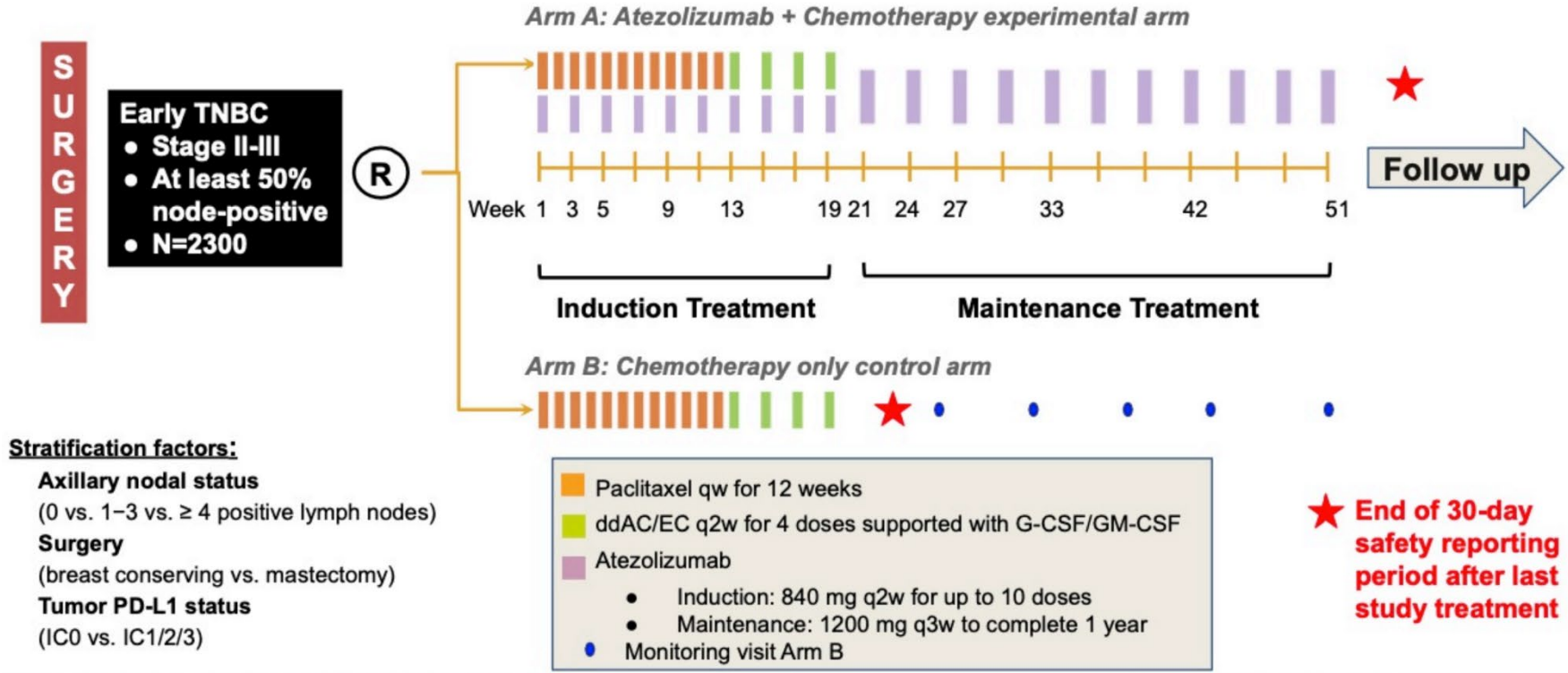
Travel support from:

AstraZeneca, Celgene, Pfizer, Roche

Checkpoint-Inhibitoren (CPi) im Faktencheck:

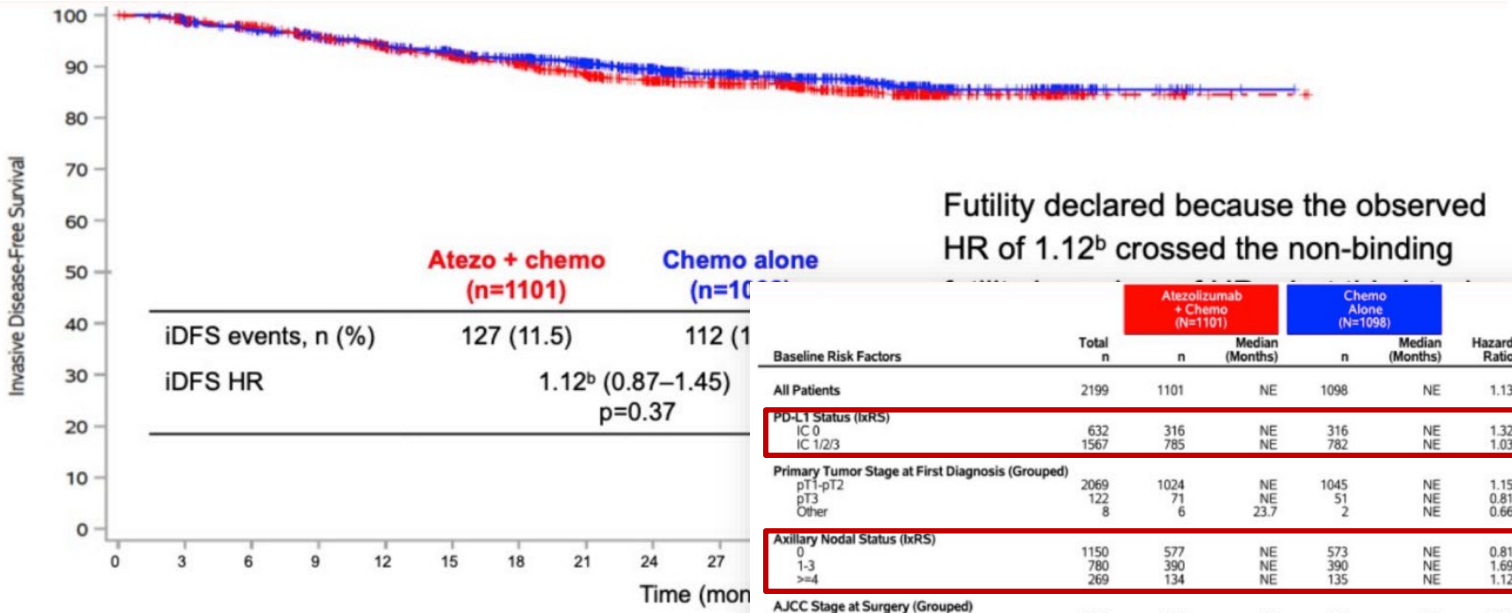
- Wann sollen sie derzeit eingesetzt werden?
  - Nur adjuvant, nur neoadjuvant, neoadjuvant und adjuvant?

ALEXANDRA (Phase III): Adjuvant Pac-ddAC/EC + Atezolizumab vs. Pac-ddAC/EC for eTNBC (N=2199, F/U ~25 mo) – Study Design



Ignatiadis M, et al. SABCS 2023 (GS01-03)

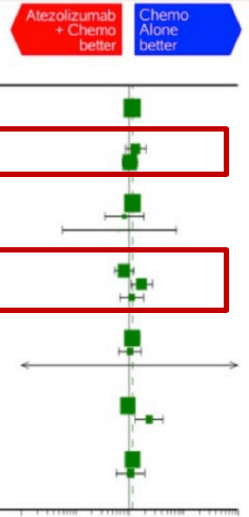
ALEXANDRA (Phase III): Adjuvant Pac-ddAC/EC + Atezolizumab vs. Pac-ddAC/EC for eTNBC (N=2199, F/U ~25 mo) – iDFS



	Atezo + chemo (n=1101)	Chemo alone (n=10
iDFS events, n (%)	127 (11.5)	112 (1
iDFS HR	1.12[b] (0.87–1.45) p=0.37	

Futility declared because the observed HR of 1.12[b] crossed the non-binding

Baseline Risk Factors	Total n	Atezolizumab + Chemo (N=1101) n	Atezolizumab + Chemo (N=1101) Median (Months)	Chemo Alone (N=1098) n	Chemo Alone (N=1098) Median (Months)	Hazard Ratio	95% Wald CI
All Patients	2199	1101	NE	1098	NE	1.13	(0.87, 1.45)
PD-L1 Status (IxRS)							
IC 0	632	316	NE	316	NE	1.32	(0.87, 2.01)
IC 1/2/3	1567	785	NE	782	NE	1.03	(0.75, 1.43)
Primary Tumor Stage at First Diagnosis (Grouped)							
pT1-pT2	2069	1024	NE	1045	NE	1.15	(0.88, 1.51)
pT3	122	71	NE	51	NE	0.81	(0.35, 1.86)
Other	8	6	23.7	2	NE	0.66	(0.06, 7.54)
Axillary Nodal Status (IxRS)							
0	1150	577	NE	573	NE	0.81	(0.54, 1.22)
1-3	780	390	NE	390	NE	1.69	(1.08, 2.64)
>=4	269	134	NE	135	NE	1.12	(0.68, 1.85)
AJCC Stage at Surgery (Grouped)							
Stage II	1875	935	NE	940	NE	1.15	(0.85, 1.56)
Stage III	318	161	NE	157	NE	1.03	(0.64, 1.65)
Other	6	5	NE	1	NE	>999.99	(0.00, NE)
Pooled Age Group 1							
<65	1820	916	NE	904	NE	0.95	(0.71, 1.26)
>=65	379	185	NE	194	NE	2.33	(1.28, 4.24)
Baseline ECOG Assessment Score							
0	1782	887	NE	895	NE	1.15	(0.87, 1.51)
1	417	214	NE	203	NE	1.06	(0.58, 1.95)



Hazard ratios and the associated Wald confidence intervals were estimated using *unstratified* Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.

Ignatiadis M, et al. SABCS 2023 (GS01-03)

Neoadjuvante Checkpoint-Inhibitor Studien beim eTNBC

21. ANNUAL SCIENTIFIC MEETING 2024

Studie, Phase	N	CPi	Chemotherapie	Therapie adjuvant	pCR Raten	Überleben
KEYNOTE-522, Phase III[1]	1174	Pembrolizumab	Carbo/Pac → **AC**	Pembro 1 Jahr	**64.8%** vs. 51.2%, $p < 0.001$	**3-Jahres EFS 84.5%** vs. 76.8%, HR 0.63, $p < 0.00031$
NeoPACT, Phase II[2]	117	Pembrolizumab	Carbo/Doc	SOC	**60%**	**2-Jahres EFS 88%**
I-SPY2, rand. Phase II[3]	29 TNBC	Pembrolizumab	Pac → AC	SOC	**60%** vs. 22%	**3-Jahres EFS 93% (overall)**
IMpassion031, Phase III[4,5]	333	Atezolizumab	nPac → AC	Atezo 1 Jahr	**58%** vs. 41%, $p = 0.0044$	**2- Jahres EFS 85%** vs 80% HR 0.76, ns
NeoTripaPDL1, Phase III[6,7]	280	Atezolizumab	Carbo/nPac	AC/EC/FEC	**48.6%** vs. 44.4% $p = 0.48$	**5-Jahres EFS 70.6** vs 74.9 HR 1.076, ns
NCI10013, Phase II[8]	67	Atezolizumab	Carbo/Pac	AC dosisdicht	**55.6%** vs. 18.8% $p = 0.018$	
GeparNuevo, Phase II[9]	174	Durvalumab	Window → nPac → **AC**	SOC	**53.4%** vs. 44.2% OR 1.45	**3-Jahres DDFS 91.7%** vs. 78.4%, HR 0.31, $p = 0.005$ **3-Jahres OS 95.2%** vs. 83.5%, HR 0.24, $p = 0006$
I-SPY2, Phase II[10]	21 TNBC	Durvalumab	Pac → AC + Olaparib	SOC	**47%** vs. 27%	
∑	**2195**	**Pembrolizumab (N=1320)** Atezolizumab (N=680) Durvalumab (N=195)	**+AC (N=1731)** +Carbo (N=1638)	**+CPi adj (N=1507)** +Ctx adj (N=347)	**Δ 13,6 - 25%**	**Δ 2/3-Jahres EFS: 7,7 - 13%**

1.Schmid P. NEJM 2020 und 2022; 2. Sharma P. JCO 2022; 3. Nanda R. JAMA Oncol 2020; 4. Mittendorf. Lancet Oncol 2020; 5. Barrias H.C. ESMO BC 2023, Abstract LBA1; 6. Gianni L. ESMO 2023, Abstract LBA19; 7.Gianni L. Ann Oncol 2022; 8. Ademuyiwa FO. NPJ Breast Cancer 2022; 9. Loibl S. Ann Oncol 2019 und 2022; 10. Pusztai L. Cancer Cell 2021.)

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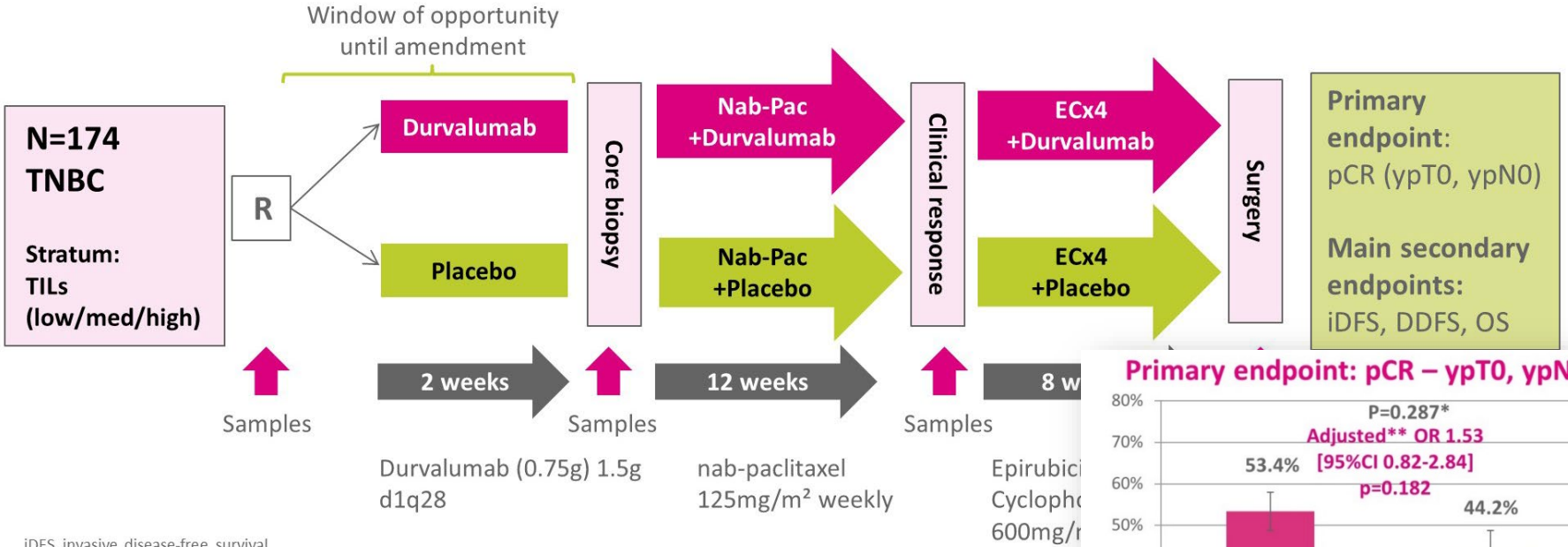
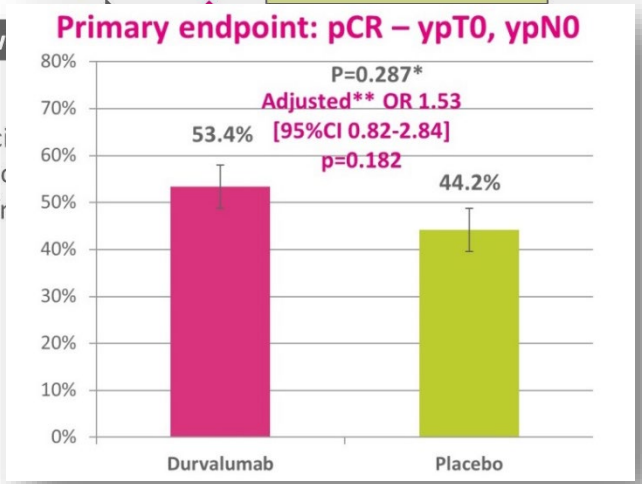
GeparNUEVO (Phase II): Neoadjuvant nPac → EC + Durvalumab vs. nPac → EC + Placebo for eTNBC (N=174, F/U 44 mo) - Study Design, pCR

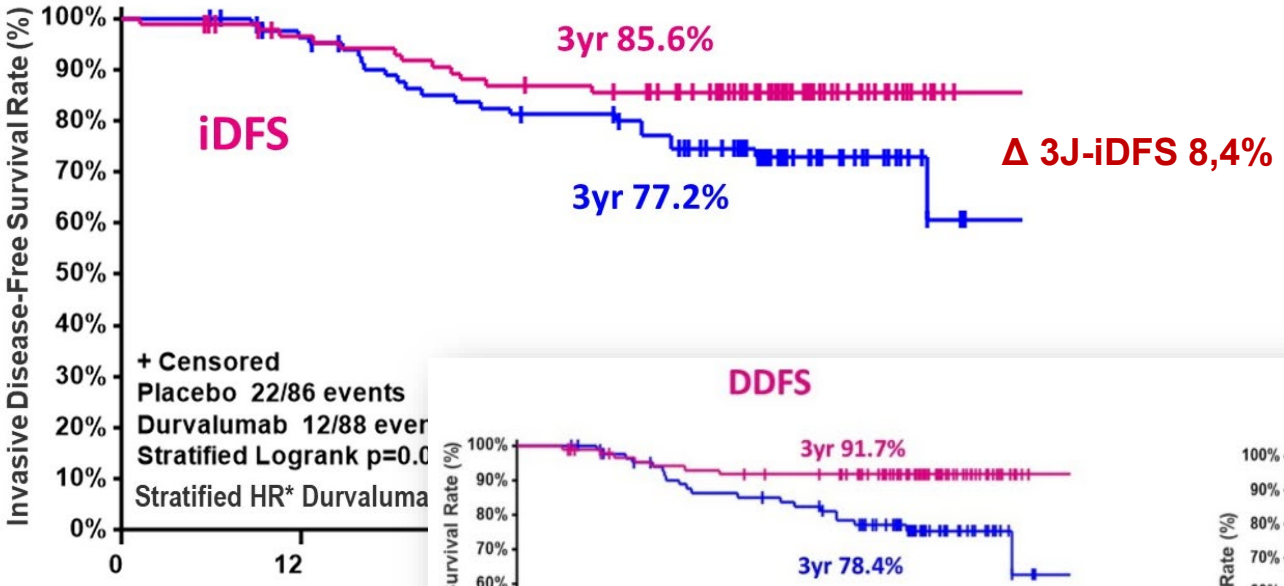


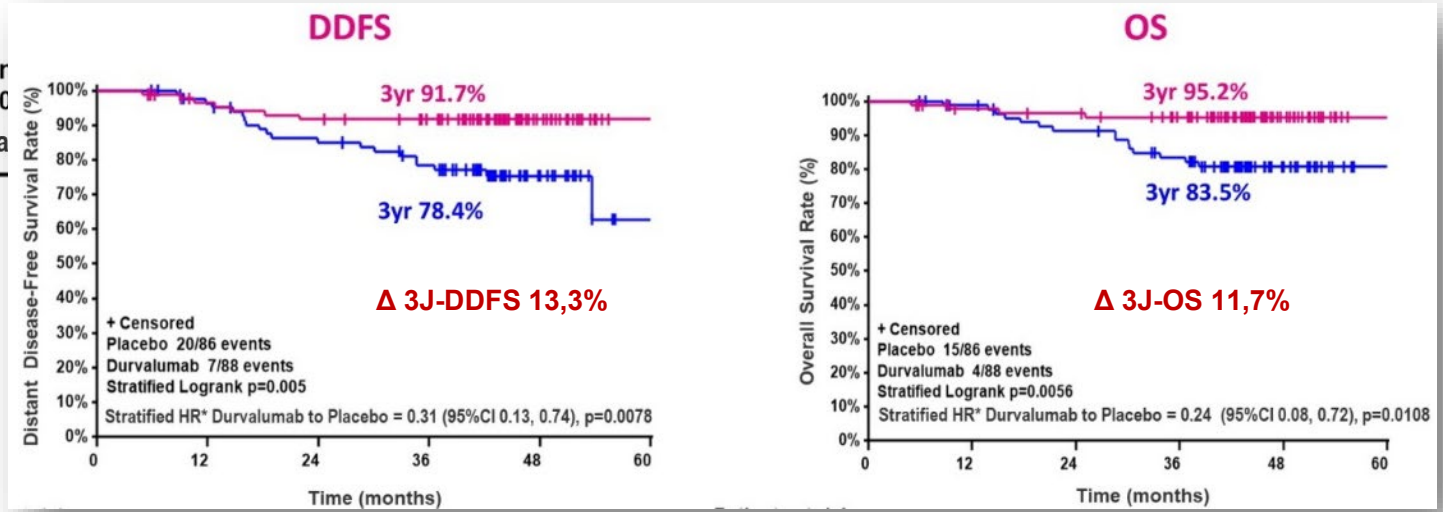
iDFS, invasive disease-free survival
DDFS, distance disease-free survival
OS, overall survival



Loibl S, et al. ASCO 2021 (abs 506)

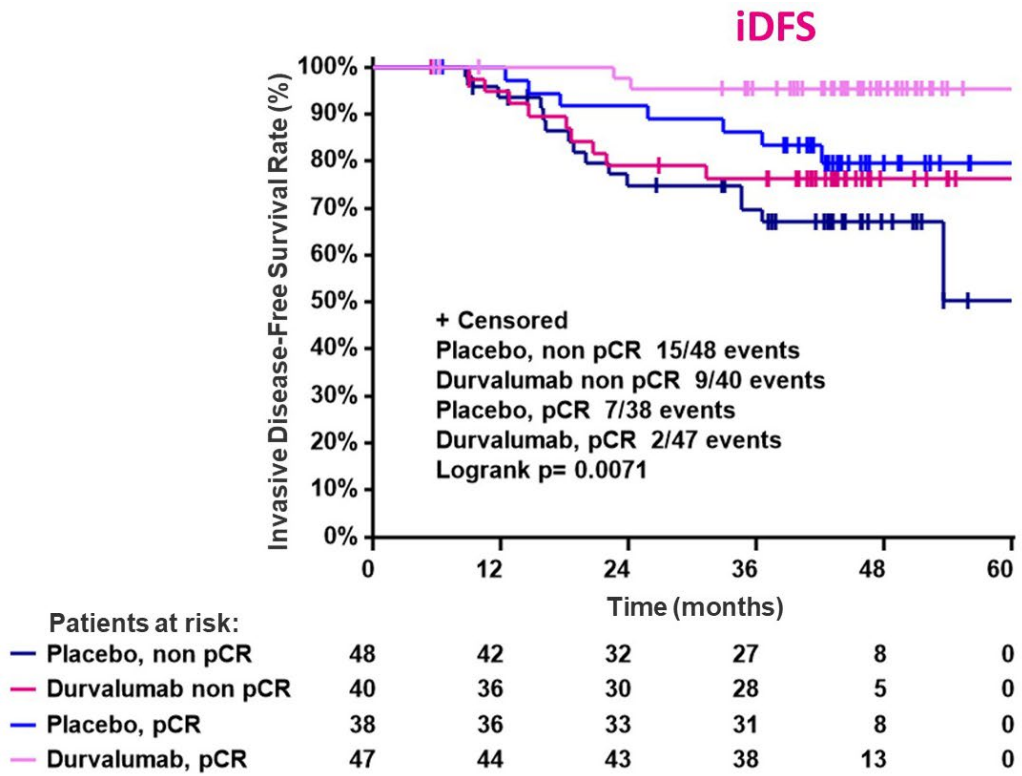
GeparNUEVO (Phase II): Neoadjuvant nPac → EC + Durvalumab vs. nPac → EC + Placebo for eTNBC (N=174, F/U 44 mo) – iDFS, DDFS, OS





Loibl S, et al. ASCO 2021 (abs 506)

GeparNUEVO (Phase II): Neoadjuvant nPac → EC + Durvalumab vs. nPac → EC + Placebo for eTNBC (N=174, F/U 44 mo) - iDFS by pCR and Tx



3yr 95.5%

3yr 86.1%

3yr 76.3%

3yr 69.7%

Δ_{pCR} 3J-EFS 9,0%

$\Delta_{non\text{-}pCR}$ 3J-EFS 6,6%

HR (pCR vs non-pCR) 0.34 (95%CI 0.16-0.73)
log-rank p=0.004

Loibl S, et al. ASCO 2021 (abs 506)

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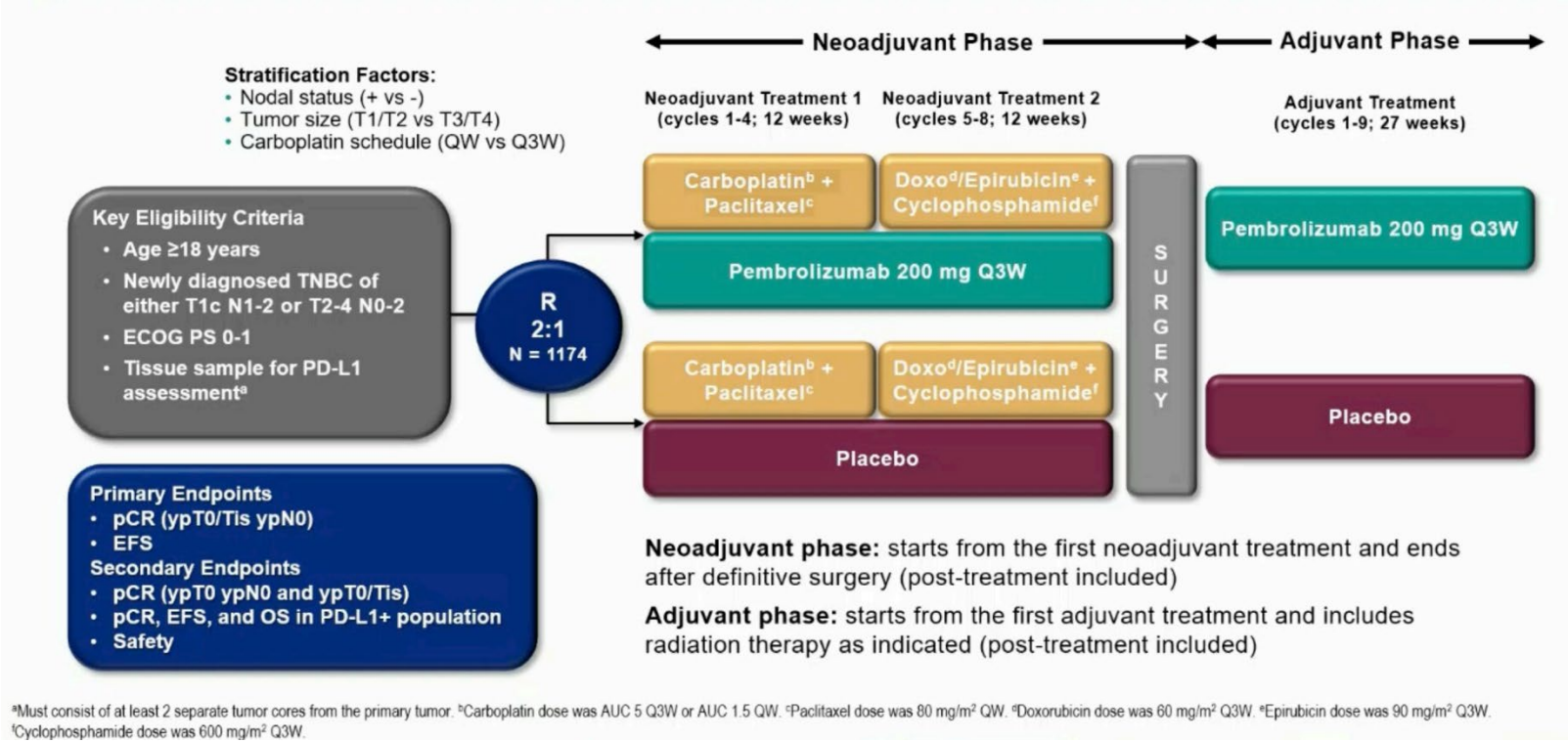
KEYNOTE-522 (Phase III): Neo-/adjuvant Standard + Pembrolizumab vs. Standard + Placebo for eTNBC (N=1174, F/U 63 mo) – Study Design



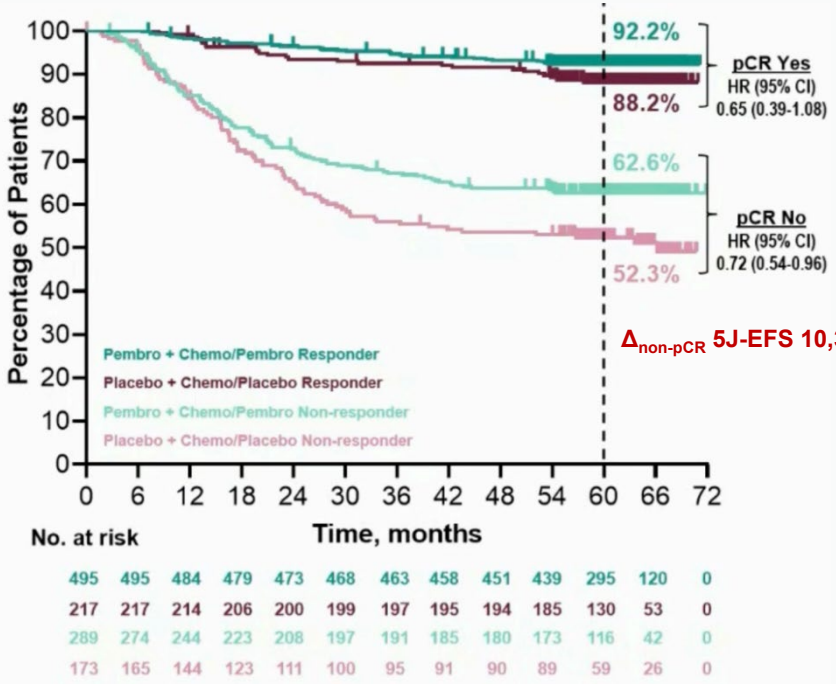
[a]Must consist of at least 2 separate tumor cores from the primary tumor. [b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW. [c]Paclitaxel dose was 80 mg/m² QW. [d]Doxorubicin dose was 60 mg/m² Q3W. [e]Epirubicin dose was 90 mg/m² Q3W. [f]Cyclophosphamide dose was 600 mg/m² Q3W.

Schmid P, et al. ESMO 2023 (LBA18)

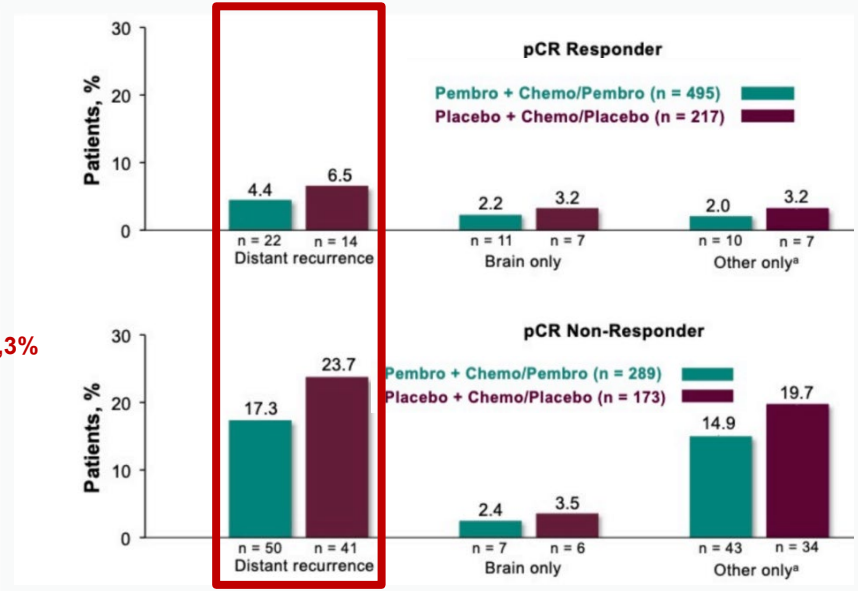
KEYNOTE-522 (Phase III): Neo-/adjuvant Standard + Pembrolizumab vs. Standard + Placebo for eTNBC (N=1174, F/U 63 mo) – EFS by pCR and Tx

Δ_{all} 5J-EFS 9,2%

Δ_{pCR} 5J-EFS 4,0%

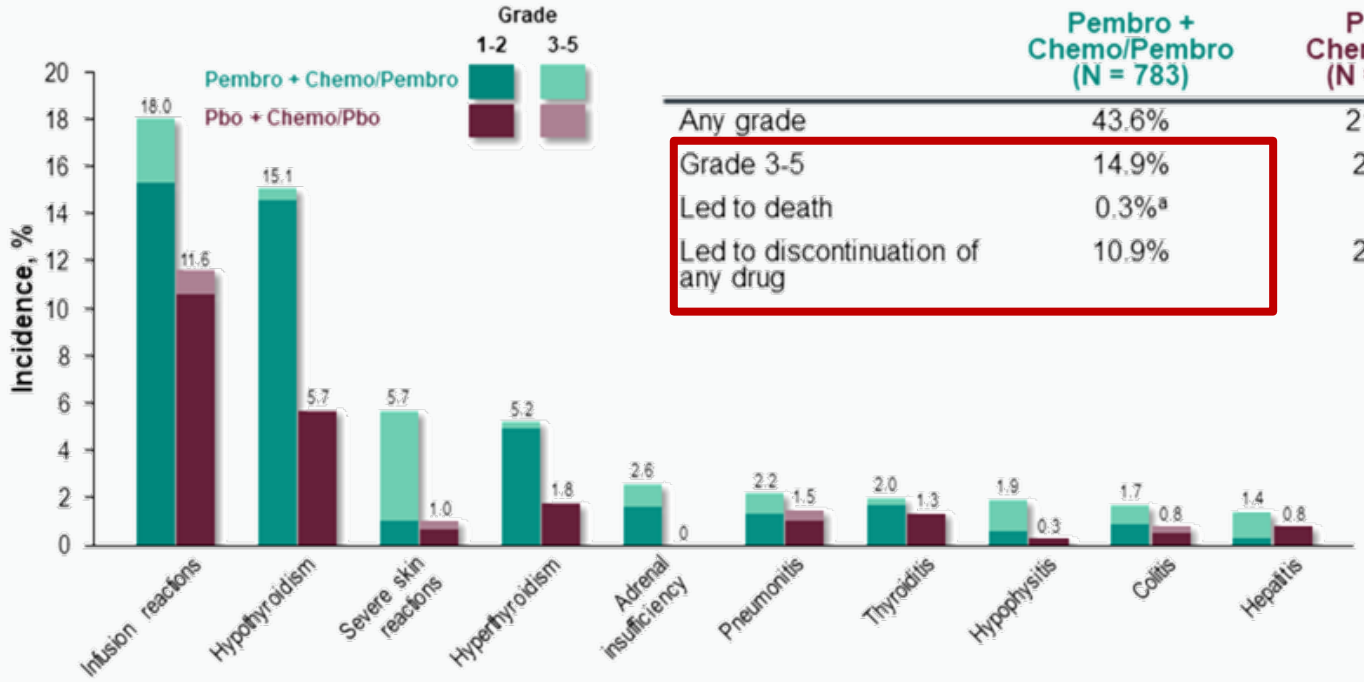


$\Delta_{non\text{-}pCR}$ 5J-EFS 10,3%



Schmid P, et al. SABCS 2023 (LBA01-01)

KEYNOTE-522 (Phase III): Neo-/adjuvant Standard + Pembrolizumab vs. Standard + Placebo for eTNBC (N=1174, F/U 63 mo) – Immun-related Adverse Events



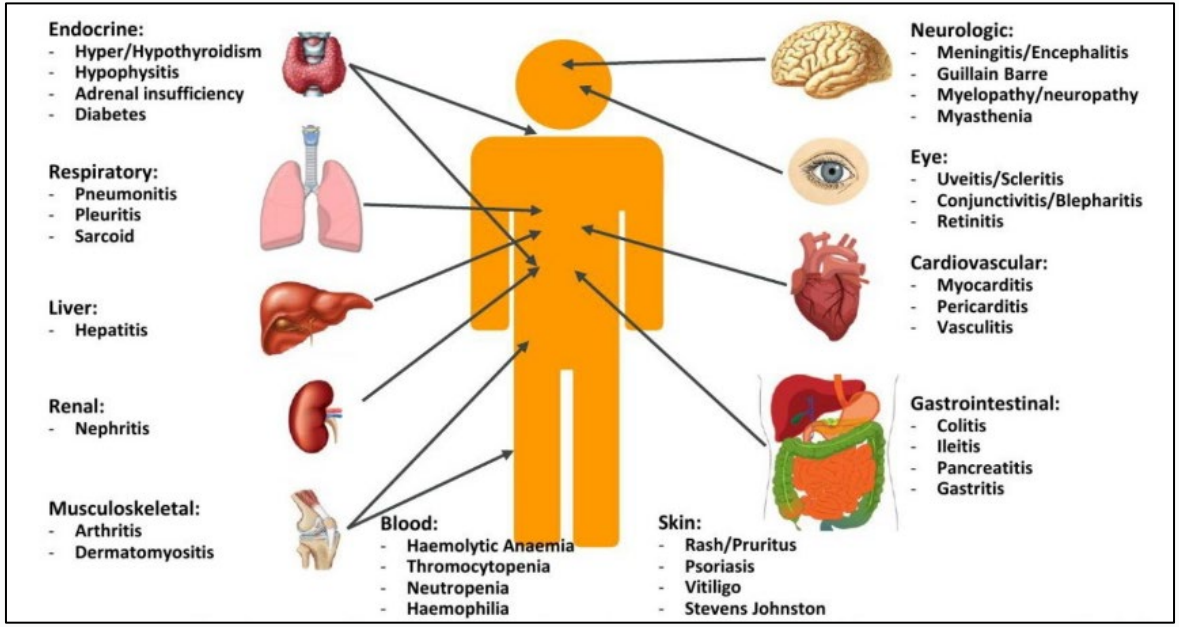
	Pembro + Chemo/Pembro (N = 783)	Pbo + Chemo/Pbo (N = 389)
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	10.9%	2.6%

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

[a] 1 patient from **pneumonitis** and 1 patient from **autoimmune encephalitis**.

Schmid P, et al. ESMO 2021 (Virtual Plenary)

Immun-related Adverse Events



- ***Alle*** **Organsysteme können betroffen sein**
- **Die Symptome sind *unspezifisch***
- **Die Zeit bis zum *Auftreten hochgradig variabel* (auch bis zu 1 Jahr nach Therapieende)**

Schmid P, et al. Educational SABCS 2019 (ES1-2)

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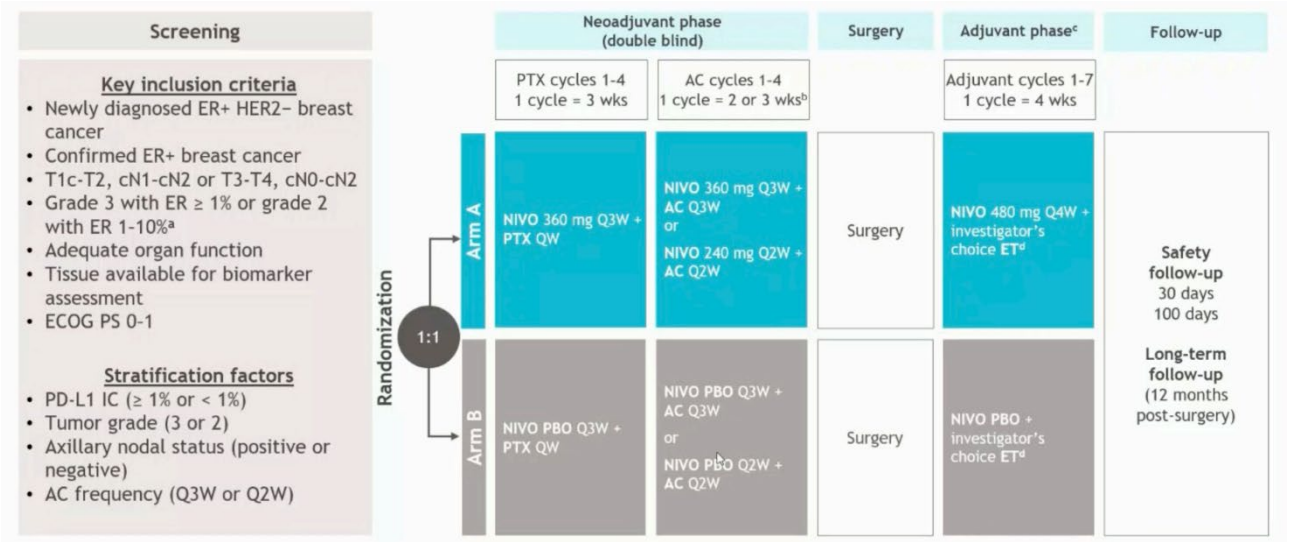
Checkpoint-Inhibitoren (CPi) im Faktencheck:

- Wann sollen sie derzeit eingesetzt werden?
  - Nur adjuvant, nur neoadjuvant, neoadjuvant und adjuvant

Checkpoint-Inhibitoren (CPi) im Faktencheck:

- Wann sollen sie derzeit eingesetzt werden?
  - Nur adjuvant, nur neoadjuvant, neoadjuvant und adjuvant
- Bei welchem Subtyp?
  - eTNBC, HR+HER2- eBC, ect.?

CheckMate (Phase III): NACT + Nivolumab vs. NACT + Placebo → OP → ET + Nivolumab vs. ET + Placebo for ER+ HER2- eBC (N=510) – Study Design



Primary endpoint

- pCR in the mITT population[a]

Secondary endpoints

- pCR[a] in the PD-L1+ population[b]
- RCB class (0/1/2/3) frequency and RCB 0-1 rate
- RCB class frequency and RCB 0-1 rate in the PD-L1+ population
- Safety and tolerability

Exploratory endpoint

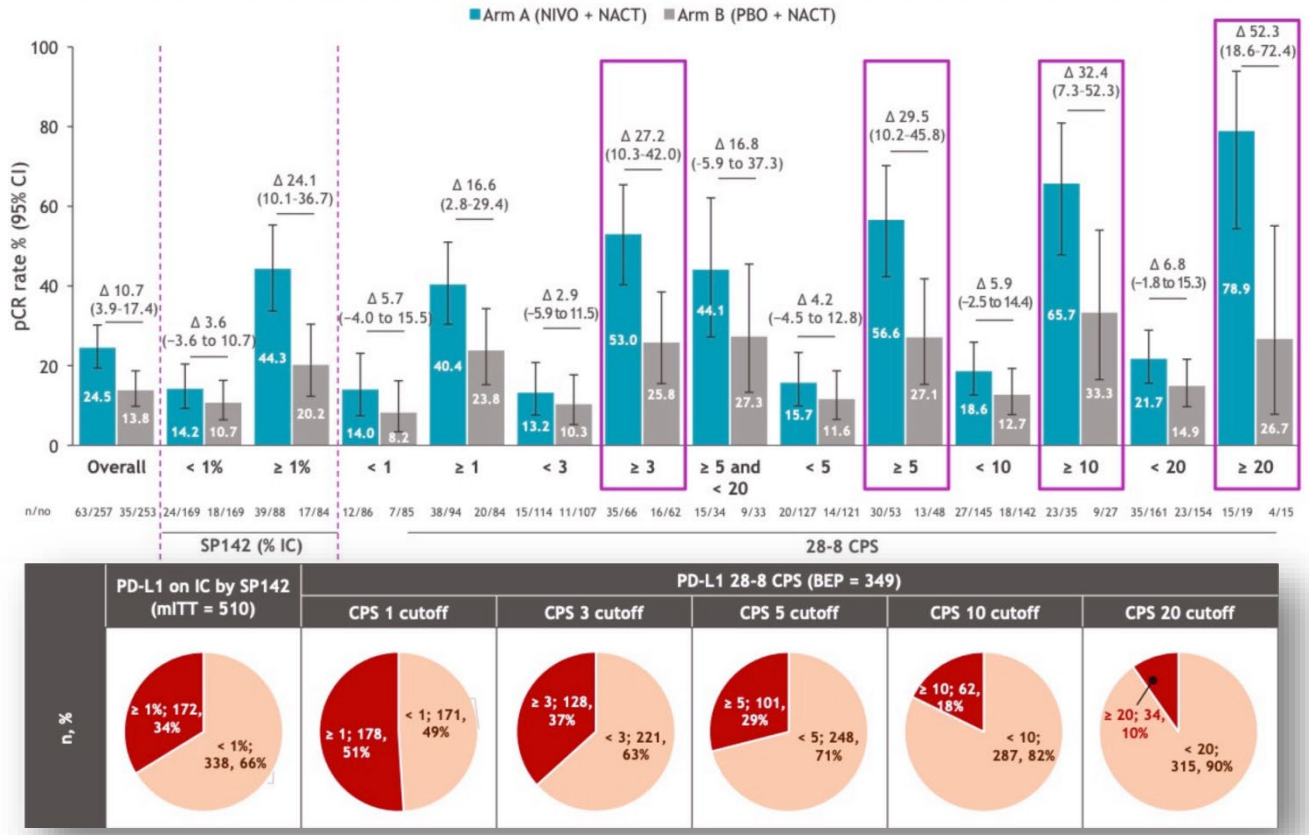
- EFS (unavailable for this presentation)

- 99% Grad 3
- 44% Stadium III
- 80% N+
- 34% PD-L1 ≥ 1% (SP142) bzw. 51% (28-8 CPS)

- Primary endpoint: pCR
- EFS only *exploratory*

Loi S, et al. ESMO 2023 (LBA20)

CheckMate (Phase III): NACT + Nivolumab vs. NACT + Placebo → OP → ET + Nivolumab vs. ET + Placebo for ER+ HER2- eBC (N=510) – pCR by PD-L1



Δ_{pCR} 16,6 - 52,3%

- Welches Δ_{pCR} rechtfertigt die zusätzliche Toxizität?
- *Keine* Überlebensdaten

Loi S, et al. SABCS 2023 (GS01-01)

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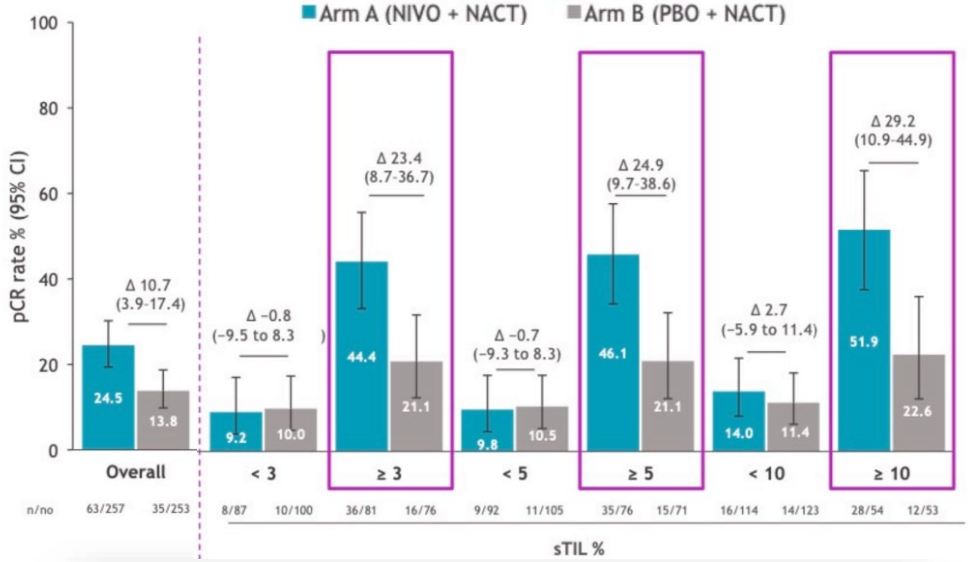
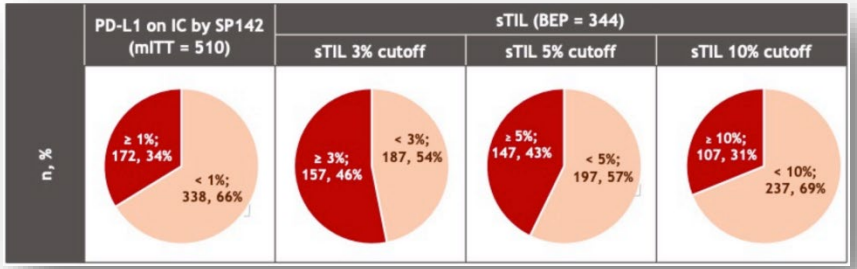
CheckMate (Phase III): NACT + Nivolumab vs. NACT + Placebo → OP → ET + Nivolumab vs. ET + Placebo for ER+ HER2- eBC (N=510) – pCR by sTILs





Δ_{pCR} 23,4 - 29,2%

- Welches Δ_{pCR} rechtfertigt die zusätzliche Toxizität?
- *Keine* Überlebensdaten

Loi S, et al. SABCS 2023 (GS01-01)

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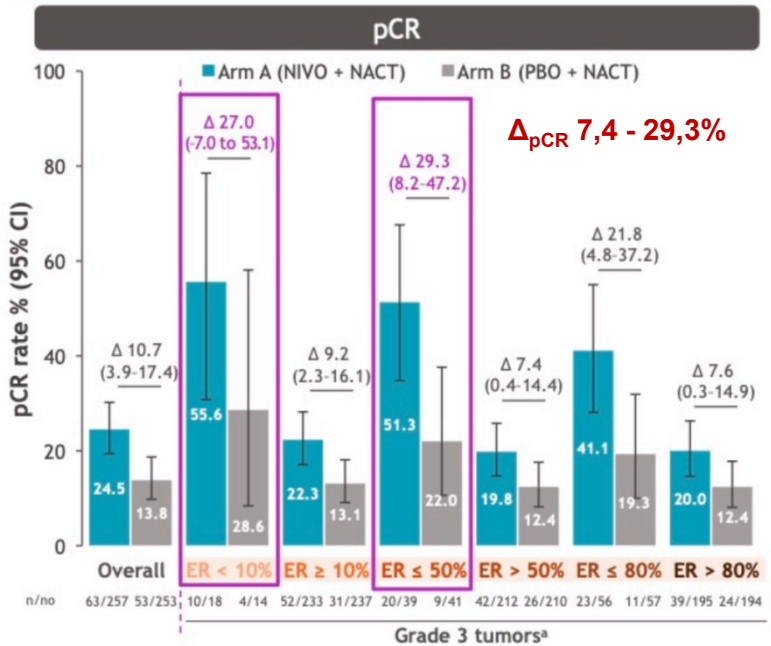
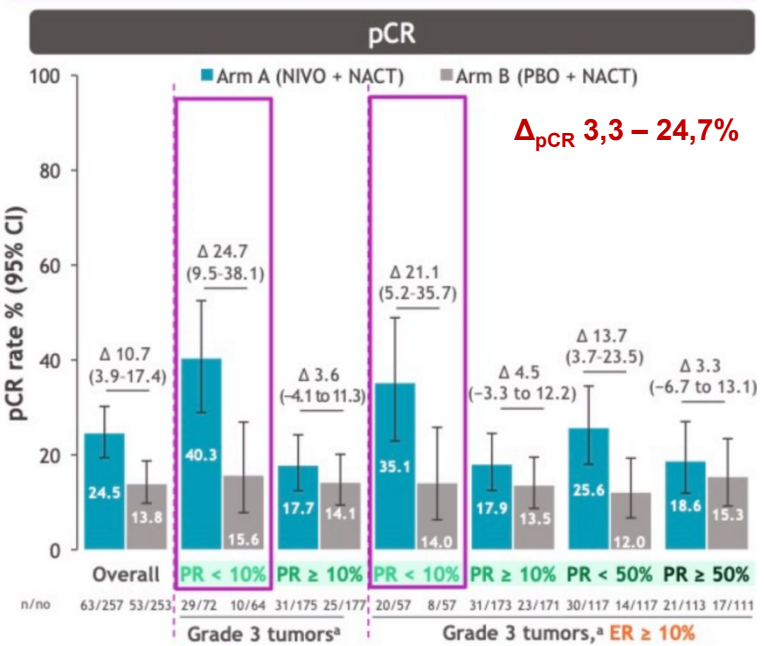
CheckMate (Phase III): NACT + Nivolumab vs. NACT + Placebo → OP → ET + Nivolumab vs. ET + Placebo for ER+ HER2- eBC (N=510) – pCR by ER/PR





- **Welches Δ_{pCR} rechtfertigt die zusätzliche Toxizität?**
- ***Keine* Überlebensdaten**

Loi S, et al. SABCS 2023 (GS01-01)

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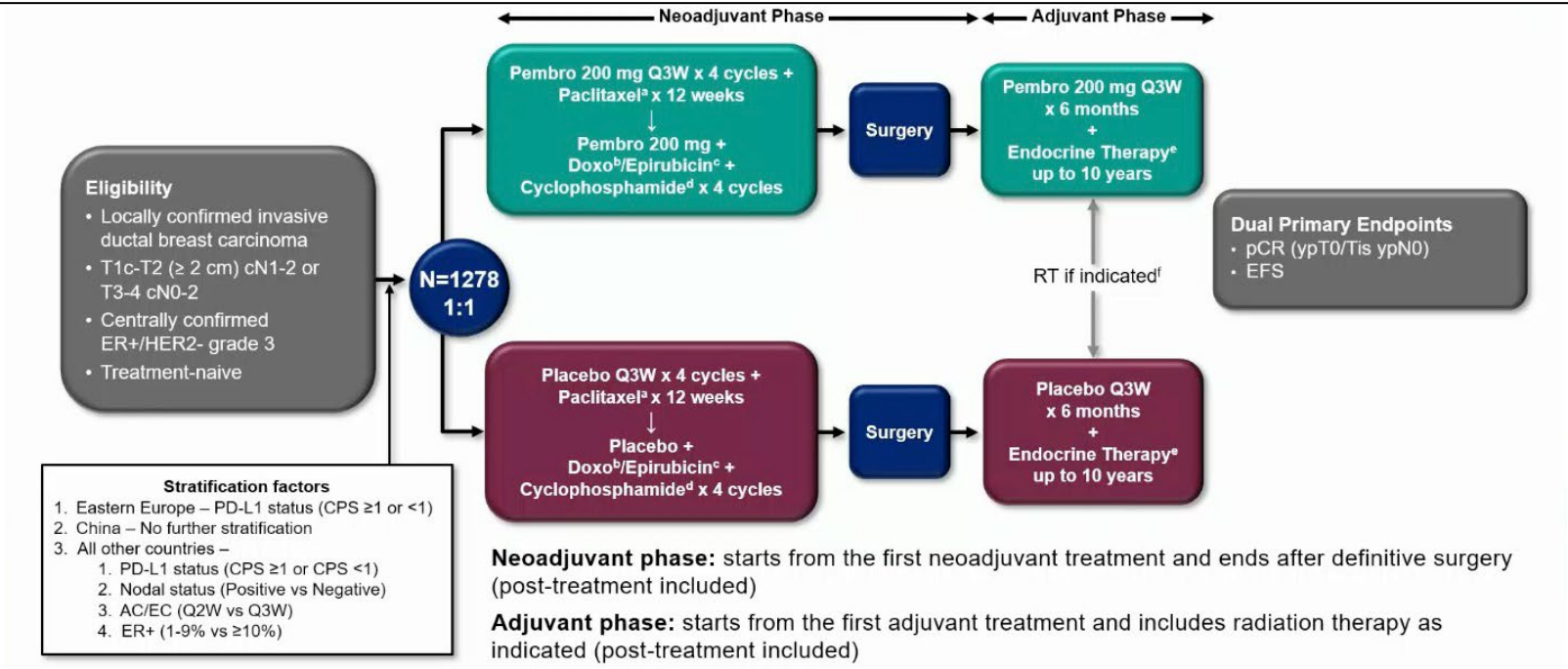
KEYNOTE-756 (Phase III): Neo/-adjuvant Pembrolizumab + Ctx vs. Placebo + Ctx for ER+ HER2- eBC (N=1278, F/U 33.2 mo) – Study Design

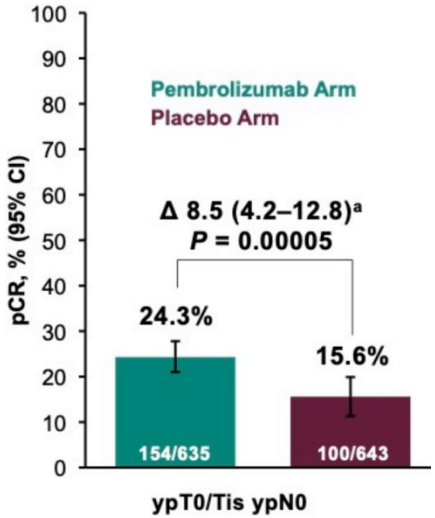


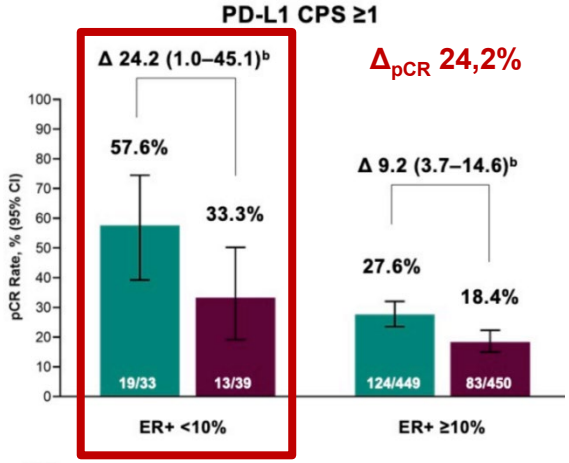
- **100% Grad 3**
- **90% N+**
- **76% PD-L ≥ 1% (CPS)**

- **Co-primary endpoints: pCR *and* EFS**

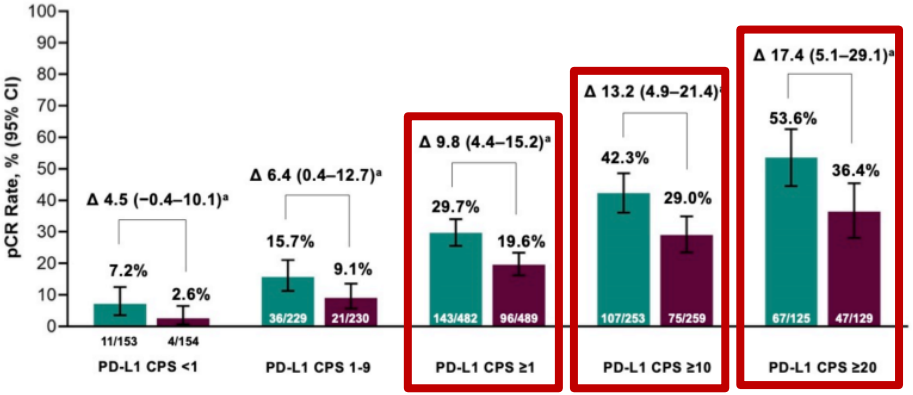
Cardoso F, et al. ESMO 2023 (LBA21)

KEYNOTE-756 (Phase III): Neo/-adjuvant Pembrolizumab + Ctx vs. Placebo + Ctx for ER+ HER2- eBC (N=1278, F/U 33.2 mo) – pCR by PD-L1, ER





Δ_{pCR} 24,2%



Δ_{pCR} 6,4 – 17,4%

- Welches Δ_{pCR} rechtfertigt die zusätzliche Toxizität?
- *Bisher keine* Überlebensdaten

O´Shaugnessy J , et al. SABCS 2023 (GS01-02)

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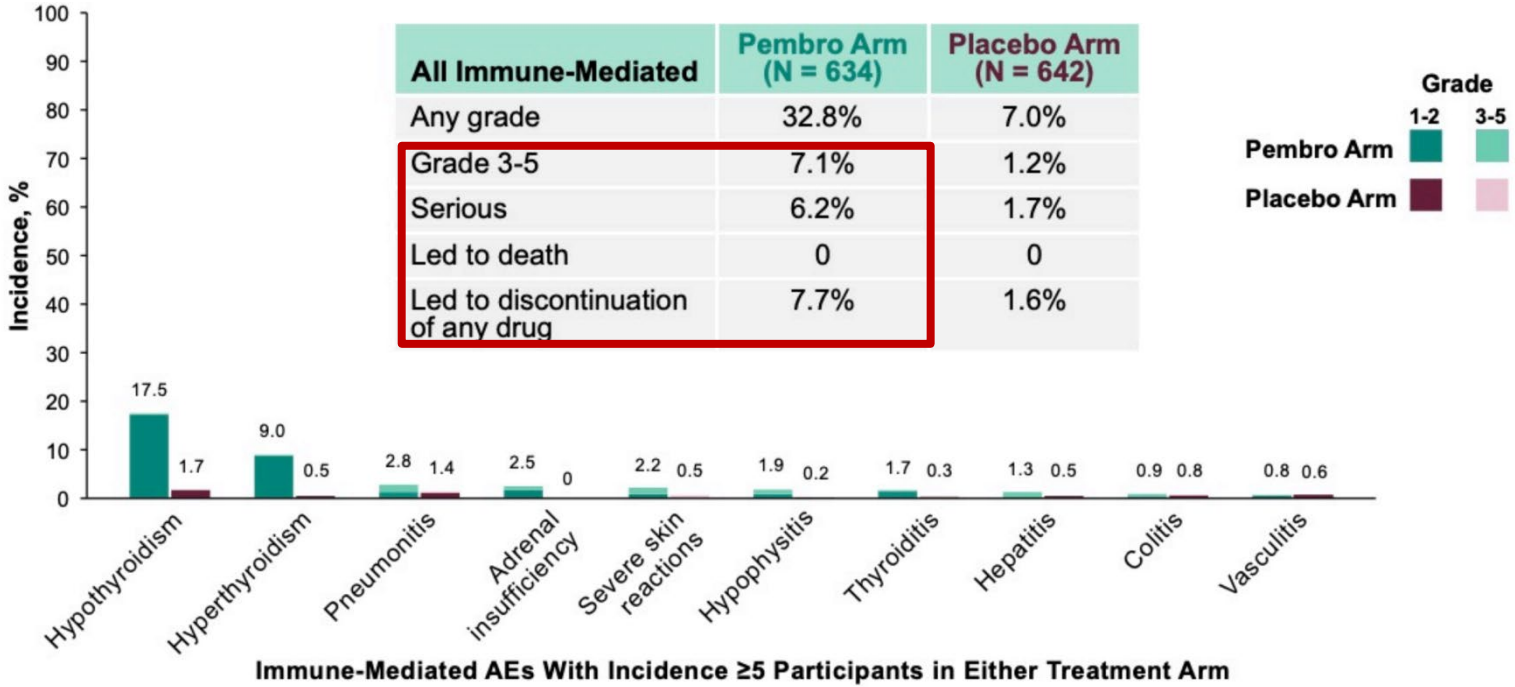
KEYNOTE-756 (Phase III): Neo/-adjuvant Pembrolizumab + Ctx vs. Placebo + Ctx for ER+ HER2- eBC (N=1278, F/U 33.2 mo) – IRAEs

All Immune-Mediated	Pembro Arm (N = 634)	Placebo Arm (N = 642)
Any grade	32.8%	7.0%
Grade 3-5	7.1%	1.2%
Serious	6.2%	1.7%
Led to death	0	0
Led to discontinuation of any drug	7.7%	1.6%



Welches Δ_{pCR} rechtfertigt die zusätzliche Toxizität?

O´Shaugnessy J , et al. SABCS 2023 (GS01-02)

GBG GERMAN BREAST GROUP

Checkpoint-Inhibitoren (CPi) im Faktencheck:

- Wann sollen sie derzeit eingesetzt werden?
  - Nur adjuvant, nur neoadjuvant, neoadjuvant und adjuvant
- Bei welchem Subtyp?
  - eTNBC, HR+HER2- eBC, ect.

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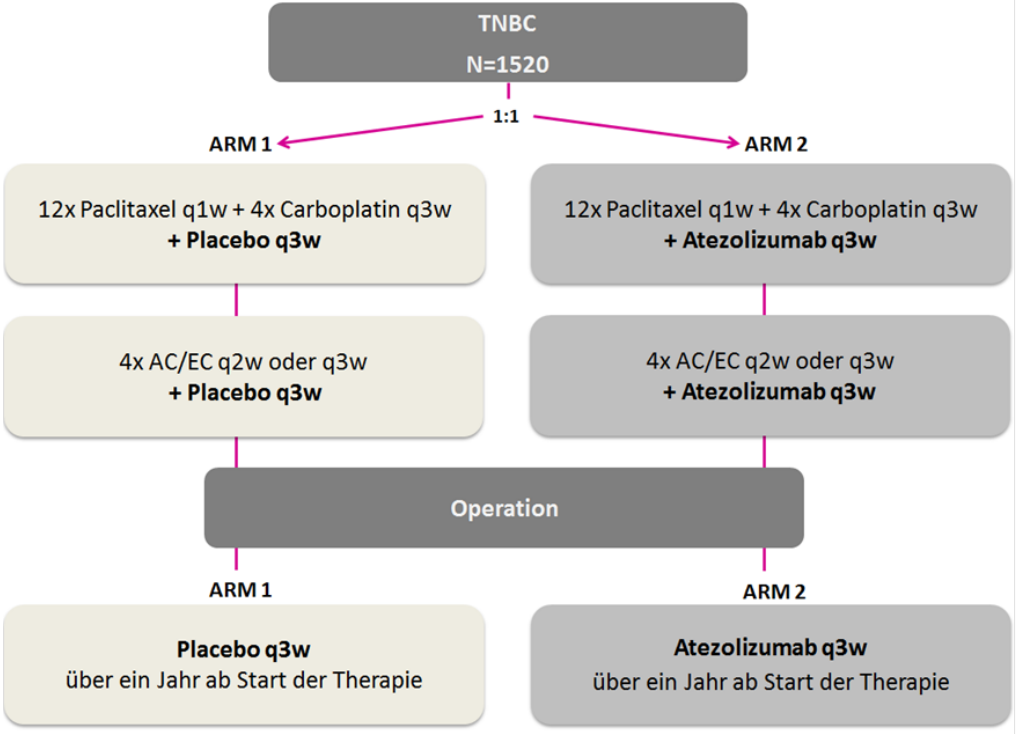
NCT

Studiendesign GeparDouze: Wirkung von Atezolizumab?



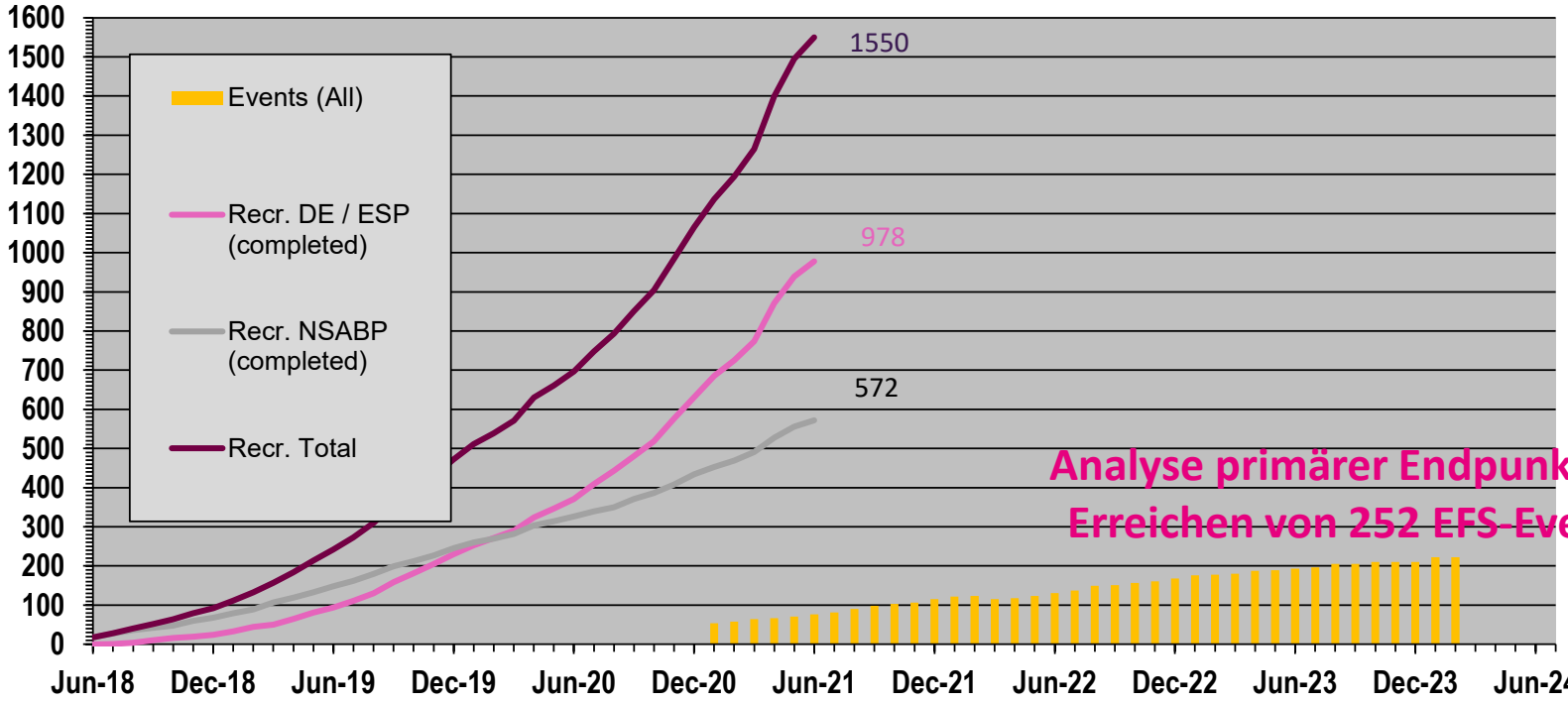
Strata:
- Gruppe (NSABP Foundation Inc., GBG)
- Tumorgröße (1.1-3.0cm; >3.0cm)
- Applikation EC/AC (q2w; q3w)
- Klinischer Nodalstatus (positiv; negativ)
- PD-L1 Status (positiv, negativ, unbestimmbar)

Zentrale Testung:
- HR, HER2, Ki67, TILs
- PD-L1 ab Amendment 1

Dosierungen:
- Carboplatin AUC 5
- Paclitaxel 80mg/m^2
- Doxorubicin (A) 60mg/m^2
- Epirubicin (E) 90mg/m^2
- Cyclophosphamid (C) 600mg/m^2

GeparDouze Events

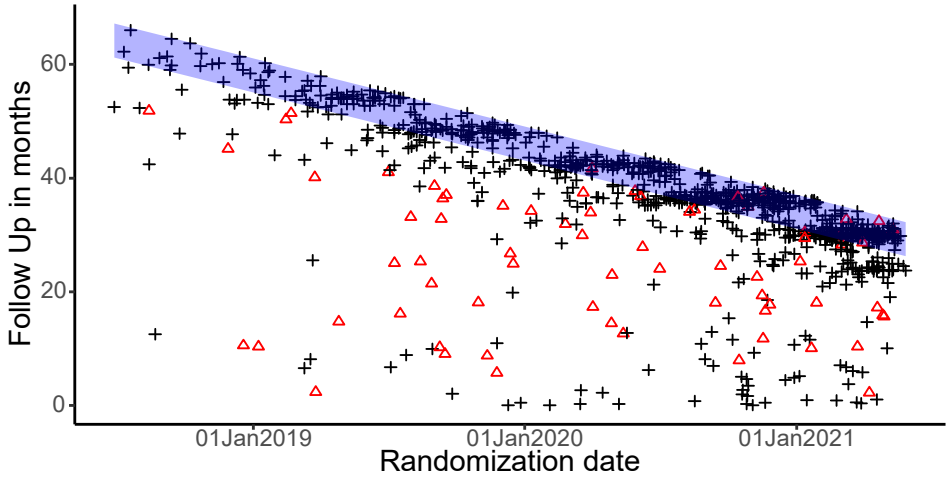
Rekrutierungsende 31.05.2021



Analyse primärer Endpunkt bei Erreichen von 252 EFS-Events

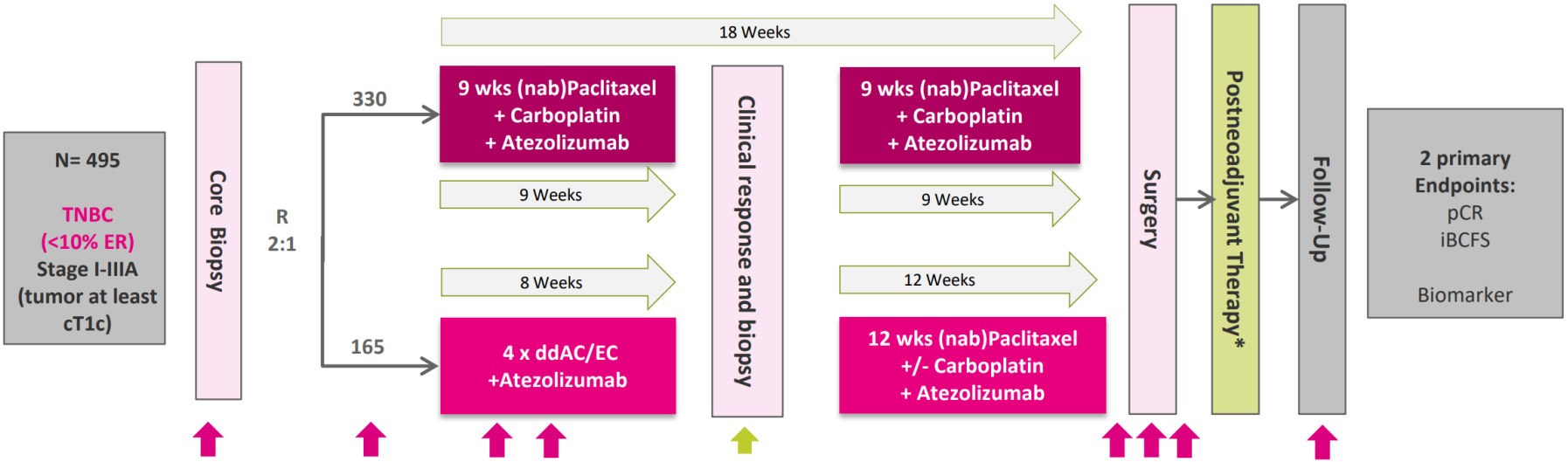
GeparDouze Scatterplot (01.02.2024)

Anzahl Patienten GER+ ESP	978
Anzahl von Patienten ohne FU	3
FU Completeness	90.9%



Bitte: Aktuelles FU erheben, zeitnahe Dokumentation der ausstehenden Bögen und Beantwortung der Queries!

Studiendesign GeparBOOG: Brauchen wir Anthrazykline?



Stratification Factors:
- sTIL (<10% vs. >=10%-50% vs. >50%)
- Tumor Size (≤2cm vs >2cm)
- cN0 vs. cN+

- Patients continue with atezolizumab after surgery until 52 weeks after the first dose with exception of patients with cT1c at primary diagnosis
- Non-pCR g*BRCA* mutant patients may receive olaparib per standard of care
- Non-pCR gBRCA1/2 wildtype patients may receive capecitabine per standard of care

↑ Mandatory collection of tumor tissue and/or liquid biomaterial

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NCT

Heilung durch Innovation, Kompetenz und Partnerschaft – führend in der Brustkrebs-Forschung

Vielen Dank für Ihre Aufmerksamkeit

GBG
GERMAN
BREAST
GROUP