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TNBC-Update

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Germantown, TN

Conflict of Interest

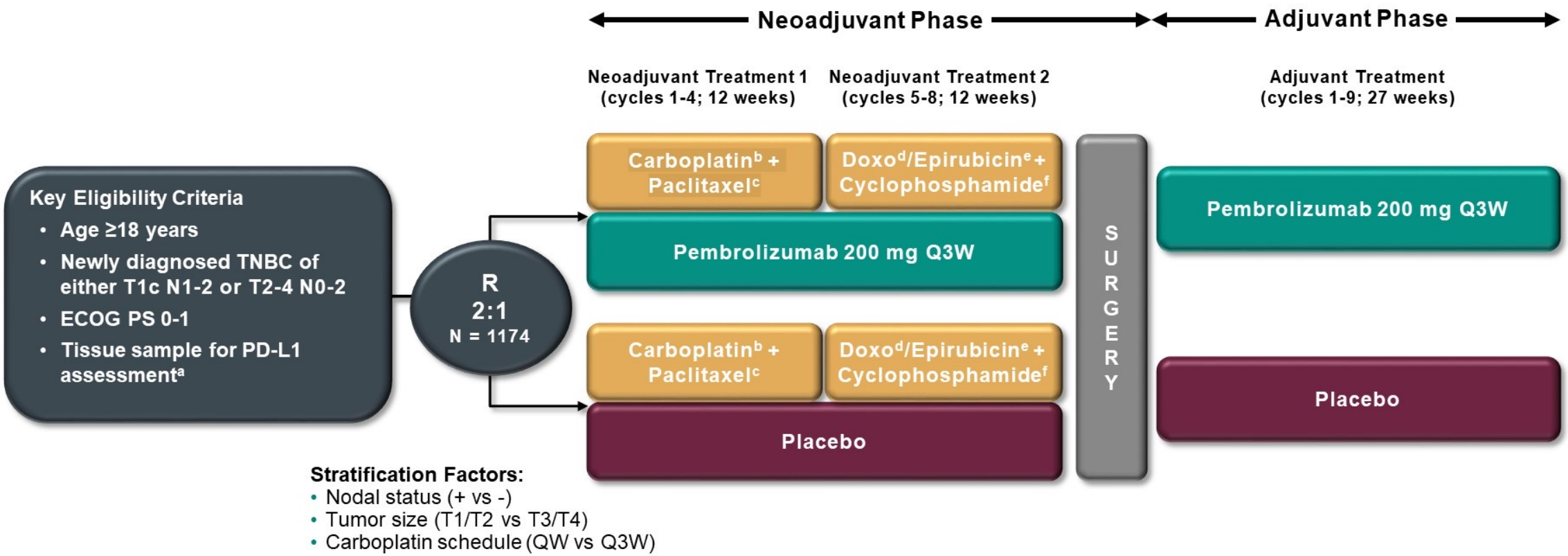
- CONSULTING FEES: Roche/Genetech, Novartis, Eli Lilly, Gilead, Puma, Pfizer, AstraZeneca, Biotheranuatics, Daiichi Sankyo, Concerto AI, Sanofi
- FEES FOR NON-CME SERVICES: Eli Lilly
- CONTRACTED RESEARCH: Roche/Genetech, Puma, Celcuity, Merck, BMS, Eli Lilly, GTx inc, Astrazeneca, Pfizer, Gilead, Tesaro, Halozyme,
- Ownership: Oncodisc

Objective: State of TNBC

1. Evolving Therapies for Early TNBC
2. Evolving Therapies for metastatic TNBC
3. Will offer my opinion on treatment sequencing

Neo/Adjuvant

KEYNOTE-522 Study Design (NCT03036488)



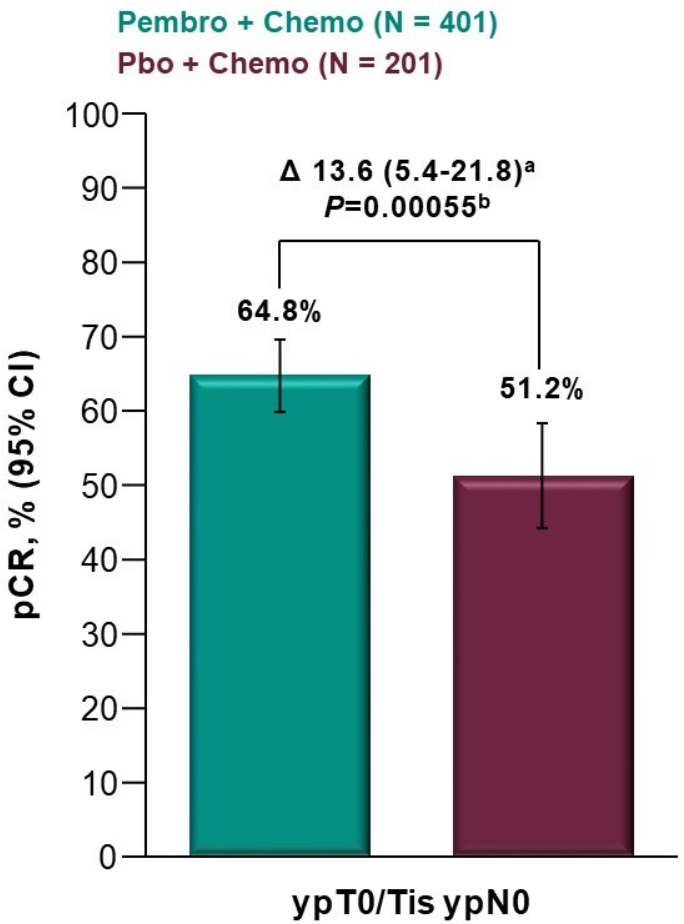
Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

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

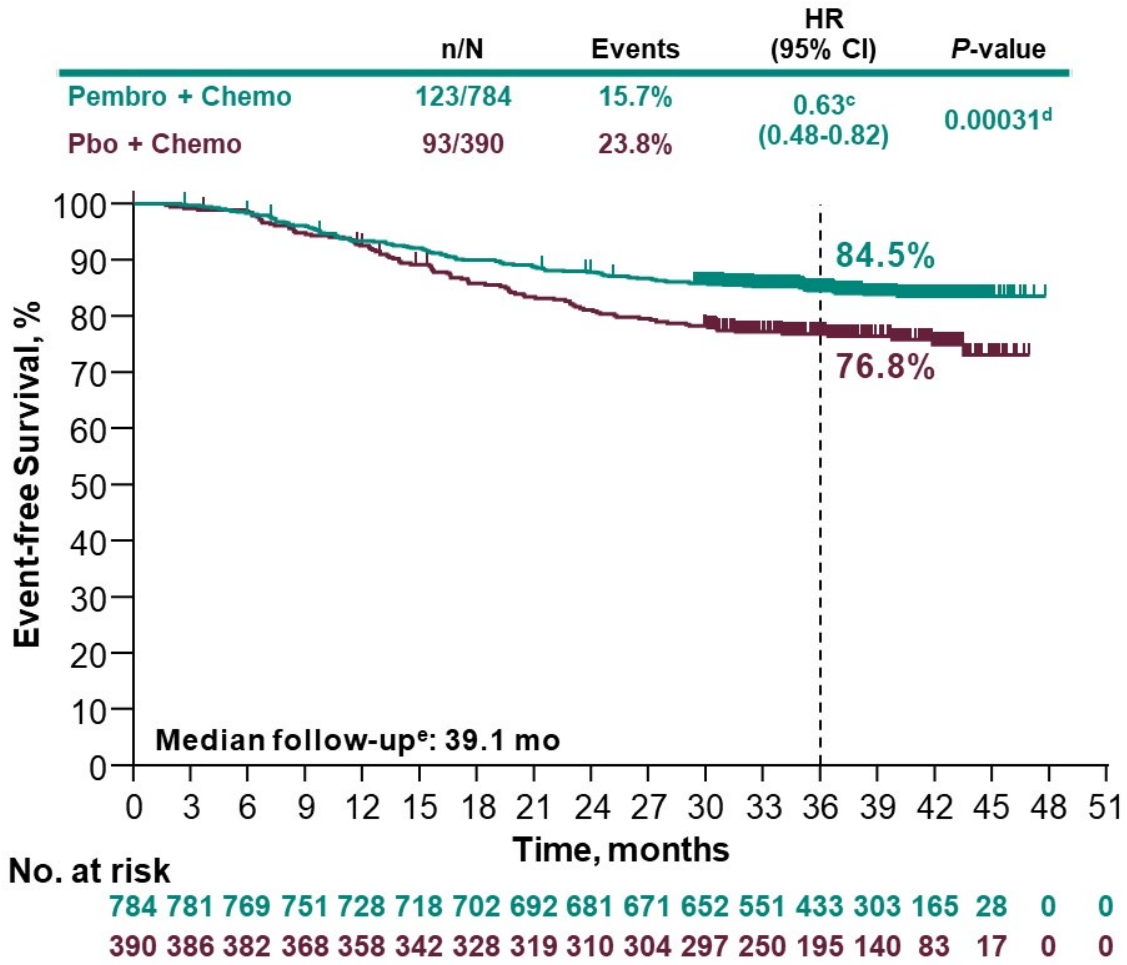
[a]Must consist of at least 2 separate tumor cores from the primary tumor. [b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW. [c]Paclitaxel dose was 80 mg/m^2 QW. [d]Doxorubicin dose was 60 mg/m^2 Q3W. [e]Epirubicin dose was 90 mg/m^2 Q3W. [f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

Primary Analyses of KEYNOTE-522

pCR at IA1[1]



EFS at IA4[2]

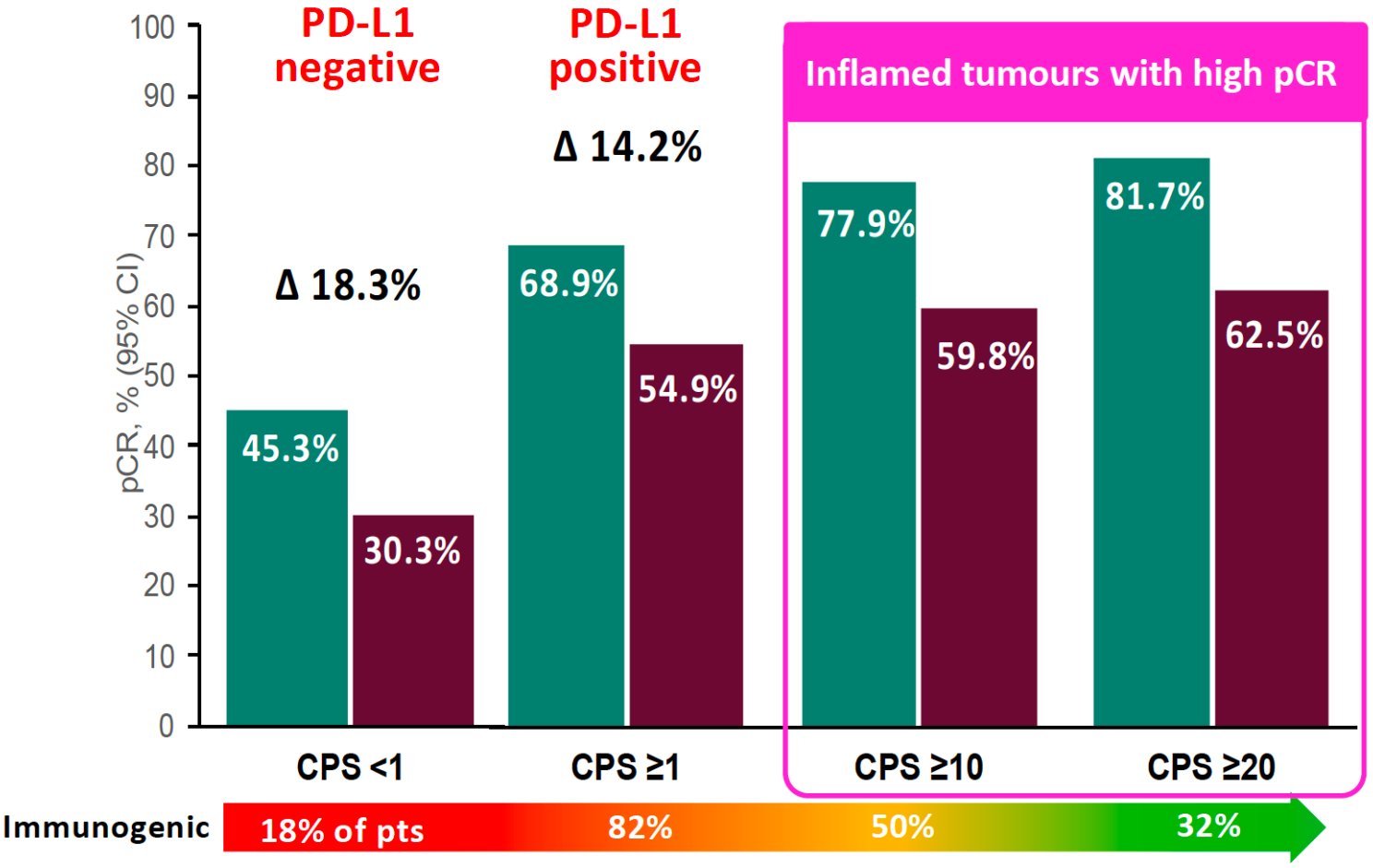


1. Schmid P, et al. *N Engl J Med* 2020;382:810-21. 2. Schmid P, et al. *N Engl J Med* 2022;386:556-67. [a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. [b]Prespecified *P*-value boundary for significance of 0.003 was crossed; 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.

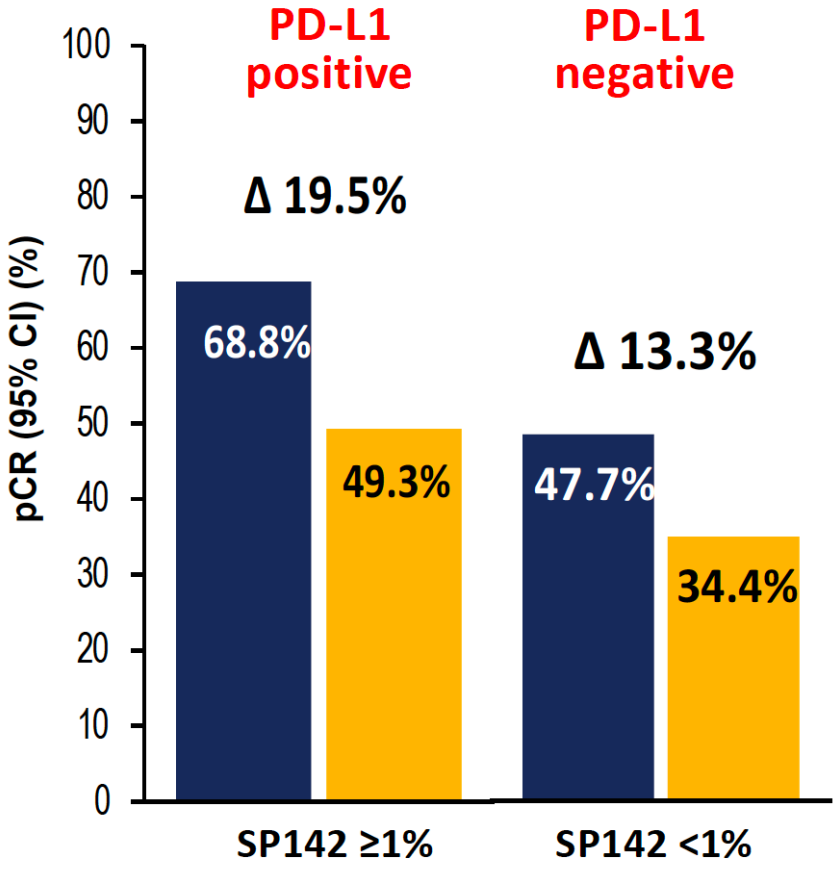
Neoadjuvant CIT in TNBC: pCR rates by PD-L1 expression

PDL1-positive and PDL1-negative patients benefit from CIT

Keynote 522

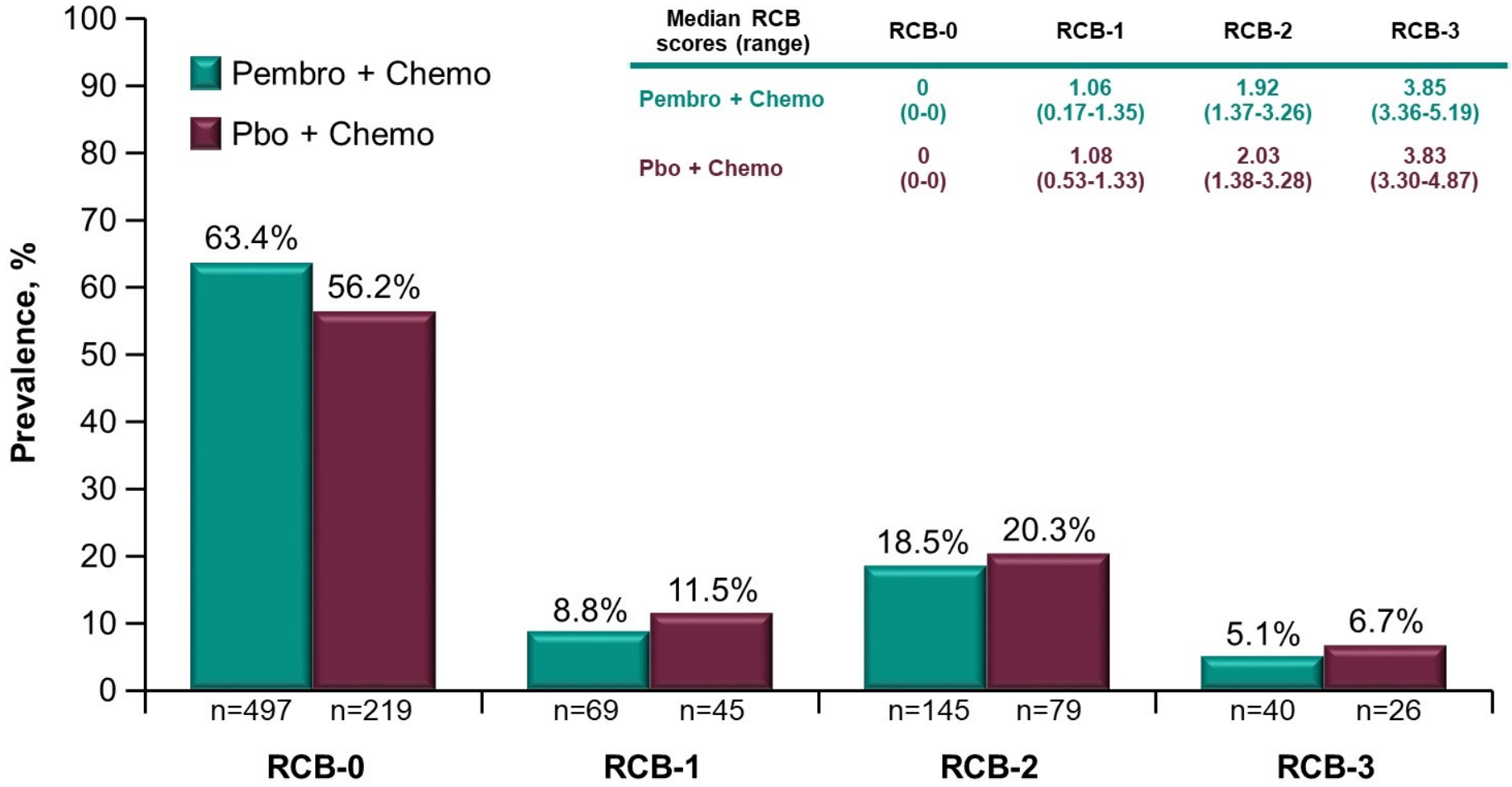


Impassion 031



Schmid P, et al. ESMO 2019, Schmid, et al NEJM 2020, Mittendorf et al, Lancet. 2020 Oct 10;396(10257):1090-1100

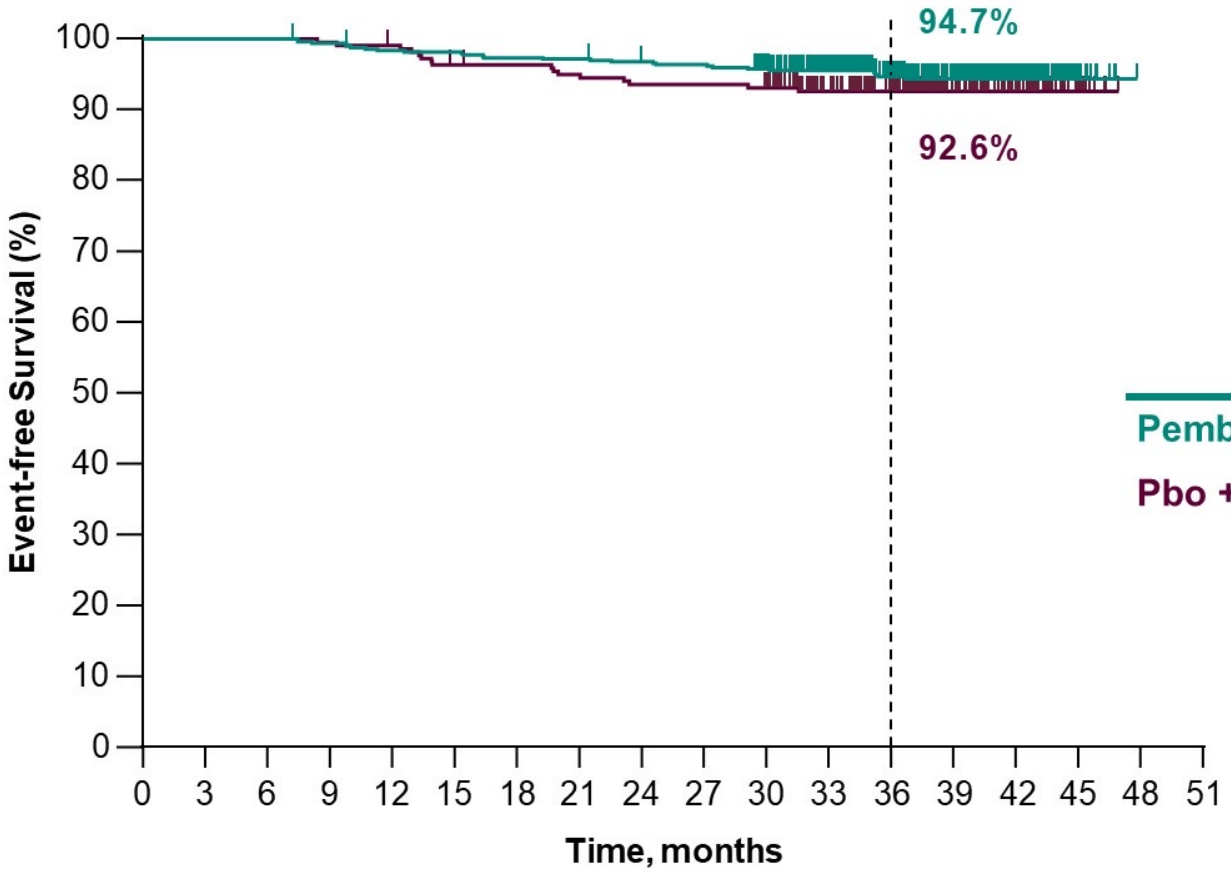
Prevalence of RCB Categories in All Patients



Median RCB scores (range)	RCB-0	RCB-1	RCB-2	RCB-3
Pembro + Chemo	0 (0-0)	1.06 (0.17-1.35)	1.92 (1.37-3.26)	3.85 (3.36-5.19)
Pbo + Chemo	0 (0-0)	1.08 (0.53-1.33)	2.03 (1.38-3.28)	3.83 (3.30-4.87)

Among all patients (n=1174), 54 patients (4.6%) had missing RCB categorical data: 33 (4.2%) in the pembro + chemo group and 21 (5.4%) in the pbo + chemo group.
Data cutoff date: March 23, 2021.

EFS in RCB-0



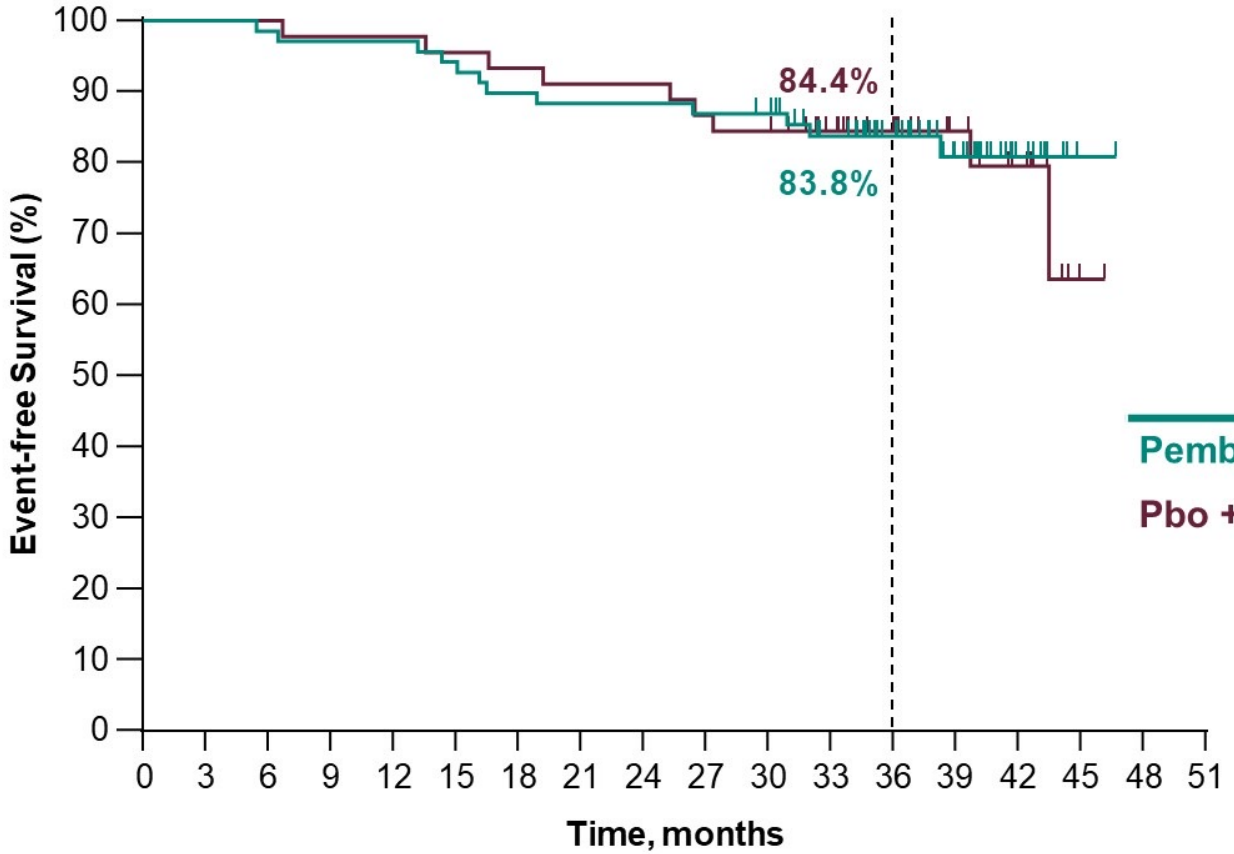
	n/N	Events	HR (95% CI)
Pembro + Chemo	26/497	5.2%	0.70[a] (0.38-1.31)
Pbo + Chemo	16/219	7.3%	

No. at risk

497	497	497	493	487	486	482	481	476	474	463	390	310	223	124	18	0	0
219	219	219	218	216	209	208	205	202	202	199	167	132	89	58	10	0	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate. Data cutoff date: March 23, 2021.

EFS in RCB-1



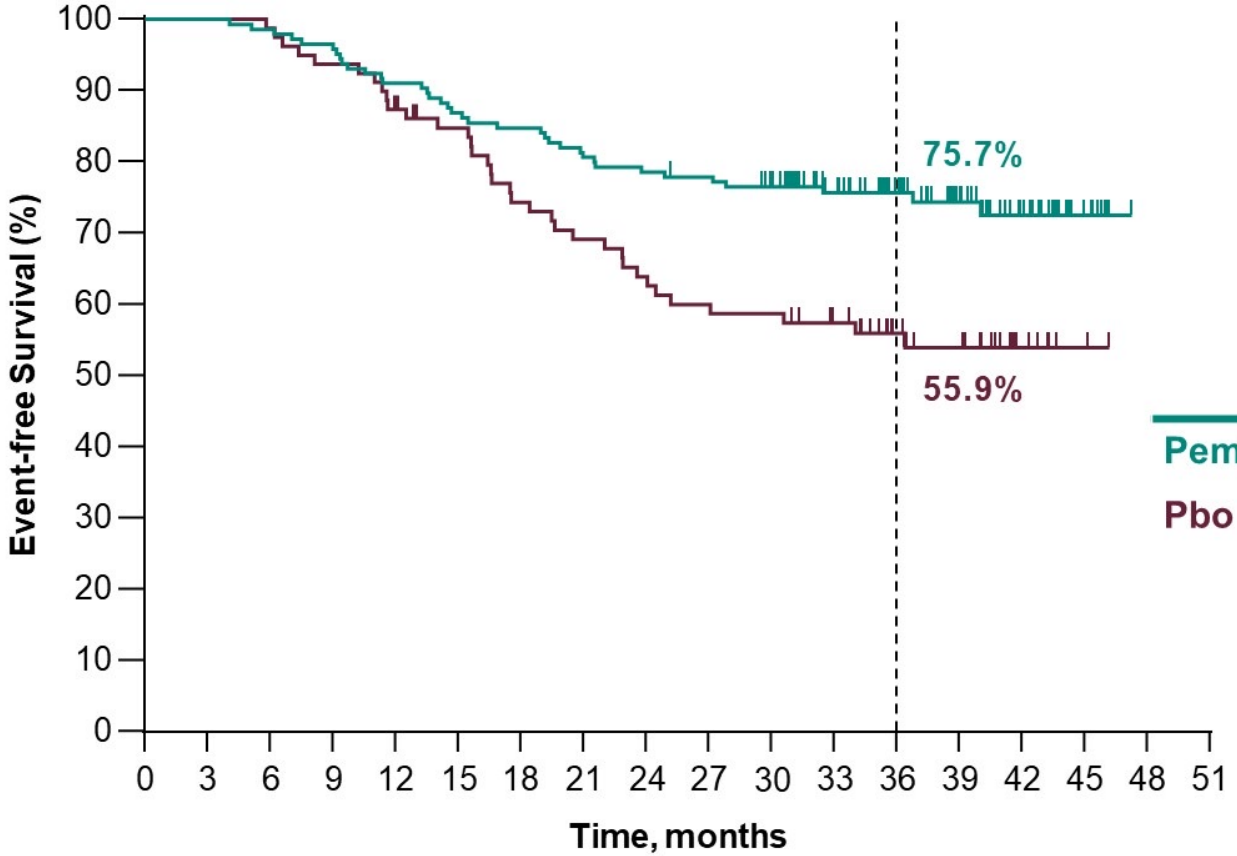
	n/N	Events	HR (95% CI)
Pembro + Chemo	12/69	17.4%	0.92[a] (0.39-2.20)
Pbo + Chemo	9/45	20.0%	

No. at risk

69	69	68	67	67	65	62	61	61	60	59	50	38	24	9	1	0	0
45	45	45	44	44	43	42	41	41	39	38	32	25	18	11	1	0	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate. Data cutoff date: March 23, 2021.

EFS in RCB-2



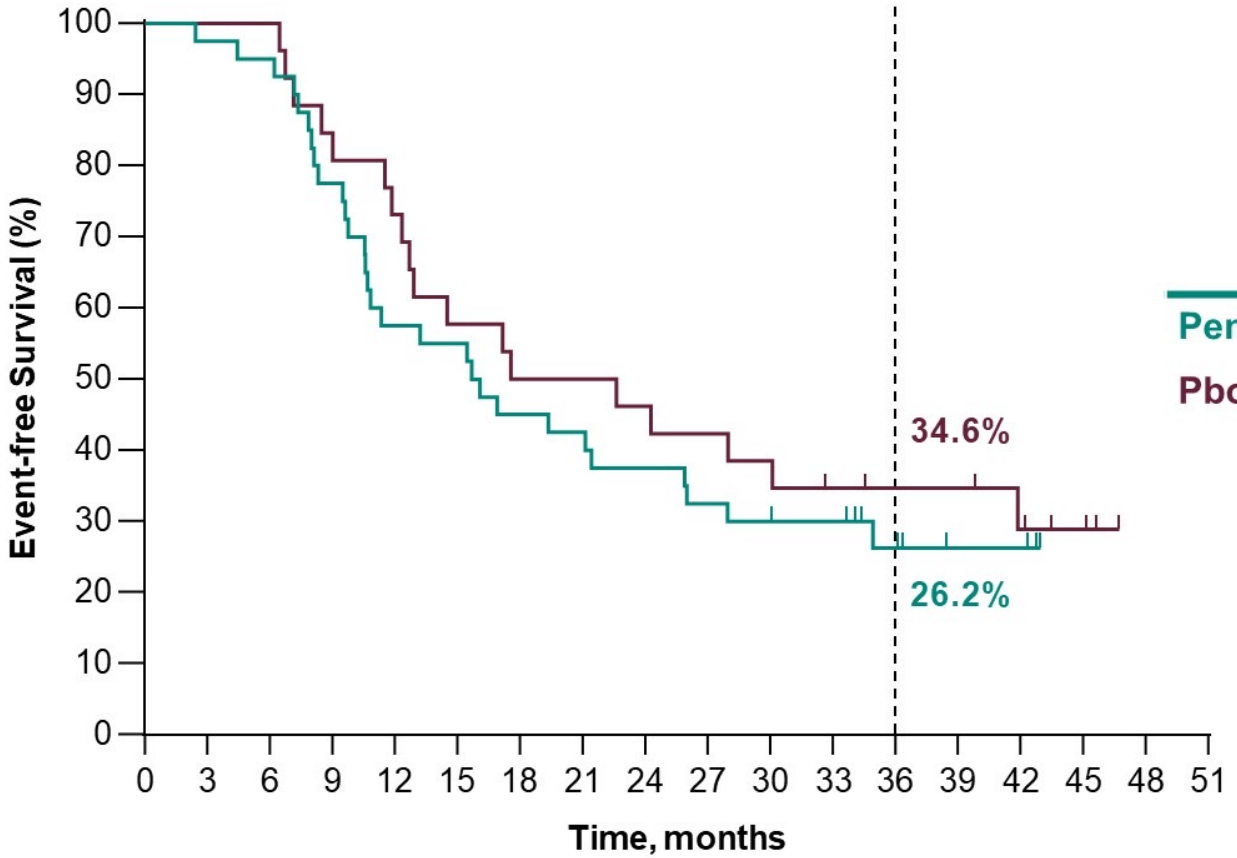
	n/N	Events	HR (95% CI)
Pembro + Chemo	37/145	25.5%	0.52[a] (0.32-0.82)
Pbo + Chemo	35/79	44.3%	

No. at risk

145	145	143	140	132	126	123	117	114	112	107	90	70	46	26	9	0	0
79	79	78	74	69	65	57	53	49	46	45	40	29	24	7	2	0	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate. Data cutoff date: March 23, 2021.

EFS in RCB-3



	n/N	Events	HR (95% CI)
Pembro + Chemo	29/40	72.5%	1.24[a] (0.69-2.23)
Pbo + Chemo	18/26	69.2%	

No. at risk

40	39	38	31	23	22	18	17	15	13	12	11	6	3	3	0	0	0
26	26	26	22	19	15	13	13	12	11	10	8	7	7	5	3	0	0

[a]Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate. Data cutoff date: March 23, 2021.

2022 ASCO ANNUAL MEETING

Neoadjuvant Phase II Study of Pembrolizumab and Carboplatin plus Docetaxel in Triple Negative Breast Cancer (NeoPACT)

Priyanka Sharma, Shane R. Stecklein, Rachel Yoder, Joshua M. Staley, Kelsey Schwensen, Anne O'Dea, Lauren Nye, Manana Elia, Deepti Satelli, Gregory Crane, Rashna Madan, Maura F. O'Neil, Jamie Wagner, Kelsey E. Larson, Christa Balanoff, Milind A. Phadnis, Andrew K. Godwin, Roberto Salgado, Qamar J. Khan, Joyce O'Shaughnessy

NCI Designated Cancer Center

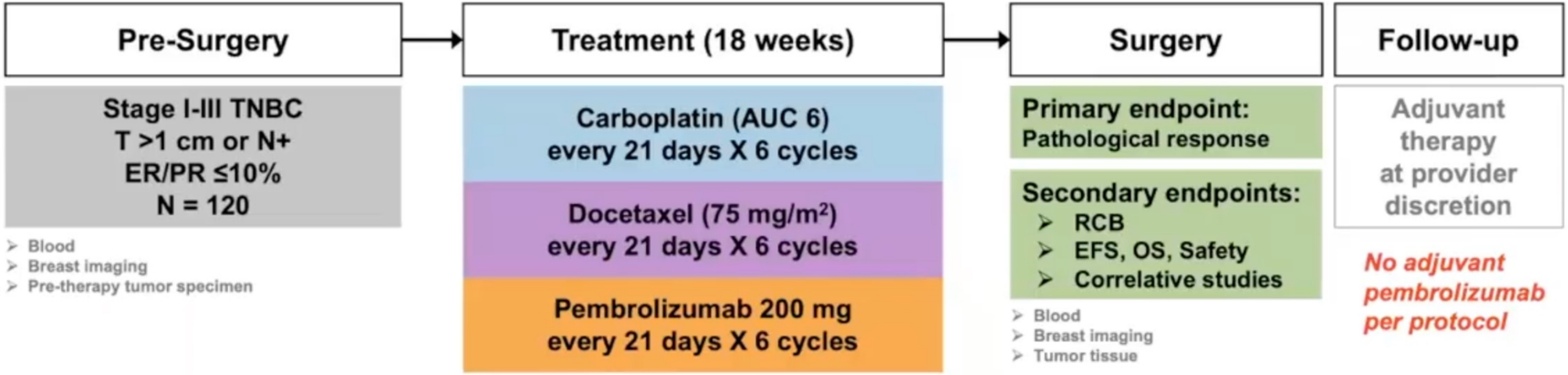
NCI Community Oncology Research Program

THE UNIVERSITY OF KANSAS CANCER CENTER

PRESENTED BY:
Priyanka Sharma, M.D.

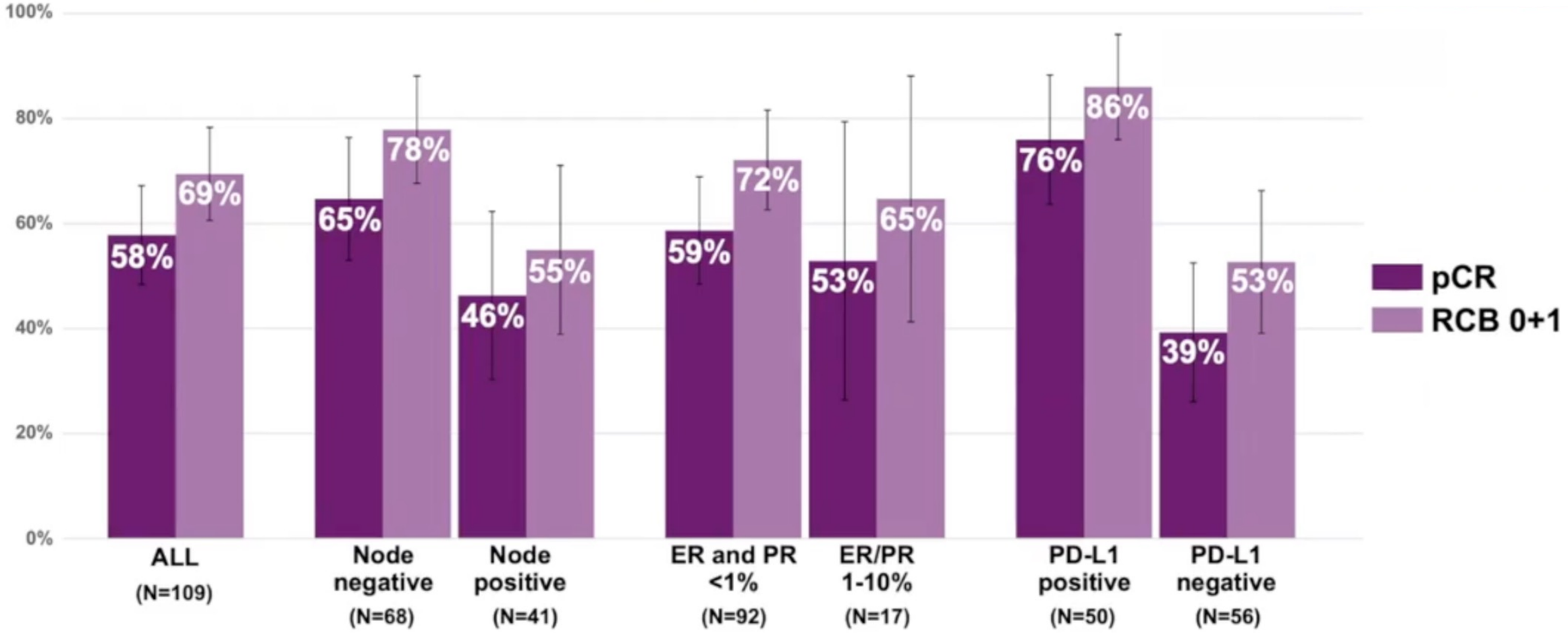
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Study Design-- NeoPACT



Sites: University of Kansas and Baylor University Medical Center

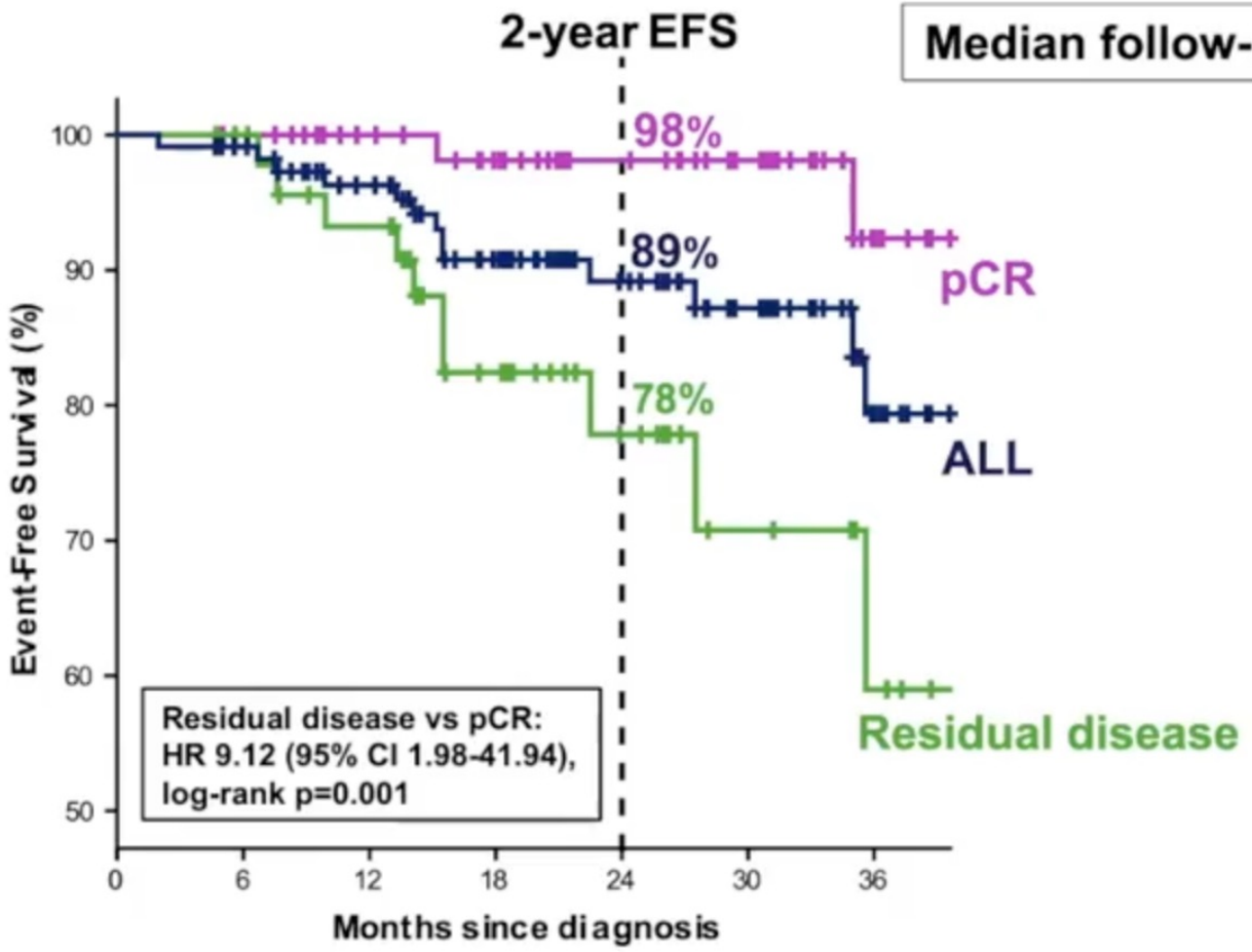
RESULTS: Pathologic Complete Response



- No patients had disease progression during neoadjuvant treatment.
- **Among patients with stage II-III disease and ER & PR IHC <1%, pCR and RCB 0+1 rates were 59% and 69%, respectively.**
- **pCR in TNM stage I, II, and III disease was 69%, 59%, and 43%, respectively.**

Error bars represent 95% binomial confidence intervals

RESULTS: Event Free Survival



Number at risk							
All	113	108	95	75	54	37	18
pCR	63	62	55	48	38	28	13
Residual disease	49	46	40	27	16	9	5

Survival analysis includes all patients in the ITT population except for N=2 who are awaiting surgery

Adverse event (AEs)

Grade 3 or higher treatment- related AEs (TRAEs) were observed in 26.9% of patients

- Most common grade 3 or higher TRAEs were
  - Diarrhea 4.3%
  - Anemia 3.5%
  - Peripheral sensory neuropathy 2.6%

Treatment discontinuation due to AEs

- TRAEs led to discontinuation of any drug in 12% of patients
- discontinuation of pembrolizumab due to TRAE occurred in 7% of patients
- Discontinuation of chemotherapy due to TRAE occurred in 10% of patients

[a] Treatment-related AEs that occurred in at least 10% of patients are reported.
[b] Grade 1=40.0%, Grade 2=18.3%, Grade 3=4.3%, Grade 4=0%.
[c] Peripheral sensory neuropathy was mainly grade 1 (26.9%), with 10.4% and 2.6% of patients experiencing grade 2 and 3 peripheral neuropathy, respectively (Grade 4=0%).

Immune-Mediated Aes (iAEs)

Treatment-related iAEs were observed in 27.0% of patients.

- 4.3% experienced grade 3 or higher iAE.
  - Most common grade 3 or higher iAE was colitis (1.7%)
  - No cases of hypophysitis or adrenal insufficiency were noted

Treatment-related iAE	All grades (N=115)	Grade 1-2	Grade 3-4[a]
Any iAE	31 (27.0%)	26 (22.6%)	5 (4.3%)
Rash	21 (18.3%)	21 (18.3%)	0 (0%)
Hypothyroidism	4 (3.5%)	4 (3.5%)	0 (0%)
Colitis	2 (1.7%)	0 (0%)	2 (1.7%)
Myocardial infarction[a,b]	1 (0.9%)	0 (0%)	1 (0.9%)
Inflammatory dermatitis	1 (0.9%)	0 (0%)	1 (0.9%)
Autoimmune disorder	1 (0.9%)	0 (0%)	1 (0.9%)
Hyperthyroidism	1 (0.9%)	1 (0.9%)	0 (0%)
Thyroiditis	1 (0.9%)	1 (0.9%)	0 (0%)
Cranial nerve palsy	1 (0.9%)	1 (0.9%)	0 (0%)
Focal meningomyelitis	1 (0.9%)	1 (0.9%)	0 (0%)

[a] N=1 grade 5 event.
[b] Myocardial infarction requiring percutaneous coronary intervention with diagnosis of coronary artery disease 2 weeks following first cycle of study treatment. Following this event, subject was removed from study treatment per treating provider and started on alternative chemotherapy. Patient suffered another myocardial infarction 3 weeks after stopping study treatment, leading to death.
[c] GAD65-positive autoimmune encephalitis.

Summary Current Therapy Sequence

Neo-Adjuvant/Adjuvant Chemotherapy

- **AC-paclitaxel + Carboplatin + Pembrolizumab –**(**T** ≥ 2cm and/or N+)
- **Taxotere Cytoxan x 4/6 –**(**T** ≤ 2cm)
- **AC-paclitaxel** --T ≤ 2cm
- **AC-paclitaxel + Carboplatin--** pembrolizumab contraindicated
- Taxotere + carboplatin +/- pembrolizumab- when appropriate

Adjuvant

1. **pCR:**
   - **Pembrolizumab**-- can exclude if intolerable or pt preference
2. **Non-pCR**
   - **Pembrolizumab**
   - **Pembrolizumab + Capecitabine**-- Especially if RCB II/III
   - **Pembrolizumab + Olaparib**—If gBRCA positive
   - **Capecitabine**– if **not** pembrolizumab candidate
   - **Olaparib**—if gBRCA and **not** pembrolizumab candidate

Study- Pembrolizumab 200mg q3WK + Olaparib 300MG bid (N)	Toxicities (%)
Keynote 365 cohort A –mCRPC (84)[1]	○ Common-all grades • Nausea (33) • Anemia (31) ○ Grade >=3-TRAEs (35) ○ Grade 5 – (2)
KeyLYNK 007- Advance solid tumors (168)[2]	○ Common- all grades • Nausea (39) • Anemia (30) • Fatigue (16) ○ Grade 3-4 (36)
Phase II Niraparib and Pembrolizumab mTNBC (55)[3]	○ Grade All • Nausea (55) • Fatigue (44) • Anemia 35) • Thrombocytopenia (25) ○ Grade 3 AE's (58)- Fatigue, Anemia, Thrombocytopenia

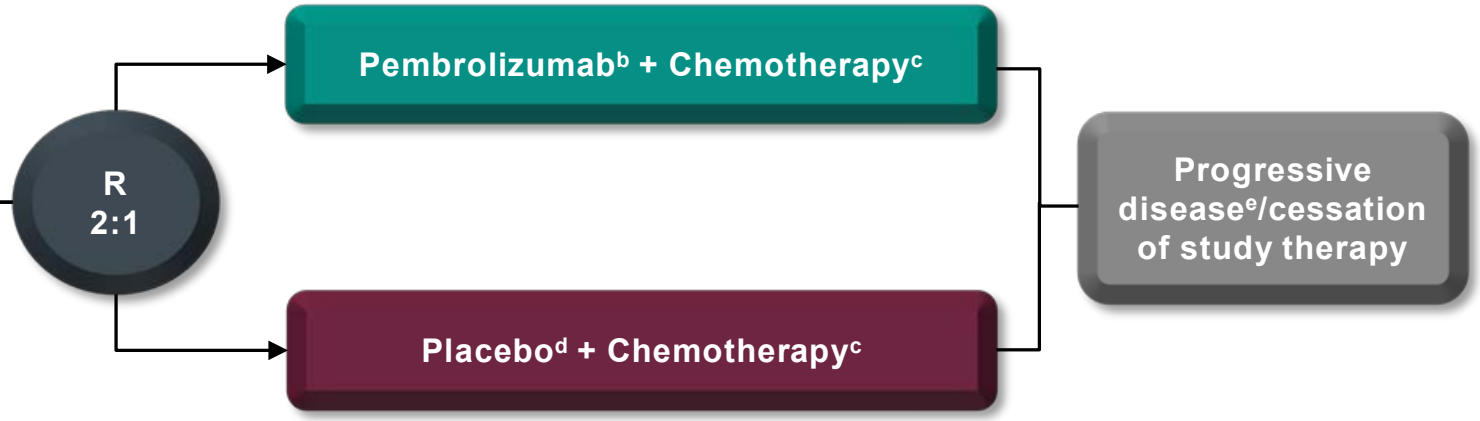
Study--Pembrolizumab 200mg q3WK + Xeloda 1000mg/m2 bid (N)	Toxicities (%)
Phase II mBC (30)[4]	○ Common-all grades occurring in >= 50% pts • Hyperglycemia (87) • Elevate ALK (67) • Amenia (60) • Fatigue (57) • Lymphopenia (53) • Elevated AST (53) • Nausea (53) Diarrhea (50) ○ Grade >3 in >=10% • Lymphopenia (20) • Hand Foot (13) • Elevated ALK (10) • Anemia (10)

1. Yu et al, JCO GU cancer symposium 2020, 2. Maio et al, Clinical Cancer Research 2021, 3. Vinayak et al Jama Oncology 2019, 4. Shah J Immuno Cancer, 2020

Metastatic

KEYNOTE-355 Study Design (NCT02819518)

Key Eligibility Criteria
- Age ≥18 years
- Central determination of TNBC and PD-L1 expression[a]
- Previously untreated locally recurrent inoperable or metastatic TNBC
- De novo metastasis or completion of treatment with curative intent ≥6 months prior to first disease recurrence
- ECOG performance status 0 or 1
- Life expectancy ≥12 weeks from randomization
- Adequate organ function
- No systemic steroids
- No active CNS metastases
- No active autoimmune disease

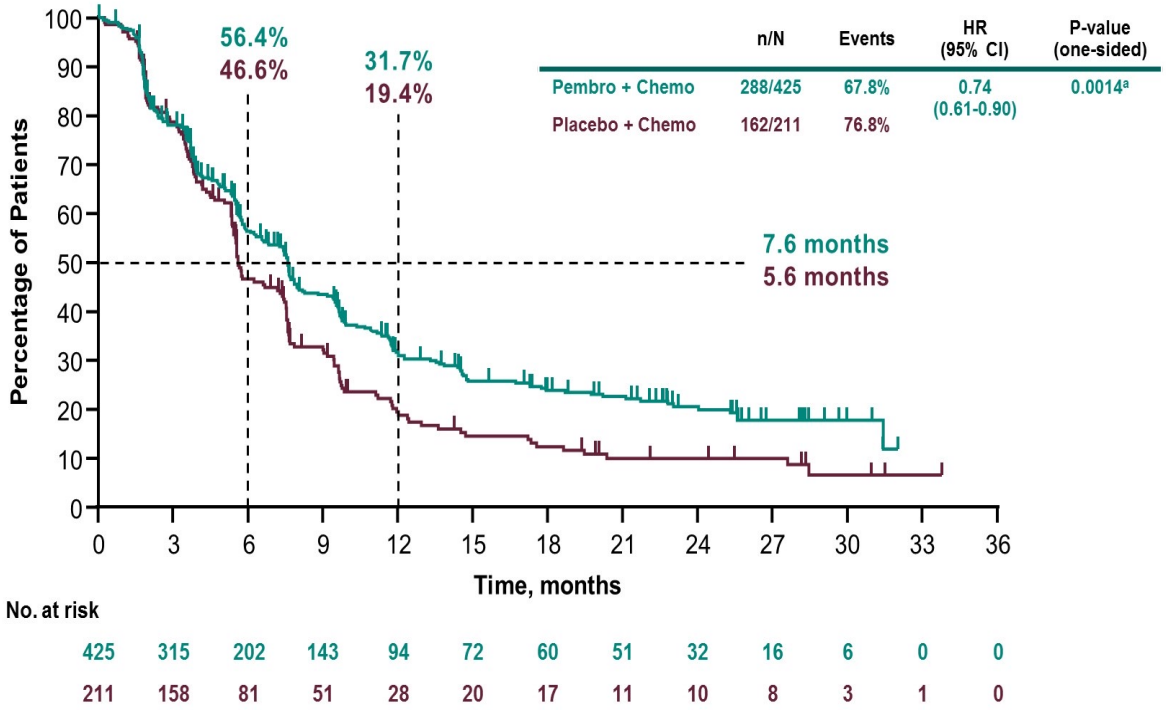


Stratification Factors:
- Chemotherapy on study (taxane or gemcitabine-carboplatin)
- PD-L1 tumor expression (CPS ≥1 or CPS <1)[f]
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes or no)

[a]Based on a newly obtained tumor sample from a locally recurrent inoperable or metastatic site (an archival tumor sample was used with permission from the study sponsor if a new tumor biopsy was not obtainable). [b]Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W). [c]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. [d]Normal saline. [e]Treatment may be continued until confirmation of progressive disease. [f]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 viable tumor cells x 100).

Progression Free Survival by PD-L1 expression

Progression-Free Survival: PD-L1 CPS ≥1



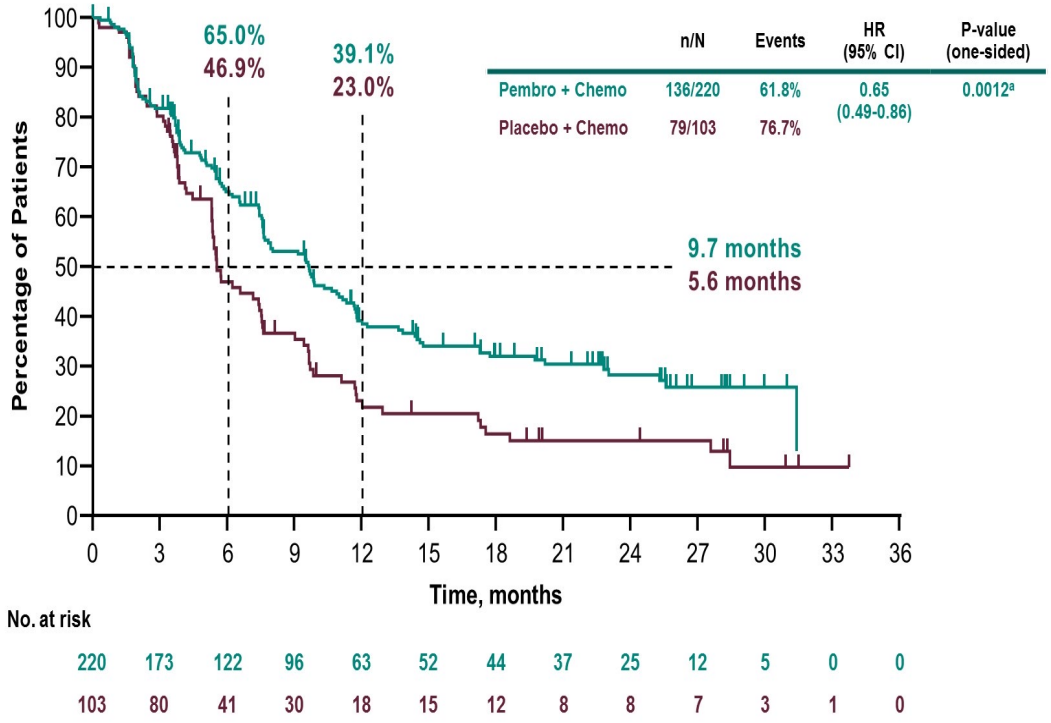
	n/N	Events	HR (95% CI)	P-value (one-sided)
Pembro + Chemo	288/425	67.8%	0.74 (0.61-0.90)	0.0014[a]
Placebo + Chemo	162/211	76.8%		

No. at risk

425	315	202	143	94	72	60	51	32	16	6	0	0
211	158	81	51	28	20	17	11	10	8	3	1	0

[a]Prespecified *P* value boundary of 0.00111 not met.
Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff December 11, 2019.

Progression-Free Survival: PD-L1 CPS ≥10



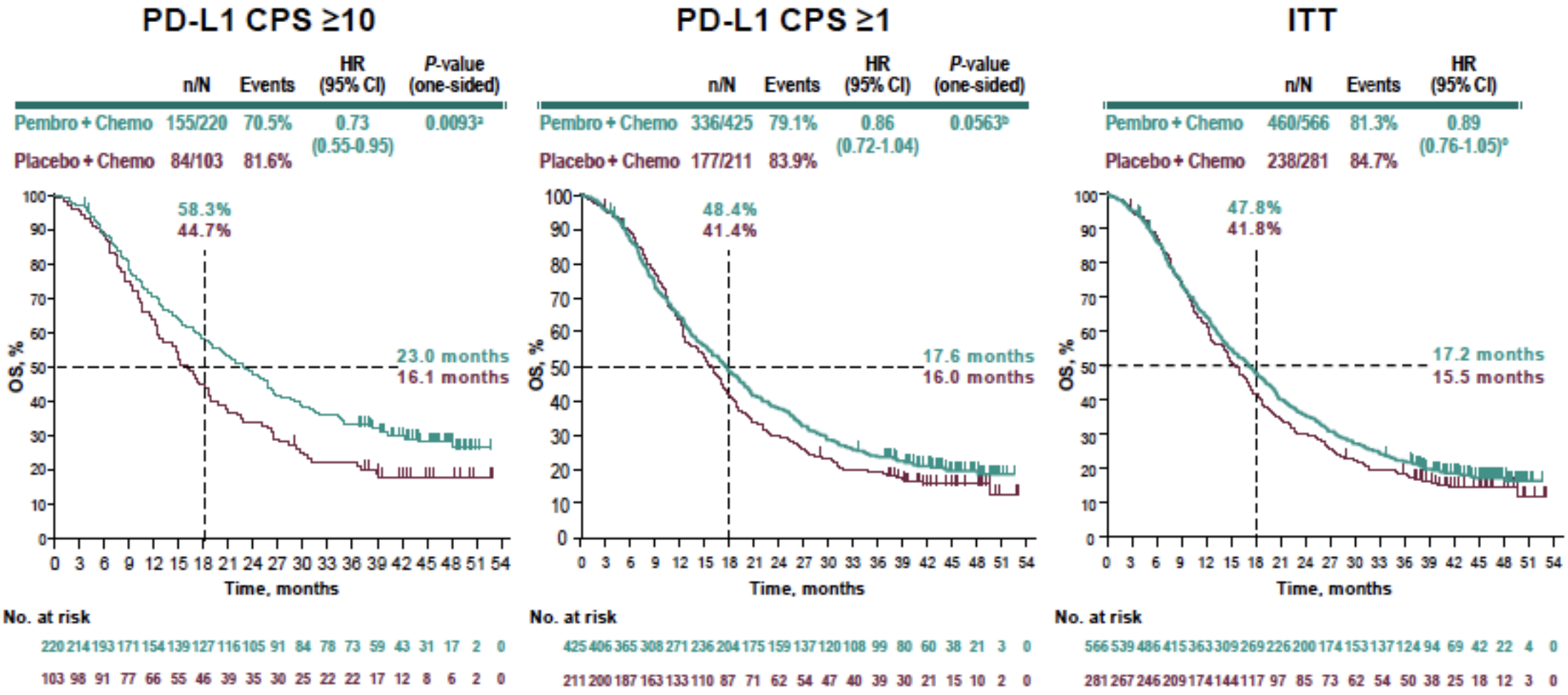
	n/N	Events	HR (95% CI)	P-value (one-sided)
Pembro + Chemo	136/220	61.8%	0.65 (0.49-0.86)	0.0012[a]
Placebo + Chemo	79/103	76.7%		

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

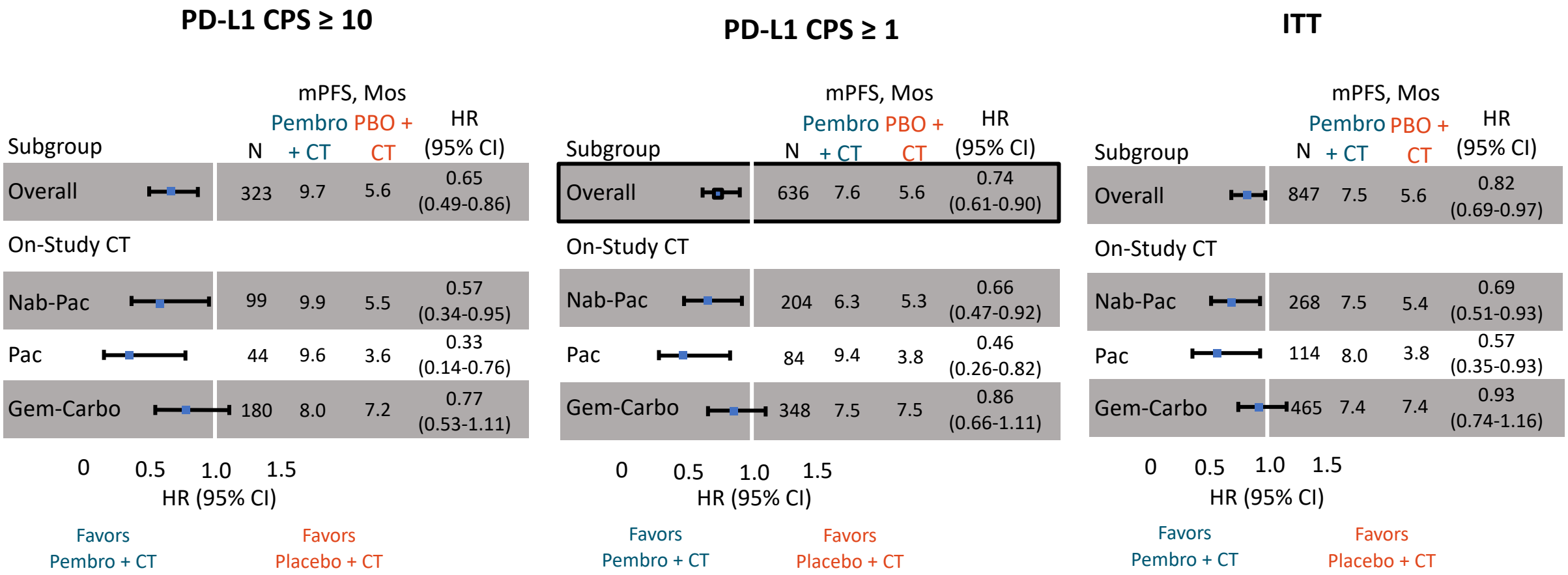
[a]Prespecified *P* value boundary of 0.00411 met.
Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff December 11, 2019.

Overall Survival at Final Analysis



[a]Prespecified *P*-value boundary of 0.0113 met. [b]Prespecified *P*-value boundary of 0.0172 not met. [c]Statistical significance not tested due to the prespecified hierarchical testing strategy. Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff: June 15, 2021.

KEYNOTE-355: PFS by Chemotherapy Regimen Across Subgroups

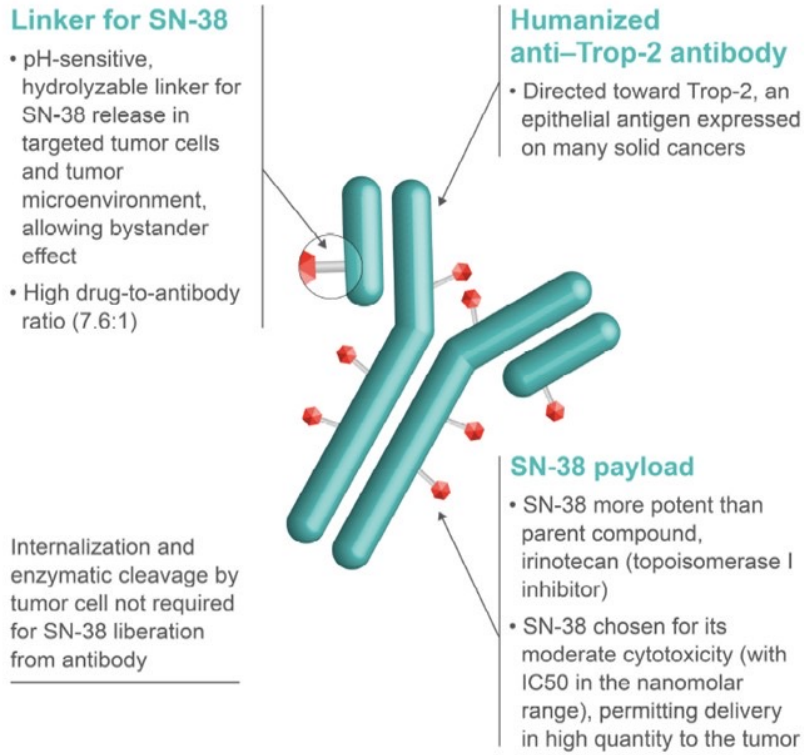


Hope Rugo. SABCS 2020. Abstr GS3-01..

Slide credit: clinicaloptions.com

SACITUZMAB GOVITECAN (SG)

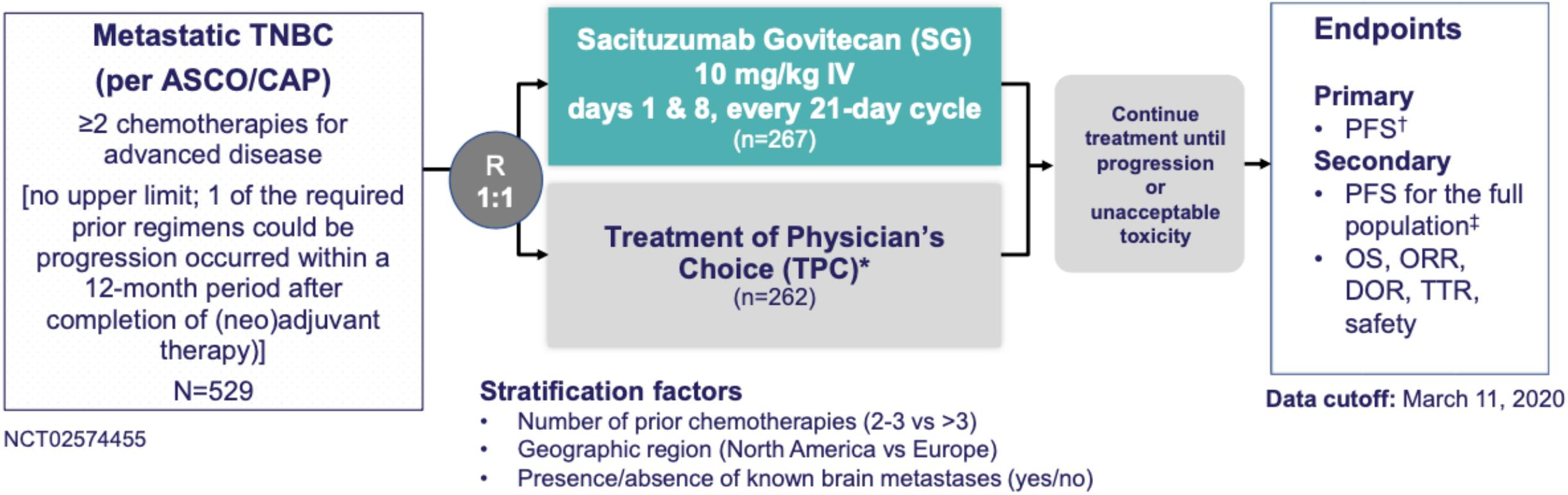
- Trop-2, a transmembrane calcium signal transducer linked to tumor progression and poor prognosis, is highly expressed in approximately 80% of breast cancers regardless of subtype[6,7]
- SG is approved for patients with mTNBC with ≥2 prior therapies (≥1 in the metastatic setting)[8,9]
- In the IMMU-132-01 phase 1/2 study, SG showed encouraging clinical activity in patients with previously treated metastatic HR+/HER2- breast cancer (N=54)[10]
  - ORR by investigator assessment: 31.5% (prior CDK4/6i use subgroup, 25%)
  - Median PFS by investigator assessment: 5.5 months (95% CI, 3.6-7.6)
  - Median OS: 12 months (95% CI, 9.0-18.2)
  - A manageable safety profile consistent with that in other studies of SG[11]



ADC, antibody-drug conjugate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; ORR, objective response rate; mTNBC, metastatic triple-negative breast cancer; OS, overall survival, PFS, progression-free survival.

1. Goldenberg DM, et al. *Expert Opin Biol Ther.* 2020;20:871-885. 2. Nagayama A, et al. *Ther Adv Med Oncol.* 2020;12:1758835920915980.3. Goldenberg DM, et al. *Oncotarget.* 2015;6:22496-224512. 4. Cardillo TM, et al. *Bioconjugate Chem.* 2015;26:919-931. 5. Govindan SV, et al. *Mol Cancer Ther.* 2013;12:968-978. 6. Ambrogi F, et al. *PLoS One.* 2014;9:e96993. 7. Trerotola M, et al. *Oncogene.* 2013;32(2):222-233. 8. TRODELVY™ (sacituzumab govitecan-hziy). Prescribing Information. Gilead Sciences, Inc.; April 2021. 9. European Medicines Agency:Trodelvy, INN-sacituzumab govitecan, https://www.ema.europa.eu/en/documents/product-information/trodelvy-epar-product-information_en.pdf, March 2022. 10. Kalinsky K, et al. *Ann Oncol. 2020*;31:1709-1718. 11. Bardia A, et al. *N Engl J Med.* 2021;384:1529-1541.

ASCENT: A Phase 3 Confirmatory Study of Sacituzumab Govitecan in Refractory/Relapsed mTNBC



NCT02574455

Stratification factors
- Number of prior chemotherapies (2-3 vs >3)
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

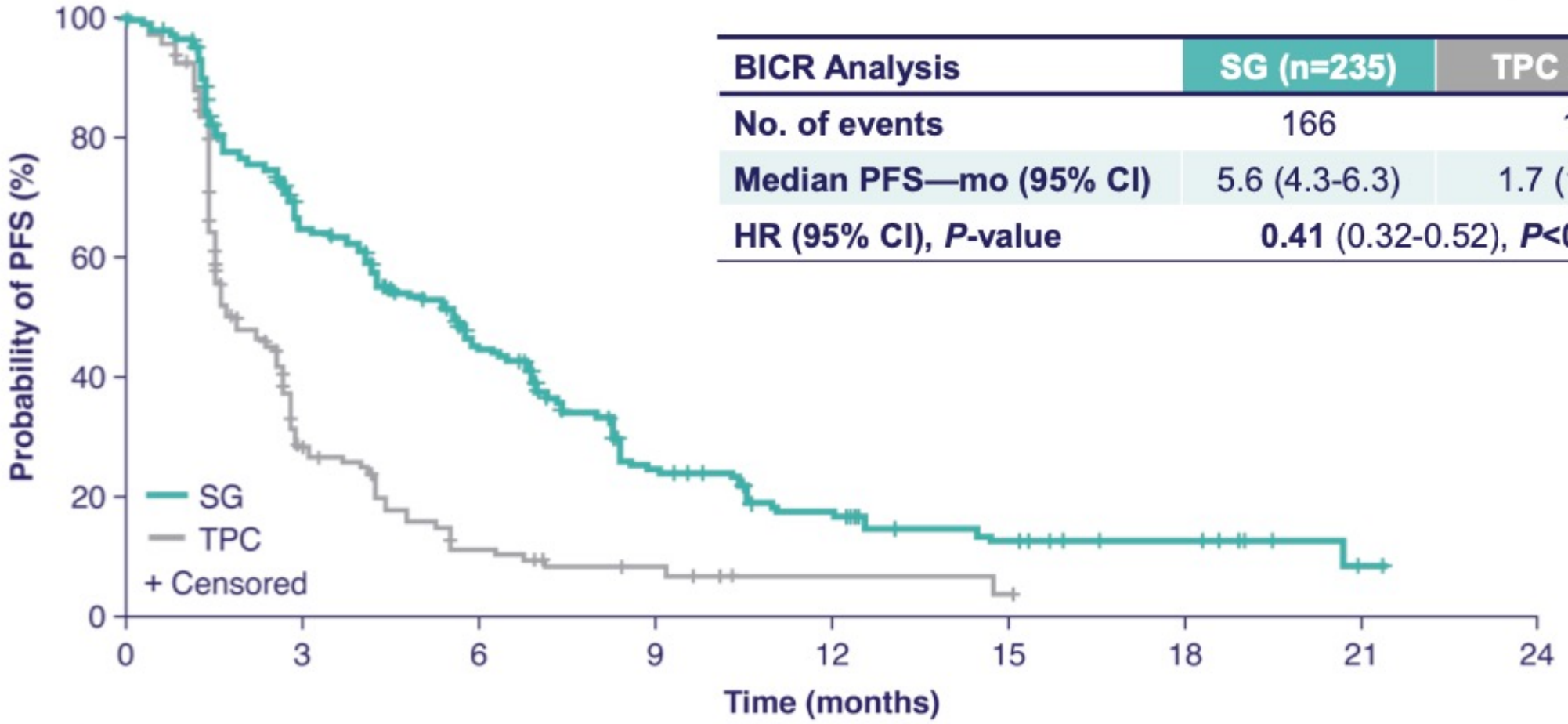
Data cutoff: March 11, 2020

ASCENT was halted early due to compelling evidence of efficacy per unanimous DSMC recommendation. Here, we report the primary results from ASCENT, including PFS and OS.

TPC arm (n)= eribulin (139), vinorelbine (52), gemcitabine (38), capecitabine (33)

Bardia NEJM 2021

Progression Free Survival (BICR Analysis)

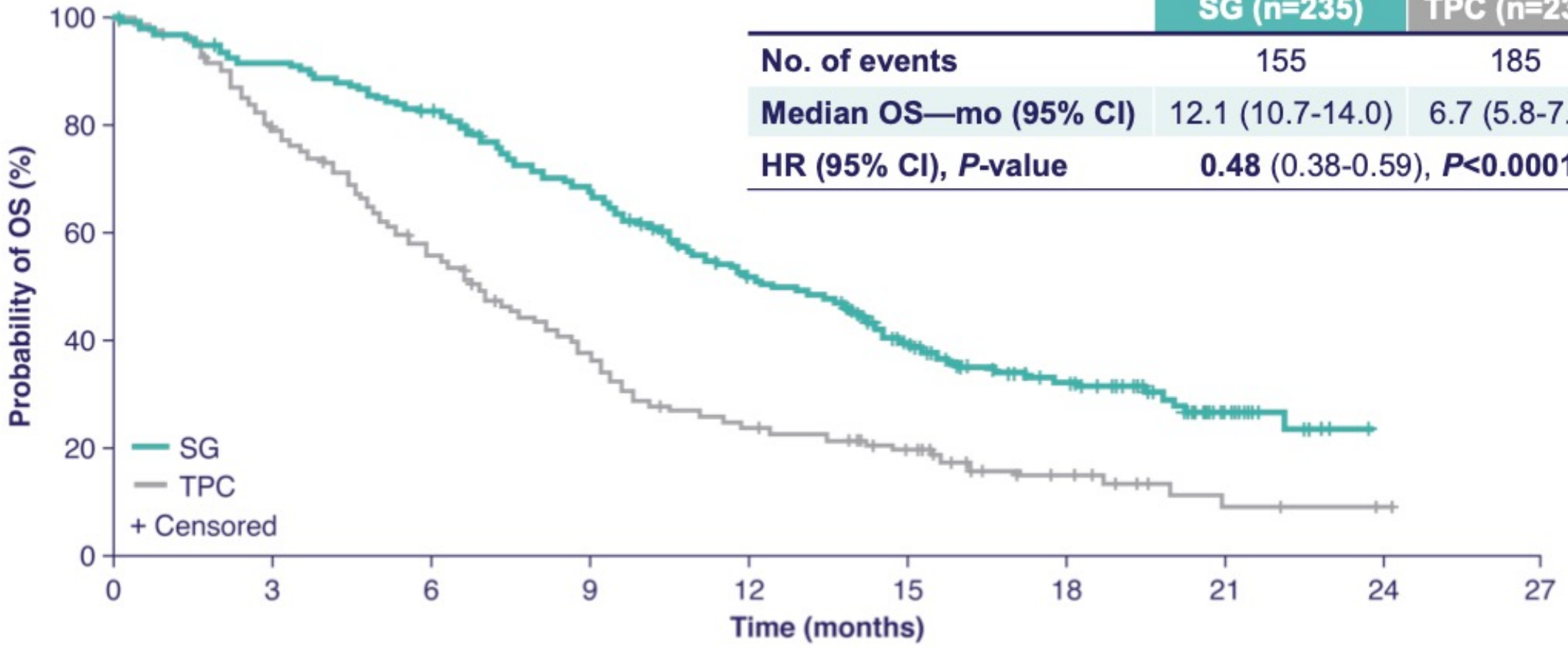


BICR Analysis	SG (n=235)	TPC (n=233)
No. of events	166	150
Median PFS—mo (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
HR (95% CI), *P*-value	**0.41** (0.32-0.52), ***P*<0.0001**	

Primary endpoint (PFS) assessed by independent central review in the brain metastases-negative population, as pre-defined in the study protocol.
Secondary endpoint (PFS) assessed in the full population (brain metastases-positive and -negative) and PFS benefit was consistent (HR=0.43 [0.35-0.54], *P*<0.0001).
BICR, blind independent central review; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Overall Survival

	SG (n=235)	TPC (n=233)
No. of events	155	185
Median OS—mo (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
HR (95% CI), *P*-value	**0.48** (0.38-0.59), ***P*<0.0001**	

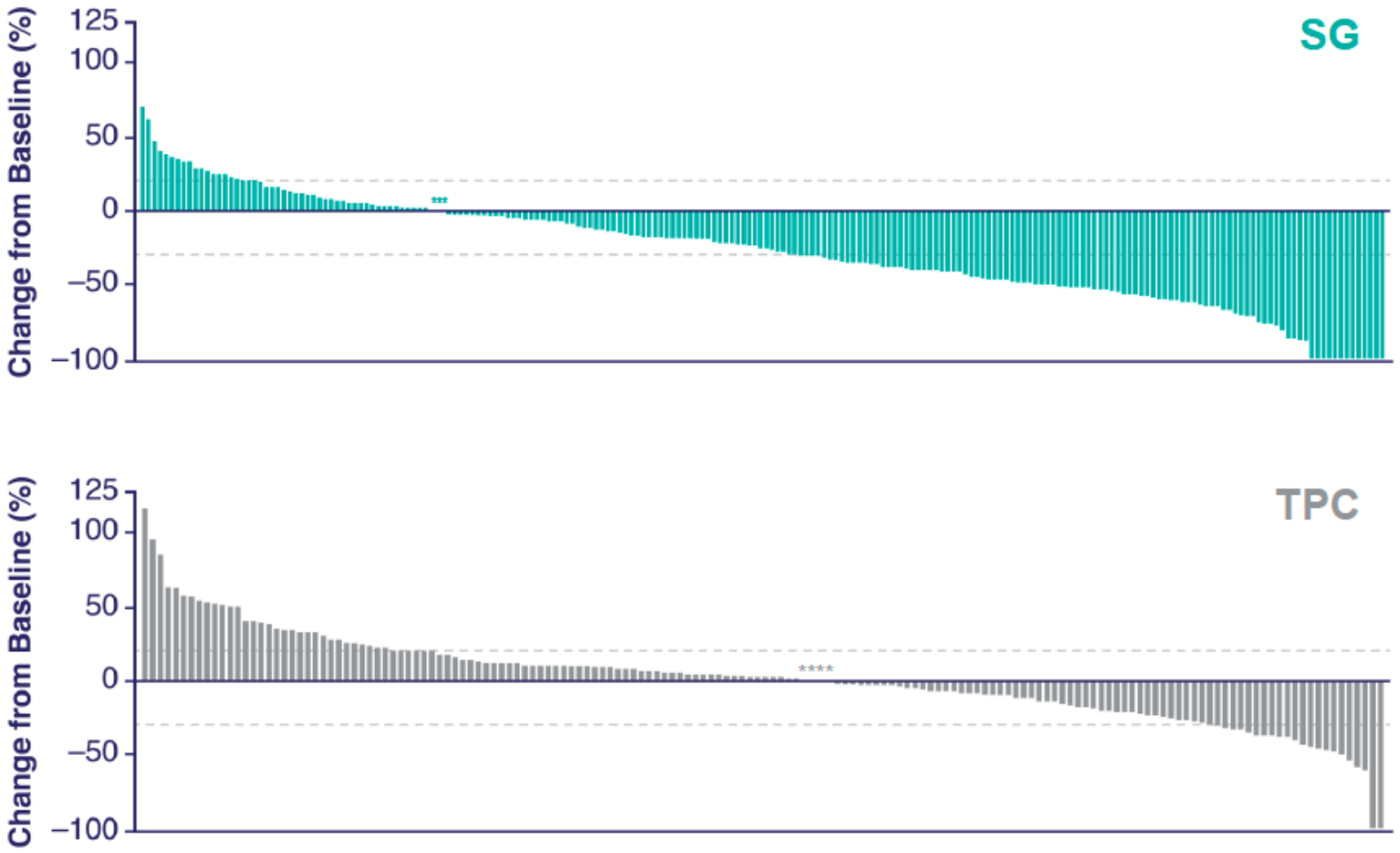


Number of patients at risk

SG	235	228	220	214	206	197	190	174	161	153	135	118	107	101	90	70	52	43	37	30	21	13	8	1	0	0
TPC	233	214	200	173	156	134	117	99	87	74	56	50	45	41	37	30	20	14	11	7	4	3	3	2	1	0

Assessed by independent central review in the brain metastases-negative population.
OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Overall Response and Best Percent Change From Baseline in Tumor Size

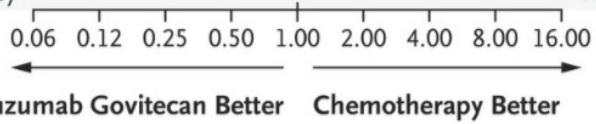


	SG (n=235)	TPC (n=233)
ORR—no. (%)	**82 (35)**	**11 (5)**
***P*-value**	**<0.0001**	
CR	10 (4)	2 (1)
PR	72 (31)	9 (4)
CBR—no. (%)	**105 (45)**	**20 (9)**
***P*-value**	**<0.0001**	
Median DOR —mo (95%CI)	**6.3 (5.5–9.0)**	**3.6 (2.8–NE)**
***P*-value**	**0.057**	

Assessed by independent central review in brain metastases-negative population.
*Denotes patients who had a 0% change from baseline in tumor size.
BICR, blind independent central review; CBR, clinical benefit rate (CR + PR + SD ≥6 mo); CR, complete response; DOR, duration of response; ORR, objective response rate; PR, partial response; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TTR, time to response.

Subgroup Analysis

Subgroup	No. of Patients	Progression-free Survival		Hazard Ratio for Disease Progression or Death (95% CI)
		Sacituzumab govitecan	Chemotherapy	
		mo (95% CI)		
All patients	468	5.6 (4.3–6.3)	1.7 (1.5–2.6)	0.41 (0.32–0.52)
Age				
<65 yr	378	4.6 (3.7–5.7)	1.7 (1.5–2.5)	0.46 (0.35–0.59)
≥65 yr	90	7.1 (5.8–8.9)	2.4 (1.4–2.9)	0.22 (0.12–0.40)
Race				
White	369	5.7 (4.3–6.8)	1.7 (1.5–2.6)	0.39 (0.30–0.51)
Black	56	5.4 (2.8–7.4)	2.2 (1.5–2.9)	0.45 (0.24–0.86)
Asian	18	NE (1.3–NE)	1.5 (1.2–NE)	0.40 (0.08–2.08)
Previous therapies				
2 or 3	330	5.8 (4.2–7.1)	1.6 (1.5–2.5)	0.39 (0.29–0.52)
>3	138	5.6 (3.0–6.5)	2.5 (1.5–2.8)	0.48 (0.32–0.72)
Geographic region				
North America	298	4.9 (4.0–6.3)	2.0 (1.5–2.6)	0.44 (0.33–0.60)
Rest of the world	170	5.9 (4.2–6.9)	1.6 (1.4–2.7)	0.36 (0.24–0.53)
Previous use of PD-1 or PD-L1 inhibitors				
Yes	127	4.2 (3.2–5.6)	1.6 (1.4–2.3)	0.37 (0.24–0.57)
No	341	6.2 (4.9–7.1)	2.1 (1.5–2.7)	0.42 (0.32–0.56)
Liver metastasis				
Yes	199	4.2 (2.8–5.8)	1.5 (1.4–2.4)	0.48 (0.34–0.67)
No	269	6.8 (4.6–8.0)	2.3 (1.6–2.7)	0.36 (0.26–0.50)
Initial diagnosis of TNBC				
Yes	322	5.7 (4.3–6.9)	1.6 (1.5–2.6)	0.38 (0.29–0.51)
No	146	4.6 (3.7–6.9)	2.3 (1.5–2.8)	0.48 (0.32–0.72)



Bardia, NEJM 2021

TRAEs (All Grade, >20%; Grade ¾, >5% of Patients)

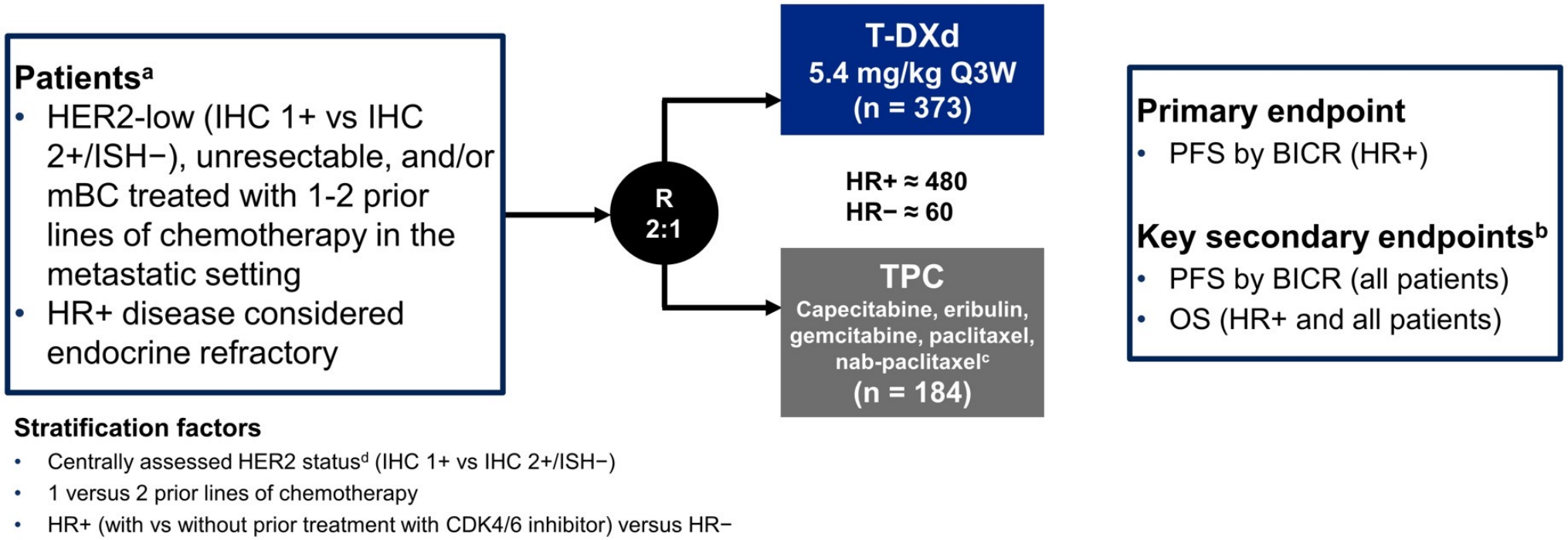
		SG (n=258)			TPC (n=224)		
	TRAE*	All grade %	Grade 3, %	Grade 4, %	All grade, %	Grade 3, %	Grade 4, %
Hematologic	**Neutropenia†**	**63**	**46**	**17**	**43**	**27**	**13**
	Anemia‡	**34**	**8**	**0**	**24**	**5**	**0**
	Leukopenia§	16	10	1	11	5	1
	Febrile neutropenia	6	5	1	2	2	<1
Gastrointestinal	**Diarrhea**	**59**	**10**	**0**	12	<1	0
	Nausea	**57**	**2**	**<1**	**26**	**<1**	**0**
	Vomiting	29	1	<1	10	<1	0
Other	**Fatigue**	**45**	**3**	**0**	**30**	**5**	**0**
	Alopecia	**46**	**0**	**0**	**16**	**0**	**0**

- Key grade ≥3 TRAEs (SG vs TPC): neutropenia (51% vs 33%), diarrhea (10% vs <1%), leukopenia (10% vs 5%), anemia (8% vs 5%), and febrile neutropenia (6% vs 2%)
  - G-CSF usage was 49% in the SG arm vs 23% in the TPC arm
  - Dose reductions due to TRAEs were similar (22% SG vs 26% TPC)
- No severe cardiovascular toxicity, no grade >2 neuropathy or grade >3 interstitial lung disease with SG
- No treatment-related deaths with SG; 1 treatment-related death (neutropenic sepsis) with TPC
- AEs leading to treatment discontinuation were low for SG and TPC: 4.7% and 5.4%
- Patients received a median of 7 treatment cycles of SG, with a median treatment duration of 4.4 months (range, 0.03-22.9)

*Patients may report more than 1 event per preferred term. AEs were classified according to the MedDRA systems of preferred terms and system organ class and according to severity by NCI CTCAE v4.03. †Combined preferred terms of 'neutropenia' and 'decreased neutrophil count'. ‡Combined preferred terms of 'anemia' and 'decreased hemoglobin'. §Combined preferred terms of 'leukopenia' and 'decreased white blood cell count'.
G-CSF, granulocyte-colony stimulating factor; SG, sacituzumab govitecan; TPC, treatment of physician's choice; TRAE, treatment-related AE.

DESTINY-BREAST04: FIRST RANDOMIZED PHASE 3 STUDY OF T-DXd FOR HER2-LOW mBC

An open-label, multicenter study (NCT03734029)



Stratification factors

- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.

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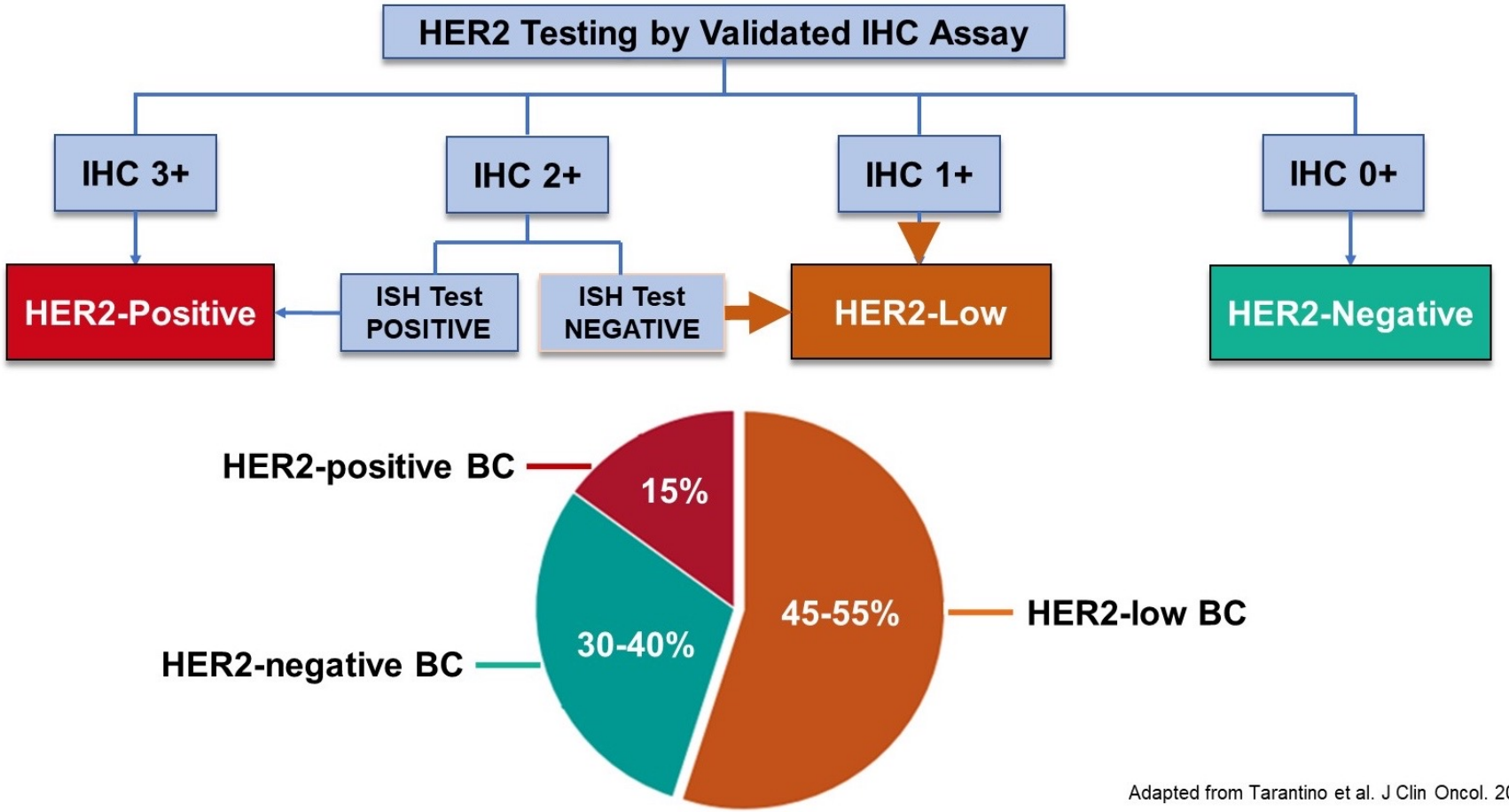
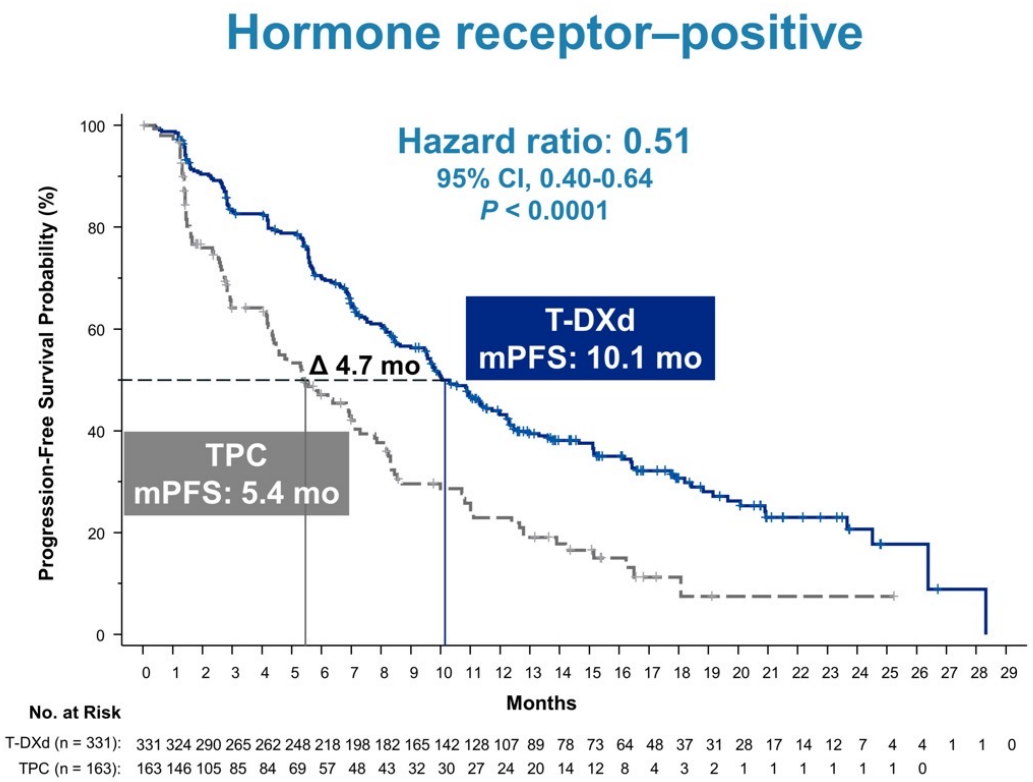
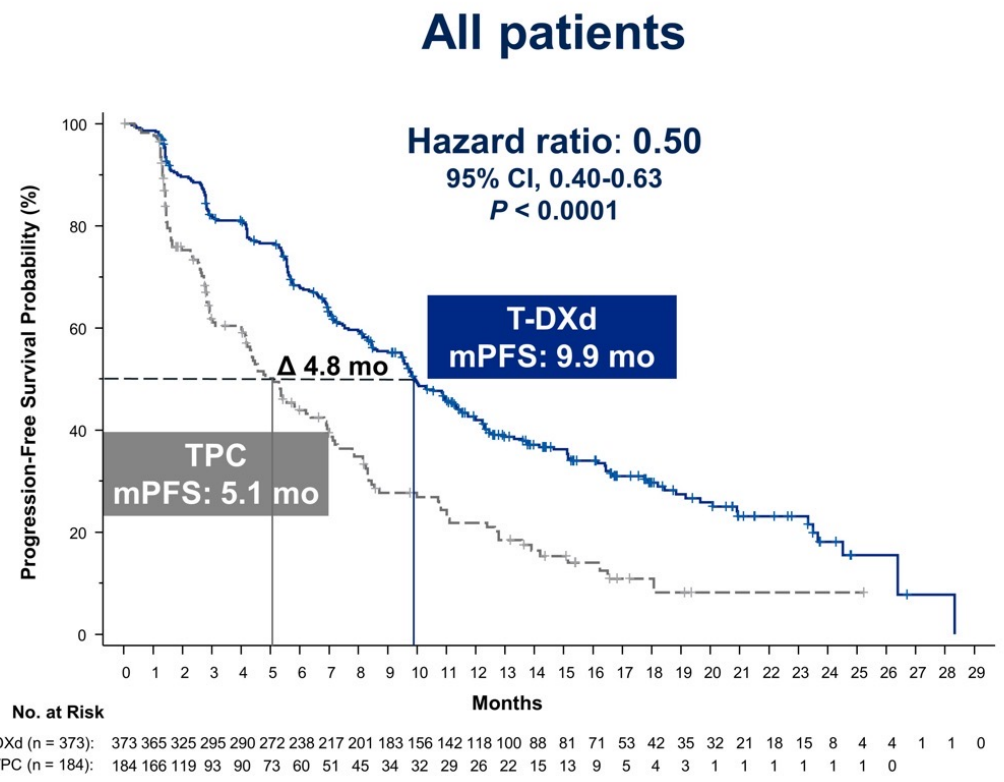
PROPOSAL OF AN ALGORITHM FOR DEFINING HER2-LOW BC



LoRusso, P ASCO 2022

PFS IN HR+ AND ALL PATIENTS





PFS by blinded independent central review.
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

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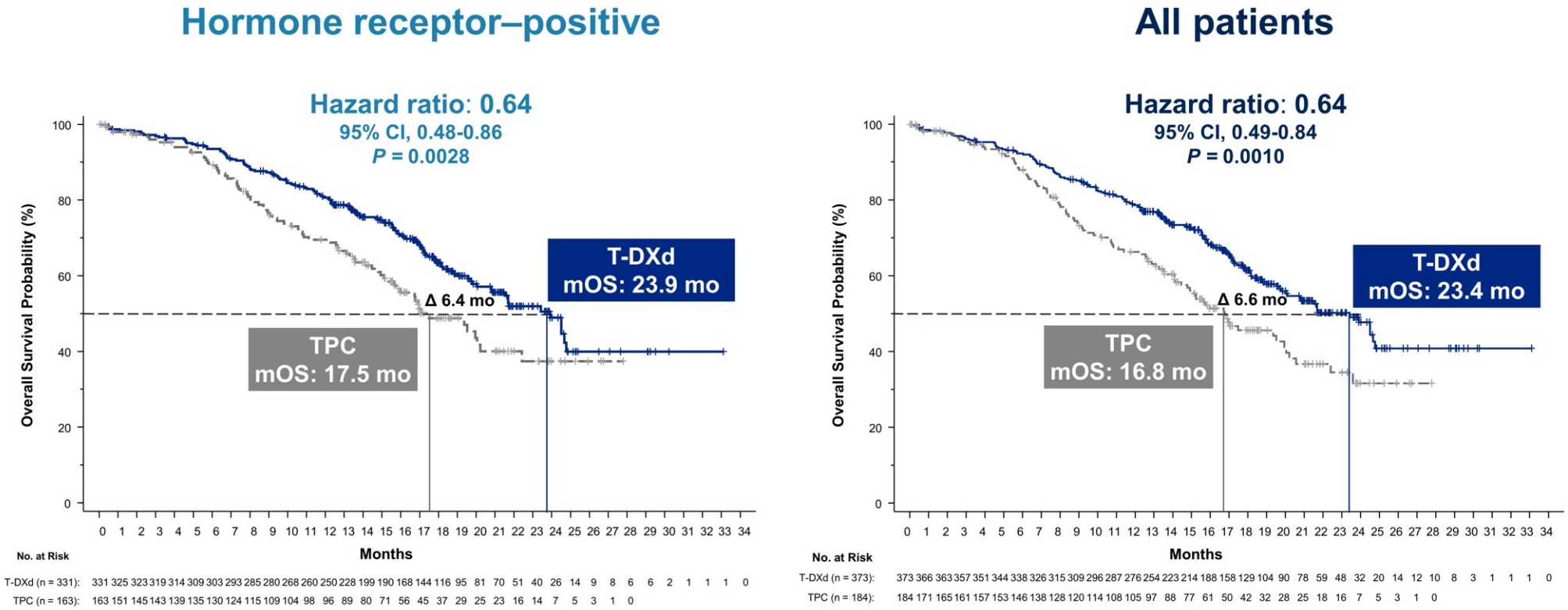
OS IN HR+ AND ALL PATIENTS



HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

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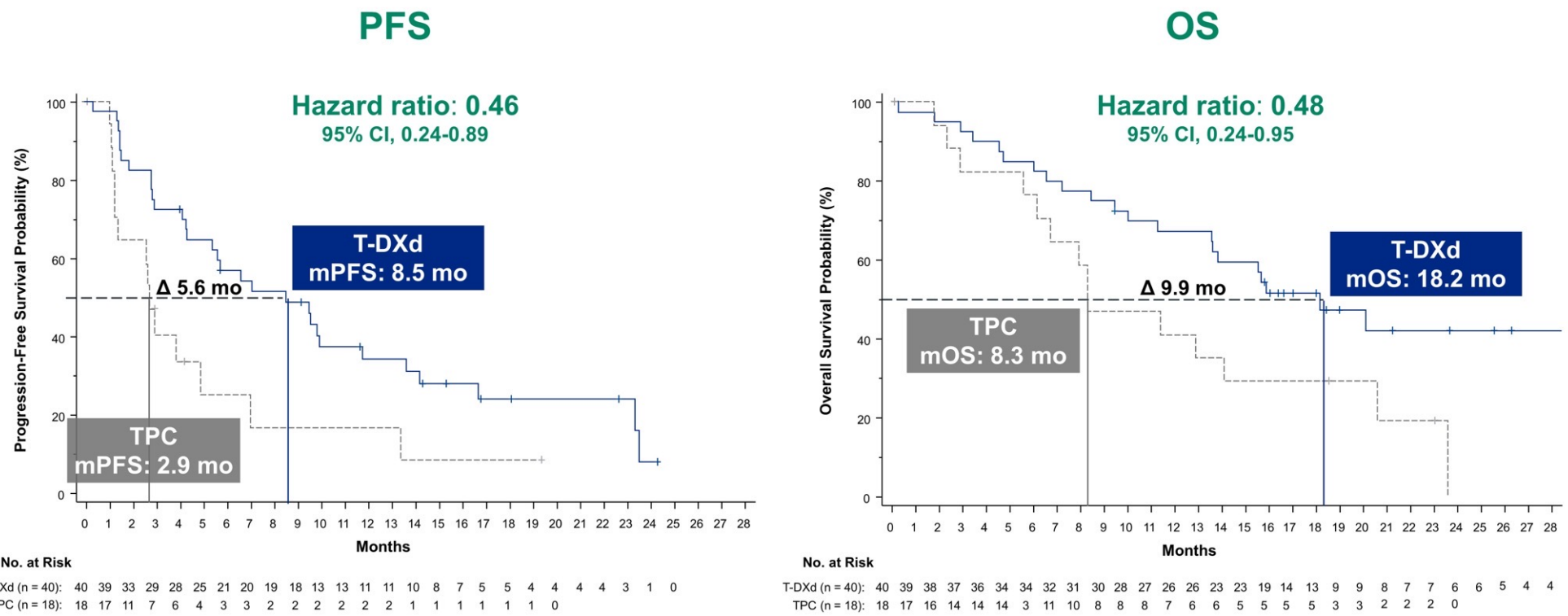
PFS AND OS IN HR– (EXPLORATORY ENDPOINTS)



HR, hormone receptor; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
For efficacy in the hormone receptor–negative cohort, hormone receptor status is based on data from the electronic data capture corrected for misstratification.

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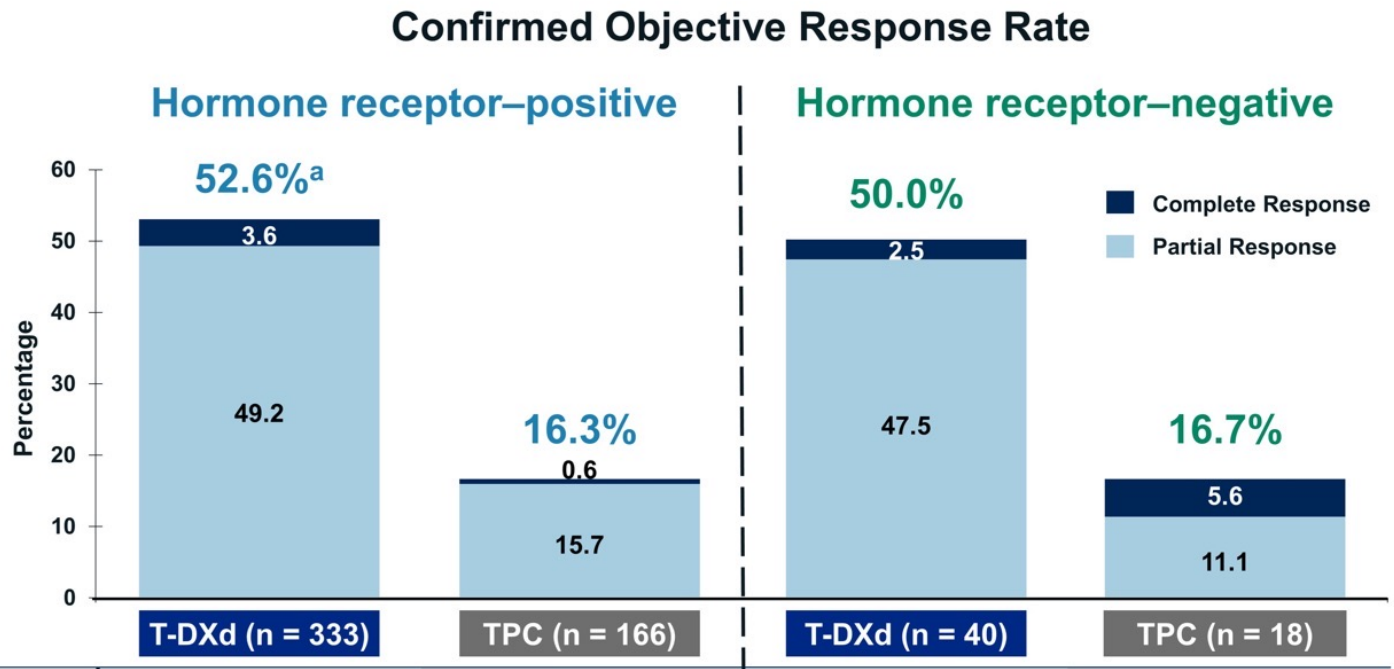
CONFIRMED ORR



	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

Hormone receptor status is based on data from the electronic data capture corrected for misstratification.
ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]The response of 1 patient was not confirmed. [b]Clinical benefit rate is defined as the sum of complete response rate, partial response rate, and more than 6 months' stable disease rate, based on blinded independent central review.

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ANTITUMOR ACTIVITY AND SAFETY OF TRASTUZUMAB DERUXTECAN IN PATIENTS WITH HER2-LOW–EXPRESSING ADVANCED BREAST CANCER: RESULTS FROM A PHASE IB STUDY

mPFS-11 mos

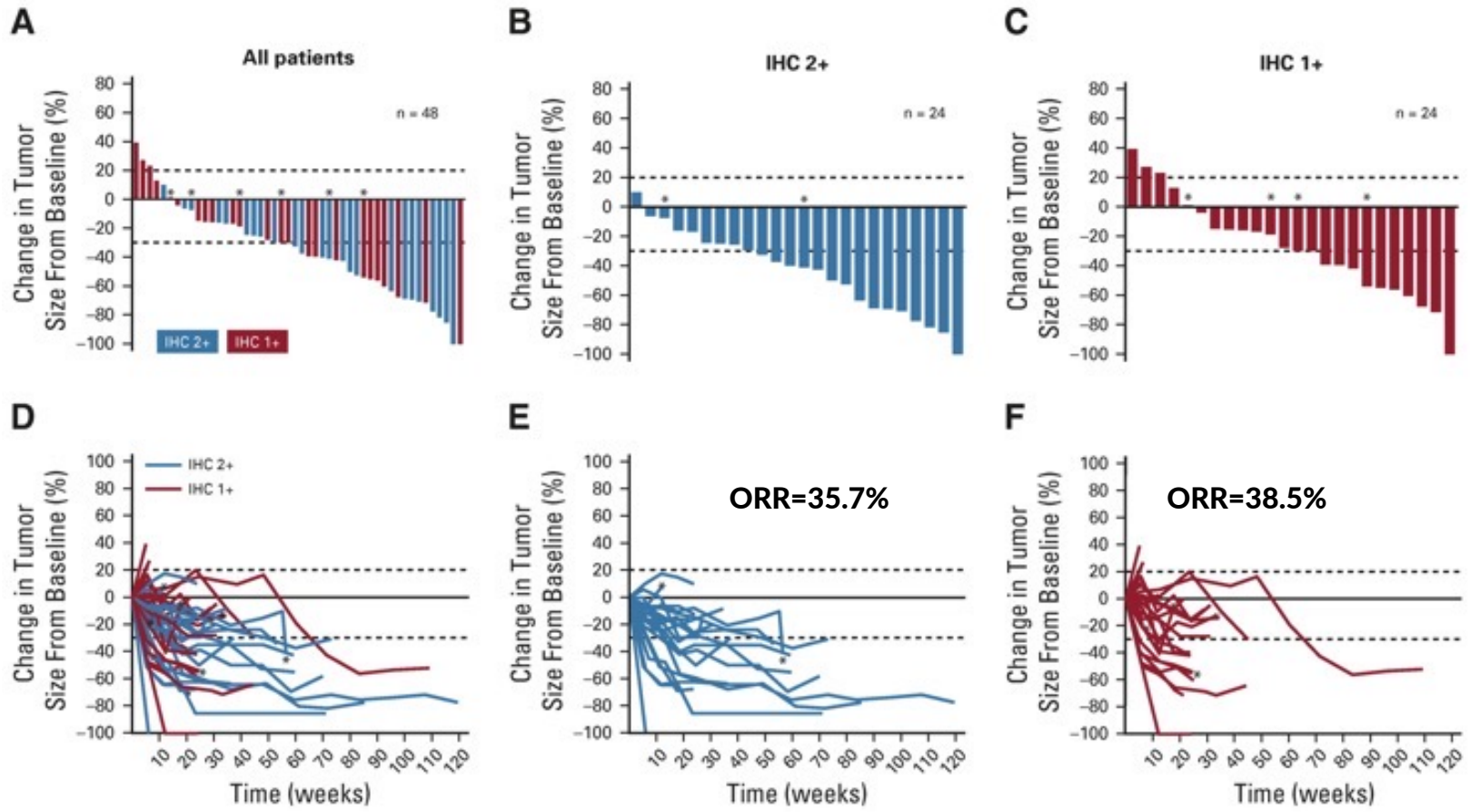

FIG 1. Best percent change in tumor size and percent change in tumor size, respectively, over time for individual patients in (A, D) the entire human epidermal growth factor receptor 2 (HER2)-low population, (B, E) the HER2 immunihistochemistry (IHC) 2+ group, and (C, F) the HER2 IHC 1+ group. Data cutoff was February 1, 2019. Dotted lines denote 30% decrease and 20% increase in tumor size cutoffs for partial response and progressive disease, respectively. Tumor responses shown are per independent central review. The IHC status subgroups represent the IHC status as determined by local assessment. (*) HR negative. HR, hormone receptor.

Shanu Modi; Haeseong Park; Rashmi K. Murthy; Hiroji Iwata; Kenji Tamura; Junji Tsurutani; Alvaro Moreno-Aspitia; Toshihiko Doi; Yasuaki Sagara; Charles Redfern; Ian E. Krop; Caleb Lee; Yoshihiko Fujisaki; Masahiro Sugihara; Lin Zhang; Javad Shahidi; Shunji Takahashi; Journal of Clinical Oncology 2020 381887-1896.

ADVERSE EVENTS OF SPECIAL INTEREST

Adjudicated as drug-related ILD/pneumonitis[a]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 371)	13 (3.5)	24 (6.5)	5 (1.3)	0	3 (0.8)	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)

Left ventricular dysfunction[b]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
Ejection fraction decreased						
T-DXd (n = 371)	1 (0.3)	14 (3.8)	1 (0.3)	0	0	16 (4.3)
TPC (n = 172)	0	0	0	0	0	0
Cardiac failure[c]						
T-DXd (n = 371)	0	1 (0.3)	1 (0.3)	0	0	2 (0.5)
TPC (n = 172)	0	0	0	0	0	0

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Median time to onset of ILD/pneumonitis for patients with T-DXd was 129.0 days (range, 26-710). [b]Left ventricular dysfunction was reported in a total of 17 (4.6%) patients in the T-DXd arm. One patient initially experienced ejection fraction decrease, then later developed cardiac failure. [c]Both patients with cardiac failure were reported to have recovered.

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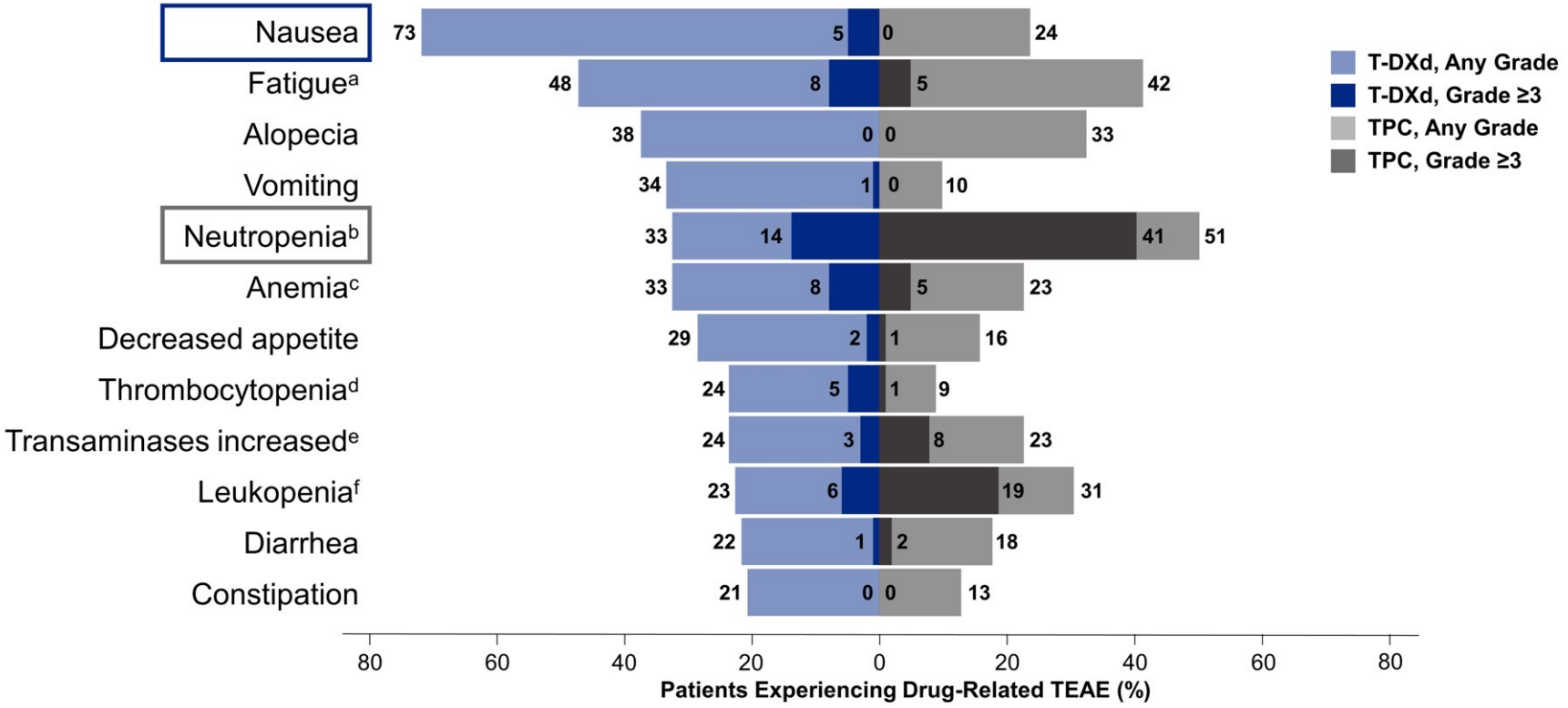
DRUG-RELATED TEAEs IN ≥20% OF PATIENTS



T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms neutrophil count decreased and neutropenia. [c]This category includes the preferred terms hemoglobin decreased, red-cell count decreased, anemia, and hematocrit decreased. [d]This category includes the preferred terms platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal. [f]This category includes the preferred terms white-cell count decreased and leukopenia.

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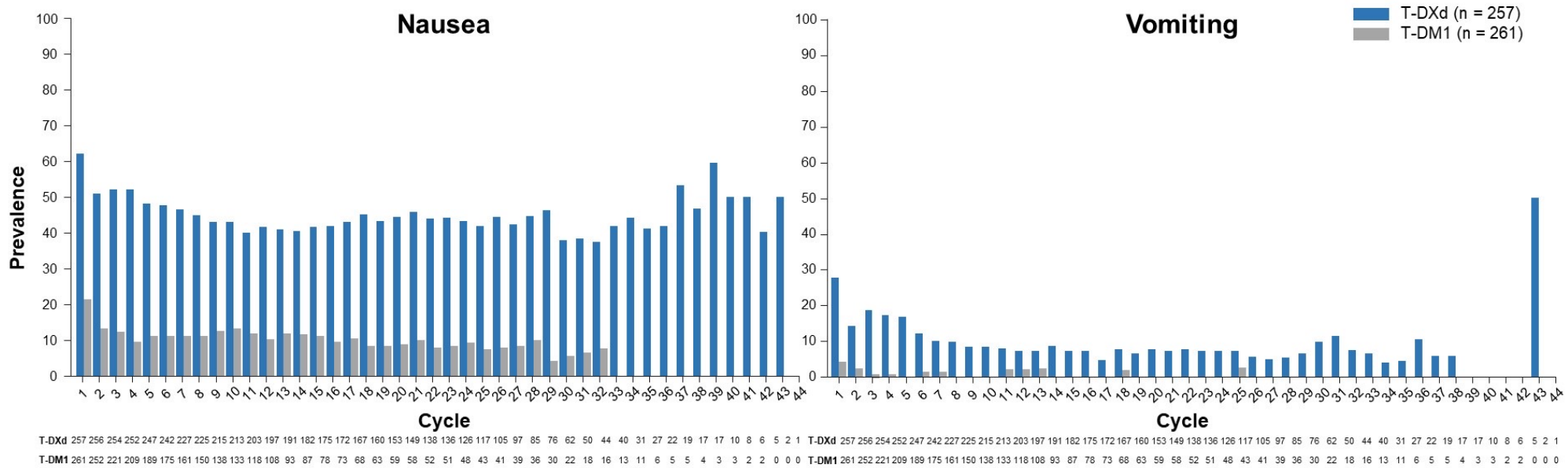
PREVALENCE OF NAUSEA AND VOMITING: DB03



- The prevalence of nausea and vomiting was higher with T-DXd than with T-DM1 and was relatively consistent over time
- Majority of events with T-DXd were grade 1 and 2 and resolved, and one patient discontinued study drug due to vomiting
  - Antiemetic prophylaxis recommendations were updated during the study based on emerging data supporting the moderately emetogenic potential of T-DXd[1,2]

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Prevalence was defined as the number of patients who had the event starting at a particular cycle or still ongoing at that cycle divided by the number of patients on treatment at that cycle.
1. Hesketh PJ et al. *J Clin Oncol.* 2020;38(24):2782-2797. 2. Modi S et al. *N Engl J Med.* 2020;382:610-621.

Summary Current Therapy mTNBC

First-line MBC

Comprehensive profiling

- **Pembrolizumab + chemo if PDL1+**
- **Olaparib/Talazoparib if BRCA + and PDL1 –**
- **Chemotherapy (taxane, xeloda, gem/carbo) if BRCA/PDL1-**
- **Clinical trial**
- **Sacituzumab-** pt progressed within 6 months of [AC-TC]P

Second-line MBC

- **Olaparib/Talazoparib if BRCA+ and PDL1 (+ or -)**
- **Sacituzumab**
- **Chemotherapy (taxane, xeloda, gem/carbo)**
- **Clinical trial**

Third-line and beyond MBC

- **Sacituzumab (if not in 2nd line)**
- **Chemotherapy**
- **TDxD- if prior sacituzumab**
- **Clinical trial**

- *NTRK Fusion:* larotrectinib or entrectinib
- *MSI-H/dMMR*: pembrolizumab or dostarlimab-gxly
- *TMB-H:* pembrolizumab
- *Somatic gBRCA 1/2 or PAPLB-2 Mutation* olaparib or talazoparib

- **Comfort measures**

Consider repeat molecular profile through liquid ctDNA on progression
Or repeat biopsy for HER2 expression testing in pt who are HER2 0

Thank You

- The West Cancer Center and Research Institute