Neoadjuvante Therapie
Was bringt uns die Zukunft

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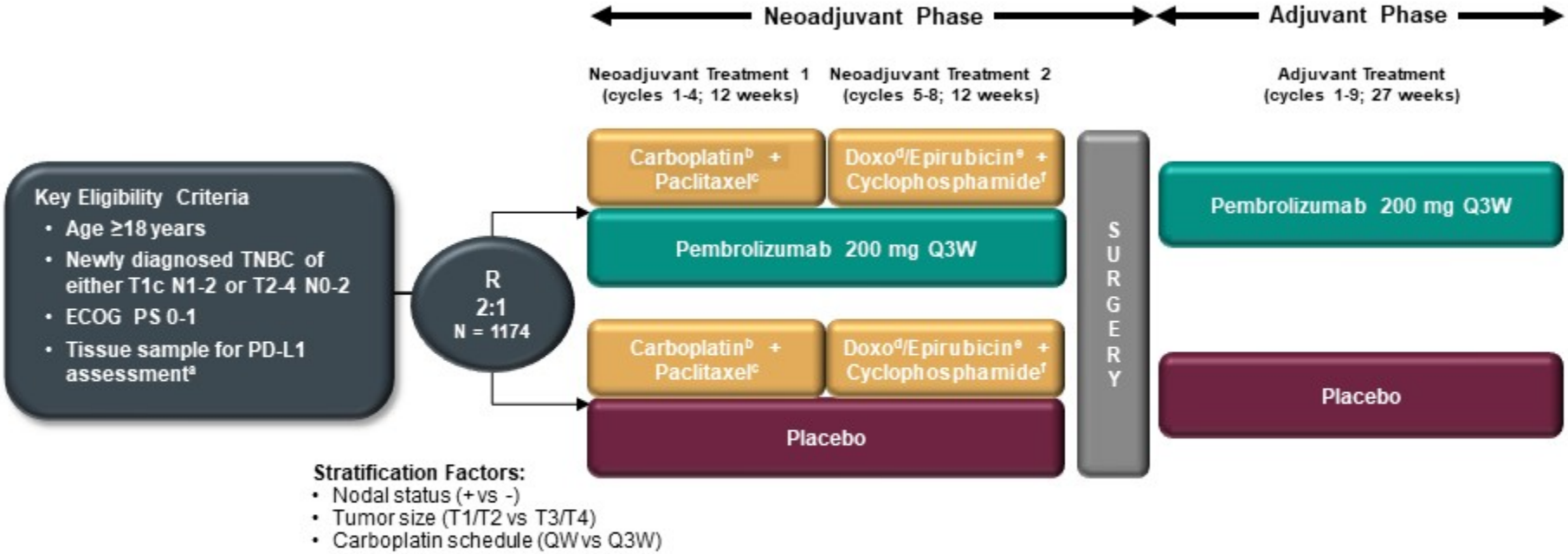
Neoadjuvante Therapie – Was bringt uns die Zukunft

Triple negatives Mammakarzinom

HER2 positives Mammakarzinom

KEYNOTE-522 Study Design (NCT03036488)



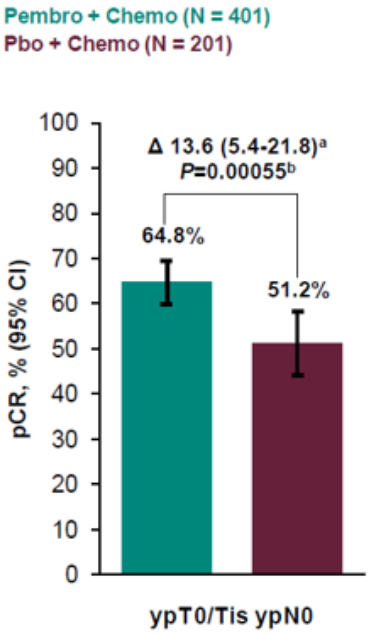
Stratification Factors:
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (QW vs Q3W)

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

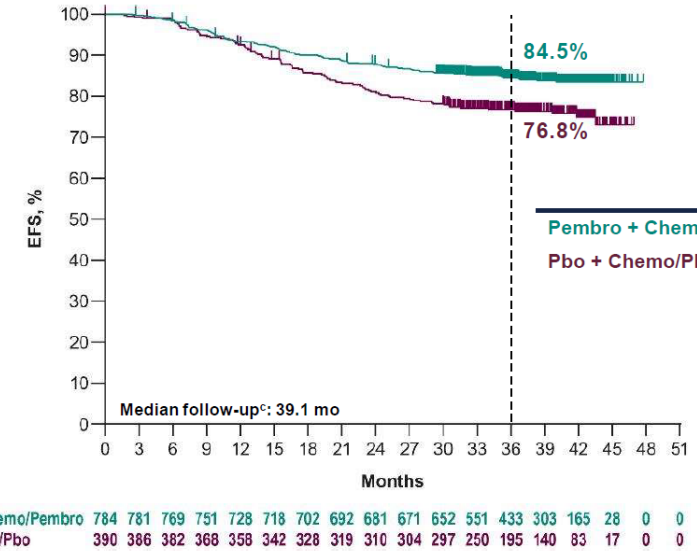
Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[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.

Primary pCR Endpoint at IA1[1]



Statistically Significant and Clinically Meaningful EFS at IA4

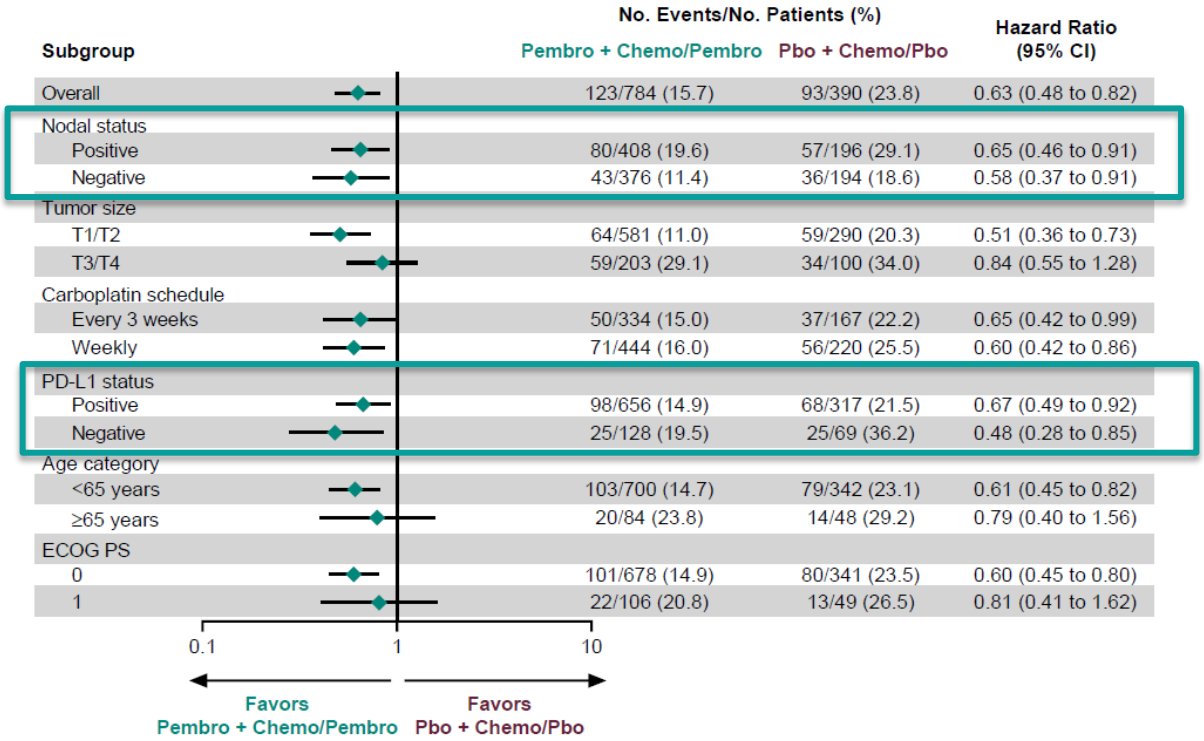


	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[a] (0.48-0.82)	0.00031[b]
Pbo + Chemo/Pbo	23.8%		

Summary of First EFS Events by Category

Event	All Subjects, N = 1174	
	Pembro + Chemo/Pembro N = 784	Pbo + Chemo/Pbo N = 390
Any EFS event	123 (15.7%)	93 (23.8%)
Progression of disease that precludes definitive surgery	14 (1.8%)	15 (3.8%)
Local recurrence[a]	28 (3.6%)	17 (4.4%)
Distant recurrence	60 (7.7%)	51 (13.1%)
Secondary primary malignancy[b]	6 (0.8%)	4 (1.0%)
Death	15 (1.9%)	6 (1.5%)

EFS in Patient Subgroups



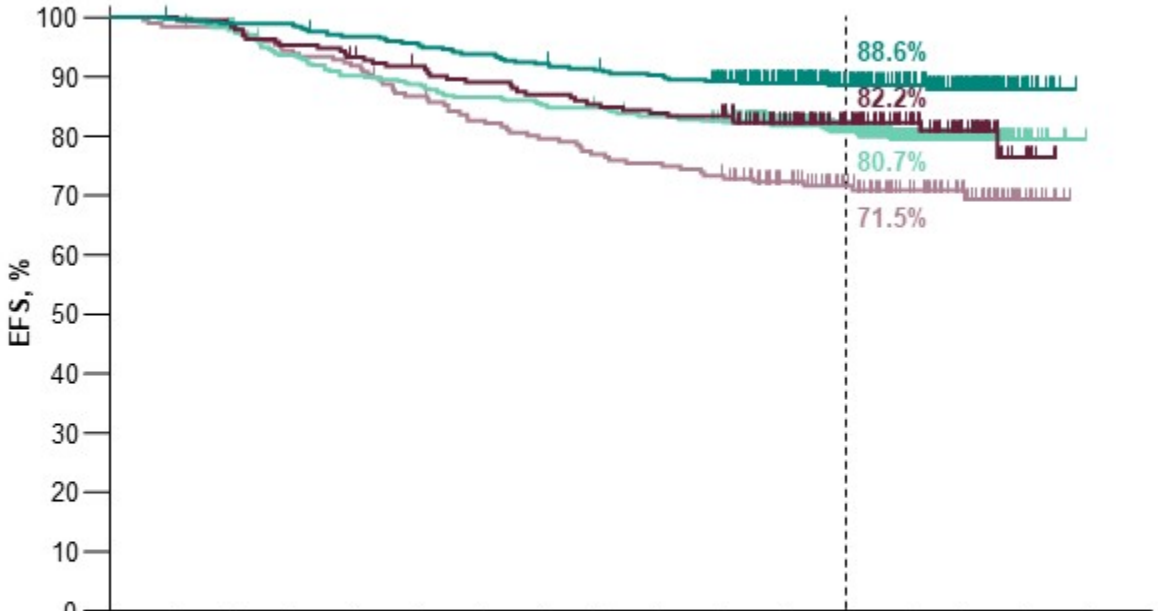
EFS by Nodal Status

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

7.2%

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

9.5%



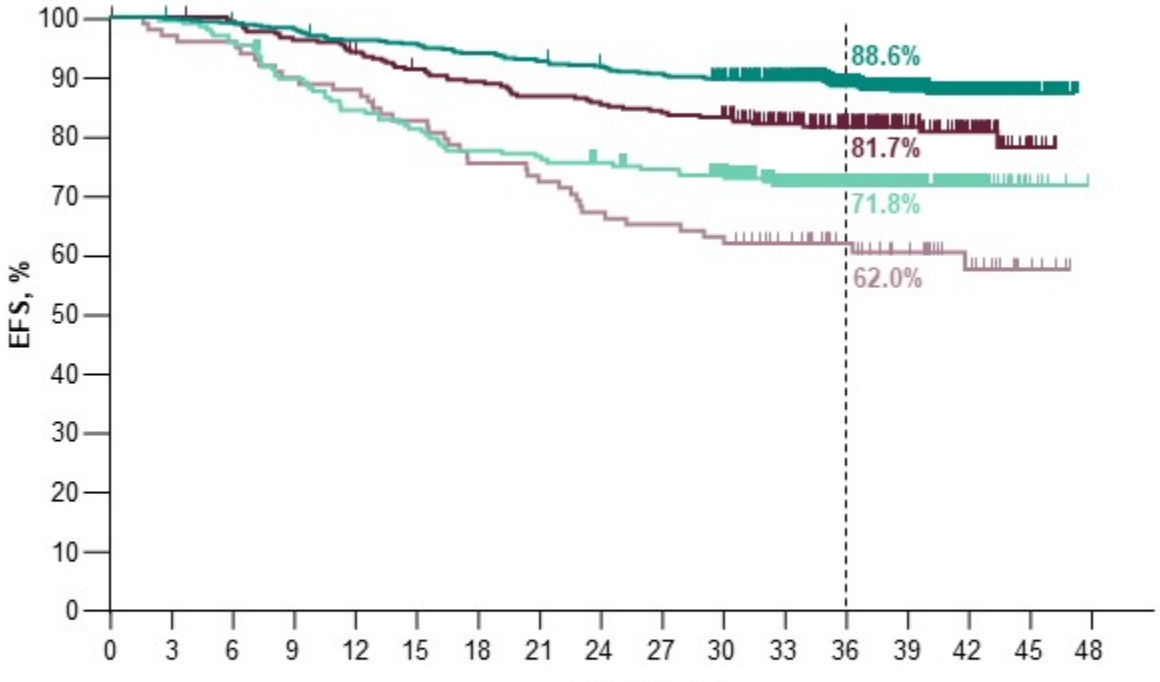
No. at risk																	
Pembro+Chemo/Pembro, Node Negative	376	374	371	371	362	358	351	345	338	335	322	272	212	151	81	16	0
Pbo+Chemo/Pbo, Node Negative	194	193	190	184	179	174	169	165	162	159	157	131	101	71	39	7	0
Pembro+Chemo/Pembro, Node Positive	408	407	398	380	366	360	351	347	343	336	330	279	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.

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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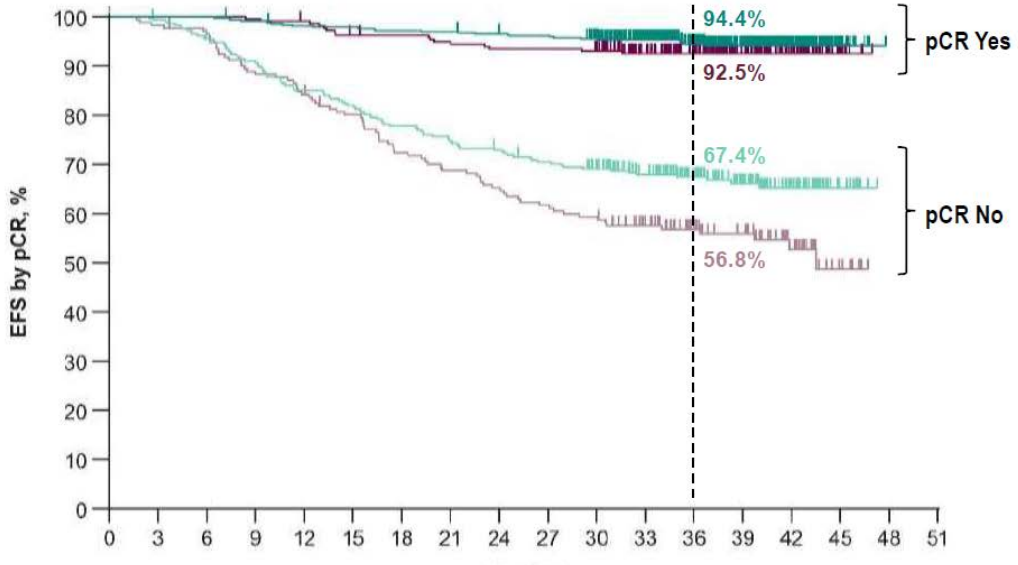
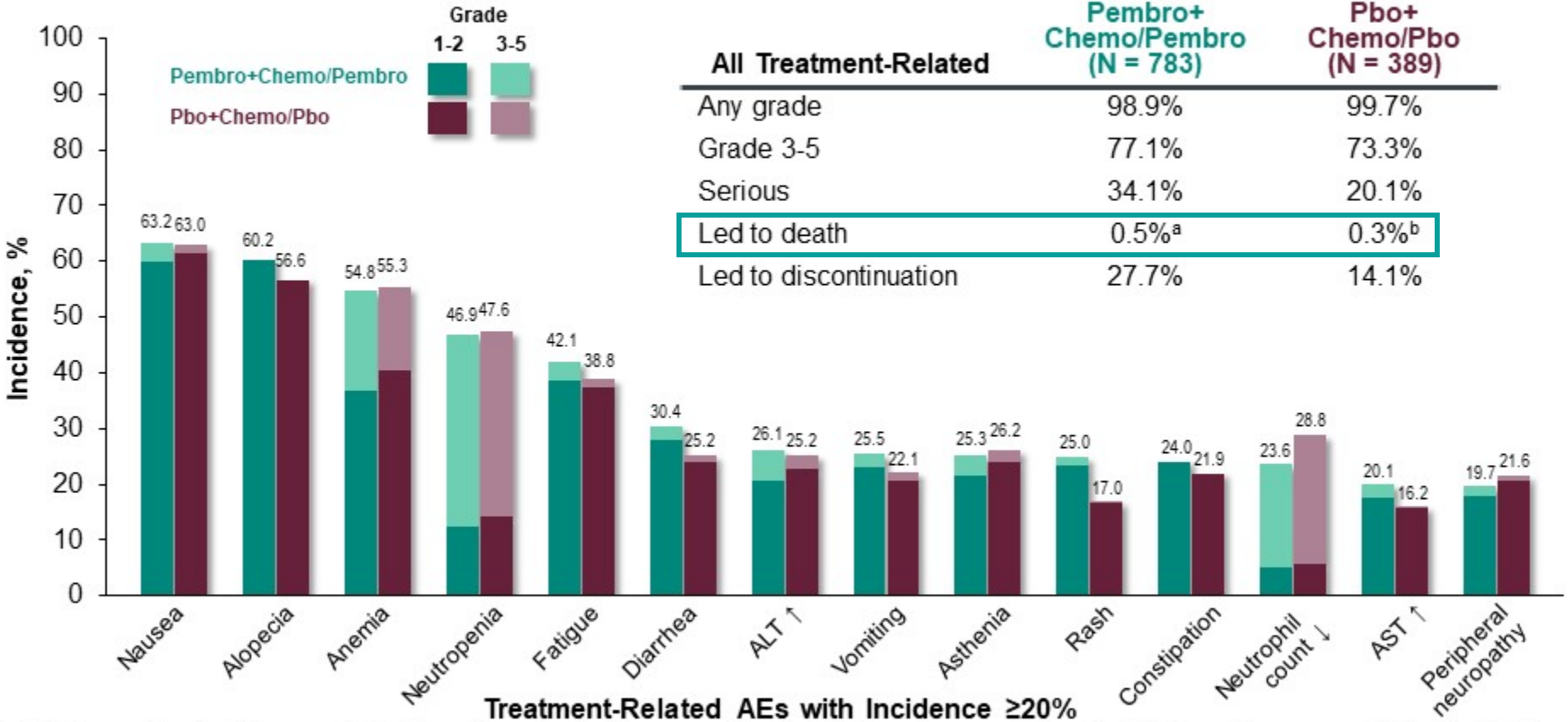
EFS by pCR (ypT0/Tis ypN0)



No. at Risk																		
Pembro + Chemo/Pembro Responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
Pbo + Chemo/Pbo Responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
Pembro + Chemo/Pembro Non-Responder	290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
Pbo + Chemo/Pbo Non-Responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

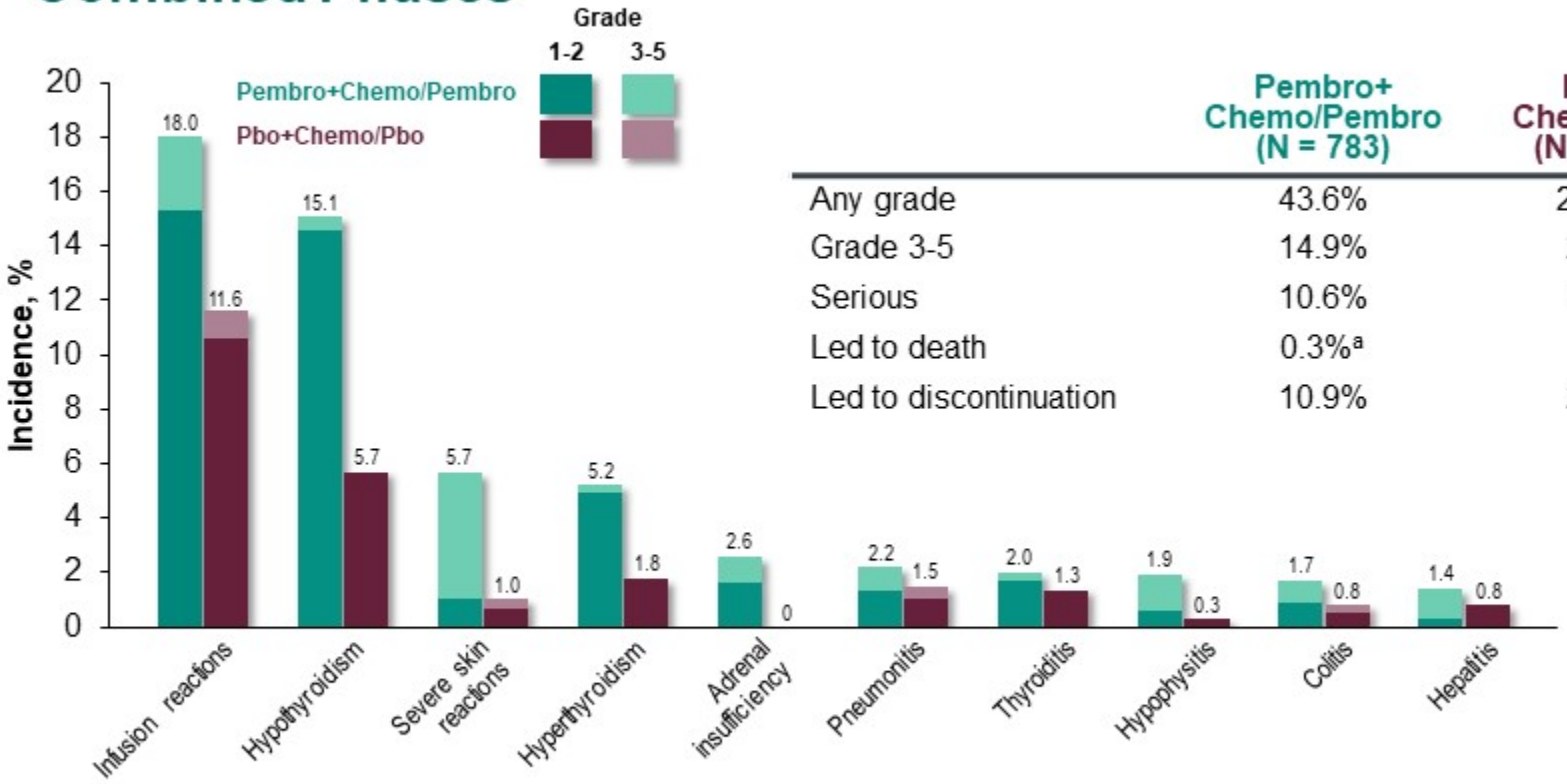
Treatment-Related AEs in Combined Phases

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.

Immune-Mediated AEs and Infusion Reactions in Combined Phases

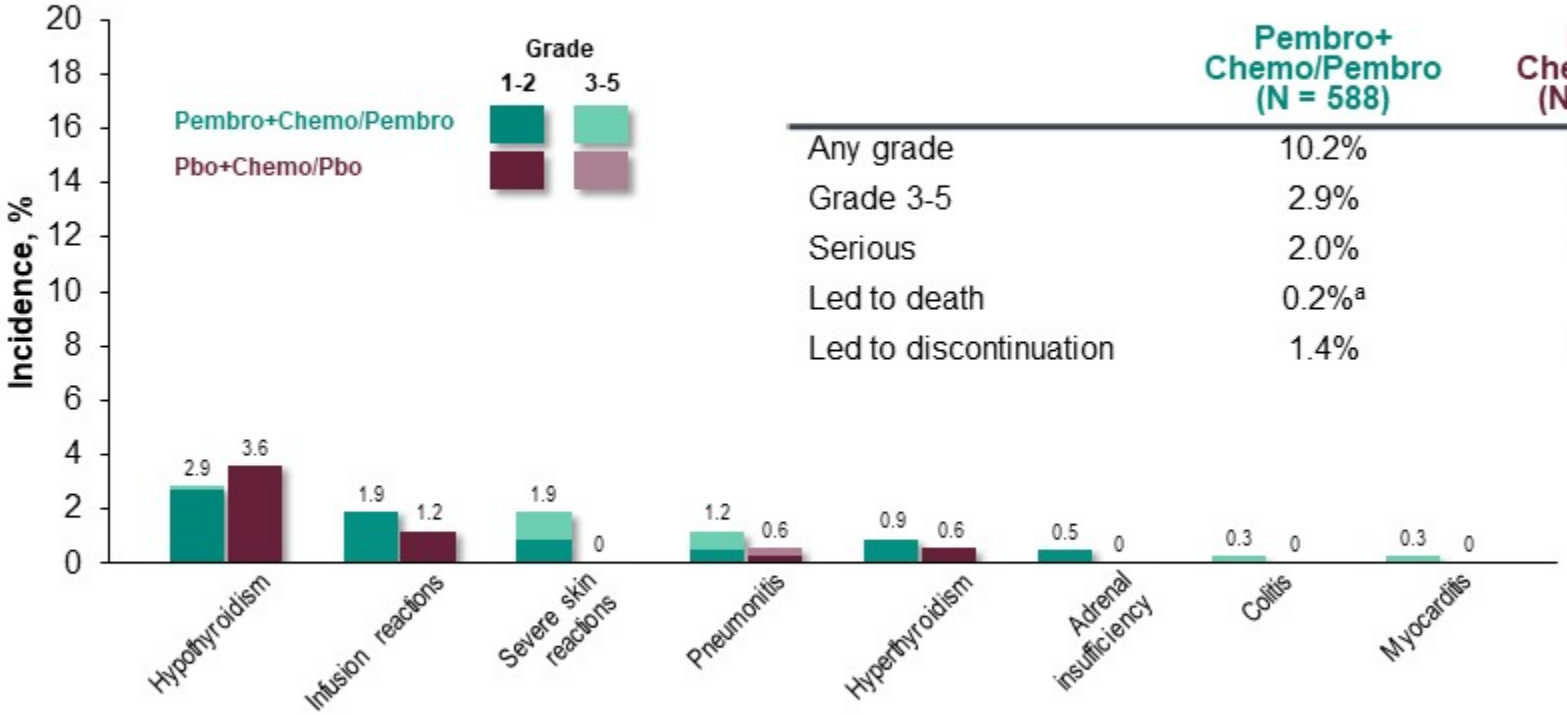


	Pembro+ Chemo/Pembro (N = 783)	Pbo+ Chemo/Pbo (N = 389)
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%
Serious	10.6%	1.3%
Led to death	0.3%[a]	0
Led to discontinuation	10.9%	2.6%

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.

Immune-Mediated AEs and Infusion Reactions in Adjuvant Phase

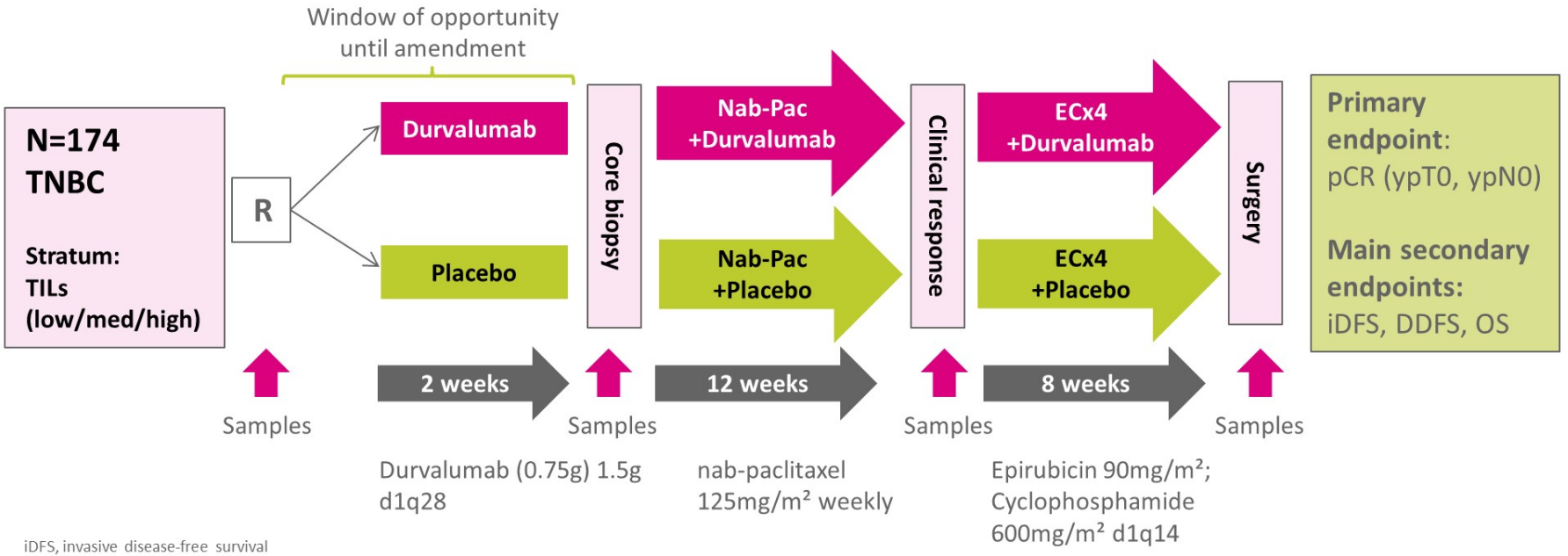


	Pembro+ Chemo/Pembro (N = 588)	Pbo+ Chemo/Pbo (N = 331)
Any grade	10.2%	6.0%
Grade 3-5	2.9%	0.3%
Serious	2.0%	0.3%
Led to death	0.2%[a]	0
Led to discontinuation	1.4%	0.3%

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.

Study Design

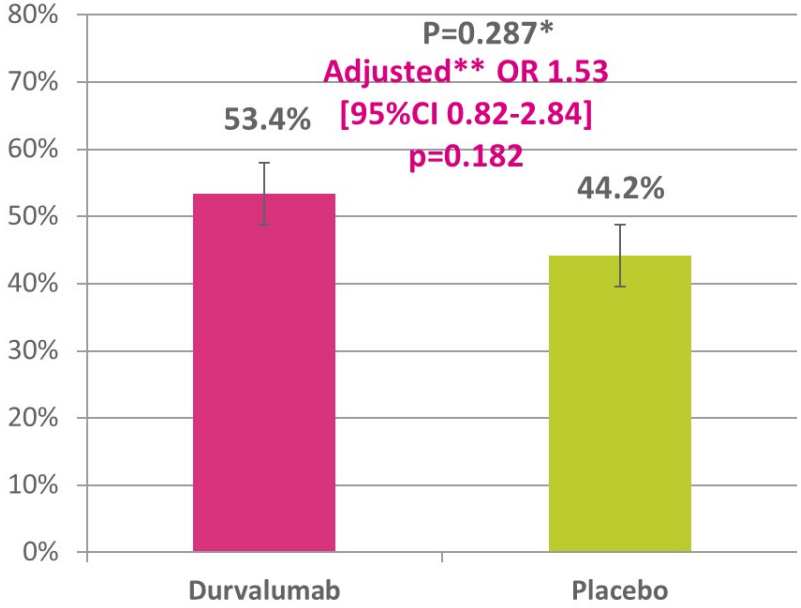


iDFS, invasive disease-free survival
DDFS, distance disease-free survival
OS, overall survival

Loibl S, et al. Ann Oncol 2019

Efficacy Endpoints

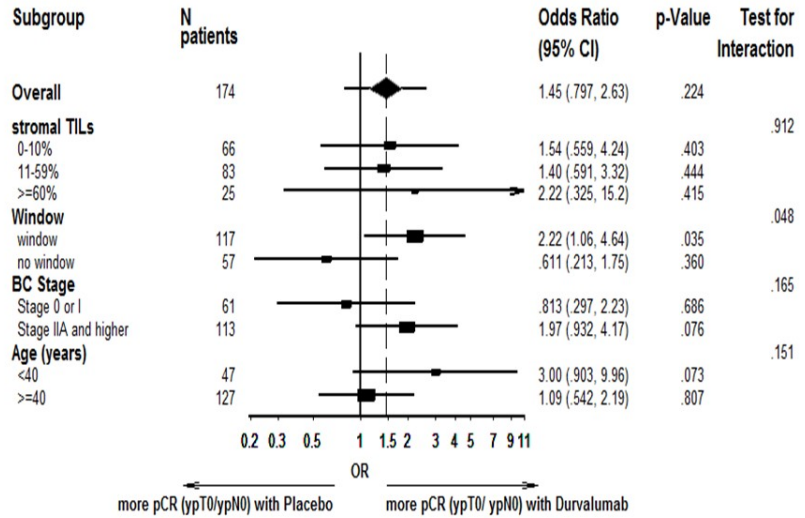
Primary endpoint: pCR – ypT0, ypN0



* Continuous corrected χ^2 test
** For stratification factor (TIL groups)

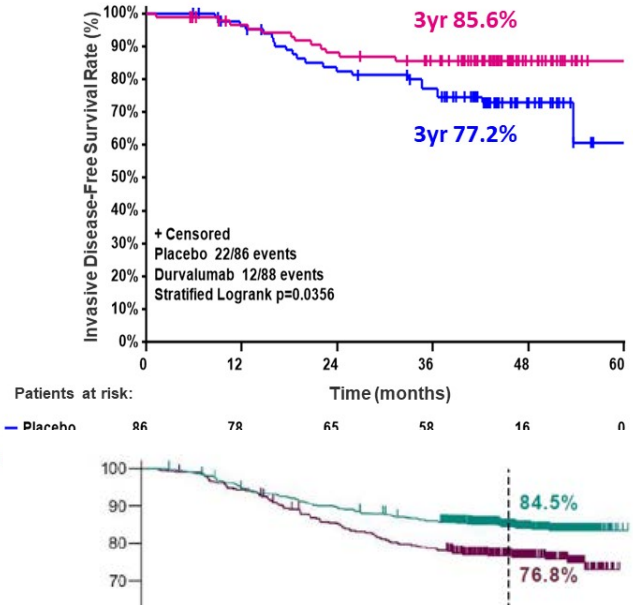
Loibl S, et al. Ann Oncol 2019

Subgroup Analyses (predefined)

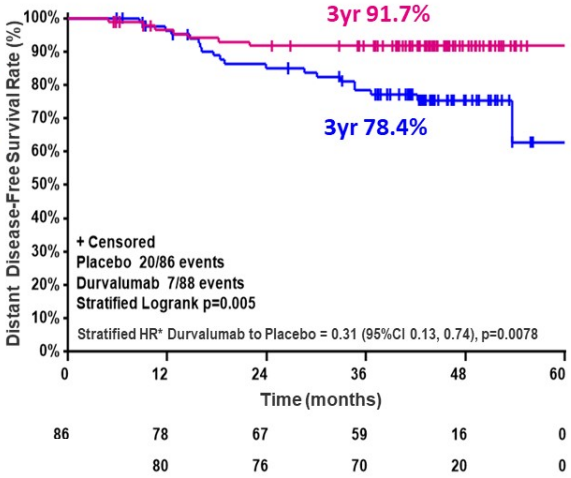


iDFS, DDFS and OS Between Treatment Arms

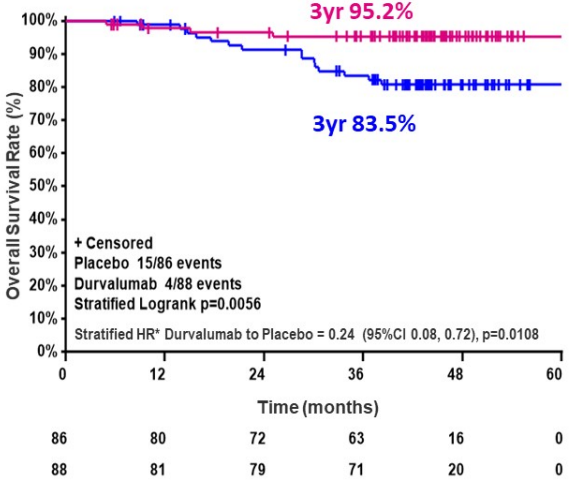
iDFS



DDFS



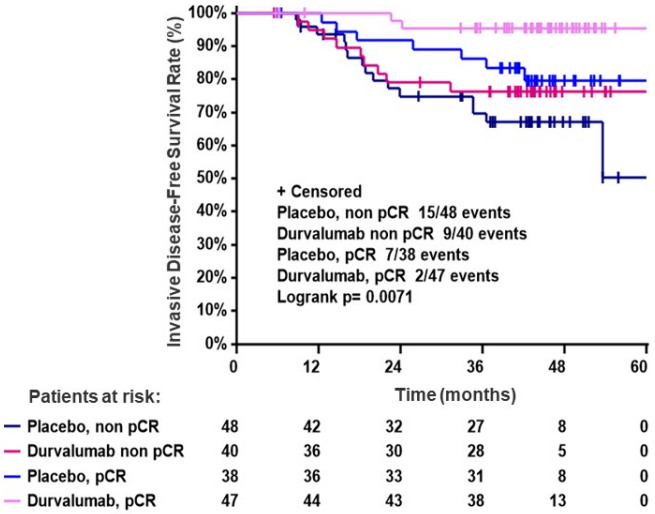
OS



* Stratified by sTILs

iDFS, DDFS and OS by pCR and Treatment Arm

iDFS

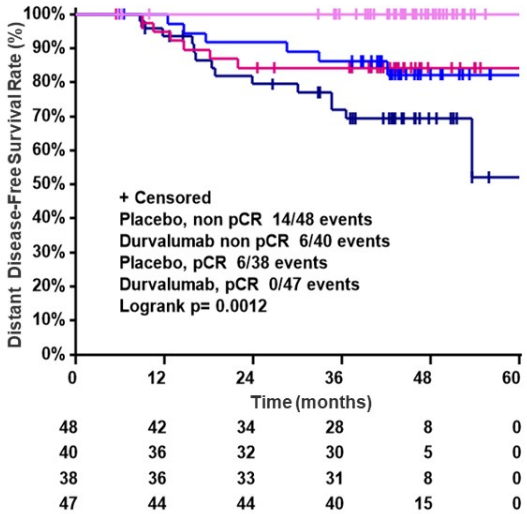


Patients at risk:

Placebo, non pCR	48	42	32	27	8	0
Durvalumab non pCR	40	36	30	28	5	0
Placebo, pCR	38	36	33	31	8	0
Durvalumab, pCR	47	44	43	38	13	0

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

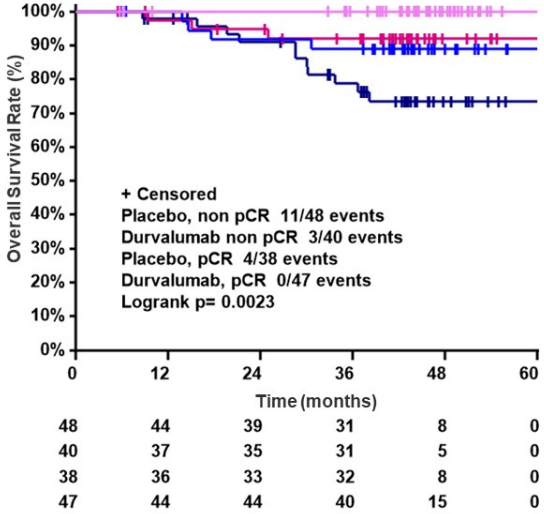
DDFS



Placebo, non pCR	48	42	34	28	8	0
Durvalumab non pCR	40	36	32	30	5	0
Placebo, pCR	38	36	33	31	8	0
Durvalumab, pCR	47	44	44	40	15	0

HR (non-pCR vs pCR) 0.28
(95%CI 0.11-0.69)
log-rank p=0.003

OS



Placebo, non pCR	48	44	39	31	8	0
Durvalumab non pCR	40	37	35	31	5	0
Placebo, pCR	38	36	33	32	8	0
Durvalumab, pCR	47	44	44	40	15	0

HR (non-pCR vs pCR)=0.27
(95%CI 0.09-0.81)
log-rank p=0.012

Neoadjuvante Therapie - Was bringt uns die Zukunft Triple negatives Mammakarzinom

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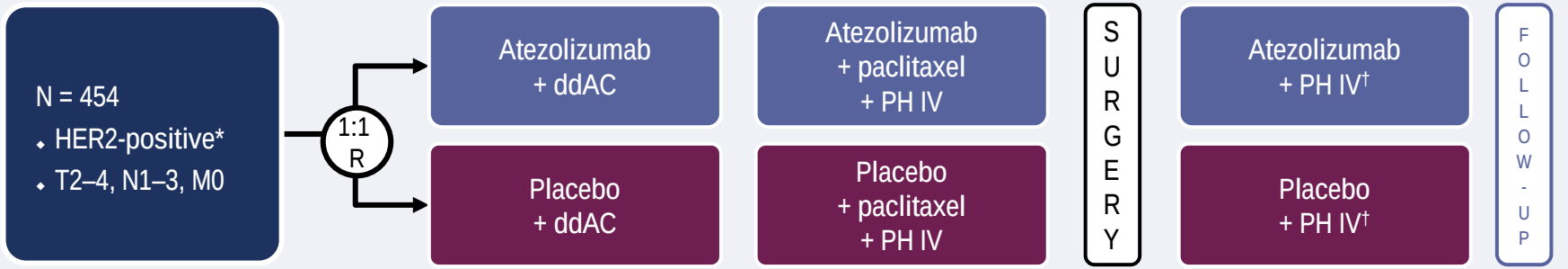
- pCR kein alleiniger primärer Endpunkt in neoadjuvanten (Immuntherapie) Studien
- Alle Pat mit TNBC > 2cm zusätzlich Immuntherapie? **Prädiktoren**
- Optimale Therapie bei TNBC < 2cm und cN0 ? **Deeskalation**
- **Adjuvante Therapie** nach primärer Chemo-Immuntherapie:
  - *wenn **pCR** weiter Immuntherapie erforderlich?*
  - *wenn **keine pCR**:*
    33% mit Rezidiv nach 3 Jahren: Wechsel der Therapie, z.B. Sacituzumab Govitecan (Saskiastudie) oder andere Therapie
  - *Molekulare Sequenzierung und zielgerichtete Therapie*
- **Zirkulierende DNA** zum Monitoring sinnvoll? Frühe Intervention bei MRD?

IMpassion050: Study design



Stratification factors:
- Stage T2 vs. T3-4
- ER-positive and/or PgR-positive vs. ER-negative and PgR-negative*
- PD-L1 IC 0 vs. IC 1/2/3*

Co-primary endpoints: pCR (ypT0/is ypN0) in the ITT and PD-L1-positive (IC 1/2/3; staining in ≥1% of tumour area) populations‡

Secondary endpoints: pCR in the PD-L1-negative (IC 0) population, EFS, OS, safety

Atezolizumab was given at 840 mg q2w during Cycles 1–4 and 1200 mg q3w thereafter; ddAC, at 60 mg/m^2/600 mg/m^2 q2w; paclitaxel, at 80 mg/m^2 qw; P, at 840 mg during Cycle 5 and 420 mg q3w thereafter; H, at 8 mg/kg during Cycle 5 and 6 mg/kg q3w thereafter.

* Centrally assessed. Inclusion of patients with hormone receptor-positive disease was capped at 50%.

† Patients with residual disease could switch HER2-directed therapy to trastuzumab emtansine 3.6 mg/kg q3w at the discretion of the treating physician.

‡ Following a study amendment to co-power for PD-L1-positivity. PD-L1 staining was assessed using the VENTANA SP142 antibody.

ddAC, dose-dense doxorubicin and cyclophosphamide; EFS, event-free survival; ER, oestrogen receptor; H, trastuzumab; ITT, intent-to-treat; IV, intravenous; OS, overall survival; P, pertuzumab; pCR, pathological complete response (ypT0/is ypN0); PD-L1 IC, PD-L1-expressing tumour-infiltrating immune cells as percentage of tumour area; PgR, progesterone receptor; q2w, every 2 weeks, q3w, every 3 weeks, qw, every week.

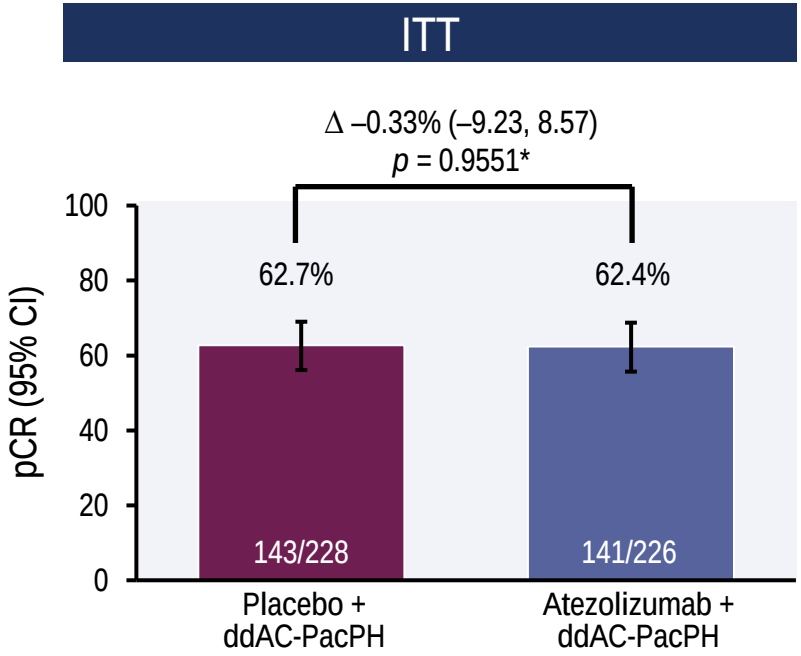
Huober J et al. 2021

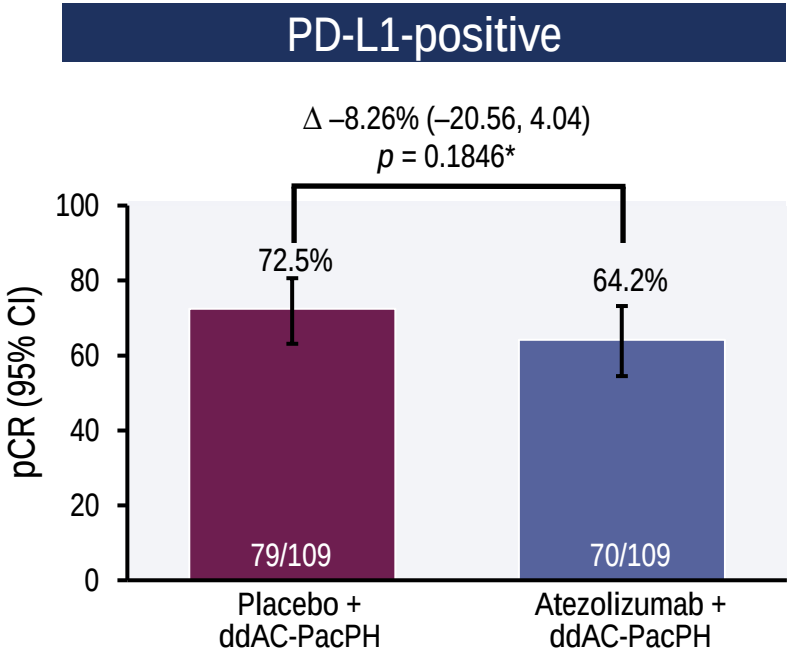
IMpassion050: Baseline demographics and disease characteristics in the ITT population

	Placebo + ddAC-PacPH (n = 228)	Atezolizumab + ddAC-PacPH (n = 226)
Age		
Median, years	50.0	50.0
<65, n (%)	207 (90.8)	204 (90.3)
≥65, n (%)	21 (9.2)	22 (9.7)
Sex, n (%)		
Female	227 (99.6)	225 (99.6)
Male	1 (0.4)	1 (0.4)
Race, n (%)		
White	142 (62.3)	149 (65.9)
Asian	66 (28.9)	62 (27.4)
Black or African American	13 (5.7)	8 (3.5)
American Indian or Alaska Native	1 (0.4)	1 (0.4)
Multiple or unknown	6 (2.6)	6 (2.7)
ECOG Performance Status, n (%)		
0	215 (94.3)	215 (95.1)
1	13 (5.7)	11 (4.9)
Staging of primary tumour, n (%)		
T2	151 (66.2)	150 (66.4)
T3–4	77 (33.8)	76 (33.6)
Staging of regional lymph nodes, n (%)		
N1	157 (68.9)	169 (74.8)
N2	46 (20.2)	38 (16.8)
N3	25 (11.0)	19 (8.4)
Hormone receptor status, n (%)		
ER-positive and/or PgR-positive	117 (51.3)	116 (51.3)
ER-negative and PgR-negative	111 (48.7)	110 (48.7)
PD-L1 status, n (%)		
IC 0 (negative)	119 (52.2)	117 (51.8)
IC 1/2/3 (positive)	109 (47.8)	109 (48.2)

Baseline demographics and disease characteristics were also balanced in the PD-L1-positive population.
ddAC, dose-dense doxorubicin and cyclophosphamide; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; H, trastuzumab; ITT, intent-to-treat; P, pertuzumab; Pac, paclitaxel; PD-L1 IC, PD-L1-expressing tumour-infiltrating immune cells as percentage of tumour area; PgR, progesterone receptor.

IMpassion050: Co-primary endpoints – pCR in the ITT and PD-L1-positive populations





https://bit.ly/3wSoe3d

* Stratified (Cochran-Mantel-Haenszel test).

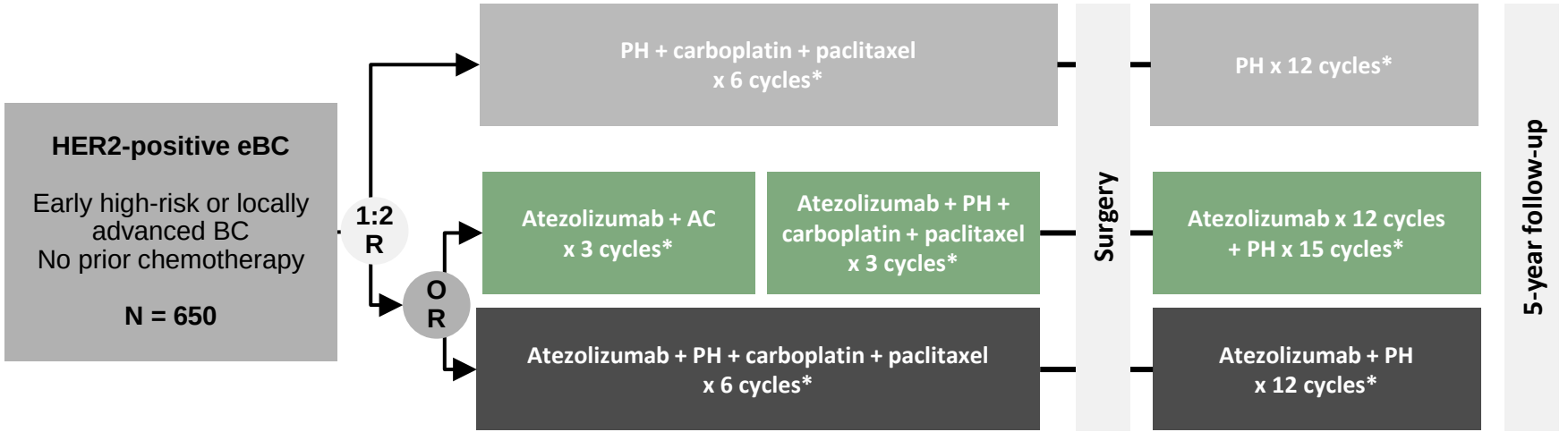
CI, confidence interval; ddAC, dose-dense doxorubicin and cyclophosphamide; H, trastuzumab; ITT, intent-to-treat; P, pertuzumab; Pac, paclitaxel; pCR, pathological complete response (ypT0/is ypN0).

IMpassion050: Deaths

Patient status	Placebo + ddAC-PacPH (n = 225)	Atezolizumab + ddAC-PacPH (n = 226)
AEs leading to death, number of patients (%)	0	5 (2.2)
Neoadjuvant phase		Alveolitis (Day 75)*
		Sepsis (Day 72)
		COVID-19 (Day 115)
		Septic shock (Day 166)*
Adjuvant phase		COVID-19 (Day 265)
Disease recurrence listed as cause of death, number of patients	3	1
Other, number of patients	1 (primary gastric cancer)	0
Total, number of patients (%)	4 (1.8)	6 (2.7)

Safety population.
Selected comorbidities and confounding factors:
Alveolitis: 81-year-old patient with vertebral fracture complicated by pneumonia in a patient with pulmonary metastasis. Sepsis: 69-year-old patient with anal fistula relapse leading to perineal ulceration and vulvar infection. Septic shock: 61-year-old patient with type 2 diabetes and urinary tract infection aggravated by severe neutropenia.
* Causality assigned to study treatment by the investigator.
ddAC, dose-dense doxorubicin and cyclophosphamide; H, trastuzumab; P, pertuzumab; Pac, paclitaxel.

APTneo study design



- **Primary Endpoint:** EFS
- **Secondary Endpoint:** pCR, cOR, DEFS, OS, safety

* Doses used in this study are as follows: atezolizumab 1200 mg IV q3w; doxorubicin 60 mg/m^2 q3w + cyclophosphamide 600 mg/m^2 q3w; carboplatin AUC2 D1 & D8 q3w; paclitaxel 90 mg/m^2 D1 & D8 q3w; pertuzumab 840 mg loading dose followed by 420 mg thereafter; trastuzumab 8 mg/kg loading dose followed by 6 mg/kg thereafter.
AC, doxorubicin + cyclophosphamide; BC, breast cancer; cOR, clinical objective response; DEFS, distant event-free survival; eBC, early breast cancer; EFS, event-free survival; pCR, pathological complete response; OS, overall survival; PH, pertuzumab–trastuzumab.

https://clinicaltrials.gov/ct2/show/NCT03595592. Accessed June 2021.

Neoadjuvante Therapie - Was bringt uns die Zukunft HER2 positives Mammakarzinom

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- Hohe pCR Rate mit Chemo und Tra+Per (63%), auch bei high risk Population (hier pCR gutes Surrogat für Langzeitprognose)

- Wertigkeit der Immuntherapie unklar (APT Neo Studie abwarten)

- **T-DXd** als Teil der neoadjuvanten Therapie:
  Destiny 11: **T-DXd** vs **T-DXd-Pac/Tra/Her** vs **ddAC-Pac/Tra/Her**

- Wenn **keine pCR**:
  - Neue postneoadjuvante Konzepte
    T-DM1 vs: **T-DXd**, vs **T-DM1 +Atezolizumab** oder **T-DM1+Tucatinib**
  - Molekulare Sequenzierung und zielgerichtete Therapie

- **Zirkulierende DNA** zum Monitoring sinnvoll? Frühe Intervention bei MRD?

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