Immunonkologie bei frühem Brustkrebs - Welches Target ist relevant?

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22. ASM FRANKFURT /MAIN

Annual Scientific Meeting der German Breast Group
Frankfurt, 6.-7. März 2025

GBG GERMAN BREAST GROUP

Conflicts of Interest

Honoraria from:

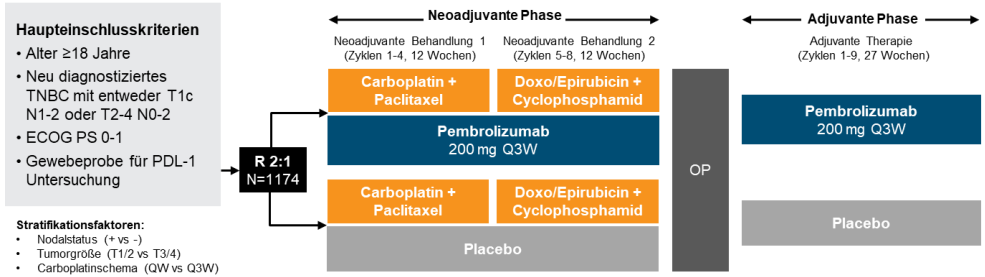
Amgen, AstraZeneca, Aurikamed, Bayer, Celgene, ClinSol, Clovis Oncology, coma UroGyn, Connectmedica, Daiichi Sankyo, Gilead, GSK, if-kongress, I-MED, iOMEDICO, Lilly, MCI Deutschland, med publico, Metaplan, MSD, Mylan, NanoString Technologies, Novartis, onkowissen.de, Pfizer, Pierre Fabre, promedicis,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

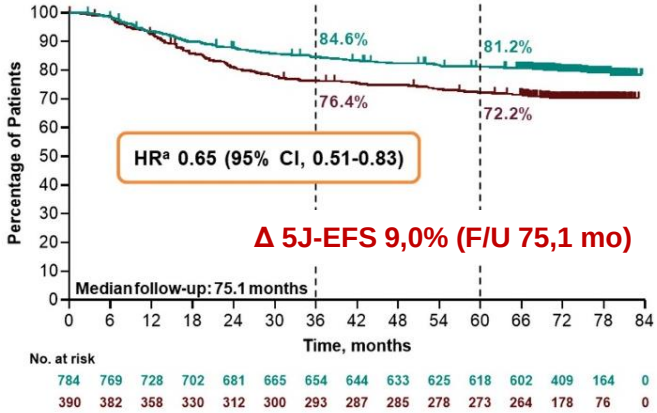
Travel support from:

AstraZeneca, Celgene, Daiichi Sankyo, Gilead, Pfizer, Roche

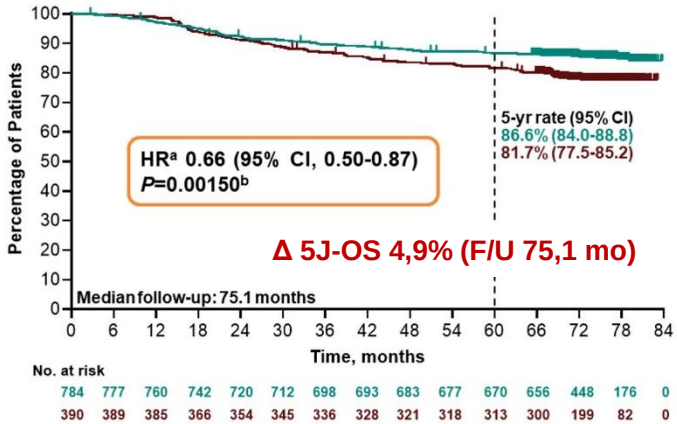
NCT

KEYNOTE-522 (Phase III): Neo/adjuvant SOC + Pembrolizumab vs. SOC + Placebo for eTNBC (N=1174, F/U 75,1 mo) – Study Design, EFS (Primary Endpoint), OS



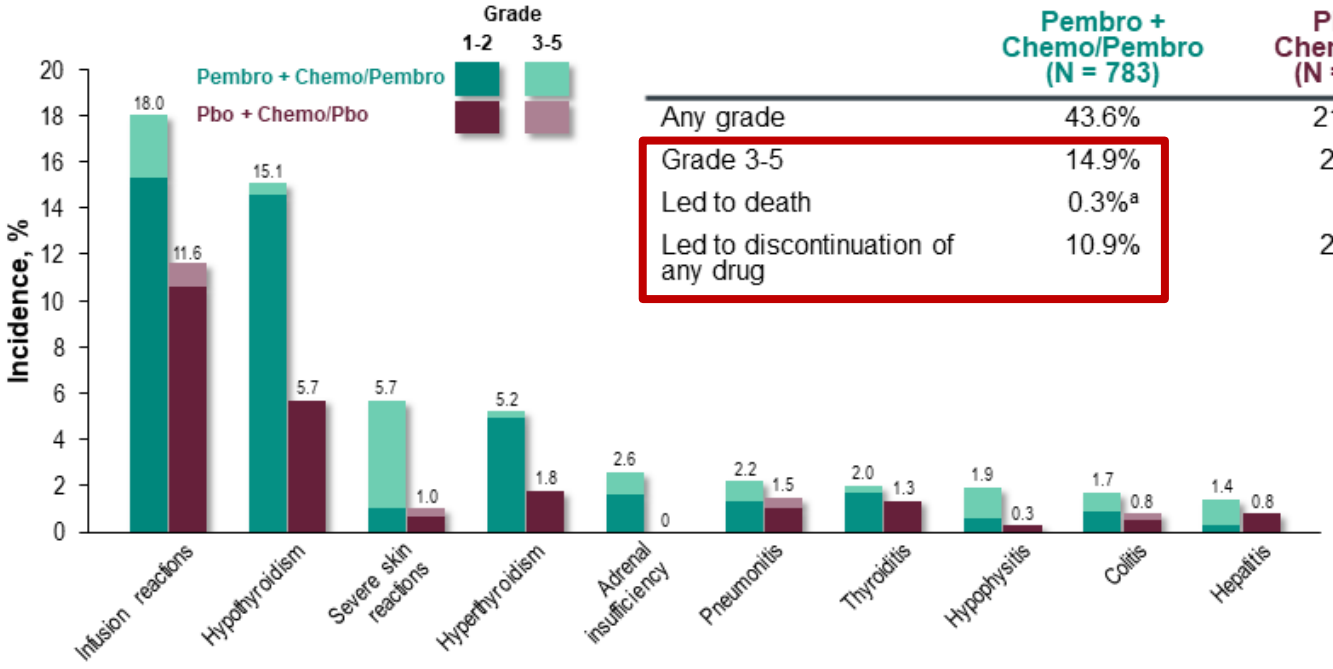


	Pts w/ Event
Pembro + Chemo/Pembro	20.3%
Placebo + Chemo/Placebo	29.2%



	Pts w/ Event
Pembro + Chemo/Pembro	14.7%
Placebo + Chemo/Placebo	21.8%

KEYNOTE-522 (Phase III) - Immun-related Adverse Events



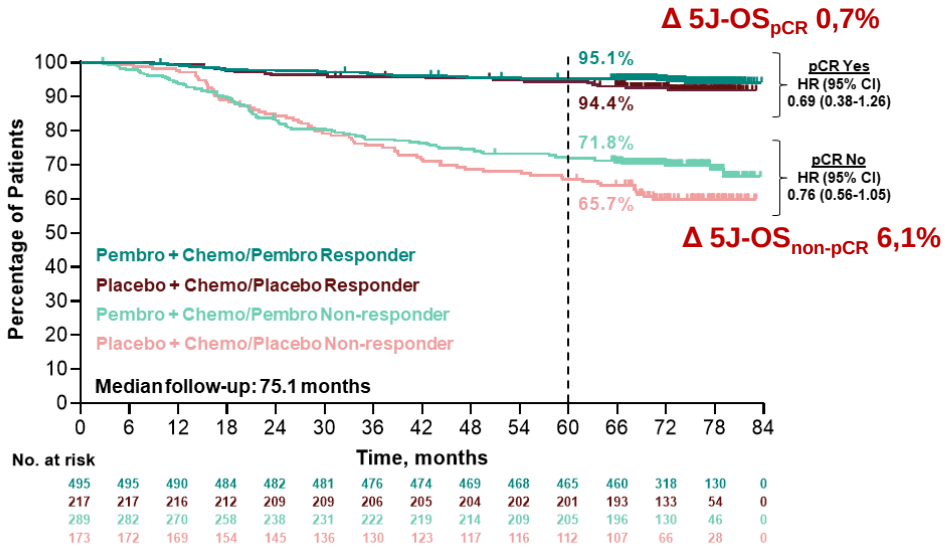
	Pembro + Chemo/Pembro (N = 783)	Pbo + Chemo/Pbo (N = 389)
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%
Led to death	0.3%[a]	0
Led to discontinuation of any drug	10.9%	2.6%

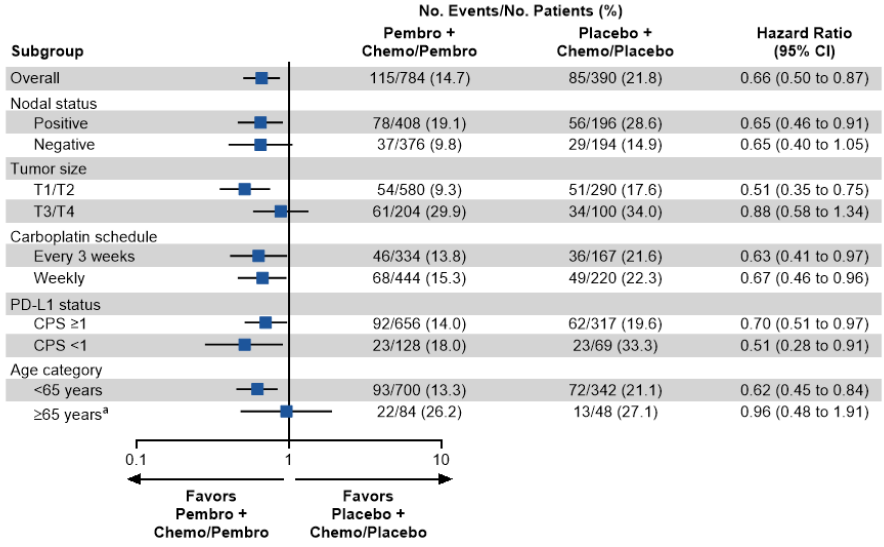
Immune-Mediated AEs and Infusion Reactions with Incidence ≥10 Patients

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

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

KEYNOTE-522 (Phase III): Neo/adjuvant SOC + Pembrolizumab vs. SOC + Placebo for eTNBC (N=1174, F/U 57,1 mo) – OS by pCR, Subgroups

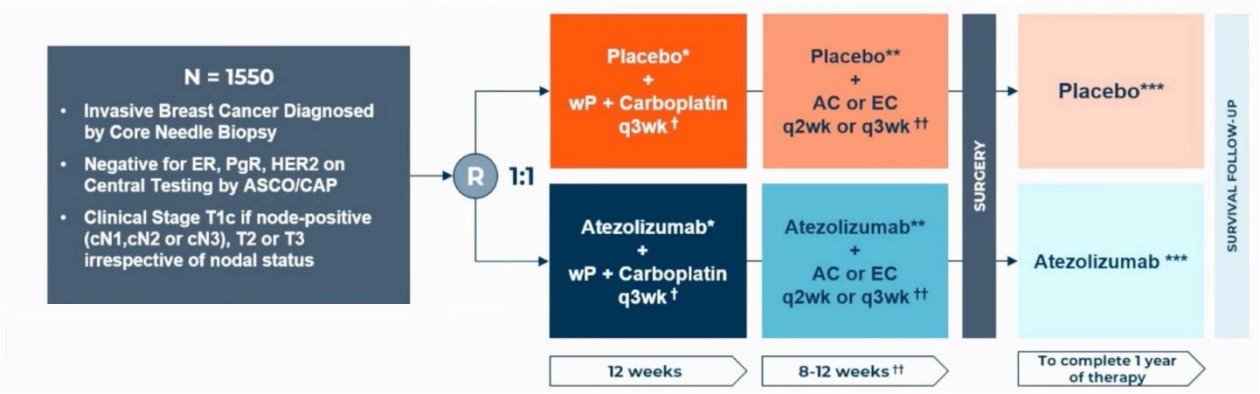


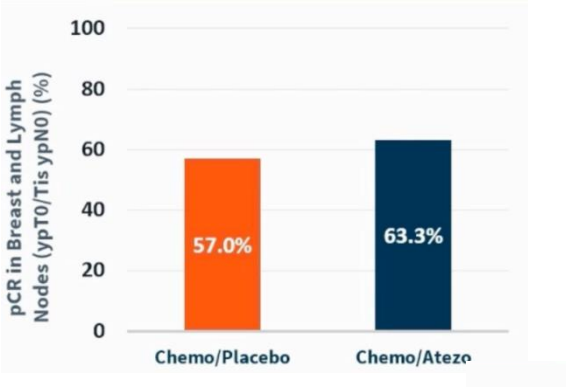


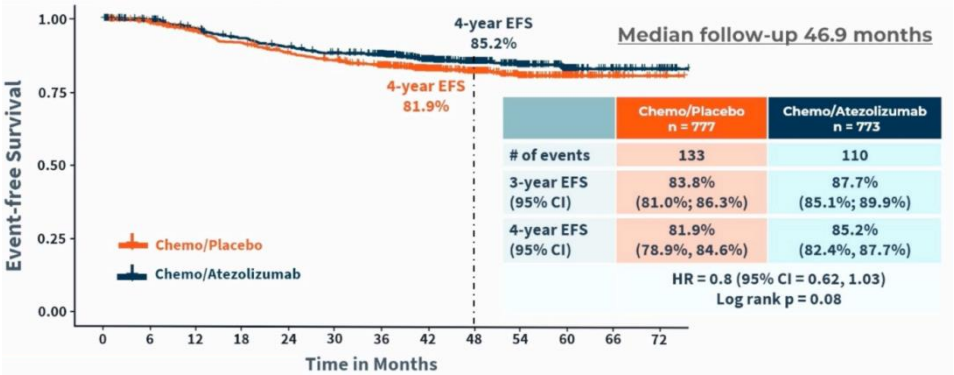
Beim **triple-negativen frühen Mammakarzinom** verbessert **ab T2** oder **bei N+** die **neoadjuvante plus adjuvante Gabe von Pembrolizumab** das **Überleben** auf Kosten einer erhöhten Toxizität. **Es existieren keine zusätzlichen prädiktiven Marker.**

Schmid P, et al. ESMO 2024 (LBA4).

NSABP B-59/GBG96-GEPARDOUZE (Phase III): Neoadjuvant SOC + Atezolizumab vs. SOC + Placebo for high-risk eTNBC (N=1550) – Study Design, pCR Rate, EFS

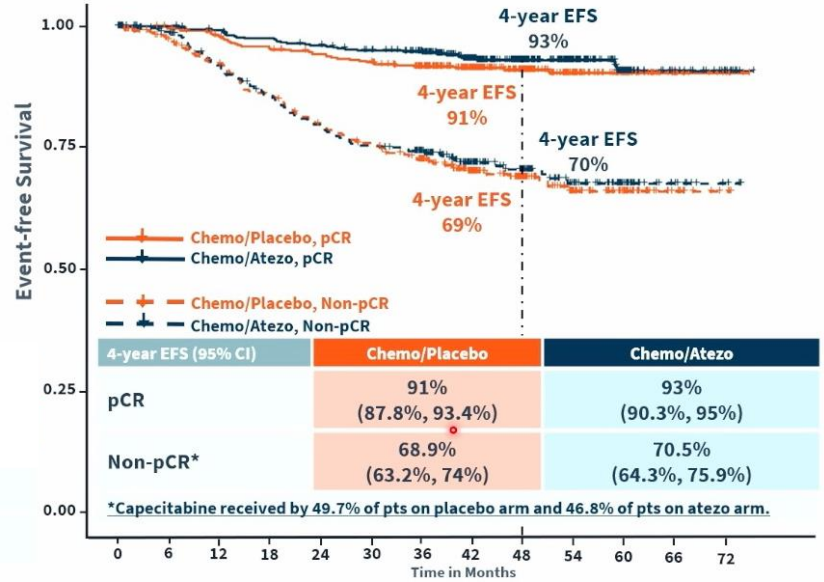






Geyer CE, et al. SABCS 2024 (GS3-05).

NSABP B-59/GBG96-GEPARDOUZE (Phase III): Neoadjuvant SOC + Atezolizumab vs. SOC + Placebo for high-risk eTNBC (N=1550) – EFS Subgroup Analysis

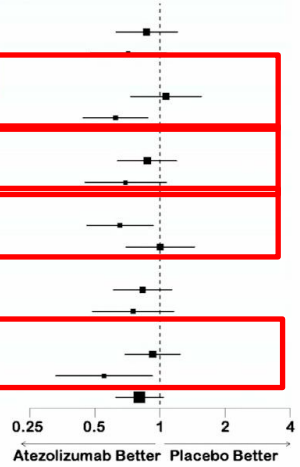


4-year EFS (95% CI)	Chemo/Placebo	Chemo/Atezo
pCR	91% (87.8%, 93.4%)	93% (90.3%, 95%)
Non-pCR*	68.9% (63.2%, 74%)	70.5% (64.3%, 75.9%)

*Capecitabine received by 49.7% of pts on placebo arm and 46.8% of pts on atezo arm.

Subgroup	N events/patients	HR (95% CI)	P	P for interaction
Group				0.457
GBG	146/978	0.868 (0.627, 1.202)	0.395	
NSABP	97/572	0.744 (0.478, 1.067)	0.100	
Clinical Nodal Status				0.039
Negative	109/901	1.066 (0.732, 1.552)	0.739	
Positive	134/649	0.623 (0.441, 0.879)	0.007	
AC/EC Schedule				0.401
Every 2 weeks	159/996	0.872 (0.638, 1.191)	0.389	
Every 3 weeks	84/554	0.694 (0.450, 1.069)	0.097	
Clinical Size of Primary Tumor				0.098
> 3.0 cm	128/647	0.653 (0.459, 0.929)	0.018	
1.1–3.0 cm	115/903	1.003 (0.696, 1.446)	0.986	
PD-L1 status				0.712
Negative/indeterminate/not available	160/853	0.831 (0.609, 1.135)	0.244	
Positive	83/697	0.752 (0.487, 1.160)	0.198	
TIL Category				0.086
<30%	180/960	0.925 (0.690, 1.239)	0.560	
>=30%	63/583	0.551 (0.330, 0.920)	0.023	
Overall	243/1550	0.805 (0.626, 1.037)	0.093	

X-axis is under log scale.

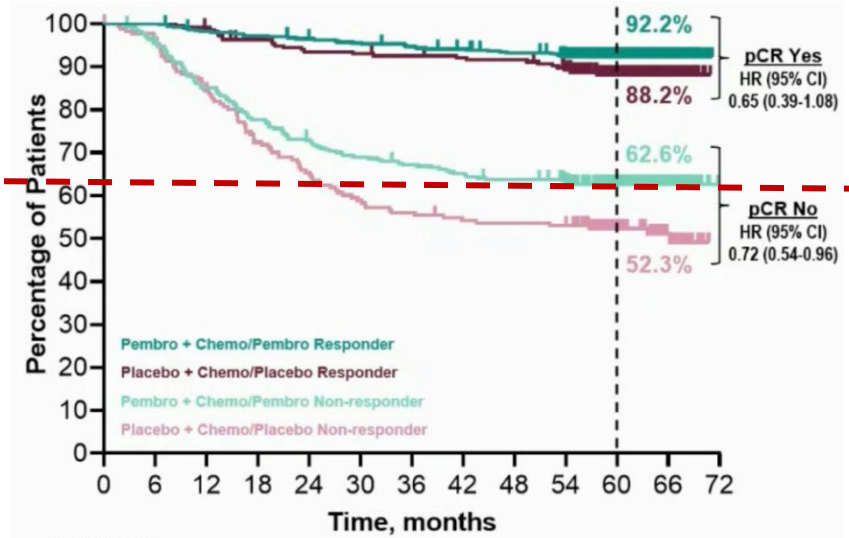


Beim **triple-negativen frühen Mammakarzinom ab T2** oder **bei N+** verbessert die **neoadjuvante plus adjuvante Gabe von Atezolizumab nicht das Ereignis-freie Überleben**. **Es existieren keine zusätzlichen prädiktiven Marker.** Trend für **höhere** Effektivität von Atezolizumab bei **hoher Tumorlast** (N+ , T > 3cm) und **TILs ≥ 30%**, **geringere** Effektivität bei **dosisdicht** EC/AC.

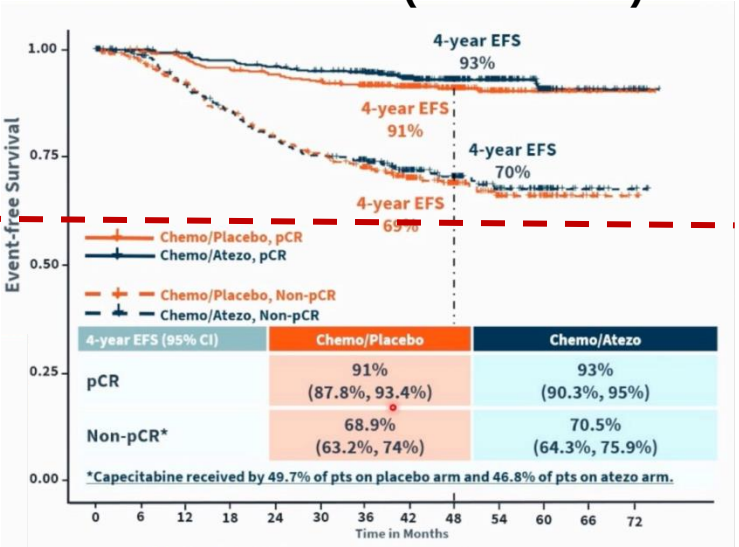
Geyer CE, et al. SABCS 2024 (GS3-05).

Immunotherapy in eTNBC: Main Differences Between KEYNOTE-522 and NSABP B-59/GBG96-GEPARDOUZE

KEYNOTE-522 (F/U 63 m)



GEPARDOUZE (F/U 46.9 m)



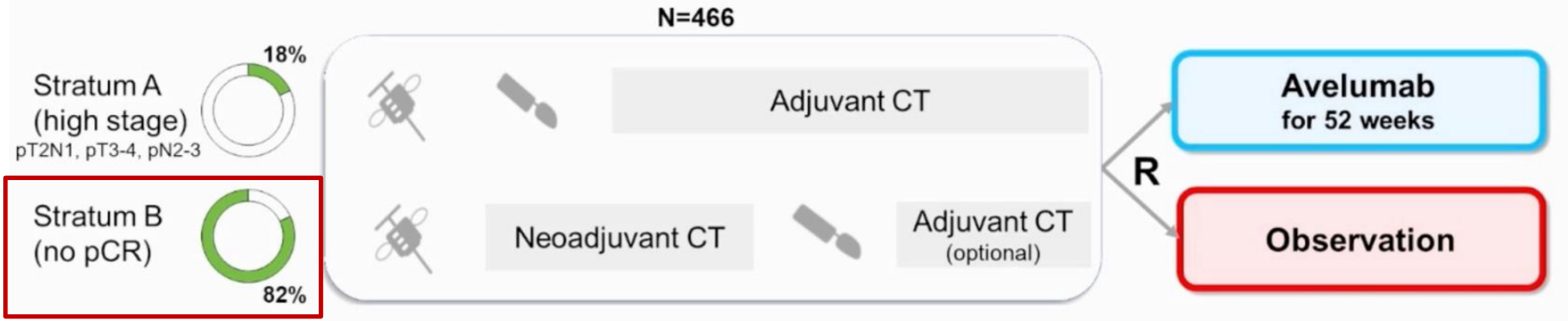
4-year EFS (95% CI)	Chemo/Placebo	Chemo/Atezo
pCR	91% (87.8%, 93.4%)	93% (90.3%, 95%)
Non-pCR*	68.9% (63.2%, 74%)	70.5% (64.3%, 75.9%)

Main Differences

- **N0: 48% vs. 59%**
- **ddEC/AC: 0 vs. 64%**
- **Capecitabine if no pCR: 0 vs. ~50%**
- **CPi Anti-PD-1 vs. Anti-PD-L1**

Schmid P, et al. ESMO 2023 (LBA18); Geyer CE, et al. SABCS 2024 (GS3-05).

A-BRAVE (Phase III): Postneo-/adjuvant Avelumab vs. Observation for high-risk eTNBC (N=466) – Study Design, 3y-DFS (Primary Endpoint), DDFS, OS

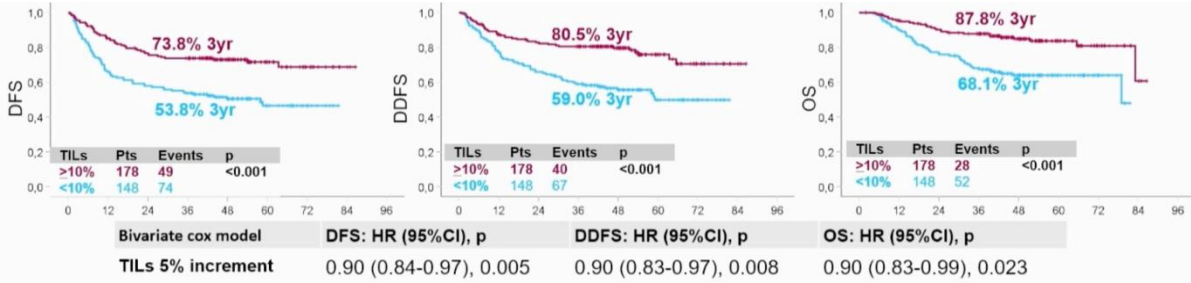


Endpoint and population			Δ 3-yr rate	HR (95% CI)
DFS	ITT	Co-primary	+ 5.1%	**0.81** (0.61-1.09)
	Post-neoadj	Co-primary	+ 6.2%	**0.80** (0.58-1.10)

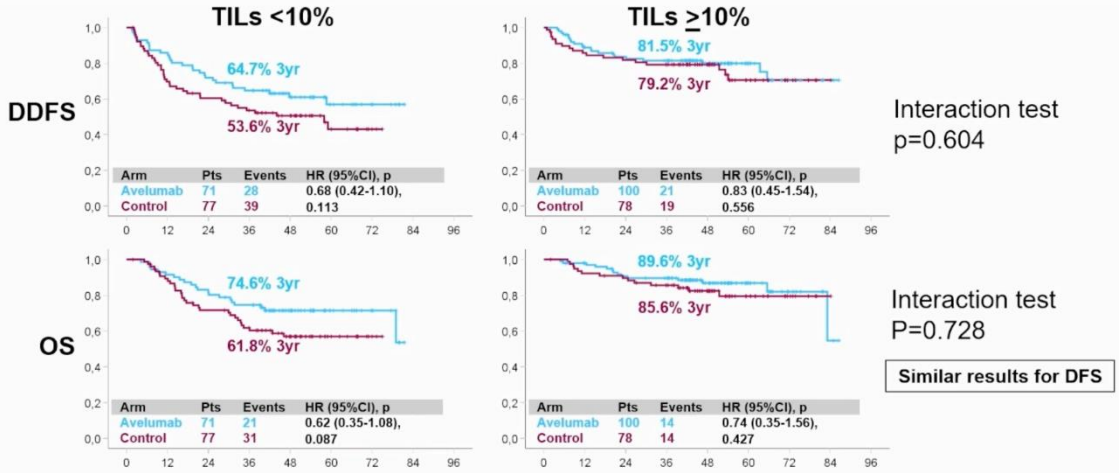
Endpoint and population			Δ 3-yr rate	HR (95% CI)
OS	ITT	Secondary	+ 8.5%	**0.66** (0.45-0.97)
DDFS	ITT	Exploratory	+ 7.5%	**0.70** (0.50-0.96)

Conte PF, et al. ASCO 2024 (LBA500); Dieci MV, et al. SABCS 2024 (RF3-02).

A-BRAVE (Phase III): Postneo-/adjuvant Avelumab vs. Observation for high-risk eTNBC (N=326) – Tumor Infiltrating Lymphocytes (TILs)



Bivariate cox model	DFS: HR (95%CI), p	DDFS: HR (95%CI), p	OS: HR (95%CI), p
TILs 5% increment	0.90 (0.84-0.97), 0.005	0.90 (0.83-0.97), 0.008	0.90 (0.83-0.99), 0.023



***TILs** are*

- **prognostic**
  in high-risk eTNBC, but
- **not predictive**
  for efficacy of avelumab

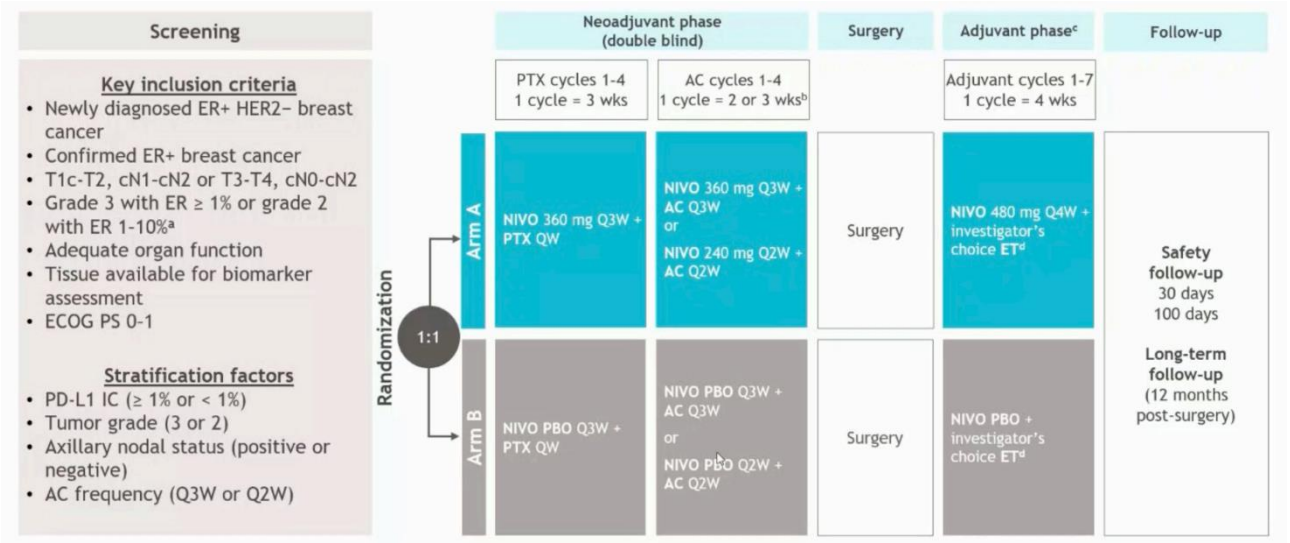
Similar results for **PD-L1 expression** and **residual cancer burden (RCB)**

(trend for better efficacy of avelumab for higher RCB)

TILs und PD-L1 Expression (prätherapeutisch) sowie **RCB** sind **nicht prädiktiv** für die Wirksamkeit von **Avelumab** beim TNBC und non-pCR nach NACT

Dieci MV, et al. SABCS 2024 (RF3-02).

CheckMate (Phase III): NACT + Nivolumab vs. NACT + Placebo → Surgery → 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

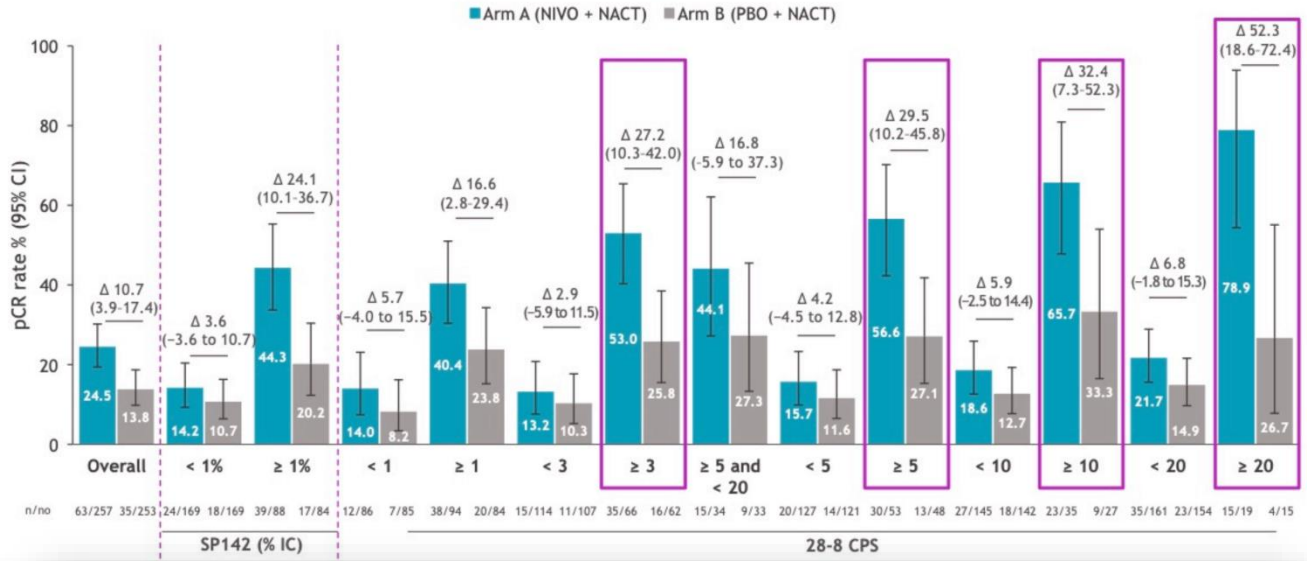
- EFS (unavailable for this presentation)

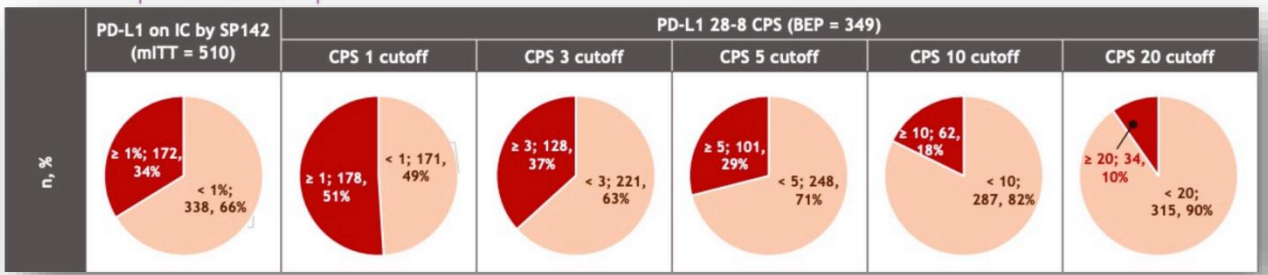
- **99% Grad 3**
- **44% Stadium III**
- **80% N+**
- **34% PD-L1 ≥ 1% (SP142)**

- **Primärer Endpunkt: pCR**
- **EFS *nur* exploratorisch**

Loi S, et al. ESMO 2023 (LBA20).

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



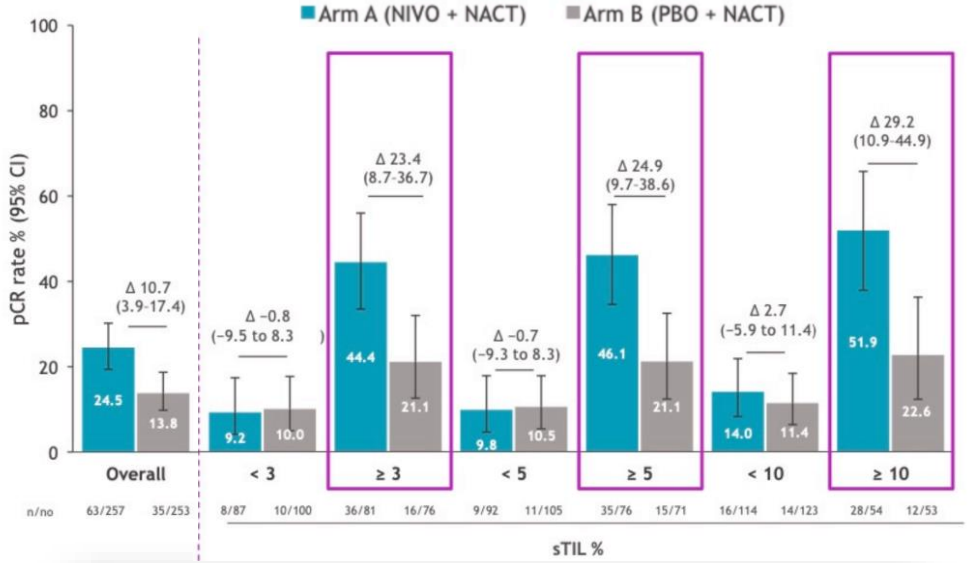


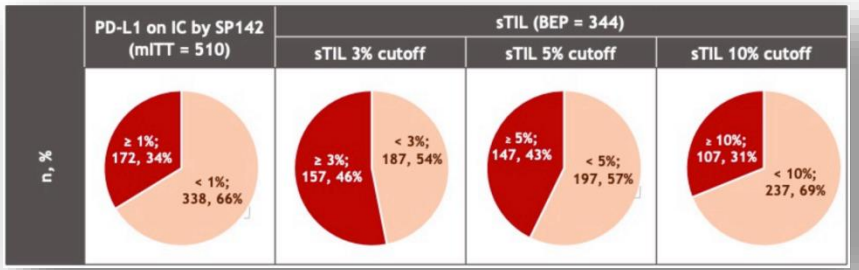
Δ_{pCR} 16,6 - 52,3%

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

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

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



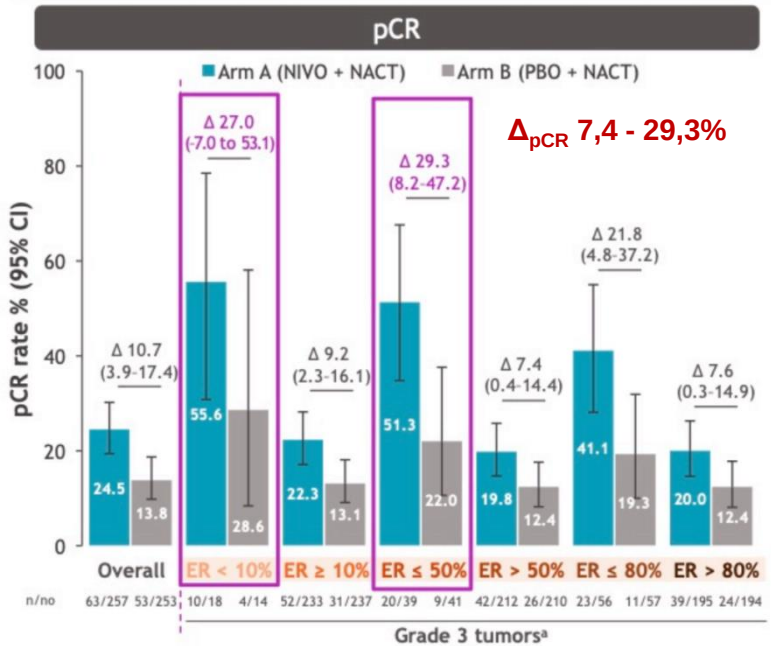


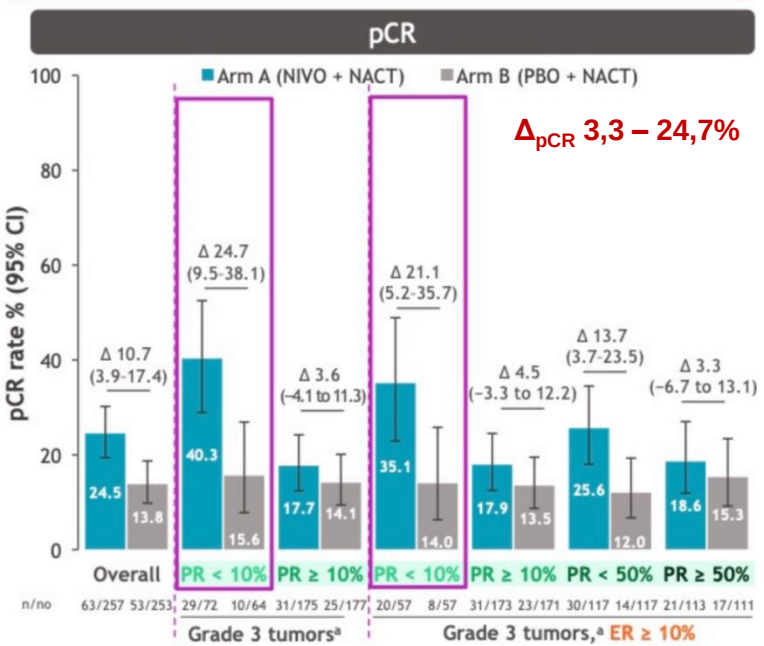
Δ_{pCR} 23,4 - 29,2%%

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

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

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

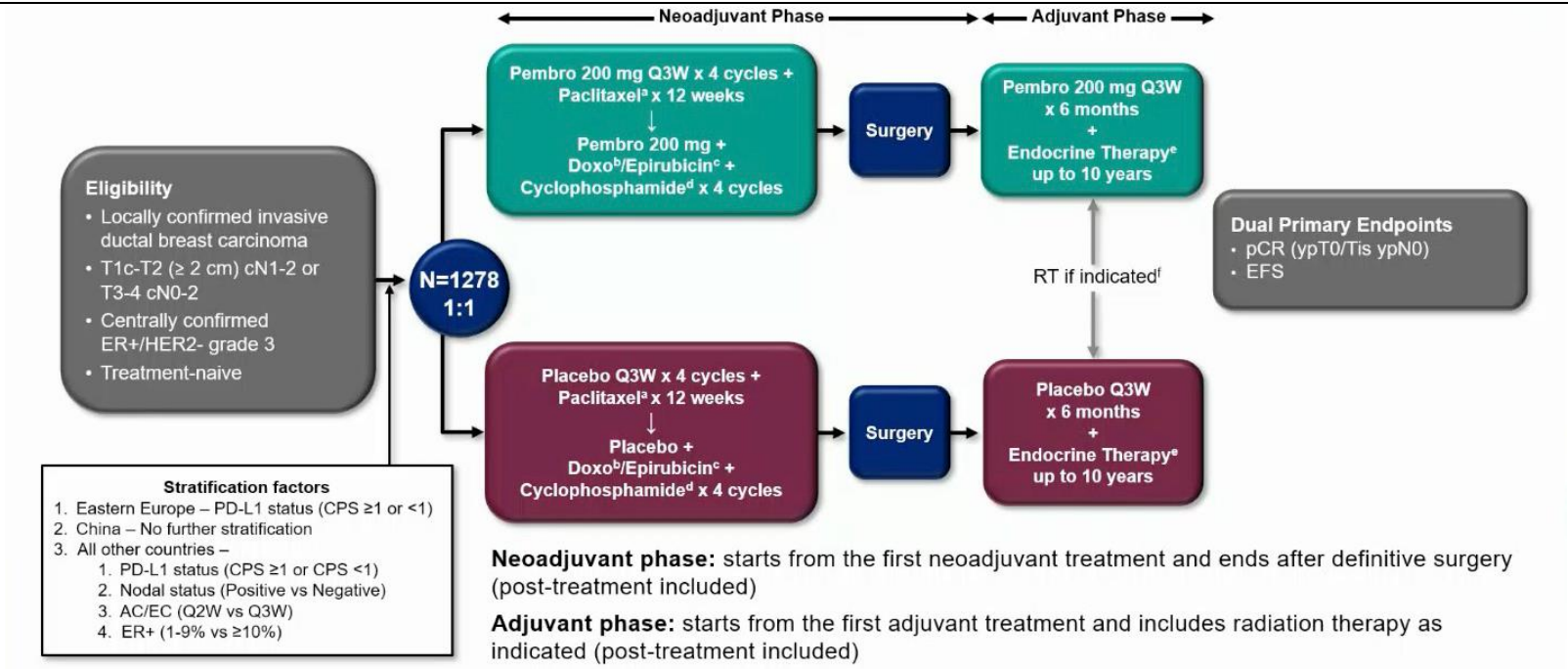




- **Welches Δ_{pCR} rechtfertigt die zusätzliche Toxizität?**
- ***Keine* Überlebensdaten**

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

KEYNOTE-756 (Phase III): Neo-/adjuvant Pembrolizumab + CT vs. Placebo + CT for ER+ HER2- EBC (N=1278, F/U 33,2 Mo) – Study Design

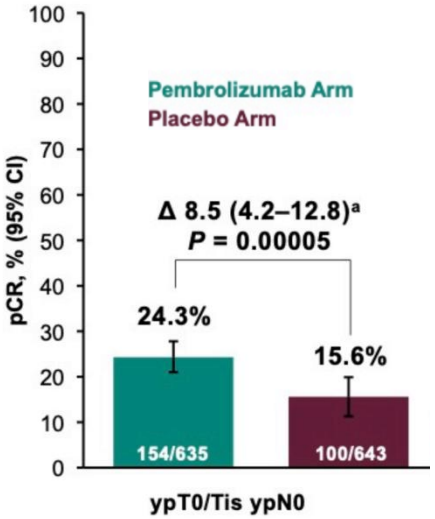


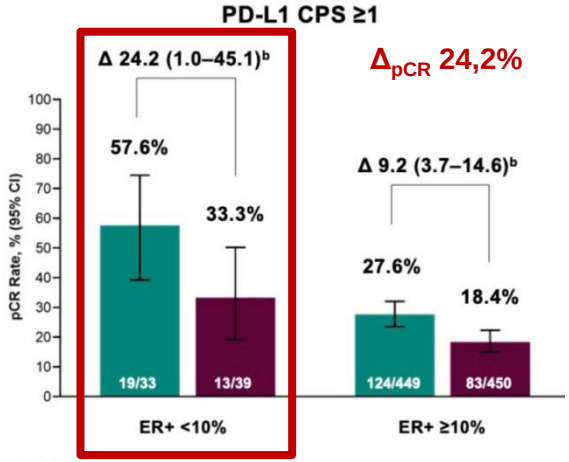
- **100% Grad 3**
- **90% N+**
- **76% PD-L ≥ 1% (CPS)**

- **Ko-primäre Endpunkte: pCR *und* EFS**

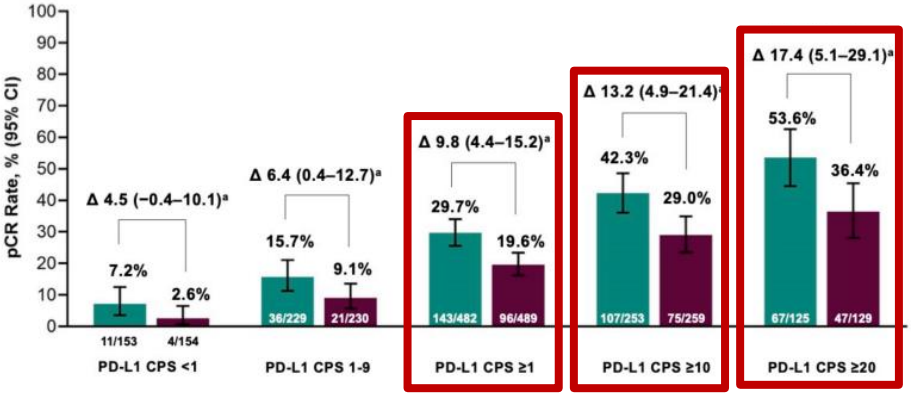
Cardoso F, et al. ESMO 2023 (LBA21).

KEYNOTE-756 (Phase III): Neo-/adjuvant Pembrolizumab + CT vs. Placebo + CT for ER+ HER2- EBC (N=1278, F/U 33,2 Mo) – pCR by PD-L1 and ER Expression





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).

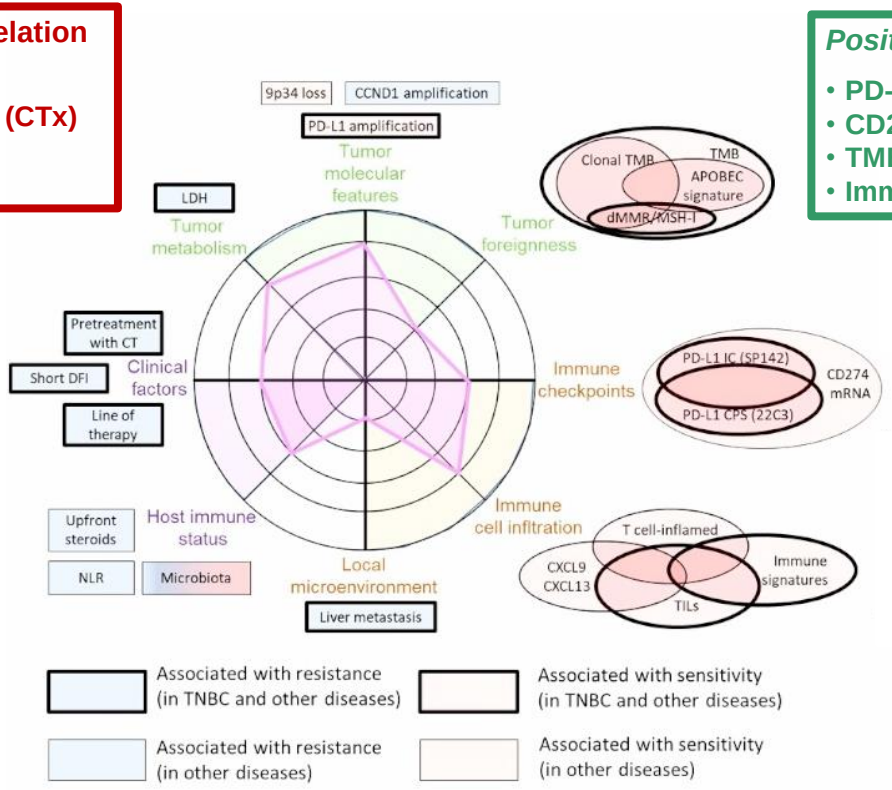
Checkpoint-Inhibitoren beim frühen Mammakarzinom

- Wann sollen sie derzeit eingesetzt werden?
  - Neoadjuvant beginnen und adjuvant komplettieren
- Bei welchem Subtyp?
  - Nur beim eTNBC ab T2 oder bei N+
- Welcher Checkpoint-Inhibitor sollte verwendet werden?
  - Pembrolizumab
- In Kombination mit welcher Chemotherapie?
  - Anthrazyklin, Cyclophosphamid, Carboplatin, Taxan
- Gibt es weitere prädiktive Marker?
  - Nein, aber weitere Analysen sind absolut sinnvoll!

Urgent Need of Precision Immunology (Rose Chart)

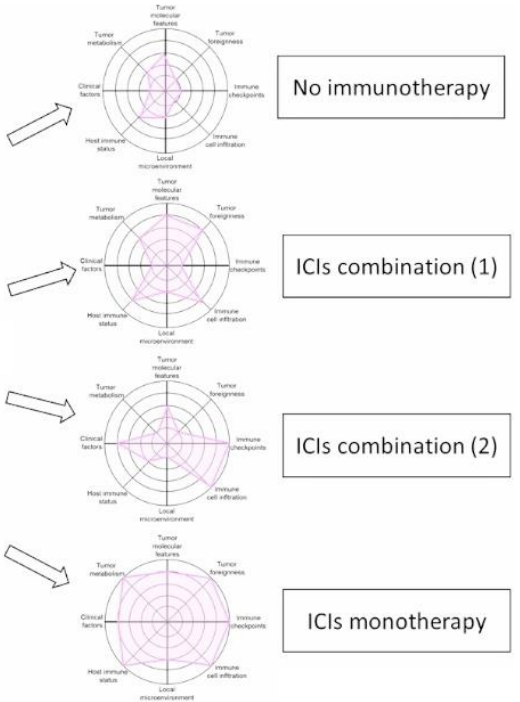
***Negative* correlation**

- **LDH**
- **Pretreatment (CTx)**
- **Short DFI**
- **Liver mets**



***Positive* correlation**

- **PD-L1 amplification**
- **CD274 mRNA↑**
- **TMB**
- **Immune signatures**



Bianchini G SABCS 2023 (GS01-01, Discussion).

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

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