

Immunotherapy in Breast Cancer: Now and the Future

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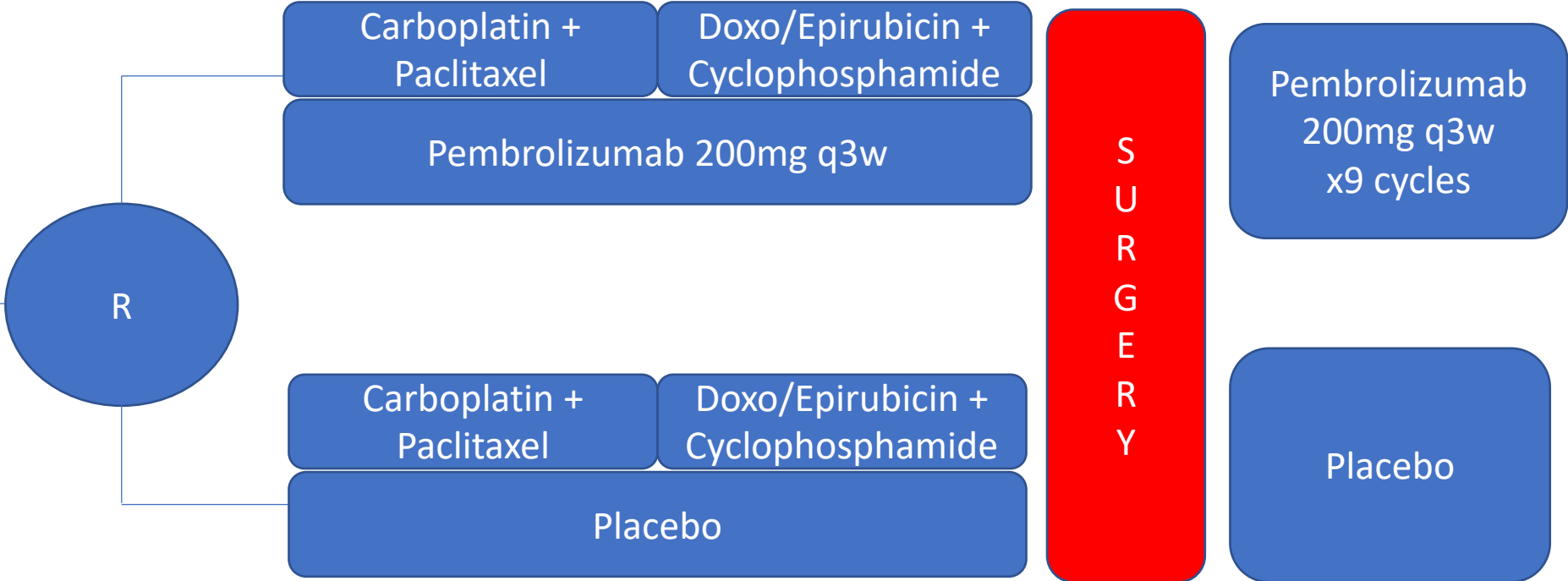
Background

- The role of immunotherapy in the treatment of metastatic 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
- Additional roles of immunotherapy in breast cancer are being investigated

Immunotherapy in TNBC

Keynote-522

- Age ≥ 18 years
- Newly diagnosed TNBC of either T1c N1-2 or T2-4 N0-2
- ECOG PS 0-1



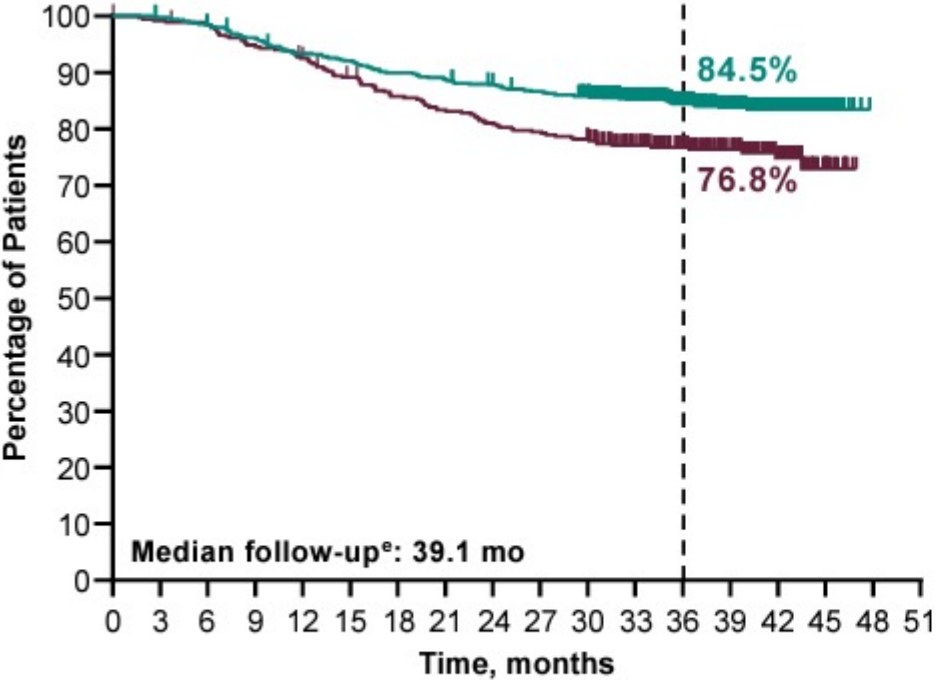
Primary Endpoints:
pCR (ypT0/Tis ypN0)
EFS in ITT

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† <i>percentage points (95% CI)</i>	P Value
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)	

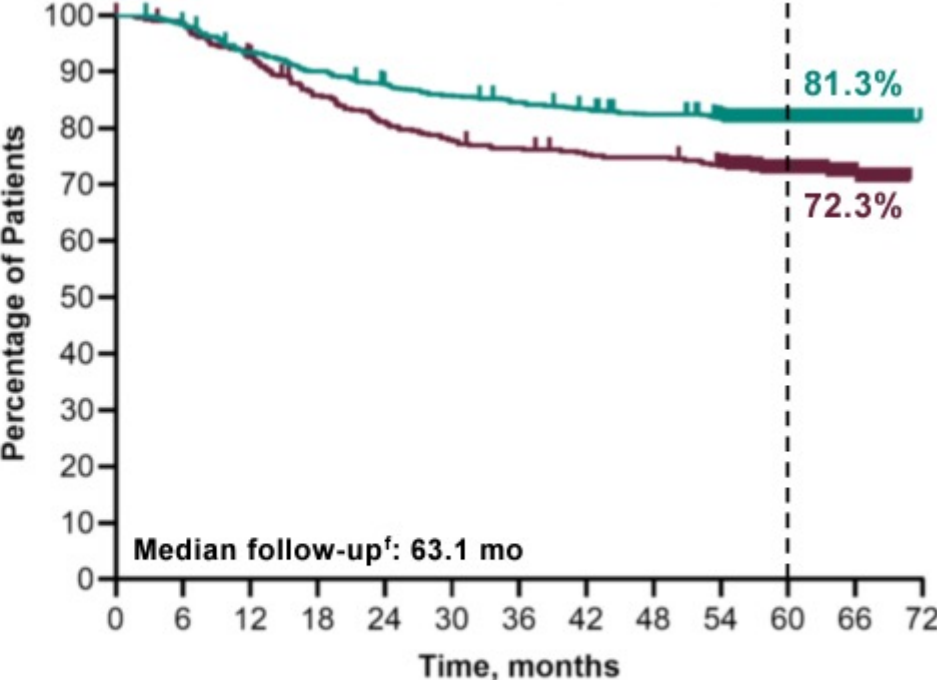
KEYNOTE-522: Results EFS



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

Median Follow-up: 39.1 mos

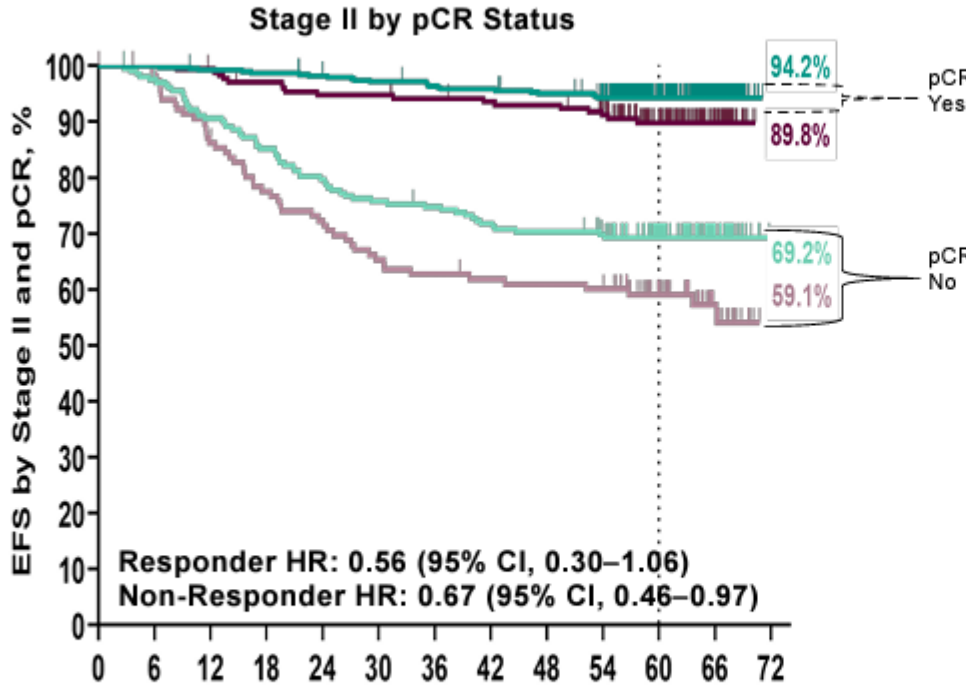


No. at risk

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

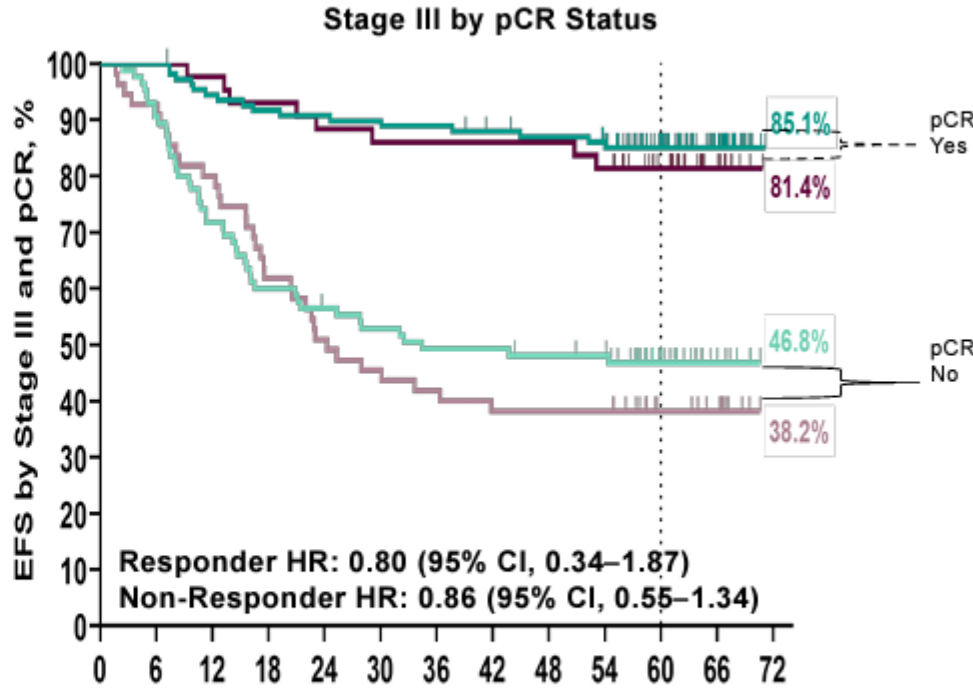
Median Follow-up: 63.1 mos

KEYNOTE-522: Results EFS by stage and pCR



	No. at risk														
	0	6	12	18	24	30	36	42	48	54	60	66	72		
Pembro + Chemo/Pembro Responder	386	386	382	380	375	371	367	365	360	351	236	90	0		
Pbo + Chemo/Pbo Responder	173	173	171	166	162	162	160	158	157	150	106	42	0		
Pembro + Chemo/Pembro Non-Responder	204	197	183	172	161	153	150	144	141	135	96	36	0		
Pbo + Chemo/Pbo Non-Responder	118	114	100	89	83	75	72	70	69	68	47	18	0		

Stage II



	No. at risk														
	0	6	12	18	24	30	36	42	48	54	60	66	72		
Pembro + Chemo/Pembro Responder	109	109	102	99	98	97	96	93	91	88	59	30	0		
Pbo + Chemo/Pbo Responder	43	43	42	40	38	37	37	37	37	35	24	11	0		
Pembro + Chemo/Pembro Non-Responder	85	77	61	51	47	44	41	41	39	38	21	7	0		
Pbo + Chemo/Pbo Non-Responder	55	51	44	34	28	25	23	21	21	21	12	8	0		

Stage III

NeoTrip

- Age ≥ 18 years
- HER2 negative, ER and PR negative
- Early high risk (T1cN1; T2N1; T3N0) versus locally advanced (T3N1; T4 a,b,c; T4d any N; any T and N2-3)
- ECOG 0-1

R

Carboplatin + nab-paclitaxel
day 1,8 every 3 weeks x 8 cycles

Atezolizumab q3w

Carboplatin + nab-paclitaxel
day 1,8 every 3 weeks x 8 cycles

Placebo

S
U
R
G
E
R
Y

AC/EC/FEC
x4 cycles

AC/EC/FEC
x4 cycles

Primary Endpoint:

- EFS

Secondary Endpoint:

- pCR

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.

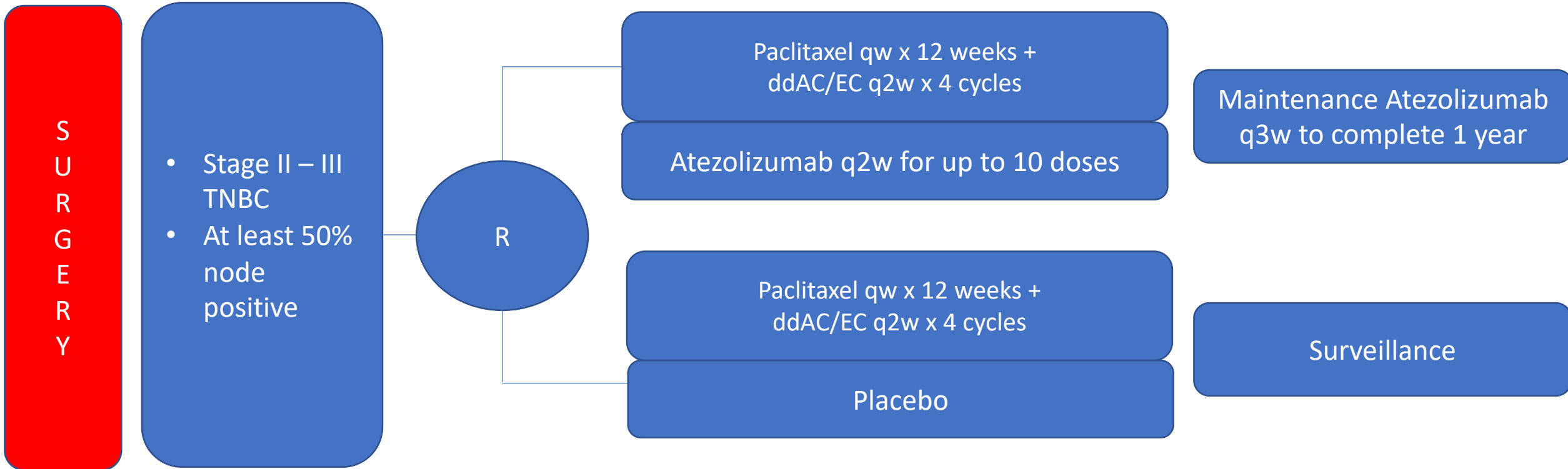
Table 3. Multivariate analysis of pCR

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)

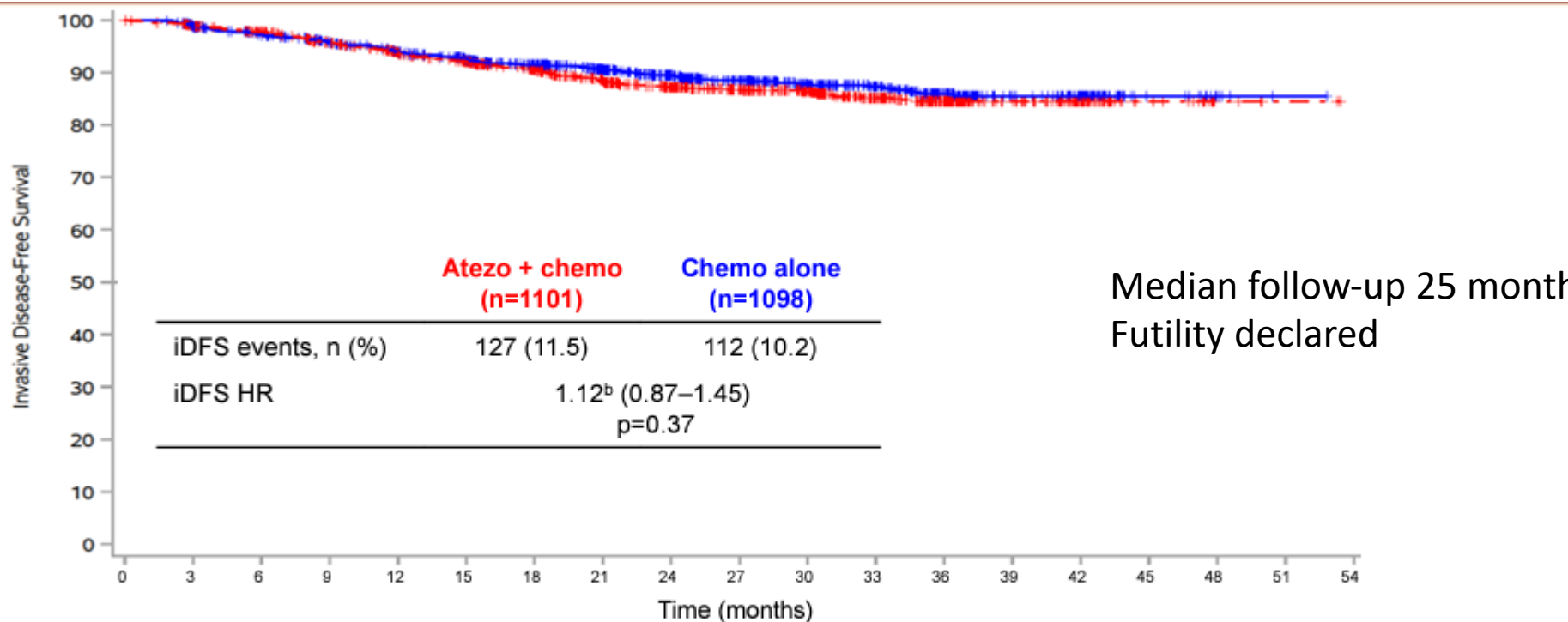
Alexandra/IMpassion030



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)

Alexandra/IMpassion030: iDFS ITT



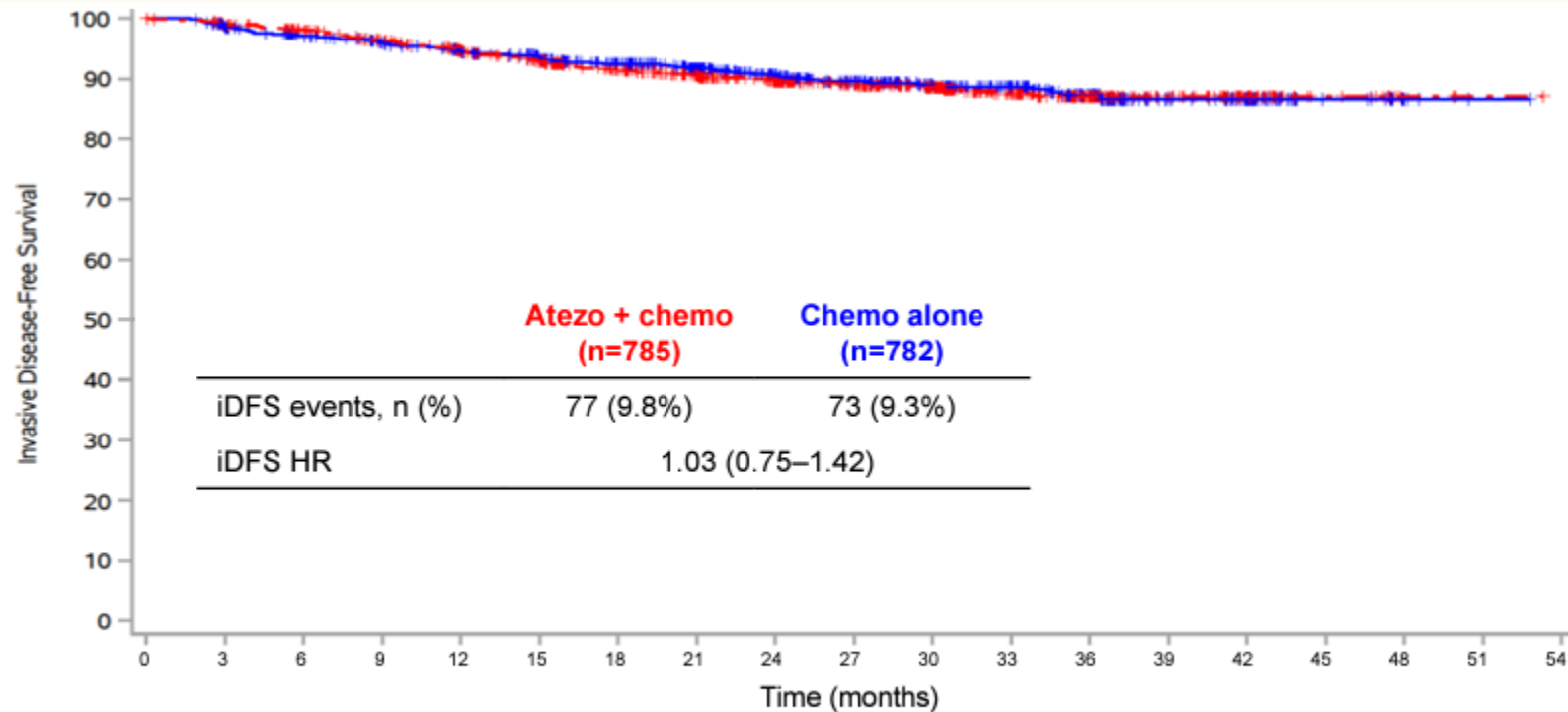
Median follow-up 25 months
Futility declared

	Atezo + chemo (n=1101)	Chemo alone (n=1098)
iDFS events, n (%)	127 (11.5)	112 (10.2)
iDFS HR	1.12 ^b (0.87–1.45) p=0.37	

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Chemo alone	1098	1022	970	923	864	812	731	663	565	471	372	289	204	109	74	17	5	1	0
Atezo + chemo	1101	1042	995	932	869	820	735	648	564	481	391	294	202	120	66	22	5	2	0

^aDefined as the interval from randomization until date of first occurrence of an iDFS event, ^bstratified by PD-L1 status, Surgery, and Axillary Nodal Status

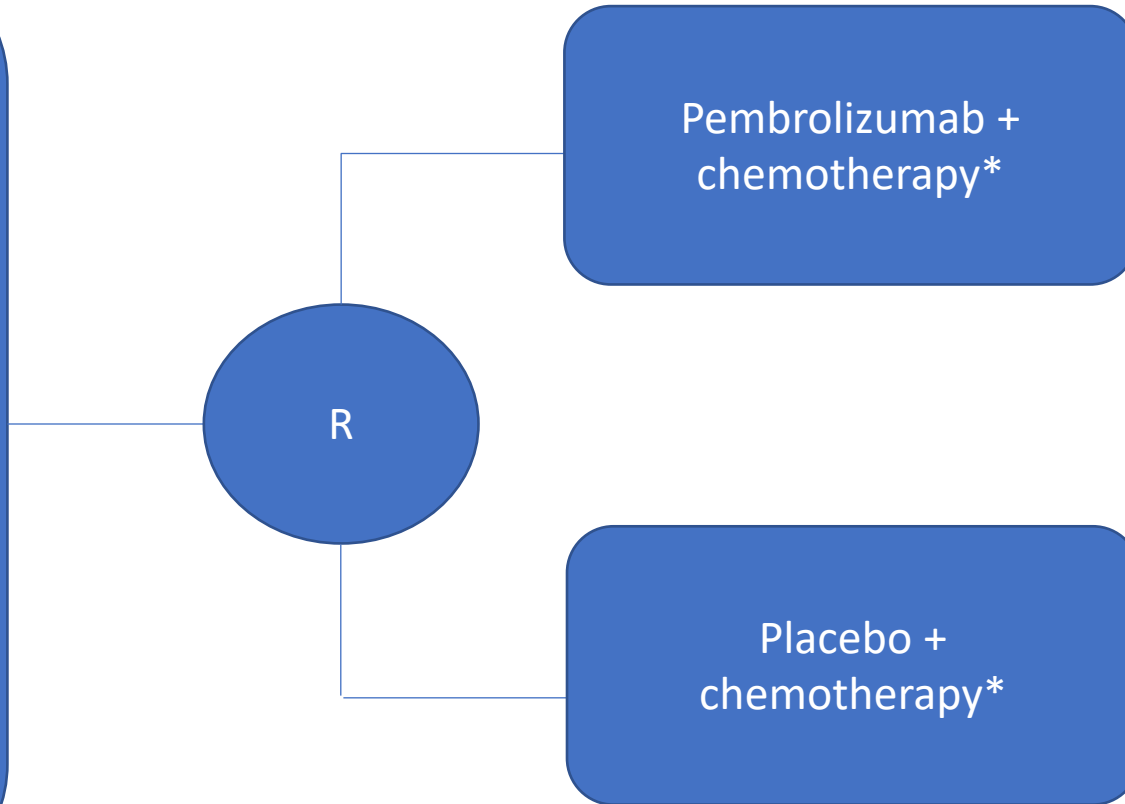
Alexandra/IMpassion030: iDFS PD-L1+ subgroup



	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
Chemo alone	782	728	691	660	622	589	534	486	416	350	276	223	154	81	53	14	4	1	0
Atezo + chemo	785	749	718	680	640	601	536	480	425	366	300	230	156	90	48	17	3	1	0

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



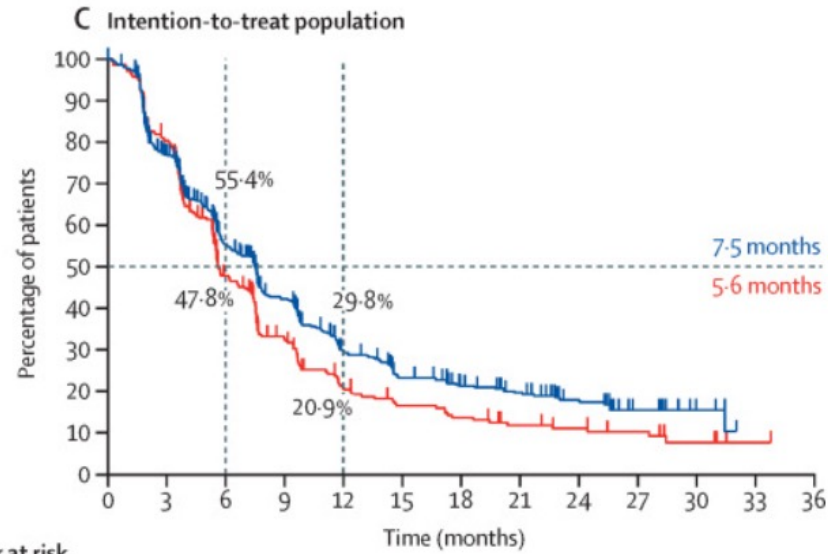
Primary Endpoints: PFS, OS

PD-L1 CPS score ≥ 10

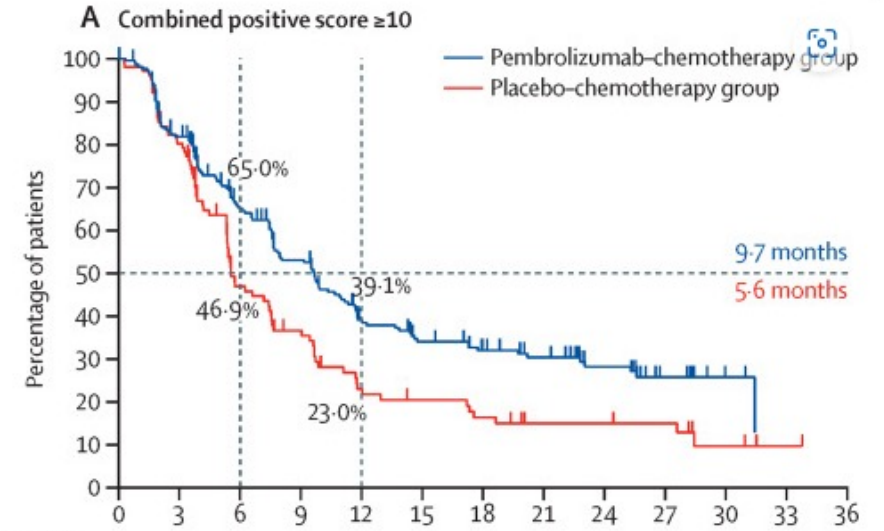
PD-L1 CPS ≥ 1

ITT Population

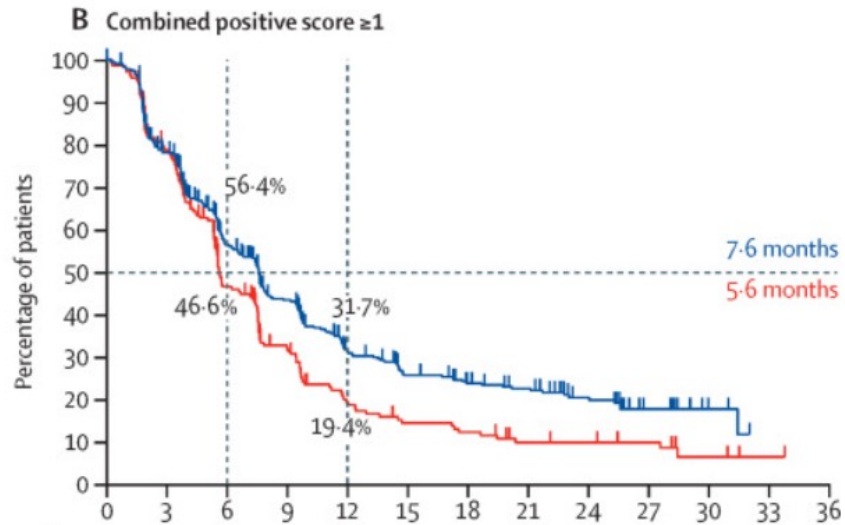
*Chemotherapy: nanoparticle albumin-bound paclitaxel, paclitaxel, or gemcitabine-carboplatin



	0	3	6	9	12	15	18	21	24	27	30	33	36
Number at risk													
Pembrolizumab-chemotherapy group	566	408	260	184	118	86	70	57	32	16	6	0	0
Placebo-chemotherapy group	281	214	108	68	39	29	24	17	14	11	5	1	0

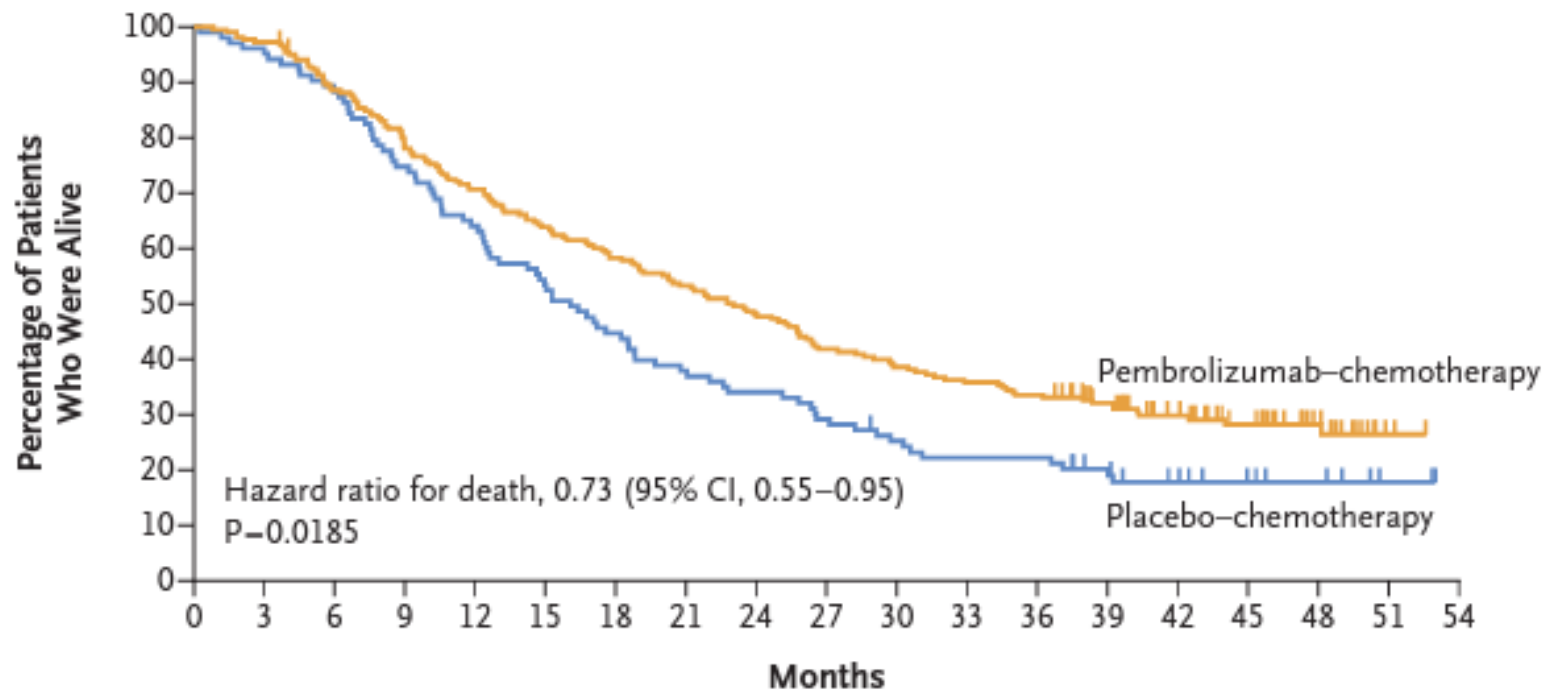


	0	3	6	9	12	15	18	21	24	27	30	33	36
Number at risk													
Pembrolizumab-chemotherapy group	220	173	122	96	63	52	44	37	25	12	5	0	0
Placebo-chemotherapy group	103	80	41	30	18	15	12	8	8	7	3	1	0



	0	3	6	9	12	15	18	21	24	27	30	33	36
Number at risk													
Pembrolizumab-chemotherapy group	425	315	202	143	94	72	60	51	32	16	6	0	0
Placebo-chemotherapy group	211	158	81	51	28	20	17	11	10	8	3	1	0

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

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

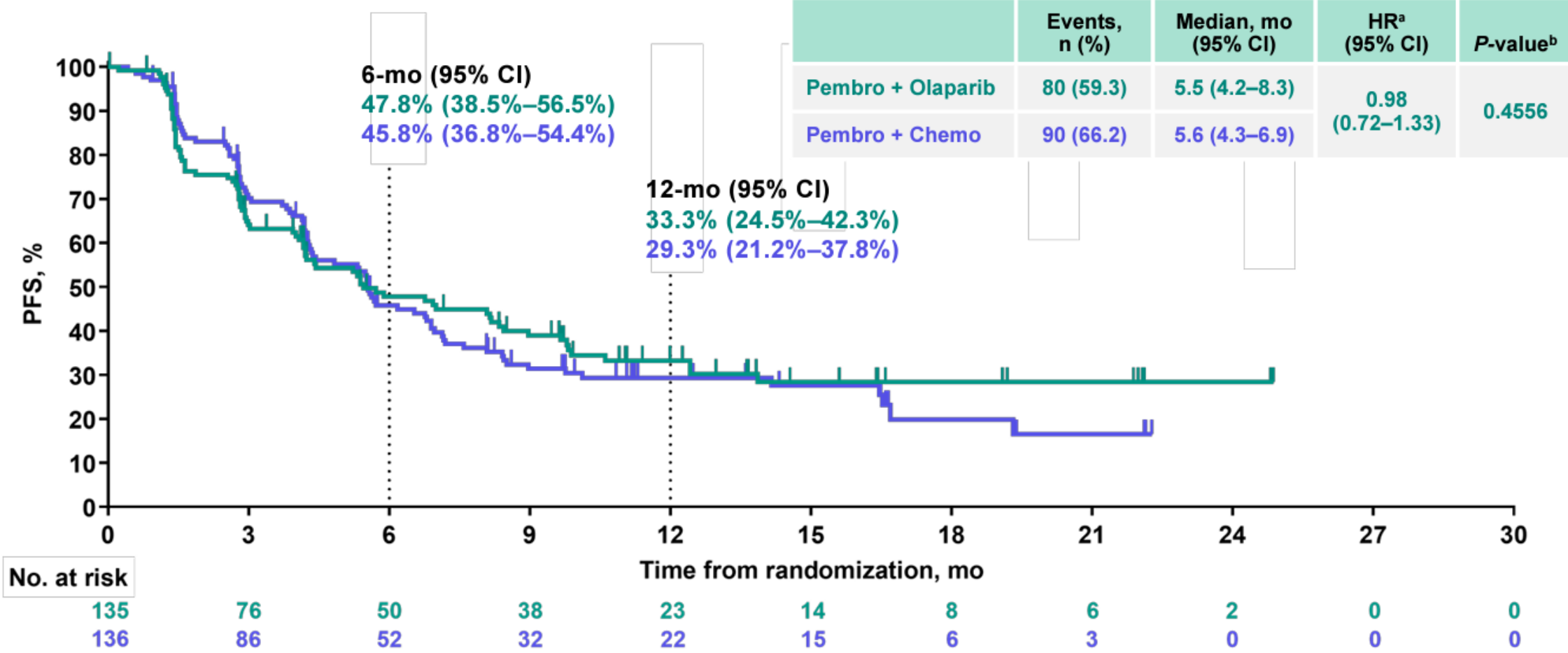
Carboplatin days 1 and 8 of each 21 day cycle
+
gemcitabine days 1 and 8 of each 21 day cycles
+
Pembro 200mg q3w for up to 25 cycles including induction

Primary Endpoints:

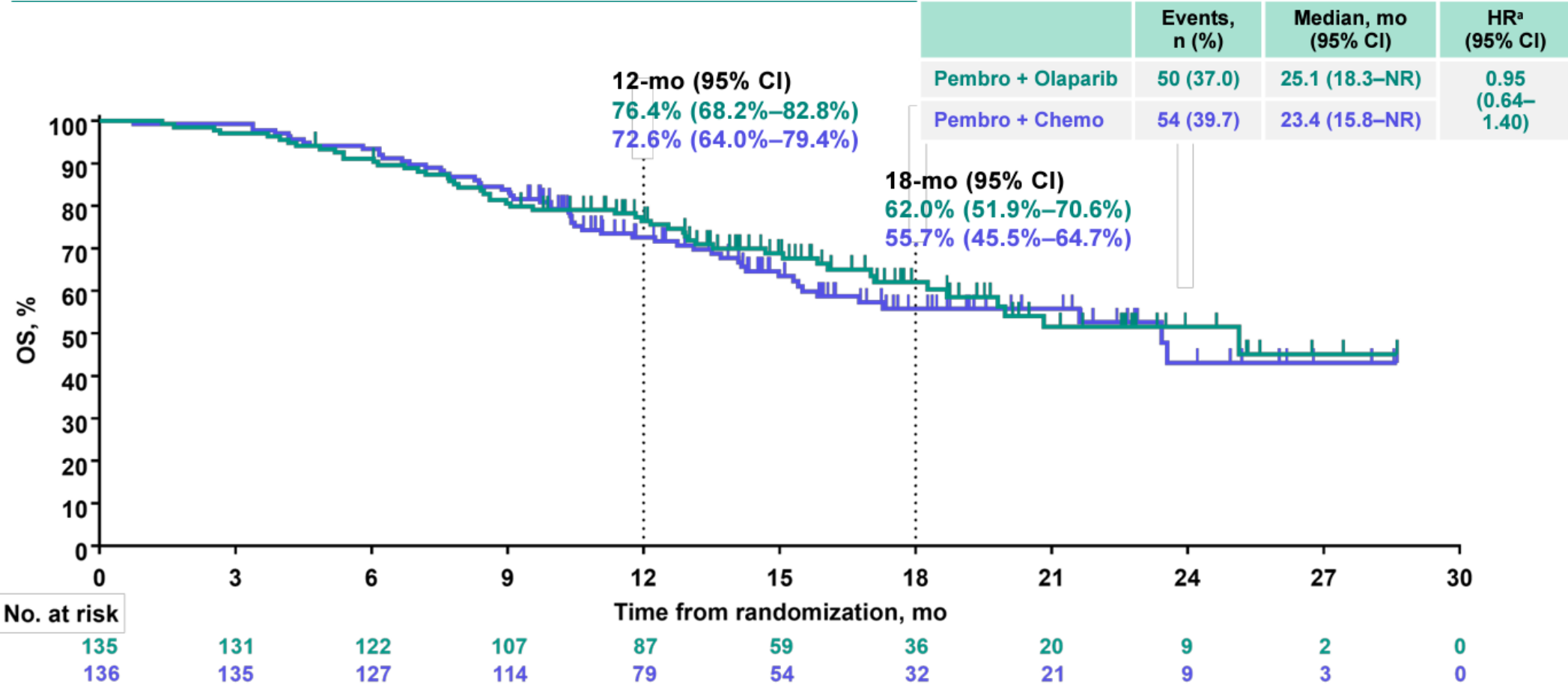
PFS

OS in ITT

KEYLYNK: PFS in ITT



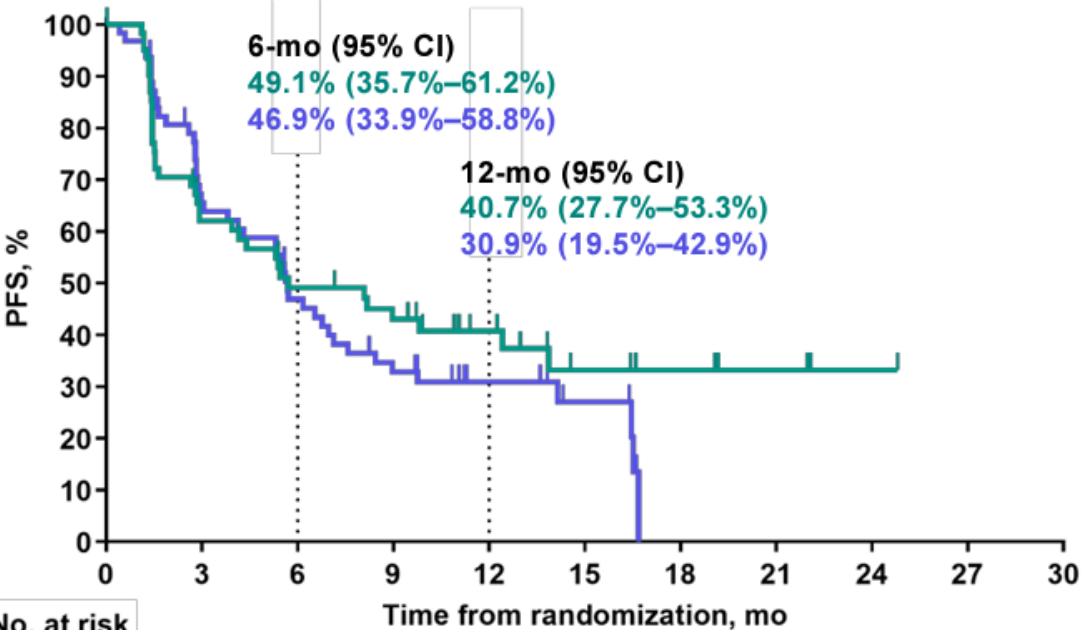
KEYLYNK: OS in ITT population



KEYLYNK: PFS CPS ≥10 and BRCAm

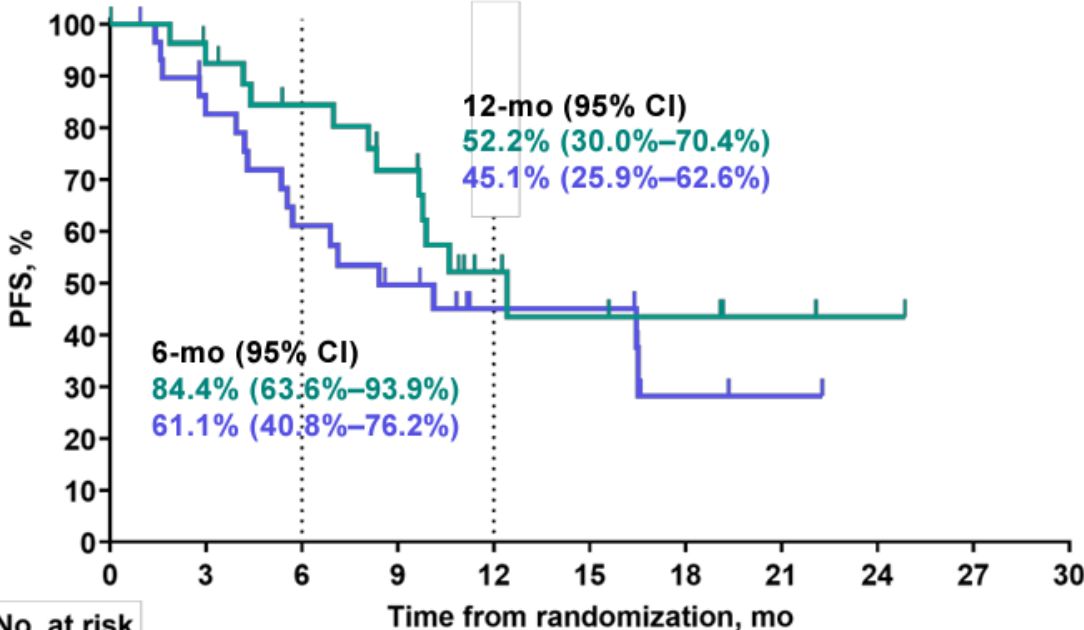
Tumor PD-L1 CPS ≥10 Population

	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)	



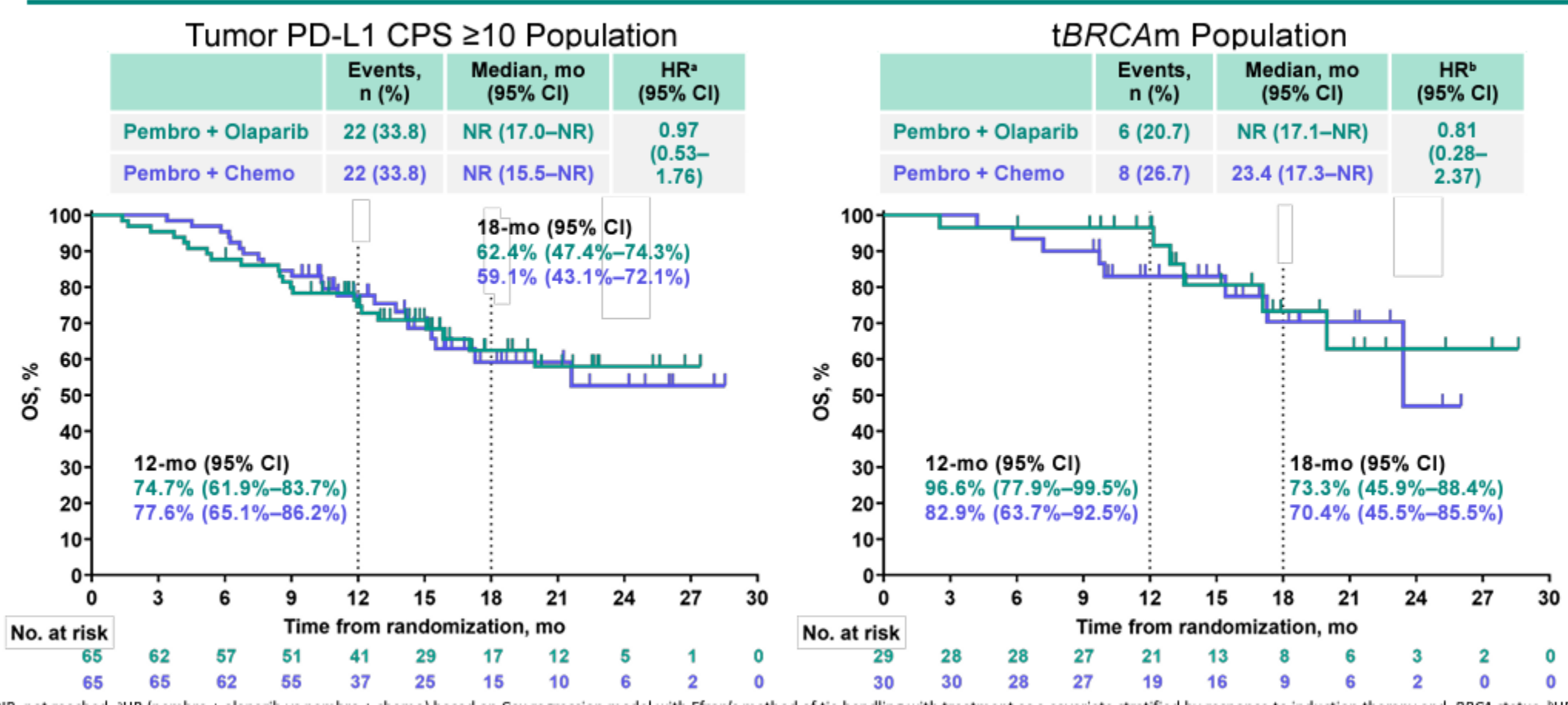
tBRCAm Population

	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; tBRCAm, tumor BRCA mutation (includes germline and somatic mutations). ^aHR (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



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.

^aThere were no grade 5 events in the pembro + olaparib group.

^b2 patients had grade 5 events in the pembro + chemo group (gastrointestinal hemorrhage and thrombotic thrombocytopenic purpura, n = 1 each).

^cImmune-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.

^dThere were no grade 5 events in either group.

Data cutoff date: December 15, 2022.

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Immunotherapy in HR+/HER2 negative breast cancer

Checkmate 7FL

- ER+/HER2 negative breast cancer
- T1c-2, cN1-2 or T3-T4, cN0-N2
- Grade 3 with ER \geq 1% or grade 2 with ER 1-10%
- ECOG PS 0-1

R

Paclitaxel weekly x 12 weeks followed by
AC q2w or q3w x 4 cycles

Nivolumab q3w

Paclitaxel weekly x 12 weeks followed by
AC q2w or q3w x 4 cycles

Placebo

S
U
R
G
E
R
Y

Nivo q4w x7
cycles
+ investigator
choice ET

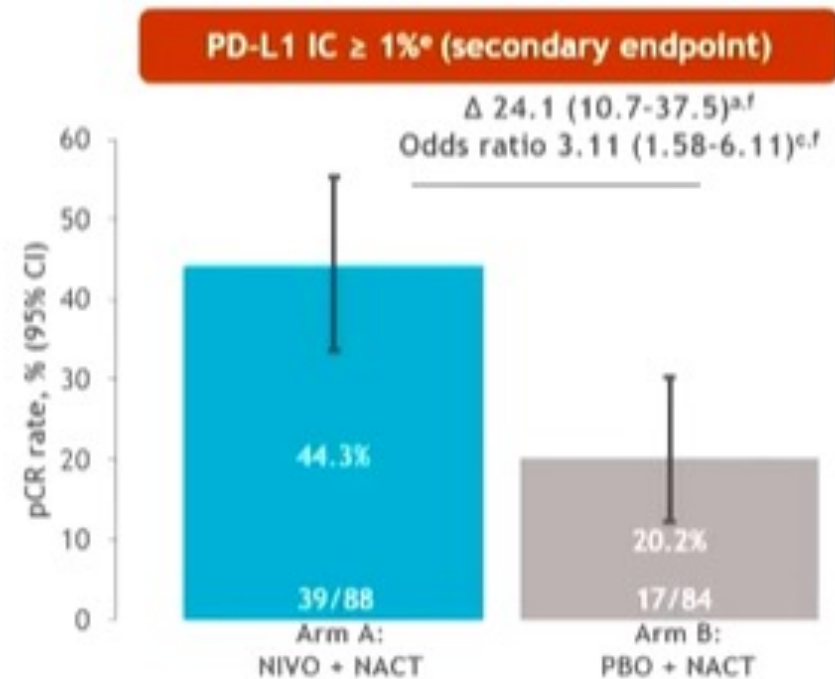
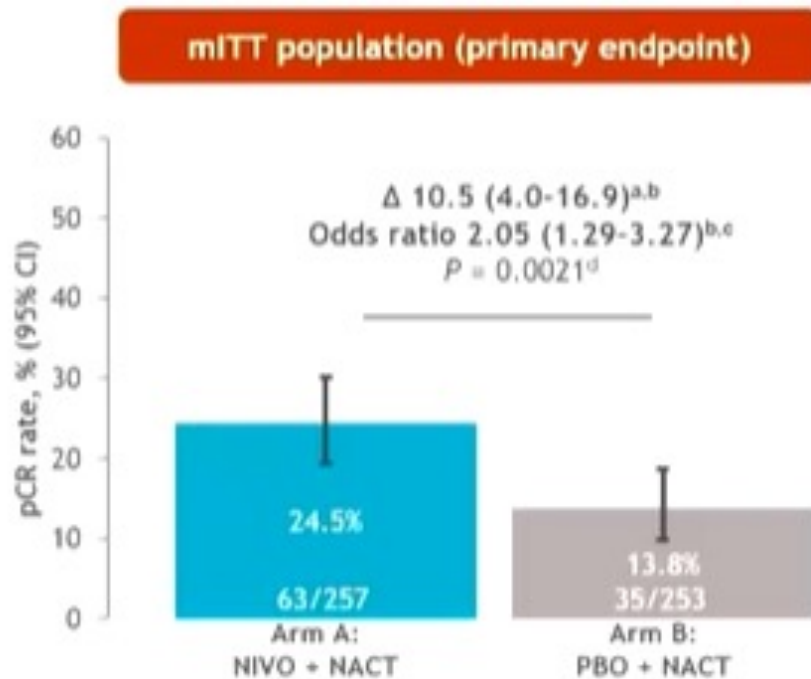
Placebo +
investigator
choice ET

Primary Endpoint:

pCR

EFS

Checkmate 7FL: pCR ITT population



KEYNOTE-756

- ER+/HER2 negative breast cancer
- Grade 3
- T1c-T2(≥ 2 cm) cN1-2 or T3-4 cN0-2
- Treatment naive

R

Paclitaxel weekly x 12 weeks followed by
AC/EC x 4 cycles

Pembrolizumab q3w

Paclitaxel weekly x 12 weeks followed by
AC/EC x 4 cycles

Placebo

S
U
R
G
E
R
Y

Pembro q3w x6
months +
endocrine
therapy

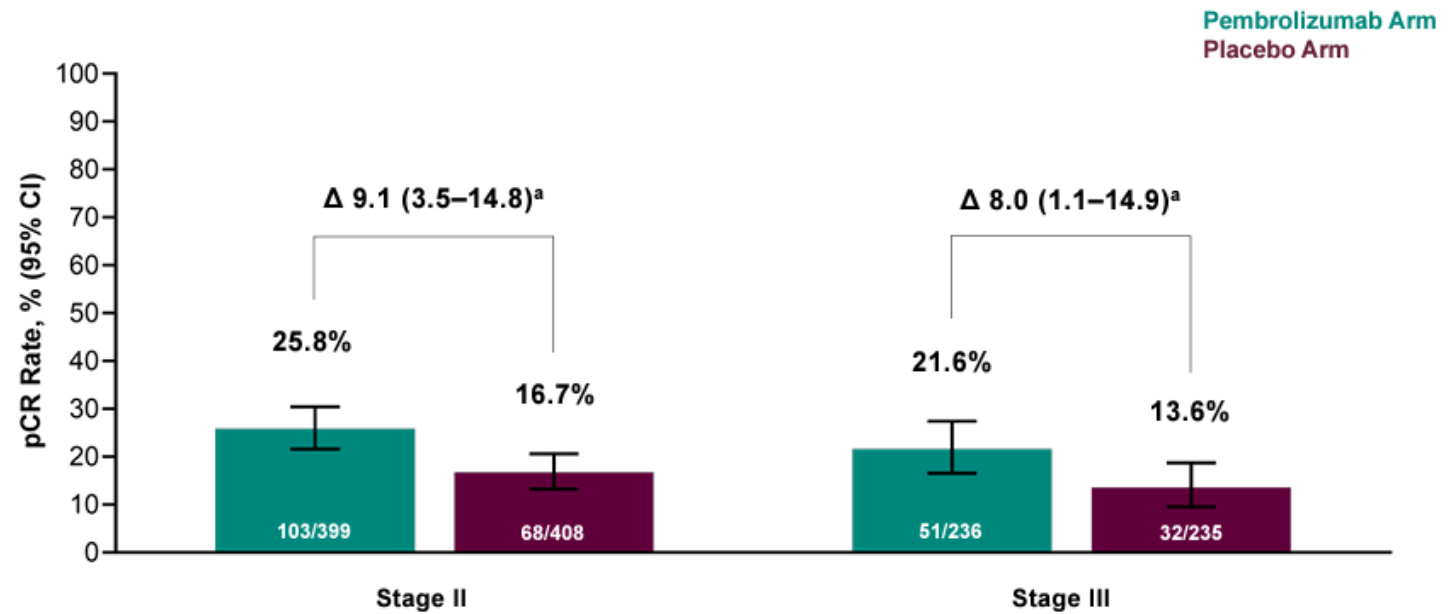
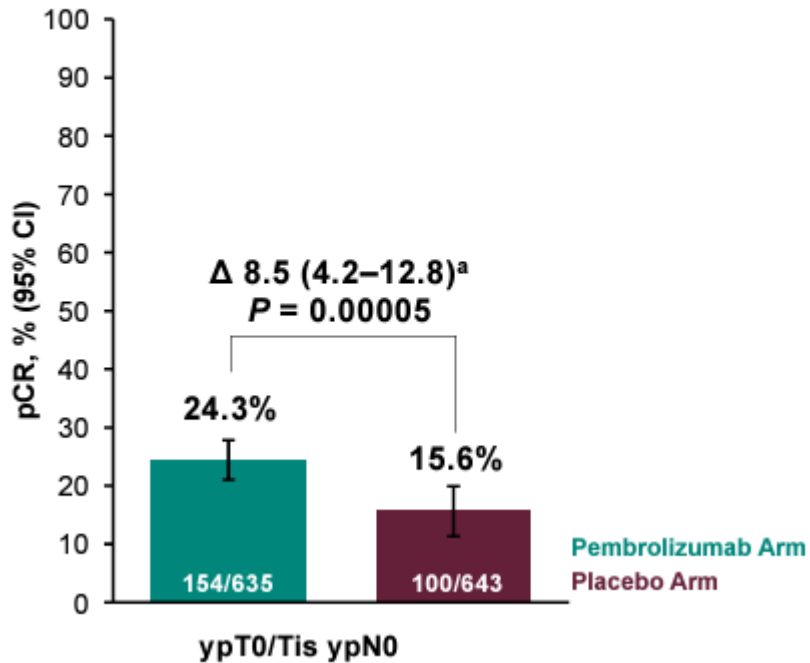
Placebo q3w x6
months +
endocrine
therapy

Primary Endpoint:

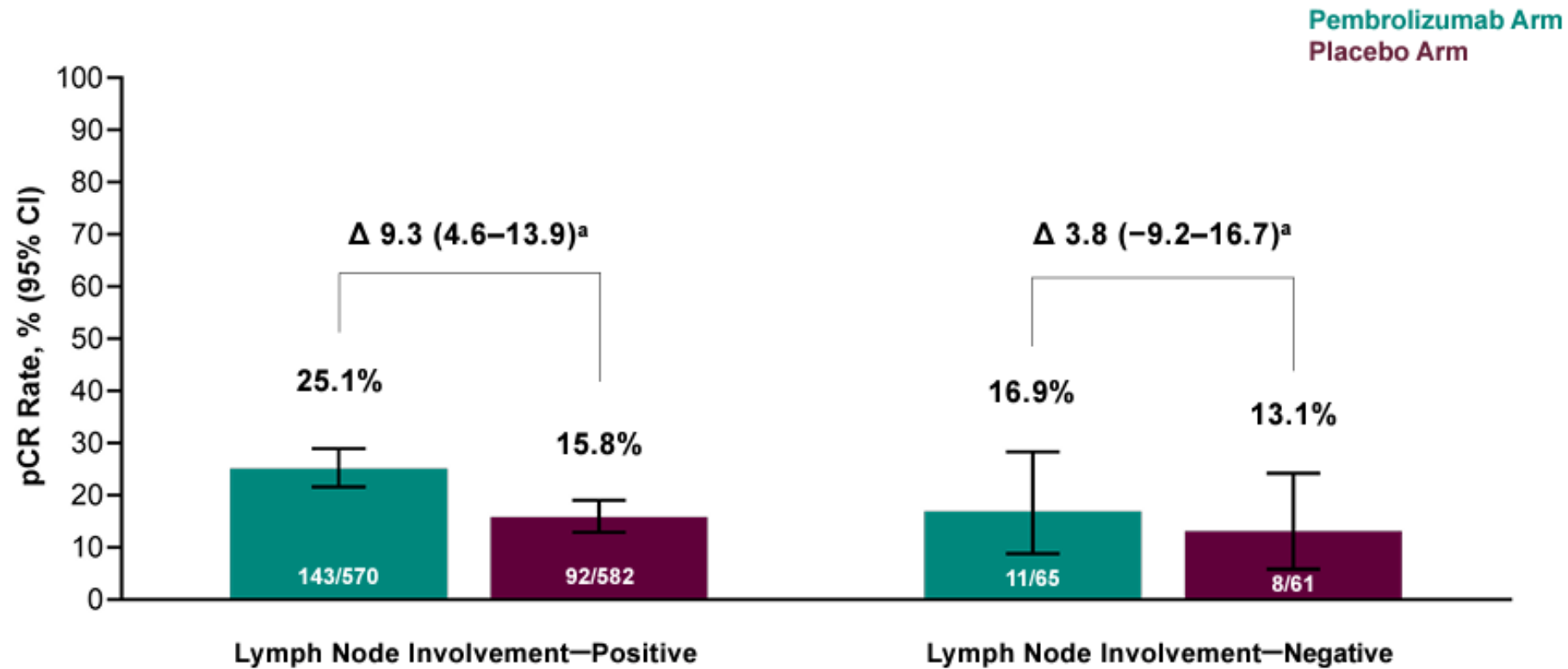
- pCR
- EFS

KEYNOTE-756: pCR

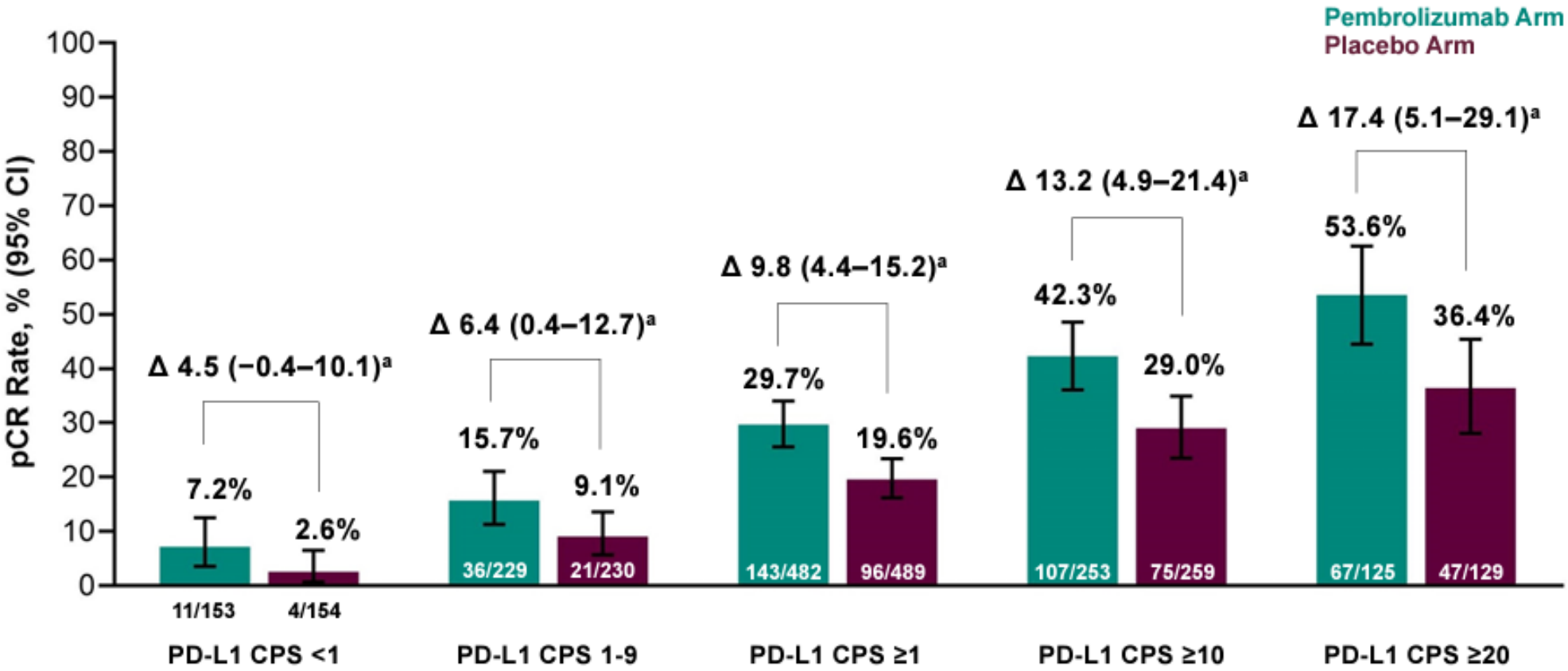
Primary Endpoint



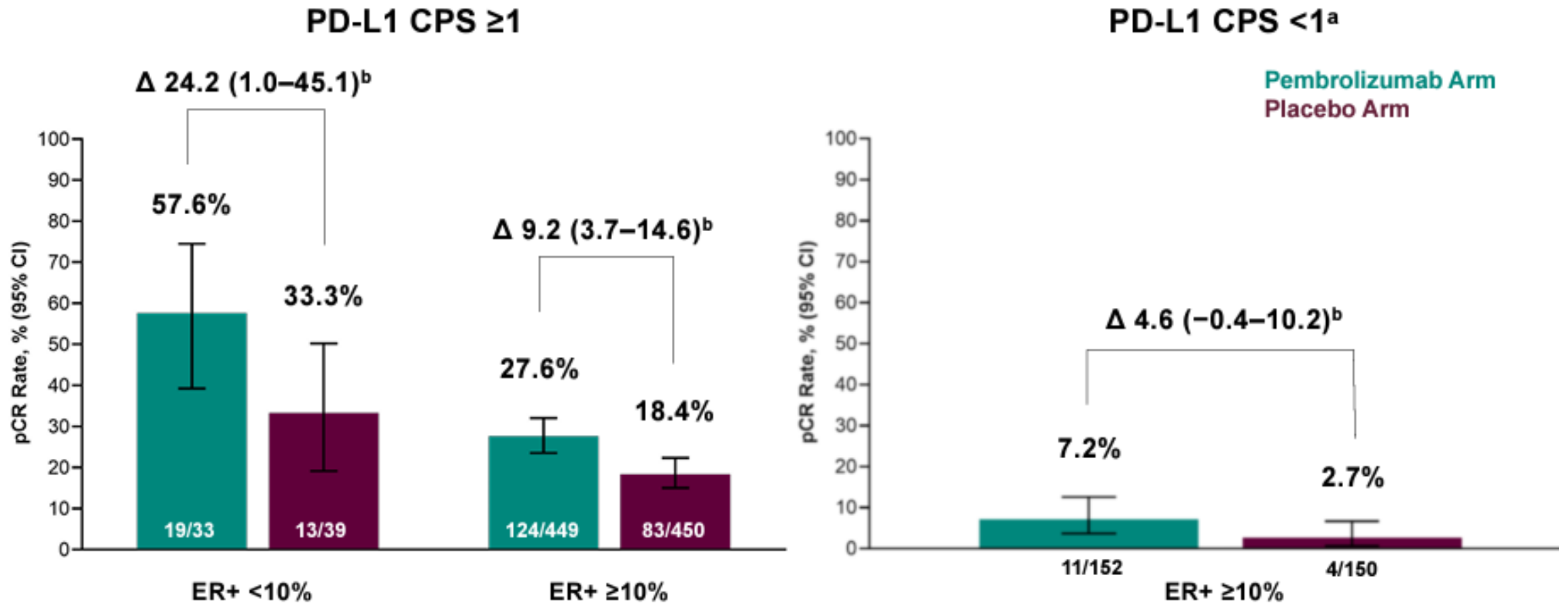
KEYNOTE-756 pCR and lymph node involvement



KEYNOTE-756: pCR by PD-L1 expression level



KEYNOTE-756: pCR by PD-L1 expression level and ER positivity



Future of Immunotherapy in Breast Cancer

- **ER+ breast cancer**
 - Will pCR translate to EFS benefit?
 - Biomarkers, gene signatures for predicting IO response
 - Added benefit of IO with other known adjuvant therapies (endocrine therapy, CDK 4/6 inhibitors)

Thank you

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