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How I treat mTNBC

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Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update

TABLE 2. Additional Recommended Reporting Comments for Specific Scenarios

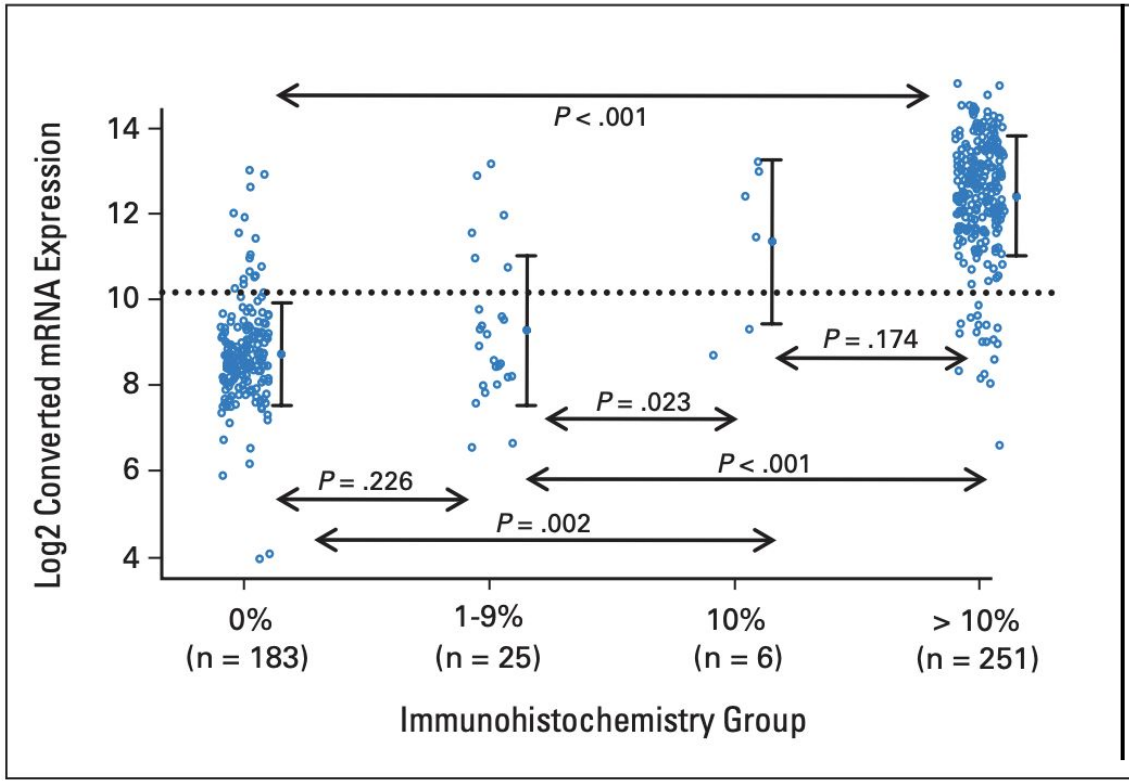
Result	Additional Recommended Comment
1%-10% cells staining	The cancer in this sample has a low level (1%-10%) of ER expression by IHC. There are limited data on the overall benefit of endocrine therapies for patients with low level (1%-10%) ER expression, but they currently suggest possible benefit, so patients are considered eligible for endocrine treatment. There are data that suggest invasive cancers with these results are heterogeneous in both behavior and biology and often have gene expression profiles more similar to ER-negative cancers.
No internal controls and ER is 0%-10%	No internal controls are present, but external controls are appropriately positive. If needed, testing another specimen that contains internal controls may be warranted for confirmation of ER status.

Abbreviations: ER, estrogen receptor; IHC, immunohistochemistry.

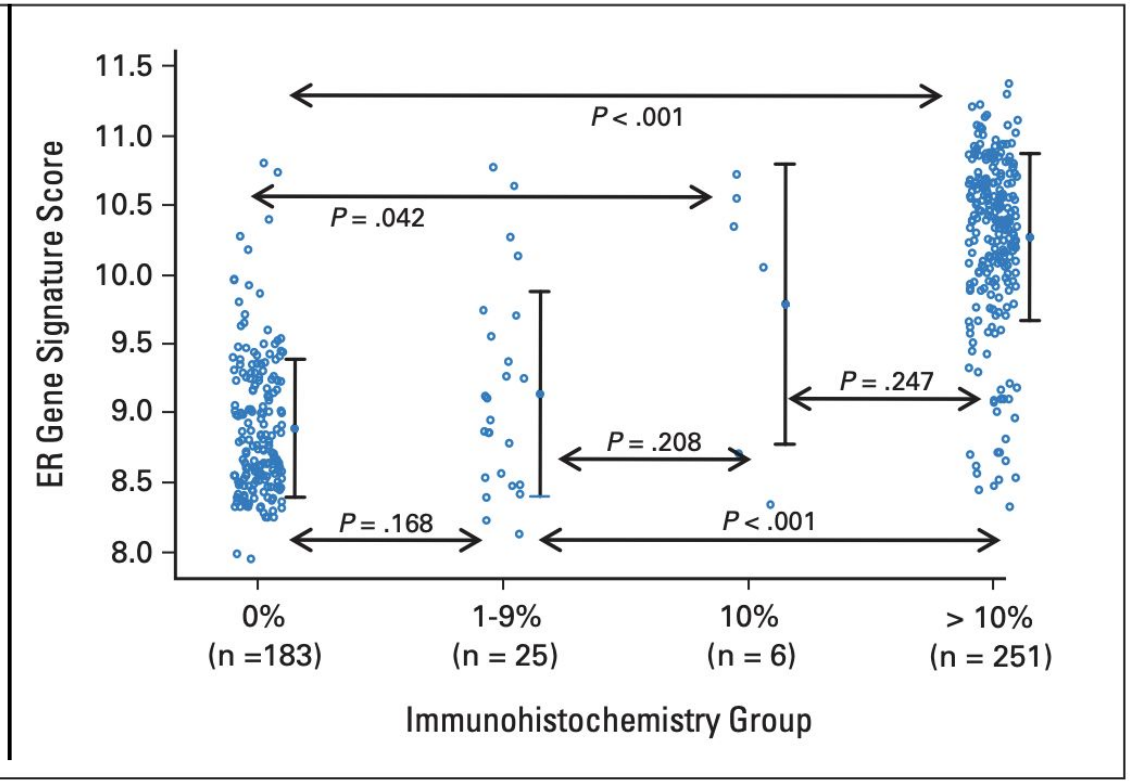
Allison et al., JCO 2020

Gene Expression comparison by ER IHC stain

ESR1-mRNA

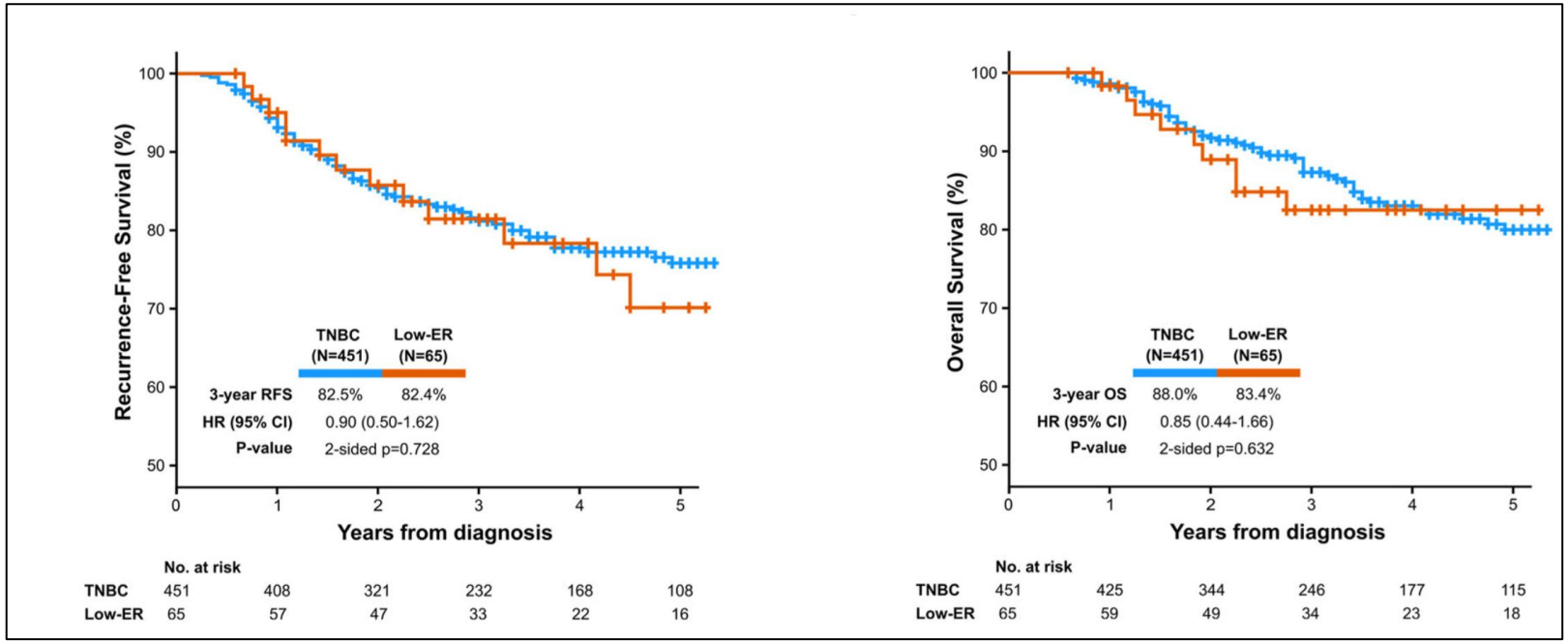


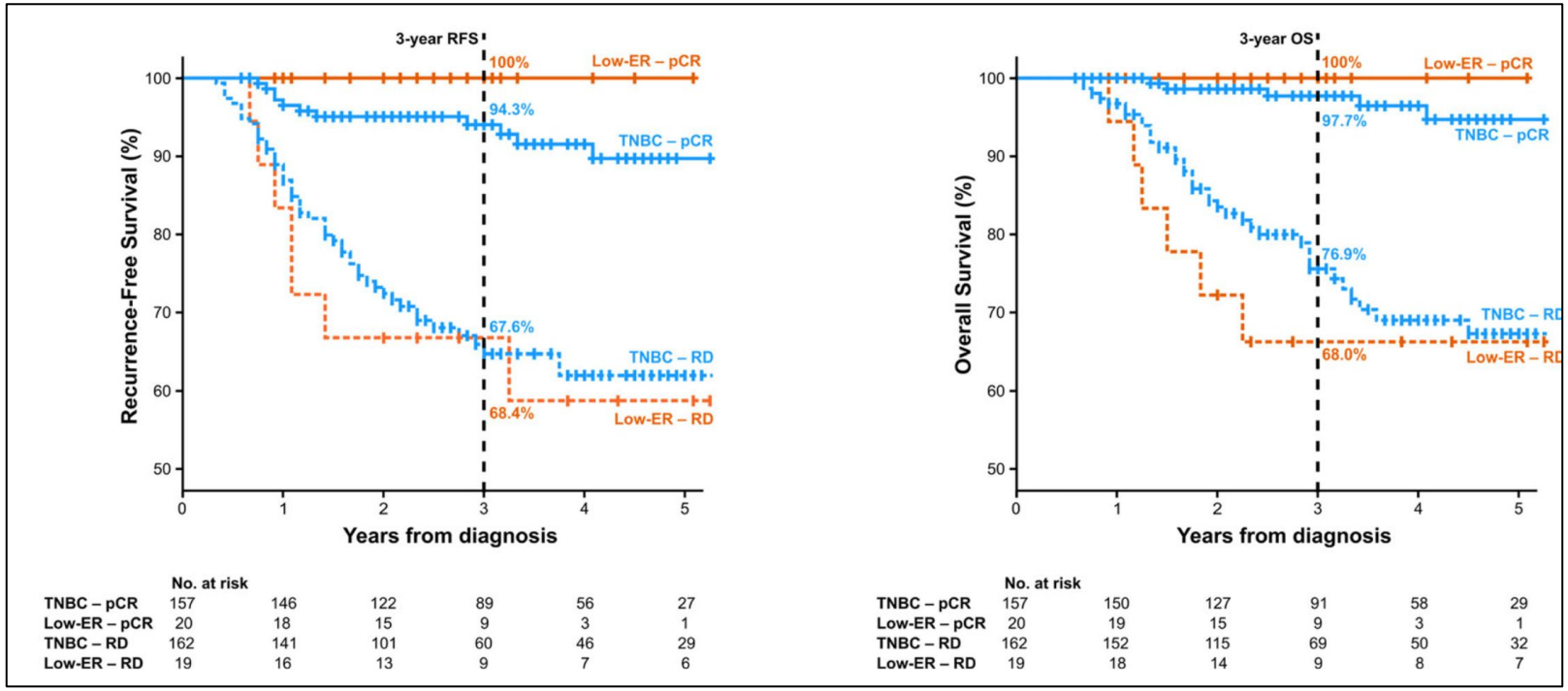
ER associated Genes



Iwamoto, Pustzai et al JCO 2012

TNBC vs ER-LOW Outcomes





Yoder, Sharma et al NPJ Breast Cancer 2022

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

R 2:1

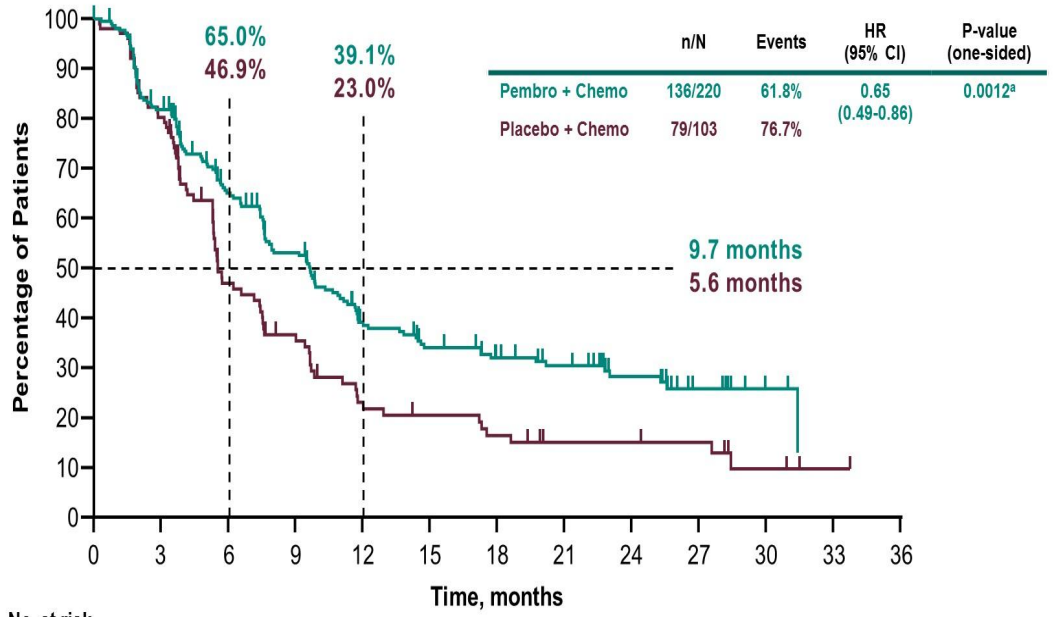
- Pembrolizumab[b] + Chemotherapy[c]
- Placebo[d] + Chemotherapy[c]

→ Progressive disease[e]/cessation of study therapy

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).

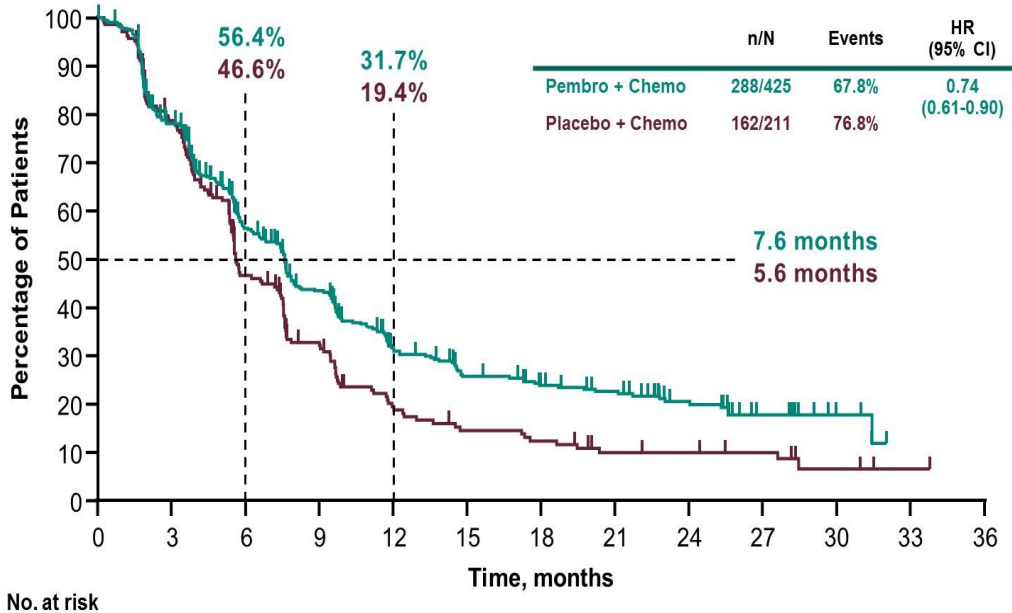
Progression-Free Survival: PD-L1 CPS ≥10



	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%		

[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.

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%		

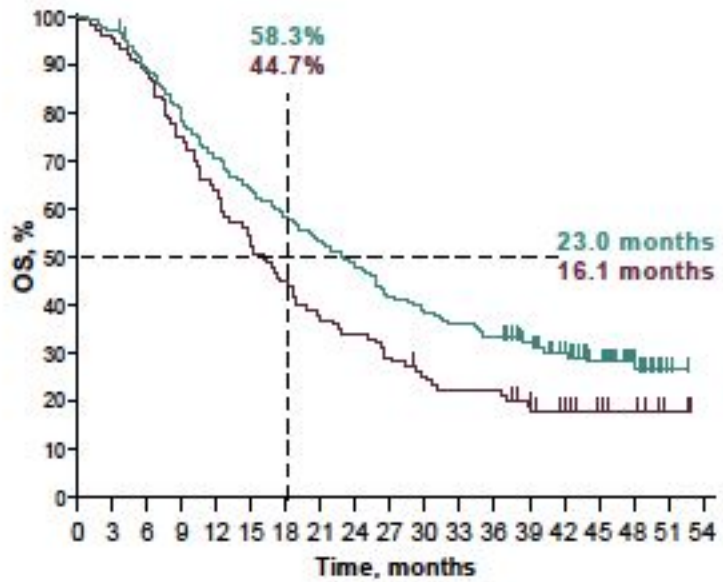
[a]Prespecified *P* value boundary of 0.00111 not met.
Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff December 11, 2019.

San Antonio Breast Cancer Symposium®, December 7-10, 2021

Overall Survival at Final Analysis

PD-L1 CPS ≥10

	n/N	Events	HR (95% CI)	*P*-value (one-sided)
Pembro + Chemo	155/220	70.5%	0.73 (0.55-0.95)	0.0093[a]
Placebo + Chemo	84/103	81.6%		

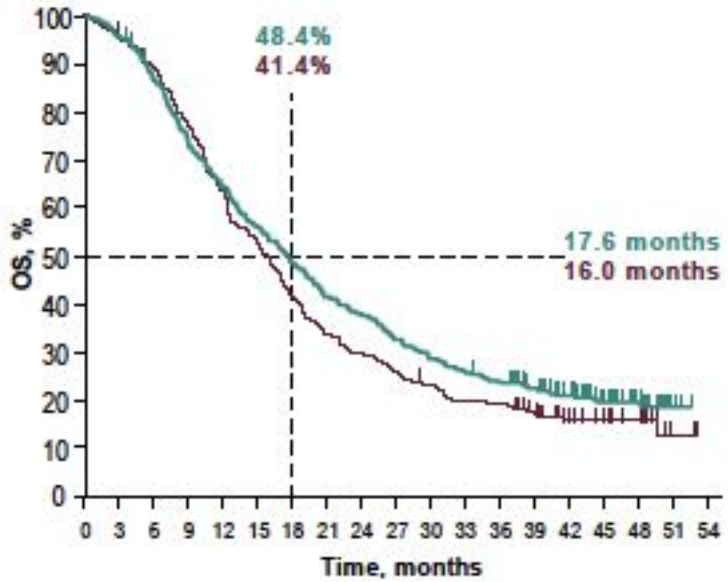


No. at risk

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

PD-L1 CPS ≥1

	n/N	Events	HR (95% CI)	*P*-value (one-sided)
Pembro + Chemo	336/425	79.1%	0.86 (0.72-1.04)	0.0563[b]
Placebo + Chemo	177/211	83.9%		

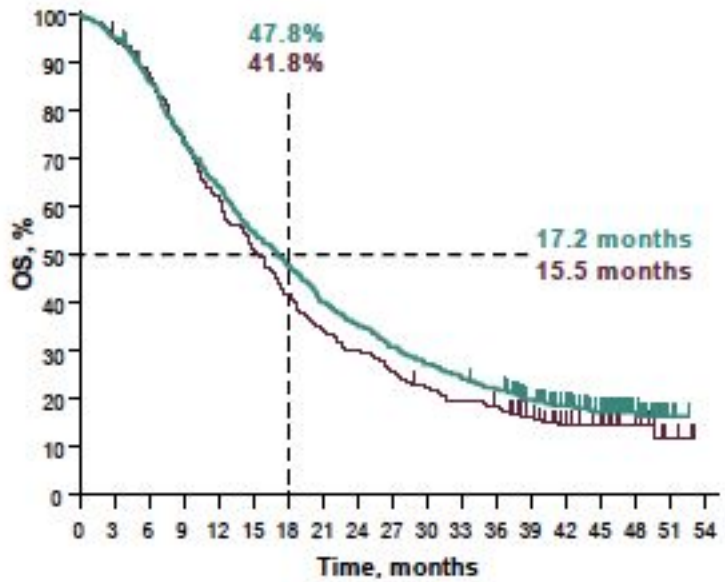


No. at risk

425	406	365	308	271	236	204	175	159	137	120	108	99	80	60	38	21	3	0
211	200	187	163	133	110	87	71	62	54	47	40	39	30	21	15	10	2	0

ITT

	n/N	Events	HR (95% CI)
Pembro + Chemo	460/566	81.3%	0.89 (0.76-1.05)[c]
Placebo + Chemo	238/281	84.7%	



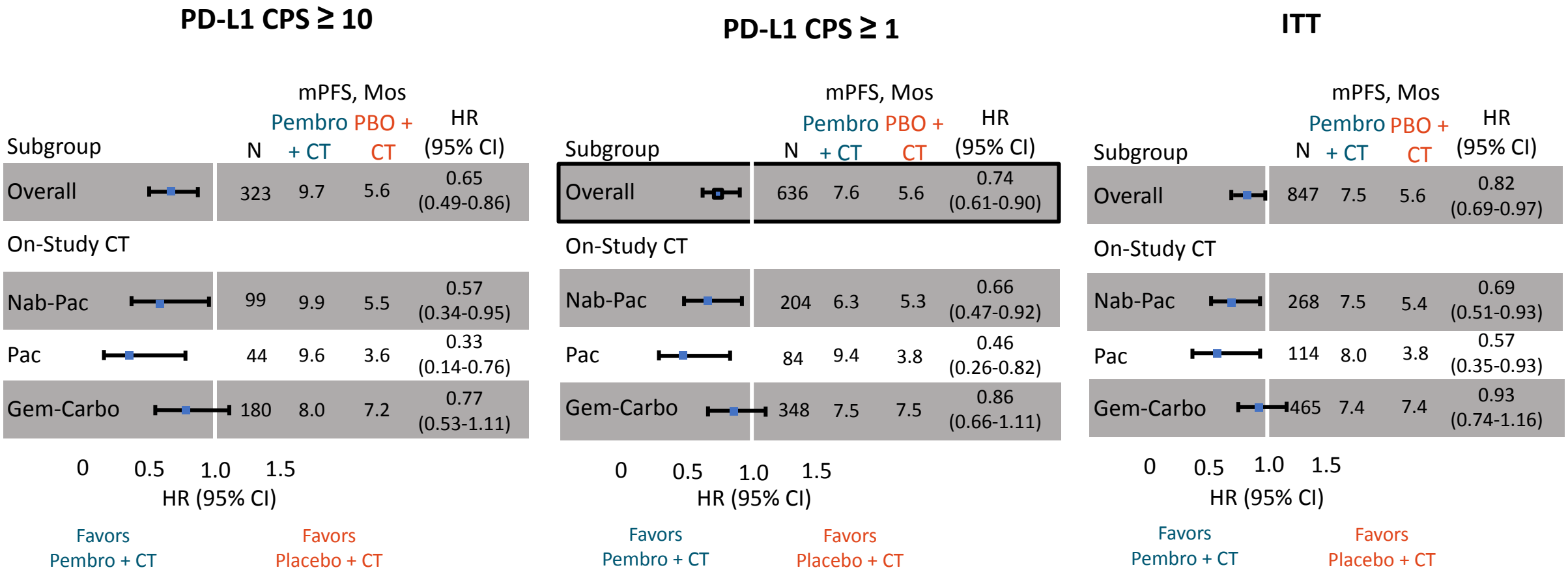
No. at risk

566	539	486	415	363	309	269	226	200	174	153	137	124	94	69	42	22	4	0
281	267	246	209	174	144	117	97	85	73	62	54	50	38	25	18	12	3	0

[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.

Javier Cortes, MD

KEYNOTE-355: PFS by Chemotherapy Regimen Across Subgroups



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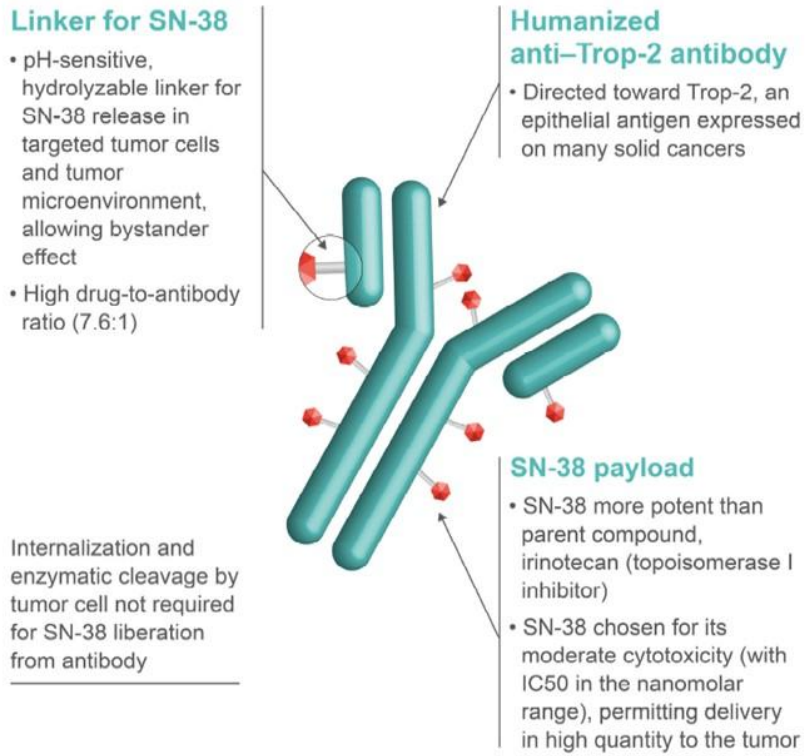
Slide credit: clinicaloptions.com

SACITUZMAB GOVITECAN (SG)

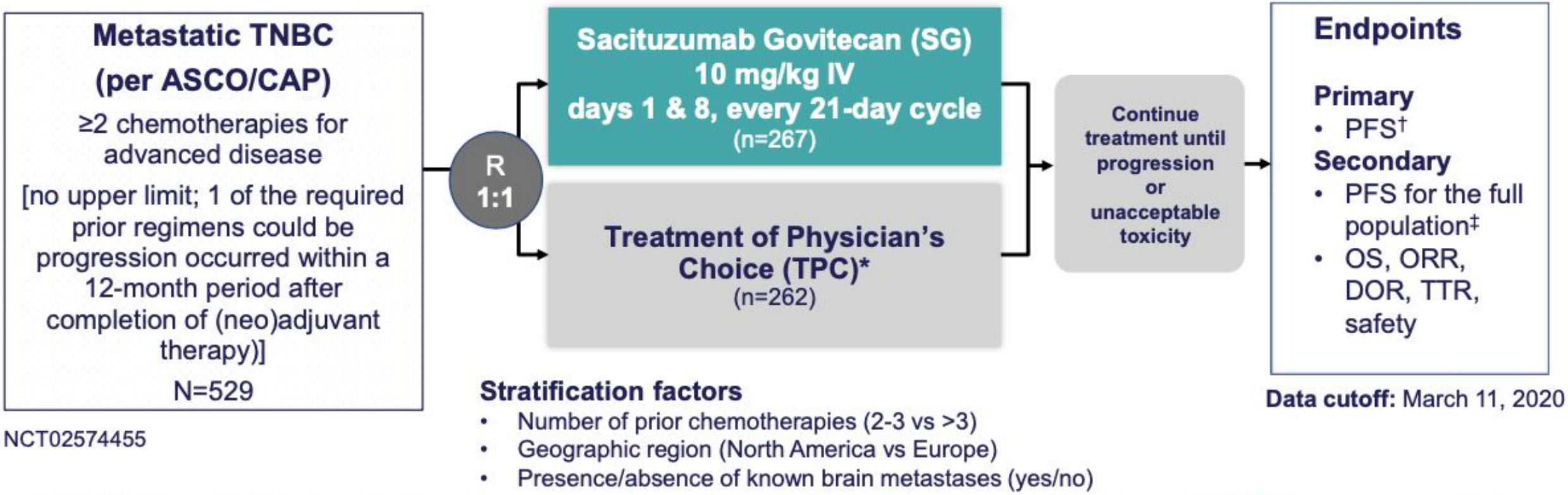
- Trop-2, a transmembrane calcium signal transducer linked to tumor progression and poor prognosis, is highly expressed in approximately 80% of breast cancers regardless of subtype[6,7]
- SG is approved for patients with mTNBC with ≥2 prior therapies (≥1 in the metastatic setting)[8,9]
- In the IMMU-132-01 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)

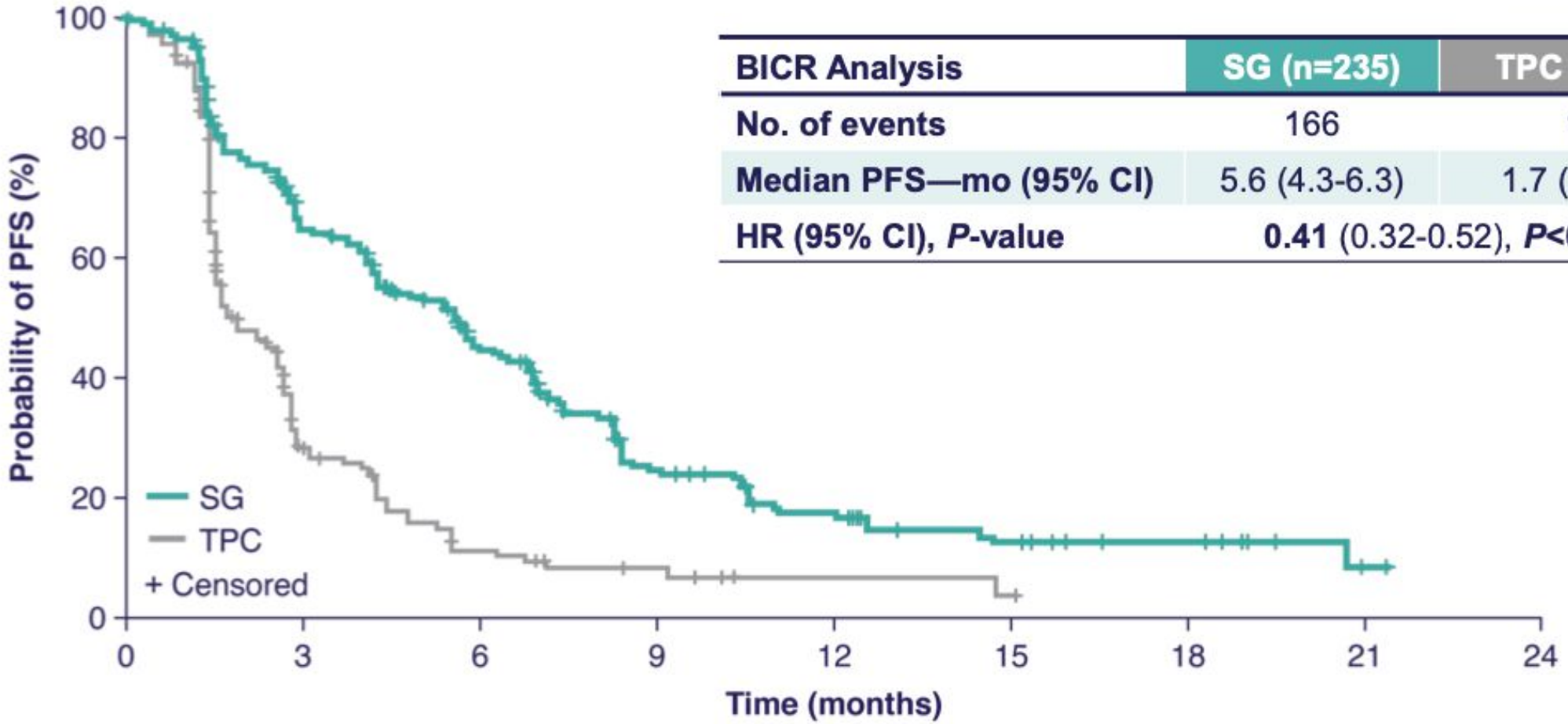
Data cutoff: March 11, 2020

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**	

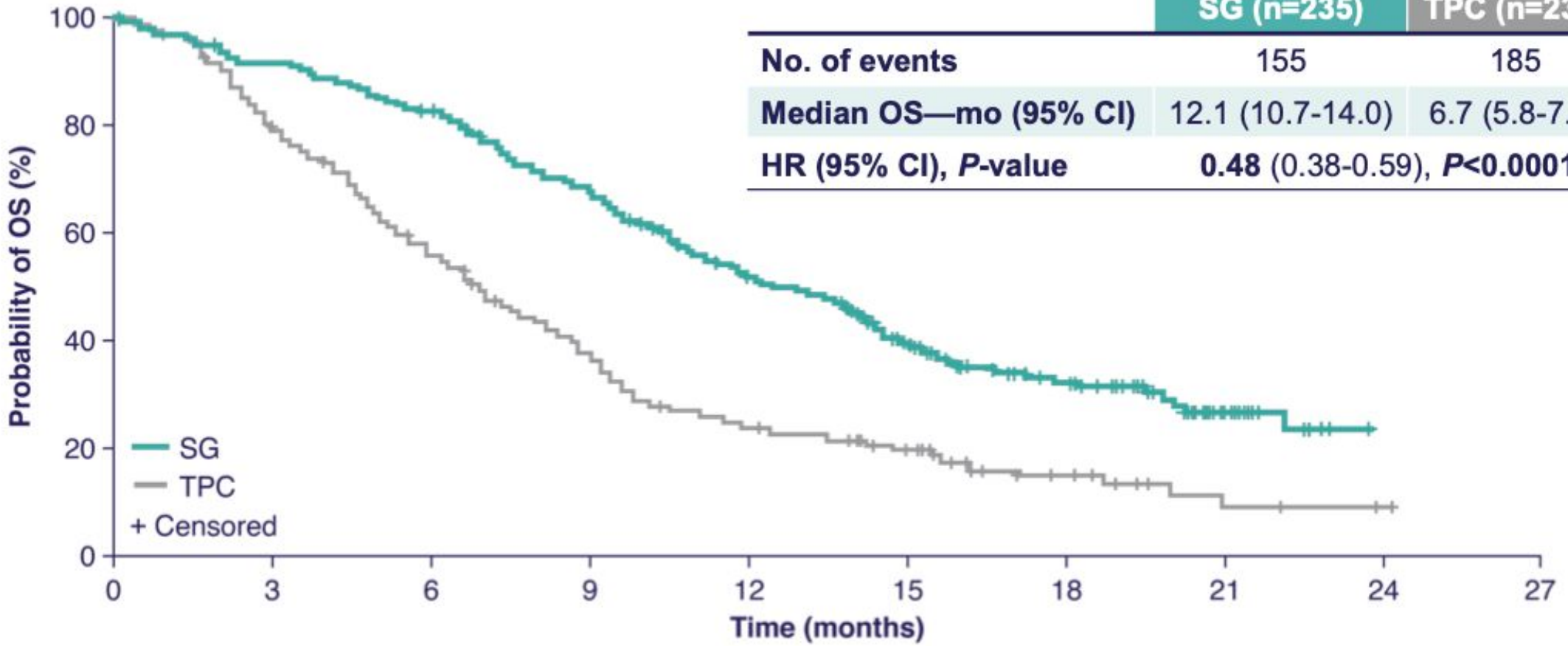
Number of patients at risk

SG	235	222	166	134	127	104	81	63	54	37	33	24	22	16	15	13	9	8	8	5	3	1	0
TPC	233	179	78	35	32	19	12	9	7	6	4	2	2	2	2	1	0	0	0	0	0	0	0

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**	

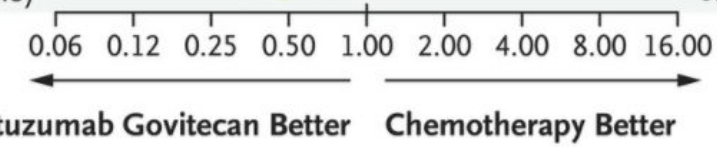


Number of patients at risk

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

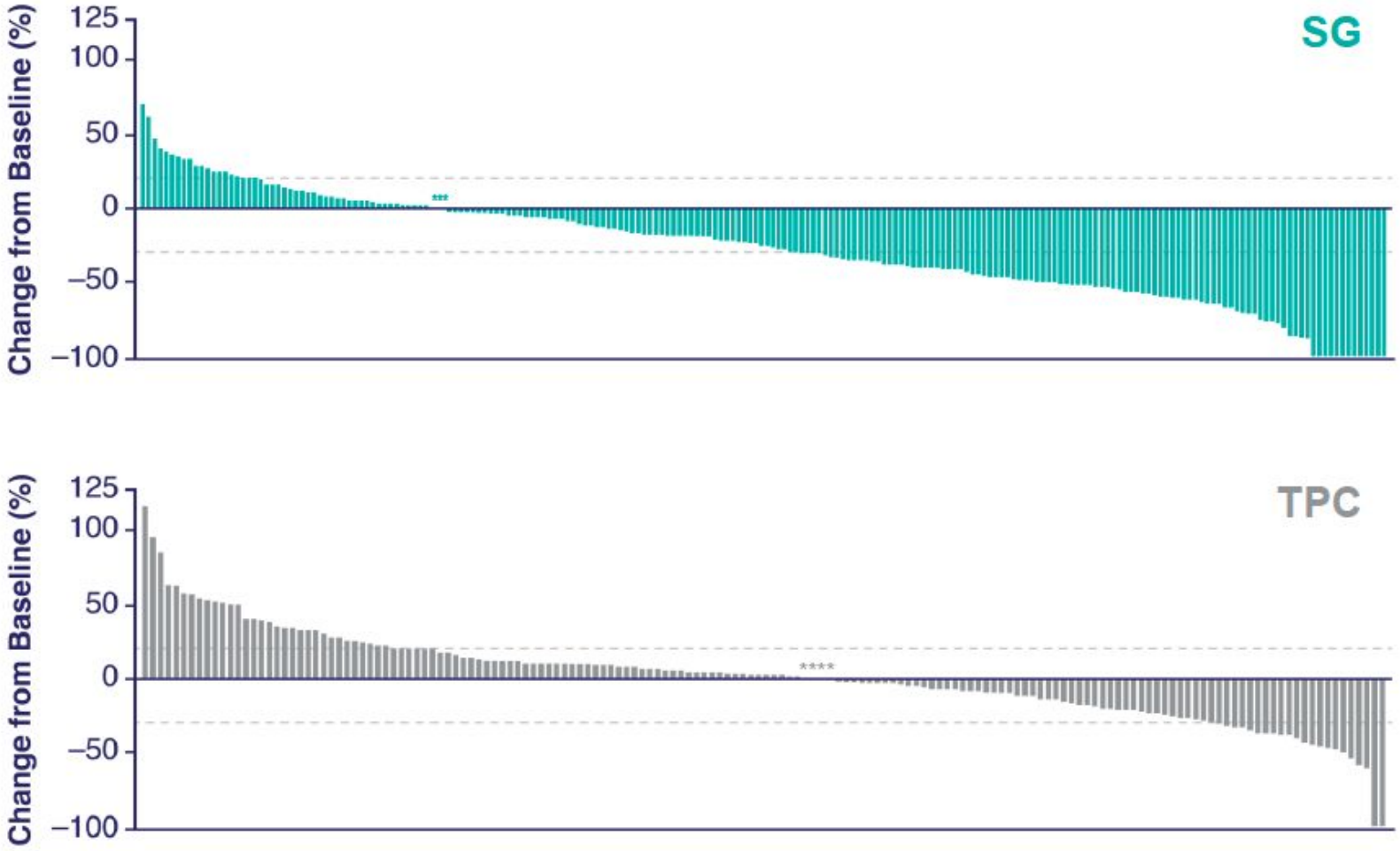
Assessed by independent central review in the brain metastases-negative population.
OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

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

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.

TRAEs (All Grade, >20%; Grade 3/4, >5% of Patients)

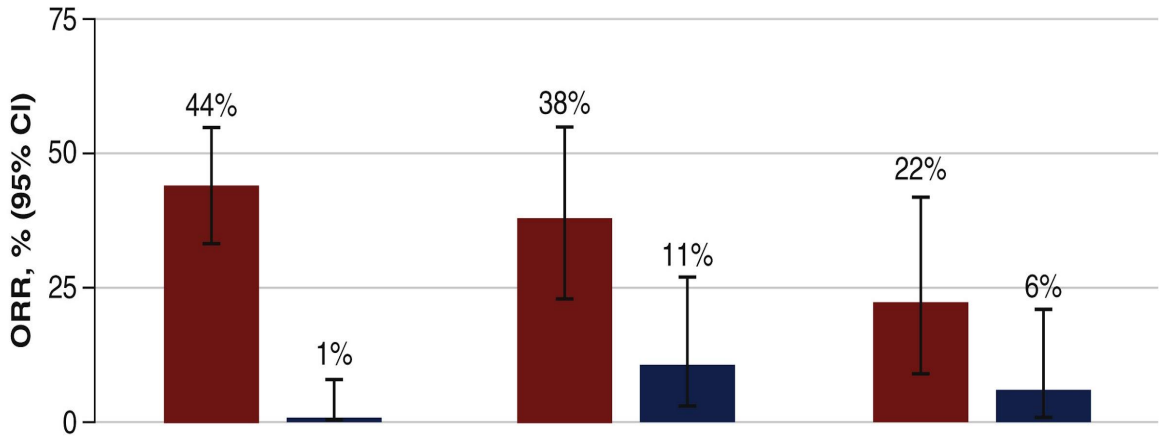
		SG (n=258)			TPC (n=224)		
	TRAE*	**All grade %**	**Grade 3, %**	**Grade 4, %**	**All grade, %**	**Grade 3, %**	**Grade 4, %**
Hematologic	**Neutropenia†**	**63**	**46**	**17**	**43**	**27**	**13**
	Anemia‡	**34**	**8**	**0**	**24**	**5**	**0**
	Leukopenia§	16	10	1	11	5	1
	Febrile neutropenia	6	5	1	2	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)

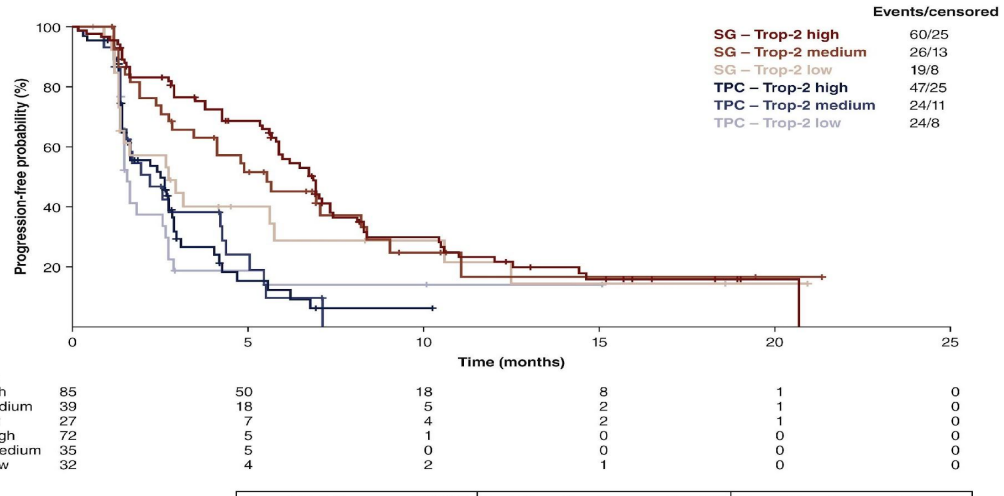
*Patients may report more than 1 event per preferred term. AEs were classified according to the MedDRA systems of preferred terms and system organ class and according to severity by NCI CTCAE v4.03. †Combined preferred terms of 'neutropenia' and 'decreased neutrophil count'. ‡Combined preferred terms 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.

Clinical Response by Trop Expression

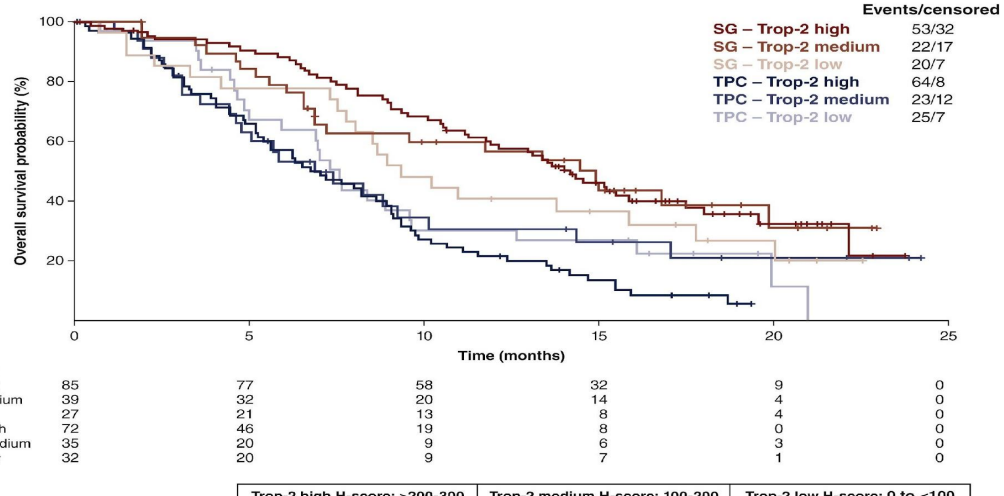
	SG	TPC
Trop-2 expression, *n* (%)	151 (64)	139 (60)
(High) H-score >200-300	85/151 (56)	72/139 (52)
(Medium) H-score 100-200	39/151 (26)	35/139 (25)
(Low) H-score 0 to <100[a]	27/151 (18)	32/139 (23)



	Trop-2 high H-score: >200-300 (*n* = 157)		Trop-2 medium H-score: 100-200 (*n* = 74)		Trop-2 low H-score: 0 to <100 (*n* = 59)	
	SG (*n* = 85)	TPC (*n* = 72)	SG (*n* = 39)	TPC (*n* = 35)	SG (*n* = 27)	TPC (*n* = 32)
ORR, % (*n*)	44 (37)	1 (1)	38 (15)	11 (4)	22 (6)	6 (2)
95% CI	33-55	0-8	23-55	3-27	9-42	1-21



	Trop-2 high H-score: >200-300		Trop-2 medium H-score: 100-200		Trop-2 low H-score: 0 to <100	
	SG (*n* = 85)	TPC (*n* = 72)	SG (*n* = 39)	TPC (*n* = 35)	SG (*n* = 27)	TPC (*n* = 32)
Median PFS (mo)	6.9	2.5	5.6	2.2	2.7	1.6

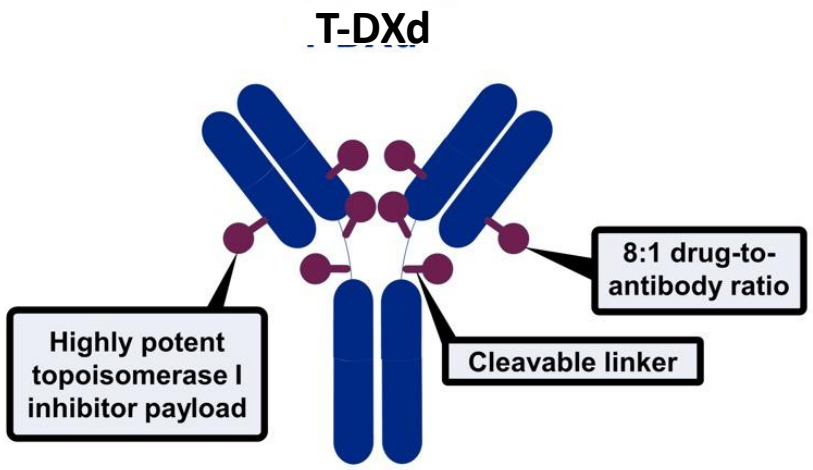


	Trop-2 high H-score: >200-300		Trop-2 medium H-score: 100-200		Trop-2 low H-score: 0 to <100	
	SG (*n* = 85)	TPC (*n* = 72)	SG (*n* = 39)	TPC (*n* = 35)	SG (*n* = 27)	TPC (*n* = 32)
Median OS (mo)	14.2	6.9	14.9	6.9	9.3	7.6

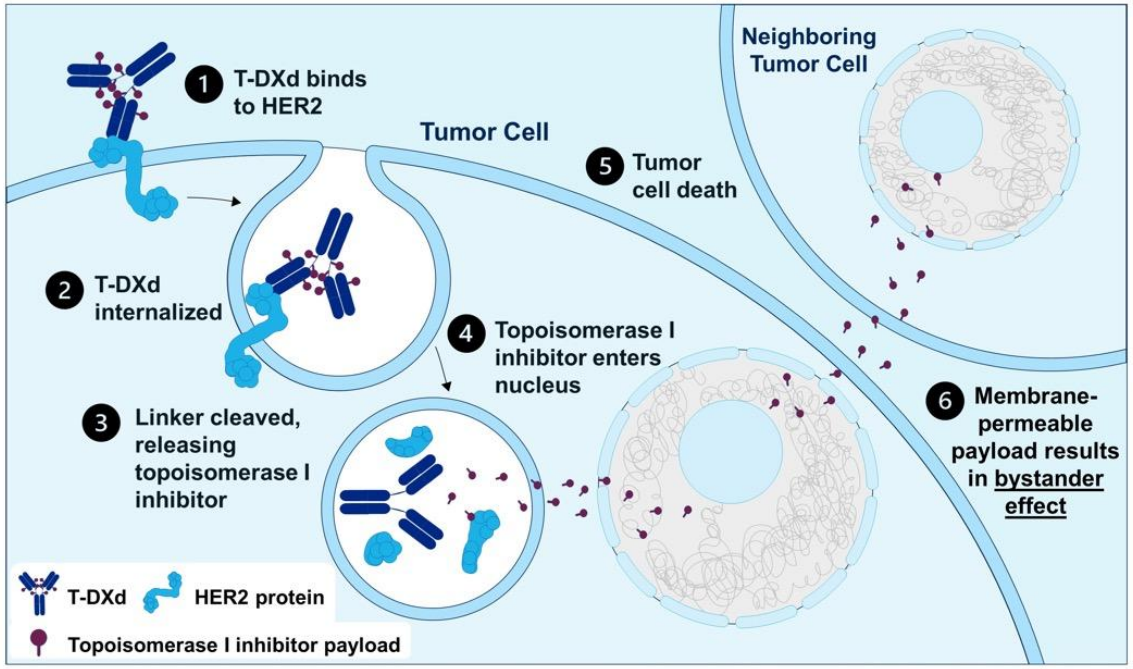
Bardia et al., Annals of Oncology 2021

Targeted Approach

T-DXd MOA, Bystander Effect, and Rational For Targeting HER2-LOW mBC



Internalization of T-DXd leads to release of the DXd payload and subsequent cell death in the target tumor cell and neighboring tumor cells through the bystander effect[1,2]

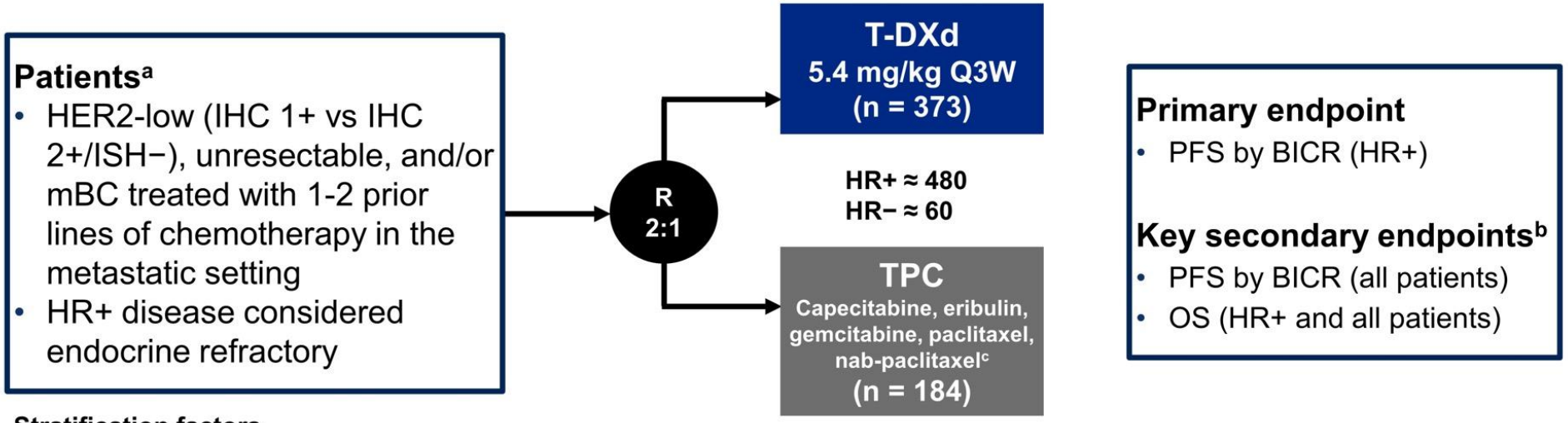


Adapted with permission from Modi S, et al. *J Clin Oncol* 2020;38:1887-96. CC BY ND 4.0.

Nakada T et al. Chem Pharm Bull 2019. Ogitani Y, et al. Clin Cancer Res 2-16. Modi S, et al. JCO 2-2-. Modi, S ASCO 2022

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

An open-label, multicenter study (NCT03734029)



Stratification factors

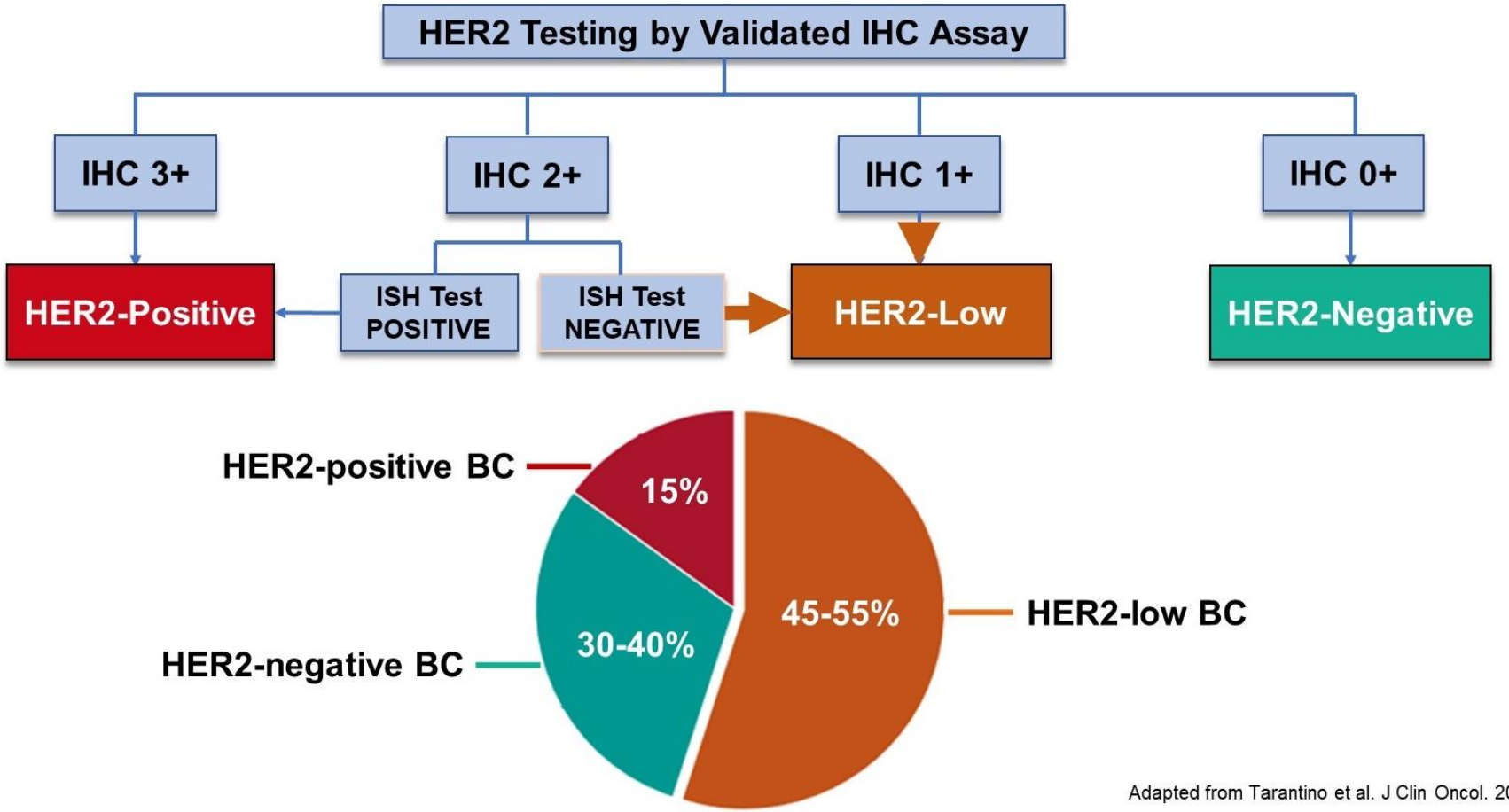
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

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.

Modi, S ASCO 2022

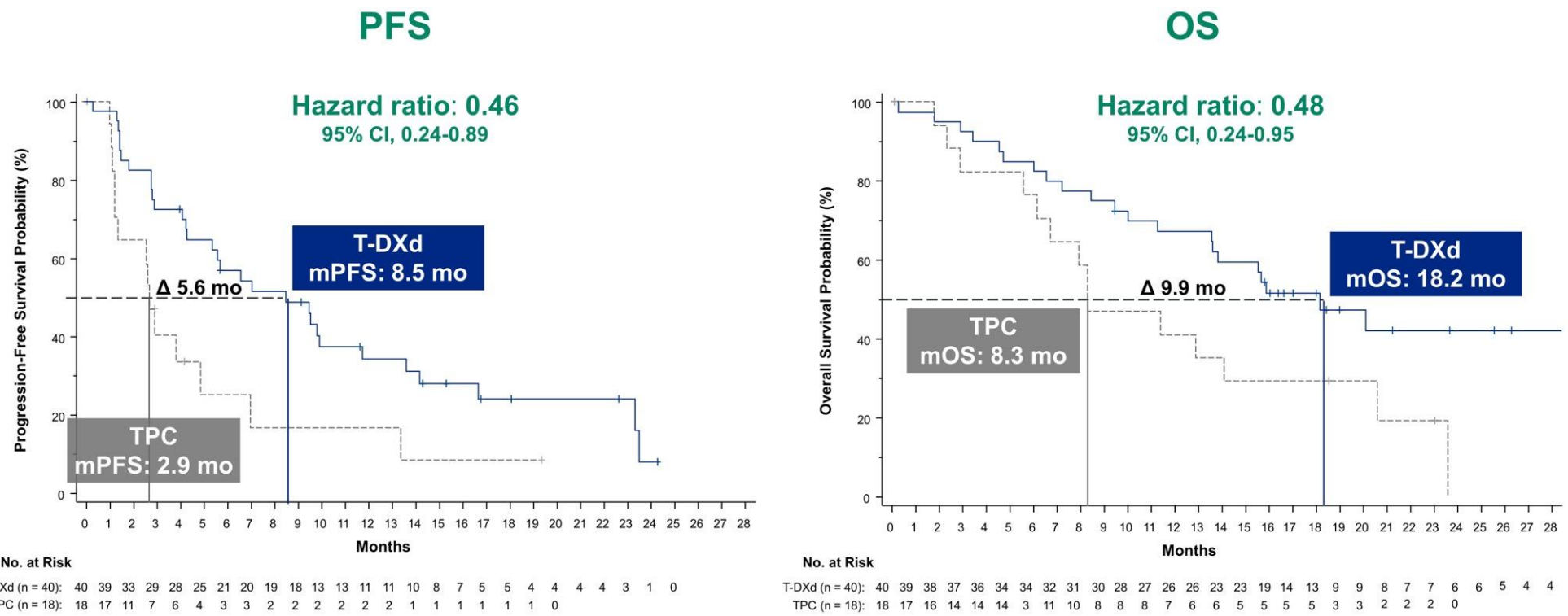
PROPOSAL OF AN ALGORITHM FOR DEFINING HER2-LOW BC



Adapted from Tarantino et al. J Clin Oncol. 2020 38(17)

LoRusso, P ASCO 2022

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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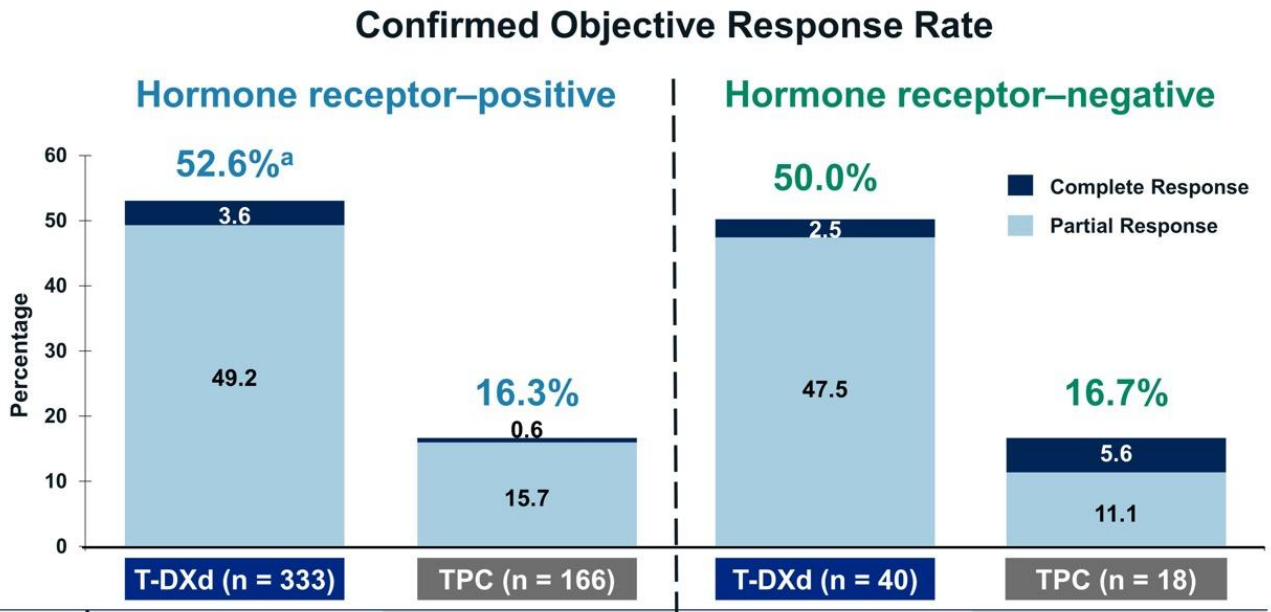
CONFIRMED ORR



	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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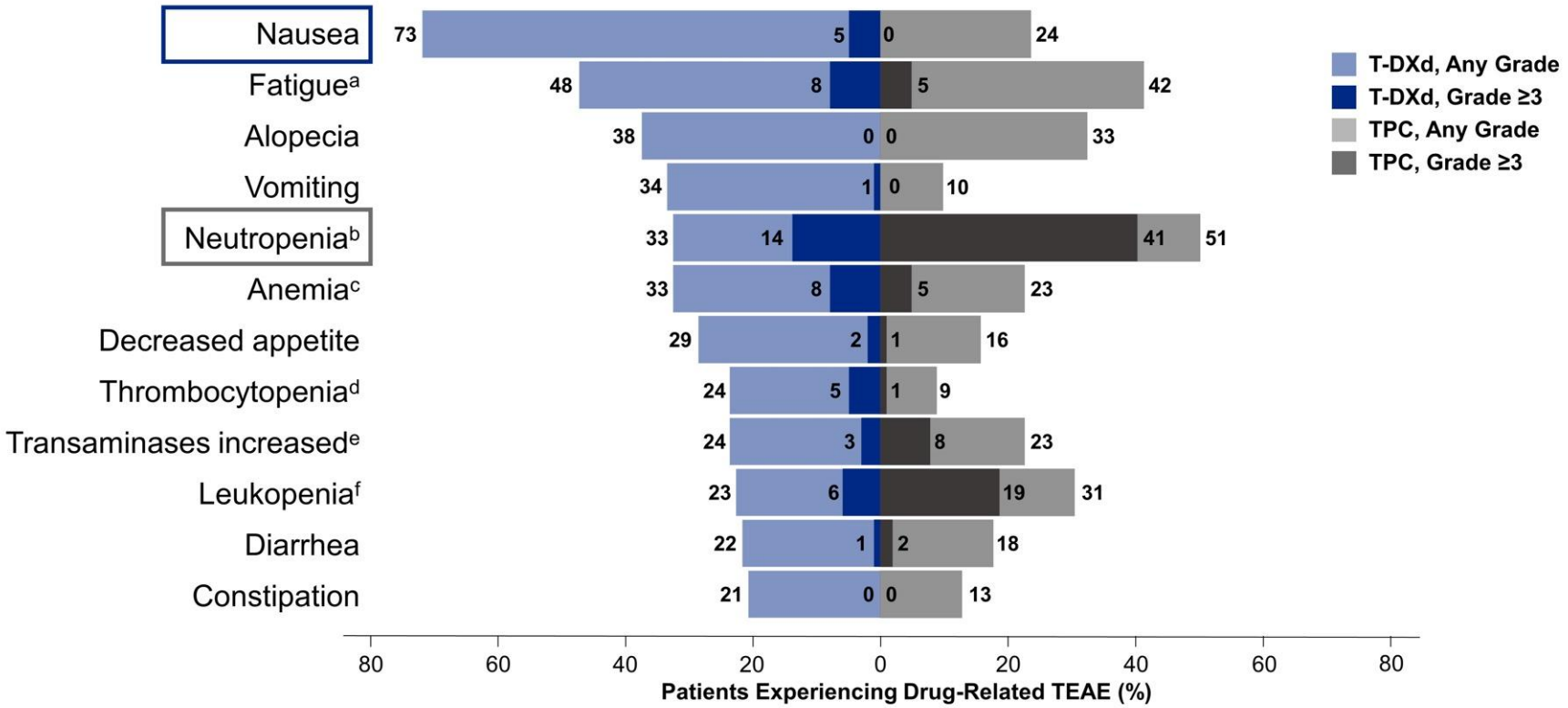
DRUG-RELATED TEAEs IN ≥20% OF PATIENTS



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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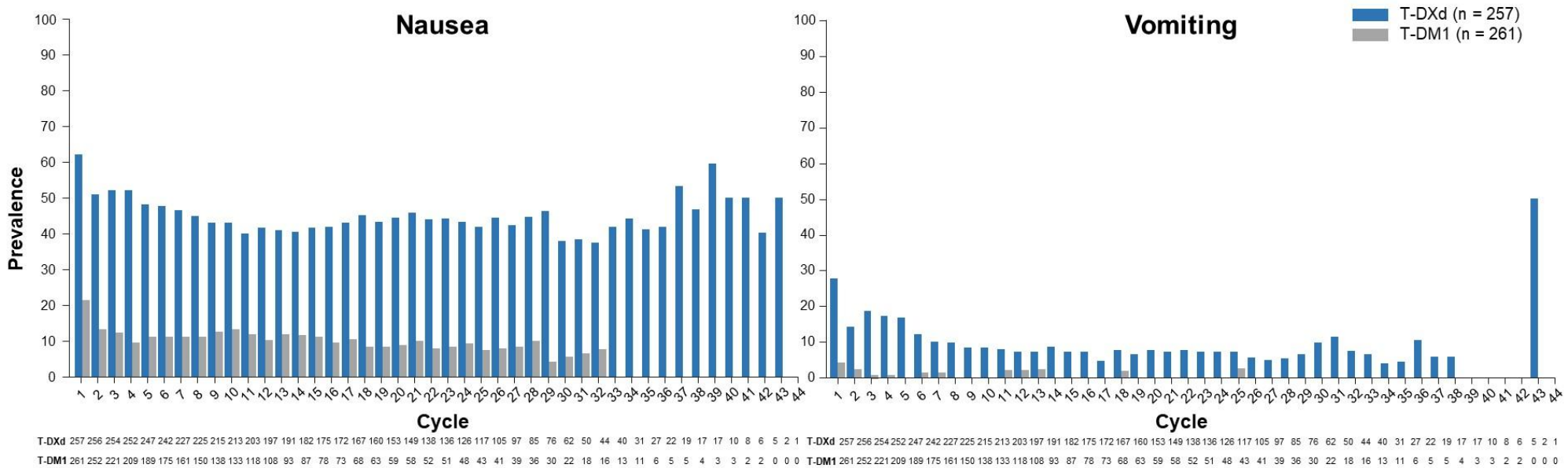
PREVALENCE OF NAUSEA AND VOMITING



- 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.

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.

Modi, S ASCO 2022

HOW TO SELECT HER2-LOW PATIENTS FOR T-DXD?

Median PFS by Tumor Sample Characteristics Among Patients Enrolled in DESTINY-Breast04

	Number of Events		Median PFS, Months (95% CI)		
Subgroup	**T-DXd**	**TPC**	**T-DXd**	**TPC**	**Hazard Ratio (95% CI)**
Tumor location					
Primary (n = 196)	96/136	43/60	9.6 (7.1-11.3)	4.2 (1.6-6.4)	**0.47** (0.32-0.70)
Metastases (n = 359)	145/235	84/124	10.9 (9.5-12.3)	5.4 (4.3-7.1)	**0.50** (0.38-0.66)
Specimen type					
Biopsy (n = 448)	189/299	103/149	10.9 (9.6-12.0)	5.3 (4.2-6.9)	0.46 (0.35-0.59)
Excision/resection (n = 108)	53/73	24/35	7.5 (5.7-9.9)	3.0 (1.4-11.0)	0.57 (0.33-1.0)

PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Prat A et al. San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18.

HOW TO SELECT HER2-LOW PATIENTS FOR T-DXD?

Median PFS by Tumor Sample Characteristics Among Patients Enrolled in DESTINY-Breast04

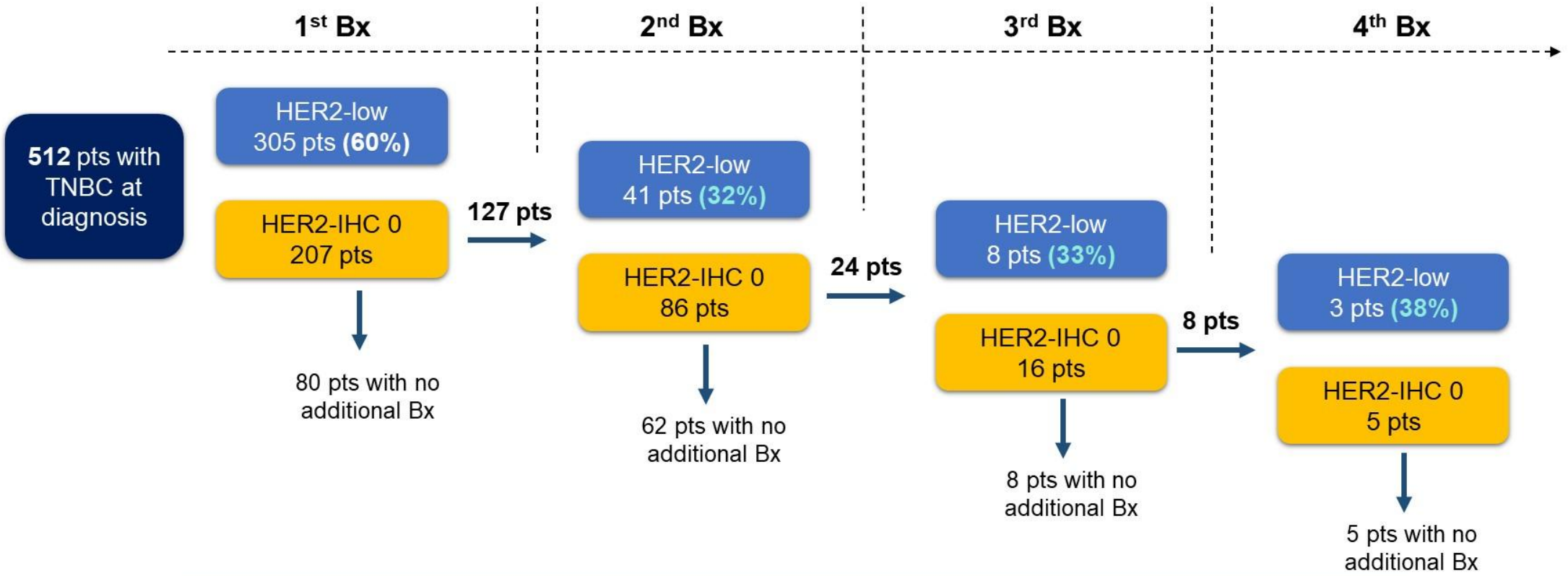
	Number of Events		Median PFS, Months (95% CI)		
Subgroup	**T-DXd**	**TPC**	**T-DXd**	**TPC**	**Hazard Ratio (95% CI)**
Collection type					
Archival tissue (n = 482)	203/324	109/158	10.3 (8.6-12.0)	5.3 (4.2-7.0)	**0.48** (0.37-0.61)
Newly obtained tissue (n = 75)	40/49	18/26	9.7 (5.6-10.9)	4.8 (2.8-6.9)	**0.57** (0.30-1.1)
Tumor specimen collection date					
2013 and earlier (n = 29)	11/19	9/10	7.0 (2.8-NE)	6.8 (1.4-11.1)	0.78 (0.24-2.54)
2014-2018 (n = 175)	76/126	33/49	11.4 (9.5-15.1)	4.3 (1.6-7.0)	0.44 (0.28-0.70)
2019 or later (n = 310)	137/203	75/107	9.8 (8.4-11.3)	5.1 (4.1-7.1)	0.49 (0.37-0.66)
Missing (n = 43)	19/25	10/18	6.6 (2.8-10.8)	2.8 (1.2-8.3)	0.54 (0.20-1.4)

- For patients enrolled in DESTINY-Breast04, efficacy of T-DXd compared with TPC was consistent regardless of tumor sample characteristics

PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Prat A et al. San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18.

Results (Part 1) – Impact of Repeat Bxs:

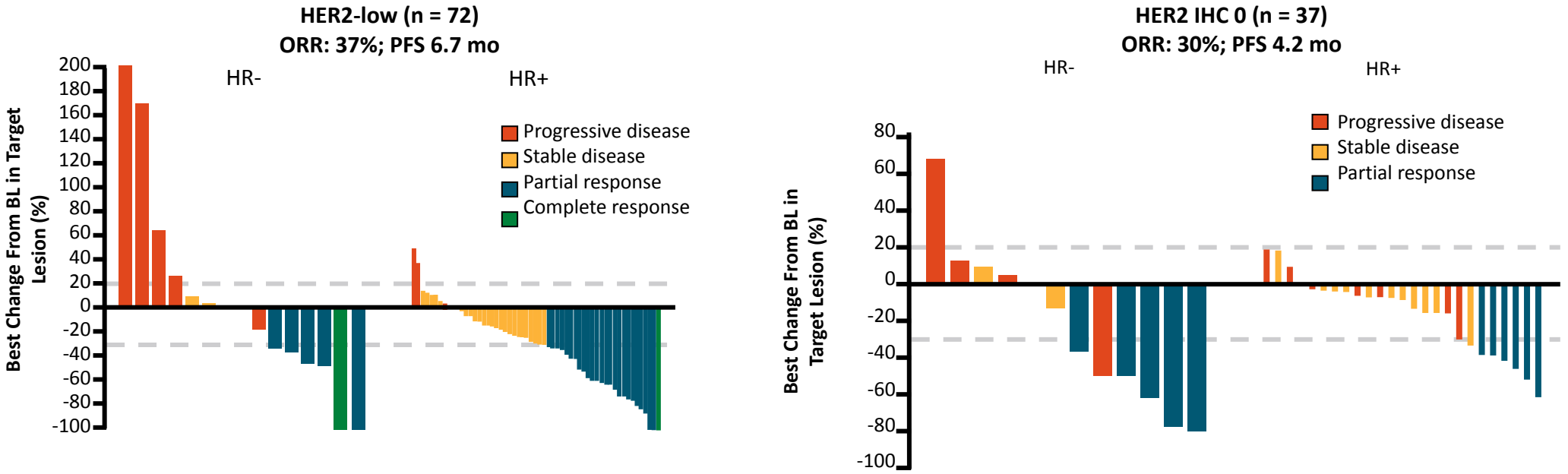
Detection of HER-low in successive serial Bxs for pts without a prior HER2-low result



With each successive Bx, a new HER2-low result was detected for 1/3 of patients with prior only HER2-IHC 0 results

PRESENTED BY: Yael Bar, MD, PhD ybar@mgh.harvard.edu @BarYaelMD

PHASE II DAISY TRIAL: BEST OVERALL RESPONSE ACCORDING TO HER2 EXPRESSION LEVELS WITH T-DXD IN METASTATIC BC



Do current data justify expanding the role of T-DXd beyond HER2 low?

Dieras. SABCS 2021. Abstr PD8-02. Trastuzumab deruxtecan PI.

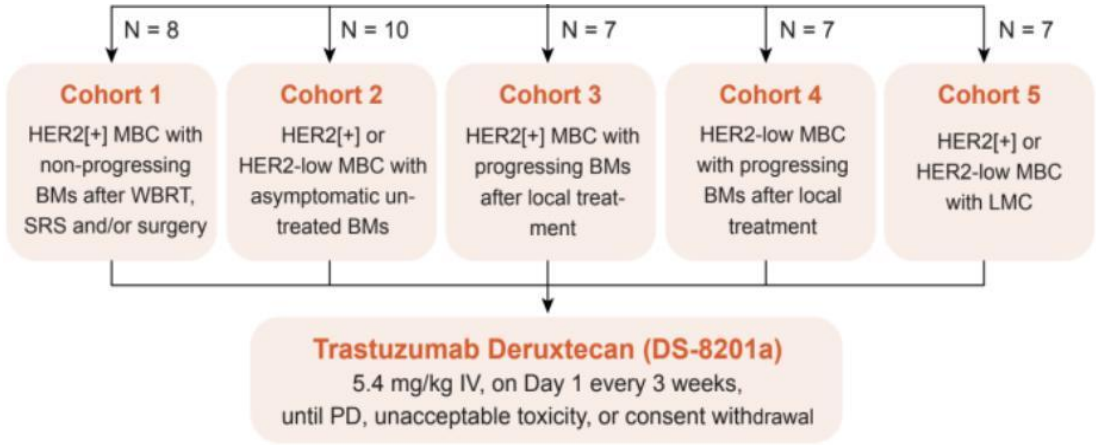
WHAT'S THE ACTIVITY OF T-DXD AMONG PATIENTS WITH HER2-LOW BRAIN METS?

DAISY (stable) - ORR 30% (3/10)

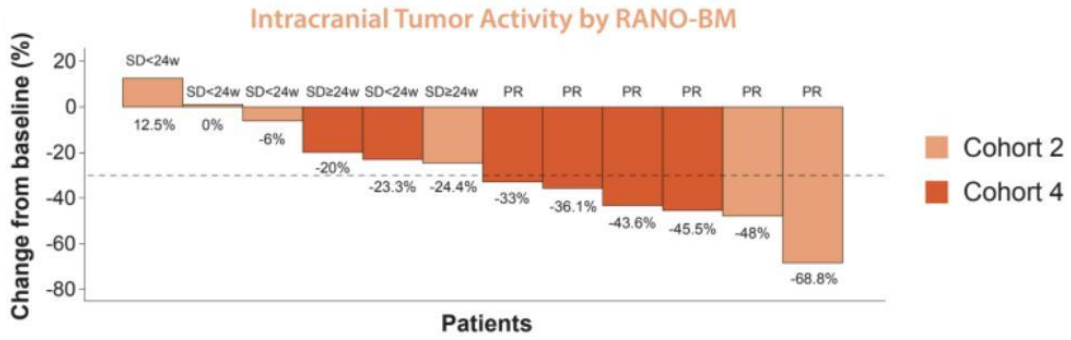
	Overall *n*=24	Cohort 1 *n*=12	Cohort 2 *n*=10	Cohort 3 *n*=2
Confirmed BOR % (*n*) [95% CI]	62.5 (15/24) [40.6-81.2]	91.7 (11/12) [61.5-99.8]	30 (3/10) [6.7-65.2]	50 (1/2) [1.3-98.7]
CBR % (n) [95% CI]	70.8 (17/24) [48.9; 87.4]	91.7 (11/12) [61.5-99.8]	50 (5/10) [18.7-81.3]	50 (1/2) [1.3-98.7]
mPFS (months) [95% CI]	8.5 [4.4-12.2]	13 [7.1-NR]	4.1 [2.3-11.7]	NA [2.0-NR]
Death, % (n)	29.2 (7/24)	25.0 (3/12)	40 (4/10)	0 (0/2)

Table 2. *Overall T-DXd activity in patients with BMs*

DEBBRAH (active) - ORR 50% (6/12)



Waterfall Plots of Best Response Based on Intracranial Lesions in HER2-Low Patients With Measurable Lesions



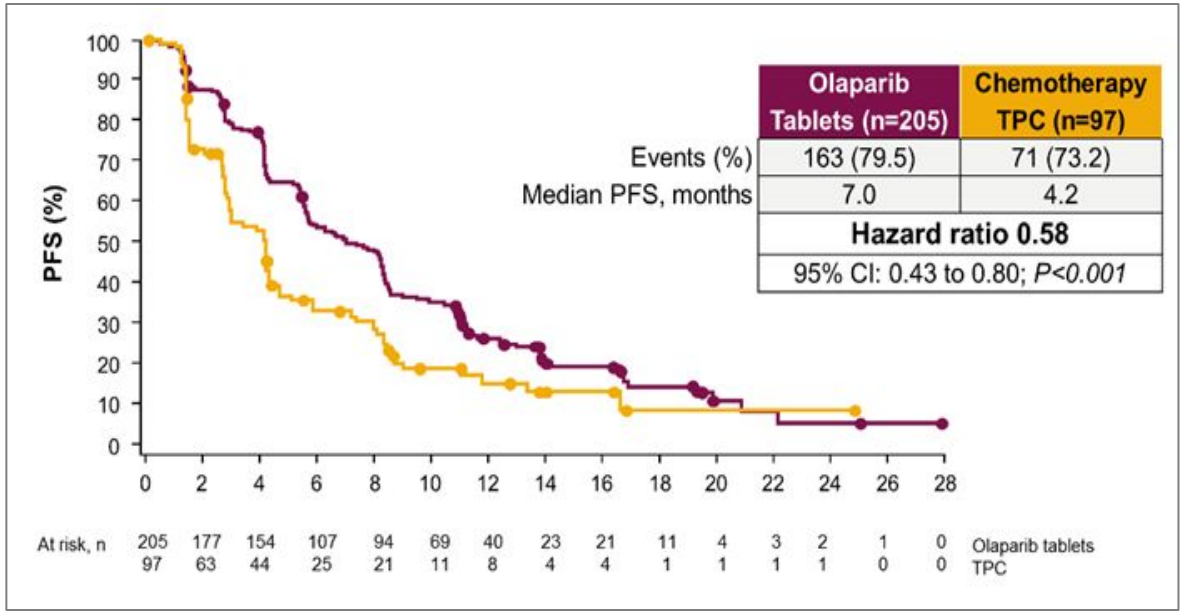
Epaillard N. et al ESMO 22; Perez-Gargia JM et al. SABCS22

Synthetic Lethality

PARP inhibitors improve PFS in gBRCA+ patients with MBC

OlympiAD

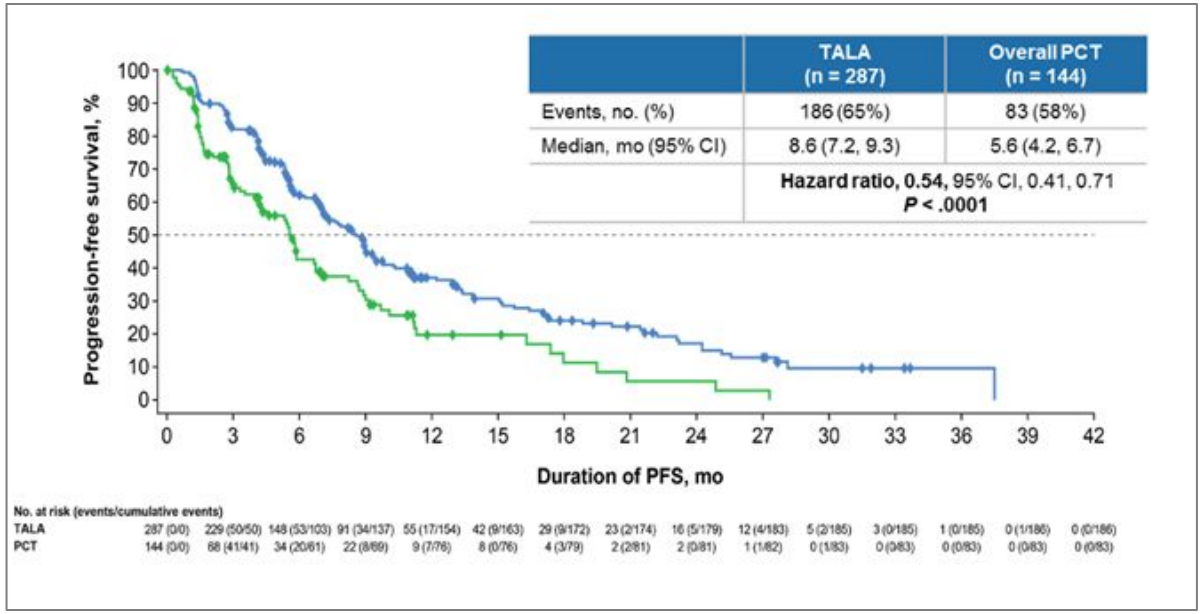
ER/PR -: 50%
HR +: 50%



	Olaparib Tablets (n=205)	Chemotherapy TPC (n=97)
Events (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
Hazard ratio 0.58		
95% CI: 0.43 to 0.80; *P<0.001*		

EMBRACA

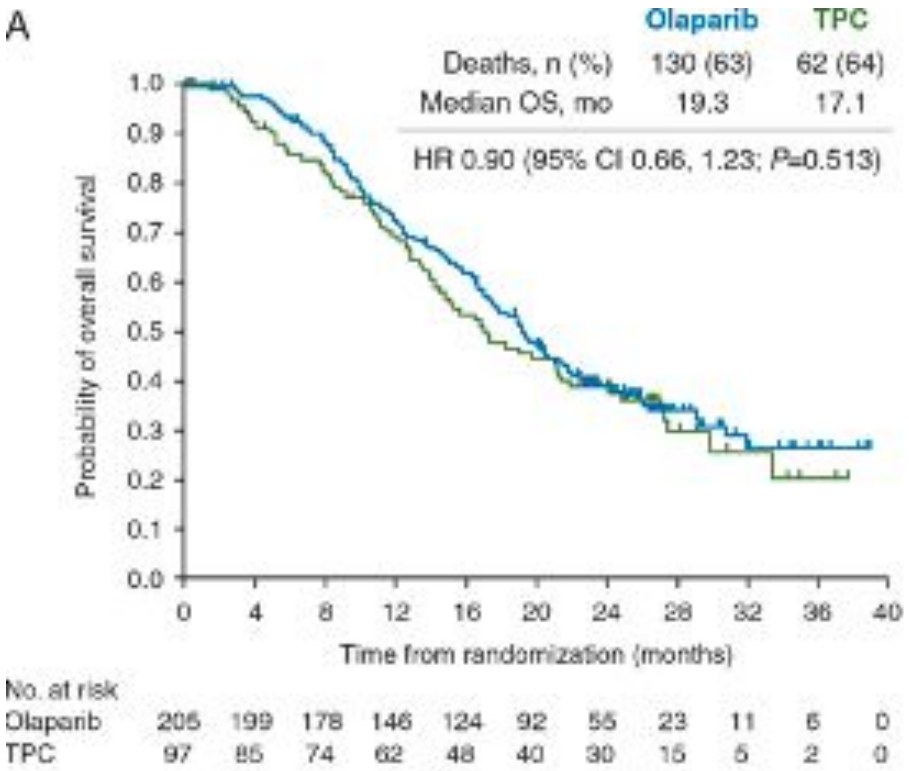
ER/PR -: 45%
HR +: 55%

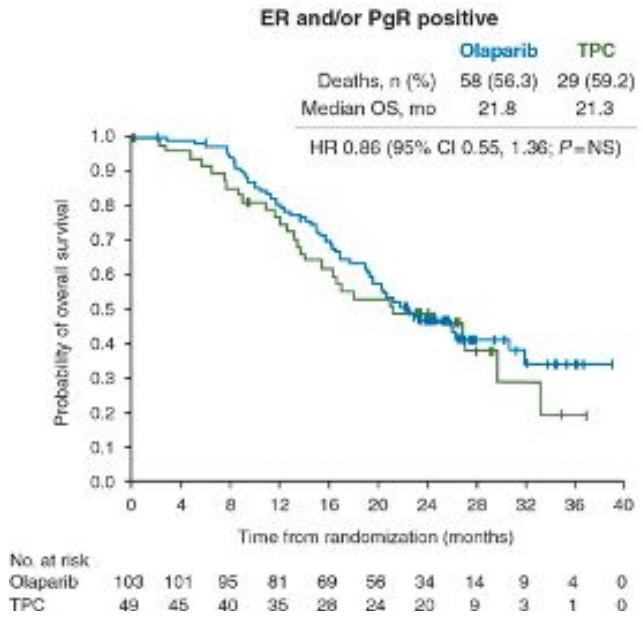


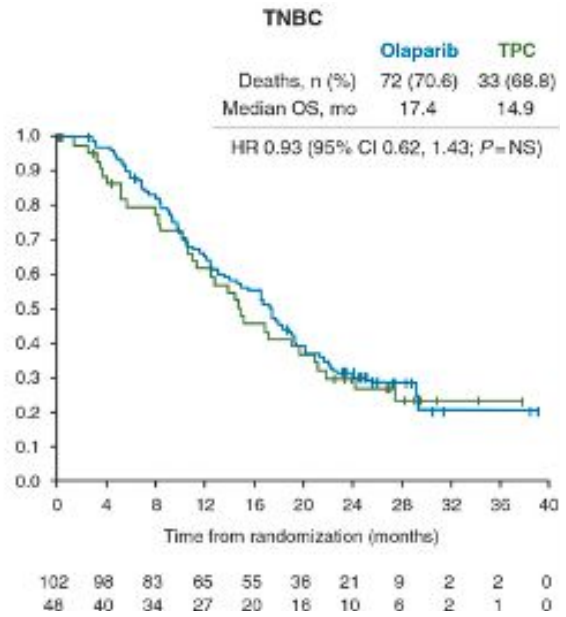
	TALA (n = 287)	Overall PCT (n = 144)
Events, no. (%)	186 (65%)	83 (58%)
Median, mo (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
	Hazard ratio, 0.54, 95% CI, 0.41, 0.71 ***P* < .0001**	

Robson M et al. *New Engl J Med*. 2017;377(6):523-533. Litton JK et al. *N Engl J Med*. 2018;379(8);753-763.

OlympiAD: Final OS



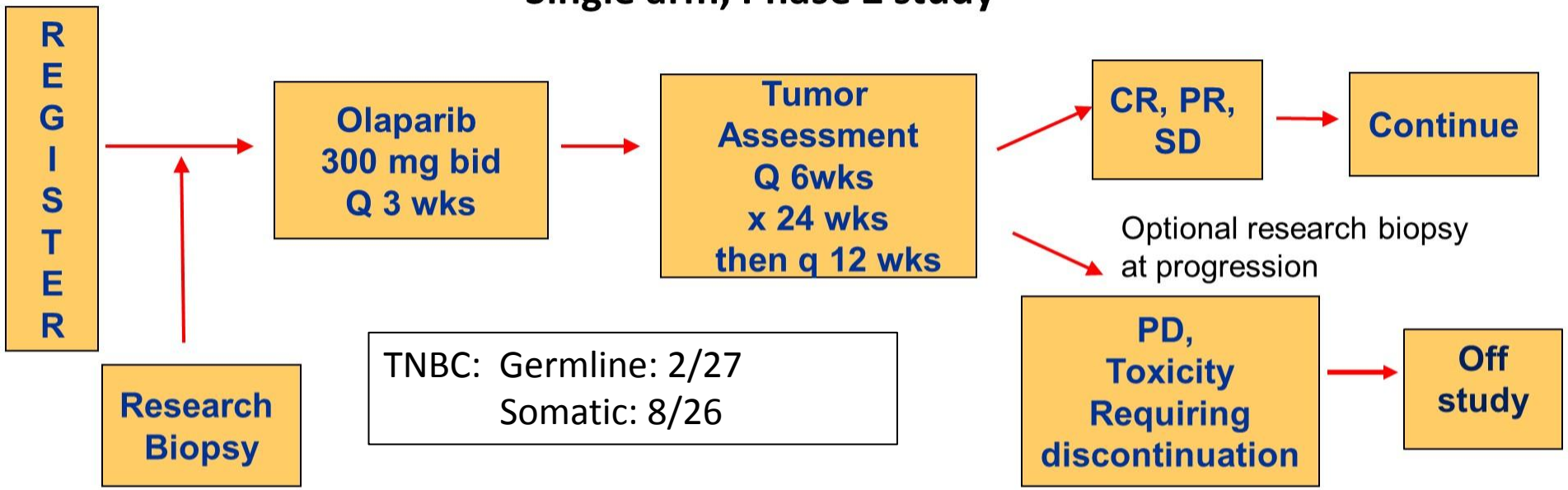




Robson et al., Annals of Oncology

Schema: Olaparib Expanded

Single arm, Phase 2 study

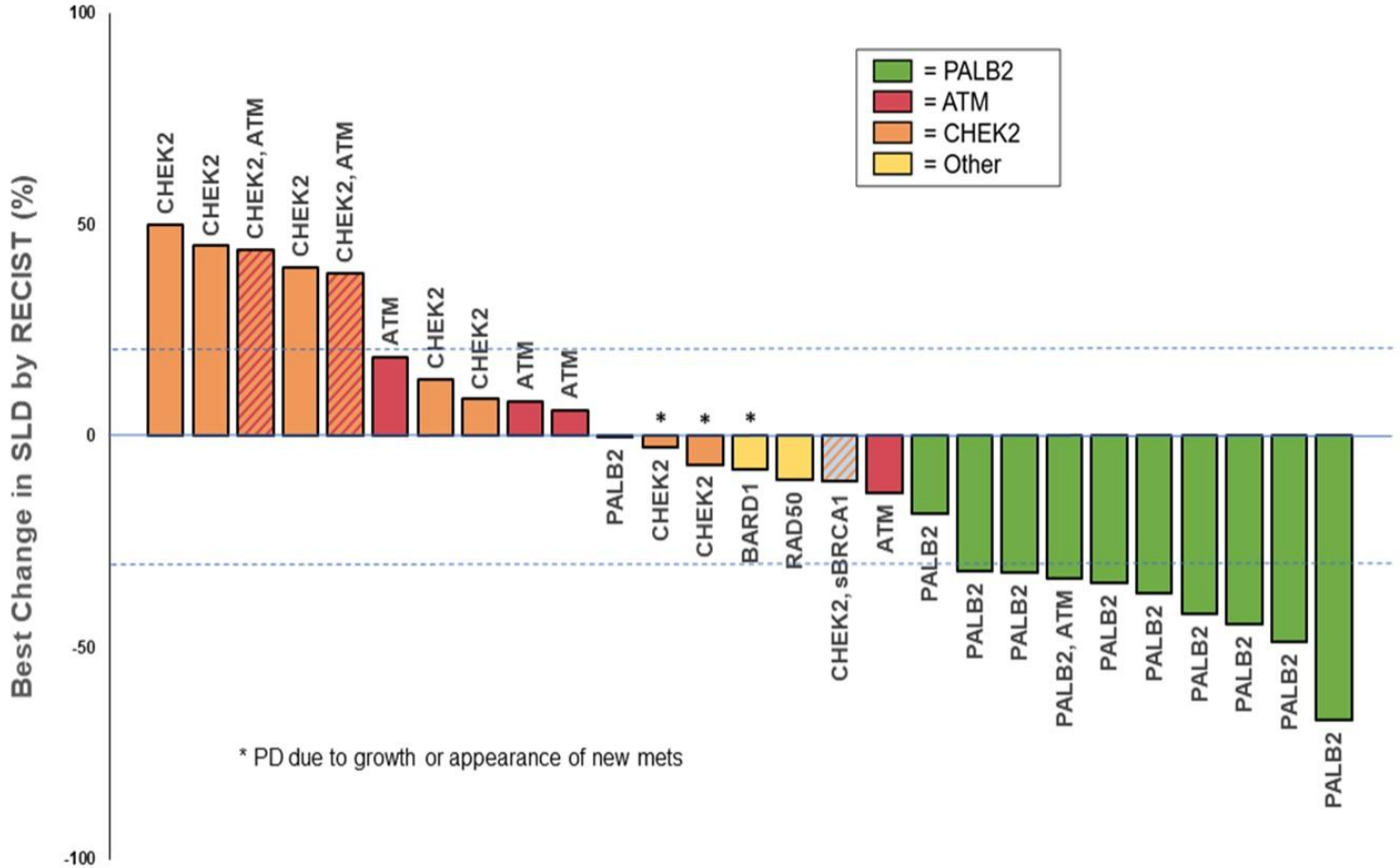


Cohort 1: Germline Mutation
Cohort 2: Somatic Mutation

s*BRCA1/2* allowed if g*BRCA* negative

ATM, ATR, BAP1, BARD1, BLM, BRIP1 (FANCJ), CHK1 (CHEK1), CHEK2 , CDK12, FANCA, FANCC, FANCD2, FANCF, MRE11A, NBN (NBS1), PALB2, RAD50, RAD51C, RAD51D, WRN

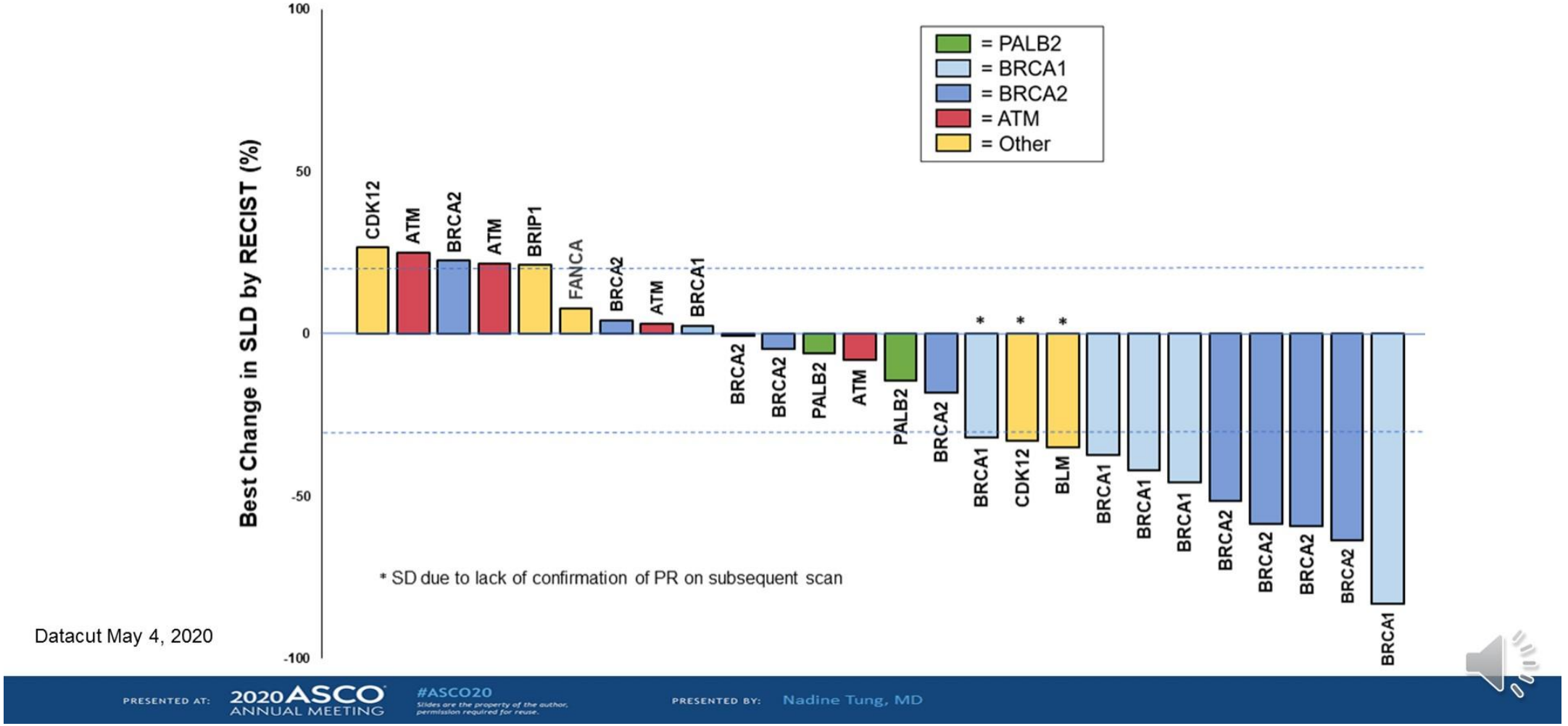
Best Overall Responses: Cohort 1 (Germline)



Datacut May 4, 2020

Presented By Nadine Tung at ASCO 2020

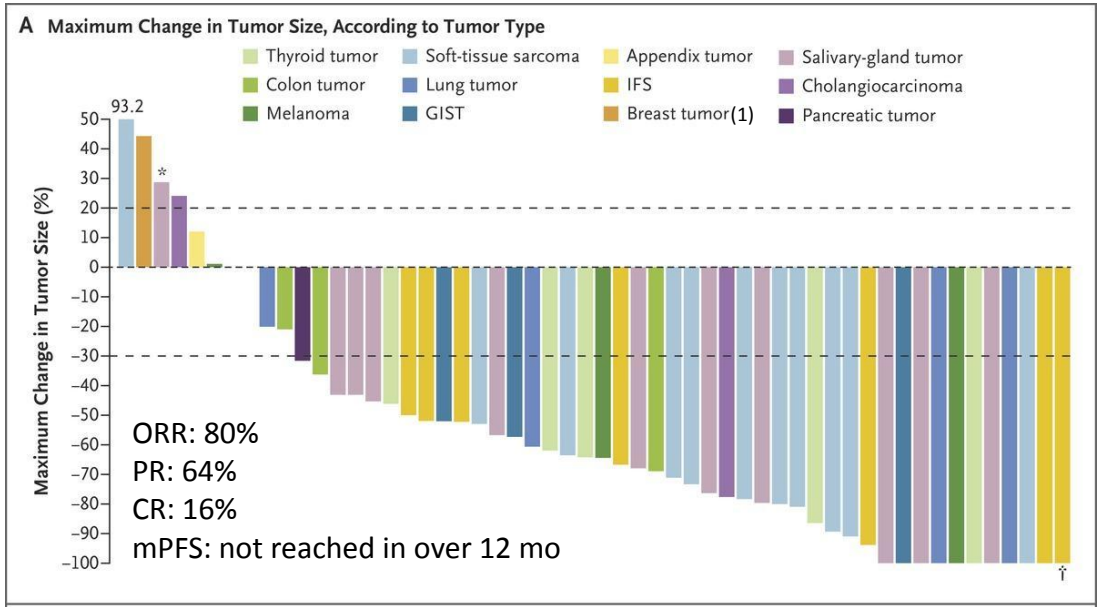
Best Overall Responses: Cohort 2 (Somatic)

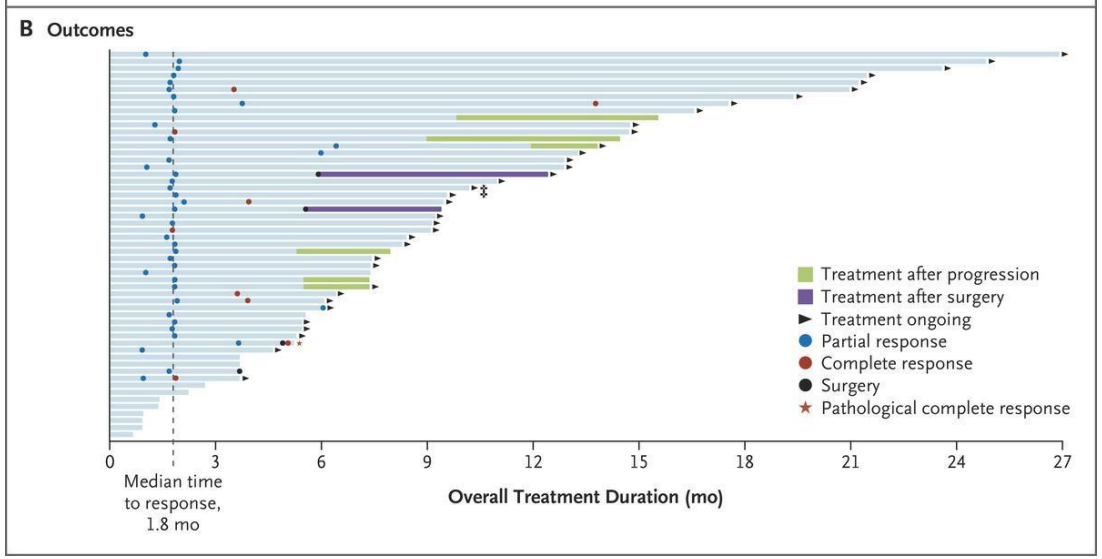


Presented By Nadine Tung at ASCO 2020

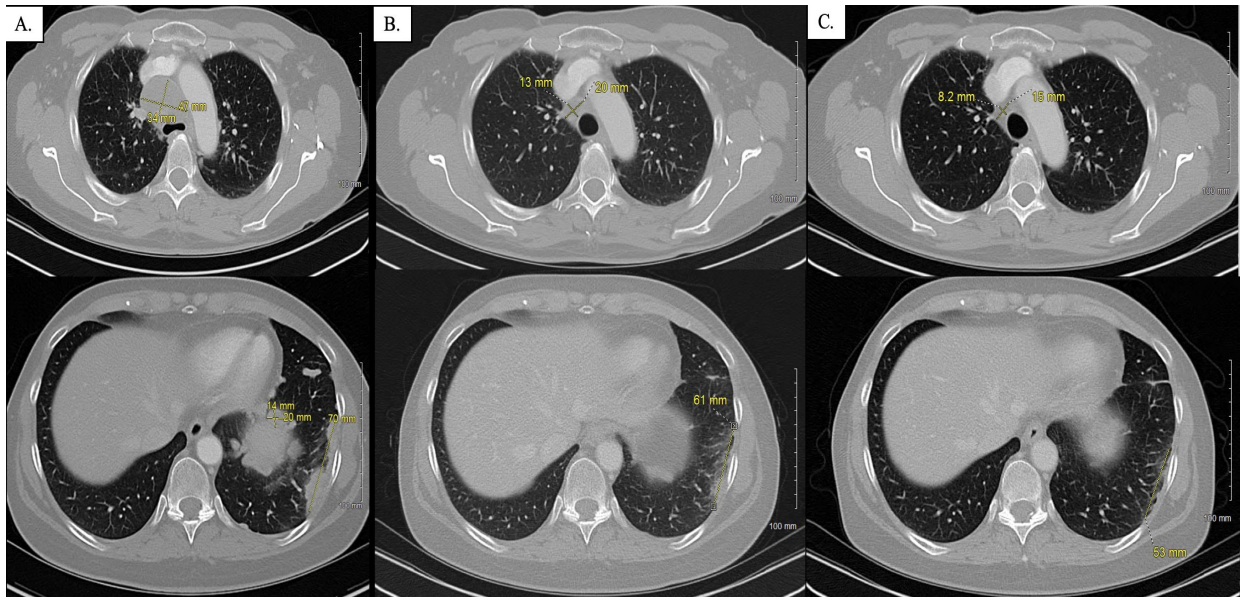
NRTK FUSIONS

Larotrectinib[1]





Case of 45 y/o Caucasian female-Deep PR after 3 months



Found in over 90% of secretory breast cancers
0.15% of all breast cancers
87% are basal like phenotype

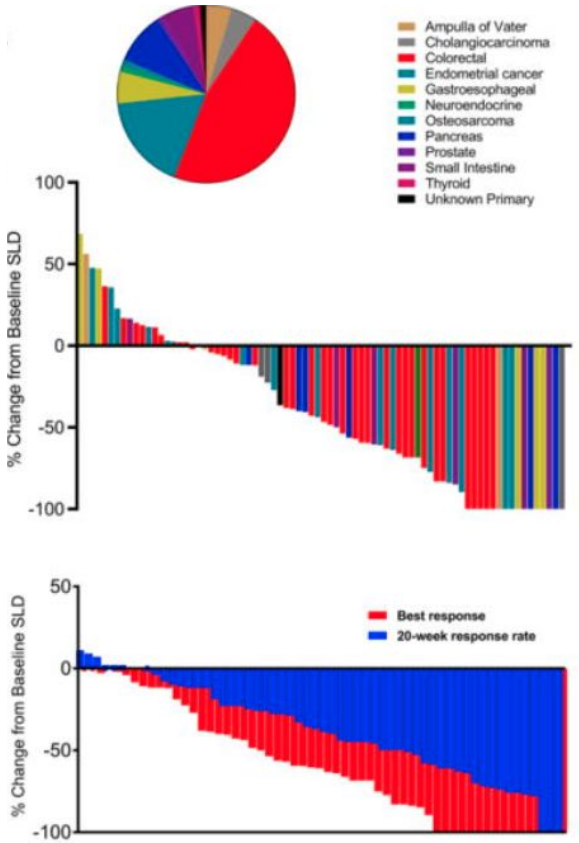
1. Drilon et al NEJM 2018, 2. Singh and Vidal BMJ Case Report 2022

TMB MSI-H and dMMR

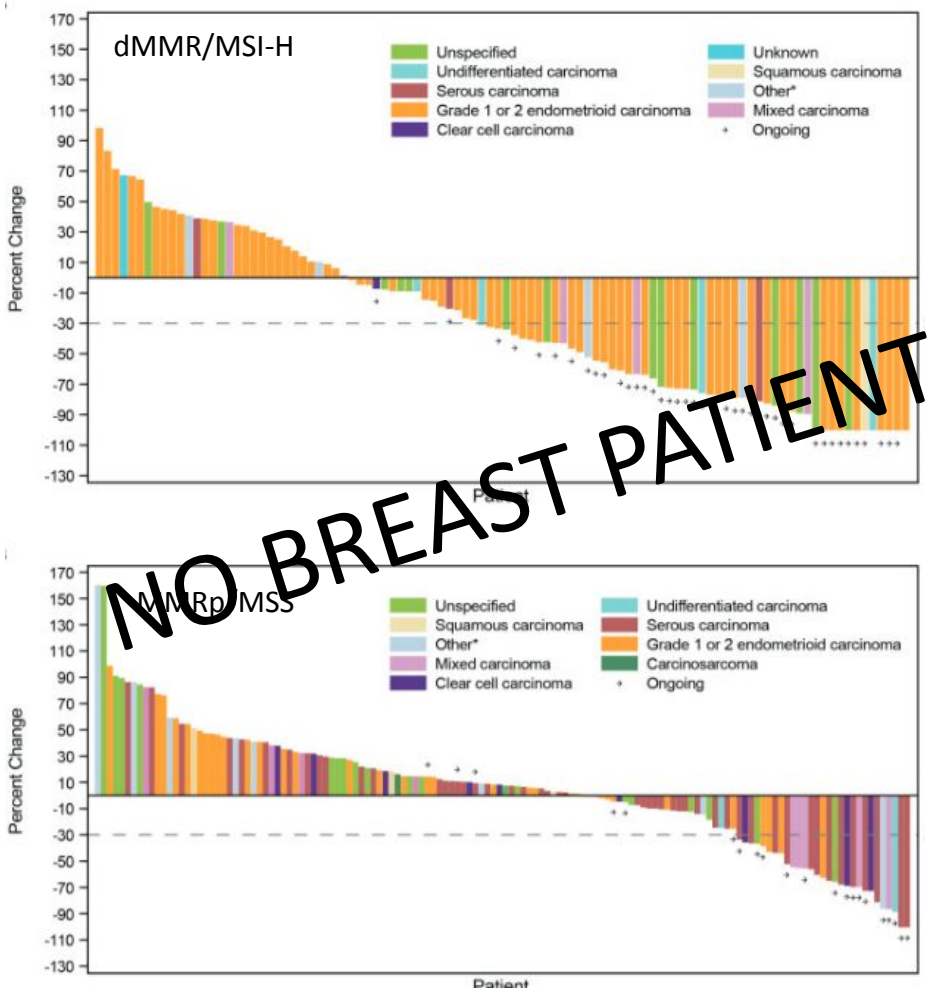
MSI-H/ dMMR or TMB-H-Tumor Agnostic

Pembrolizumab[1]

dMMR

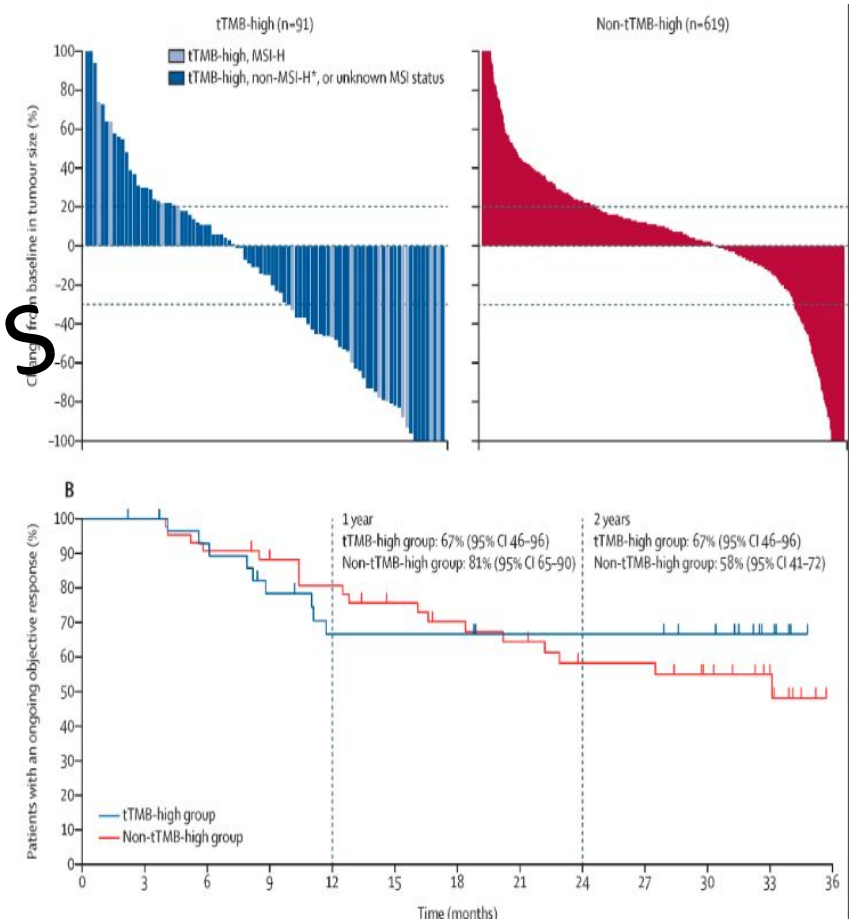


Dostarlimab[2]



Pembrolizumab[3]

TMB-H

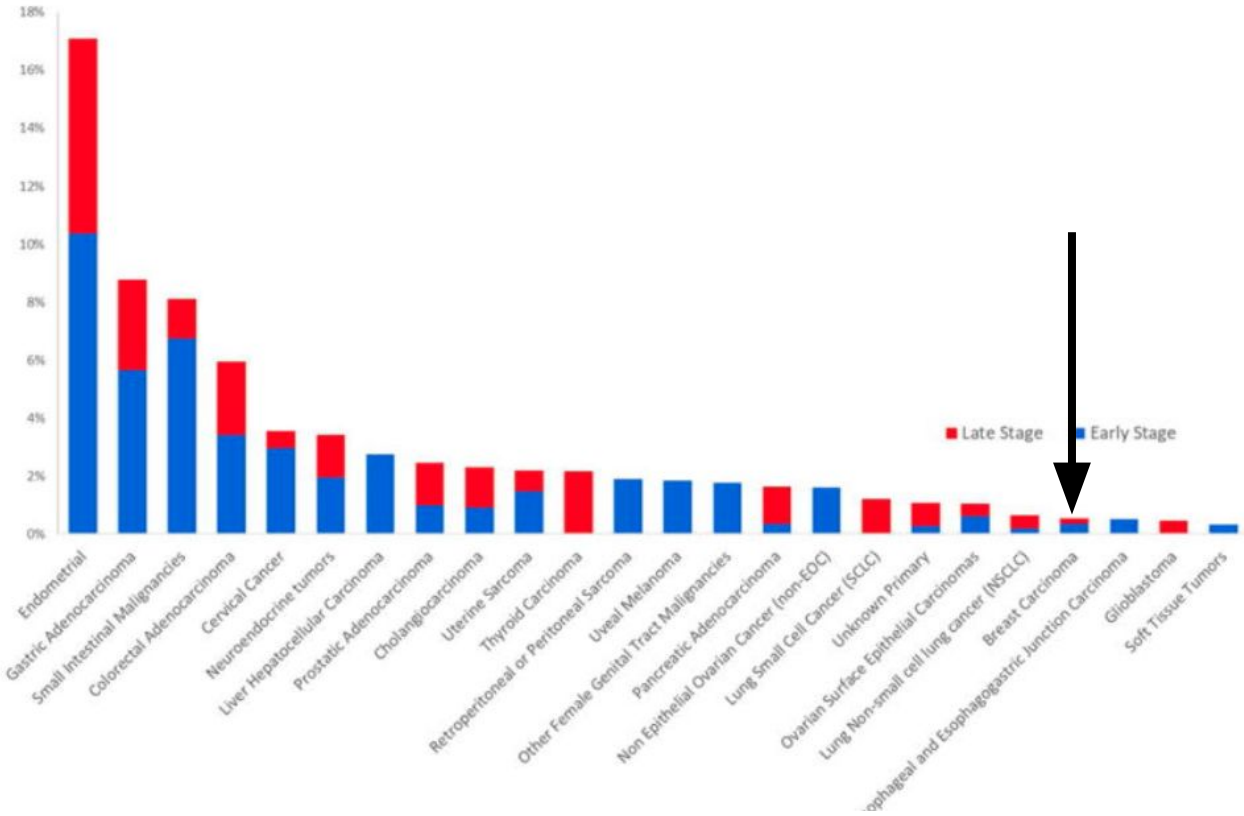


NO BREAST PATIENTS

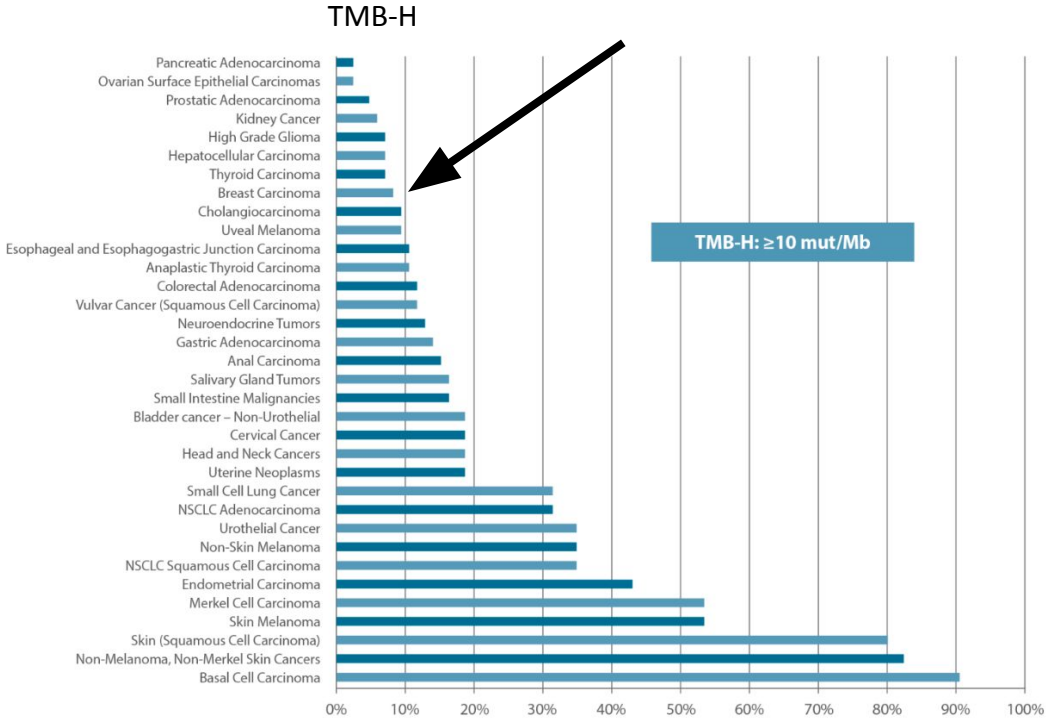
1. Le et al., Science 2017 and 2. Oaknin et al., J Immunother Cancer 2022, 3. Marabelle et al., The Lancet 2020

dMMR and TMB-H is uncommon in breast Cancer

dMMR

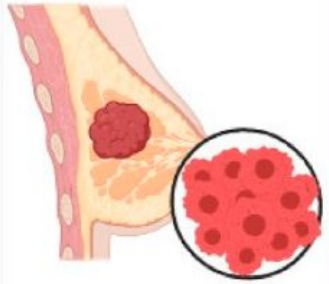


TMB-H

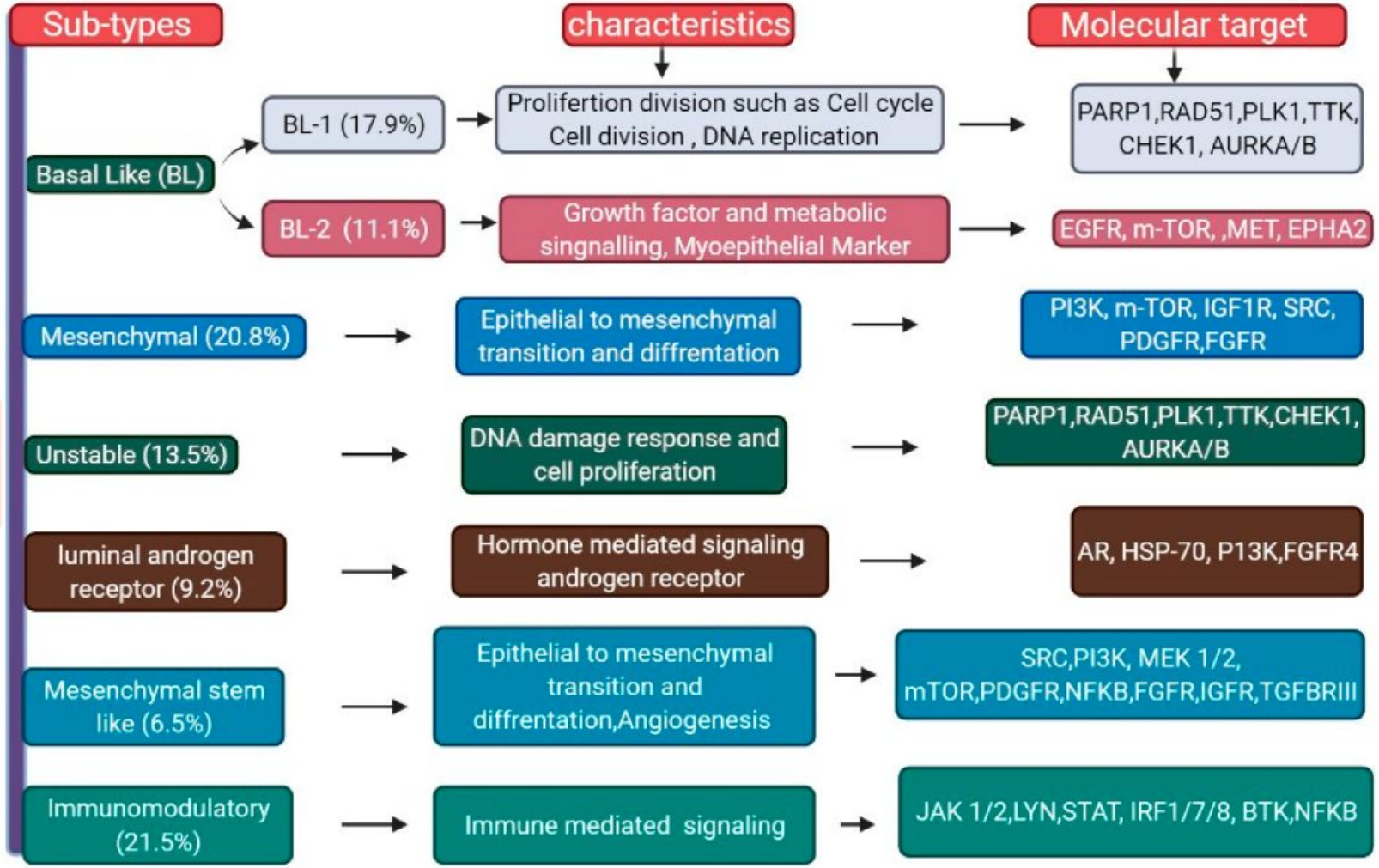


Le et al., Science 2017 and Carislifesciences.com

Biomarkers with Research Implications in TNBC



Classification of triple negative breast cancer



ADC's
HER3
TROP
HER4
Immune-Target
CDH6

MRD: Using ctDNA quantification techniques to assist in detection of early treatment failure and whether treatment changes can augment disease course

Conclusion

- TNBC remains a large unmet need for effective tolerable therapies
- However few, targeted approaches are available and should be investigated when appropriate
- Germline testing should be offered to all (early and or late stage) patients with TNBC
- Molecular comprehensive testing should be performed on all mTNBC patients
  - Preferable in the 1st line setting
- HER2 low is an important marker/subtype and should be identified in every metastatic breast cancer patient
- Clinical Trials is an important arsenal in the treatment of TNBC at all stage of the disease. I encourage practitioners to always seek clinical trial options for their TNBC patients.

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**

Second-line MBC

- **Olaparib/Talazoparib if BRCA+ and PDL1 (+ or -)**
- **Sacituzumab**
- **TDxD if HER2 low**
- **Chemotherapy (microtubulin inhibitor, capecitabine, gem/carbo)**
- **Clinical trial**

Third-line and beyond MBC

- **Sacituzumab (if not in 2nd line)**
- **TDxD (if HER2 low and not used in 2nd line)**
- **Chemotherapy**
- **TDxD- if prior sacituzumab**
- **Clinical trial**
- *NTRK Fusion:* larotrectinib or entrectinib
- RET fusion: selpercatinib
- *MSI-H/dMMR*: pembrolizumab or dostarlimab-gxly
- *TMB-H:* pembrolizumab
- *Somatic gBRCA 1/2 or PAPLB-2 Mutation* olaparib or talazoparib
- *BRAF mutation: dabrafenib and trametinib*

- **Comfort measures**

Consider repeat molecular profile through liquid ctDNA on progression

Thank You

- The West Cancer Center and Research Institute