Current and Future Directions of Immunotherapy in Breast Cancer

13th Annual Winter Cancer Symposium
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Avan Armaghani, MD, FACP
Associate Member
Department of Breast Oncology
Moffitt Cancer Center

Background

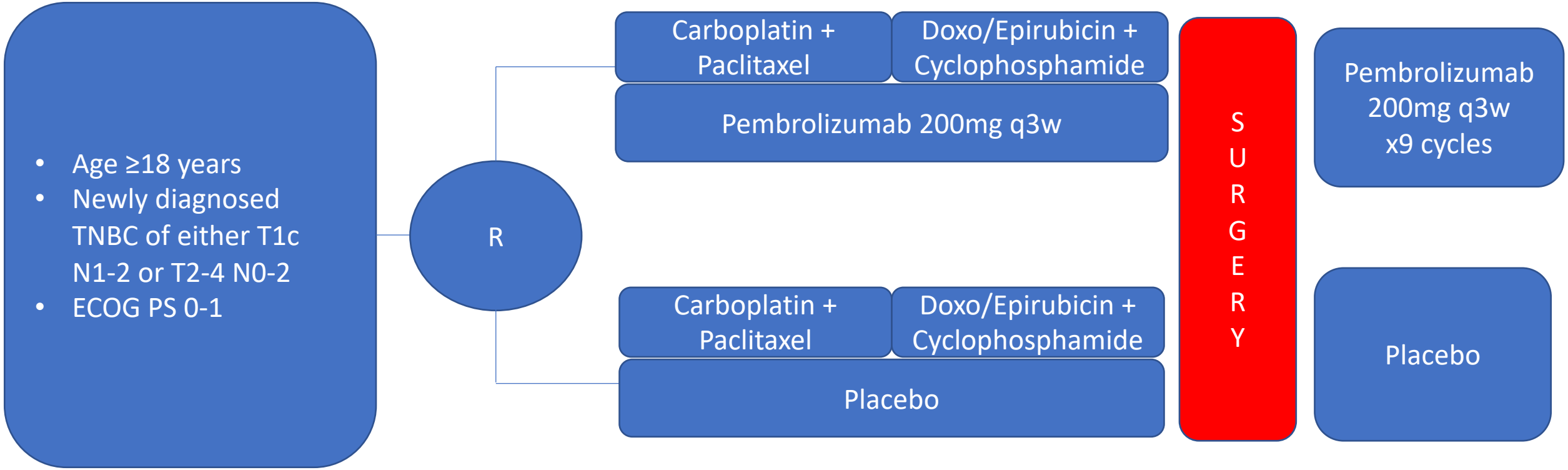
- The role of immunotherapy in the treatment of breast cancer continues to evolve

- Immunotherapy in combination with chemotherapy is standard of care for neoadjuvant treatment of stage II-III TNBC and PDL1 positive metastatic TNBC

- Emerging data provides evidence for role immunotherapy in HR+, HER2 negative breast cancers

Immunotherapy in TNBC

Keynote-522



Primary Endpoints:
pCR (ypT0/Tis ypN0)
EFS in ITT

Schmid et al. NEJM 2020

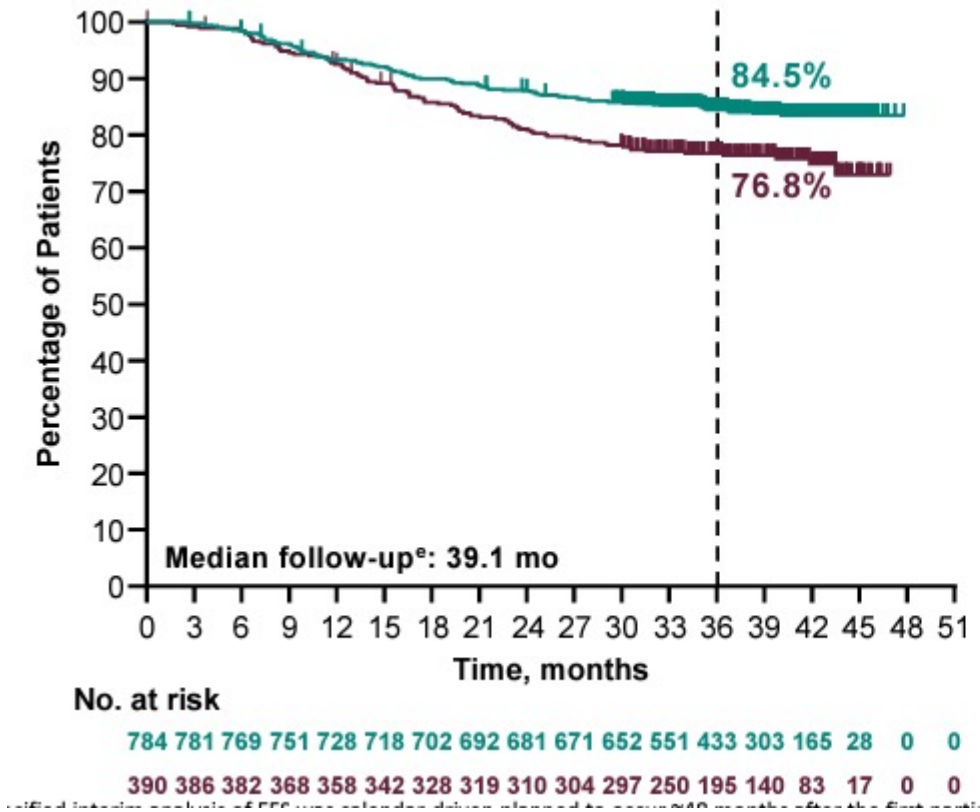
KEYNOTE-522: Results pCR

Table 2. Pathological Complete Response, According to Pathological Stage.*

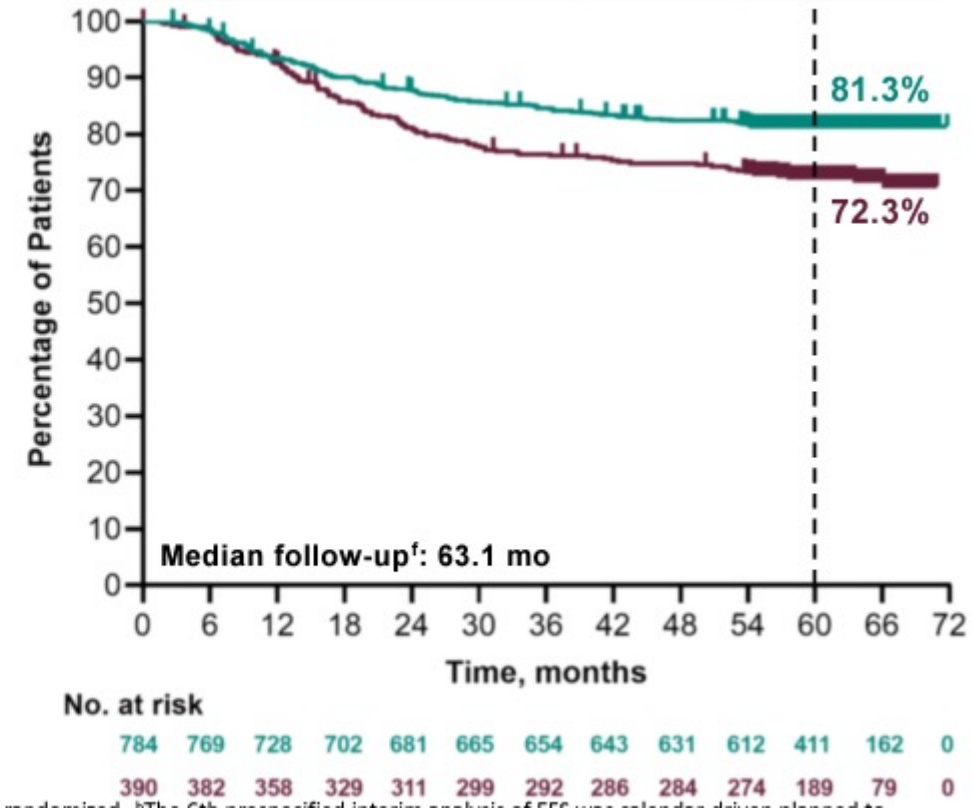
Variable	Pembrolizumab–Chemotherapy (N=401)	Placebo–Chemotherapy (N=201)	Estimated Treatment Difference†	P Value
			percentage points (95% CI)	
Pathological stage ypT0/Tis ypN0				
No. of patients	260	103		
Percentage of patients with response (95% CI)	64.8 (59.9–69.5)	51.2 (44.1–58.3)	13.6 (5.4–21.8)	P<0.001
Pathological stage ypT0 ypN0				
No. of patients	240	91		
Percentage of patients with response (95% CI)	59.9 (54.9–64.7)	45.3 (38.3–52.4)	14.5 (6.2–22.7)	
Pathological stage ypT0/Tis				
No. of patients	275	108		
Percentage of patients with response (95% CI)	68.6 (63.8–73.1)	53.7 (46.6–60.8)	14.8 (6.8–23.0)	

Schmid et al. NEJM 2020

KEYNOTE-522: Results EFS



Median Follow-up: 39.1 mos

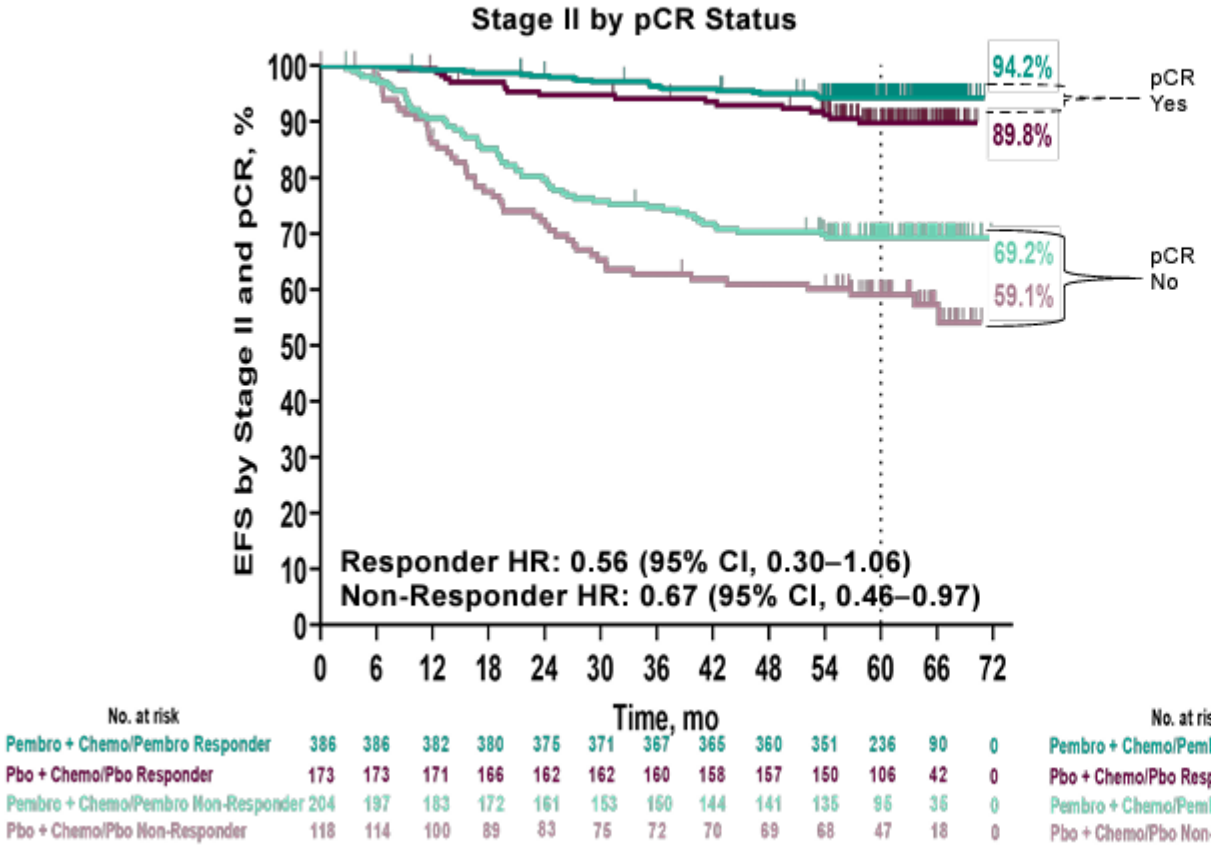


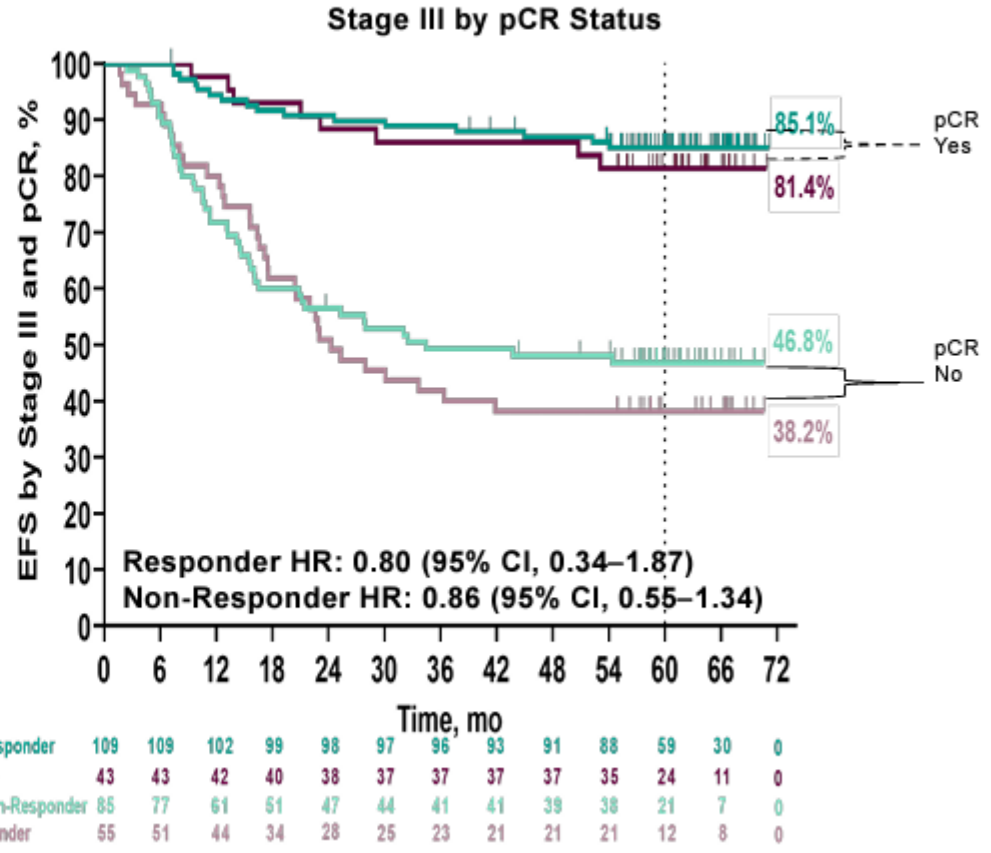
Median Follow-up: 63.1 mos

Schmid et al. NEJM 2022

Schmid et al. ESMO 2023

KEYNOTE-522: Results EFS by stage and pCR



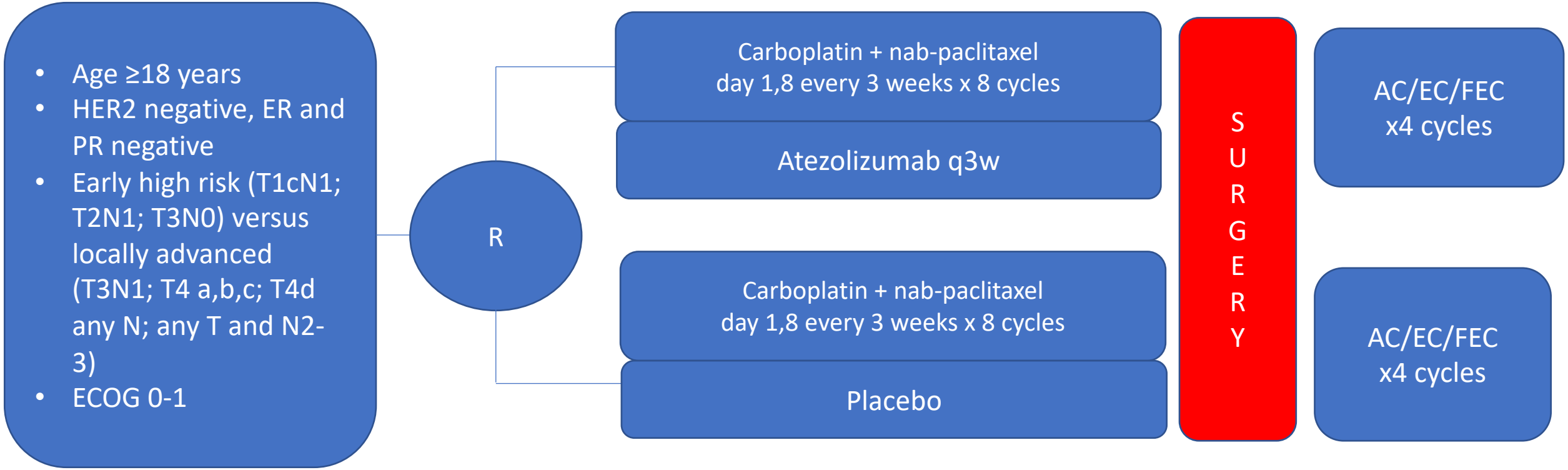


Stage II

Stage III

Schmid et al. ESMO 2023

NeoTrip



Primary Endpoint:
- EFS

Secondary Endpoint:
- pCR

Gianni et al. Ann Oncol 2022

Table 2. Pathological complete response

	Atezo (n = 138)		No atezo (n = 142)	
	n	%	n	%
pCR	67	48.6	63	44.4
95% CI for pCR rate		40.0-57.2		36.0-52.9
Crude absolute difference in pCR rate (95% CI)	4.2 (−7.4 to 15.6)			
OR	1.18 (0.74-1.89)			
P value	0.48			

Atezo, atezolizumab; CI, confidence interval; OR, odds ratio; pCR, pathological complete response.

Table 3. Multivariate analysis of pCR

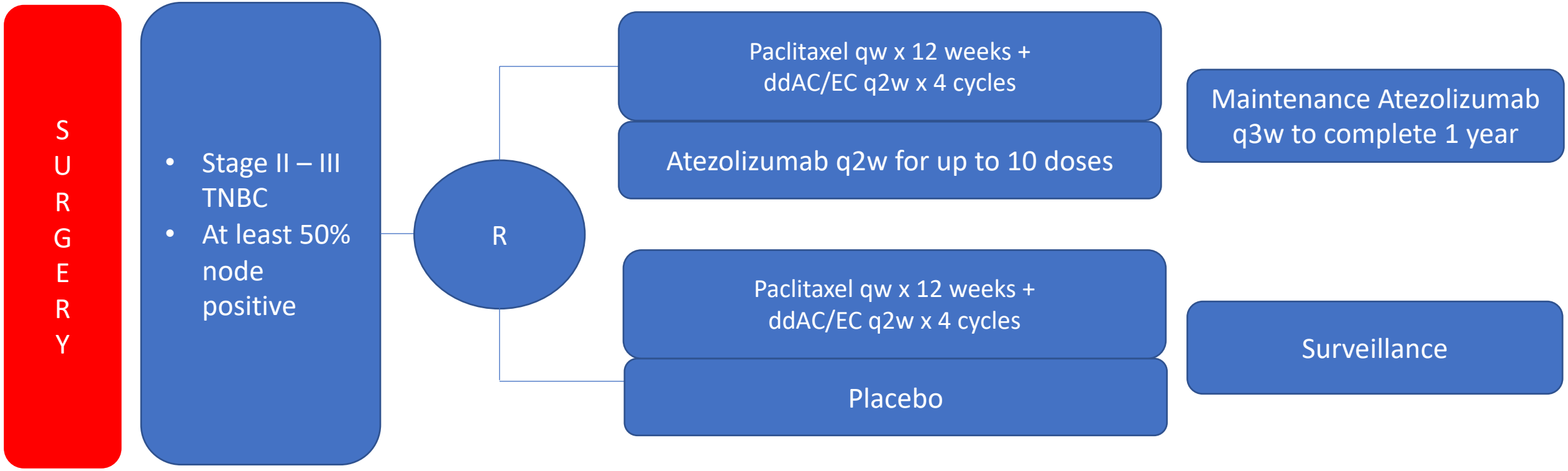
Variable	Effect	Odds ratio (95% CI)	P value
Treatment	Atezo versus no atezo	1.11 (0.88-1.40)	0.39
PD-L1 expression	Positive versus negative	2.08 (1.64-2.65)	<0.0001
Disease stage	Early high risk versus locally advanced	0.84 (0.66-1.06)	0.14

Atezo, atezolizumab; CI, confidence interval; pCR, pathological complete response; PD-L1, programmed death-ligand 1.

Median follow-up 54 months:
5 year EFS 70.6% with atezo v 74.9% without atezo (p value .66)

Gianni et al. Ann Oncol 2022
Gianni et al. ESMO 2023

Alexandra/IMpassion030

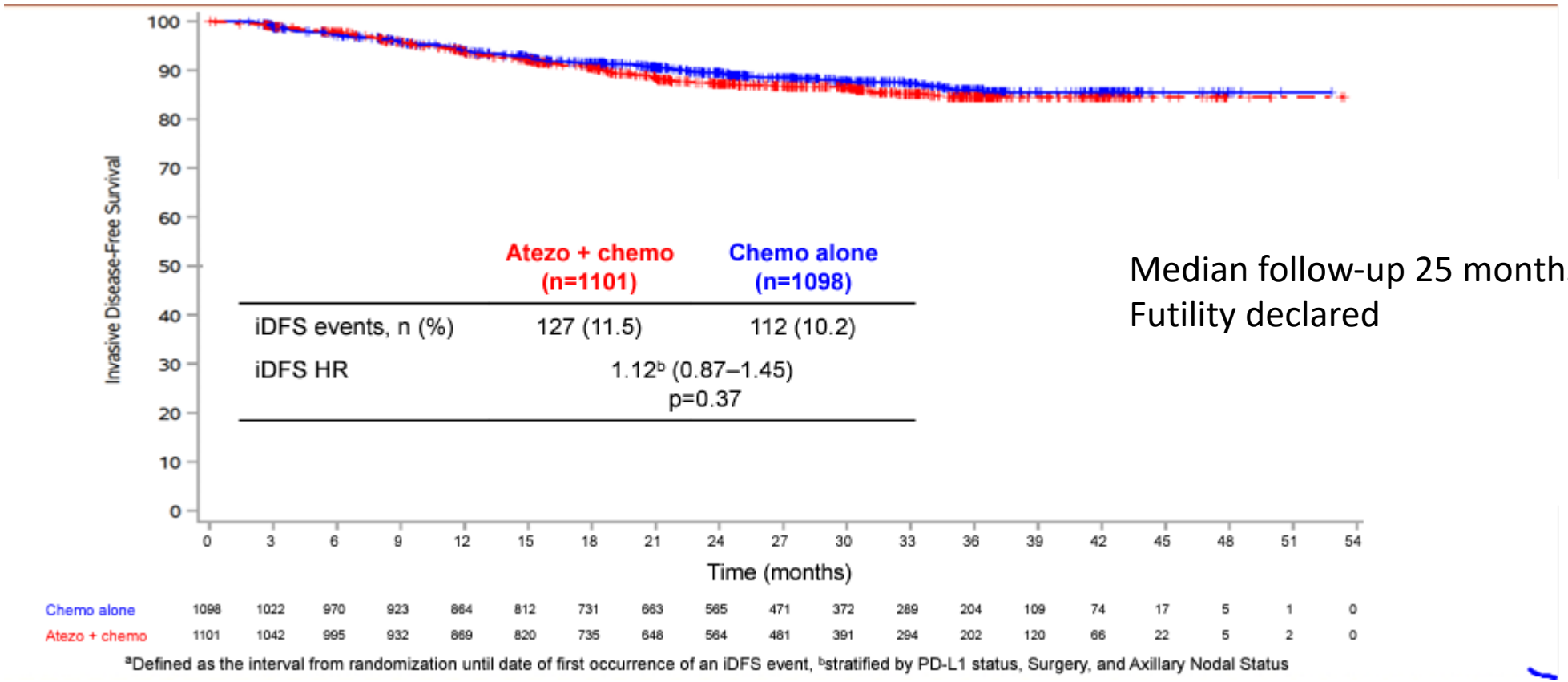


Primary Endpoint:
- iDFS ITT

Secondary Endpoints:
- iDFS in PD-LD1+
- iDFS node +
- iDFS including second primary non-breast invasive cancer
- Overall survival (OS)
- Relapse free interval (RFI)
- Distant Relapse free interval (DRFI)
- Disease free survival (DFS)

Ignatiadis et al. SABCS 2023

Alexandra/IMpassion030: iDFS ITT

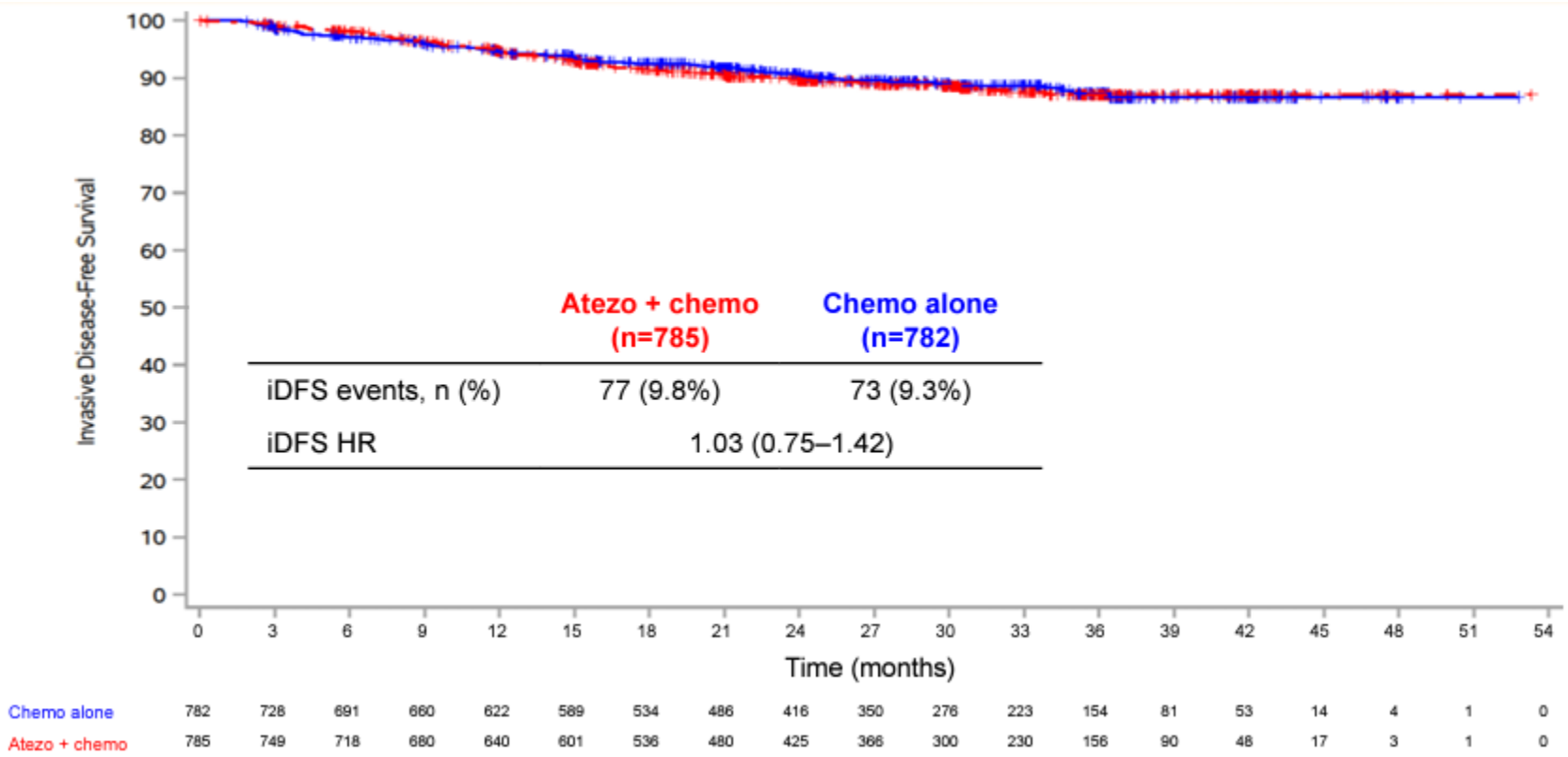


[a]Defined as the interval from randomization until date of first occurrence of an iDFS event, [b]stratified by PD-L1 status, Surgery, and Axillary Nodal Status

Median follow-up 25 months
Futility declared

Ignatiadis et al. SABCS 2023

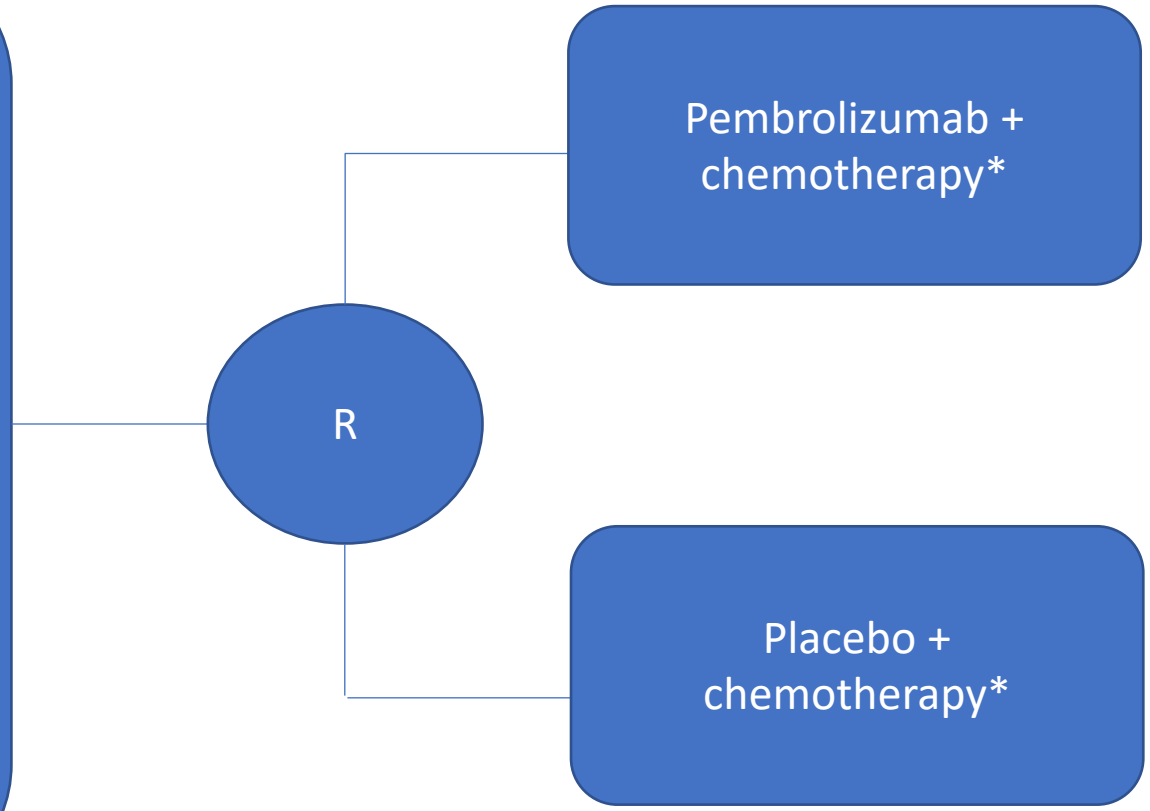
Alexandra/IMpassion030: iDFS PD-L1+ subgroup



Ignatiadis et al. SABCS 2023

Keynote-355

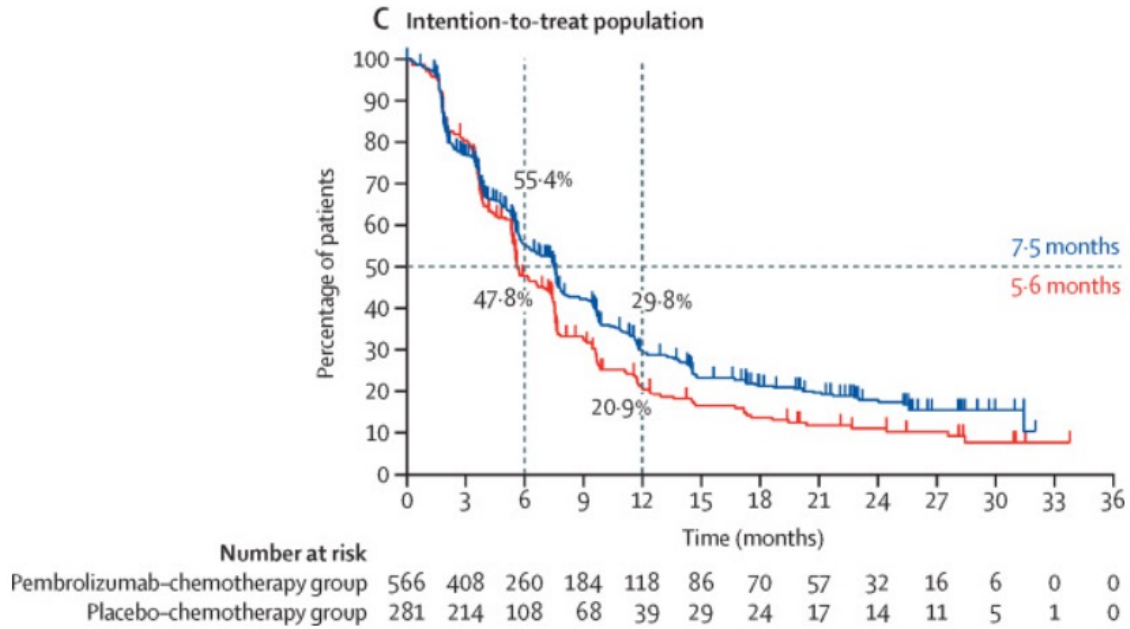
- Age ≥18 years
- Central determination of TNBC and PD-L1 expression
- Previously untreated locally recurrent inoperable or metastatic TNBC
- De novo metastasis or completion of treatment with curable intent ≥6 months prior to first disease recurrence
- ECOG PS 0 or 1
- No active CNS metastases

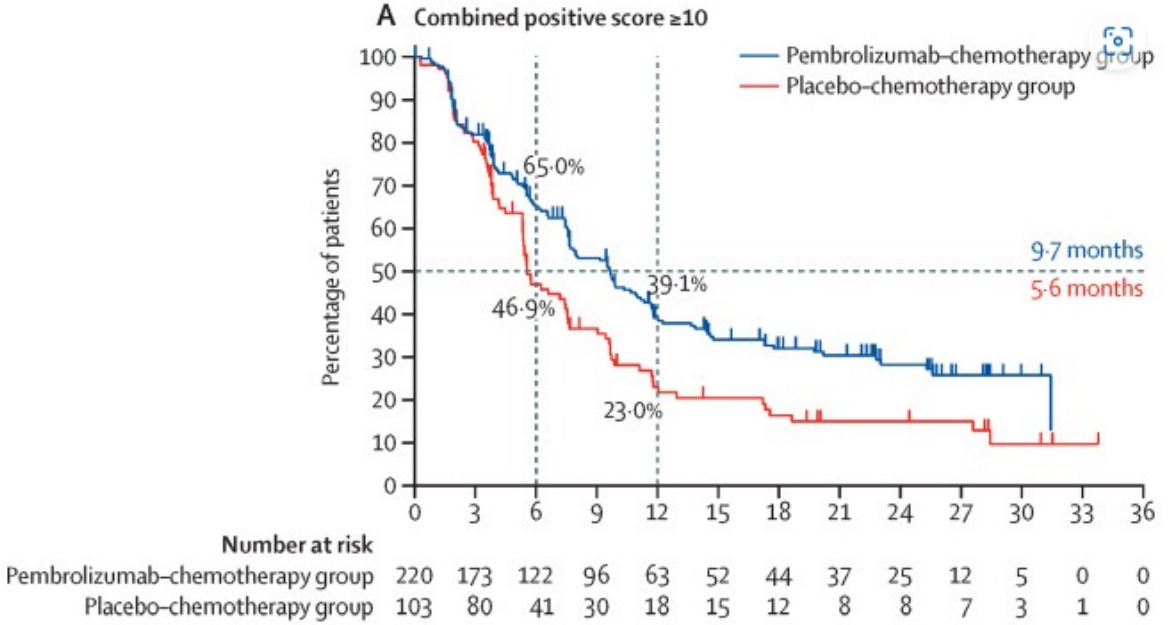


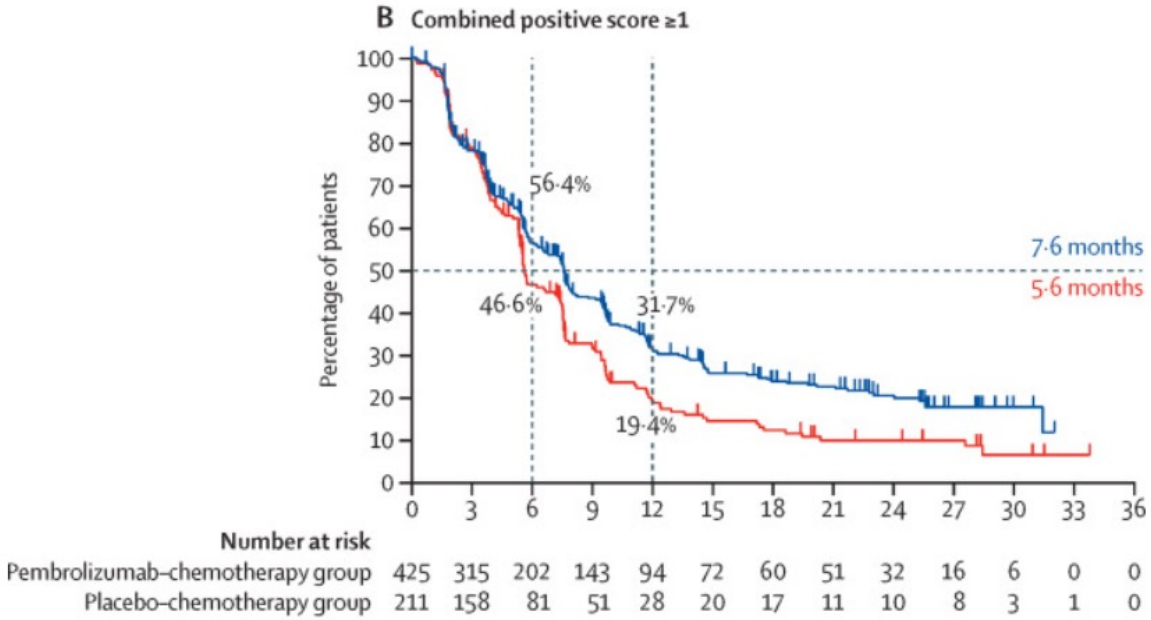
Primary Endpoints: PFS, OS
PD-L1 CPS score ≥ 10
PD-L1 CPS ≥ 1
ITT Population

*Chemotherapy: nanoparticle albumin-bound paclitaxel, paclitaxel, or gemcitabine-carboplatin

Cortes J et al. Lancet 2020

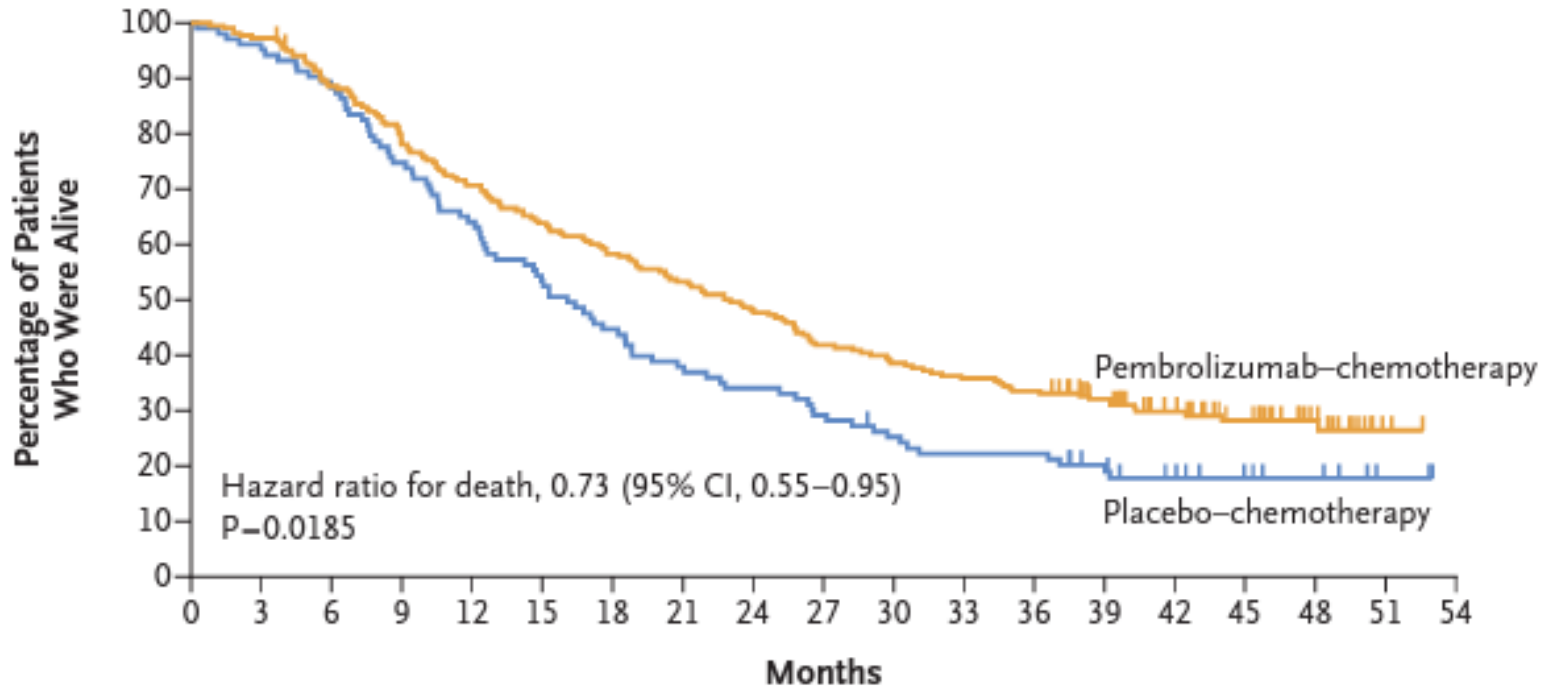






Cortes J et al. Lancet 2020

A Overall Survival in the CPS-10 Subgroup



No. at Risk

Pembrolizumab–chemotherapy	220	214	193	171	154	139	127	116	105	91	84	78	73	59	43	31	17	2	0
Placebo–chemotherapy	103	98	91	77	66	55	46	39	35	30	25	22	22	17	12	8	6	2	0

Cortes J et al. NEJM 2022

KEYLYNK

- Age ≥18 years
- Locally recurrent inoperable or metastatic TNBC not previously treated in the metastatic setting
- Interval between treatment with curative intent and recurrence ≥6 months
- Confirmed PD-L1 status

Carboplatin days 1 and 8 of each 21 day cycle
+
gemcitabine days 1 and 8 of each 21 day cycle
+
pembrolizumab q3w

4-6 cycles

R

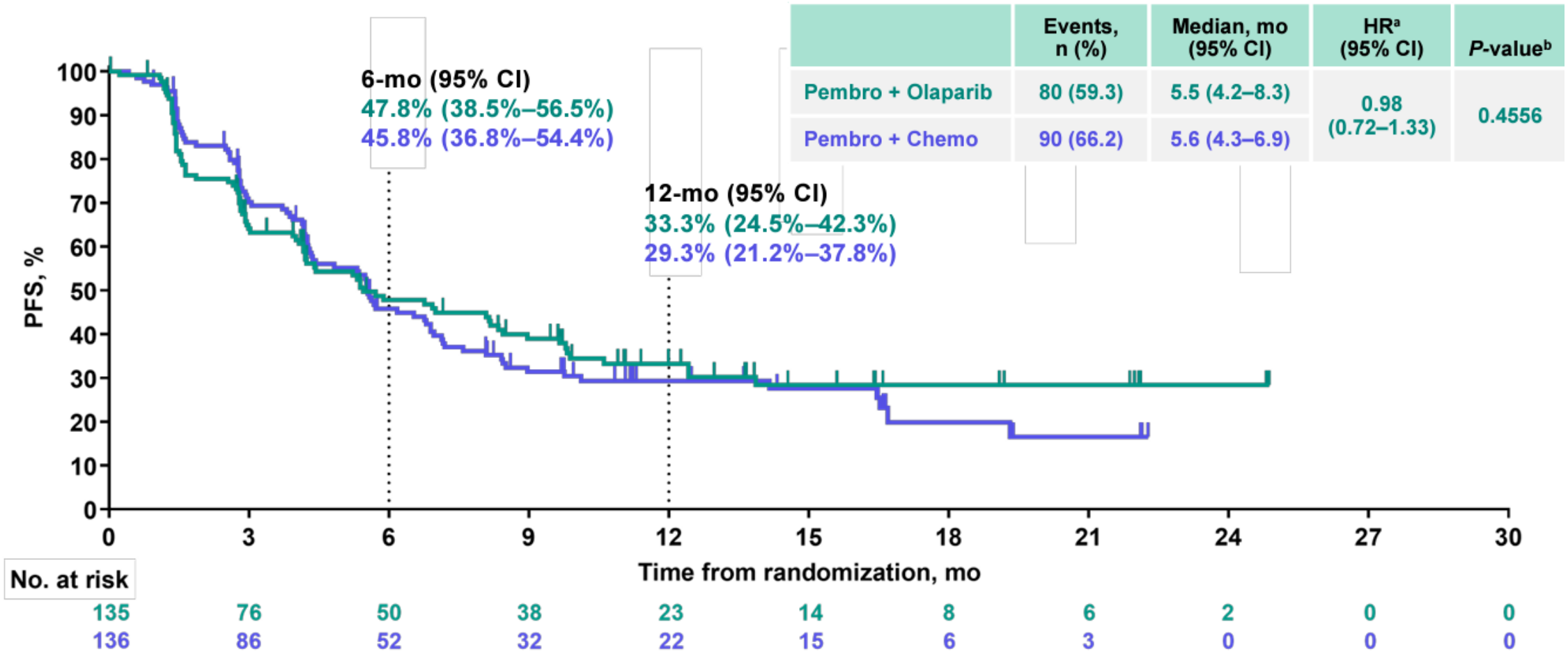
Olaparib 300mg twice daily
+
Pembro 200mg q3w up to 35 cycles including induction

Carboplatin days 1 and 8 of each 21 day cycle
+
gemcitabine days 1 and 8 of each 21 day cycles
+
Pembro 200mg q3w for up to 25 cycles including induction

Primary Endpoints:
PFS
OS in ITT

Rugo et al. SABCS 2023

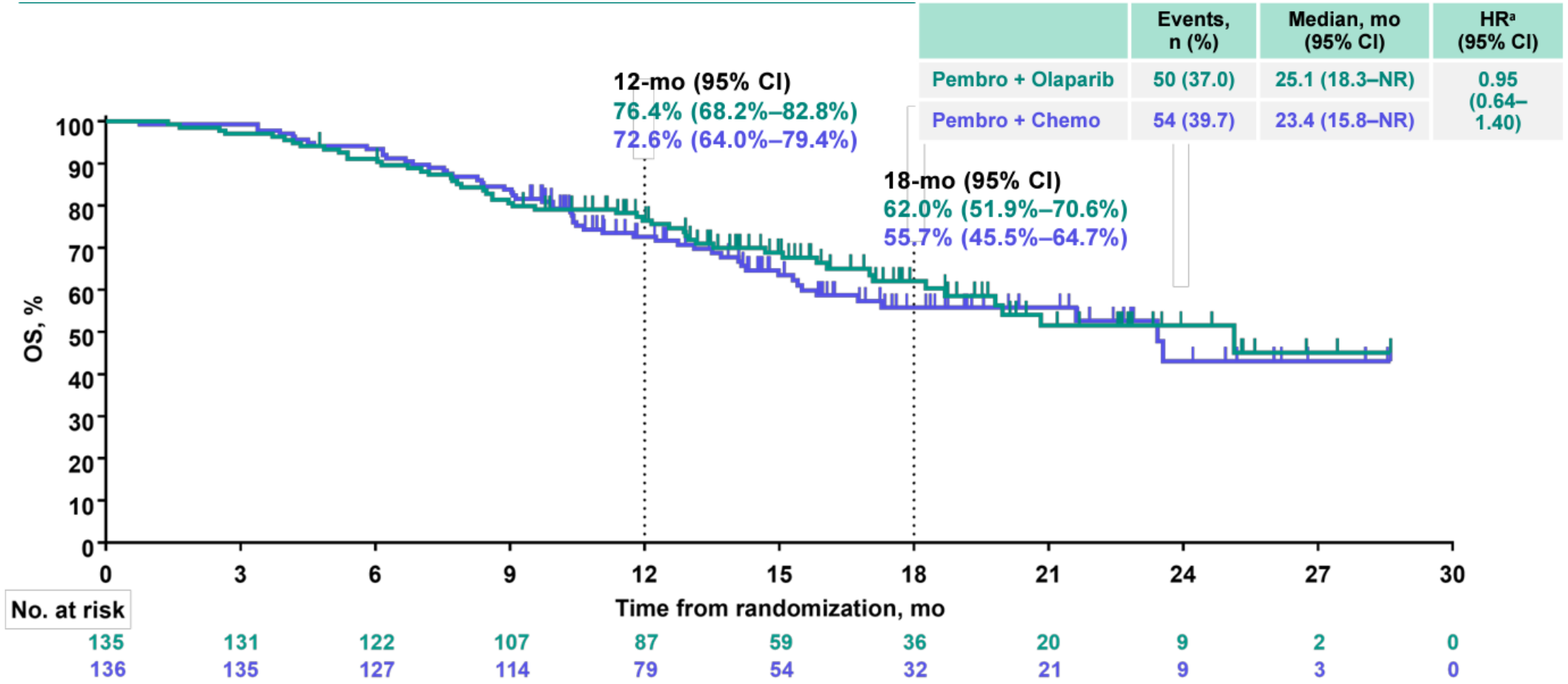
KEYLYNK: PFS in ITT



	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)	*P*-value[b]
Pembro + Olaparib	80 (59.3)	5.5 (4.2–8.3)	0.98 (0.72–1.33)	0.4556
Pembro + Chemo	90 (66.2)	5.6 (4.3–6.9)		

Rugo et al. SABCS 2023

KEYLYNK: OS in ITT population



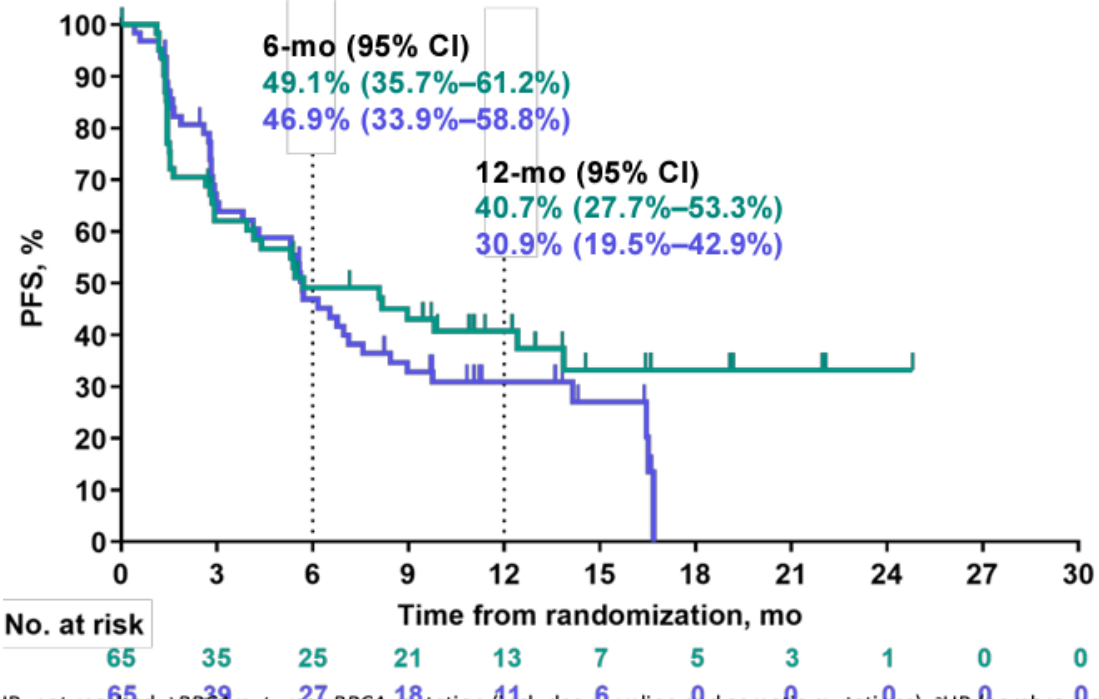
	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)
Pembro + Olaparib	50 (37.0)	25.1 (18.3–NR)	0.95 (0.64–1.40)
Pembro + Chemo	54 (39.7)	23.4 (15.8–NR)	

Rugo et al. SABCS 2023

KEYLYNK: PFS CPS ≥10 and BRCAm

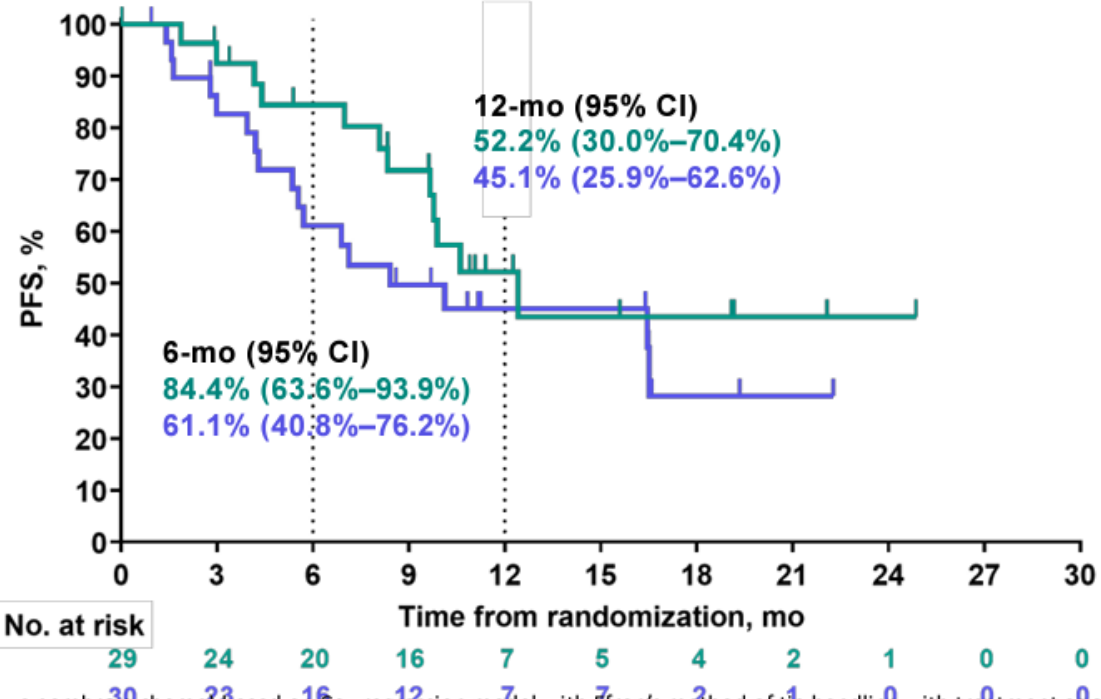
Tumor PD-L1 CPS ≥10 Population

	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)
Pembro + Olaparib	36 (55.4)	5.7 (2.9–13.9)	0.92 (0.59–1.43)
Pembro + Chemo	45 (69.2)	5.7 (3.8–7.6)	



t*BRCA*m Population

	Events, n (%)	Median, mo (95% CI)	HR[b] (95% CI)
Pembro + Olaparib	12 (41.4)	12.4 (8.3–NR)	0.70 (0.33–1.48)
Pembro + Chemo	17 (56.7)	8.4 (5.4–NR)	

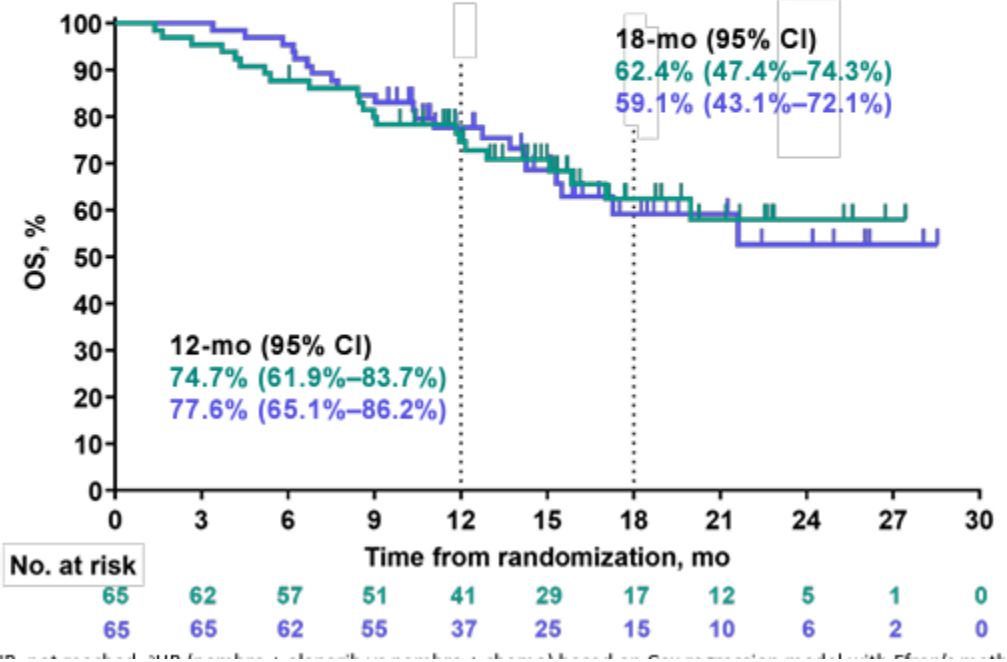


IR, not reached; t*BRCA*m, tumor *BRCA* mutation (includes germline and somatic mutations). [a]HR (pembro + olaparib vs pembro + chemo) based on Cox regression model with Efron's method of tie handling with treatment as a

KEYLYNK: OS CPS ≥10 and BRCAm

Tumor PD-L1 CPS ≥10 Population

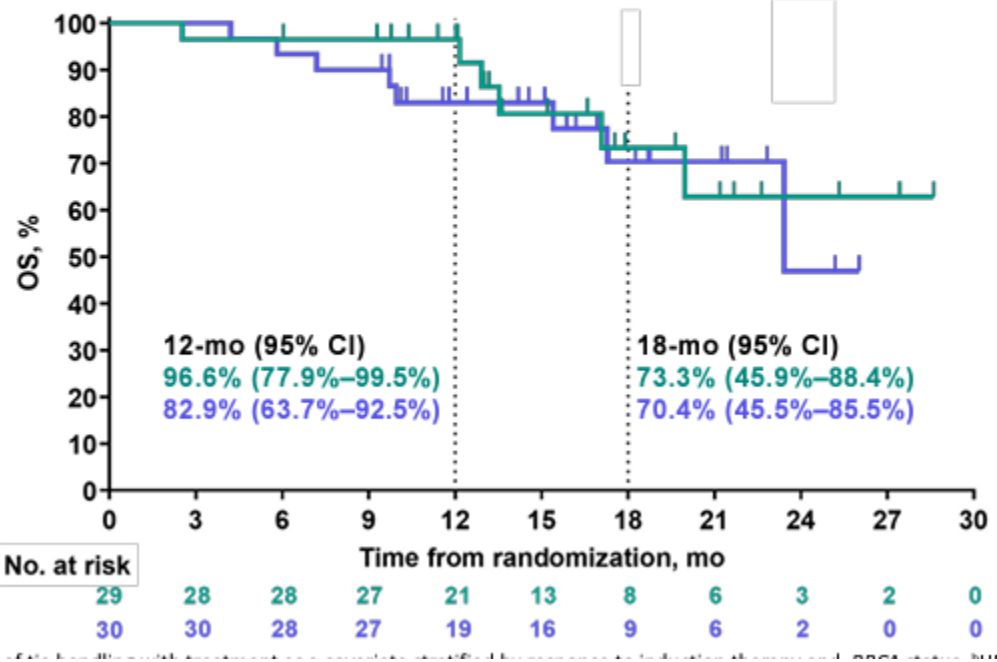
	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)
Pembro + Olaparib	22 (33.8)	NR (17.0–NR)	0.97 (0.53–1.76)
Pembro + Chemo	22 (33.8)	NR (15.5–NR)	



No. at risk											
65	62	57	51	41	29	17	12	5	1	0
65	65	62	55	37	25	15	10	6	2	0

t*BRCA*m Population

	Events, n (%)	Median, mo (95% CI)	HR[b] (95% CI)
Pembro + Olaparib	6 (20.7)	NR (17.1–NR)	0.81 (0.28–2.37)
Pembro + Chemo	8 (26.7)	23.4 (17.3–NR)	



No. at risk											
29	28	28	27	21	13	8	6	3	2	0
30	30	28	27	19	16	9	6	2	0	0

Rugo et al. SABCS 2023

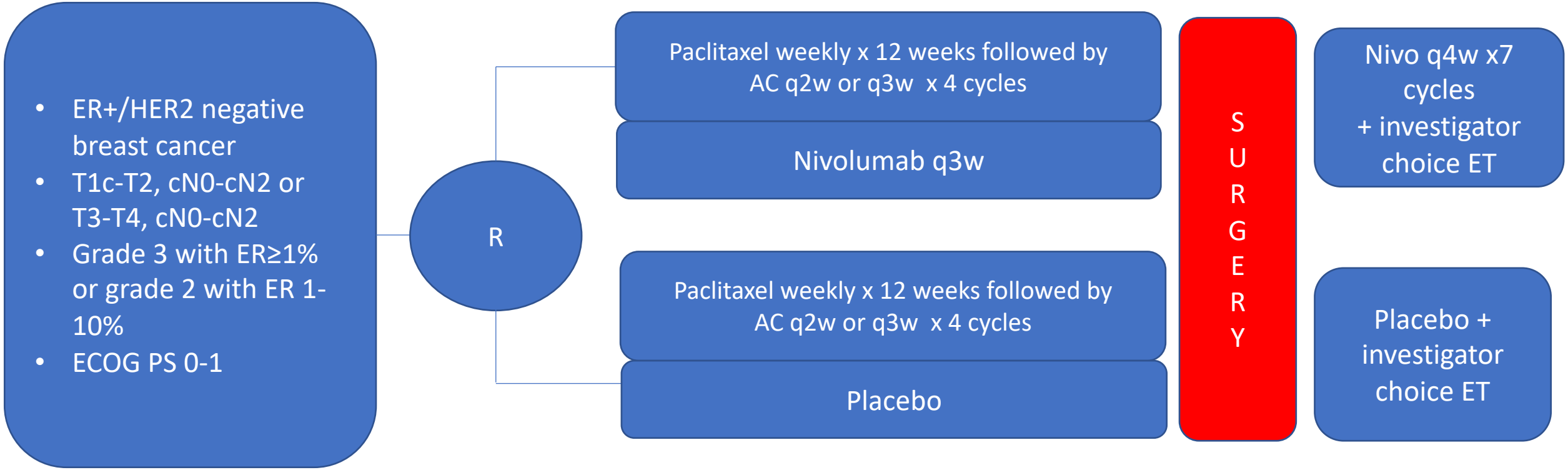
KEYLYNK: Adverse events

	Pembro + Olaparib n = 135	Pembro + Chemo n = 133
Treatment-related AEs		
Any grade treatment-related AEs	114 (84.4)	128 (96.2)
Grade 3–5 treatment-related AEs	44 (32.6)[a]	91 (68.4)[b]
Treatment-related AEs leading to discontinuation of any treatment	12 (8.9)	26 (19.5)
Immune-Mediated AEs and Infusion Reactions[c]		
Any grade	26 (19.3)	31 (23.3)
Grade 3/4[d]	6 (4.4)	6 (4.5)
Led to discontinuation of any treatment	0	4 (3.0)

Data are n (%) of patients.
[a]There were no grade 5 events in the pembro + olaparib group.
[b]2 patients had grade 5 events in the pembro + chemo group (gastrointestinal hemorrhage and thrombotic thrombocytopenic purpura, n = 1 each).
[c]Immune-mediated AEs and infusion reactions were based on a list of preferred terms intended to capture known risks of pembrolizumab and were considered regardless of attribution to study treatment by the investigator.
[d]There were no grade 5 events in either group.
Data cutoff date: December 15, 2022.

Immunotherapy in HR+/HER2 negative breast cancer

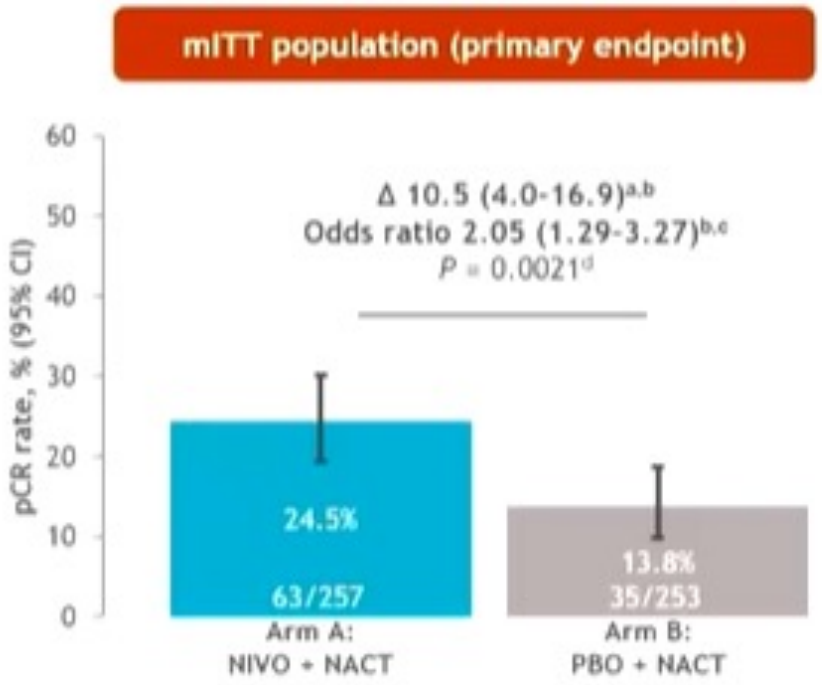
Checkmate 7FL

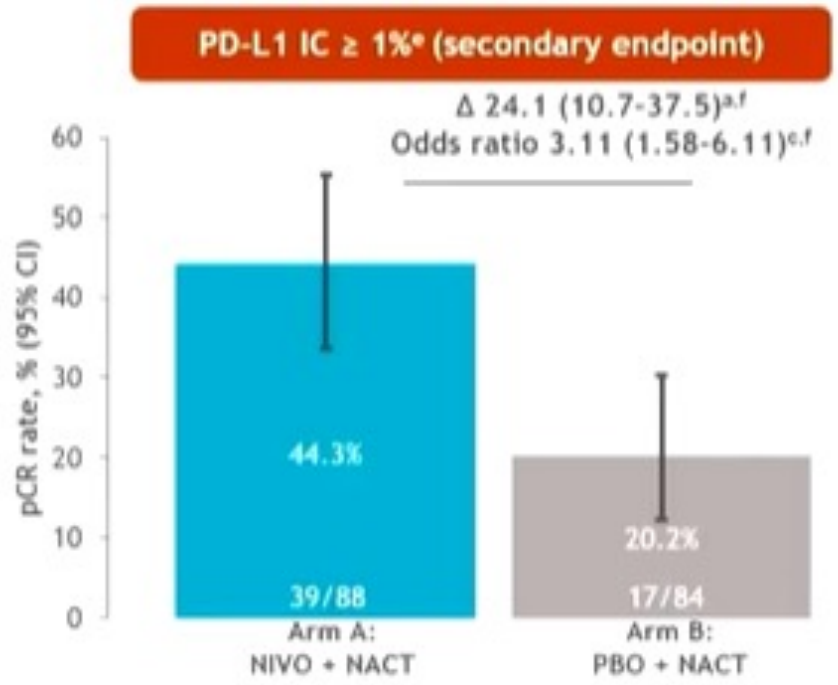


Primary Endpoint:
pCR
EFS

Loi et al. ESMO 2023, SABCS2023

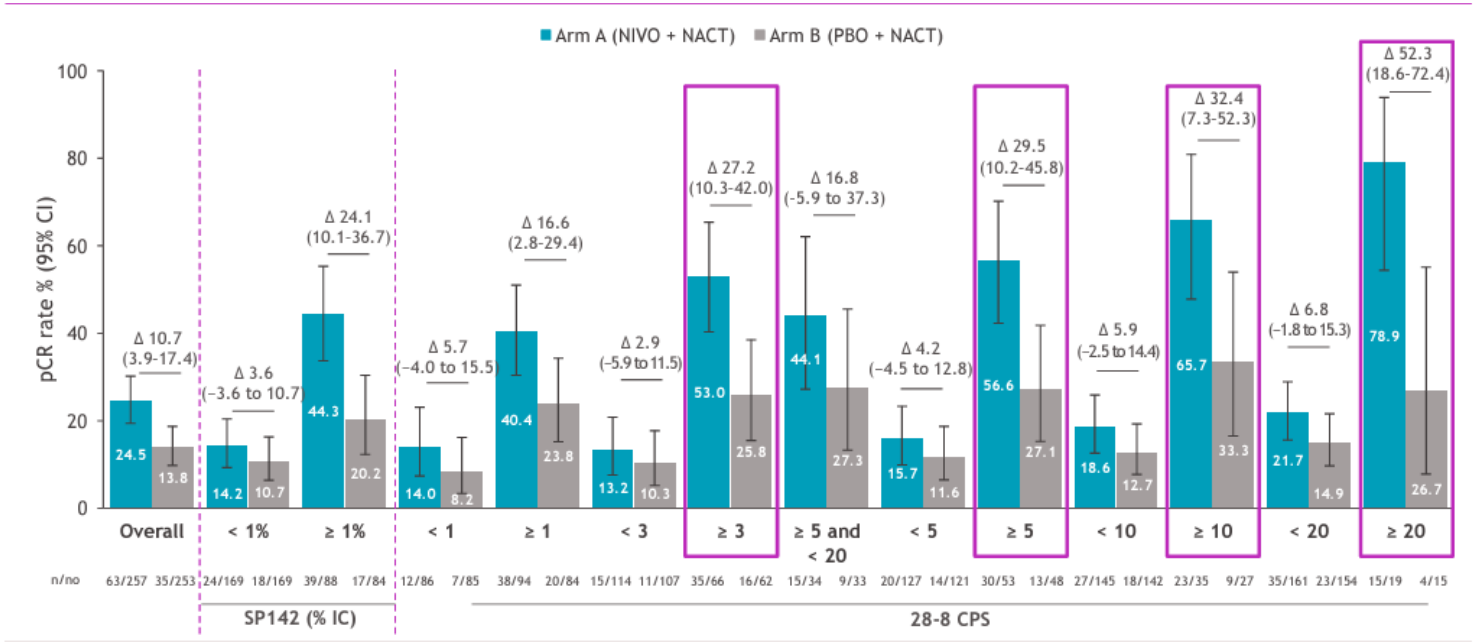
Checkmate 7FL: pCR ITT population

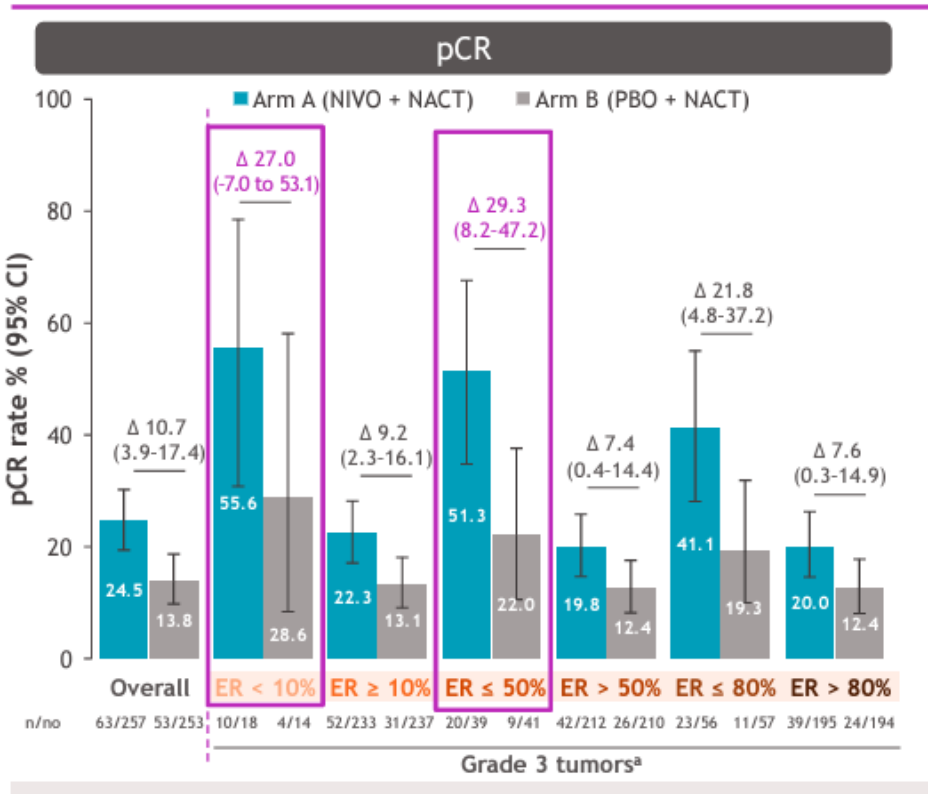




Loi et al. ESMO 2023, SABCS 2023

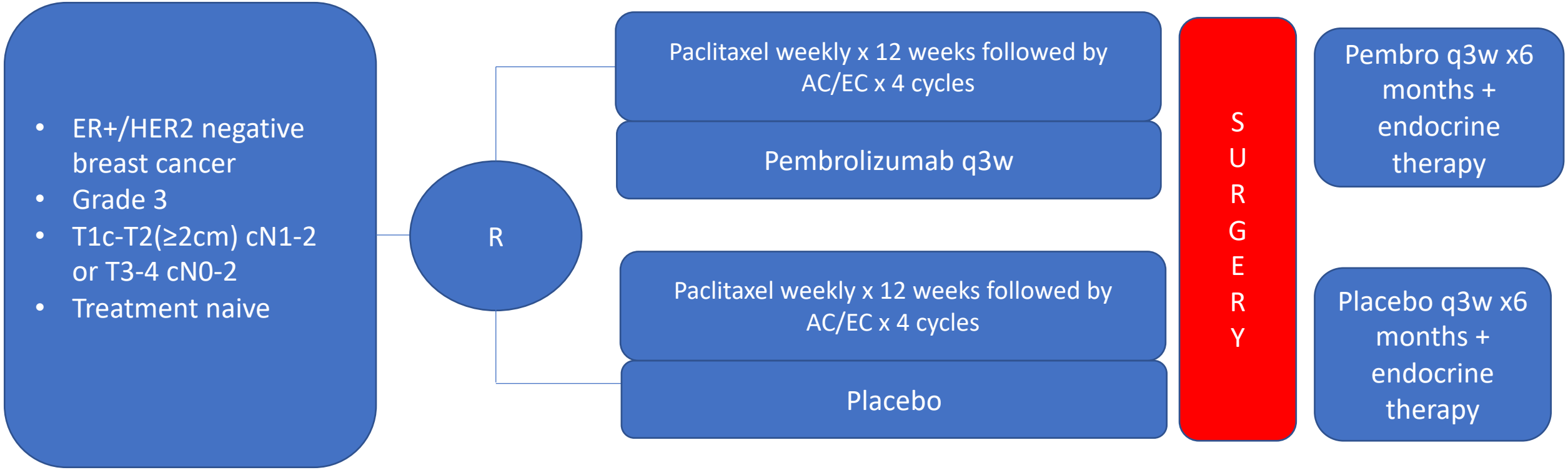
Checkmate 7FL: Key subgroup & biomarker analysis





Loi et al. SABCS 2023

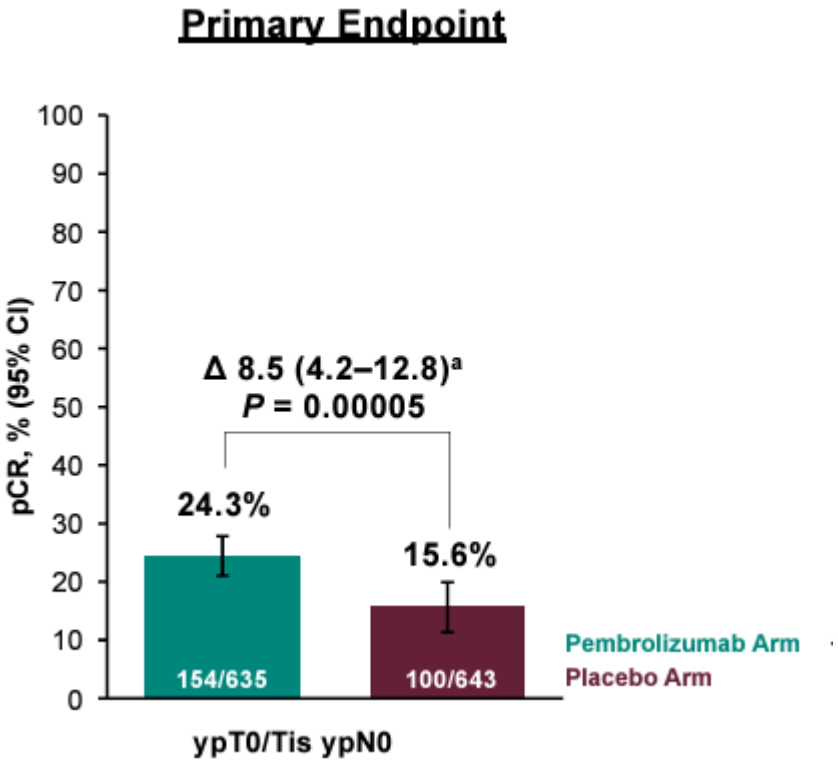
KEYNOTE-756

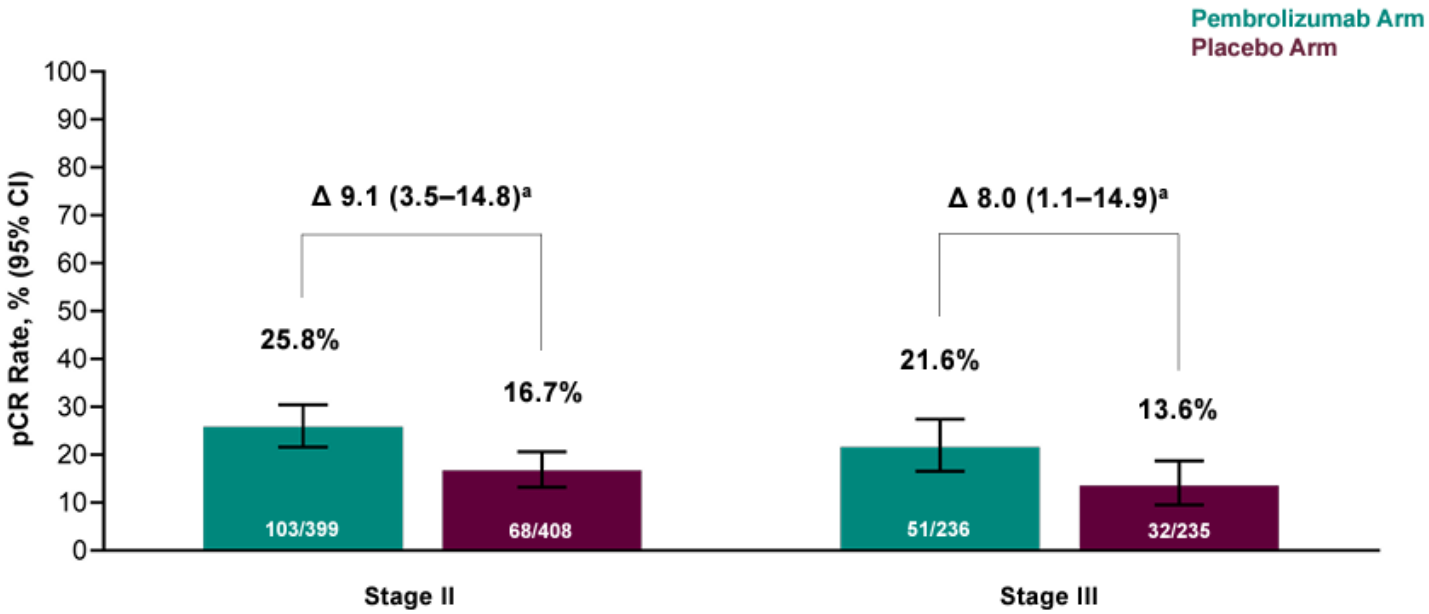


Primary Endpoint:
- pCR
- EFS

Cardosa et al. ESMO 2023
O'Shaughnessy SABCS 2023

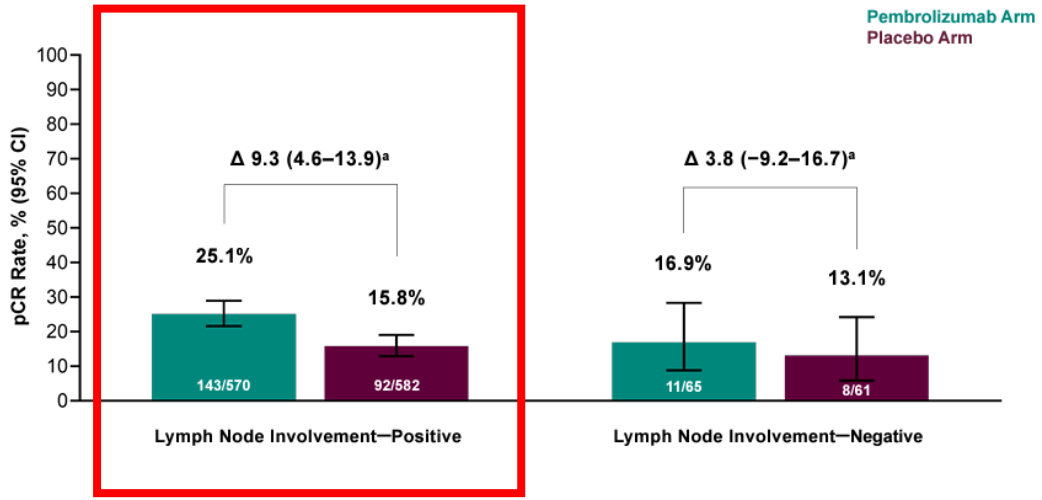
KEYNOTE-756: pCR

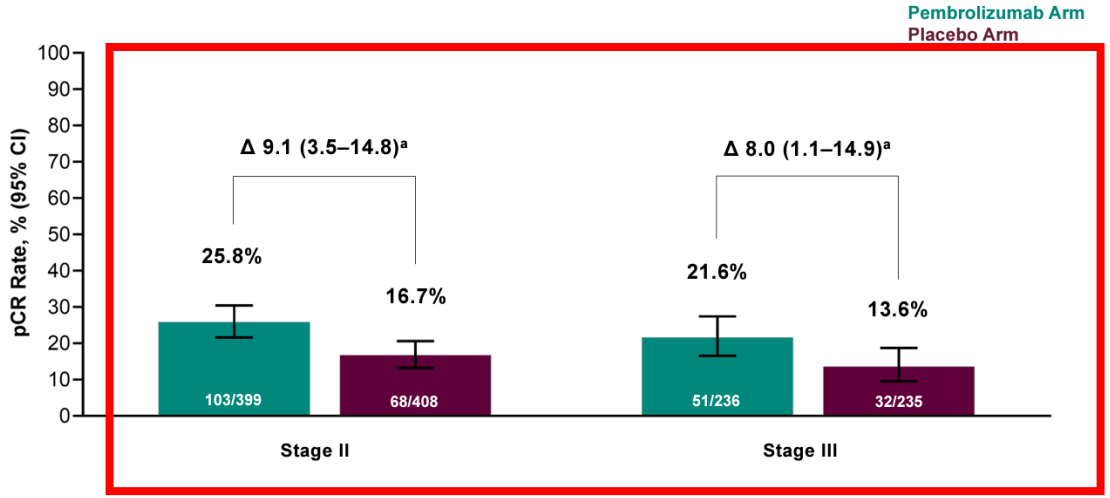


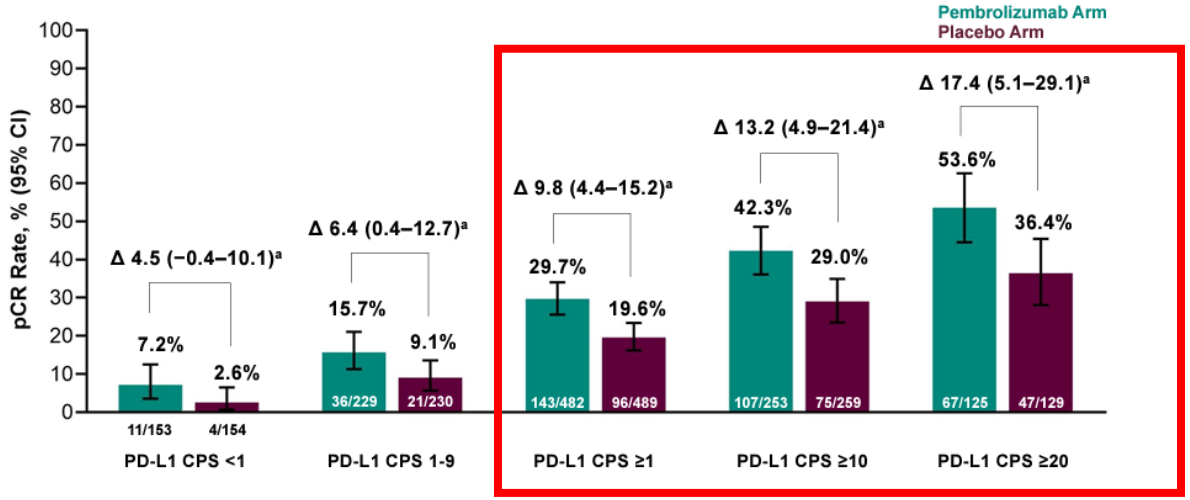


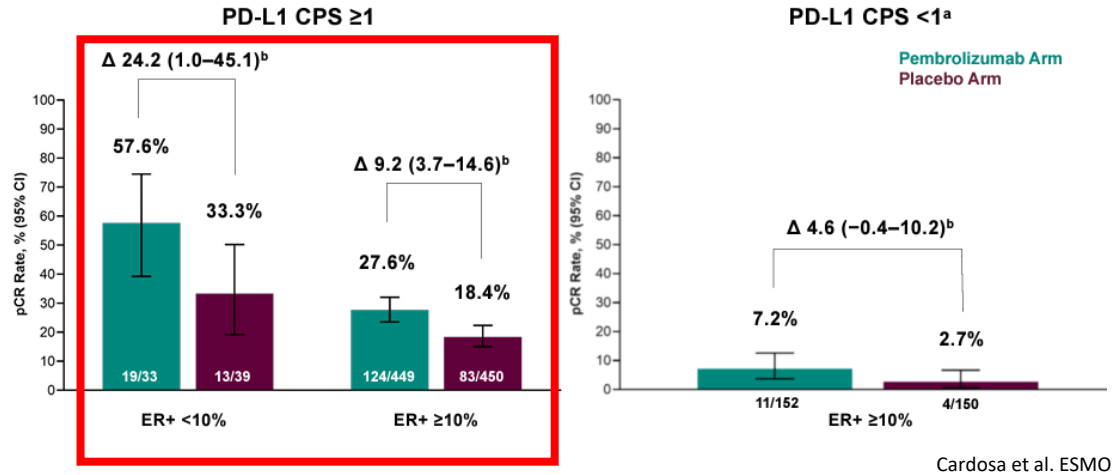
Cardosa et al. ESMO 2023
O'Shaughnessy SABCS 2023

KEYNOTE-756: Key subgroup & biomarker analysis









Cardosa et al. ESMO 2023
O'Shaughnessy SABCS 2023

Future of Immunotherapy in Breast Cancer

- **Triple negative breast cancer**
  - Additional studies for atezolizumab
    - GeparDouze/NSABP B-59
  - Adjuvant therapy strategies
    - OptimICE-PCR
    - SWOG1418
    - SASCIA, ASCENT-05/OptimICE-RD, TROPion Breast 03

Future of Immunotherapy in Breast Cancer

- **ER+ breast cancer**
  - Will pCR translate to EFS benefit?
  - Which biomarkers are best to predict pCR/EFS?
  - What is the added benefit of IO with other known adjuvant therapies (endocrine therapy, CDK 4/6 inhibitors)

Additional questions to consider

- What is the optimal chemotherapy partner?
- Timing of IO administration- does it matter?
- Combination therapies (IO or other agents)
- Can we better predict and prevent irAEs?

Thank you!

avan.armaghani@moffitt.org