Advancing care with Antibody Drug Conjugates for Her2 Negative Breast cancer

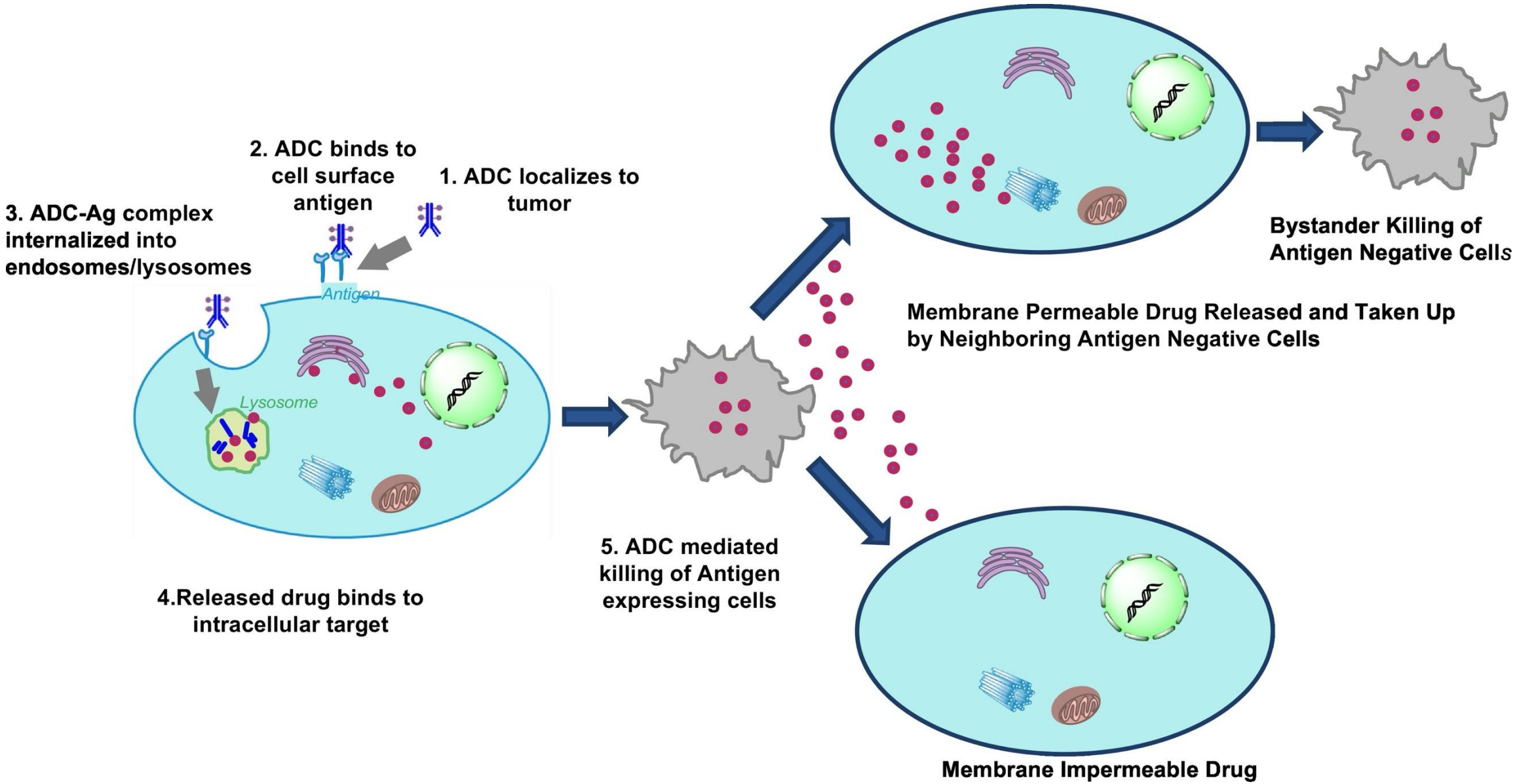
Suchita Pakkala, MD
Emory Winship Midtown

Updates in Cancer Therapies
Saturday December 7, 2024

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

Cancer Specific Antibody drug conjugate (ADC)



Trail PA, et al. *Pharmacol Ther.* 2018;181:126–142.

TROPiCS-02

Sacituzumab in HR+/HER2- Advanced Breast Cancer

Trop-2 expressed in ~85-90% all breast cancer subtypes

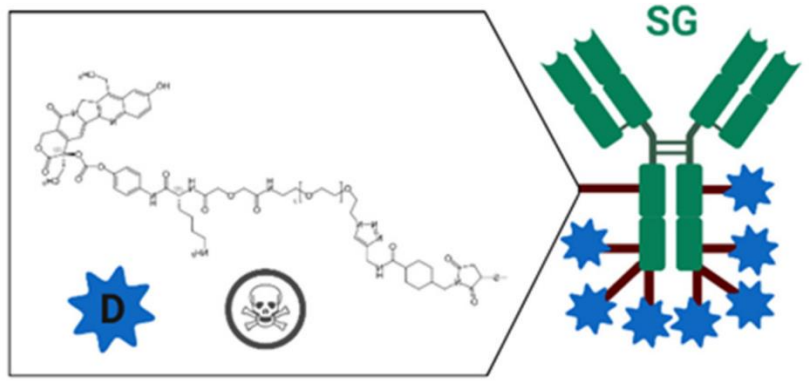
Target Antigen: TROP2

mAb isotype: IgG1

Linker type: cleavable

Payload (class): SN-38, active metabolite of irinotecan (Camptothecin)
Payload action: Topoisomerase-1 inhibitor

DAR: 8



HR+/HER2− MBC after:

- ≥ 1 ET, taxane, CDK4/6i (any setting
- 2-4 prior chemo for MBC

~ 3 prior chemo MBC

R 1:1

N=543

Sacituzumab govitecan

Chemo of MD's choice* (capecitabine, vinorelbine, gemcitabine or eribulin)

**~50% eribulin, 20% gem, 20% vin, <10% cape*

Endpoints

Primary

- **PFS by BICR**

Secondary

- OS
- ORR, DOR, CBR
- PRO
- Safety

Rugo H et al. ESMO 2022. Abstract LBA76. Corti C et al. Cancers. 2021; 13 (12):2898

Demographics and Baseline Characteristics[1]

	SG (n=272)	TPC (n=271)
Female, n (%)	270 (99)	268 (99)
Median age, y (range)	57 (29–86)	55 (27–78)
<65 y, n (%)	199 (73)	204 (75)
≥65 y, n (%)	73 (27)	67 (25)
Race or ethnic group, n (%)		
White	184 (68)	178 (66)
Black	8 (3)	13 (5)
Asian	11 (4)	5 (2)
Other[a] / Not reported[b]	69 (25)	75 (28)
ECOG PS, n (%)		
0	116 (43)	126 (46)
1	156 (57)	145 (54)
Visceral metastases at baseline, n (%)	259 (95)	258 (95)
Liver metastases,[c] n (%)	229 (84)	237 (87)
De novo metastatic breast cancer, n (%)	78 (29)	60 (22)

	SG (n=272)	TPC (n=271)
Median time from initial metastatic diagnosis to randomization, mo (range)	48.5 (1.2–243.8)	46.6 (3.0–248.8)
Prior chemotherapy in (neo)adjuvant setting, n (%)	173 (64)	184 (68)
Prior endocrine therapy use in the metastatic setting ≥6 mo, n (%)	235 (86)	234 (86)
Prior CDK4/6 inhibitor use, n (%)		
≤12 months	161 (59)	166 (61)
>12 months	106 (39)	102 (38)
Unknown	5 (2)	3 (1)
Median prior chemotherapy regimens in the metastatic setting, n (range)[d]	3 (0-8)	3 (1-5)

[a]Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander. [b]Not reported indicates local regulators did not allow collection of race or ethnicity information. [c]Presence of baseline target/non-target liver metastases per RECIST1.1 by local investigator review. [d]The reported number of prior therapies were miscounted at screening for some patients; 9 patients received prior chemotherapy regimens in the metastatic setting outside the per protocol range for inclusion criteria and were included in the intent-to-treat population.

CDK, cyclin-dependent kinase; ECOG PS, Eastern Cooperative Oncology Group performance status, (neo)adjuvant, neoadjuvant or adjuvant; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

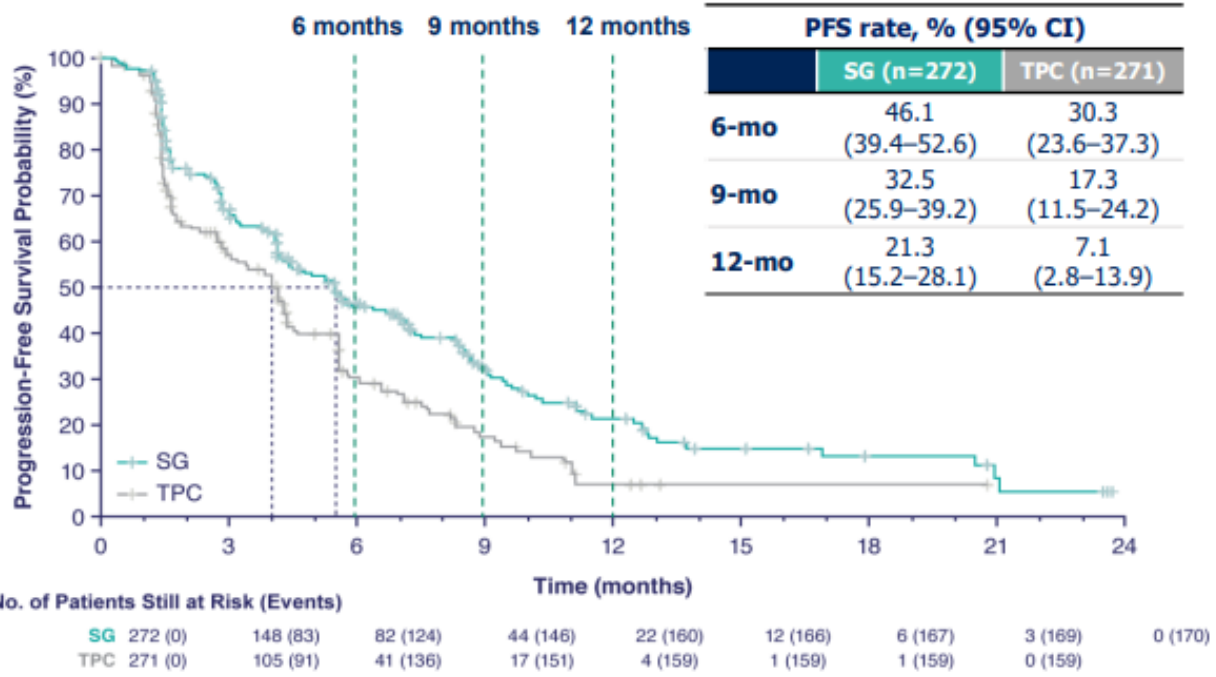
1. Rugo HS, et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. (epub ahead of print).

TROPiCS-02

Sacituzumab Improved PFS and OS

PFS[1]

BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



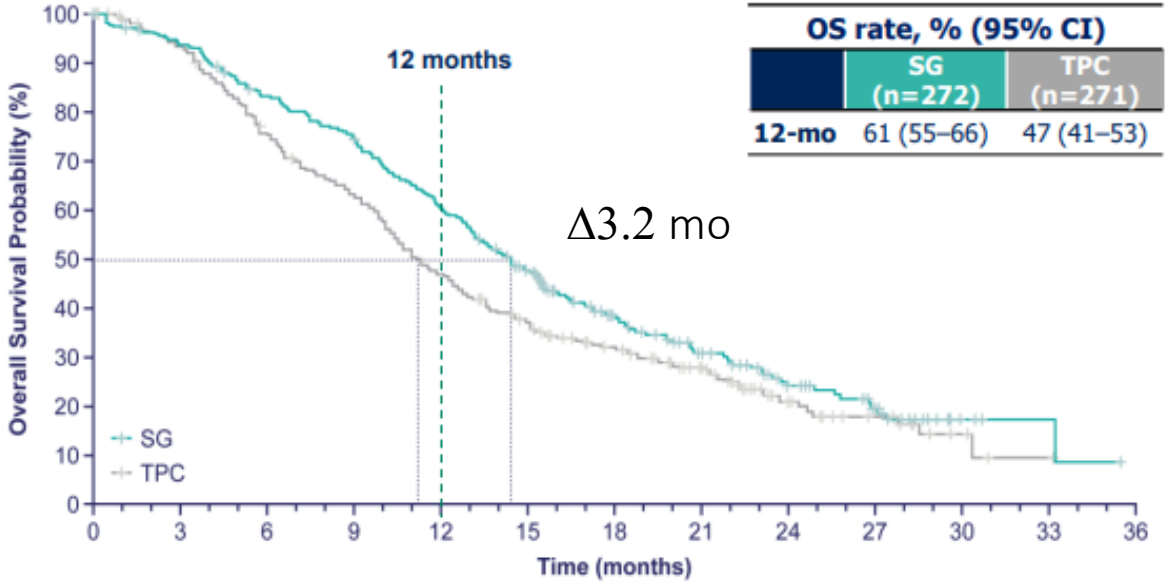
PFS rate, % (95% CI)	SG (n=272)	TPC (n=271)
6-mo	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-mo	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-mo	21.3 (15.2–28.1)	7.1 (2.8–13.9)

No. of Patients Still at Risk (Events)

SG	272 (0)	148 (83)	82 (124)	44 (146)	22 (160)	12 (166)	6 (167)	3 (169)	0 (170)
TPC	271 (0)	105 (91)	41 (136)	17 (151)	4 (159)	1 (159)	1 (159)	0 (159)	

OS[2]

	SG (n=272)	TPC (n=271)
Median OS, mo (95% CI)	14.4 (13.0–15.7)	11.2 (10.1–12.7)
Stratified HR (95% CI)	**0.79** (0.65–0.96)	
Stratified Log Rank *P* value	*P*=0.020	



OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	61 (55–66)	47 (41–53)

No. of Patients Still at Risk (Events)

SG	272 (0)	252 (16)	221 (44)	197 (67)	160 (104)	120 (137)	80 (158)	53 (173)	31 (183)	20 (188)	4 (190)	2 (190)	0 (191)
TPC	271 (0)	246 (16)	196 (64)	164 (95)	122 (137)	92 (163)	70 (174)	49 (183)	23 (193)	13 (196)	5 (198)	1 (199)	0 (199)

Median follow-up was 10.2 months.
BICR, blinded independent central review; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Rugo H et al. J clin Oncol. 2022; 40: 3365-3376
Rugo H et al. ESMO 2022. Abstract LBA76

TROPiCS-02: Response Rates and Subgroup Analysis

BICR analysis	SG (n=272)	TPC (n=271)
ORR, n (%)	57 (21)	38 (14)
Odds ratio (95% CI)	1.63 (1.03–2.56), *P*=0.035	
Best overall response, n (%)		
CR	2 (1)	0
PR	55 (20)	38 (14)
SD	142 (52)	106 (39)
SD ≥6 mo	35 (13)	22 (8)
PD	58 (21)	76 (28)
NE	15 (6)	51 (19)
CBR,[a] n (%)	92 (34)	60 (22)
Odds ratio (95% CI)	1.80 (1.23–2.63), *P*=0.003	
Median DOR, mo (95% CI)	8.1 (6.7–9.1)	5.6 (3.8–7.9)

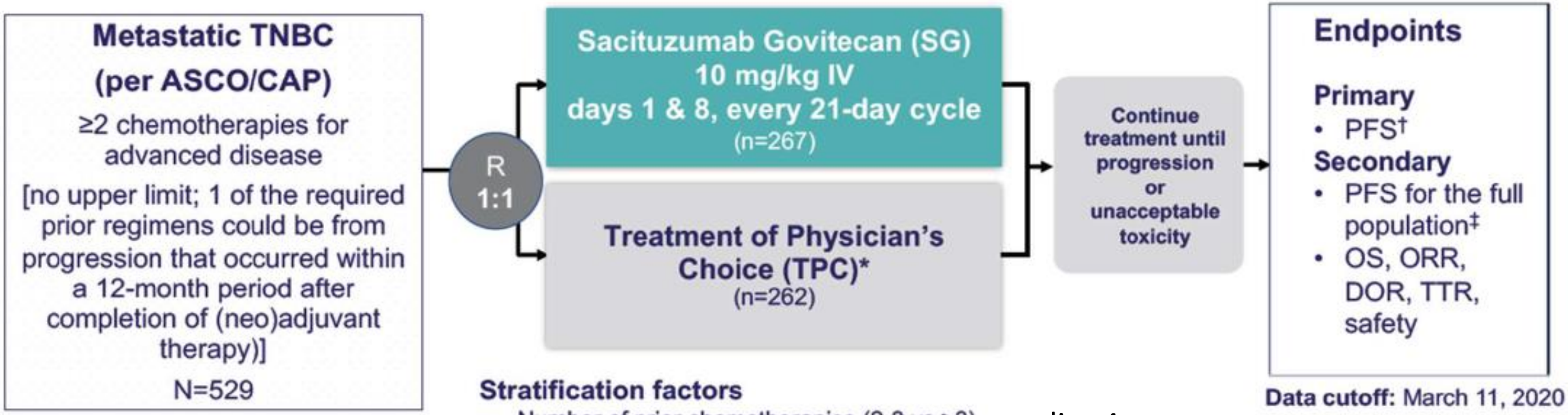
Significant improvement in ORR and Prolonged DOR

- ~95% of evaluable samples had Trop-2 expression
  - Response, PFS, OS benefit and similar safety profile seen across all Trop-2 subgroups including those with low expression (H-Score ≤10, but smaller subset n= 34 vs. 45)
- 52% were HER2 low, 40% HER2 0 (null)
  - Improved DOR and PFS with similar safety profile in HER2 low/null

Rugo H et al. ESMO 2022. Abstract LBA76
Rugo H et al. SABCS 2022; GS5-11

Schmid P et al. ESMO2022. Abstract 214MO

ASCENT: Sacituzumab in Refractory mTNBC



NCT02574455

Stratification factors

- Number of prior chemotherapies (2-3 vs >3) -median 4
- Geographic region (North America vs Europe)
- Presence/absence of known brain metastases (yes/no)

Data cutoff: March 11, 2020

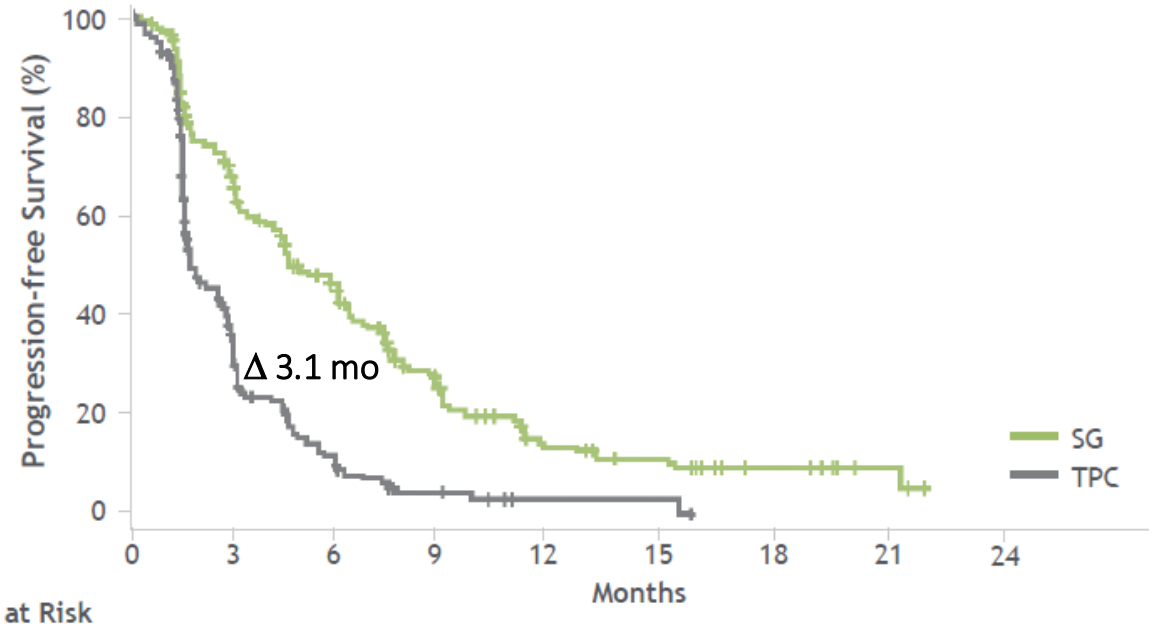
* TPC options: capecitabine, eribulin, gemcitabine, vinorelbine

	SG (n=235)	TPC (n=233)
Previous anticancer regimens† —median no. (range)	4 (2-17)	4 (2-14)
Most common previous chemotherapy—no. (%)		
Taxane‡	235 (100)	233 (100)
Anthracycline§	191 (81)	193 (83)
Cyclophosphamide	192 (82)	192 (82)
Carboplatin	147 (63)	160 (69)
Capecitabine	147 (63)	159 (68)
Most common sites of disease¶—no. (%)		
Lung only	108 (46)	97 (42)
Liver	98 (42)	101 (43)
Bone	48 (20)	55 (24)

Bardia et al. ESMO 2020. LBA17; N Engl J Med. 2021;384(16):1529-1541.

ASCENT: Sacituzumab Improves PFS and OS

Progression Free Survival



No. at Risk

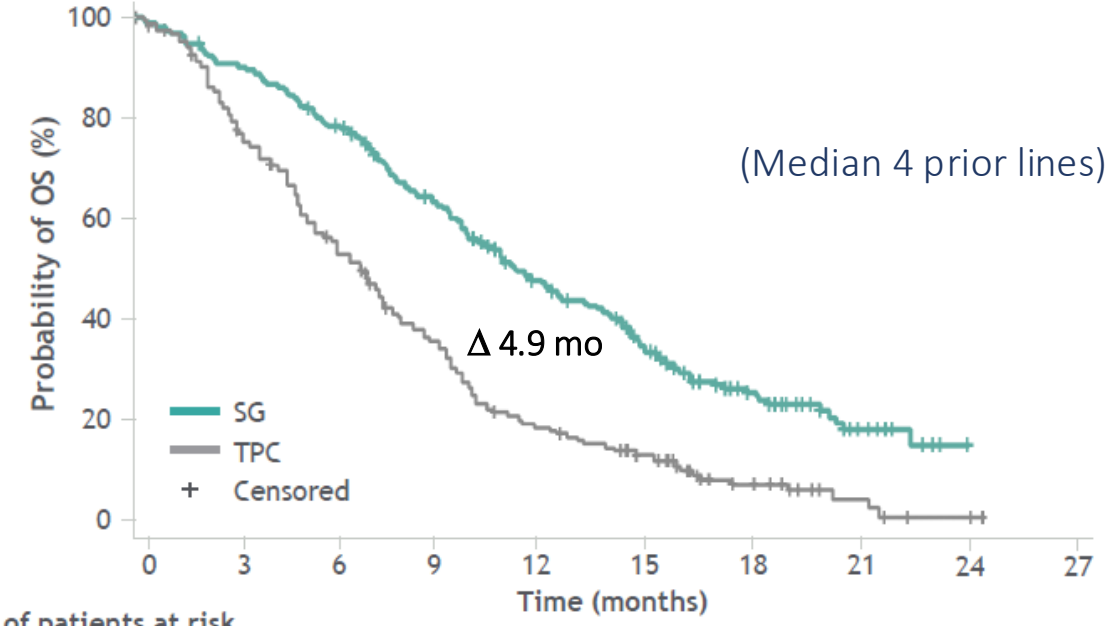
SG	267	145	82	38	23	14	8	1
TPC	262	41	13	6	2	1	0	0

	SG (n=267)	TPC (n=262)
Median PFS –mo (95% CI)	4.8 (4.1-5.8)	1.7 (1.5-2.5)
HR (95% CI)	0.43 (0.35-0.54)	

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)
6.9 (5.8-7.4)	2.5 (1.5-2.9)	5.6 (2.9-8.2)	2.2 (1.4-4.3)	2.7 (1.4-5.8)	1.6 (1.4-2.7)

Overall Survival

(Median 4 prior lines)



No. of patients at risk

SG	267	260	250	242	232	219	208	189	174	164	145	127	116	109	98	76	56	46	39	31	21	13	8	1	0	0
TPC	262	239	222	192	174	150	132	113	97	84	64	58	52	46	42	34	24	17	14	9	6	5	3	2	1	0

	SG (n=267)	TPC (n=262)
Median OS –mo (95% CI)	11.8 (10.5-13.8)	6.9 (5.9-7.7)
HR (95% CI)	0.51 (0.41-0.62)	

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)
14.2 (11.3-17.5)	6.9 (5.3-8.9)	14.9 (6.9-NE)	6.9 (4.6-10.1)	9.3 (7.5-17.8)	7.6 (5.0-9.6)

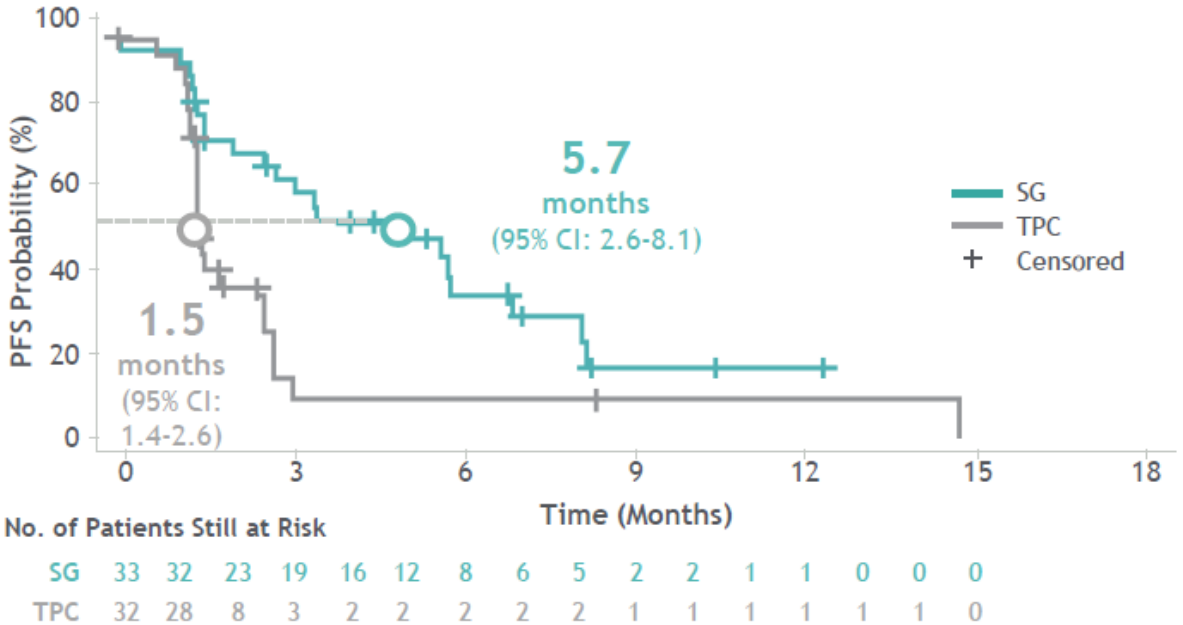
PFS and OS Benefits with Sacituzumab seen across Trop 2 expression subgroups and especially in high/medium expressers

Bardia A, et al. *JCO* 2024;42 (15):1738-1744

Bardia A et al. Ann Oncol. 2021;32(9):1148-1156

Subgroup Analysis: PFS and OS in the 2L Metastatic Setting in the BMNeg Population

Progression Free Survival

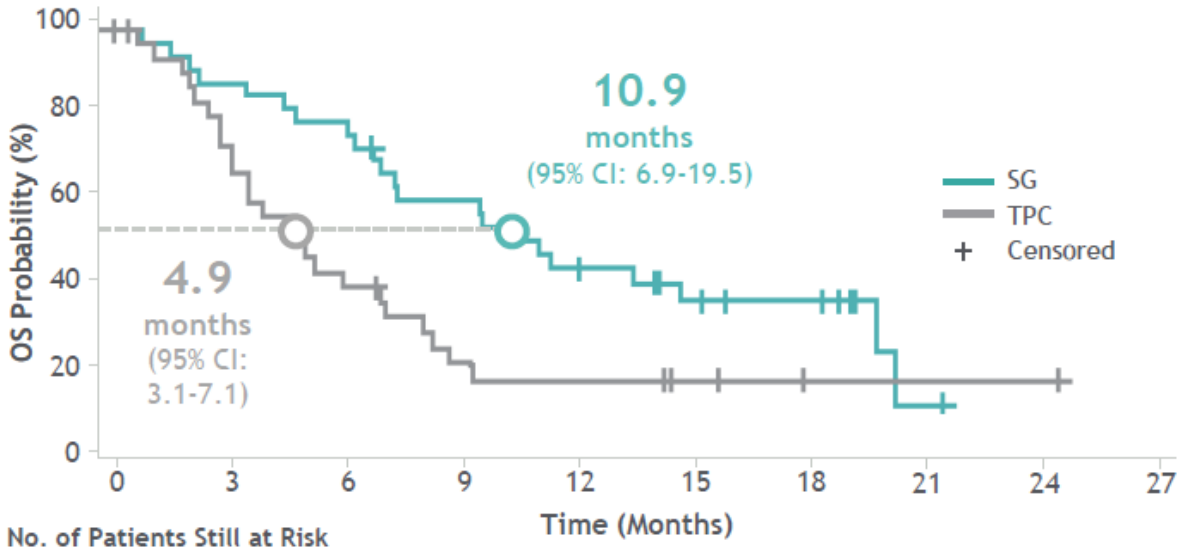


No. of Patients Still at Risk

SG	33	32	23	19	16	12	8	6	5	2	2	1	1	0	0	0	
TPC	32	28	8	3	2	2	2	2	2	1	1	1	1	1	1	0	

BICR Analysis	SG (n=33)	TPC (n=32)
No. of events	21	23
Median PFS—mo (95% CI)	5.7 (2.6-8.1)	1.5 (1.4-2.6)
HR (95% CI)	0.41 (0.22-0.76)	

Overall Survival



No. of Patients Still at Risk

SG	33	32	31	29	28	26	26	21	19	19	17	15	13	13	11	9	7	7	7	4	2	1	0	0	0	0
TPC	32	29	27	22	17	14	12	10	8	6	5	5	5	5	5	3	2	2	1	1	1	1	1	1	1	0

	SG (n=33)	TPC (n=32)
No. of events	22	24
Median OS—mo (95% CI)	10.9 (6.9-19.5)	4.9 (3.1-7.1)
HR (95% CI)	0.51 (0.28-0.91)	

Patients treated with SG vs. TPC demonstrated improved mPFS of 5.7 vs 1.5 months and mOS of 10.9 vs 4.9 months

Assessed by independent central review in the brain metastasis-negative population who recurred ≤12 months after (neo)adjuvant chemotherapy and received 1 line of therapy in the metastatic setting, prior to study enrollment.

Carey, LA et al. NPJ Breast cancer 2022;8 (1): 72

ASCENT: Adverse Events

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

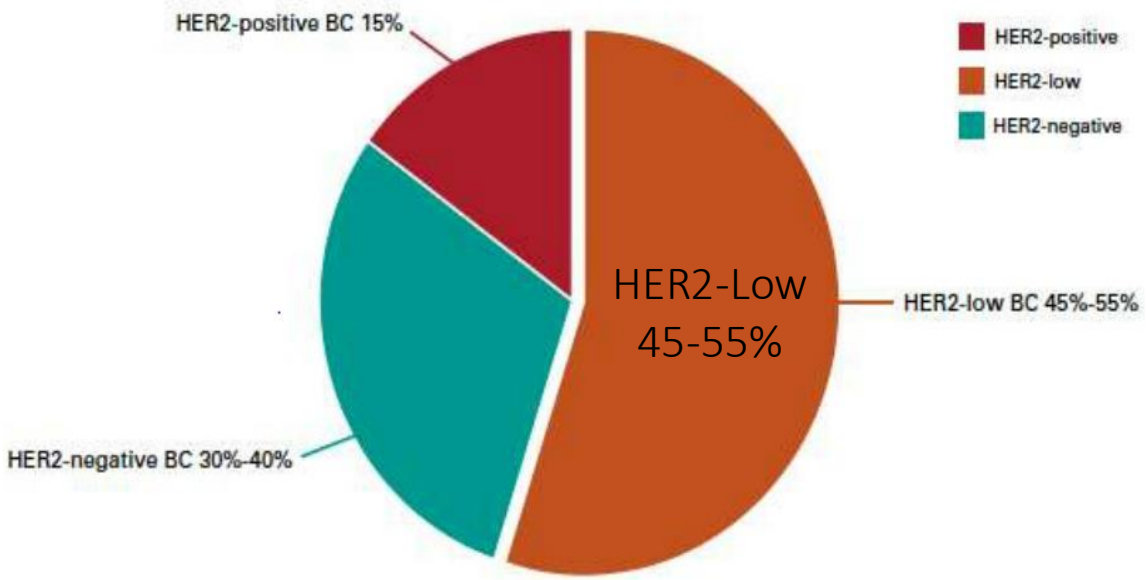
		SG (n=258)			TPC (n=224)		
	TRAE*	**All grade %**	**Grade 3, %**	**Grade 4, %**	**All grade, %**	**Grade 3, %**	**Grade 4, %**
Hematologic	**Neutropenia†**	**63**	**46**	**17**	**43**	**27**	**13**
	Anemia‡	**34**	**8**	**0**	**24**	**5**	**0**
	Leukopenia§	16	10	1	11	5	1
	Febrile neutropenia	6	5	1	2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

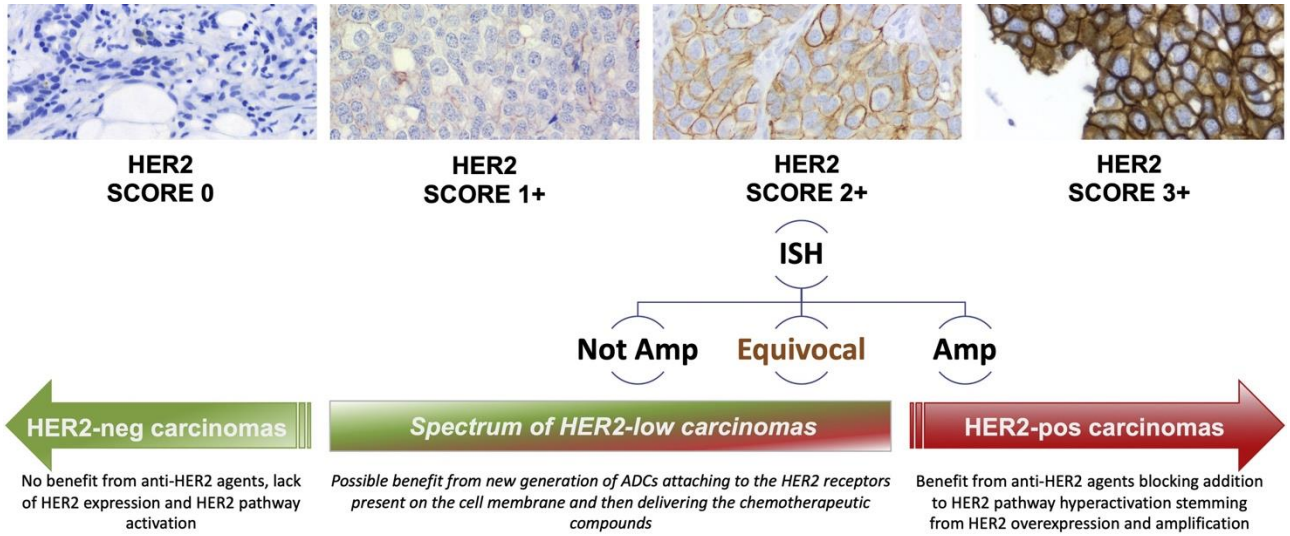
Dose interruptions[1]	61%	33%
Dose reductions[2]	22%	26%
Treatment discontinuation[2]	4.7%	5.4%

Fewer dose modifications and discontinuations due to AEs were observed in SG vs. TPC patients

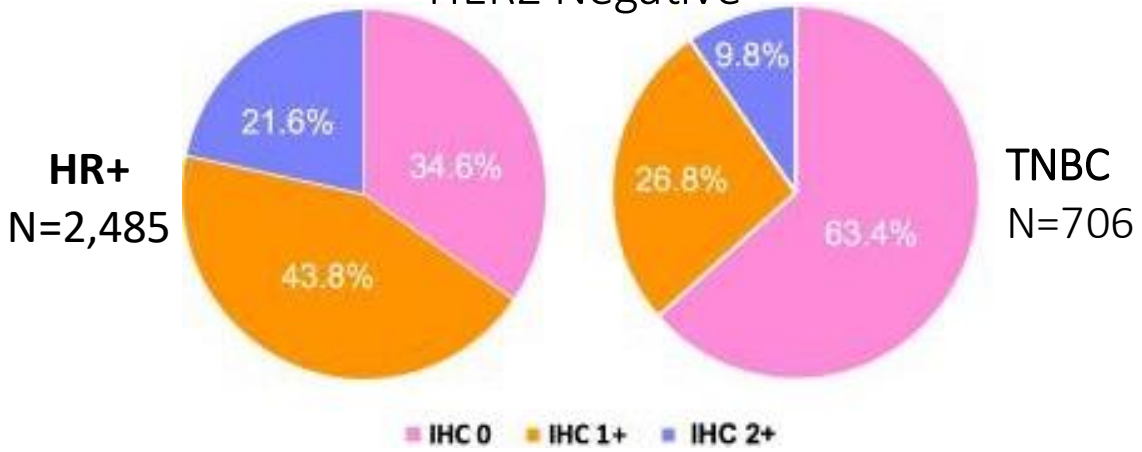
Rugo H et al. npj Breast Cancer 8, 98 (2022)

Prevalence by HER2 expression





HER2 Negative



HER2 Low Disease

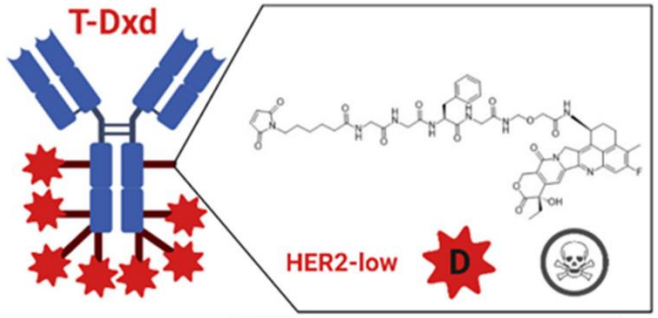
- 65% HR+ vs. 37% TNBC
- Change through disease course

(Primary vs. Recurrent, Pre vs. Post neoadjuvant)

- Clinically and Prognostically similar to Her2 0

Tarantino P et al. J Clin Oncol. 2020;38(17):1951-1962 Schettni F, et al. NPJ Breast Cancer 2021; 7 (1): 1
Marchiò C, Annaratone L et al. Semin Cancer Biol. 2021 Jul;72:123-135 Viale, G et al. J Clin Oncol. 2022; 40(16):1087

DESTINY-Breast-04
T-DXd in HER2-low Advanced Breast Cancer



Target Antigen: HER2 (trastuzumab vehicle)
mAb isotype: IgG1
Linker type: cleavable
Payload (class): Dxd (Camptothecin)
Payload action: Topoisomerase-1 inhibitor
DAR: 8

Patients[a]
- HER2-low (IHC 1+ vs IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

HR+ ≈ 480
HR− ≈ 60

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[b]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

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−

Chemotherapy, n (%)	
Eribulin	94 (51.1)
Capecitabine	37 (20.1)
Nab-paclitaxel	19 (10.3)
Gemcitabine	19 (10.3)
Paclitaxel	15 (8.2)

Modi S, et al. ASCO 2022. Abstract LBA3. Modi S, et al. NEJM 2022. Corti C et al. Cancers. 2021; 13 (12):2898

DESTINY-Breast-04: Baseline Characteristics

	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Age, median (range), years	57 (32-80)	56 (28-80)	58 (32-80)	56 (28-80)
HER2 status (IHC), n (%)				
1+	193 (58)	95 (58)	215 (58)	106 (58)
2+/ISH−	138 (42)	68 (42)	158 (42)	78 (42)
ECOG performance status, %				
0	187 (56)	95 (58)	200 (54)	105 (57)
1	144 (44)	68 (42)	173 (46)	79 (43)
Hormone receptor,[a] n (%)				
Positive	328 (99)	162 (99)	333 (89)	166 (90)
Negative	3 (1)	1 (1)	40 (11)	18 (10)
Brain metastases at baseline, n (%)	18 (5)	7 (4)	24 (6)	8 (4)
Liver metastases at baseline, n (%)	247 (75)	116 (71)	266 (71)	123 (67)
Lung metastases at baseline, n (%)	98 (30)	58 (36)	120 (32)	63 (34)

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]Hormone receptor status is based on data collected using the interactive web/voice response system at the time of randomization, which includes misstratified patients.

Modi S, et al. ASCO 2022. Abstract LBA3. Modi S, et al. NEJM 2022

DESTINY-BREAST-04: Prior Treatments

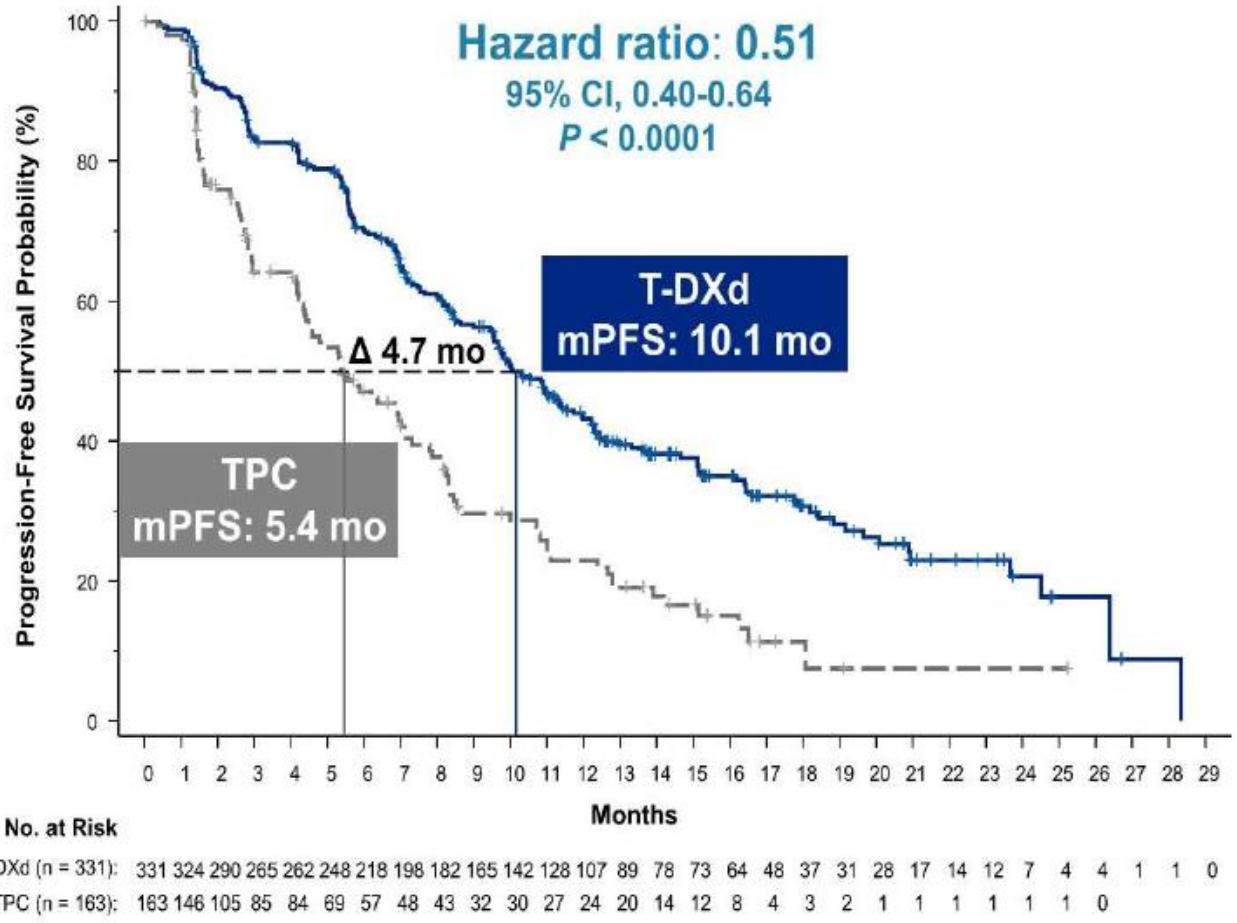
	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Lines of systemic therapy (metastatic setting)				
Number of lines, median (range)	3 (1-9)	3 (1-8)	3 (1-9)	3 (1-8)
Number of lines, n (%)				
1	23 (7)	14 (9)	39 (10)	19 (10)
2	85 (26)	41 (25)	100 (27)	53 (29)
≥3	223 (67)	108 (66)	234 (63)	112 (61)
Lines of chemotherapy (metastatic setting)				
Number of lines, median (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
Number of lines, n (%)				
0	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)
1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
≥3	3 (0.9)	0	6 (1.6)	0
Lines of endocrine therapy (metastatic setting)				
Number of lines, median (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
Number of lines, n (%)				
0	28 (8)	17 (10)	60 (16)	34 (18)
1	105 (32)	49 (30)	108 (29)	51 (28)
2	110 (33)	53 (33)	115 (31)	54 (29)
≥3	88 (27)	44 (27)	90 (24)	45 (24)
Prior targeted cancer therapy, n (%)				
Targeted therapy	259 (78)	132 (81)	279 (75)	140 (76)
CDK4/6 inhibitor	233 (70)	115 (71)	239 (64)	119 (65)

Based on derived data, which includes protocol deviations. CDK, cyclin-dependent kinase; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

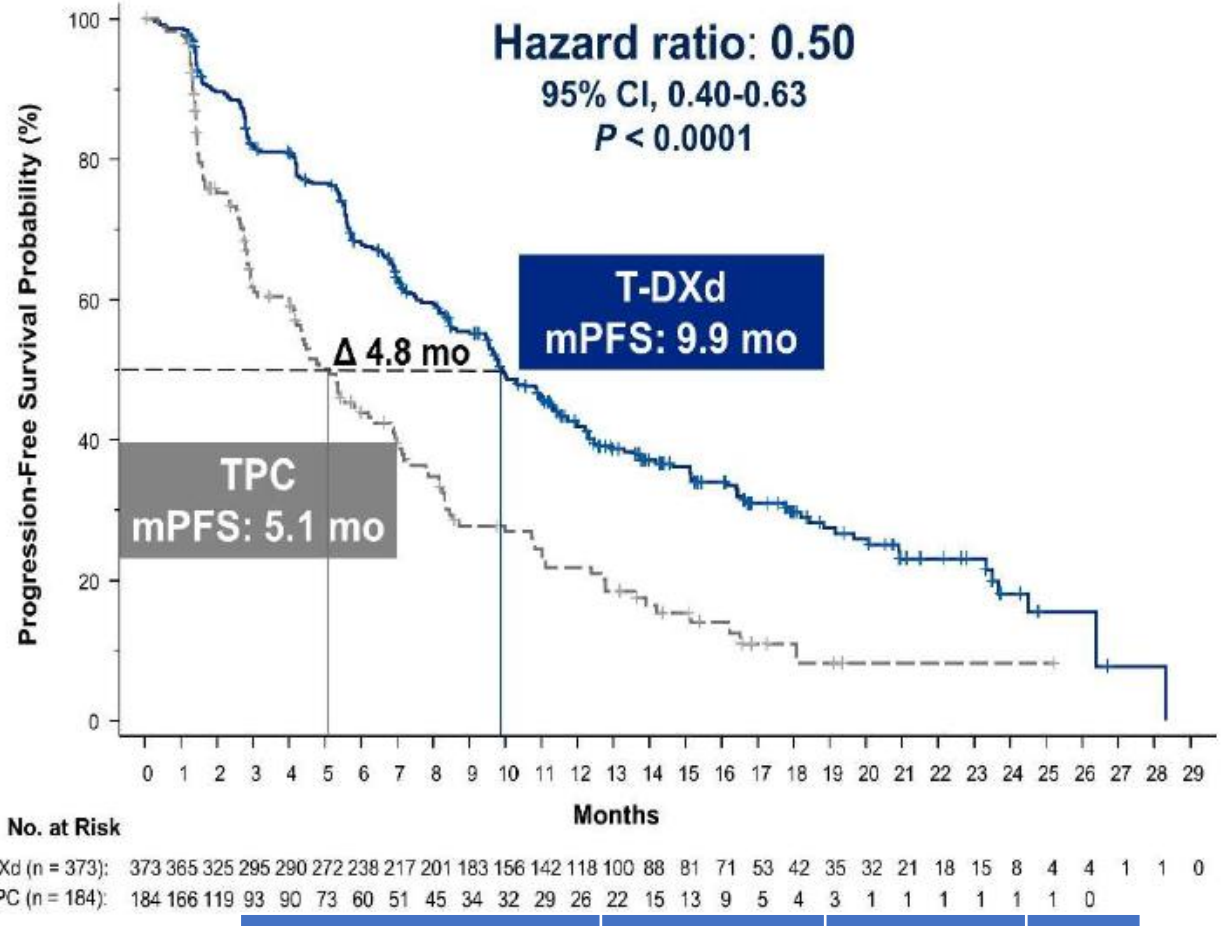
Modi S, et al. ASCO 2022. Abstract LBA3. Modi S, et al. NEJM 2022

DESTINY-BREAST-04: PFS in HR+ and ALL Patients

Hormone receptor–positive



All patients



Hormone Negative	T-DXd (40)	TPC (18)	HR
mPFS, mo	8.5 Δ5.6 2.9		0.46

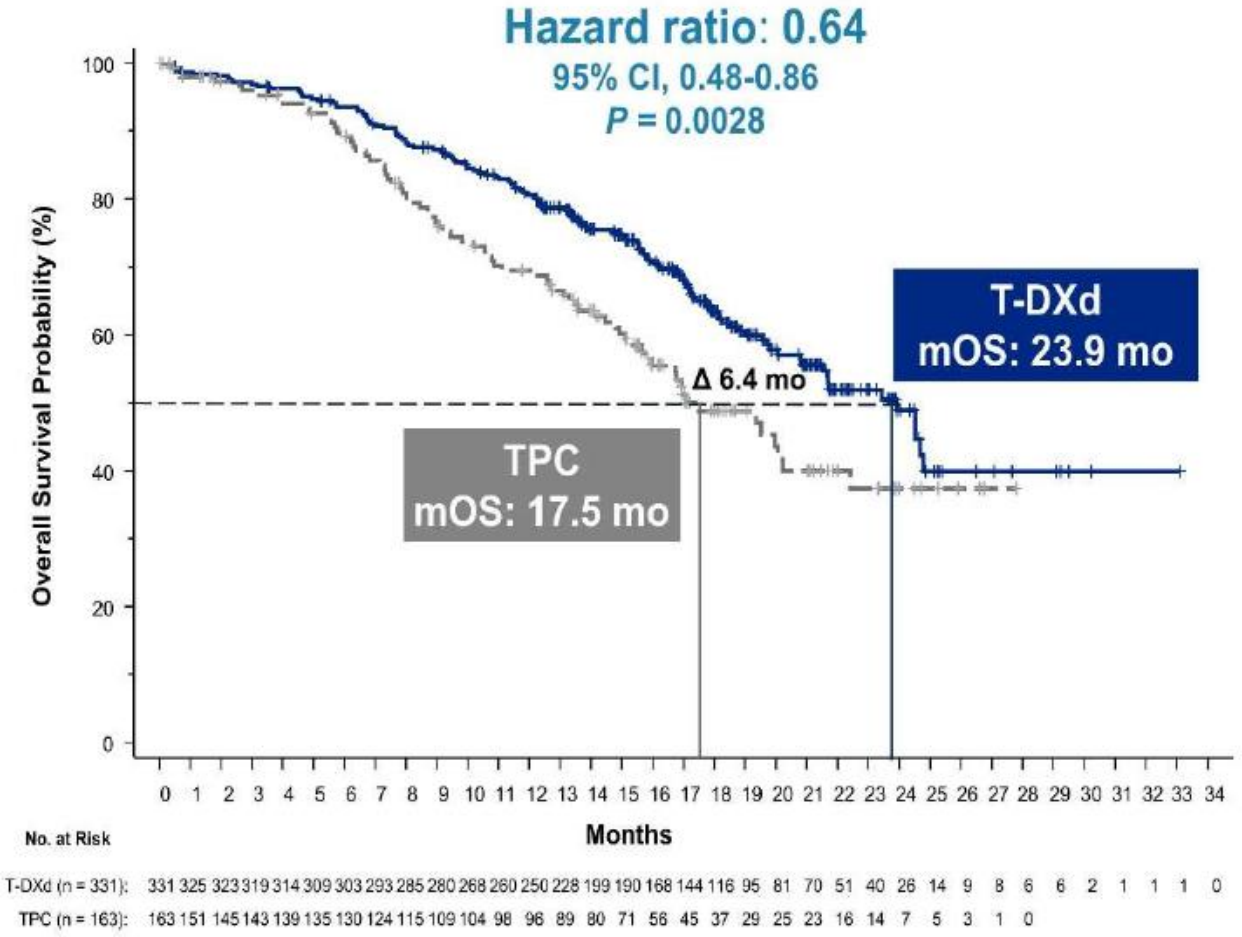
PFS by blinded independent central review.

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

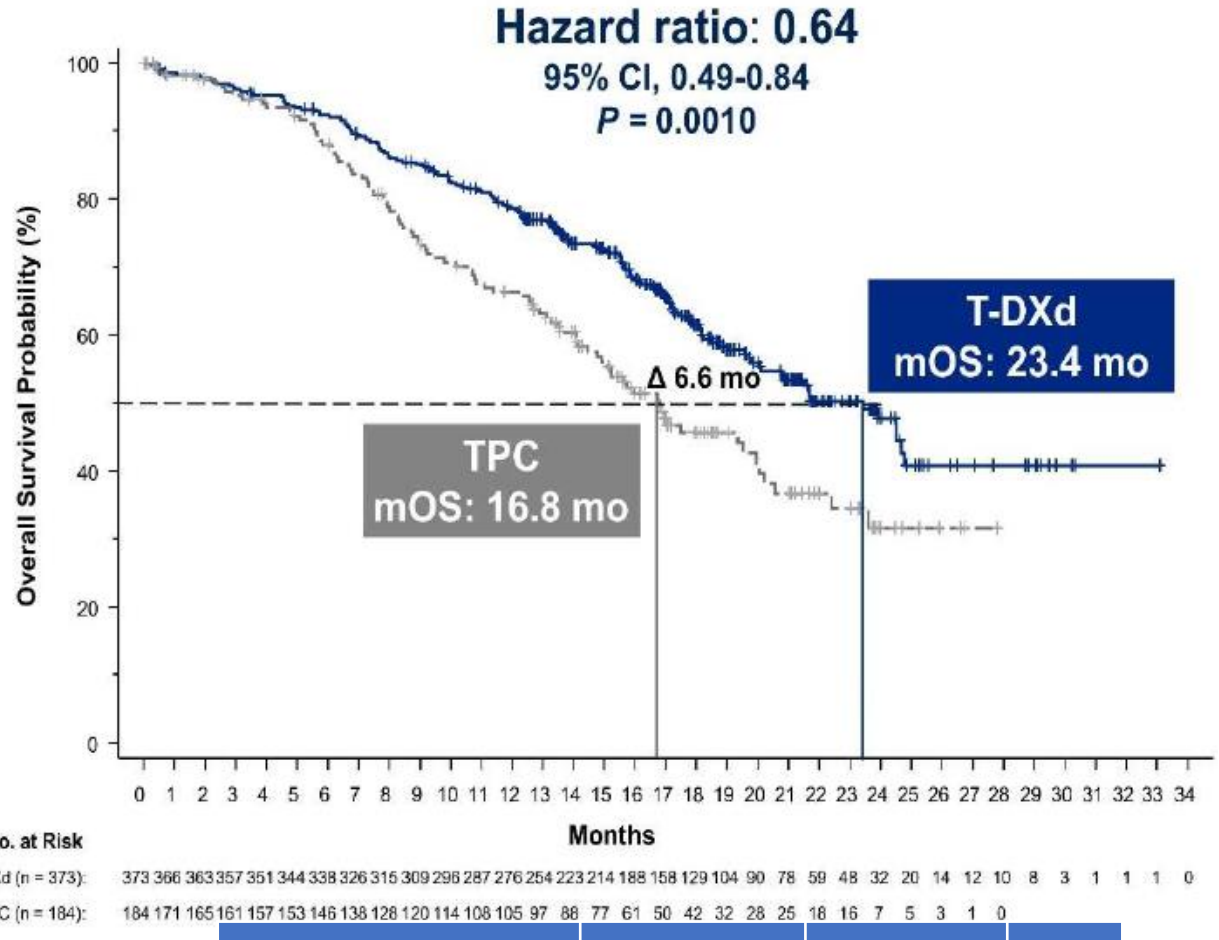
Modi S, et al. ASCO 2022. Abstract LBA3. Modi S, et al. NEJM 2022

DESTINY-BREAST-04: OS in HR+ and ALL Patients

Hormone receptor–positive



All patients

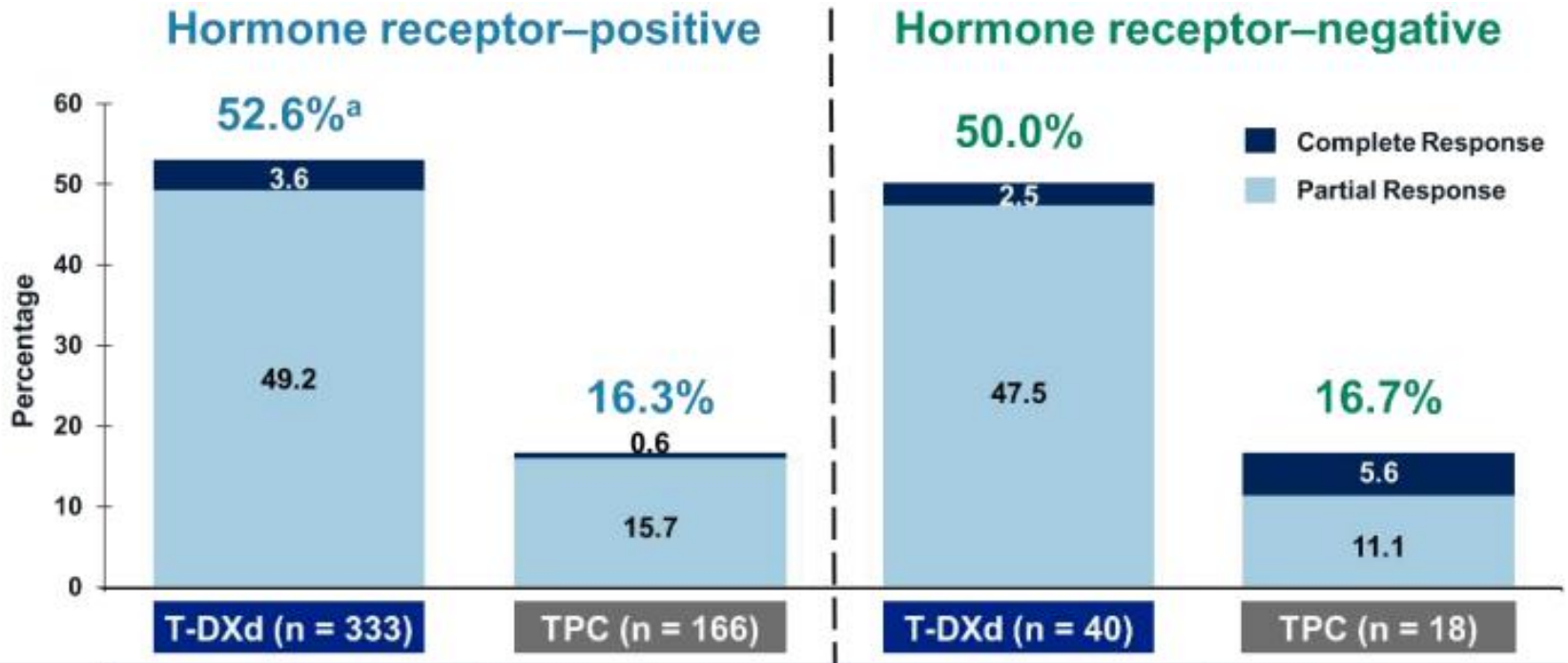


HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Hormone Negative	T-DXd (40)	TPC (18)	HR
mOS, mo	18.2 Δ9.9	8.3	0.48

Modi S, et al. ASCO 2022. Abstract LBA3. Modi S, et al. NEJM 2022

DESTINY-BREAST-04: Objective Response Rate



	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

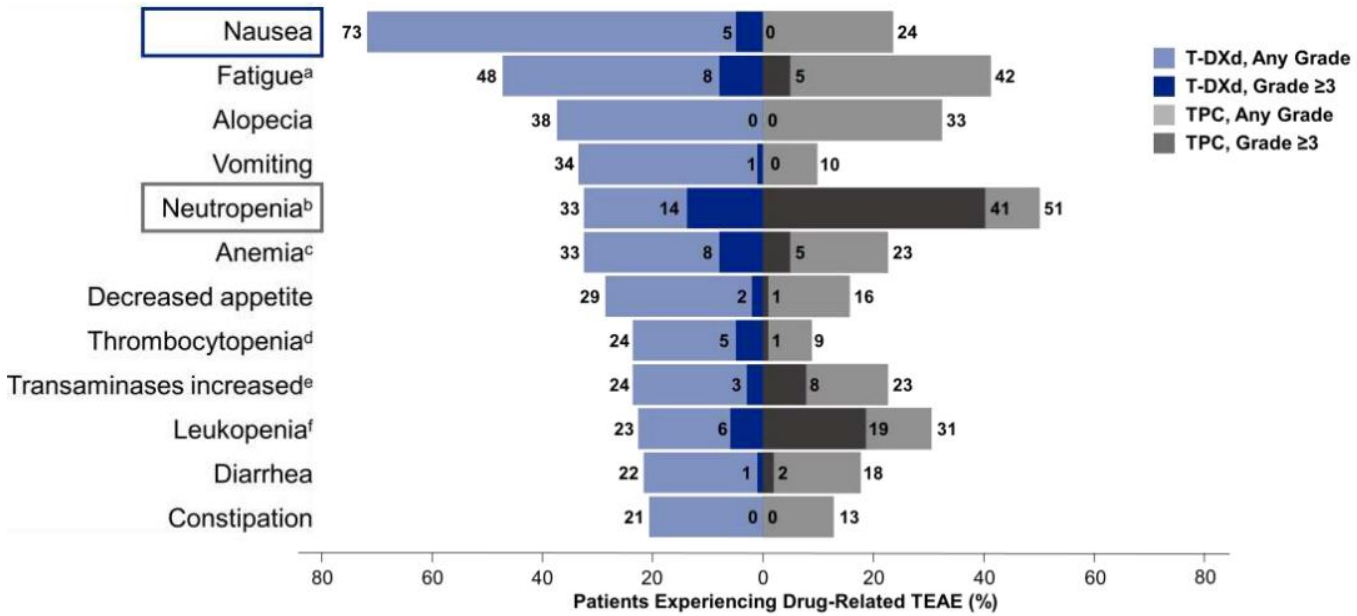
Hormone receptor status is based on data from the electronic data capture corrected for misstratification.
ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]The response of 1 patient was not confirmed. [b]Clinical benefit rate is defined as the sum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

Modi S, et al. ASCO 2022. Abstract LBA3. Modi S, et al. NEJM 2022

DESTINY-BREAST-04

Safety Analysis

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 coun 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.

		Safety analysis set[a]	
	Median treatment duration T-DXd: 8.2 months (range, 0.2-33.3) TPC: 3.5 months (range, 0.3-17.6)	**T-DXd (n = 371)**	**TPC (n = 172)**
n (%)			
Total patient-years of exposure, years[b]		283.55	63.59
TEAEs		369 (99)	169 (98)
Grade ≥3		195 (53)	116 (67)
Serious TEAEs		103 (28)	43 (25)
TEAEs associated with dose discontinuations		60 (16)	14 (8)
TEAEs associated with dose interruptions		143 (39)	72 (42)
TEAEs associated with dose reductions		84 (23)	66 (38)
TEAEs associated with deaths		14 (4)	5 (3)

AEs of Special Interest, n (%)			Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
Adjudicated as drug-related ILD/pneumonitis[a]		**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]	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

- Most common TEAE associated with treatment discontinuation
  - T-DXd: 8.2%, ILD/pneumonitis[c]
  - TPC: 2.3%, peripheral sensory neuropathy
- Most common TEAE associated with dose reduction
  - T-DXd: 4.6%, nausea and fatigue[d]
  - TPC: 14.0%, neutropenia[d]
- Total on-treatment deaths[e]
  - T-DXd: 3.8%
  - TPC: 4.7%

Modi S, et al. ASCO 2022. Abstract LBA3. Modi S, et al. NEJM 2022

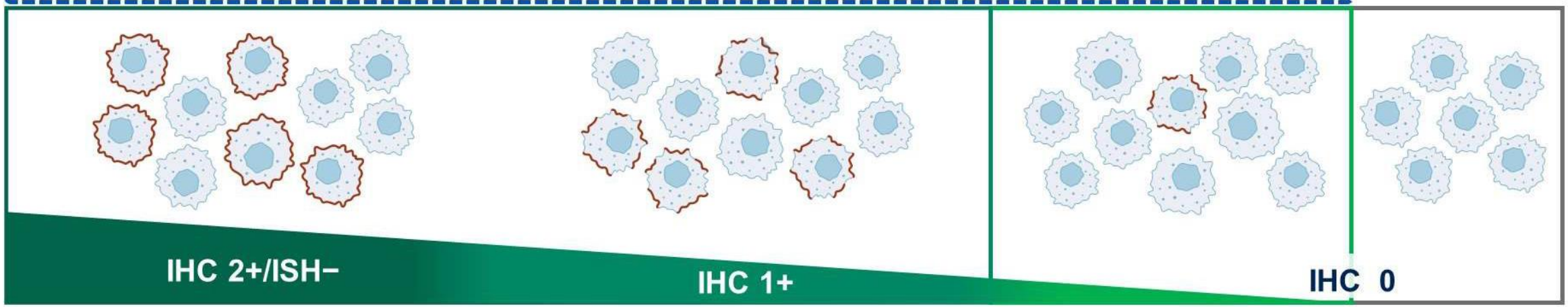
Targeting ‘low’ and ‘ultralow’ HER2-expressing tumors in mBC

HER2 IHC categories within HR+, HER2-negative (HER2−) mBC (per ASCO/CAP[1])

DESTINY-Breast06 patient population: ~85% of HR+, HER2− mBC

HER2-low ~60–65%[2,3]

HER2-ultralow ~20–25%[2–4]



IHC 2+/ISH−	IHC 1+	IHC 0	
Weak-to-moderate complete membrane staining in >10% tumor cells	Faint, incomplete membrane staining in >10% tumor cells	**Faint, incomplete membrane staining in ≤10% tumor cells**	Absent / no observable membrane staining

ASCO/CAP, American Society of Clinical Oncology / College of American Pathologists; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan

1. Wolff AC, et al. *J Clin Oncol.* 2023;41:3867–3872; 2. Denkert C, et al. *Lancet Oncol.* 2021;22:1151–1161; 3. Chen Z, et al. *Breast Cancer Res Treat.* 2023;202:313–323; 4. Mehta S, et al. *J Clin Oncol.* 2024;42(Suppl. 16):Abstract e13156

DESTINY-Breast06: a Phase 3, randomized, multicenter, open-label study (NCT04494425)

PATIENT POPULATION

- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- **Chemotherapy naïve in the mBC setting**

Prior lines of therapy

- ≥2 lines of ET ± targeted therapy for mBC
  OR
- 1 line for mBC **AND**
  - Progression ≤6 months of starting first-line ET + CDK4/6i
    OR
  - Recurrence ≤24 months of starting adjuvant ET

Stratification factors

- Prior CDK4/6i use (yes vs no)
- HER2 expression (IHC 1+ vs IHC 2+/ISH− vs IHC 0 with membrane staining)
- Prior taxane in the non-metastatic setting (yes vs no)

R 1:1

T-DXd
5.4 mg/kg Q3W
(n=436)

HER2-low = 713
HER2-ultralow = 153†

TPC
(n=430)

Options:
capecitabine,
nab-paclitaxel,
paclitaxel

ENDPOINTS

Primary

- PFS (BICR) in HER2-low

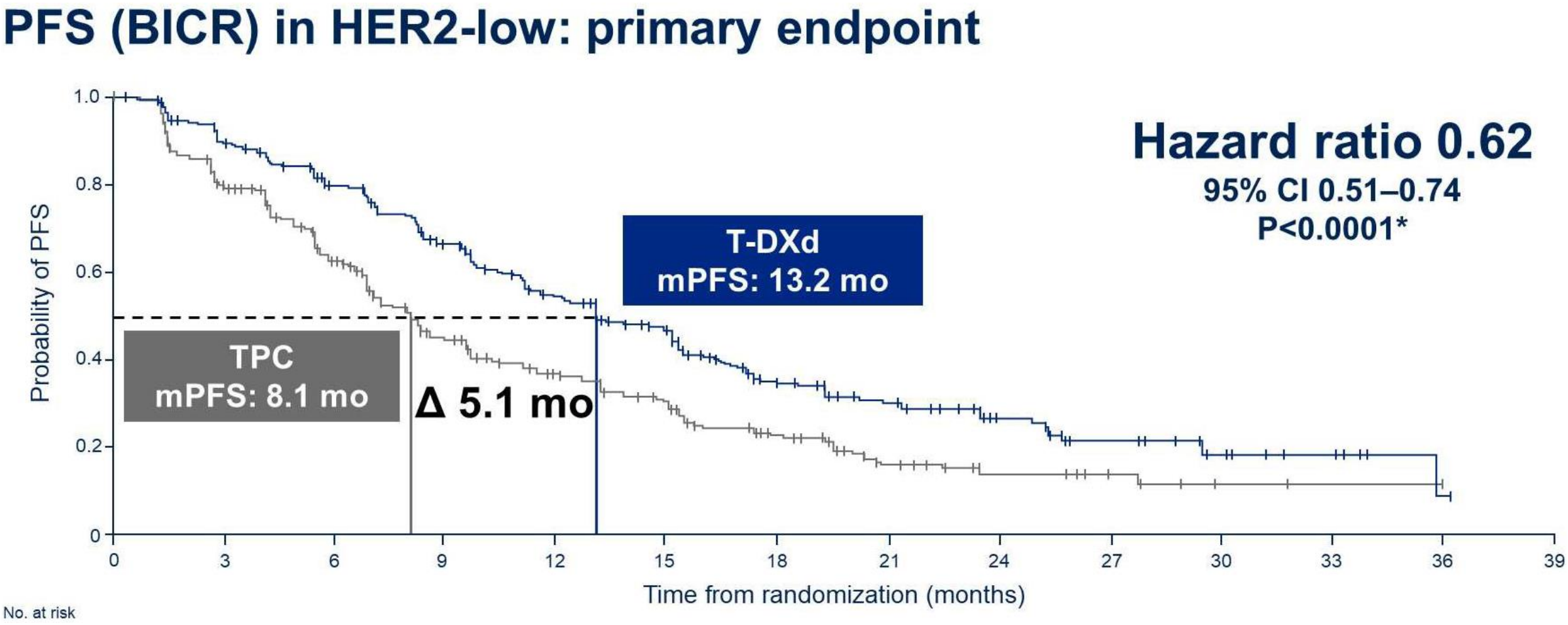
Key secondary

- PFS (BICR) in ITT (HER2-low + ultralow)
- OS in HER2-low
- OS in ITT (HER2-low + ultralow)

Median prior ET for MBC: 2
88-90% prior CDKi
47-55% prior adj/neoadj chemo

*Study enrollment was based on central HER2 testing. HER2 status was determined based on the most recent evaluable HER2 IHC sample prior to randomization. HER2-ultralow was defined as faint, partial membrane staining in ≤10% of tumor cells (also known as IHC >0<1+); †HER2-ultralow status as determined per IRT data (note: efficacy analyses in the HER2-ultralow subgroup were based on n=152 as determined per central laboratory testing data); ‡to be presented separately
BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; INV, investigator assessed; IRT, interactive response technology; ISH, in situ hybridization; ITT, intent-to-treat; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice
NCT04494425. Updated. April 12, 2024. Available from: https://clinicaltrials.gov/study/NCT04494425 (Accessed May 13, 2024)

DESTINY-Breast-06: T-DXd improved PFS in HER2-low MBC



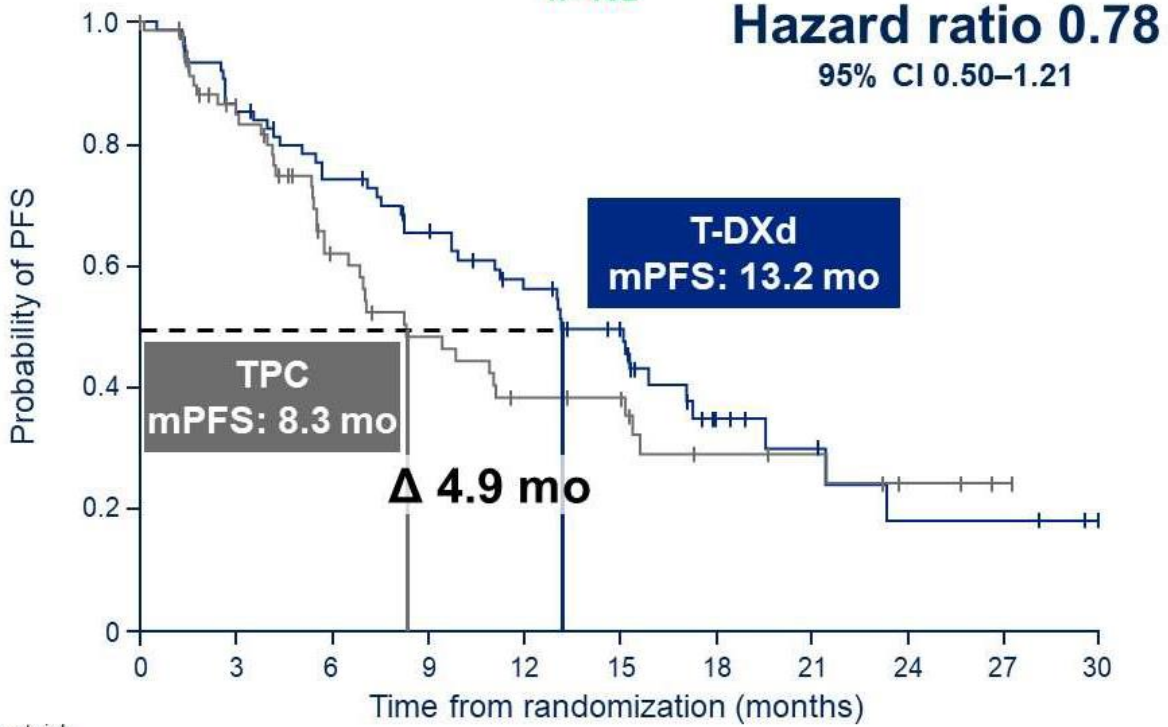
Curigliano G. Et al ASCO 2024

Bardia et al N Engl J Med 2024

PFS and OS in HER2-ultralow: prespecified exploratory analyses

PFS (BICR)

n=152

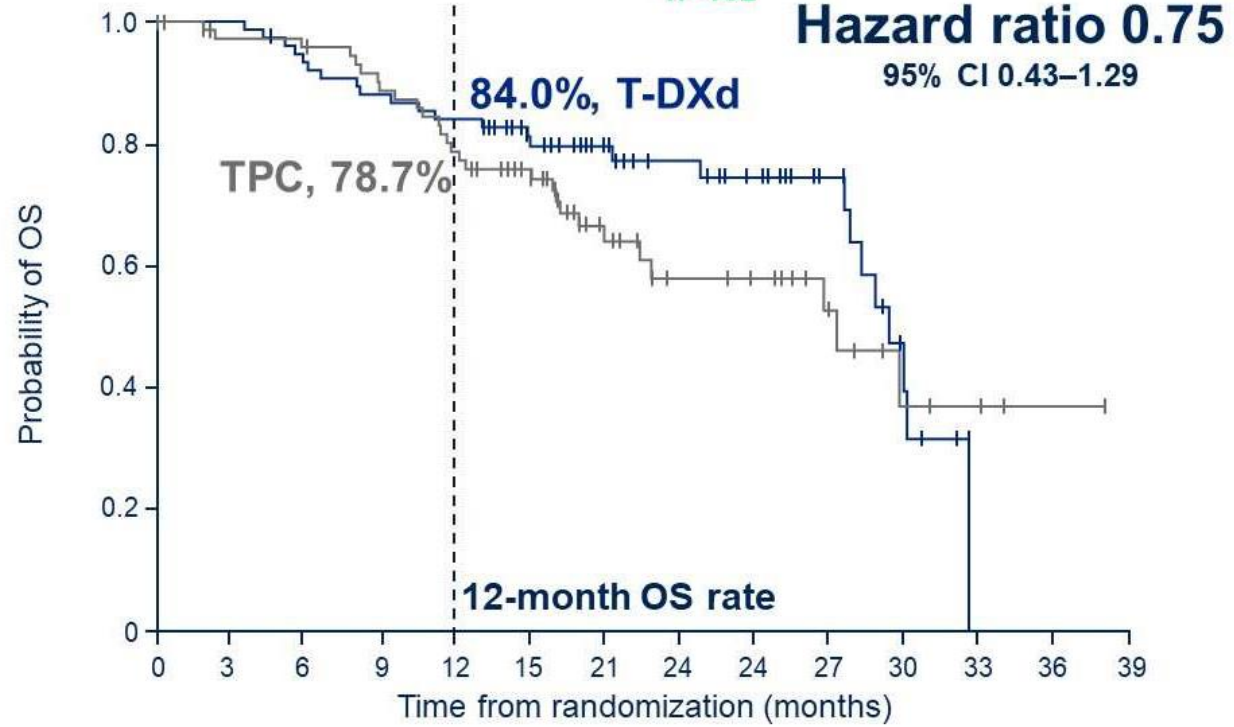


No. at risk

T-DXd	76	64	53	44	35	24	9	6	3	3	0
TPC	76	52	32	24	18	14	7	6	3	1	0

OS*

n=152



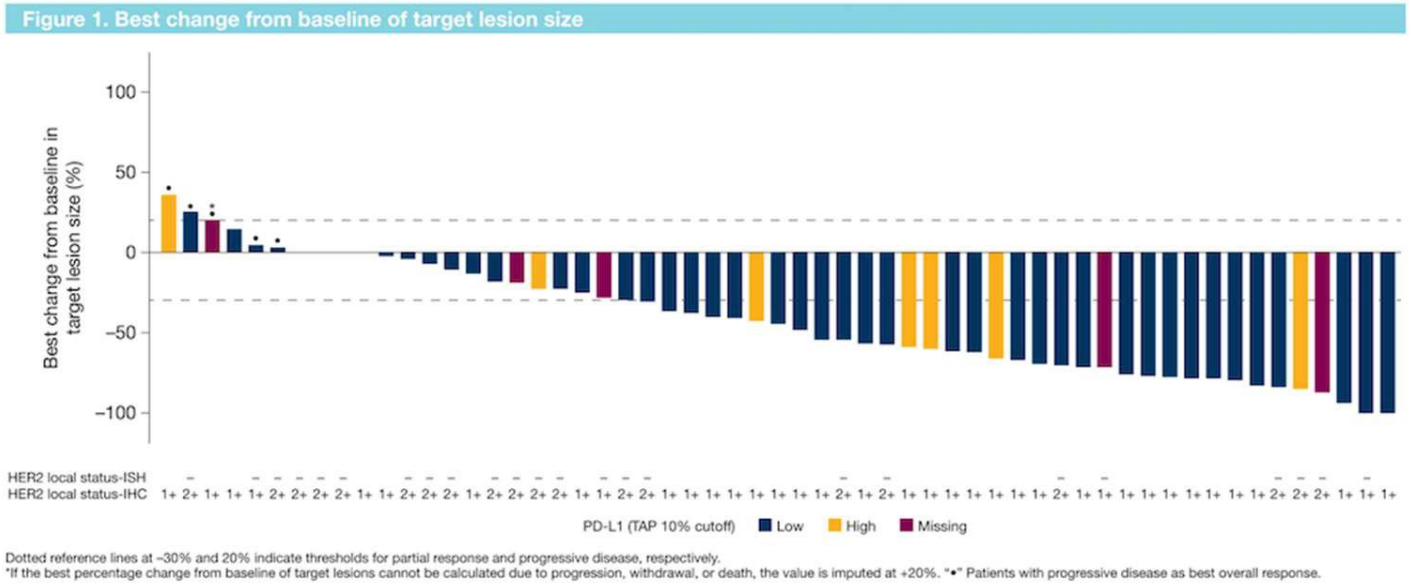
76	76	70	66	63	49	36	28	23	15	6	0	0	0
76	69	68	62	55	45	25	17	15	9	4	3	1	0

PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

*34.9% maturity (of total N for population) at this first interim analysis; median duration of follow up was 16.8 months

BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; OS, overall survival; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

BEGONIA 1st line mTNBC HER2 low Arm 6: TDXd+ Durvalumab



N=56
ORR 57%
mPFS 12.6 mo

-Notable frequent AEs: nausea, fatigue, neutropenia
-8 ILD cases (1 G5)
-43% G3/4
-Discontinuation rate 17%
-TDxd delay or reduction 51%

Table 2. Safety summary

	N=58
Any Grade AE, n (%)	57 (98.3)
Common AEs (≥20% patients, any grade)	
Nausea	45 (77.6)
Fatigue	30 (51.7)
Neutropenia	18 (31.0)
Vomiting	17 (29.3)
Alopecia	16 (27.6)
Decreased appetite	15 (25.9)
Anemia, constipation	14 (24.1) each
Asthenia, diarrhea	12 (20.7) each
Any Grade 3/4 AE	25 (43.1)
Any serious AE	12 (20.7)
Any treatment-related AE[a]	55 (94.8)
Grade 3/4	20 (34.5)
Any durvalumab AESI	43 (74.1)
Any T-DXd AESI	13 (22.4)
AE leading to T-DXd + D discontinuation	10 (17.2)
AE leading to dose interruption	32 (55.2)
AE leading to death[b]	2 (3.4)
Durvalumab dose delay	26 (44.8)
T-DXd dose delay	24 (41.4)
T-DXd dose reduction	6 (10.3)

AESI, adverse event of special interest.

Schmidt et al. SABCS Poster 2022

TROPION-Breast01: Datopotomab Deruxtecan in HR+ MBC

Dato-DXd:

- Anti-TROP2 IgG1
- Topo I inhibitor payload
- Cleavable linker
- DAR: 4
- Bystander effect

Key inclusion criteria:

- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

1:1

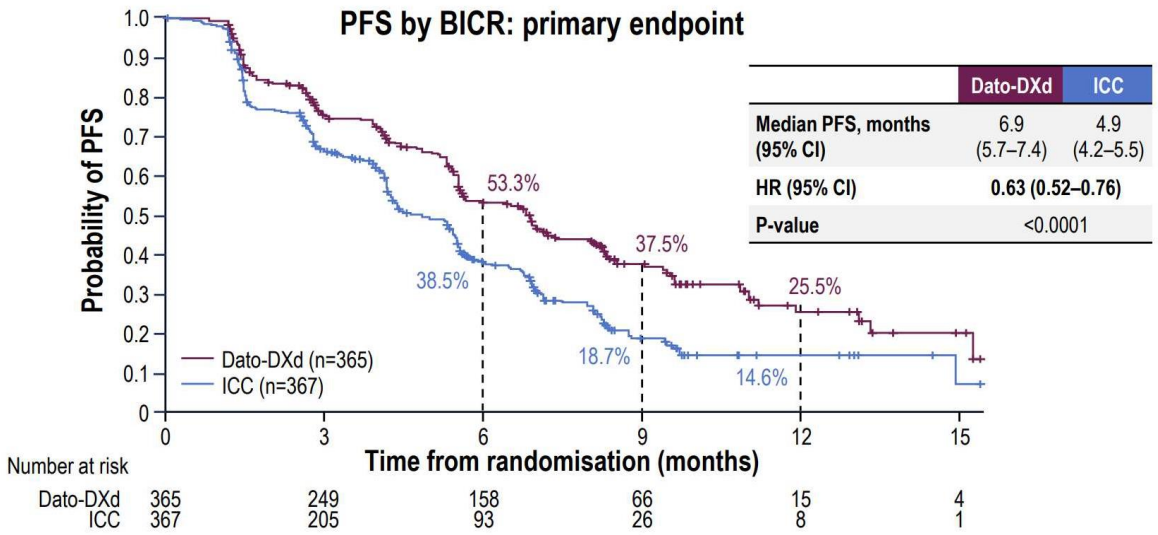
Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

Investigator's choice of chemotherapy (ICC)
as per protocol directions†
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Key secondary:** ORR, PFS (investigator assessed) and safety

Progression-Free Survival



	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.7–7.4)	4.9 (4.2–5.5)
HR (95% CI)	0.63 (0.52–0.76)	
P-value	<0.0001	

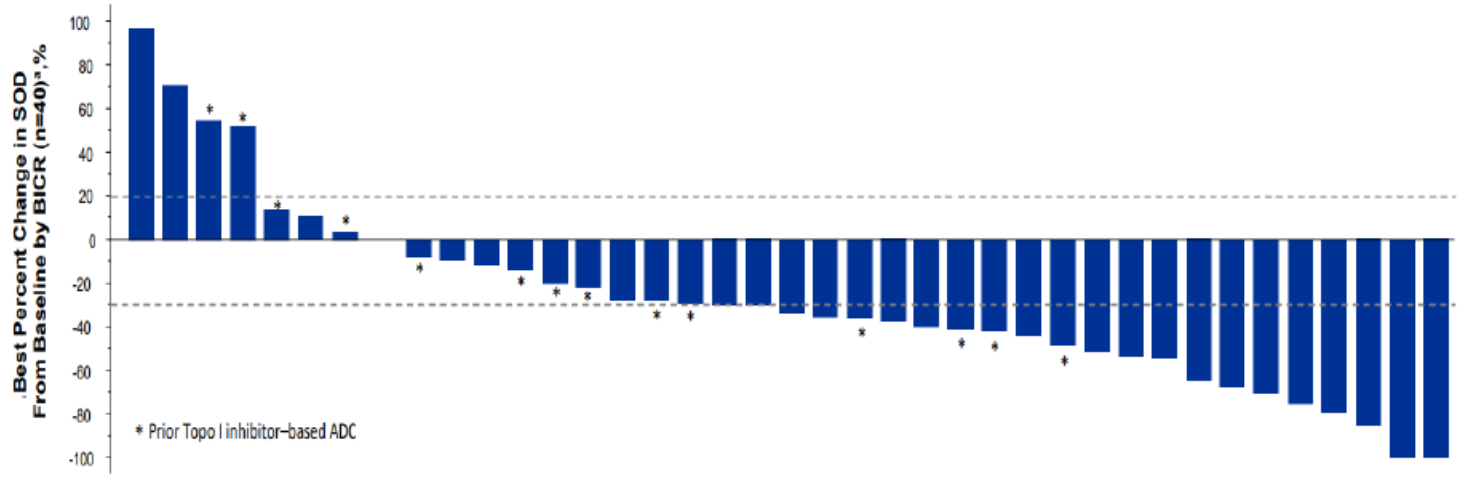
PFS by investigator assessment: Median 6.9 vs 4.5 months; HR 0.64 (95% CI 0.53–0.76)

TRAEs Occurring in >15% of Patients: Most grade 1-2, ILD 3%

System Organ Class Preferred term, n (%)	Dato-DXd (n=360)		ICC (n=351)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood and lymphatic system				
Anaemia	40 (11)	4 (1)	69 (20)	7 (2)
Neutropenia*	39 (11)	4 (1)	149 (42)	108 (31)
Eye				
Dry eye	78 (22)	2 (1)	27 (8)	0
Gastrointestinal				
Nausea	184 (51)	5 (1)	83 (24)	2 (1)
Stomatitis	180 (50)	23 (6)	46 (13)	9 (3)
Vomiting	71 (20)	4 (1)	27 (8)	2 (1)
Constipation	65 (18)	0	32 (9)	0
General				
Fatigue	85 (24)	6 (2)	64 (18)	7 (2)
Skin and subcutaneous				
Alopecia	131 (36)	0	72 (21)	0

Bardia A et al. ESMO 2023. Abstract LBA11

TROPION-PANTumor01: Dato-DXd for Refractory mTNBC



[a] Postbaseline tumor assessments were not available for 1 patient at data cutoff. Three patients were not confirmed to have a target lesion per BICR and therefore had a best overall response of non-CR/non-PD.

Prior treatment included Sacituzumab govitecan (same AB, different payload, n=11; trastuzumab deruxtecan (different AB, same payload, n=2; patritumab deruxtecan (HER3 AB, same payload), n=1.

PFS	Median (95% CI), mo	Events n/N (%)
All patients	4.4 (3.0-7.3)	29/44 (66)

OS	Median (95% CI), mo	Events n/N (%)
All patients	13.5 (10.1-16.3)	28/44 (64)

Patients, n (%)*	All TNBC patients (n=44)	Topo I inhibitor–naive patients with measurable disease at BL n=27
Objective response rate	14 (32)	12 (44)
Complete response	1 (2)	1 (4)
Partial response	13 (30)	11 (41)
Non-CR / non-PD	3 (7)	0
Stable disease	18 (41)	10 (37)
Not evaluable	1 (2)	1 (4)
Disease control rate	35 (80)	22 (81)
Clinical benefit rate[b]	17 (39)	13 (48)
Progressive disease	8 (18)	4 (15)
Duration of response, median (95% CI)	16.8 (5.6–NE)	16.8 (5.6–NE)

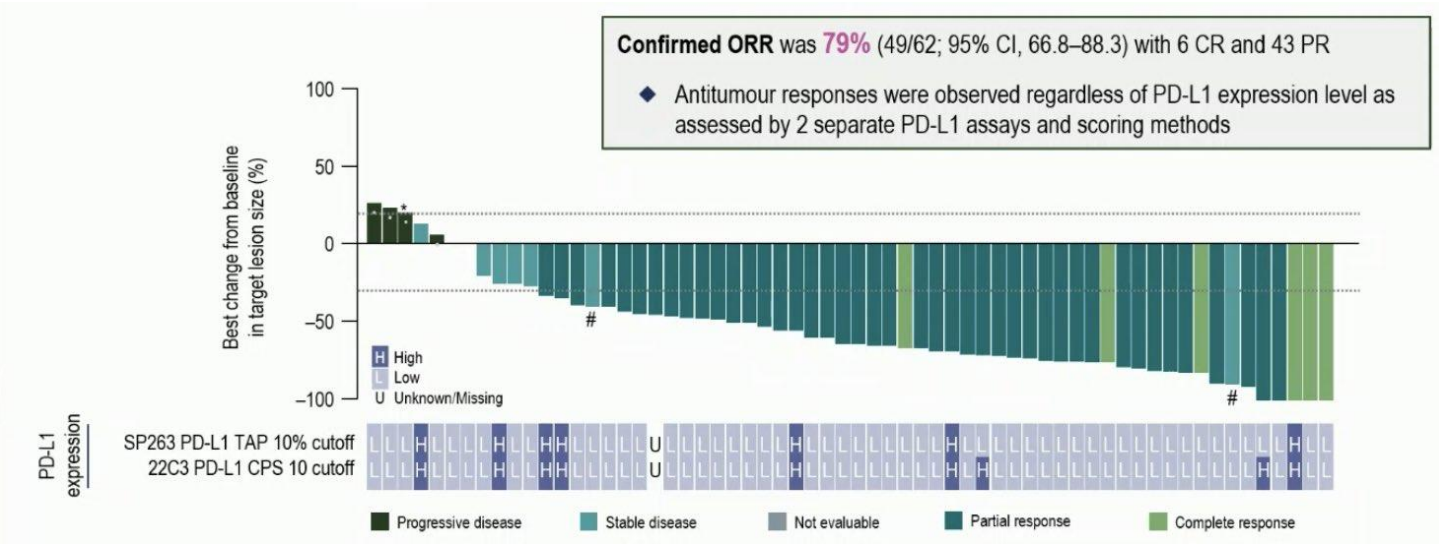
- In the overall TNBC cohort (n=44), an ORR by BICR of 32% and DCR by BICR of 80% were observed
- In patients who were treatment-naïve to topoisomerase I inhibitor-based ADC therapies (n=27), an ORR by BICR of 44% and DCR by BICR of 81% were observed 32% (n=14) had prior Topo 1 inhibitor based ADC, Median had 3 prior lines
- Mean DoR was 16.8 months in both groups

Data cutoff: July 22, 2022.

*Postbaseline tumor assessments were not available for 1 patient at data cut-off. Three patients were not confirmed to have a target lesion per BICR and therefore had a best overall response of non-CR/non-PD. bCR + PR + SD for ≥6 months..

Bardia A et al. Presented at: SABCS; Dec 6-10, 2022; San Antonio, TX. Poster P6-10-03.

BEGONIA 1st line mTNBC Arm 7: Dato-DXd+ Durvalumab



N=62
87% PDL1-
ORR 79%
mPFS 13.8 mo
DOR: 15.5 mo

-Notable frequent AEs: nausea, stomatitis, rash, dry eye, hypothyroidism (14.5%), keratitis (14.5%).
-ILD 5% (no G3/4)

Most frequently reported adverse events (≥15%) (N=62)

AE preferred term	Any grade, n (%)	Grade 3/4, n (%)
Nausea	40 (65)	0
Stomatitis	40 (65)	7 (11)
Alopecia	31 (50)	0
Constipation	29 (47)	1 (2)
Fatigue	28 (45)	1 (2)
Rash	20 (32)	0
Vomiting	16 (26)	1 (2)
Amylase increased	13 (21)	11 (18)
COVID-19	13 (21)	0
Dry eye	13 (21)	0
Decreased appetite	12 (19)	1 (2)
Pruritus	10 (16)	0
Cough	10 (16)	0

Schmidt et al. ESMO 2023

ICARUS-BREAST01: Phase 2 of Patritumab deruxtecan in HR+ MBC

- HER3 overexpressed in 30-50% of breast cancers

HER3-DXd

- Anti HER3 IgG1
- Topo 1 payload (DXd)
- Cleavable linker
- DAR: 8
- Bystander effect

KEY ELIGIBILITY CRITERIA*:

-unresectable locally advanced/metastatic BC
-HR+/HER2-neg[a]
-progression on CDK4/6inh + ET
-progression on 1 prior chemotherapy for ABC
-prior PI3K/AKT/mTORinh allowed
-no prior T-DXd

HER3-DXd 5.6 mg/kg every 3 weeks until PD or unacceptable toxicity

HER3 expression prescreening (75% membrane positivity at 10x was removed 4/21/22)

Overall membrane positivity at 10x, n (%):	
<25%	16 (16.2)
25-74%	7 (7.1)
≥75%	49 (49.4)
Unknown	27 (27.3)
Median number of systemic therapies for ABC, n [range]	2 [1;4]

	N=99	
	n	% [95%CI][a]
Confirmed ORR[b]	**53**	**53.5** [43.2; 63.6]
CR	2	2.0 [0.2;7.1]
PR	51	51.5 [41.3; 61.7]
SD	37	37.4 [27.8; 47.7]
PD	7	7.1 [2.9; 14.0]
NE[c]	2	2.0 [0.2;7.1]
CBR[d]	**62**	**62.6** [52.3;72.1]

No significant association between HER2 expression and ORR (*p-value 0.8*)[e]

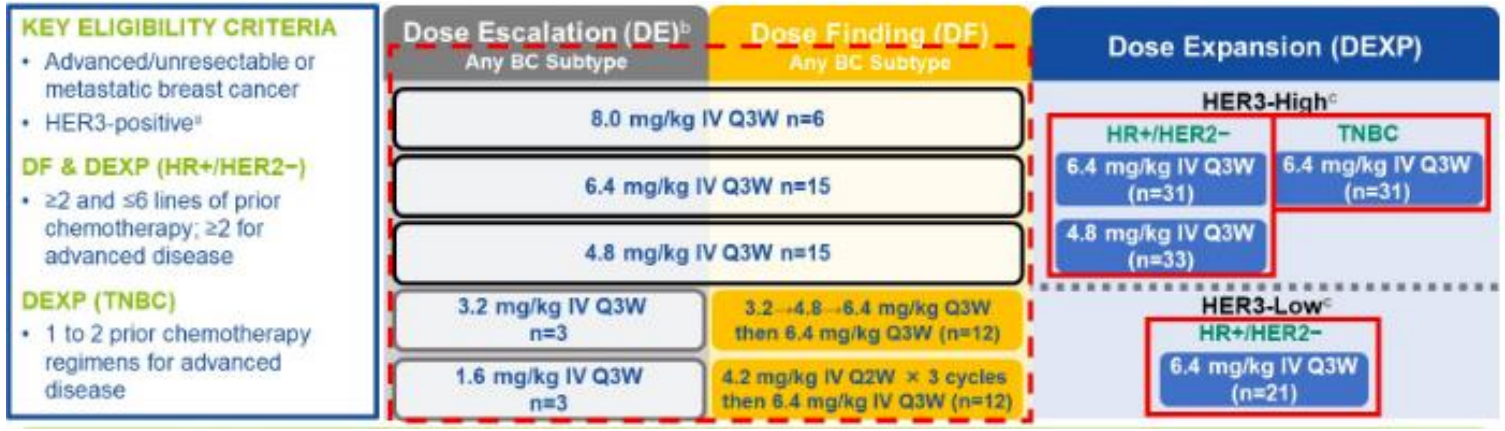
Pistilli B et al. ESMO Breast 2023.

Phase 1/2: Patritumab deruxtecan: HER3

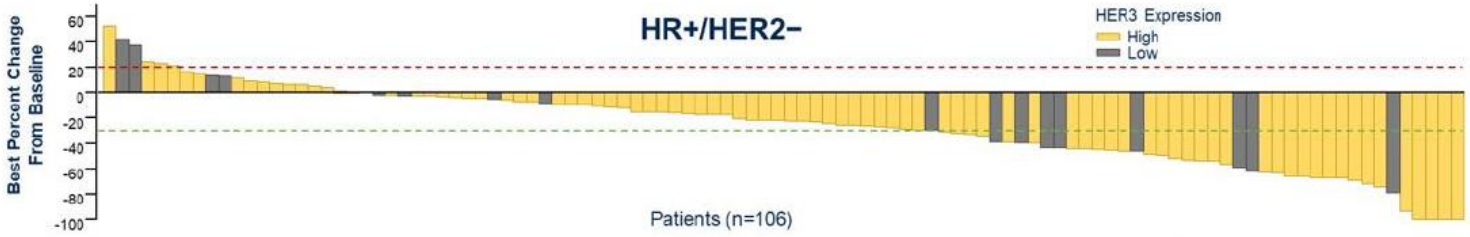
- HER3 overexpressed in 30-50% of breast cancers

HER3-DXd

- Anti HER3 IgG1
- Topo 1 payload (DXd)
- Cleavable linker
- DAR: 8
- Bystander effect



- N=113
- 90% Lung and/or Liver metastases
- Median 6 (2-13) prior lines
- Response across range of HER3+
- 6.6% patients with ILD (grade 1/2- 4.4% and 1 death)

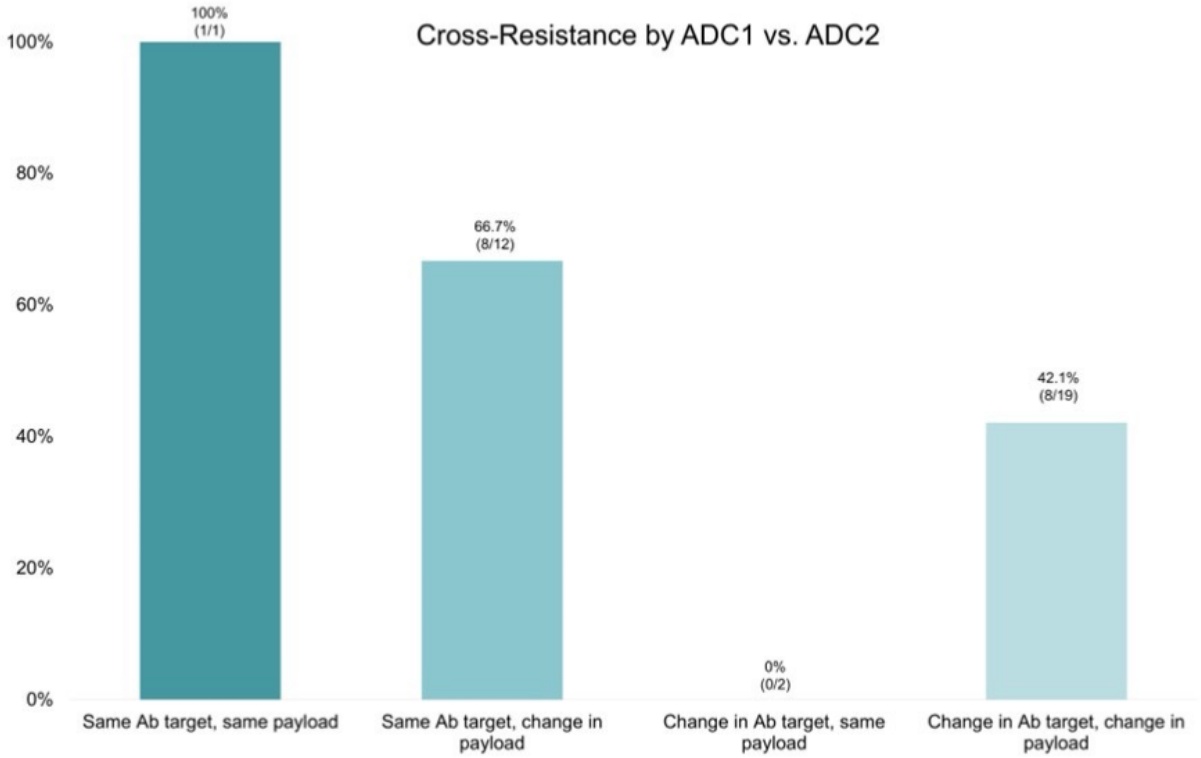


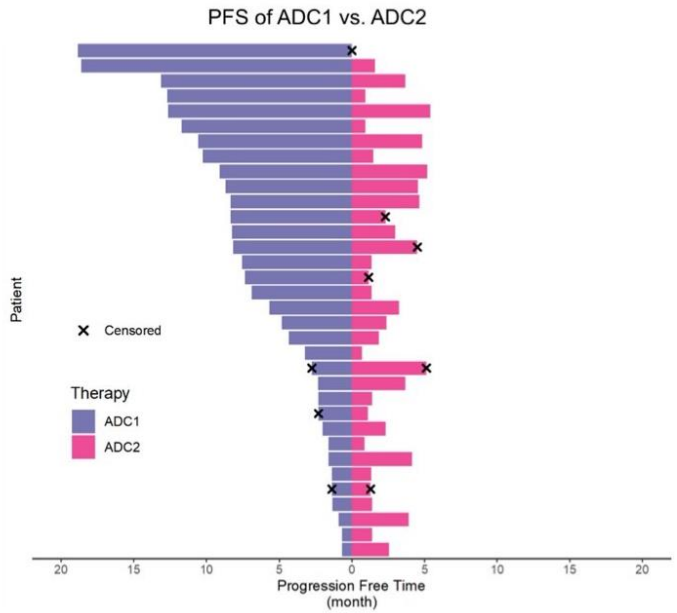
ORR	PFS	OS
30%	7.4 mo	14.6 mo

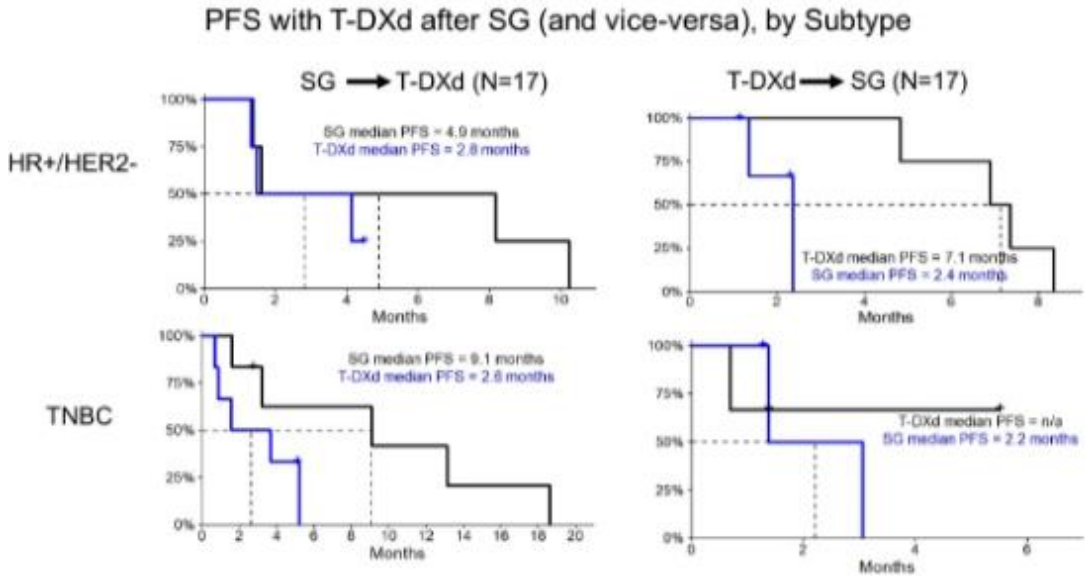
TEAEs (≥25% of all patients), %	4.8 mg/kg n=48		6.4 mg/kg n=98	
	All grade	Grade ≥3	All grade	Grade ≥3
TEAEs	**97.9**	**64.6**	**100**	**81.6**
Nausea	68.8	4.2	80.6	5.1
Platelet count decreased[b]	60.4	27.1	71.4	38.8
Neutrophil count decreased[b]	62.5	27.1	66.3	52.0
Decreased appetite	56.3	6.3	53.1	6.1
Vomiting	47.9	4.2	46.9	1.0
White blood cell count decreased[b]	45.8	10.4	45.9	23.5
Diarrhea	41.7	4.2	43.9	3.1
Anemia[b]	43.8	20.8	43.9	21.4
Aspartate aminotransferase increased	43.8	4.2	34.7	6.1
Stomatitis	25.0	0.0	34.7	1.0
Fatigue	31.3	0.0	33.7	3.1
Alanine aminotransferase increased	41.7	2.1	31.6	7.1
Constipation	22.9	0.0	29.6	0.0
Alopecia	20.8	NA	28.6	NA
Malaise	22.9	0.0	26.5	1.0

Krop I et al. ASCO 2022 abstract 1002

Sequencing Antibody Drug Conjugates (ADCs)







- 35 patients: ER+/Her2- and TNBC (n=20, 57%) patients in a single academic institution
- For TNBC subgroup, median PFS for ADC1 was 8.2 mo and median PFS for ADC2 was 3 mo
- Suggests that changing antibody target may lessen cross resistance

Abelman, R et al. Abs 1022.ASCO 2023

Conclusions: Antibody Drug Conjugates

- ADCs effective in targeting delivery of higher dose chemotherapy
- T-DXd approved for HER2-Low MBC after prior chemotherapy
- Sacituzumab approved in HR+ MBC after 2 prior lines of chemo
- Many new ADCs being investigated with promising results
- Need to better define predictors of response and how to sequence ADCs