NOVEL APPLICATIONS OF IMMUNE CHECKPOINT INHIBITORS ALONE OR IN COMBINATION WITH OTHER AGENTS FOR PATIENTS WITH EARLY AND ADVANCED TNBC; OTHER PROMISING AGENTS IN LATE-STAGE CLINICAL TRIALS

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SAN ANTONIO BREAST CANCER SYMPOSIUM®

FINANCIAL DISCLOSURE

- Professor Sherene Loi receives research funding **to her institution** from Novartis, Bristol Meyers Squibb, Merck, Roche-Genentech, Puma Biotechnology, Pfizer, Eli Lilly and Seattle Genetics. She has acted as consultant **(not compensated)** to Seattle Genetics, Pfizer, BMS, Merck, AstraZeneca and Roche-Genentech. She has acted as consultant **(paid to her institution)** to Aduro Biotech, Silverback, Novartis.

Case Presentation: Dr Rugo

58-year-old woman was diagnosed with right breast clinical stage II TNBC without germline mutation. Enrolled on the neoadjuvant I-SPY2 trial and received talazoparib/irinotecan x 3 weeks, then discontinued study therapy due to lack of response, continuing on to receive paclitaxel x 12 weeks followed by dose dense AC x 4.

She then underwent right breast lumpectomy and SLNBx which showed 2.8 cm of residual high grade TNBC, Ki67 of 80% and cellularity of 70% and 0/3 nodes.

She then received radiation therapy followed by adjuvant capecitabine x 8 cycles, followed by adjuvant off-label pembrolizumab. 6 weeks after starting pembrolizumab, she had a chest CT showing multiple small lung nodules and an intrapectoral node, which on biopsy was consistent with recurrent disease.

However, given that the documentation of recurrence occurred shortly after starting pembrolizumab, she continued on therapy with stable disease for one year, recently developing progressive disease with an increase in small lung nodules, intrapectoral lymph nodes and new soft tissue nodules in the right breast. PD-L1 testing is pending.

Case Presentation: Dr Rugo

Questions:

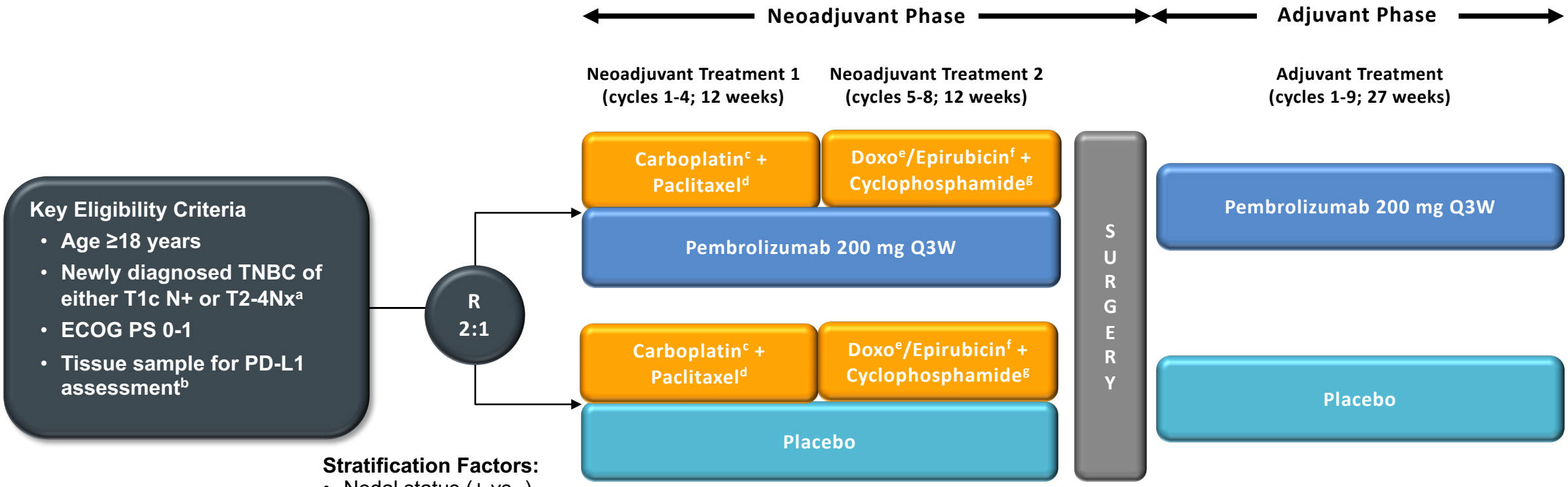
1. Have you ever or would you ever give post-neoadjuvant immune therapy outside of a clinical trial?
2. If so, would you only use immunotherapy as post-neoadjuvant therapy in patients with PD-L1+ disease?
3. Would you give immunotherapy in combination with capecitabine in this setting?

Case Presentation: Dr Robson

40-year-old BRCA germline mutation carrier s/p T1N0 TNBC 8 years ago, treated with BCT and FEC x 4 → docetaxel. Reacted to first docetaxel (anaphylactoid) and completed therapy with FEC (total epirubicin dose 600 mg/m^2). Now presented with T1bN1 (2 LN) TNBC contralateral. s/p BLM.

- What is your recommended adjuvant therapy regimen?

KEYNOTE-522 STUDY DESIGN (NCT03036488)



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

- **Primary endpoint is pCR/EFS**

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]TNBC defined by the most recent American Society of Clinical Oncology/College of American Pathologists guidelines. TN staging assessed by investigator per AJCC.
[b]Must consist of at least 2 separate tumor cores from the primary tumor.
[c]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW.
[d]Paclitaxel dose was 80 mg/m^2 QW.
[e]Doxorubicin dose was 60 mg/m^2 Q3W.
[f]Epirubicin dose was 90 mg/m^2 Q3W.
[g]Cyclophosphamide dose was 600 mg/m^2 Q3W.

BASELINE CHARACTERISTICS, ITT POPULATION

Characteristic, n (%)	All Subjects, N = 1174	
	Pembro + Chemo N = 784	Placebo + Chemo N = 390
Age, median (range), yrs	49 (22-80)	48 (24-79)
ECOG PS 1	106 (13.5)	49 (12.6)
PD-L1–positive[a]	656 (83.7)	317 (81.3)
Carboplatin schedule		
QW	449 (57.3)	223 (57.2)
Q3W	335 (42.7)	167 (42.8)
Tumor size		
T1/T2	580 (74.0)	290 (74.4)
T3/T4	204 (26.0)	100 (25.6)
Nodal involvement		
Positive	405 (51.7)	200 (51.3)
Negative	379 (48.3)	190 (48.7)

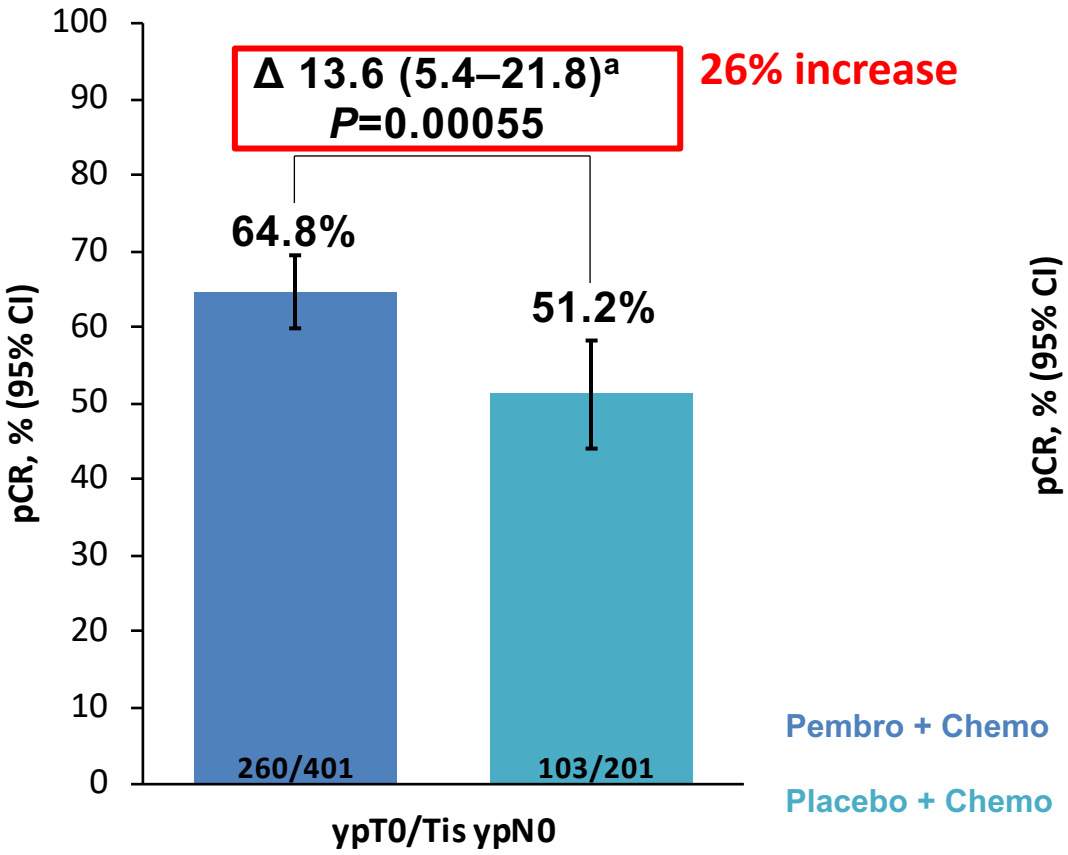
- Largely PD-L1 pos
- CPS ≥1
- 50% node neg
- Stage 1B

[a]The PD-L1 combined positive score was defined as number of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) divided by total number of tumor cells × 100. PD-L1 positivity was defined as CPS ≥1. Data cutoff date: April 24, 2019.

KEYNOTE-522: PATHOLOGICAL COMPLETE RESPONSE AT IA1

Primary Endpoint: ypT0/Tis ypN0

Statistically significant
benefit for Pembro + Chemo

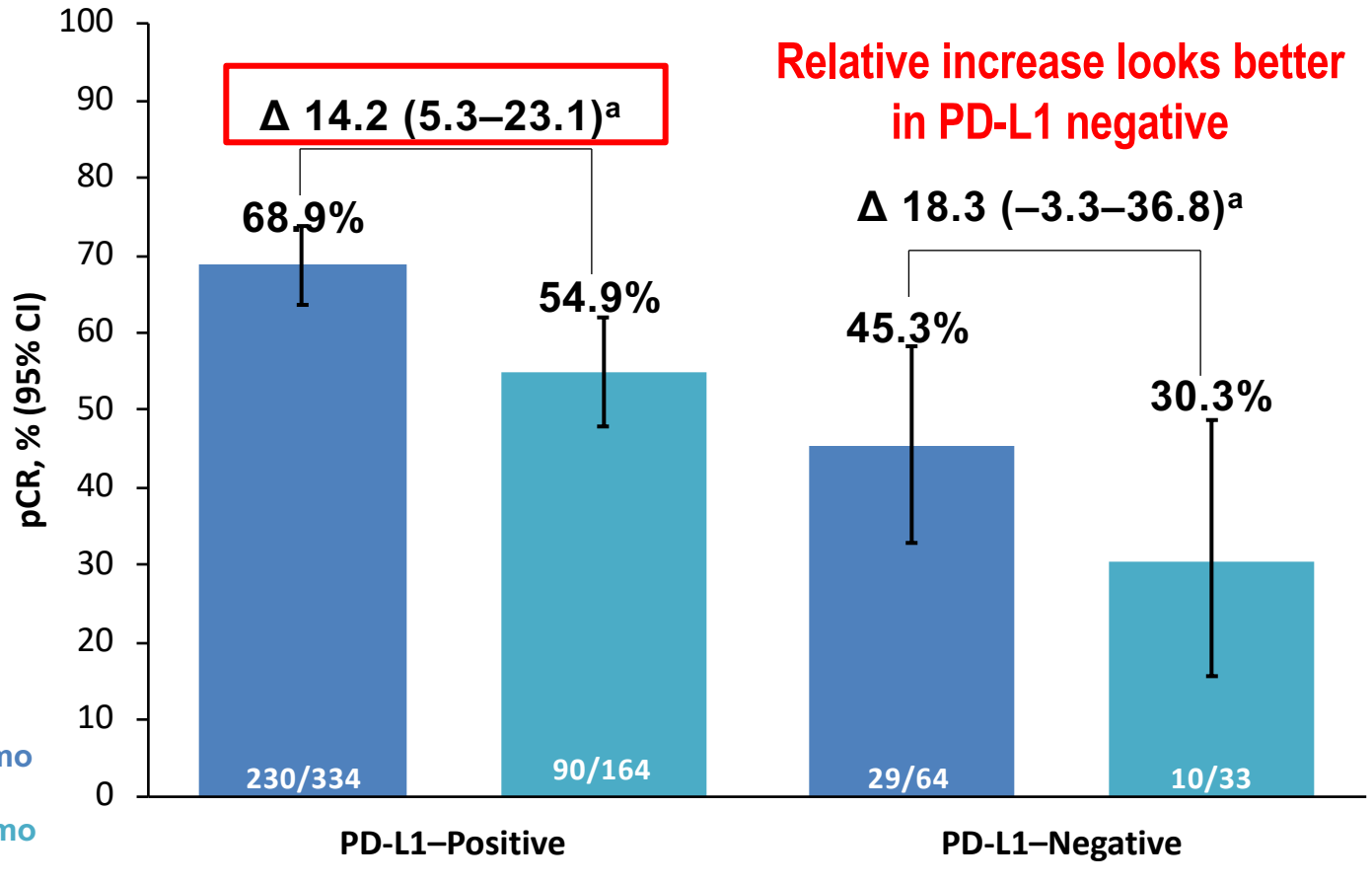


Pembro + Chemo

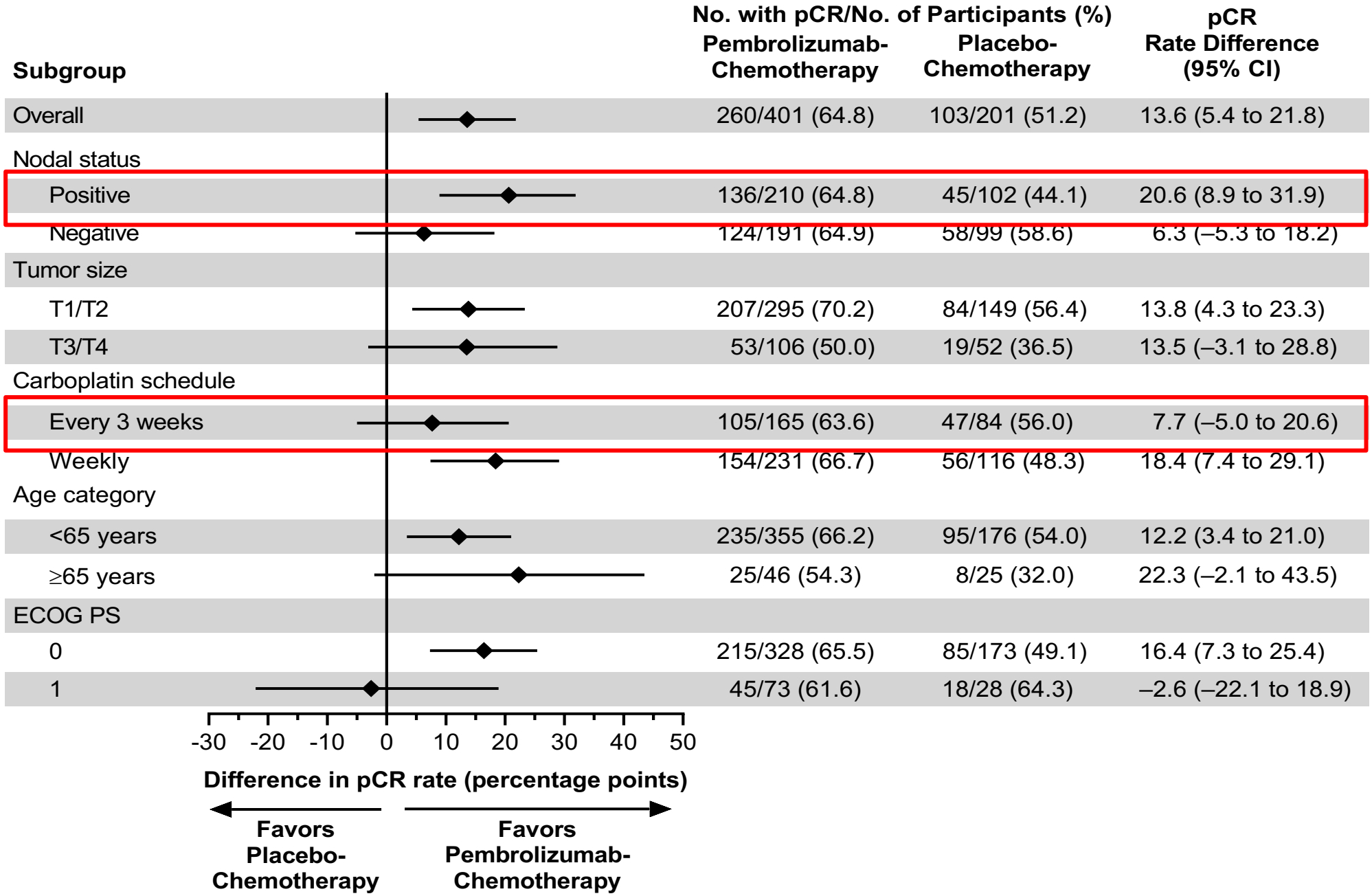
Placebo + Chemo

By PD-L1 Status[b]: ypT0/Tis ypN0

Benefit for Pembro + Chemo in
both PD-L1–positive and PD-L1–negative

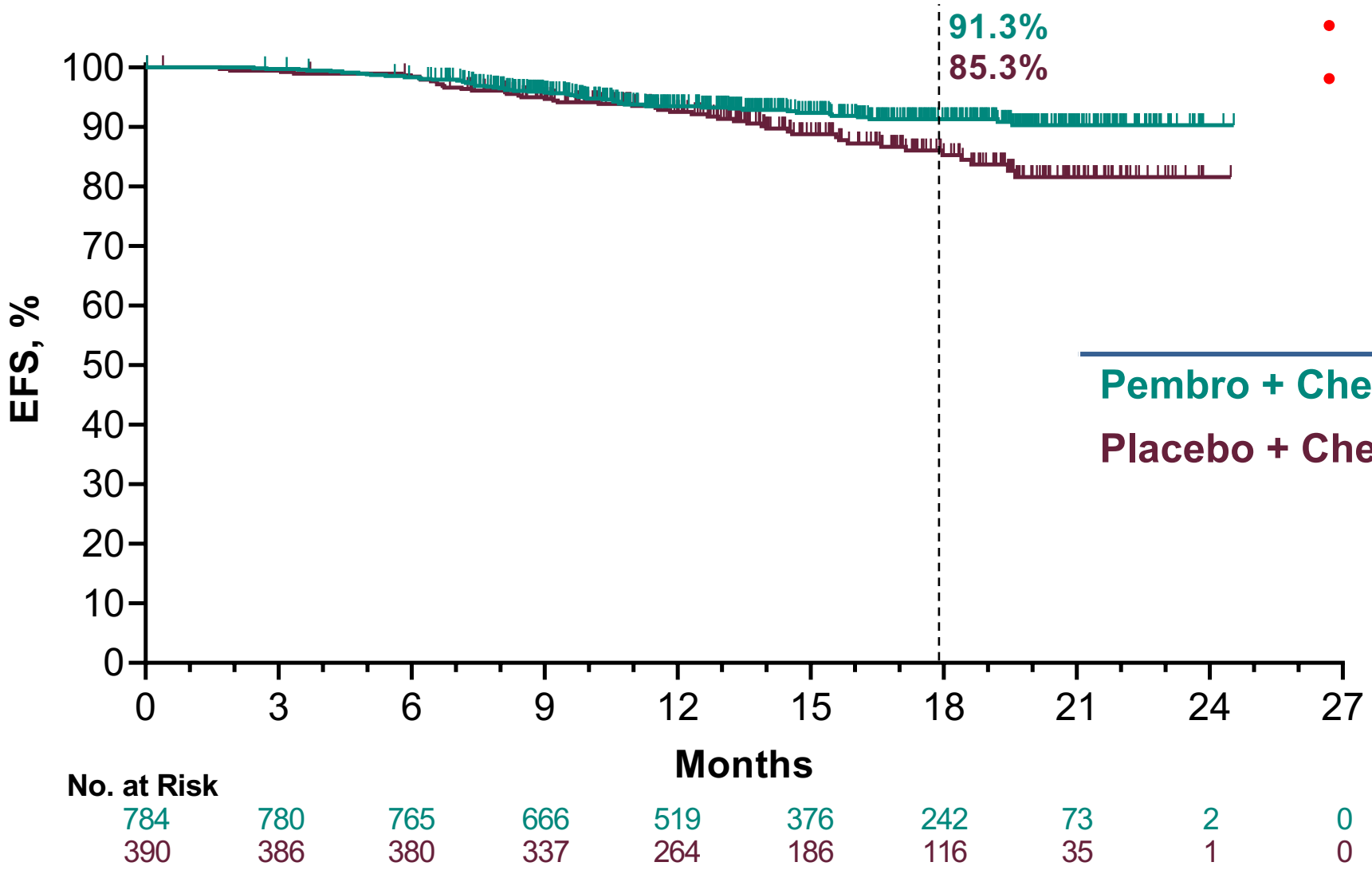


[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. [b]The PD-L1 combined positive score was defined as number of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) divided by total number of tumor cells × 100. PD-L1 positivity was defined as CPS ≥1.
Data cutoff date: September 24, 2018.


Subgroup
No. with pCR/No. of Participants (%)
Pembrolizumab-Chemotherapy
Placebo-Chemotherapy
pCR Rate Difference (95% CI)
Overall
260/401 (64.8)
103/201 (51.2)
13.6 (5.4 to 21.8)
Nodal status
Positive
136/210 (64.8)
45/102 (44.1)
20.6 (8.9 to 31.9)
Negative
124/191 (64.9)
58/99 (58.6)
6.3 (–5.3 to 18.2)
Tumor size
T1/T2
207/295 (70.2)
84/149 (56.4)
13.8 (4.3 to 23.3)
T3/T4
53/106 (50.0)
19/52 (36.5)
13.5 (–3.1 to 28.8)
Carboplatin schedule
Every 3 weeks
105/165 (63.6)
47/84 (56.0)
7.7 (–5.0 to 20.6)
Weekly
154/231 (66.7)
56/116 (48.3)
18.4 (7.4 to 29.1)
Age category
<65 years
235/355 (66.2)
95/176 (54.0)
12.2 (3.4 to 21.0)
≥65 years
25/46 (54.3)
8/25 (32.0)
22.3 (–2.1 to 43.5)
ECOG PS
0
215/328 (65.5)
85/173 (49.1)
16.4 (7.3 to 25.4)
1
45/73 (61.6)
18/28 (64.3)
–2.6 (–22.1 to 18.9)
-30 -20 -10 0 10 20 30 40 50
Difference in pCR rate (percentage points)
Favors Placebo-Chemotherapy
Favors Pembrolizumab-Chemotherapy

EVENT-FREE SURVIVAL AT IA2

- VERY EARLY look
- Low no. events (9%)
- Median FU 15.5 mo
- Similar for PD-L1 pos vs neg?
- Too early: stability of data



	Events	HR (95% CI)
Pembro + Chemo	7.4%	0.63 (0.43-0.93)
Placebo + Chemo	11.8%	

Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors.
Data cutoff April 24, 2019.

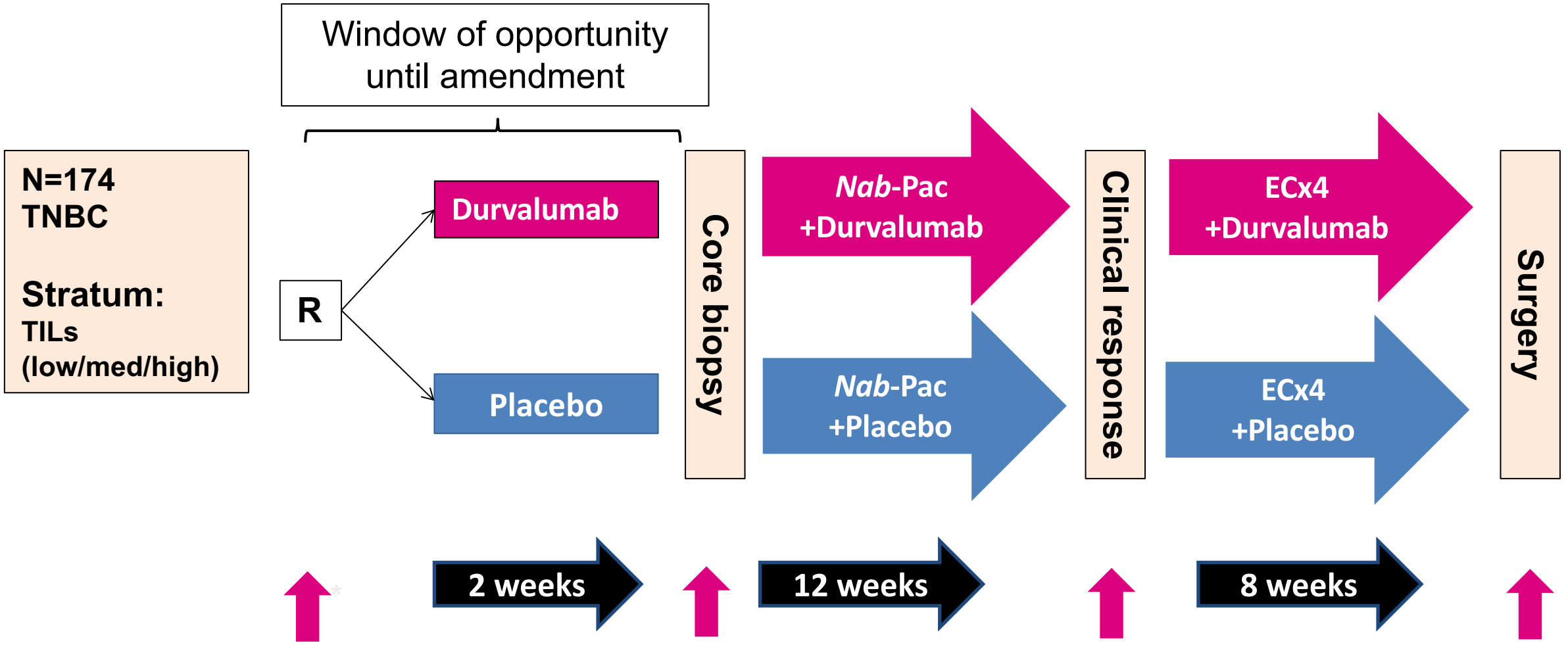
TREATMENT-RELATED AES

- Generally similar rates of Grade 3-5 during neoadjuvant phase
- Discontinuation rates
  - NEOADJUVANT 24.5% Pembro vs 13.1% Placebo
  - ADJUVANT 3.3% Pembro vs 1.3% Placebo

- Immune related – 10-15% can be permanent – more reason to wait for EFS and improved selection of patients
  - Hypothyroidism 14.9%; Hyperthyroidism 5.1%
  - Adrenal insufficiency 2.7%; Hypophysitis 1.8%
  - Pneumonitis 1.9%
  - Colitis 1.8%
  - Hepatitis 1.4%

Type 1 diabetes
Effects on fertility?

GeparNUEVO Study Design



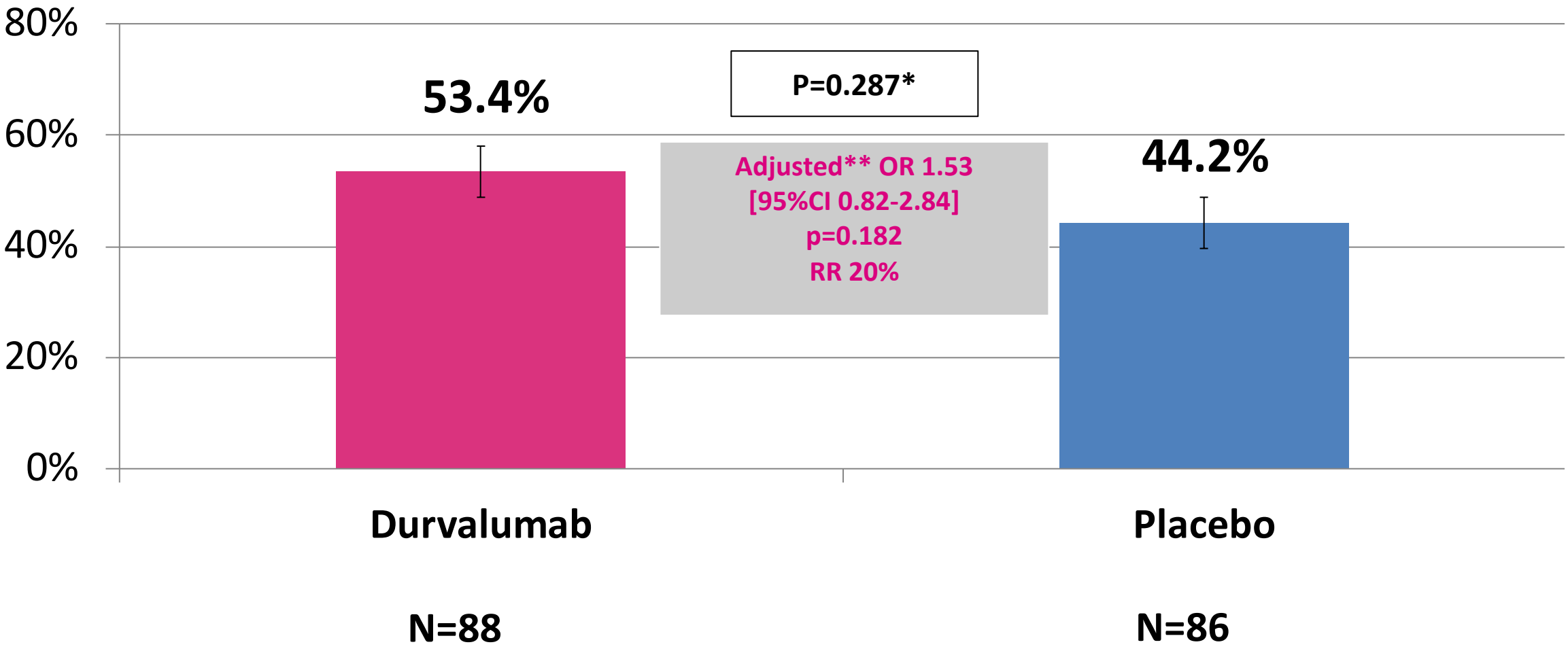
*Tissue: FFPE, fresh frozen;
Liquid biopsies: full blood; plasma, serum;

Durvalumab (0.75g) 1.5g d1q28

Nab-Paclitaxel 125mg/m² weekly

Epirubicin 90mg/m²;
Cyclophosphamide 600mg/m² d1q14

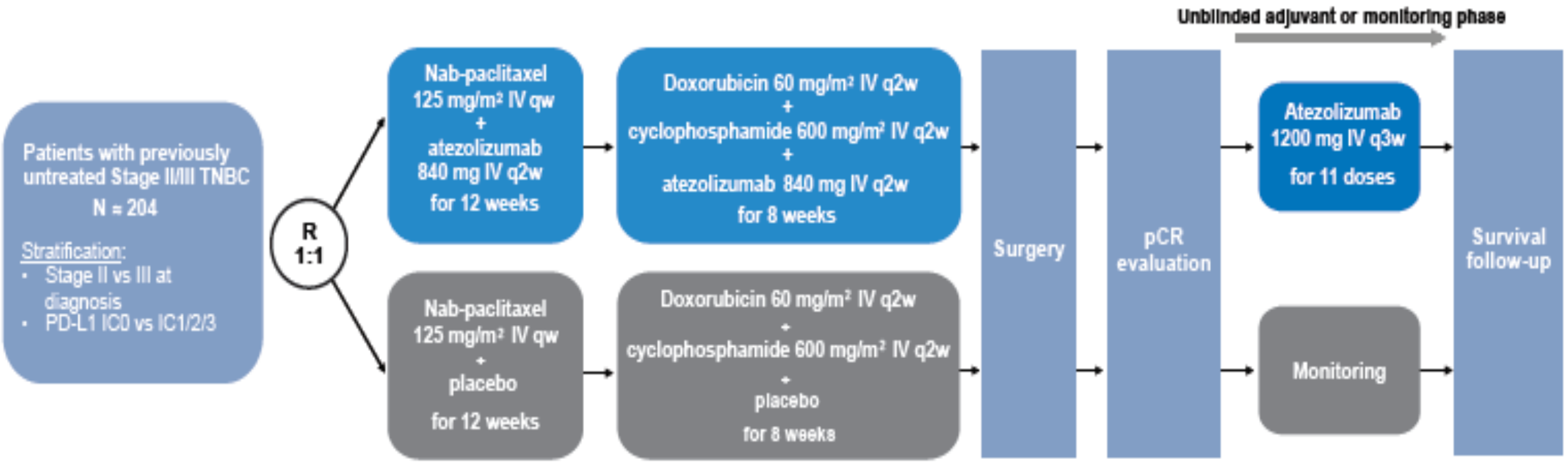
GeparNuevo: Primary Endpoint – pathological complete response pCR – ypT0, ypN0



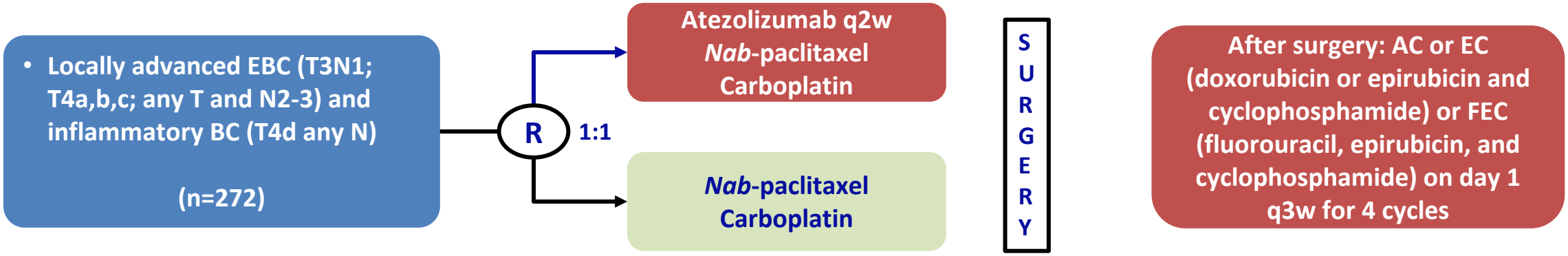
* Continuous corrected χ^2 test

** For stratification factor (TIL groups)

Neoadjuvant Atezolizumab – IMpassion031



Atezolizumab: NeoTRIP – phase III study neoadjuvant TNBC



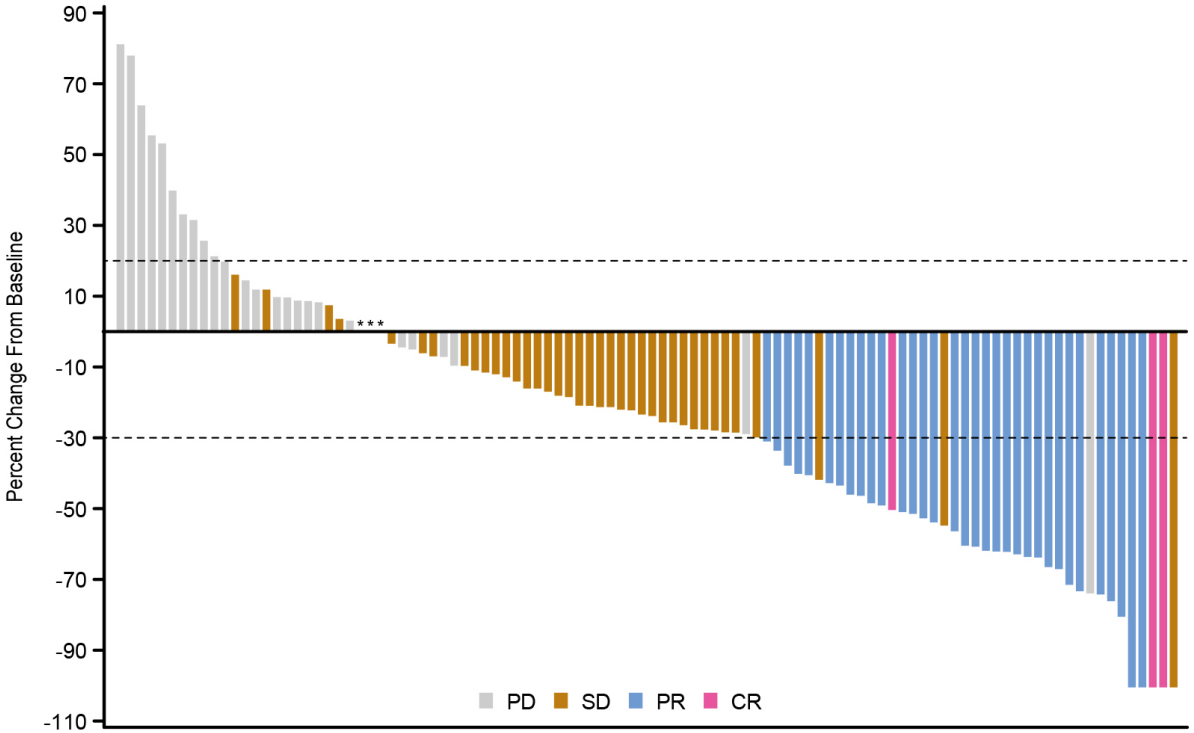
- **Carboplatin**: AUC 2 given IV on day 1 and day 8 q3w
- ***Nab*-paclitaxel**: 125mg/m^2 given IV on day 1 and day 8 q3w
- **Atezolizumab**: 1,200mg IV infusion on day 1 q3w

- **Primary endpoint**: 3 and 5 year EFS
  - 5-year EFS in control arm is assumed to be 57%. Clinically meaningful improvement to increase the 5-year EFS to 72% (HR=0.584)

ANTIBODY DRUG CONJUGATES (ADCS)

Sacituzumab Govitecan (IMMU132)

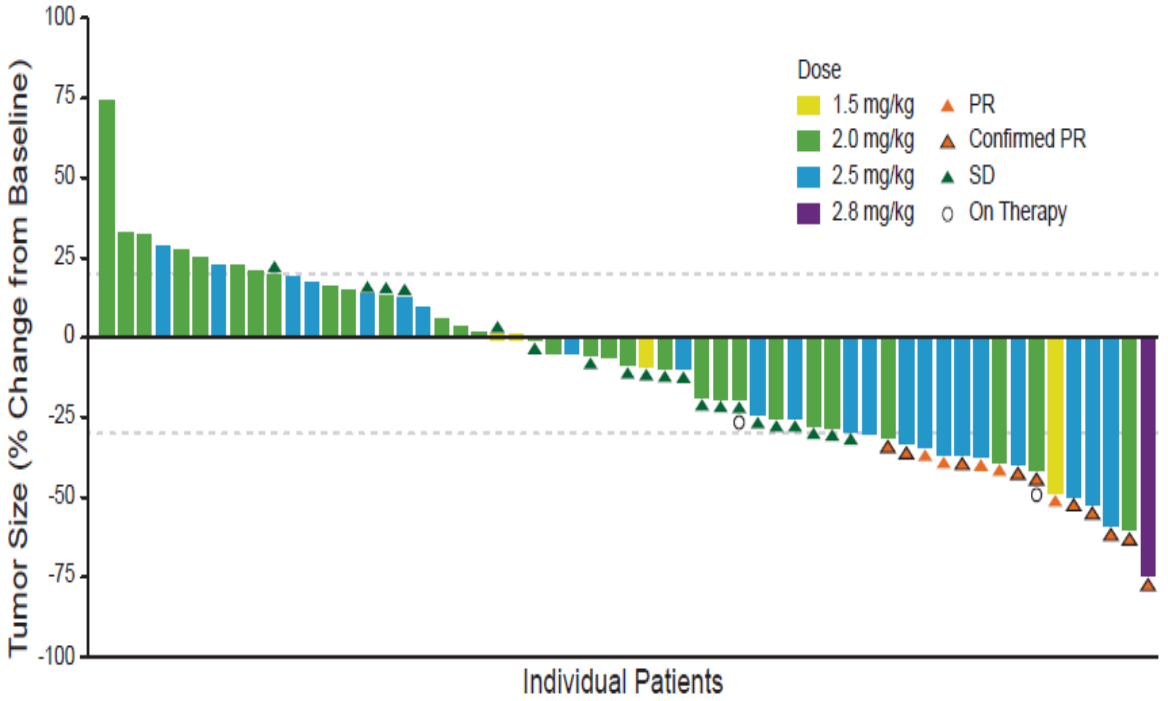
Anti-TROP2 and SN38 payload (Irinotecan)



Confirmed ORR = 33.3% (36/108)
CBR: 45.4% (49/108)

Ladiratuzumab Vedotin (LIV-1)

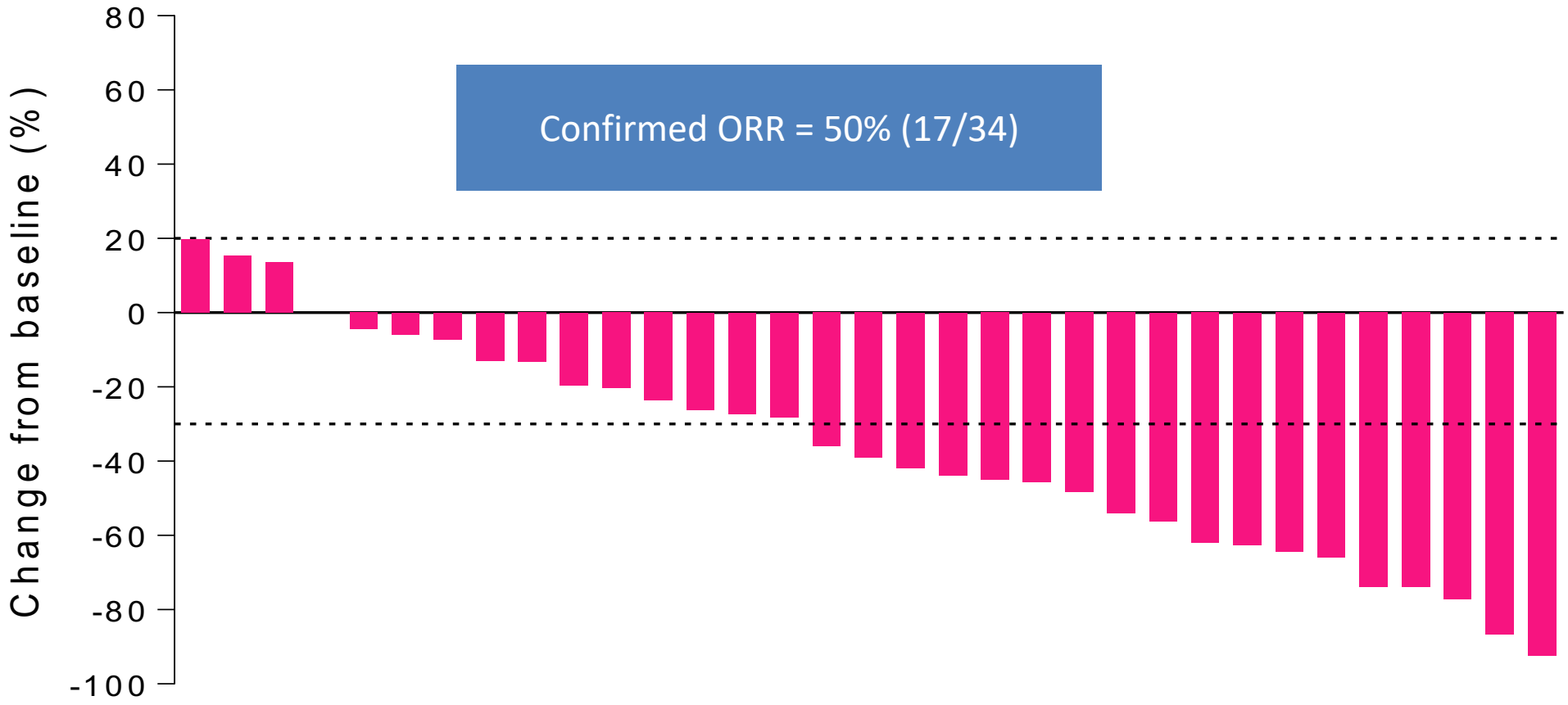
Targeting LIV1 and MMAE payload (microtubule)



Confirmed ORR = 25% (15/60)

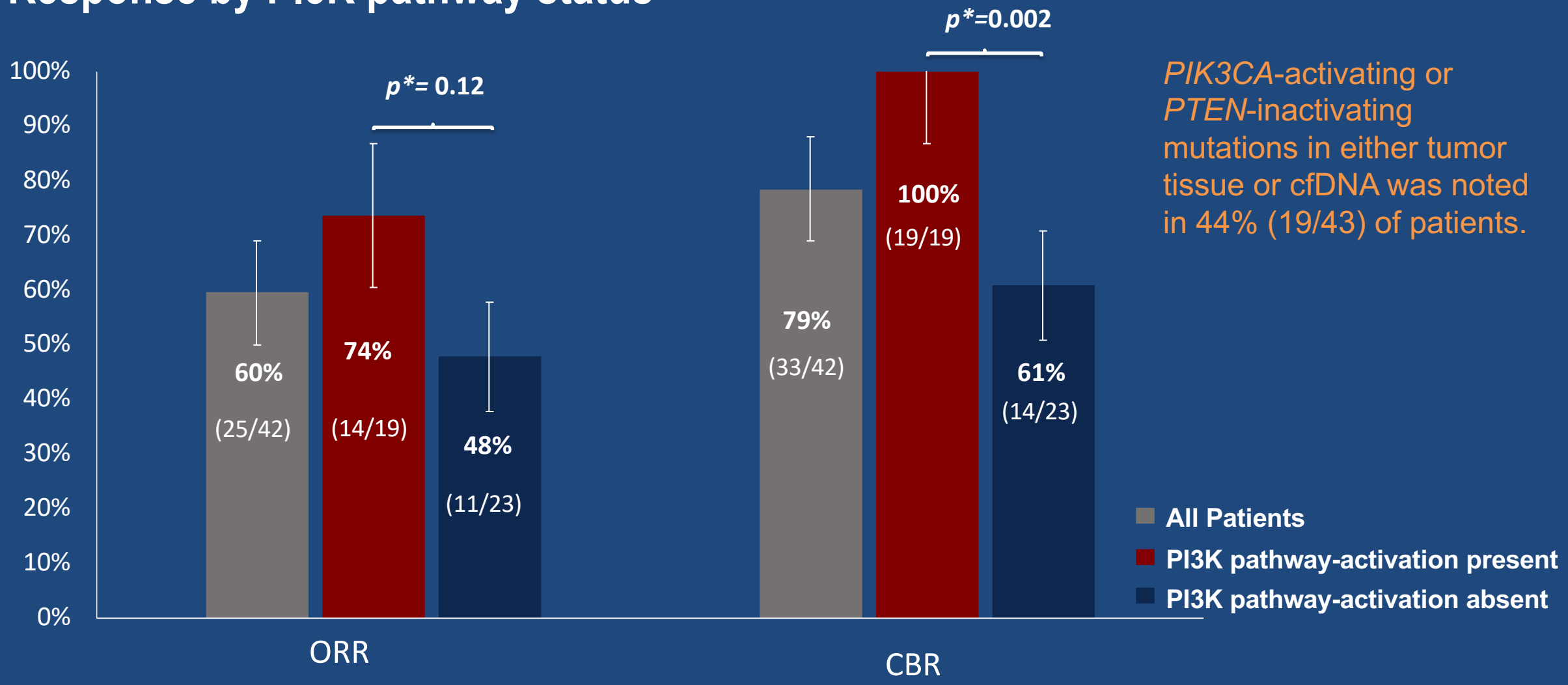
Bardia et al. *NEJM*. 2019.

TRASTUZUMAB DERUXTECAN (DS-8201A): HER2 LOW TUMORS (IHC +1,2)



Iwata H, et al. ASCO 2018. Abstract 2501.

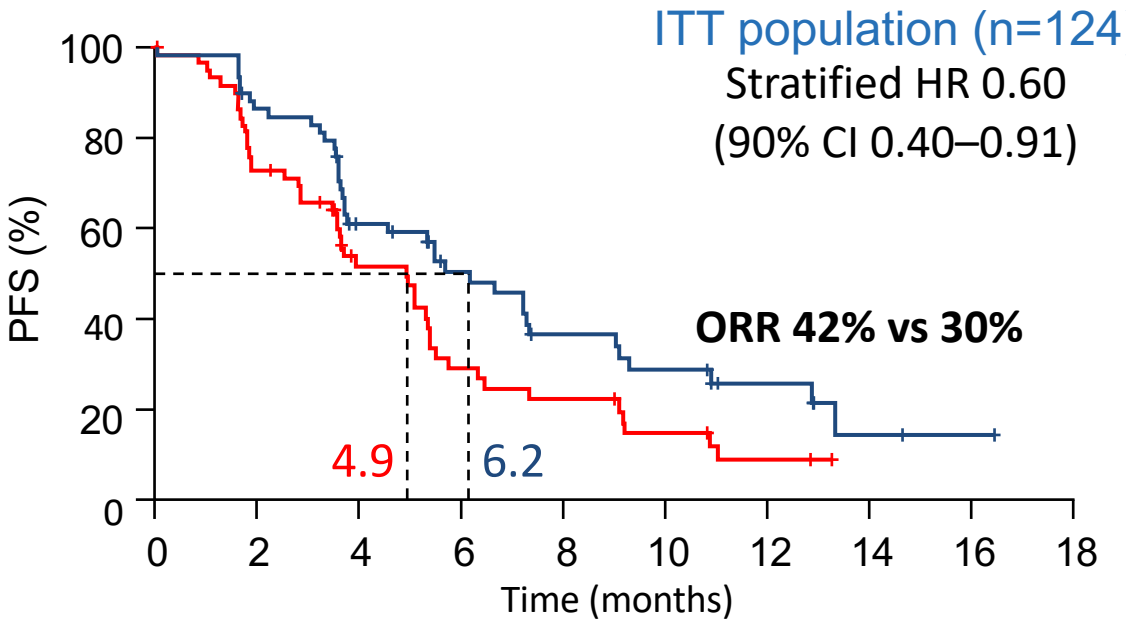
Phase I/II Study of Alpelisib (BYL719) and *Nab*-Paclitaxel in Patients with Locally Recurrent or Metastatic HER-2 Negative Breast Cancer (NCT02379247): Response by PI3K pathway status



PIK3CA-activating or *PTEN*-inactivating mutations in either tumor tissue or cfDNA was noted in 44% (19/43) of patients.

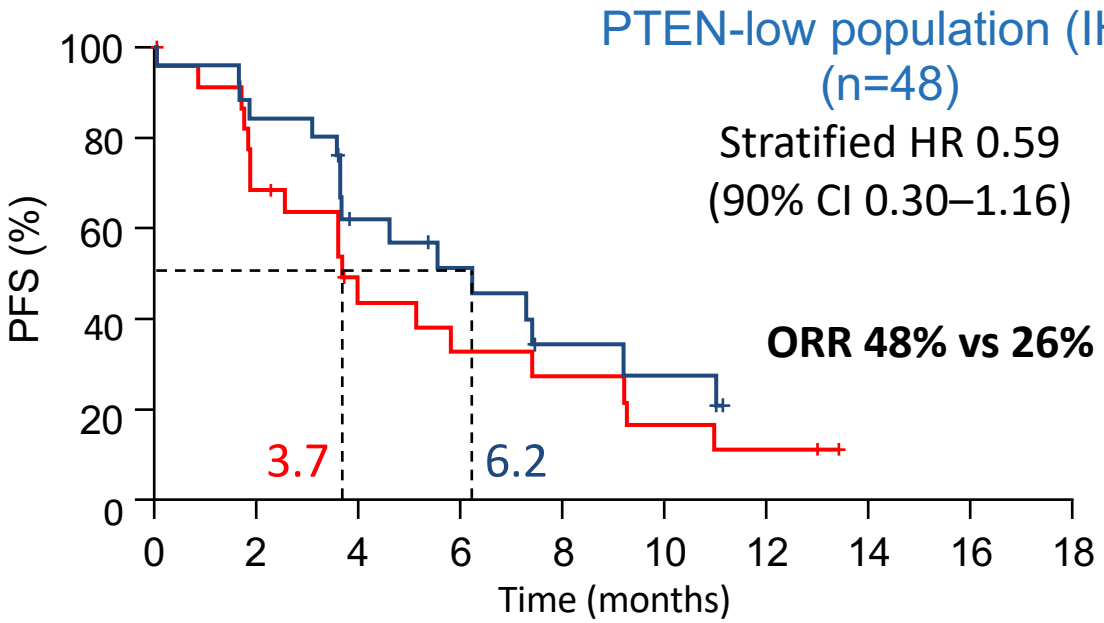
ORR=objective response rate; Clinical Benefit Rate (CBR)=Complete Response+Partial response+Stable disease ≥16 weeks; * Fisher's Exact Test

LOTUS Trial: Overview of PFS



ITT population (n=124)
Stratified HR 0.60
(90% CI 0.40–0.91)

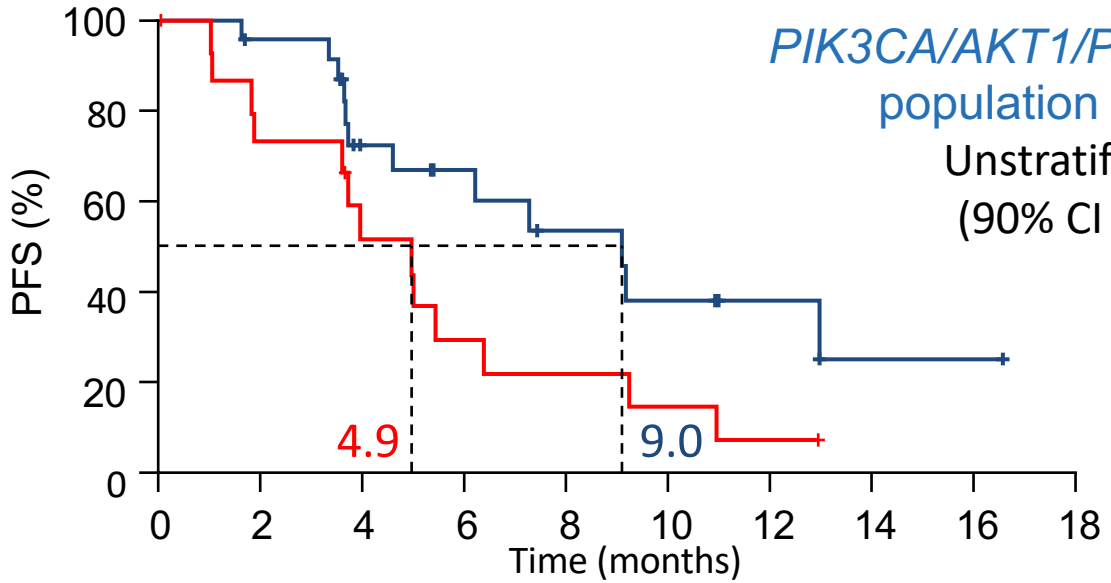
ORR 42% vs 30%



PTEN-low population (IHC) (n=48)
Stratified HR 0.59
(90% CI 0.30–1.16)

ORR 48% vs 26%

Ipatasertib + paclitaxel
Placebo + paclitaxel



PIK3CA/AKT1/PTEN-altered tumor population (NGS) (n=42)
Unstratified HR 0.44
(90% CI 0.20–0.87)

ORR 50% vs 44%

Trilaciclib plus chemotherapy versus chemotherapy alone in patients with metastatic triple-negative breast cancer: a multicentre, randomised, open-label, phase 2 trial

Antoinette R Tan, Gail S Wright, Anu R Thummala, Michael A Danso, Lazar Popovic, Timothy J Pluard, Hyo S Han, Željko Vojnović, Nikola Vasev, Ling Ma, Donald A Richards, Sharon T Wilks, Dušan Milenković, Zhao Yang, Joyce M Antal, Shannon R Morris, Joyce O'Shaughnessy

- Trial was negative for primary endpoint- no difference in neutropenia
- However OS was improved in trila arms
- Reasons unclear
- Longer duration of chemo?

Inhibits CDK4/6 and limits neutropenia

Properties	Palbo	Ribo	Abema	Trila
IC50 (nM) CDK4-CCND1	11	10	2	1
CDK6-CCND1,2,3	15	39	10	4
CDK1-CCNB1	>10000	113000	1627	NR
CDK2-CCNA-E	>10000	76000	504	NR
DLT	Neutropenia	Neutropenia, mucositis, QTcF, PE	fatigue	NR