Immunoterapia e carcinoma mammario: quali evidenze dalla letteratura?

Quali indicazioni per la pratica clinica?

Emilia Montagna
Divisione Senologia Medica
Istituto Europeo di Oncologia
Milano

Declaration of Interests

Emilia Montagna

Institutional financial interests with commercial entities:

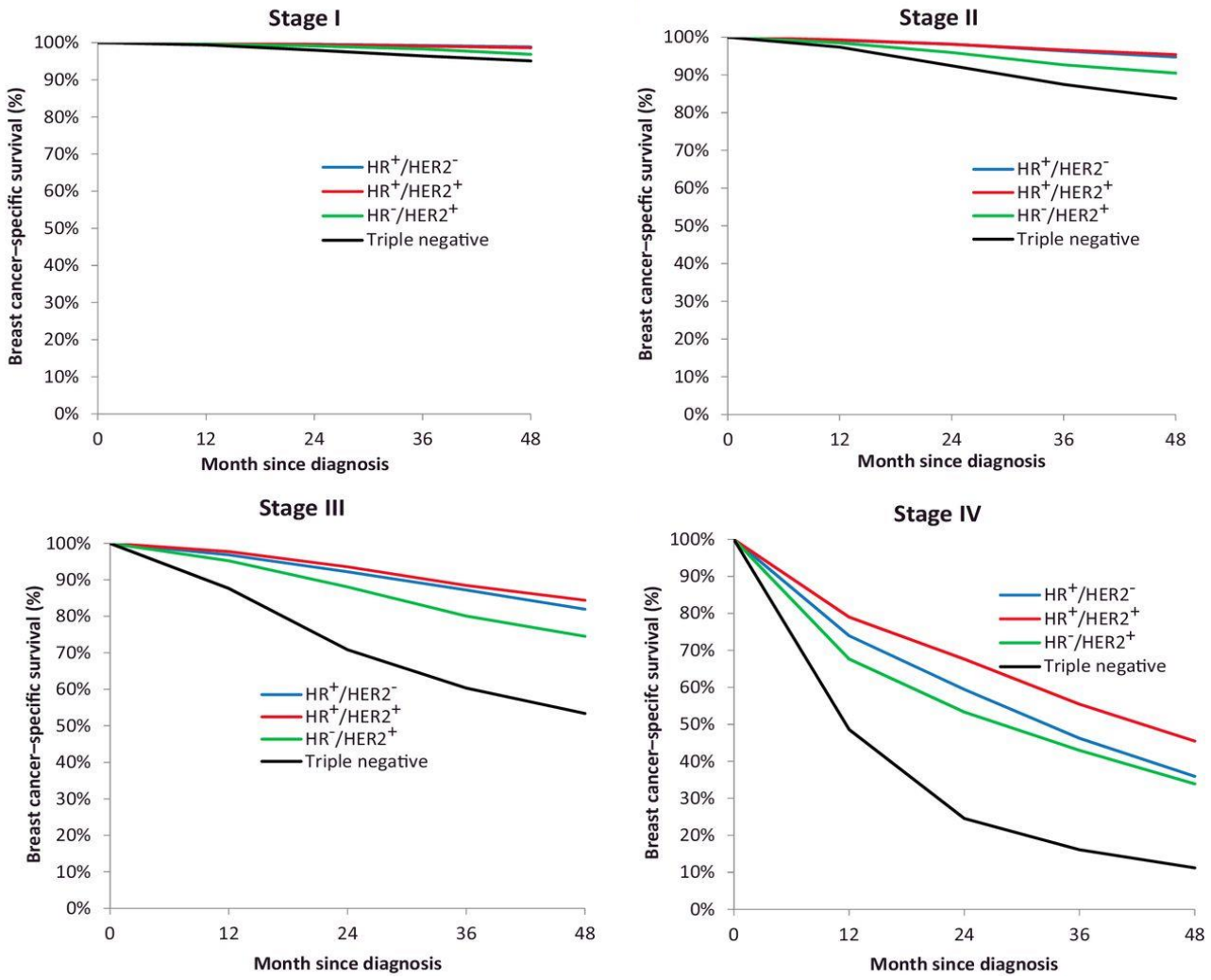
- Novartis
- Pierre fabre

- **No personal financial interests with any commercial entity**

Agenda

- Evidenze nel tumore mammario TN

TNBC IS THE MOST LETHAL BREAST CANCER SUBTYPE

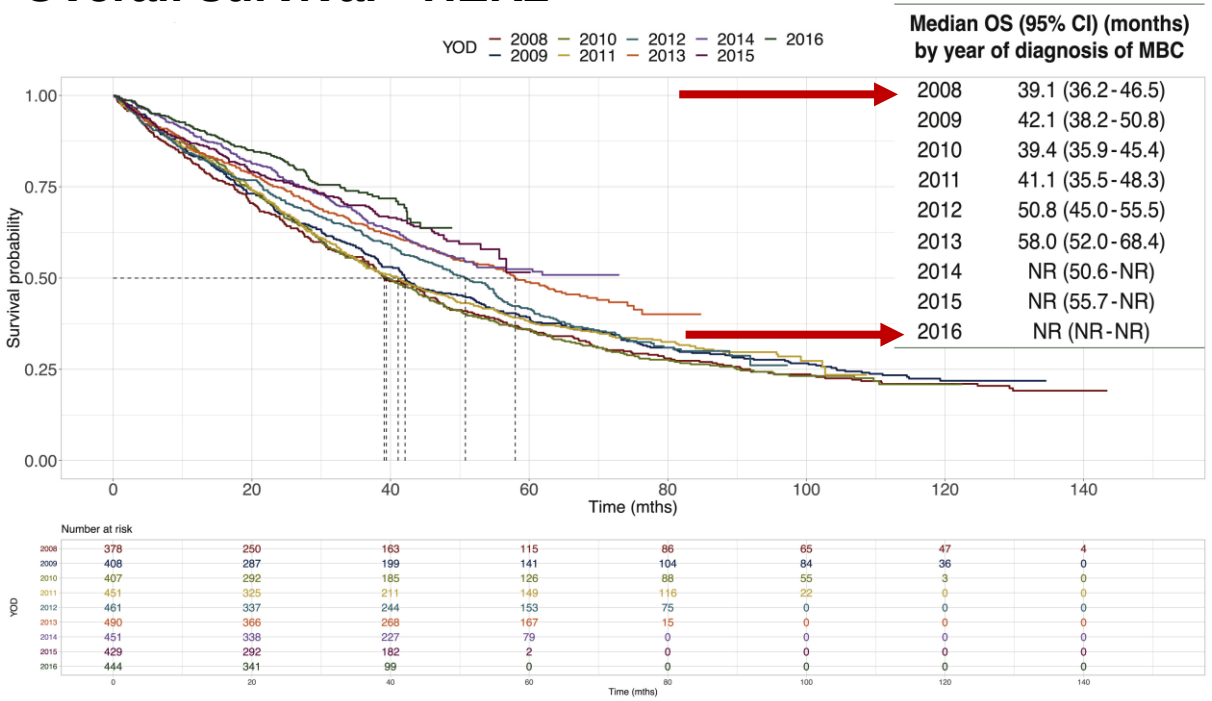


- Breast cancer–specific survival is significantly worse in TNBC compared to other subtypes
- This is much more evident in stage III and IV diseases

Howlader, Cancer Epidemiol Biomarkers Prev 2018

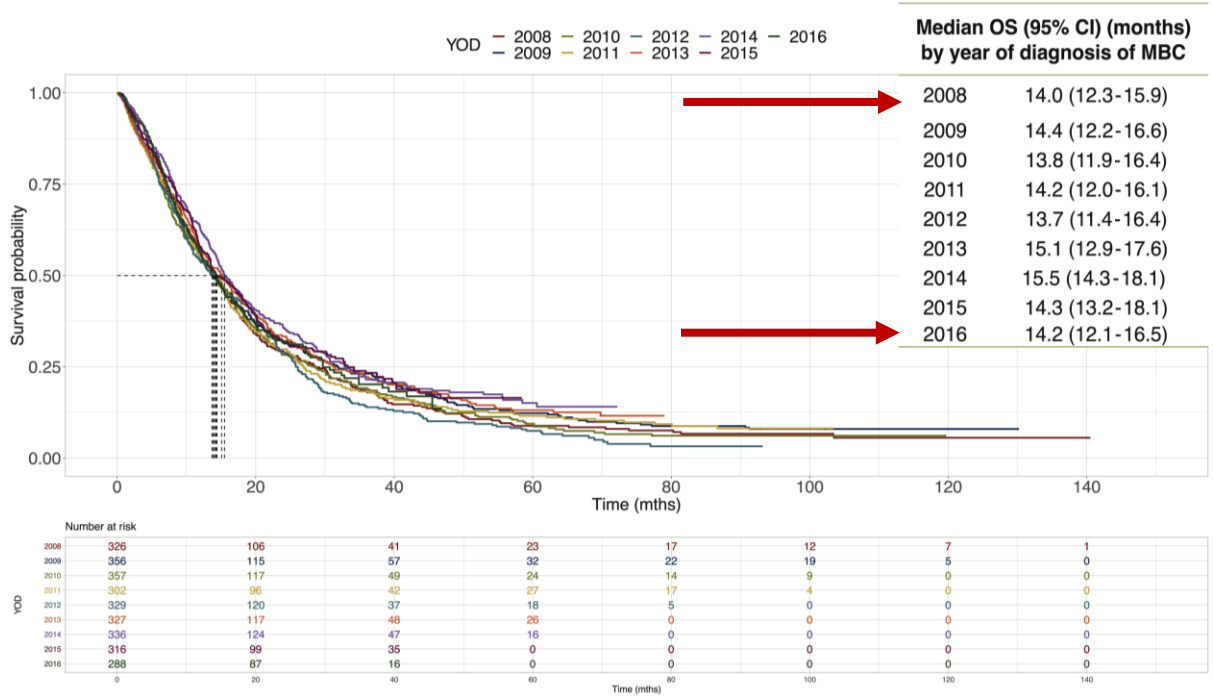
No major survival improvements for tnbc in the last decade

Overall survival - HER2+



Median OS (95% CI) (months) by year of diagnosis of MBC	
2008	39.1 (36.2-46.5)
2009	42.1 (38.2-50.8)
2010	39.4 (35.9-45.4)
2011	41.1 (35.5-48.3)
2012	50.8 (45.0-55.5)
2013	58.0 (52.0-68.4)
2014	NR (50.6-NR)
2015	NR (55.7-NR)
2016	NR (NR-NR)

Overall survival - TNBC



Median OS (95% CI) (months) by year of diagnosis of MBC	
2008	14.0 (12.3-15.9)
2009	14.4 (12.2-16.6)
2010	13.8 (11.9-16.4)
2011	14.2 (12.0-16.1)
2012	13.7 (11.4-16.4)
2013	15.1 (12.9-17.6)
2014	15.5 (14.3-18.1)
2015	14.3 (13.2-18.1)
2016	14.2 (12.1-16.5)

Median overall survival of TNBC from the onset of metastasis is <18 months

Grinda, ESMO Open 2021

Few years ago…

Current Treatment Options for Metastatic TNBC

- Sequential single-agent chemotherapy is the preferred approach for most pts with metastatic TNBC
  - Combination chemotherapy can be used for pts requiring more rapid response but does not improve OS

Taxanes	Anthracyclines	Antimetabolites	Other Microtubule Inhibitors	Platinum Agents
Paclitaxel	Doxorubicin	Capecitabine	Vinorelbine	Carboplatin
Nab-paclitaxel	Pegylated liposomal doxorubicin	Gemcitabine	Eribulin	Cisplatin
Docetaxel	Epirubicin		Ixabepilone	

- Patients should generally remain on a regimen until best response, disease progression, or significant toxicity

ZeichnerSB, et al. Breast Cancer (Auckl). 2016

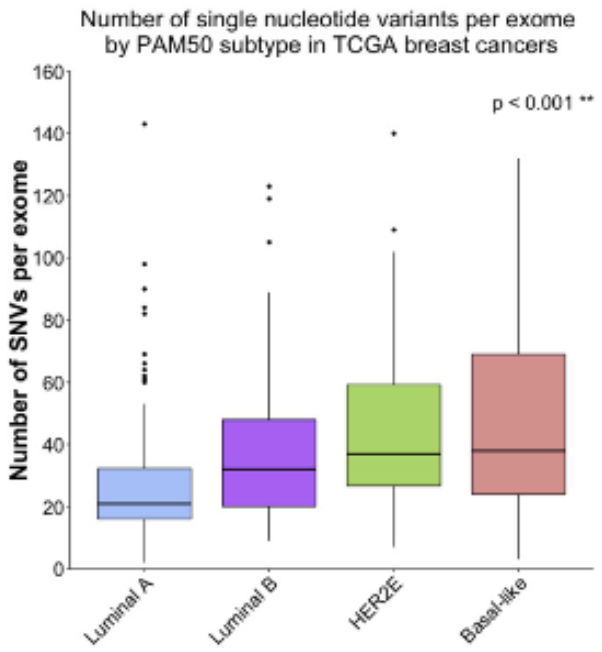
Historical outcomes in metastatic triple negative breast cancer

	ORR (%)	PFS (mo)	OS (mo)
Single agent chemotherapy			
1L	10.0-28.0	3.5-5.4	9.9-17.5
2L	6.0-18.0	2.7-3.4	9.2-15.2
Combination chemotherapy			
1L	14.8-64.3	4.8-9.0	13.9-24.2
2L+	27.0[1]-60.0	2.9-7.0	8.1-16.5

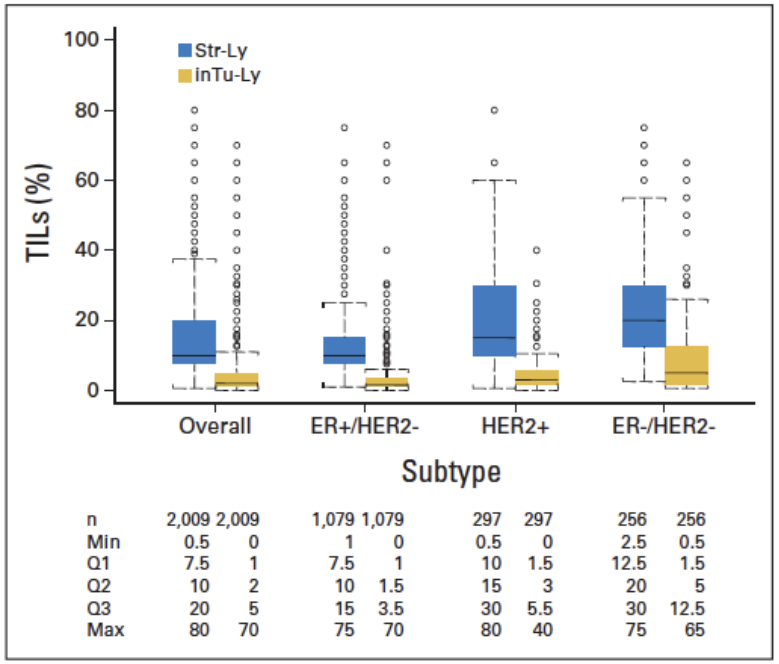
Adapted from Li CH. Breast Cancer Res. 2019

Why TNBC is a target for immunotherapy

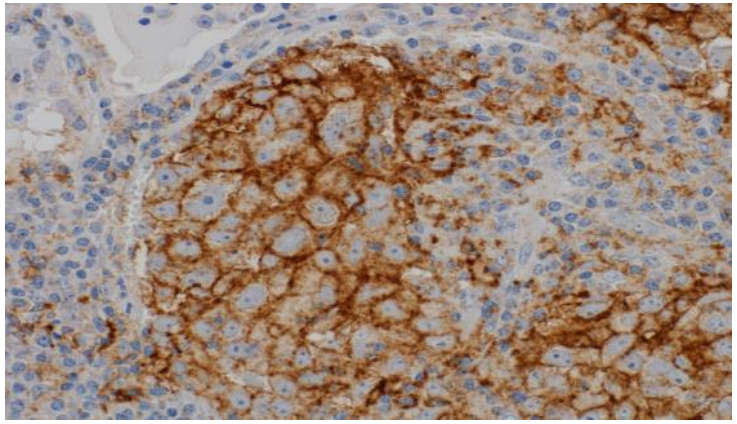
High mutation burden



T-cell infiltration

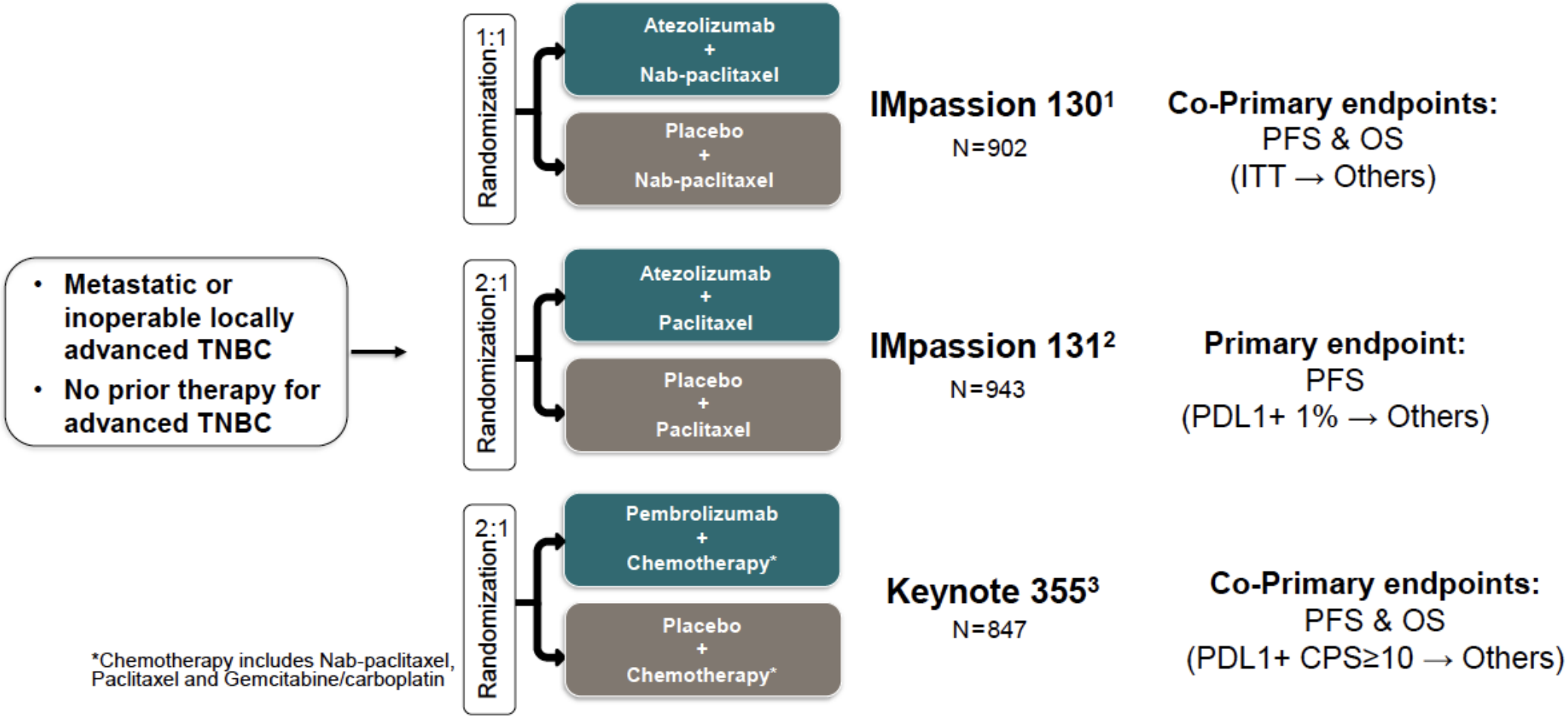


PD-L1 expression



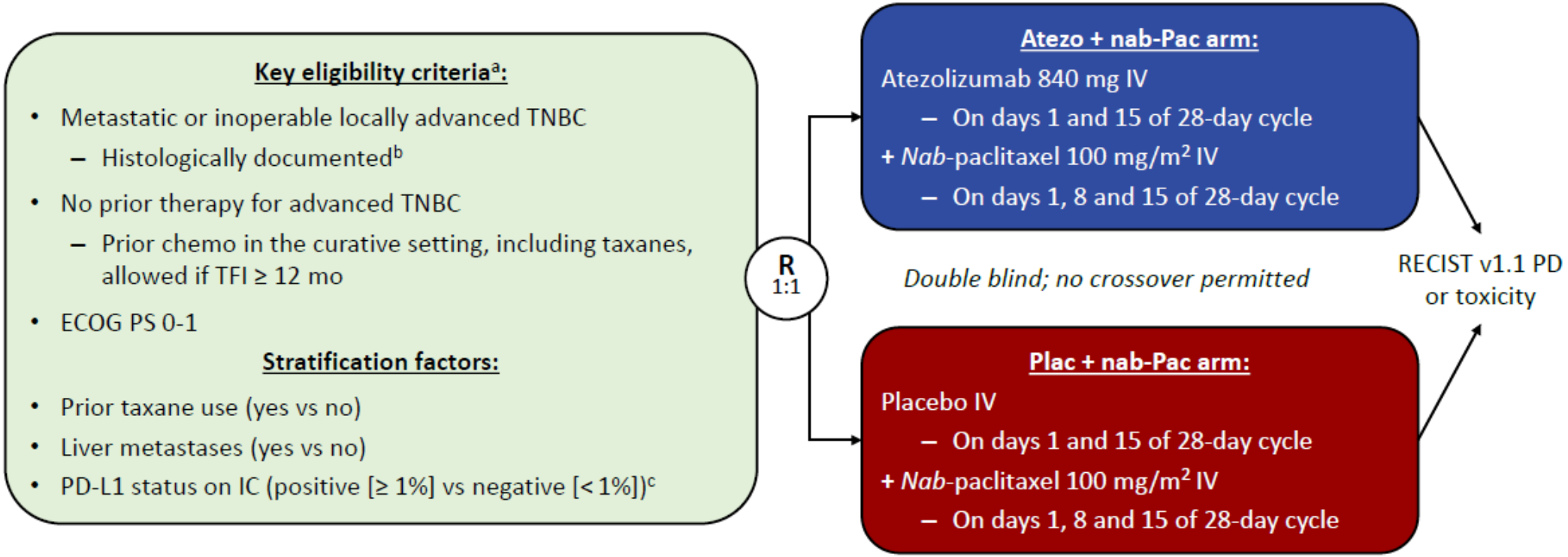
TCGA, Nature 2012
Luen, Breast 2016
Lehmann, J Clin Invest 2011
Cimino Matthews, Hum Pathol 2013
Loi, JCO 2013
Loi, Ann Oncol 2014
Chen and Mellman, Immunity 2013
Mittendorf, Cancer Immunol Res 2014

Randomized phase III studies with chemotherapy plus PD1/PDL1 inhibitors IN 1st LINE TNBC



1. Schmid, NEJM 2018; 2. Miles, Ann Oncol 2021; 3. Cortes, Lancet 2020

IMpassion130 (Phase III) – Study Design (TNBC metastatic disease)



- Co-primary endpoints were **PFS** and **OS** in the **ITT and PD-L1+ populations**[d].
- Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated.

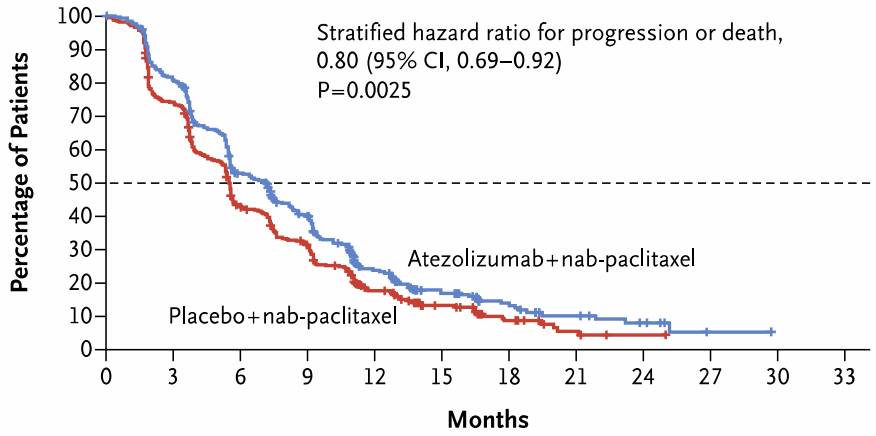
IC, tumour-infiltrating immune cell; TFI, treatment-free interval. [a] ClinicalTrials.gov: NCT02425891. [b] Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines. [c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). [d] Radiological endpoints were investigator assessed (per RECIST v1.1).

Emens et al, ESMO 2020

IMPASSION130: progression-free survival

ITT

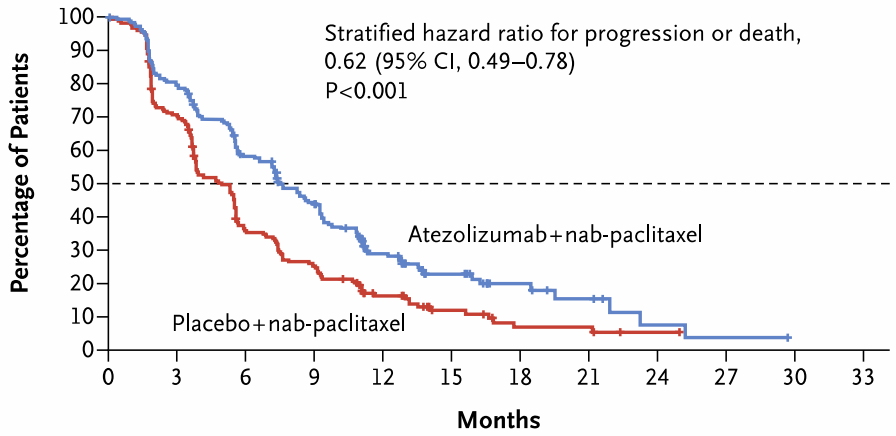
	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	358/451	7.2 (5.6–7.5)	23.7 (19.6–27.9)
Placebo+Nab-Paclitaxel	378/451	5.5 (5.3–5.6)	17.7 (14.0–21.4)



No. at Risk												
Atezolizumab+ nab-paclitaxel	451	360	226	164	77	34	20	11	6	1	NE	NE
Placebo+ nab-paclitaxel	451	327	183	130	57	29	13	5	1	NE	NE	NE

PD-L1 >1%

	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	138/185	7.5 (6.7–9.2)	29.1 (22.2–36.1)
Placebo+Nab-Paclitaxel	157/184	5.0 (3.8–5.6)	16.4 (10.8–22.0)



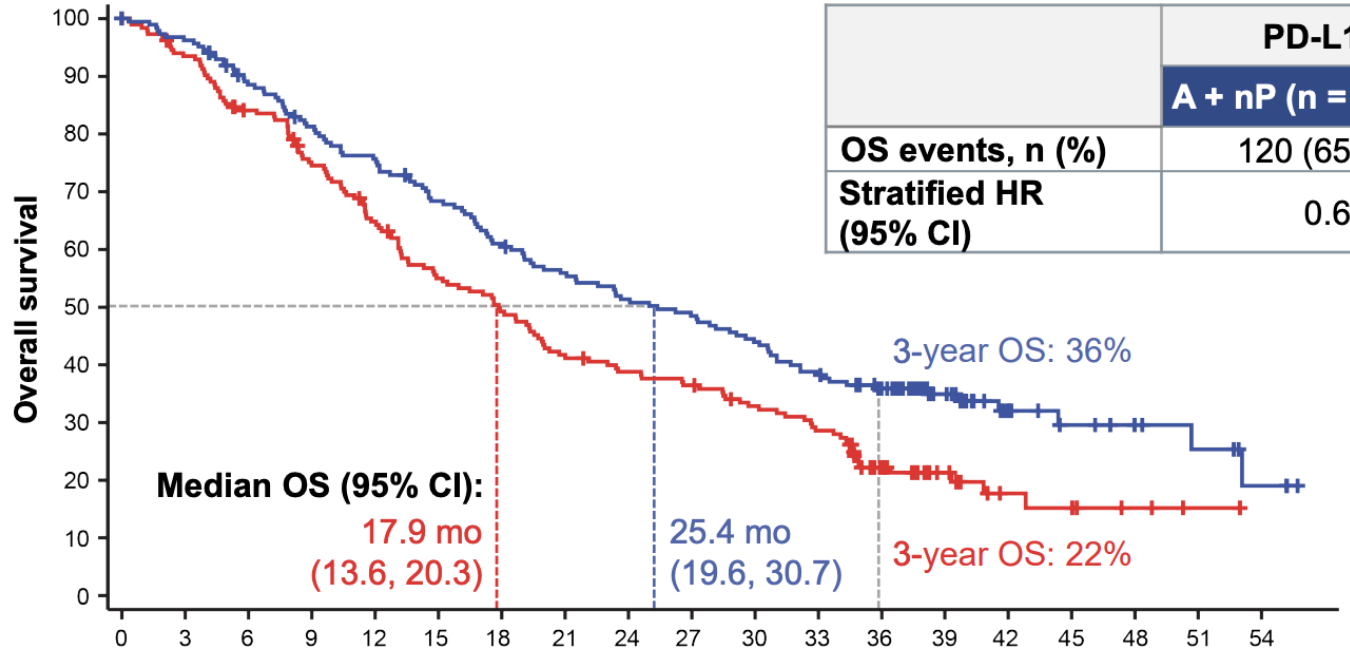
No. at Risk												
Atezolizumab+ nab-paclitaxel	185	146	104	75	38	19	10	6	2	1	NE	NE
Placebo+ nab-paclitaxel	184	127	62	44	22	11	5	5	1	NE	NE	NE

Schmid, NEJM 2018

IMpassion130 – Final OS analysis

OS in the PD-L1 IC+ population

	PD-L1 IC+ population	
	A + nP (n = 185)	P + nP (n = 184)
OS events, n (%)	120 (65)	139 (76)
Stratified HR (95% CI)	0.67 (0.53, 0.86)[a]	

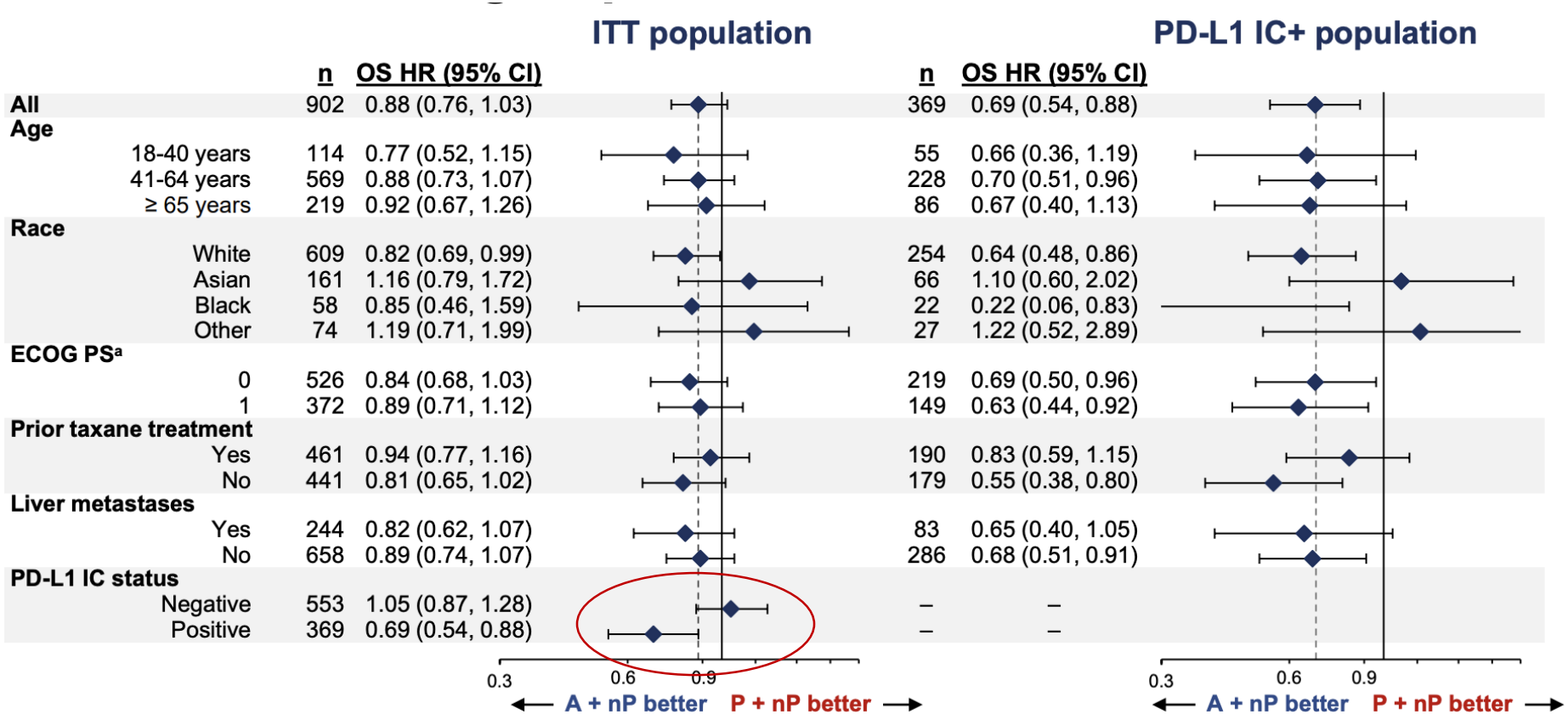


No. at risk (PD-L1+ population):																			
A + nP	185	177	160	145	135	121	108	98	90	86	77	67	56	32	17	11	9	6	3
P + nP	184	170	150	132	113	95	85	72	66	62	54	47	28	14	7	6	3	1	NE

+7.5-mo median OS improvement

Emens et al, ESMO 2020

IMpassion130 – Final OS analysis



Emens et al, ESMO 2020

IMpassion130 – Safety

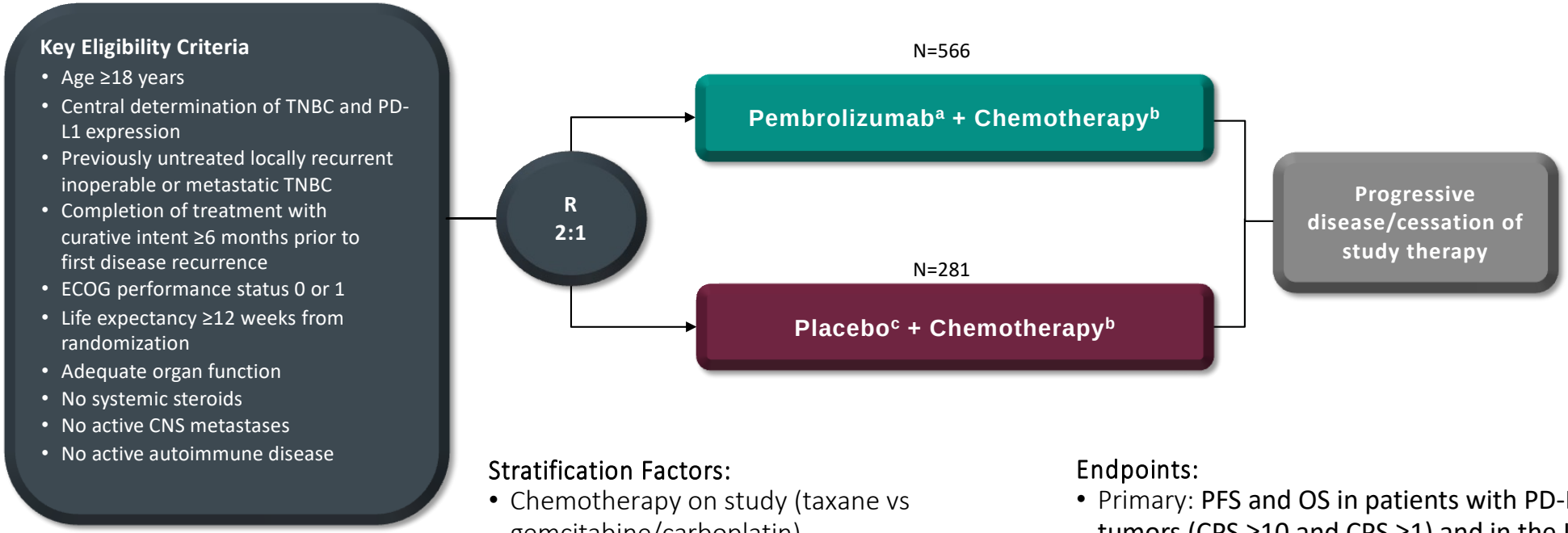
AESI, n (%)[a]	Plac + nab-Pac (n = 438)		Atezo + nab-Pac (n = 452)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hepatitis (all)	62 (14.2%)	13 (3.0%)	69 (15.3%)	23 (5.1%)
Hepatitis (diagnosis)	7 (1.6%)	1 (0.2%)	10 (2.2%)	6 (1.3%)
Hepatitis (lab abnormalities)	58 (13.2%)	12 (2.7%)	62 (13.7%)	17 (3.8%)
Hypothyroidism	19 (4.3%)	0	78 (17.3%)	0
Hyperthyroidism	6 (1.4%)	0	20 (4.4%)	1 (0.2%)
Adrenal insufficiency	0	0	4 (0.9%)	1 (0.2%)
Pneumonitis	1 (0.2%)	0	14 (3.1%)	1 (0.2%)
Colitis	3 (0.7%)	1 (0.2%)	5 (1.1%)	1 (0.2%)
Pancreatitis*	0	0	2 (0.4%)	1 (0.2%)
Diabetes mellitus	2 (0.5%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Other AESI (Rash)	114 (26.0%)	2 (0.5%)	154 (34.1%)	4 (0.9%)

There were no reported events of Guillian-Barre syndrome, Hypophysitis, Myasthenia Gravis or Myocarditis

*Enzyme elevations only

Emens et al, ESMO 2020

Keynote-355:
PEMBROLIZUMAB + CHEMOTHERAPY AS FIRST-LINE



Stratification Factors:
- Chemotherapy on study (taxane vs gemcitabine/carboplatin)
- PD-L1 tumor expression (CPS ≥1 vs CPS <1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes vs no)

Endpoints:
- Primary: **PFS and OS in patients with PD-L1+ tumors (CPS ≥10 and CPS ≥1) and in the ITT population**
- Secondary: ORR, DOR, DCR, Safety in all treated patients

[a] Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 every 28 days
Paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 every 28 days
Gemcitabine 1000 mg/m^2/carboplatin AUC 2 on days 1 and 8 every 21 days

Cortes, ASCO 2020; Cortes, Lancet 2020

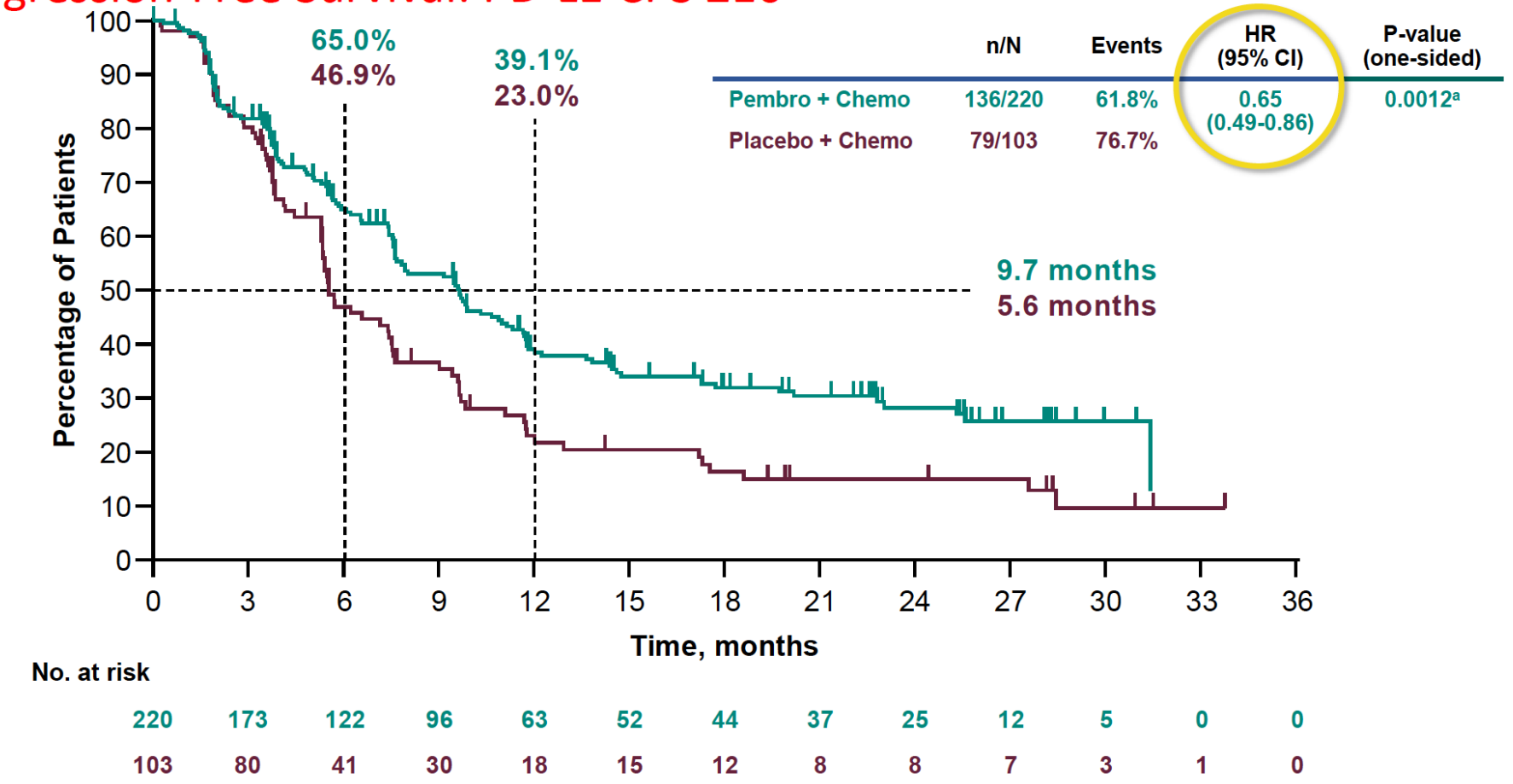
KEYNOTE 355 – Study Population allocation

Characteristic, n (%)	All Subjects, N = 847	
	Pembro + Chemo N = 566	Placebo + Chemo N = 281
Age, median (range), yrs	53 (25-85)	53 (22-77)
ECOG PS 1	232 (41.0)	108 (38.4)
PD-L1–positive CPS ≥1	425 (75.1)	211 (75.1)
PD-L1–positive CPS ≥10	220 (38.9)	103 (36.7)
Chemotherapy on study		
Taxane	255 (45.1)	127 (45.2)
Gemcitabine/Carboplatin	311 (54.9)	154 (54.8)
Prior same-class chemotherapy		
Yes	124 (21.9)	62 (22.1)
No	442 (78.1)	219 (77.9)
Disease-free interval		
de novo metastasis	168 (29.7)	84 (29.9)
<12 months	125 (22.1)	50 (17.8)
≥12 months	270 (47.7)	147 (52.3)

Rugo et al, ESMO 2021

KEYNOTE 355 - Outcomes

Progression-Free Survival: PD-L1 CPS ≥10



	n/N	Events	HR (95% CI)	P-value (one-sided)
Pembro + Chemo	136/220	61.8%	0.65 (0.49-0.86)	0.0012[a]
Placebo + Chemo	79/103	76.7%		

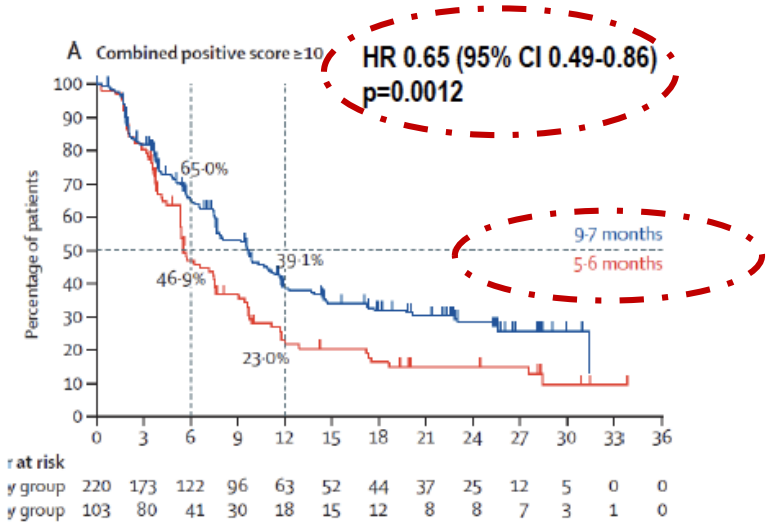
No. at risk

220	173	122	96	63	52	44	37	25	12	5	0	0
103	80	41	30	18	15	12	8	8	7	3	1	0

Presented By Javier Cortes at TBD

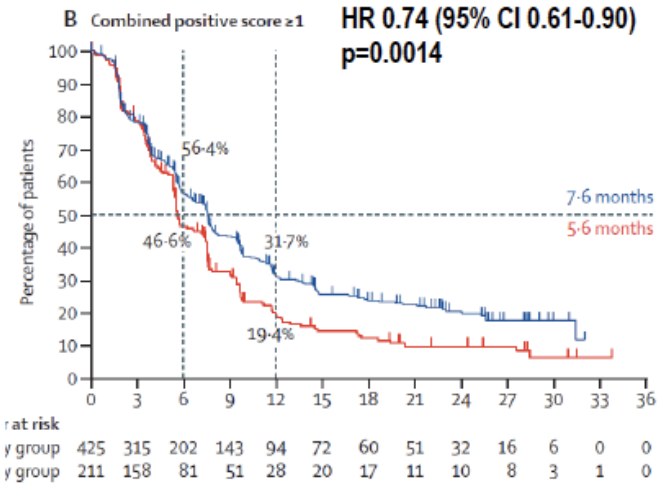
Keynote-355:
PROGRESSION-FREE SURVIVAL

PD-L1 CPS ≥10



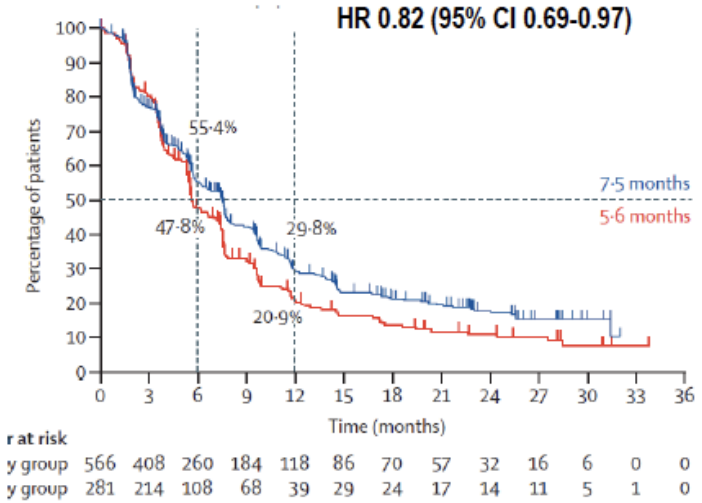
PFS superiority CPS ≥10
boundary α=0.00411

PD-L1 CPS ≥1



PFS superiority CPS ≥1
boundary α=0.00111 not met

ITT population

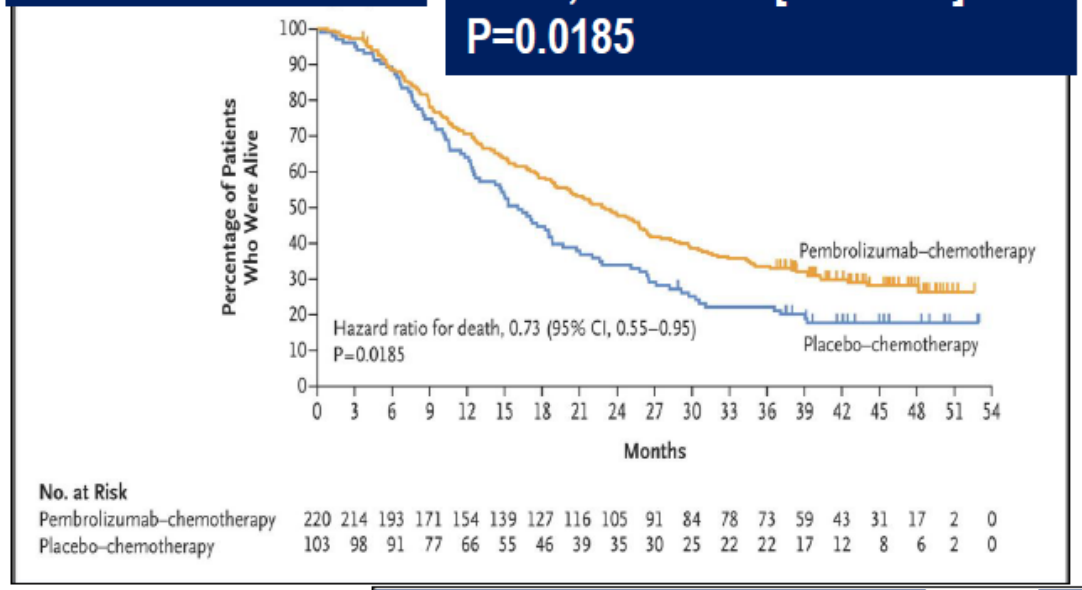


Significance not tested according to
hierarchical statistical design

Cortes, ASCO 2020; Cortes, Lancet 2020

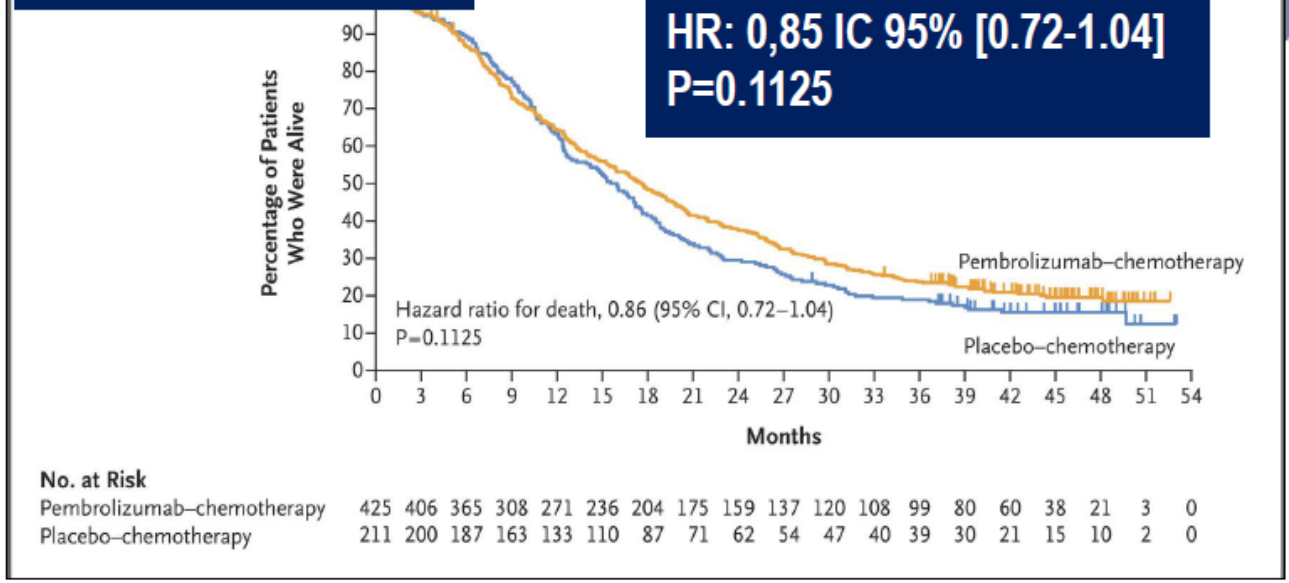
CPS-10 Subgroup

0S: 23 vs 16.1 months
HR: 0,73 IC 95% [0.55-0.95]
P=0.0185



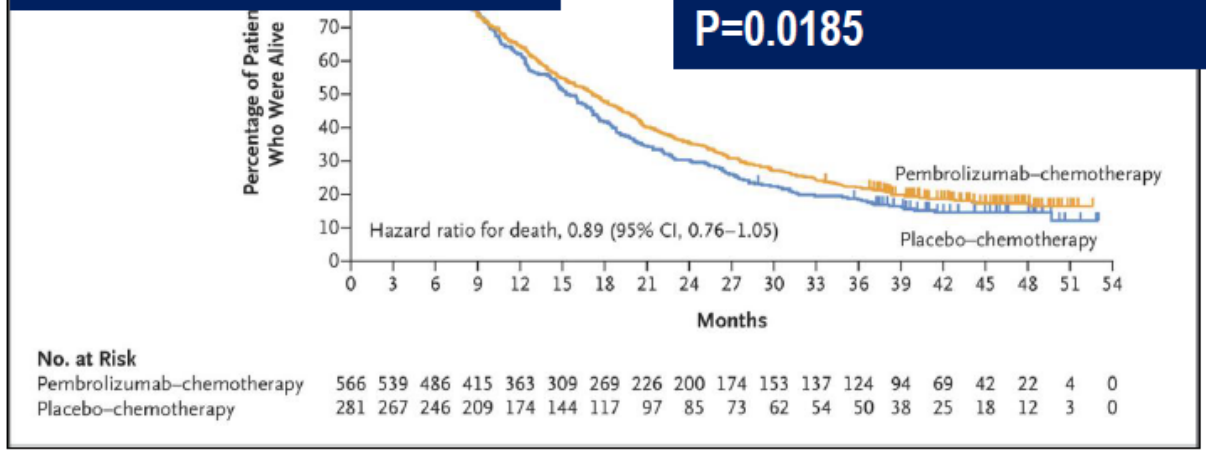
CPS-1 Subgroup

0S: 17.6 vs 16 months
HR: 0,85 IC 95% [0.72-1.04]
P=0.1125



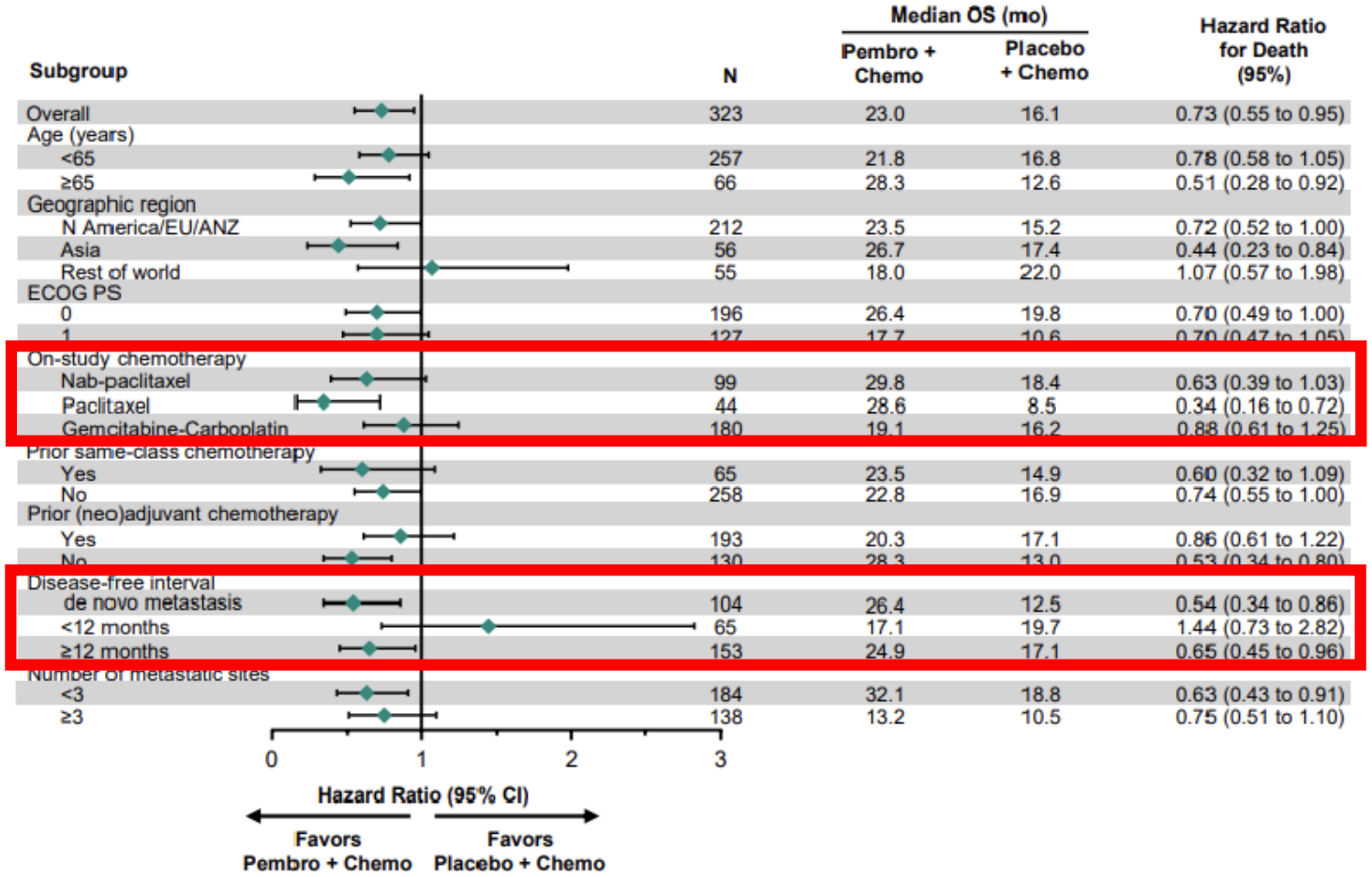
Intention to treat Population

0S: 17.2 vs 15.5 months
HR: 0,789 IC 95% [0.76-1.05]
P=0.0185



[Cortes et al, 2022]

Keynote-355:
OVERALL SURVIVAL IN SUBGROUPS CPS ≥10



Subgroup	N	Median OS (mo) Pembro + Chemo	Median OS (mo) Placebo + Chemo	Hazard Ratio for Death (95%)
Overall	323	23.0	16.1	0.73 (0.55 to 0.95)
Age (years)				
<65	257	21.8	16.8	0.78 (0.58 to 1.05)
≥65	66	28.3	12.6	0.51 (0.28 to 0.92)
Geographic region				
N America/EU/ANZ	212	23.5	15.2	0.72 (0.52 to 1.00)
Asia	56	26.7	17.4	0.44 (0.23 to 0.84)
Rest of world	55	18.0	22.0	1.07 (0.57 to 1.98)
ECOG PS				
0	196	26.4	19.8	0.70 (0.49 to 1.00)
1	127	17.7	10.6	0.70 (0.47 to 1.05)
On-study chemotherapy				
Nab-paclitaxel	99	29.8	18.4	0.63 (0.39 to 1.03)
Paclitaxel	44	28.6	8.5	0.34 (0.16 to 0.72)
Gemcitabine-Carboplatin	180	19.1	16.2	0.88 (0.61 to 1.25)
Prior same-class chemotherapy				
Yes	65	23.5	14.9	0.60 (0.32 to 1.09)
No	258	22.8	16.9	0.74 (0.55 to 1.00)
Prior (neo)adjuvant chemotherapy				
Yes	193	20.3	17.1	0.86 (0.61 to 1.22)
No	130	28.3	13.0	0.53 (0.34 to 0.80)
Disease-free interval				
de novo metastasis	104	26.4	12.5	0.54 (0.34 to 0.86)
<12 months	65	17.1	19.7	1.44 (0.73 to 2.82)
≥12 months	153	24.9	17.1	0.65 (0.45 to 0.96)
Number of metastatic sites				
<3	184	32.1	18.8	0.63 (0.43 to 0.91)
≥3	138	13.2	10.5	0.75 (0.51 to 1.10)

Rugo, ESMO 2021; Cortes, NEJM 2022

Agenda

- Evidenze nel tumore mammario TN
- Indicazioni nella pratica clinica nel TN

IMMUNOTHERAPY

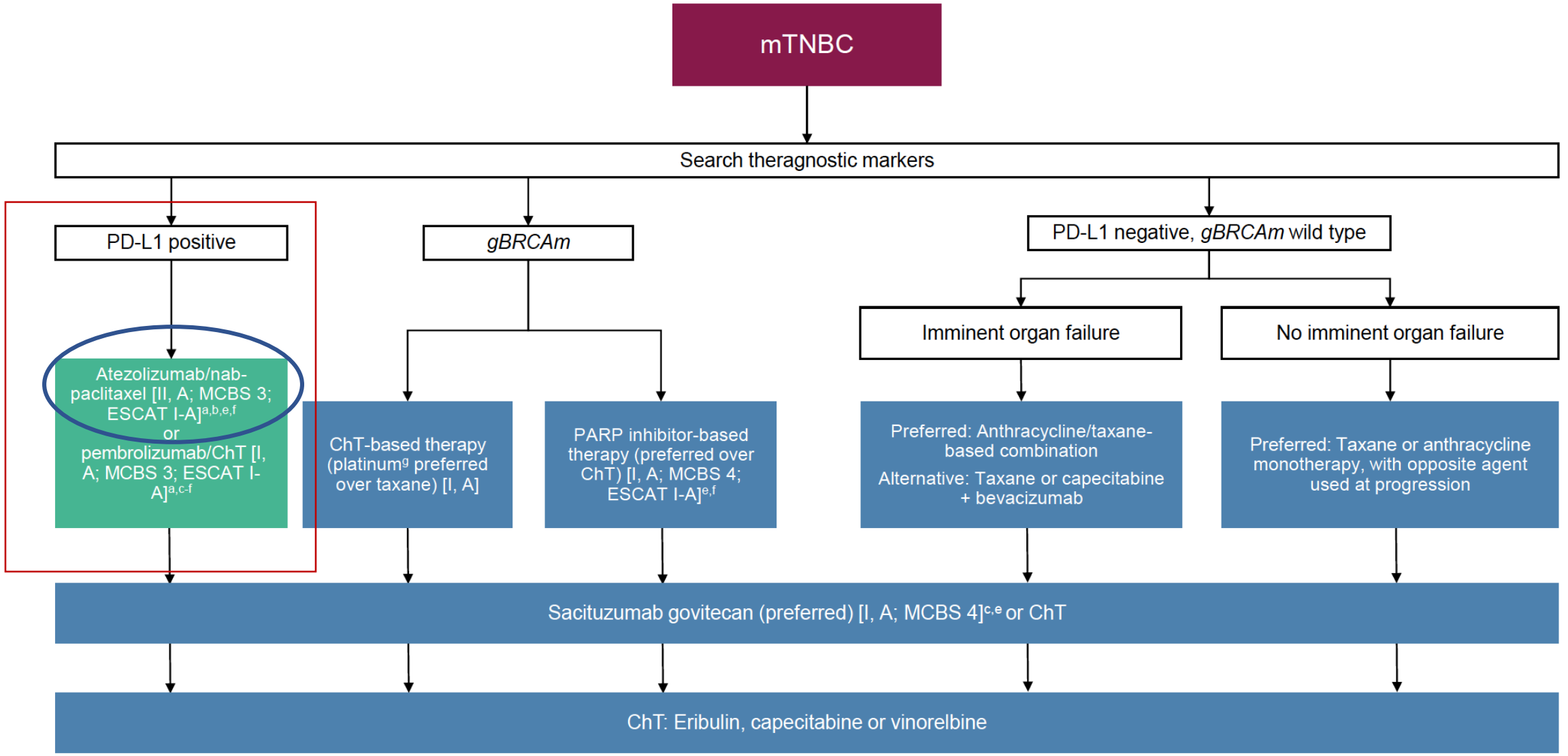
PEMBROLIZUMAB

KEYNOTE 355
(First line treatment with Pembrolizumab-CT in advanced and mTNBC)

ATEZOLIZUMAB

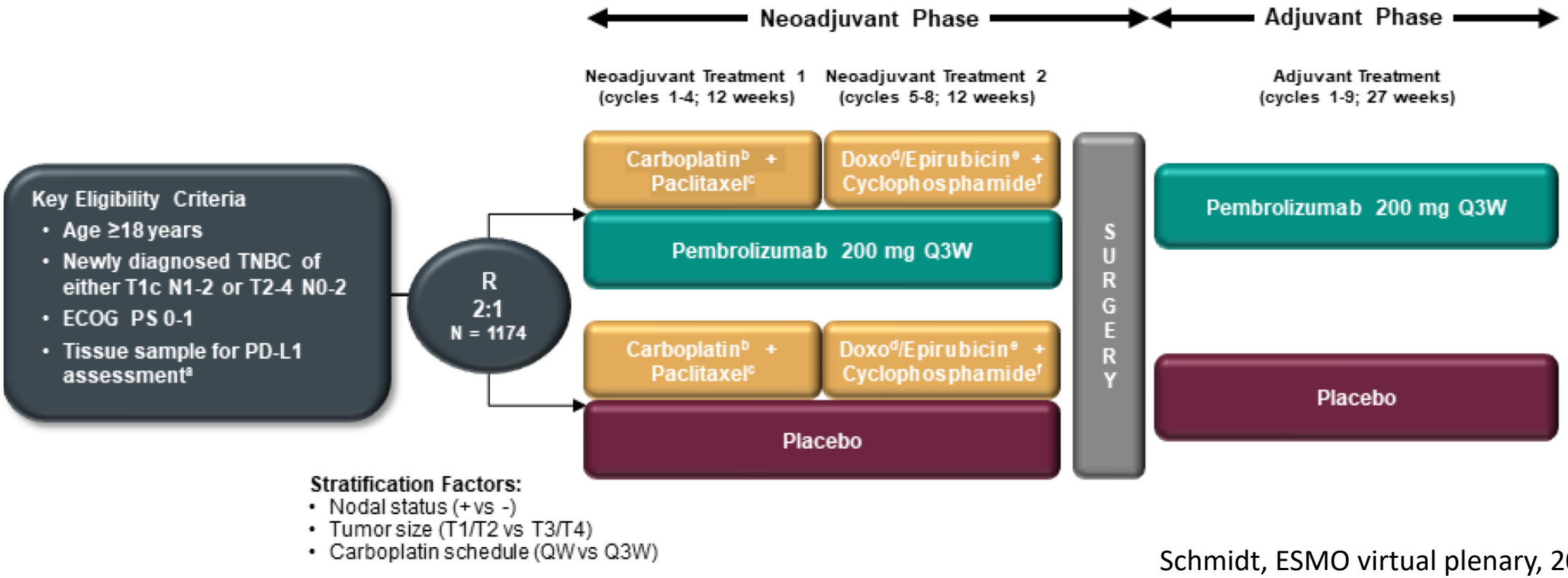
IM PASSION 130
(First line treatment with Atezoluzimab-Nab Paclitaxel in mTNBC)

METASTATIC BREAST CANCER - TNBC



Gennari et al, Annals of Onc 2021

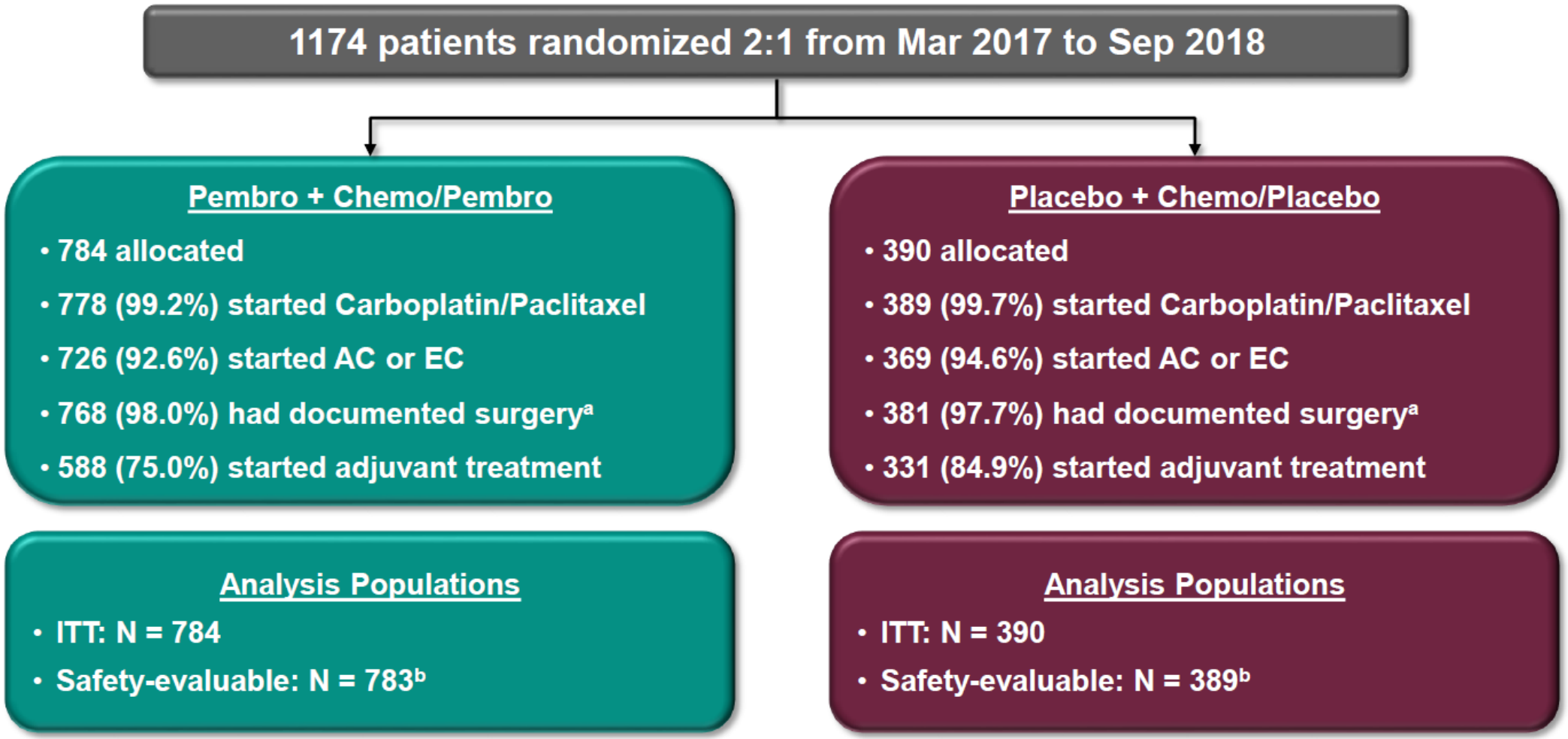
KEYNOTE 522 – Study DESIGN



Schmidt, ESMO virtual plenary, 2021

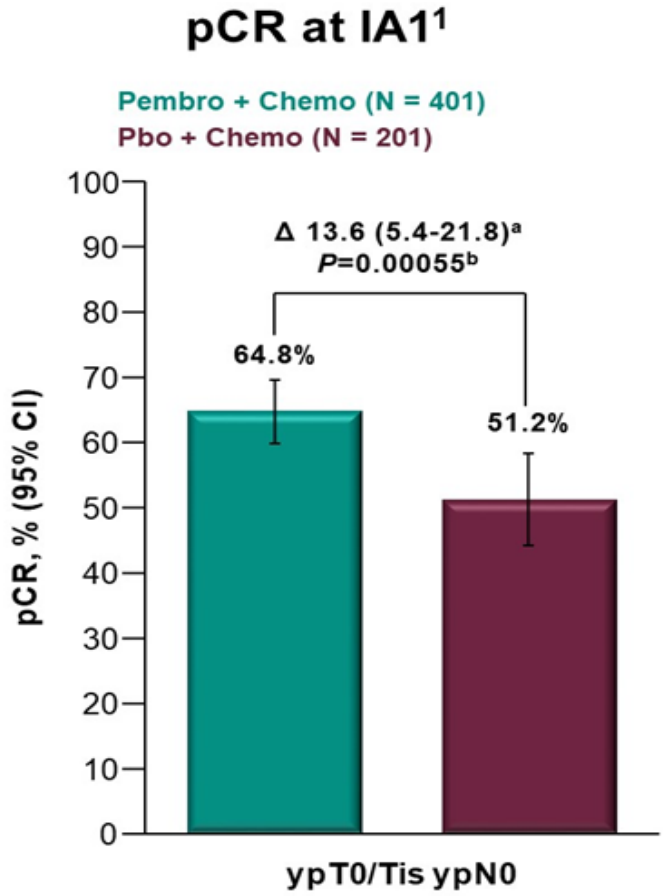
No T1a-T1b; No T1cN0; No T4d (inflammatory)

Summary of Analysis Populations



Median (range) follow-up[c]: 63.1 mo (53.9-72.0)

Primary Analyses of KEYNOTE-522

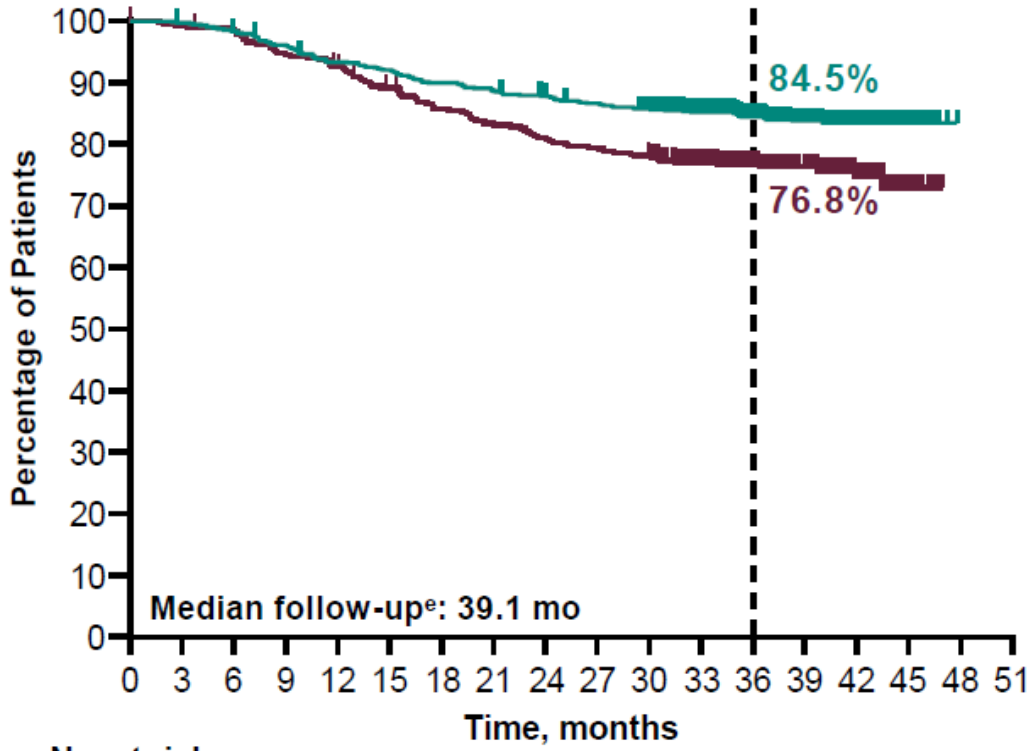


Neoadjuvant chemo plus pembrolizumab resulted in a significantlly and clinically meaningful increase in pCR of 13,6 percentage points

1. Schmid P, et al. *N Engl J Med* 2020;382:810-21. 2. Schmid P, et al. *N Engl J Med* 2022;386:556-67. [a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. [b]Prespecified *P*-value boundary for significance of 0.003 was crossed; data cutoff date: September 24, 2018. [c]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [d]Prespecified *P*-value boundary of 0.00517 was crossed. [e]Defined as the time from randomization to the data cutoff date of March 23, 2021.

EFS

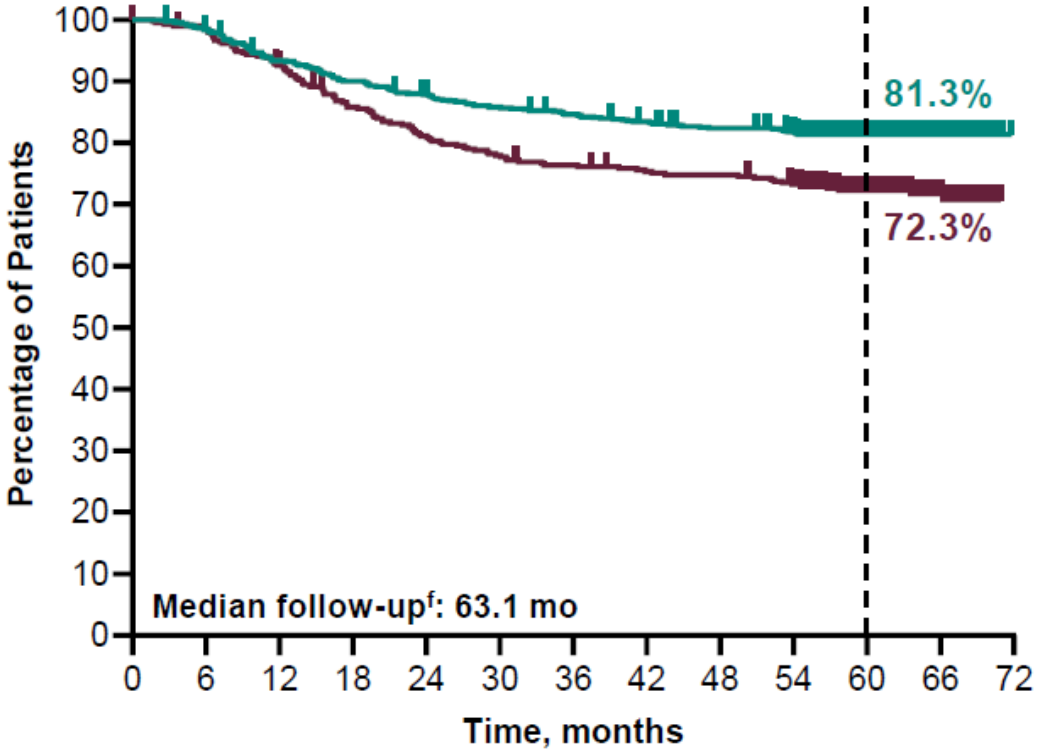
IA4[a]	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[c] (0.48-0.82)	0.00031[d]
Placebo + Chemo/Placebo	23.8%		



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

IA6[b]	Events	HR (95% CI)
Pembro + Chemo/Pembro	18.5%	0.63[c] (0.49-0.81)
Placebo + Chemo/Placebo	27.7%	



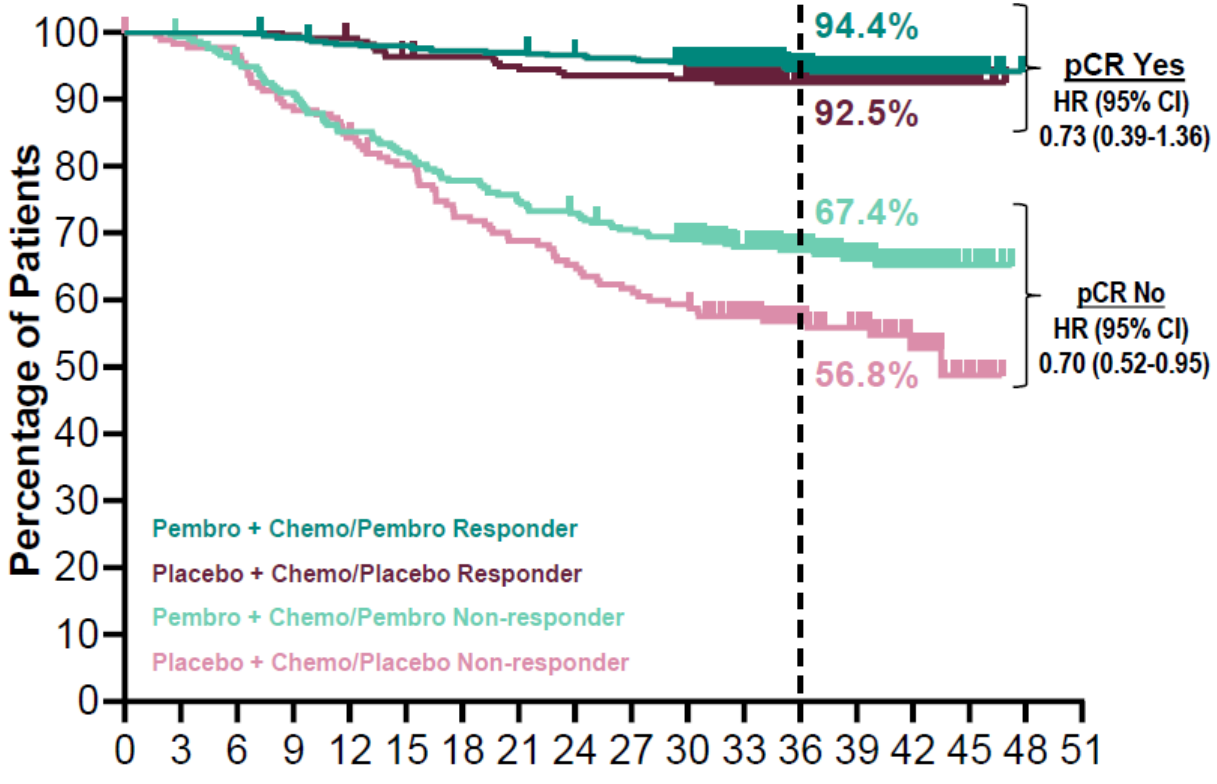
No. at risk

784	769	728	702	681	665	654	643	631	612	411	162	0
390	382	358	329	311	299	292	286	284	274	189	79	0

[a]The 4th prespecified interim analysis of EFS was calendar-driven planned to occur ~48 months after the first participant was randomized. [b]The 6th prespecified interim analysis of EFS was calendar-driven planned to occur ~72 months after the first participant was randomized. [c]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. [d]Prespecified *P*-value boundary of 0.00517 was crossed. [e]Defined as the time from randomization to the data cutoff date of March 23, 2021. [f]Defined as the time from randomization to the data cutoff date of March 23, 2023.

EFS by pCR (ypT0/Tis ypN0)

IA4

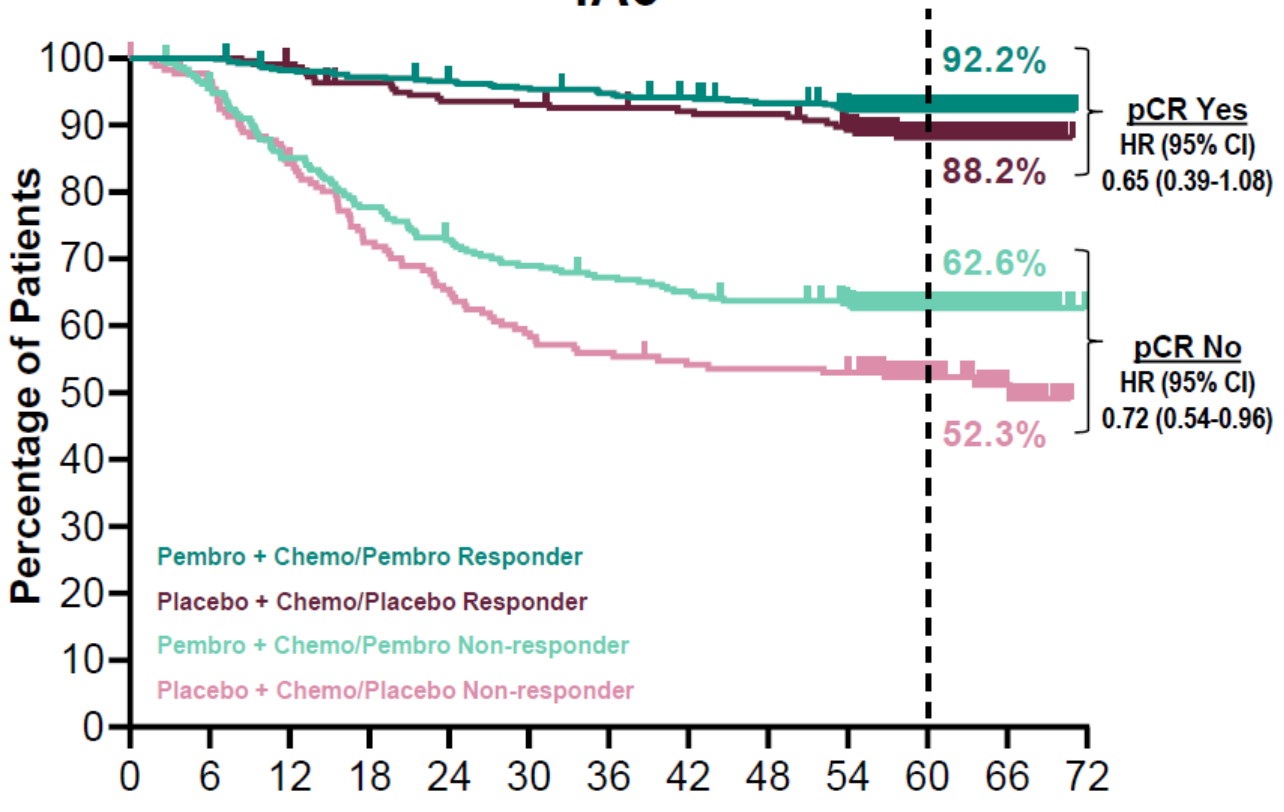


No. at risk

494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

Data cutoff date: March 23, 2021.

IA6



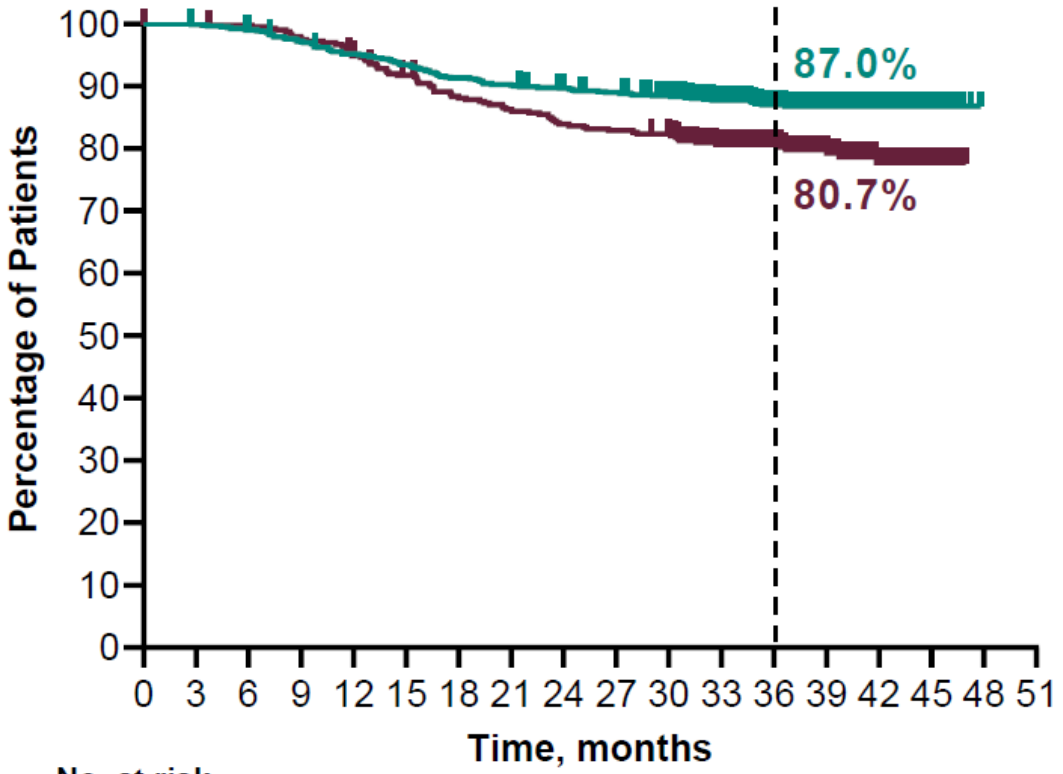
No. at risk

495	495	484	479	473	468	463	458	451	439	295	120	0
217	217	214	206	200	199	197	195	194	185	130	53	0
289	274	244	223	208	197	191	185	180	173	116	42	0
173	165	144	123	111	100	95	91	90	89	59	26	0

Data cutoff date: March 23, 2023.

Distant Progression-Free or Distant Recurrence-Free Survival

IA4	Events	HR (95% CI)
Pembro + Chemo/Pembro	12.8%	0.61[a] (0.46-0.82)
Placebo + Chemo/Placebo	20.3%	

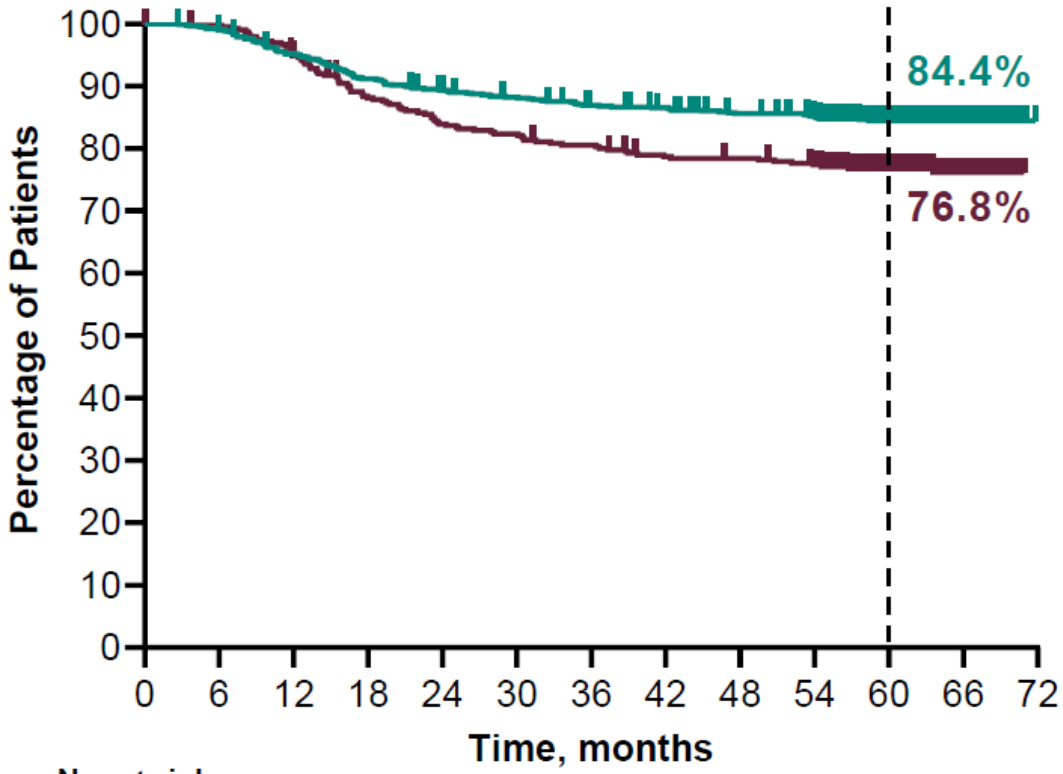


No. at risk

784	782	773	758	741	728	711	702	692	685	663	561	439	308	167	29	0	0
390	389	387	379	367	352	337	330	321	317	312	259	202	143	84	17	0	0

Data cutoff date: March 23, 2021.

IA6	Events	HR (95% CI)
Pembro + Chemo/Pembro	15.3%	0.64[a] (0.49-0.84)
Placebo + Chemo/Placebo	23.1%	



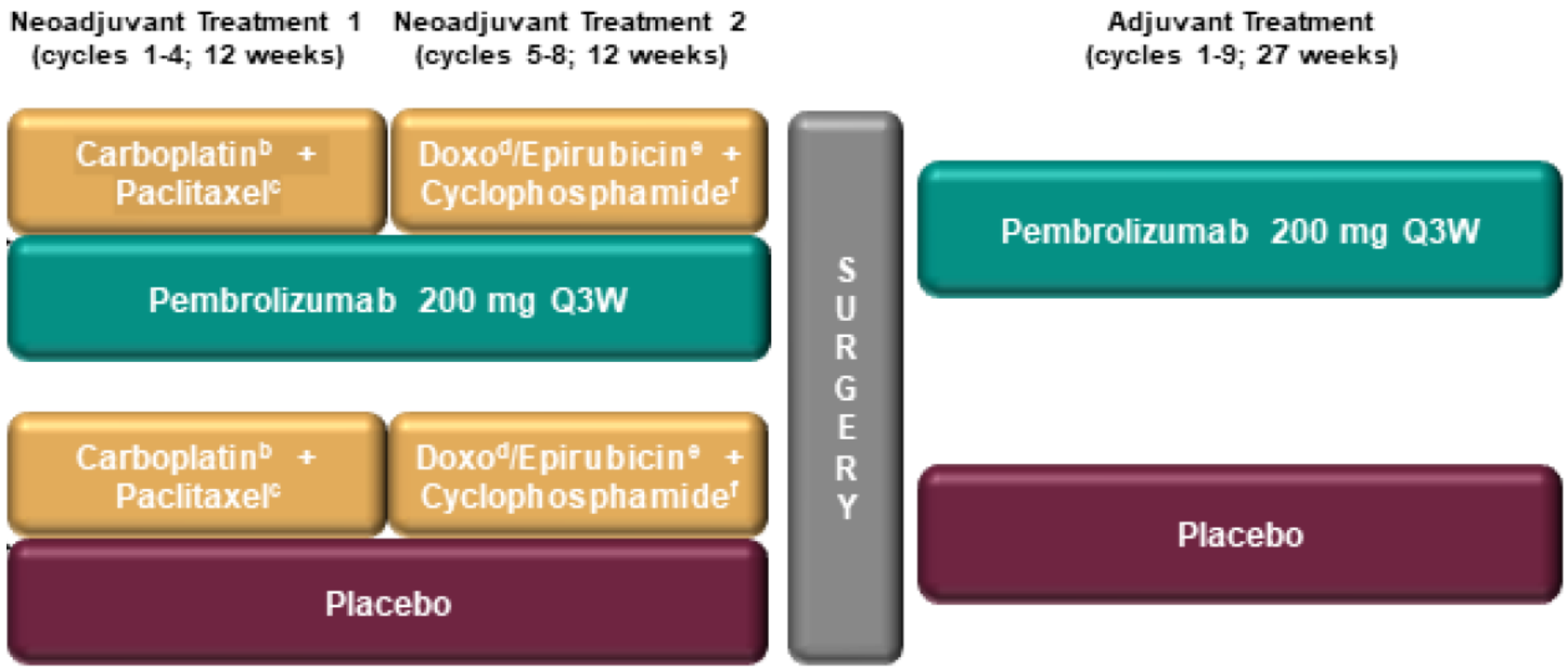
No. at risk

784	774	742	711	692	681	667	659	645	626	416	164	0
390	387	367	338	322	316	308	298	295	287	195	82	0

Data cutoff date: March 23, 2023.

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors.

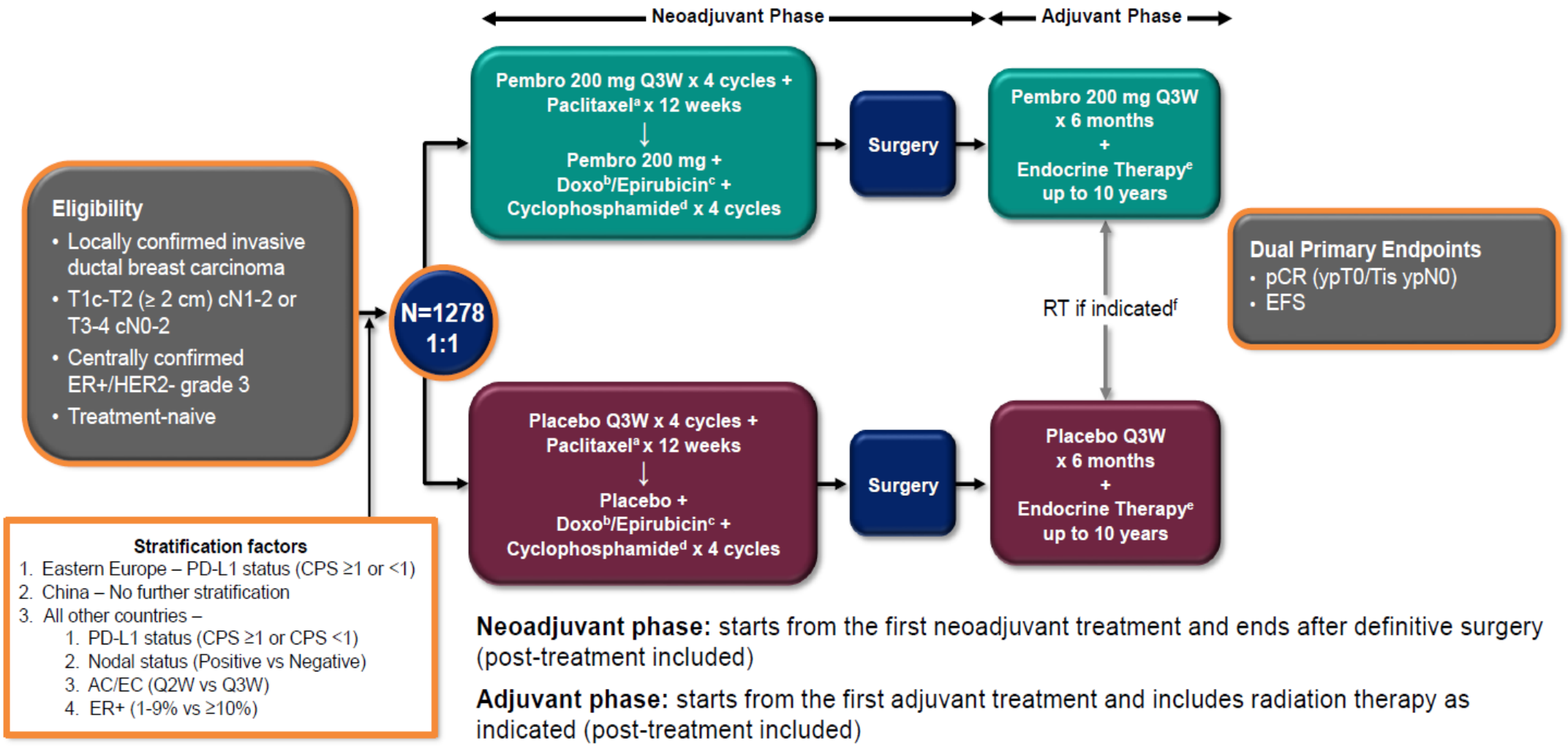
- **These results provide further support for pembro plus platinum-containing neoadjuvant chemo followed by adjuvant pembro after surgery, regardless of the pCR outcome, as a standard-of-care treatment regimen for patients with high-risk, early-stage TNBC**



Agenda

- Evidenze nel tumore mammario TN
- Indicazioni nella pratica clinica nel TN
- Evidenze nel tumore mammario luminale

KEYNOTE-756 Study Design (NCT03725059)



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

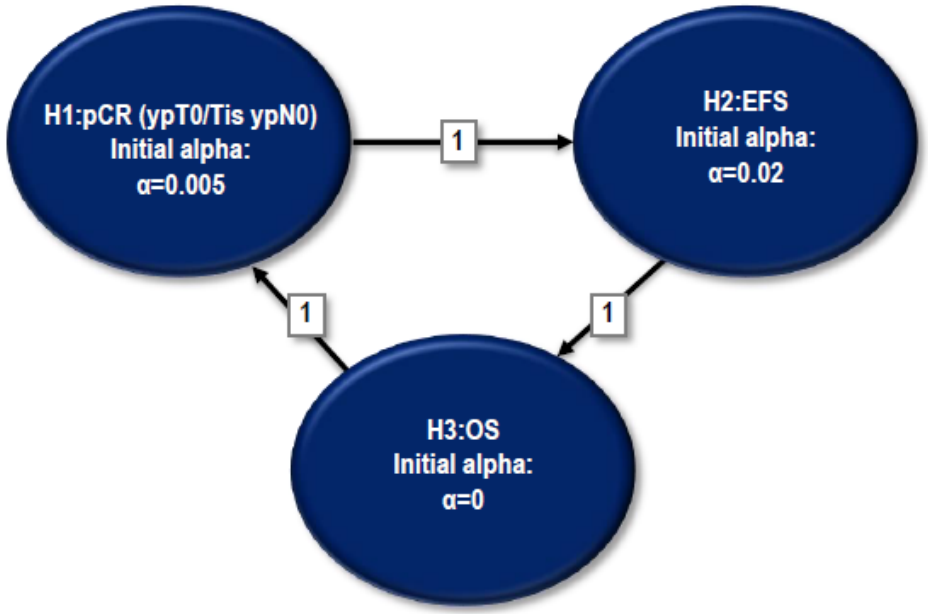
Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post-treatment included)

[a]Paclitaxel dose was 80 mg/m^2 QW. [b]Doxorubicin dose was 60 mg/m^2 Q3W. [c]Epirubicin dose was 100 mg/m^2 Q3W. [d]Cyclophosphamide dose was 600 mg/m^2 Q3W or Q2W.
[e]Endocrine therapy was administered according to institution guidelines. [f]Radiation therapy (concurrent or sequential) was administered according to institution guidelines.

Study Endpoints

- Primary Endpoints
  - pCR (ypT0/Tis ypN0)[a] assessed by the local pathologist at the time of definitive surgery in the ITT population
  - Event-free survival (EFS)[b] assessed by the investigator in the ITT population
- Secondary Endpoints
  - pCR as per alternative definitions (ypT0 ypN0 and ypT0/Tis)[a]
  - Overall survival (OS)[c]
  - pCR[a], EFS[b] and OS[c] in the PD-L1[d] CPS ≥1 population
  - Safety in all treated patients

Multiplicity:



Prespecified analysis plan allows alpha passing from successful endpoint(s) to other(s)

[a]Participants without pCR data for any reason or who received neoadjuvant chemotherapy not specified in the protocol were counted as non-pCR. [b]To be presented at a later date. [c]Tested only when EFS succeeds; to be presented at a later date. [d]PD-L1 assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100).

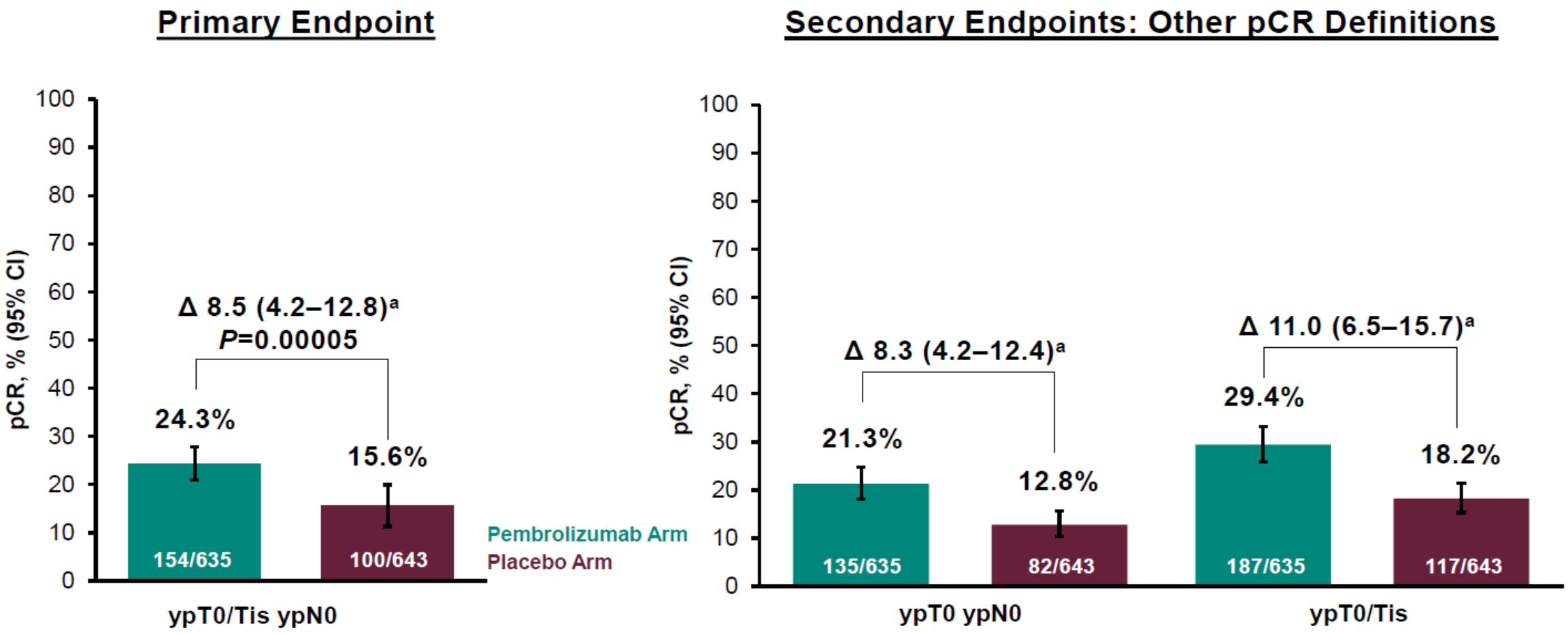
Baseline Characteristics, ITT Population

Characteristic, n (%)	All Participants[a], N = 1278	
	Pembrolizumab Arm N = 635	Placebo Arm N = 643
Age, median (range), yrs	49 (24-82)	49 (19-78)
ECOG PS 1	65 (10.2)	55 (8.6)
PD-L1[b] CPS ≥1	482 (75.9)	489 (76.0)
Anthracycline schedule		
Q3W	415 (65.4)	425 (66.1)
Q2W	183 (28.8)	187 (29.1)
Not started	37 (5.8)	31 (4.8)
Tumor size		
T1/T2	402 (63.3)	413 (64.2)
T3/T4	233 (36.7)	230 (35.8)
Nodal involvement		
Positive	570 (89.8)	582 (90.5)
Negative	65 (10.2)	61 (9.5)
ER positivity ≥10%	601 (94.6)	600 (93.3)

All GRADE 3

[a]All participants had centrally confirmed grade 3 disease. [b]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 tumor cells x 100). Data cutoff date: May 25, 2023.

Pathological Complete Response at IA1



[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by the analysis randomization stratification factors. Data cutoff date: May 25, 2023.

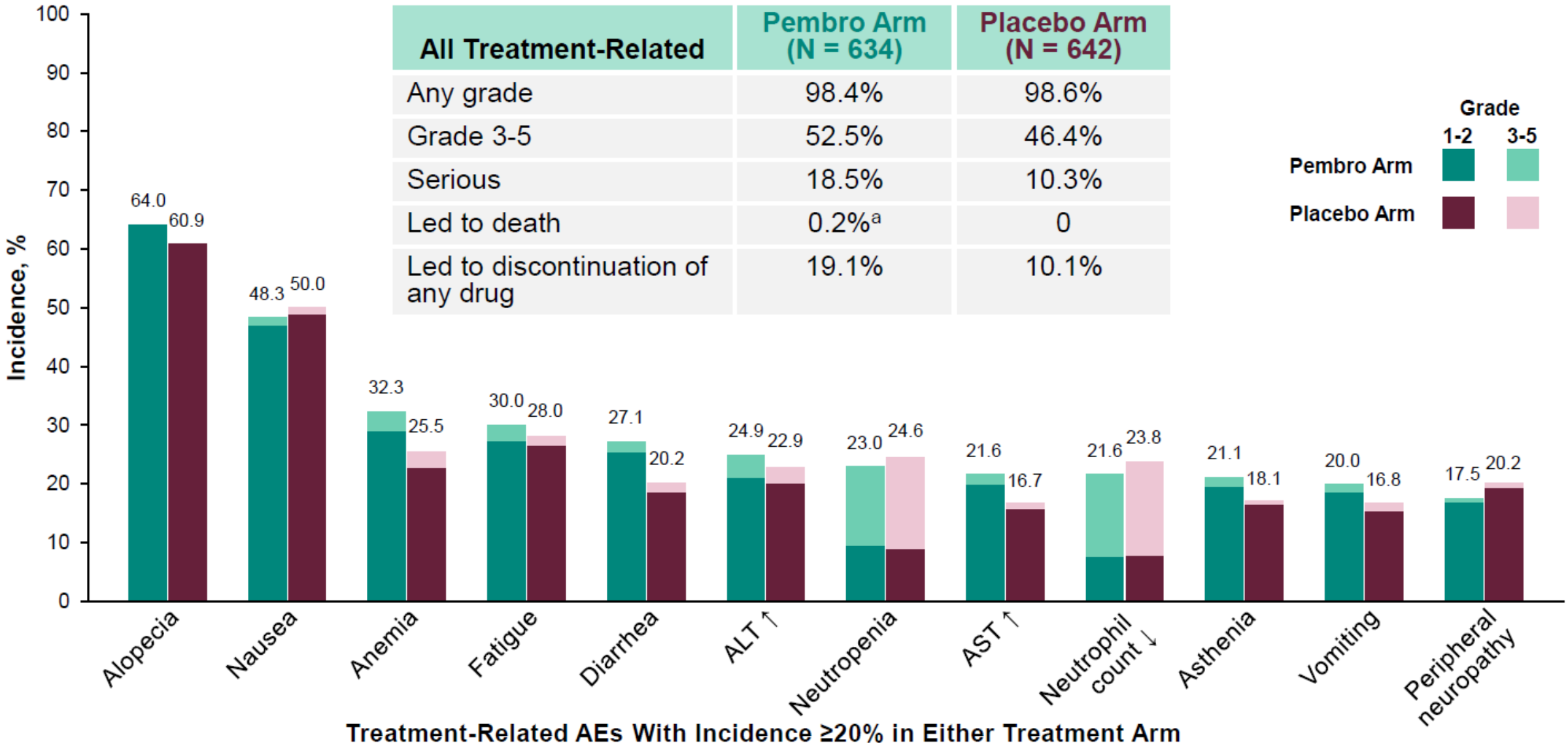
News from EBCC

- pCR rates occurred regardless of the patients' age or menopausal status. In patients younger than 50 years old, the pCR rate was 23.8% in those on pembrolizumab compared to 16.9% for those receiving placebo, and was 24.7% versus 14.2% respectively in those aged 50 or older.

- In pre-menopausal women, the pCR rate was 23.4versus 16.1% (57 out of 353) respectively, and in post-menopausal women, it was 24.8% versus 14.6%, respectively.

Treatment-Related AEs in **Neoadjuvant** Phase

All Treatment-Related	Pembro Arm (N = 634)	Placebo Arm (N = 642)
Any grade	98.4%	98.6%
Grade 3-5	52.5%	46.4%
Serious	18.5%	10.3%
Led to death	0.2%[a]	0
Led to discontinuation of any drug	19.1%	10.1%



[a]**1 patient from acute myocardial infarction, considered related to QT.** Data cutoff date: May 25, 2023.

CA209-7FL study design

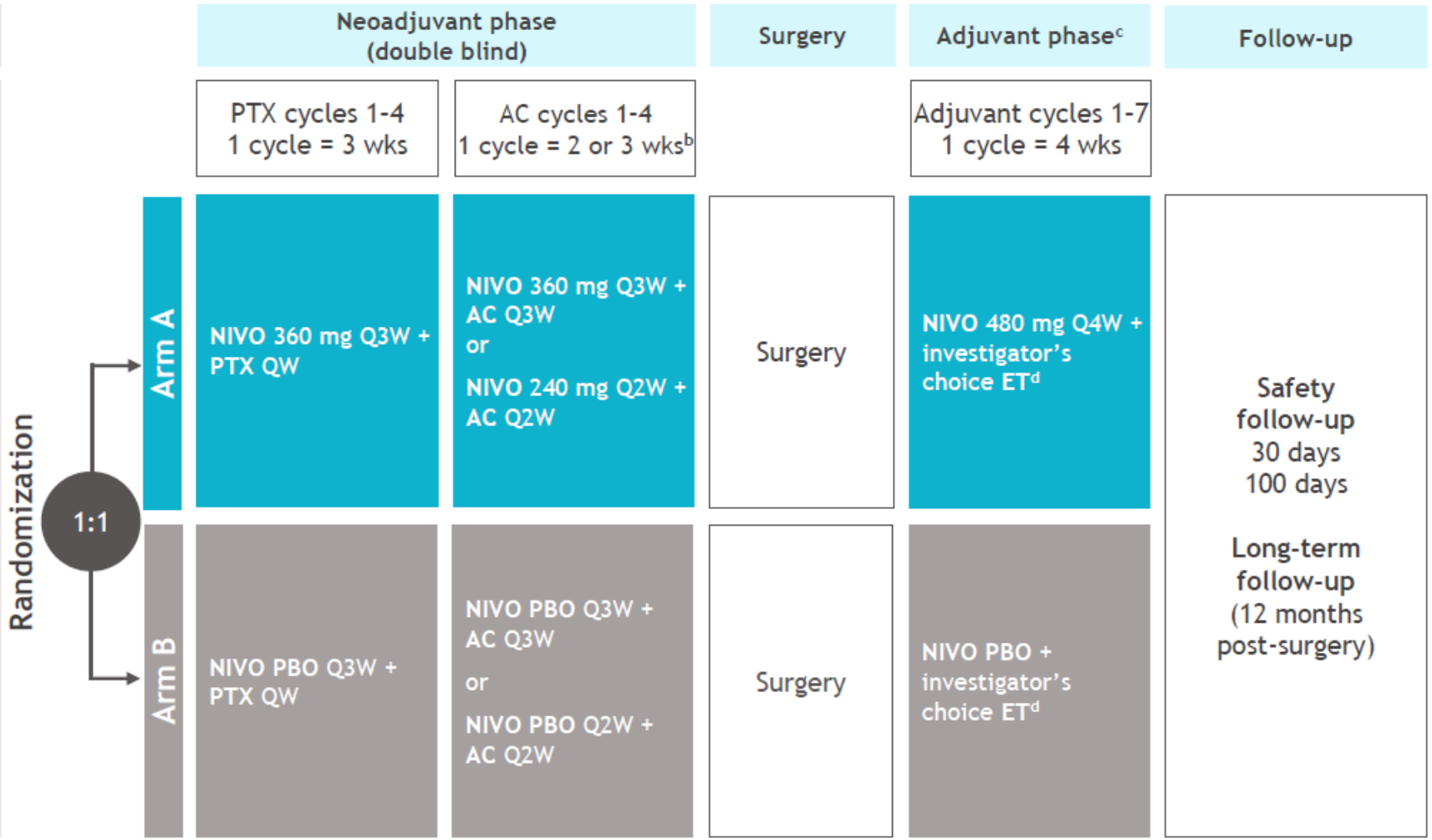
Screening

Key inclusion criteria

- Newly diagnosed ER+ HER2− breast cancer
- Confirmed ER+ breast cancer
- T1c-T2, cN1-cN2 or T3-T4, cN0-cN2
- Grade 3 with ER ≥ 1% or grade 2 with ER 1-10%[a]
- Adequate organ function
- Tissue available for biomarker assessment
- ECOG PS 0-1

Stratification factors

- PD-L1 IC (≥ 1% or < 1%)
- Tumor grade (3 or 2)
- Axillary nodal status (positive or negative)
- AC frequency (Q3W or Q2W)



[a]Grade was determined locally by investigator. [b]Investigator's choice: anthracycline dosing frequency of Q2W or Q3W for AC cycles determined by the investigator. [c]After protocol amendment 3, the study was unblinded in the adjuvant phase. Participants in arm B will not receive NIVO PBO. [d]Available ET agents included tamoxifen, letrozole, anastrozole, and exemestane.

AC, anthracycline + cyclophosphamide; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; ER+, estrogen receptor-positive; ET, endocrine therapy; HER2−, human epidermal growth factor receptor 2-negative; IC, immune cell; N, lymph node involvement; NIVO, nivolumab; PBO, placebo; PD-L1, programmed death ligand 1; PTX, paclitaxel; QXW, every X weeks; T, size and extent of primary tumor; wk, week.

Patient baseline characteristics in mITT population (n = 510)

- Of 830 patients screened, 521 were randomized in total and 510 were randomized in the primary efficacy population (mITT)

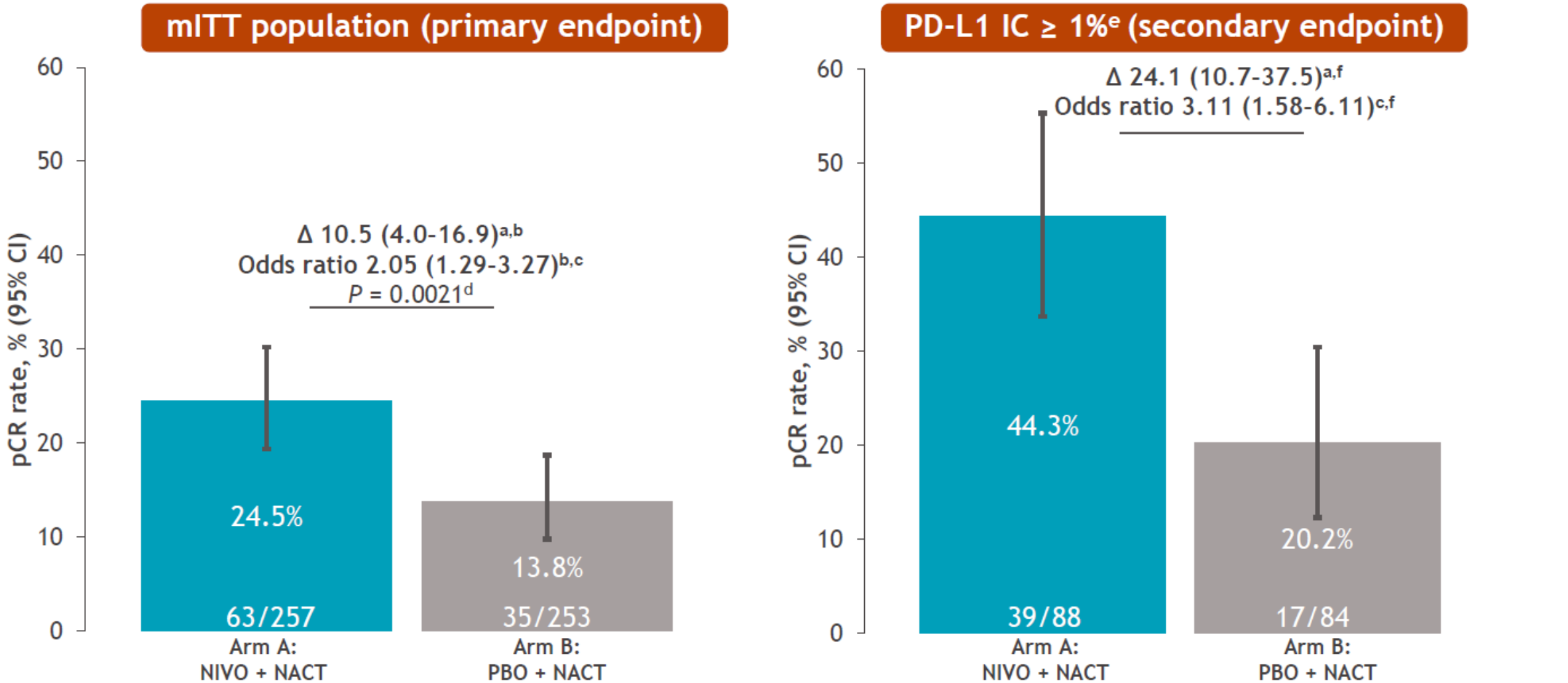
	Arm A: NIVO + NACT, n = 257	Arm B: PBO + NACT, n = 253
Median age, years (range)	50 (24-78)	51 (23-79)
ECOG PS, n (%)		
0	221 (86)	222 (88)
1	36 (14)	31 (12)
Tumor grade,[a] n (%)		
Grade 2	6 (2)	1 (< 1)
Grade 3	251 (98)	252 (> 99)
Stage[b] (TNM classification[1]), n (%)		
Stage II	135 (53)	138 (55)
Stage III	118 (46)	105 (42)
Not assigned/reported	4 (2)	7 (3)
PD-L1,[c] n (%)		
< 1%	169 (66)	169 (67)
≥ 1%	88 (34)	84 (33)
Axillary nodal status, n (%)		
Positive	205 (80)	201 (79)
Negative	52 (20)	52 (21)
AC dose-frequency chemotherapy regimen, n (%)		
Q2W	132 (51)	134 (53)
Q3W	125 (49)	119 (47)

[a]Locally assessed. [b]Arm B included 1 patient with stage I disease and 2 patients with stage IV disease. [c]PD-L1-expressing tumor-infiltrating IC as percentage of tumor area using the VENTANA SP142 assay, per central assessment. AC, anthracycline + cyclophosphamide; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, immune cell; mITT, modified intent-to-treat; NACT, neoadjuvant chemotherapy; NIVO, nivolumab; PBO, placebo; PD-L1, programmed death ligand 1; QXW, every X weeks; TNM, TNM staging system (T, size and extent of primary tumor; N, extent of spread to the lymph nodes; M, presence of metastasis). 1. AJCC Cancer Staging Manual; 8th edition, 3rd printing, Amin MB, Edge SB, Greene FL, et al (Eds), Springer, Chicago 2018.

Key changes and protocol amendments

- The treatment landscape changed in Oct 2021 with approval of adjuvant abemaciclib in high-risk primary ER+ HER2- breast cancer
- This was expected to result in a high rate of withdrawals due to safety concerns with combining CDK4/6 inhibitor with anti-PD-1, putting the co-primary EFS endpoint at risk[1-3]
- In April 2022, a protocol amendment resulted in:
  - The primary endpoint of the trial to focus solely on pCR and new enrollment ceased after 521 patients randomized
    - The primary efficacy population was modified (mITT) to include 510[a] patients enrolled across 221 sites in 31 countries from November 2019 to April 2022
  - pCR in the PD-L1+ population was evaluated as a secondary endpoint
  - EFS was changed from primary to exploratory endpoint; follow up was reduced to 1 year post surgery and adjuvant component became open label
- The safety population included all randomized patients who received ≥ 1 dose (n = 517)

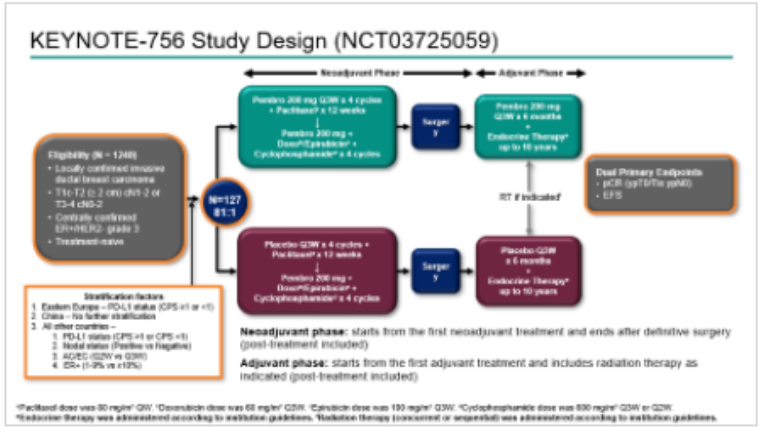
pCR rate in mITT population and by PD-L1 IC ≥ 1%



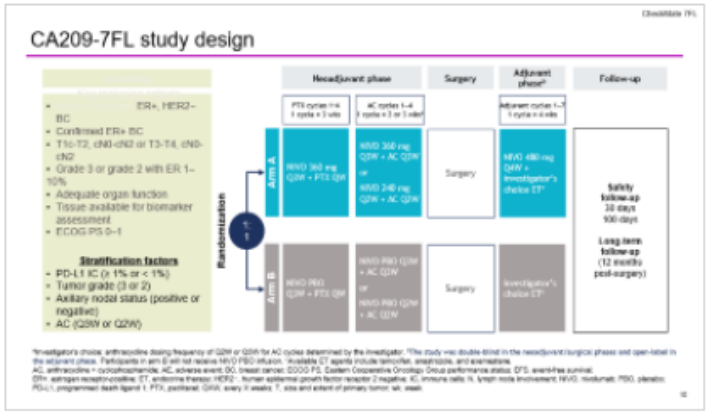
[a]Strata-adjusted difference in pCR (arm A–arm B) based on Cochran-Mantel-Haenszel method of weighting. [b]Stratified by PD-L1 by SP142 (< 1% vs ≥ 1%) and AC dose-frequency chemotherapy regimen (Q2W vs Q3W) per IRT. [c]Strata-adjusted odds ratio (arm A over arm B) using Mantel-Haenszel method. [d]Two-sided *P* value from stratified Cochran-Mantel-Haenszel test. [e]PD-L1 ICs and PD-L1-expressing tumor-infiltrating ICs as percentage of tumor area using the VENTANA SP142 assay. [f]Stratified by AC dose-frequency chemotherapy regimen.

AC, anthracycline + cyclophosphamide; CI, confidence interval; IC, immune cell; IRT, interactive response technology; mITT, modified intent-to-treat; NACT, neoadjuvant chemotherapy; NIVO, nivolumab; PBO, placebo; pCR, pathological complete response; PD-L1, programmed death ligand 1; QXW, every X weeks.

Neo-Adjuvant Trials IO + CT for ER+ HER2- Early Breast Cancer



Cardoso F et al, LBA21, ESMO 2023



Loi S et al, LBA20, ESMO 2023

Similar Trial Designs:

- both placebo controlled RCTs assessing PD1 inhibitors in combination with same NACT regimen in ER+ HER2- EBC
- different PD1 inhibitors (pembrolizumab, nivolumab)

Eligible Patients:

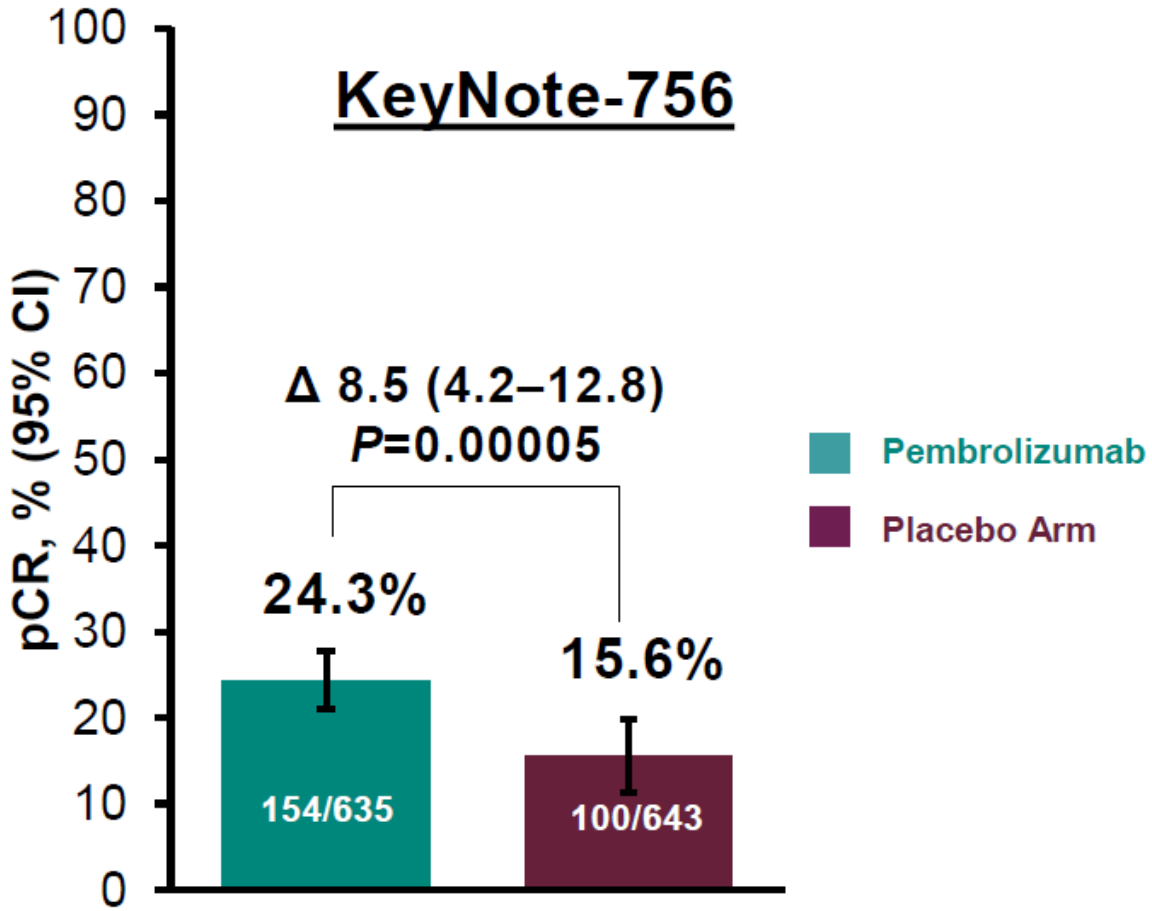
- slight differences in populations
  - All Gr 3, T1c-T2 / N1-2 or T3/T4 N0-2 in KeyNote-756
  - Gr 2/3, T1c-T2 / N0-2 or T3/T4 N0-2 in CheckMate-7FL

Similar Stratification Factors:

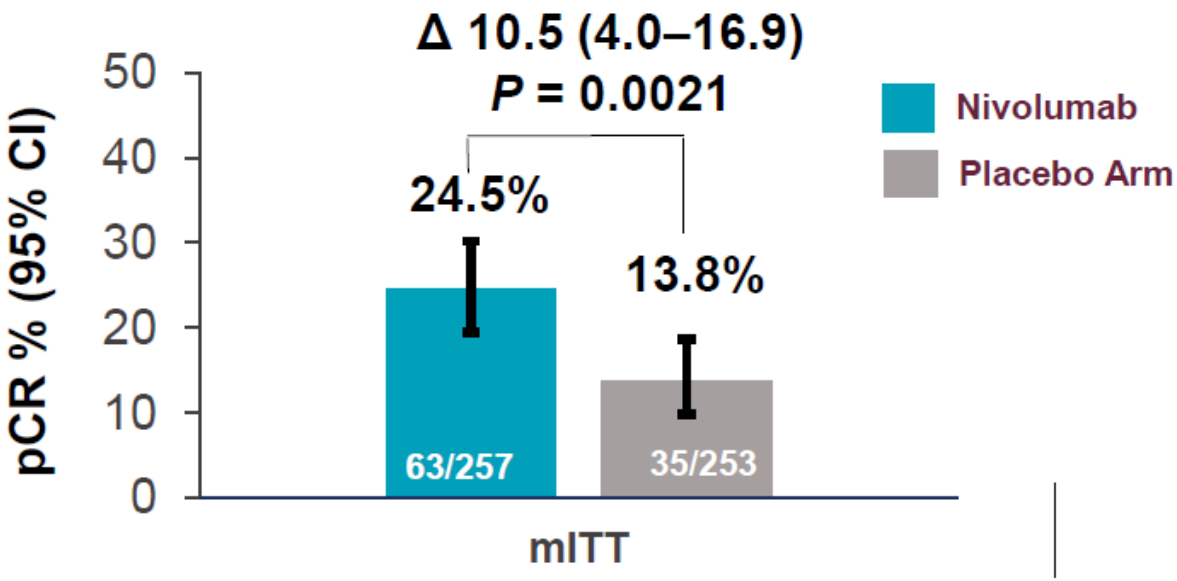
- Nodal Status, AC/EC 2w/3w schedule, PD-L1 status (but different assays used)

Stephen R D Johnston

Pathological Complete Response (ypT0/Tis ypN0)



Cardoso F et al, LBA21, ESMO 2023



Loi S et al, LBA20, ESMO 2023

Adverse Events with Neo-Adjuvant Immunotherapy in ER+ HER2- EBC

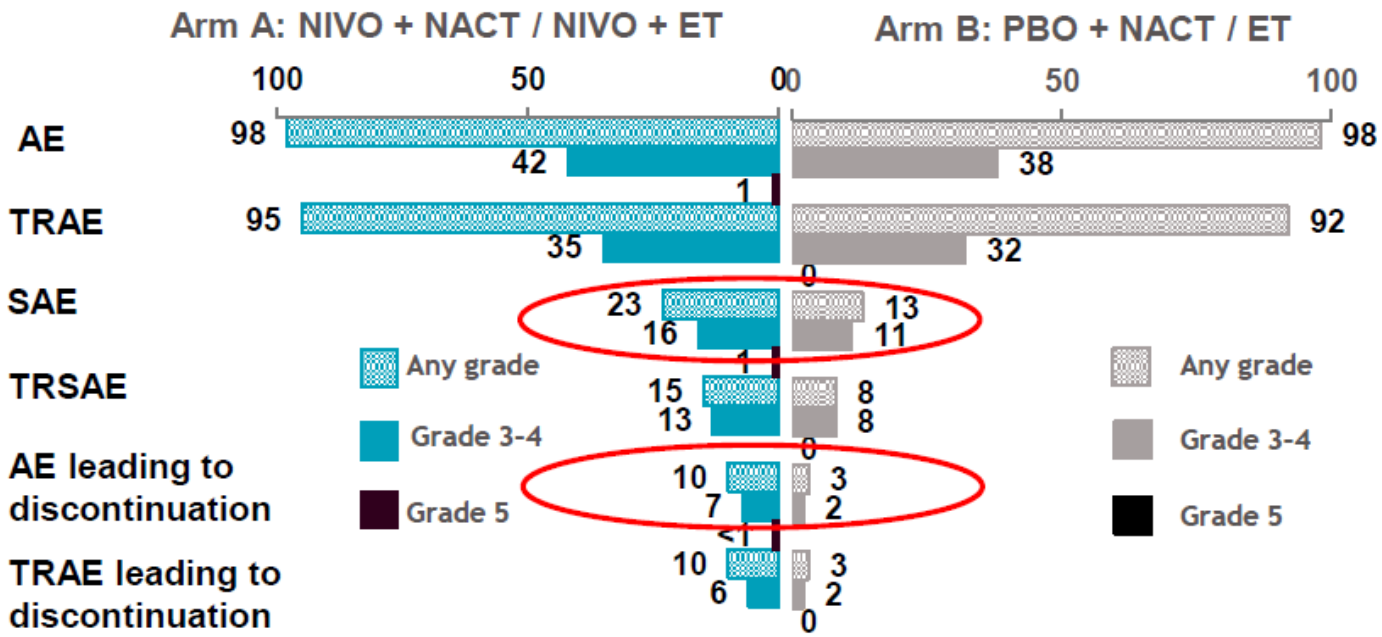
KeyNote-756

All Treatment-Related	Pembro Arm (N = 634)	Placebo Arm (N = 642)
Any grade	98.4%	98.6%
Grade 3-5	52.5%	46.4%
Serious	18.5%	10.3%
Led to death	0.2%[a]	0
Led to discontinuation of any drug	19.1%	10.1%

1 death in PEMBRO arm due to acute myocardial infarct (QT related)

Cardoso F et al, LBA21, ESMO 2023

CheckMate-7FL



2 deaths in NIVO arm due to pneumonitis, hepatitis

Loi S et al, LBA20, ESMO 2023

Neoadjuvant Immunotherapy for ER+ HER2- Early Breast Cancer

A New Paradigm ?

Can Neoadjuvant Immunotherapy improve pCR rates in ER+ HER2- EBC ?

- Yes, significant improvement in pCR seen in 2 separate studies of PD1 inhibitors, albeit rates still only 24%
- Unclear if this will translate into improved EFS

Are there subgroups of ER+ HER2- EBC who benefit most ?

- Almost certainly – higher grade, luminal B, & possibly PD-L1 positive (assay dependent)
- Need to better evaluate if genomic & immune signatures can further define those with most to gain

Are the added toxicities worth it ?

- Added toxicities well known and important in “risk / benefit” decision making of “whom to treat”

Stephen R D Johnston

Conclusioni

- Immunoterapia non indicata per tutti i tumori mammari
- Vantaggio in sopravvivenza nei pazienti con tumore mammario metastatico TN PDL 1 positivo
- Aumento della probabilità di pCR e migliore EFS nei tumori mammari TN stadio iniziale indipendentemente dall'espressione di PDL1
- Domande sull'utilizzo dell'immunoterapia in pazienti suscettibili anche ad altre terapia (es capecitabina? Olaparib?)
- Tanti quesiti sull'utilizzo della immunoterapia nei tumori luminali-> no modifica la nostra attitudine

- GRAZIE MILLE!!!!