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Redefining Treatment Across the Spectrum of HR+/HER2-Expressing Metastatic Breast Cancer

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Learning Objectives

Upon completion of this activity, participants should be better able to:

- Apply emerging data and guideline recommendations to accurately define HER2 status in breast cancer patients, thereby improving the identification of patients eligible for appropriate targeted ADC treatments
- Evaluate recent and emerging data on the efficacy of ADCs in terms of progression-free survival, objective response rate, and quality of life for patients with HR+ mBC across the HER2-expression continuum
- Evaluate how recent clinical trial results impact ADC selection and sequencing for patients with metastatic breast cancer across the HER2-expression continuum
- Employ team-based strategies to identify, mitigate, and manage potential treatment-related AEs in patients receiving ADC therapies for mBC

Navigating HER2 Expression in Breast Cancer:

Applying Emerging Data and Guidelines for Targeted ADC Treatment Eligibility

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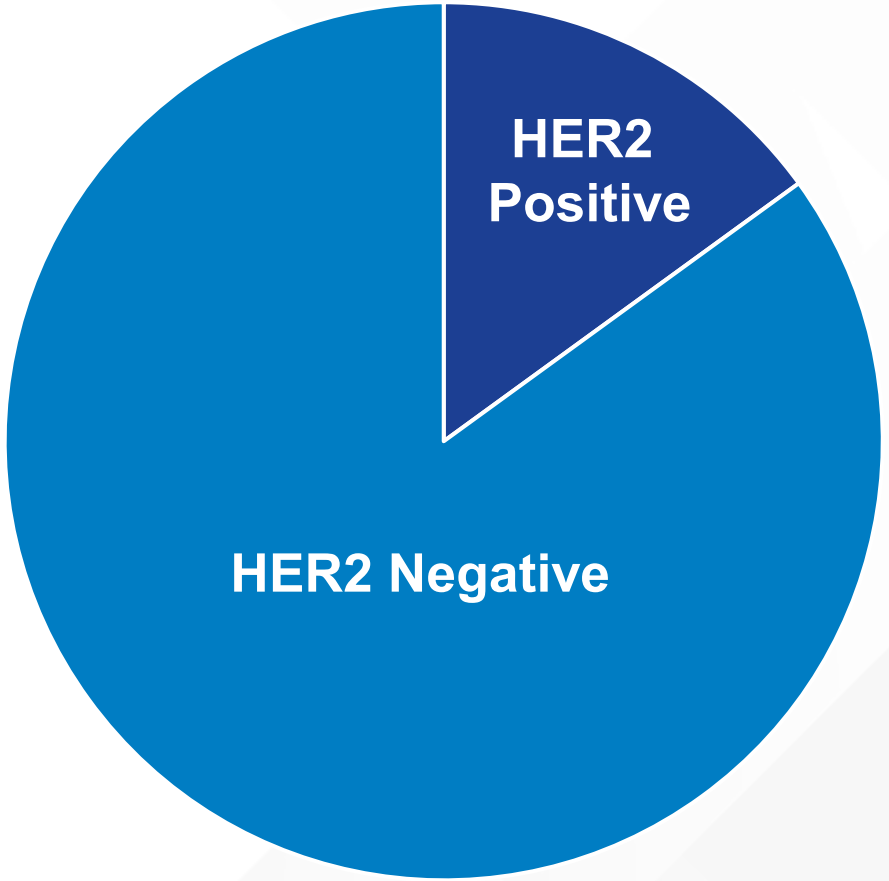
Traditional View of HER2-Positive Breast Cancer

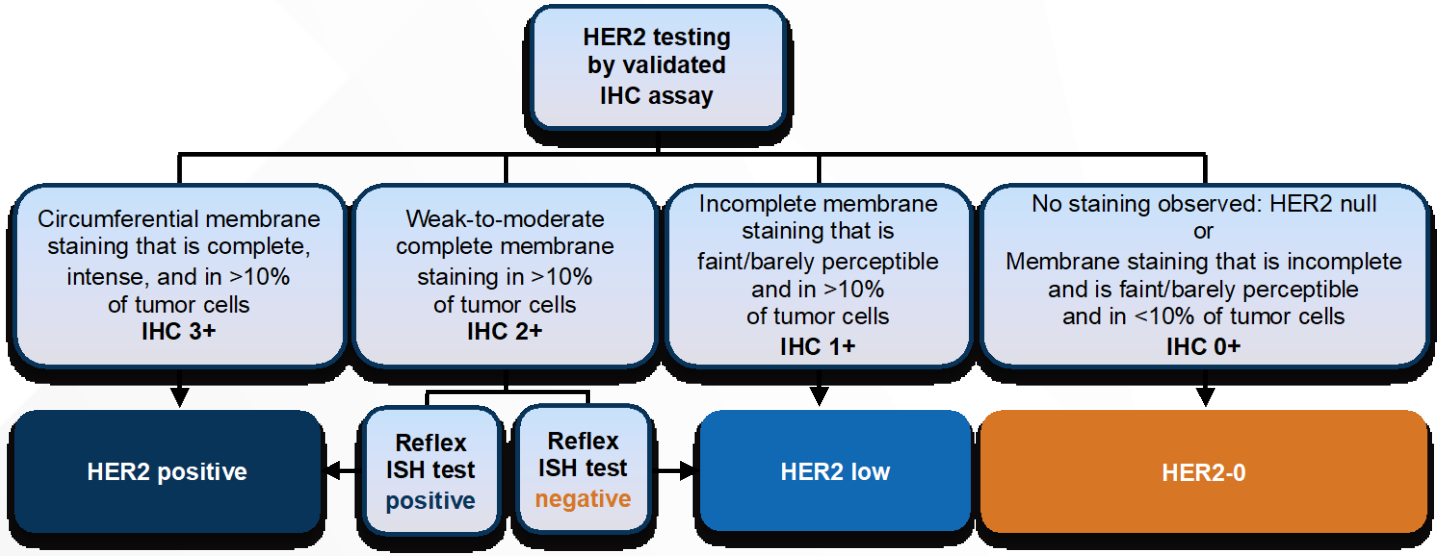
- Tumors lacking *ERBB2* overexpression or amplification are collectively defined as HER2 negative

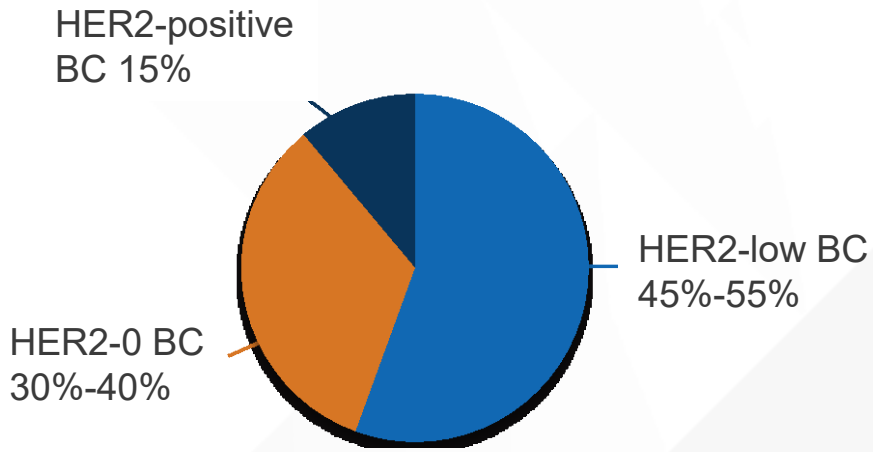


ERBB, erythroblastic leukemia viral oncogene homolog; HER2, human epidermal growth factor receptor 2.

Wolff AC, et al. *J Clin Oncol.* 2018;36(20):2105-2122.
Slide adapted from Tolaney S, Curigliano G. Debate: Is HER2-low a separate entity? SABCS 2022.

Expanding the Use of HER2 ADCs to HER2-Low Breast Cancer





ADC, antibody-drug conjugate; BC, breast cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.
Tarantino P, et al. *J Clin Oncol.* 2020;38(17):1951.

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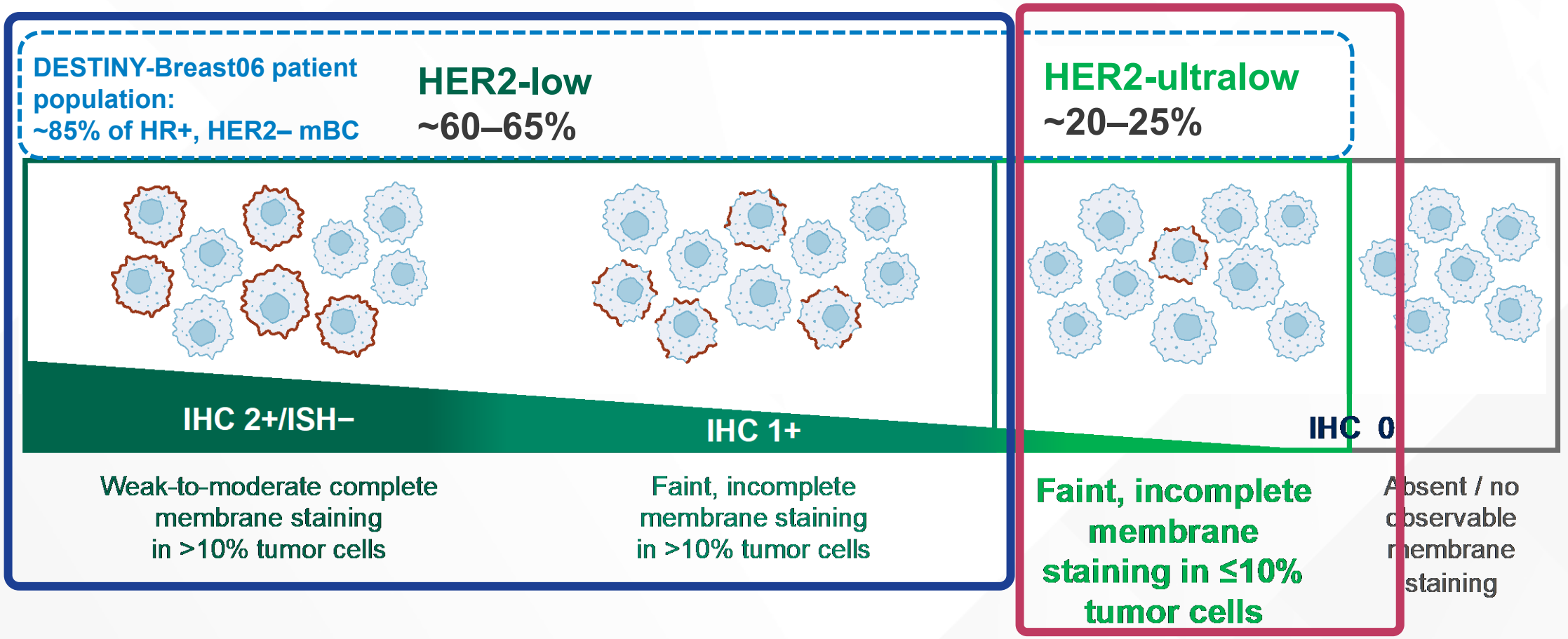
Expanding the Targetability to HER2 Low and “Ultralow”

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

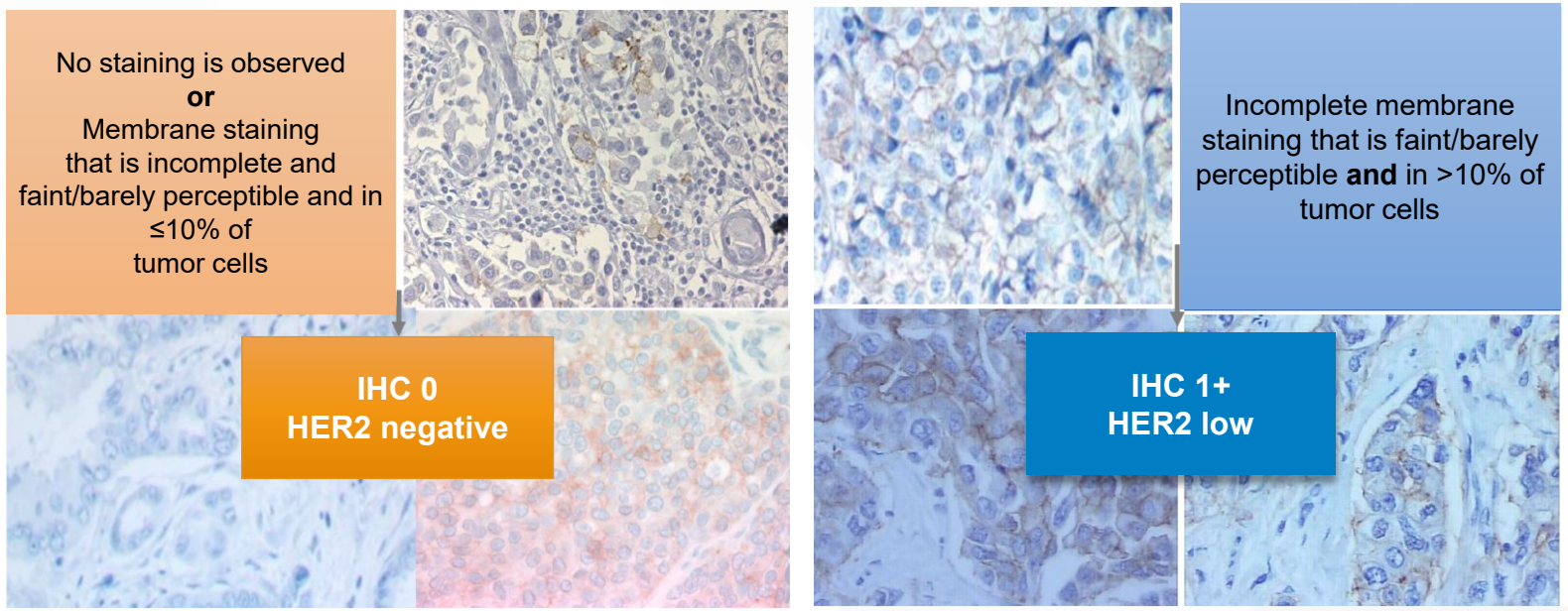


ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer.

Curigliano G, et al. ASCO 2024. Abstract LBA1000.

Low Concordance Among Pathologists Between HER2 0 & HER2 1+

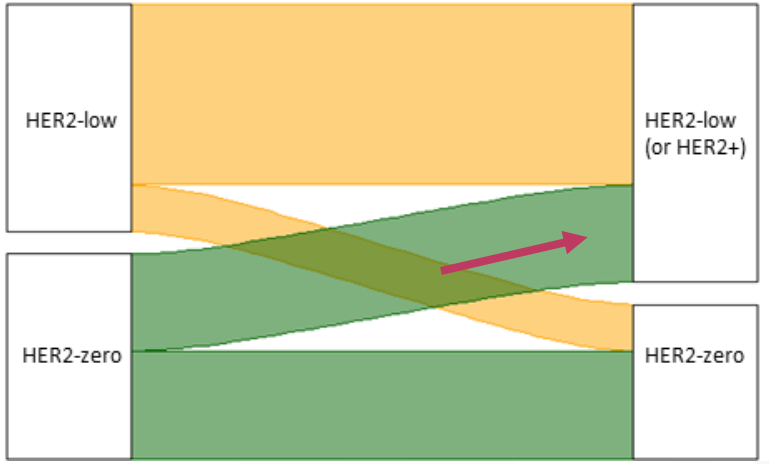
- In a recent study among 18 experienced pathologists, there was **only 26% concordance** between the designation of HER2 0 and HER2 1+
- Importantly, HER2 0 does not mean absence of HER2, as it also includes tumors with **“ultralow”** expression



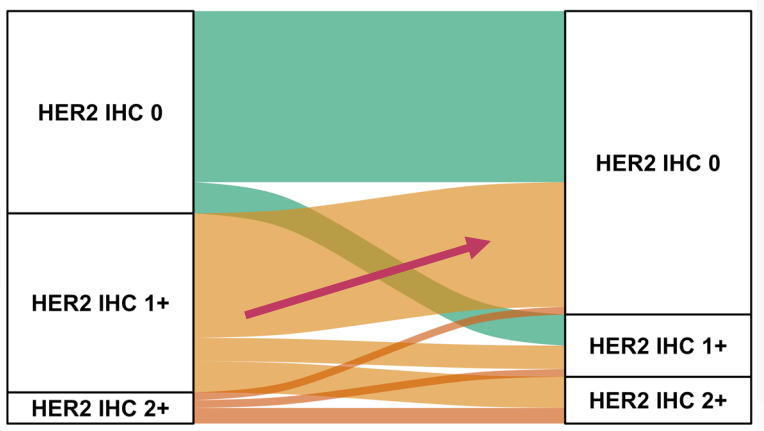
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.
Fernandez AI, et al. *JAMA Oncol.* 2022;8(4):1-4.

HER2 Low Is Unstable

- Multiple studies have confirmed the instability of HER2-low expression between primary and metastatic tumors
- The reason is unclear, but may be multifactorial: (pre)analytical factors, HER2 expression heterogeneity, biologic evolution of the disease



Matched paired primary-met TNBC

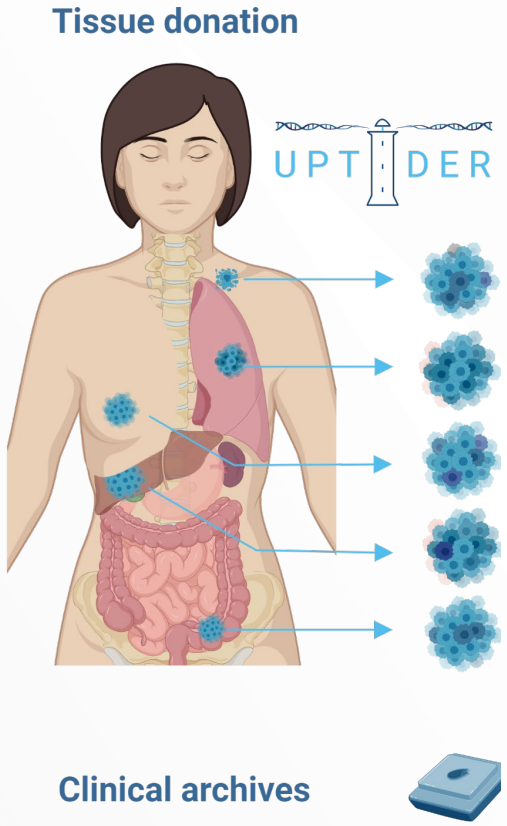


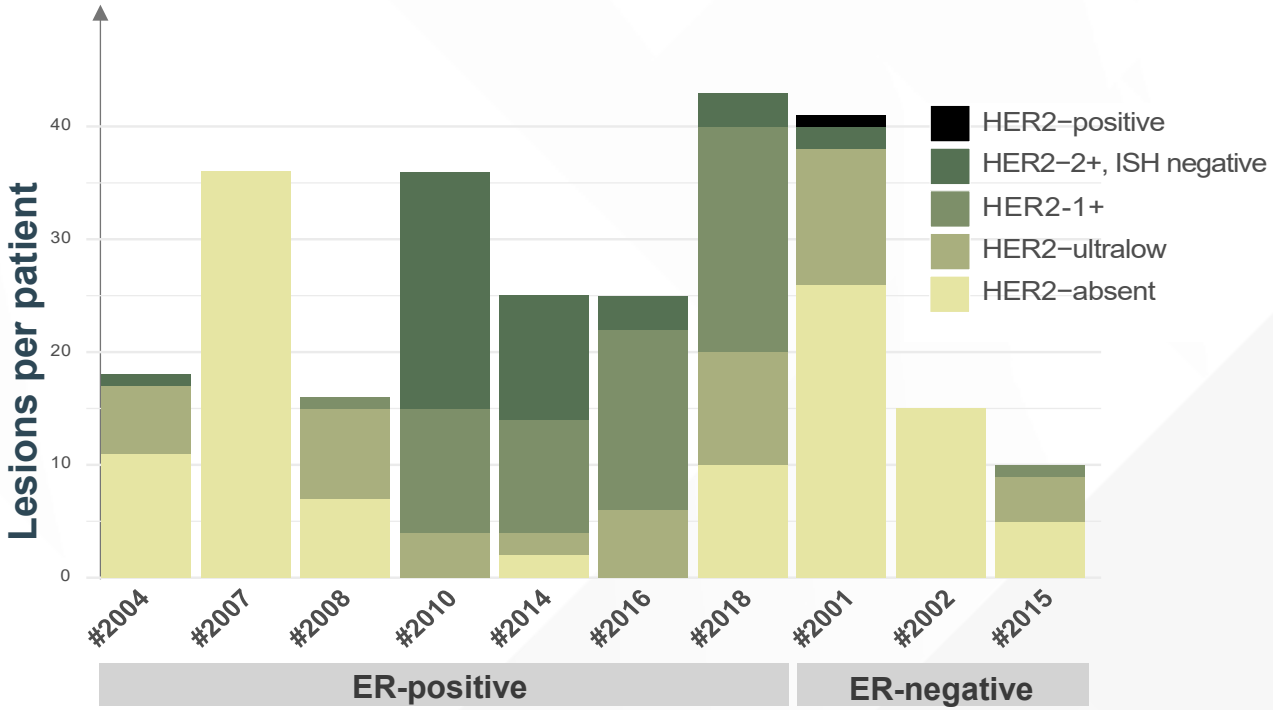
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; TNBC, triple-negative breast cancer.

1. Tarantino P, et al *Eur J Cancer.* 2022;163:35-43. 2. Miglietta F, et al. *NPJ Breast Cancer.* 2021;7(1):137. 3. Garrido-Castro A, et al. SABCS 2022. Abstract HER2-10.

Discordance Seen Within a Patient With Tissue From Different Locations at the Same Timepoint

10 patients with *HER2*-non-amplified metastatic breast cancer





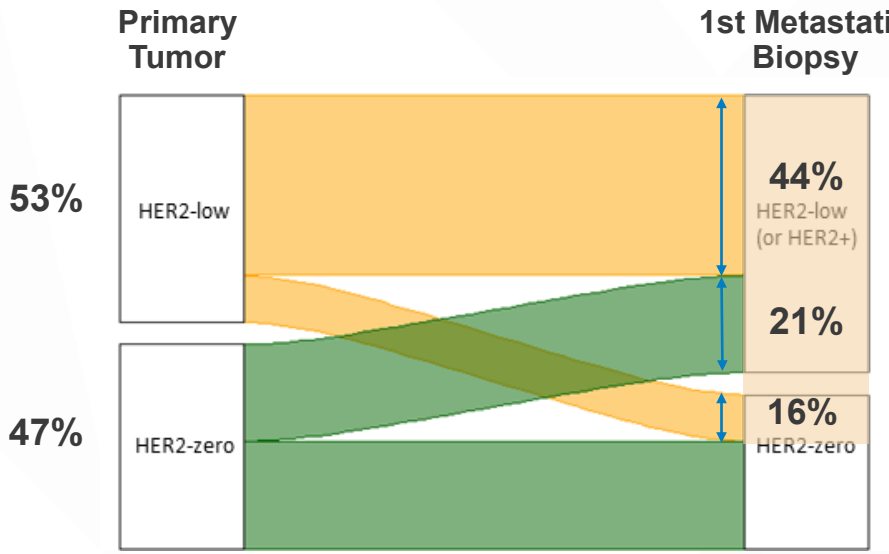
HER2-status of different metastases was highly variable within one patient, with HER2-low and zero lesions in 8/10 patients

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; ISH, in situ hybridization.

Geukens T, et al. SABCS 2022. Abstract HER2-16.

A Practical Definition of HER2-Low Breast Cancer?

- Given the complexities of assessing HER2-low and some suggestion of activity of T-DXd irrespective of timepoint of tissue collection, a practical definition of HER2 low is:
  - HER2 nonamplified tumor that showed HER2-low expression on any prior specimen in the course of disease



= 81% HER2 low according to the practical definition

HER2, human epidermal growth factor receptor 2; T-DXd, trastuzumab deruxtecan.
Adapted based on work by Paolo Tarantino, MD.
Tarantino P, et al. *Eur J Cancer*. 2022;163:35-43.

ADC Efficacy in HR+ Metastatic Breast Cancer:

Insights Across the HER2-Expression Continuum

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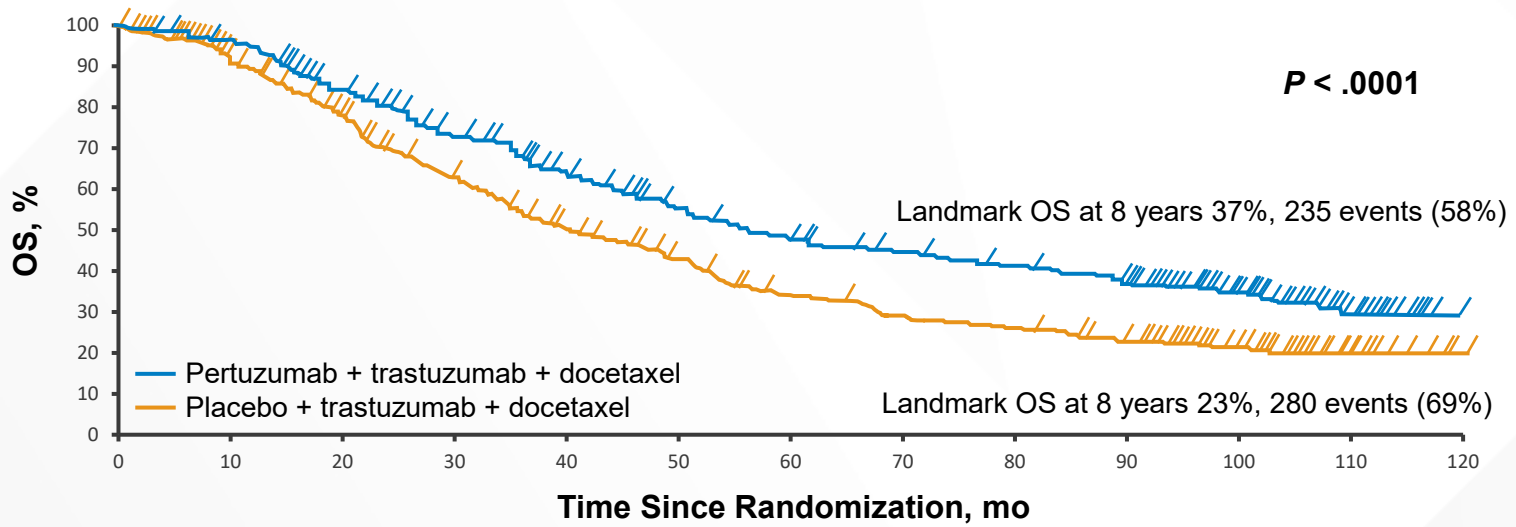
Overall Survival in Patients With Advanced *HER2*+ mBC

CLEOPATRA End-of-Study Results (median follow-up ~100 months)



No. at Risk (number censored)

Pertuzumab	402 (0)	371 (14)	318 (23)	269 (32)	228 (41)	188 (48)	165 (50)	150 (54)	137 (56)	120 (59)	71 (102)	20 (147)	0 (167)
Placebo	406 (0)	350 (19)	289 (30)	230 (36)	181 (41)	149 (48)	115 (52)	96 (53)	88 (53)	75 (57)	44 (84)	11 (115)	1 (125)

Median OS with TP-based initial therapy: **57.1 months vs 40.8 months** in the control arm

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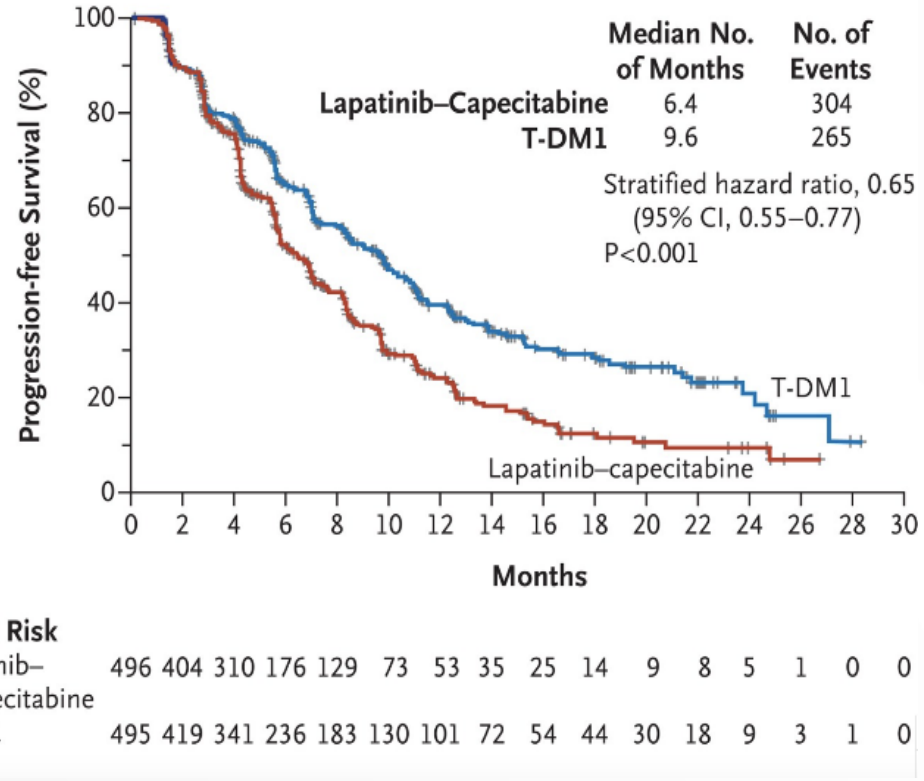
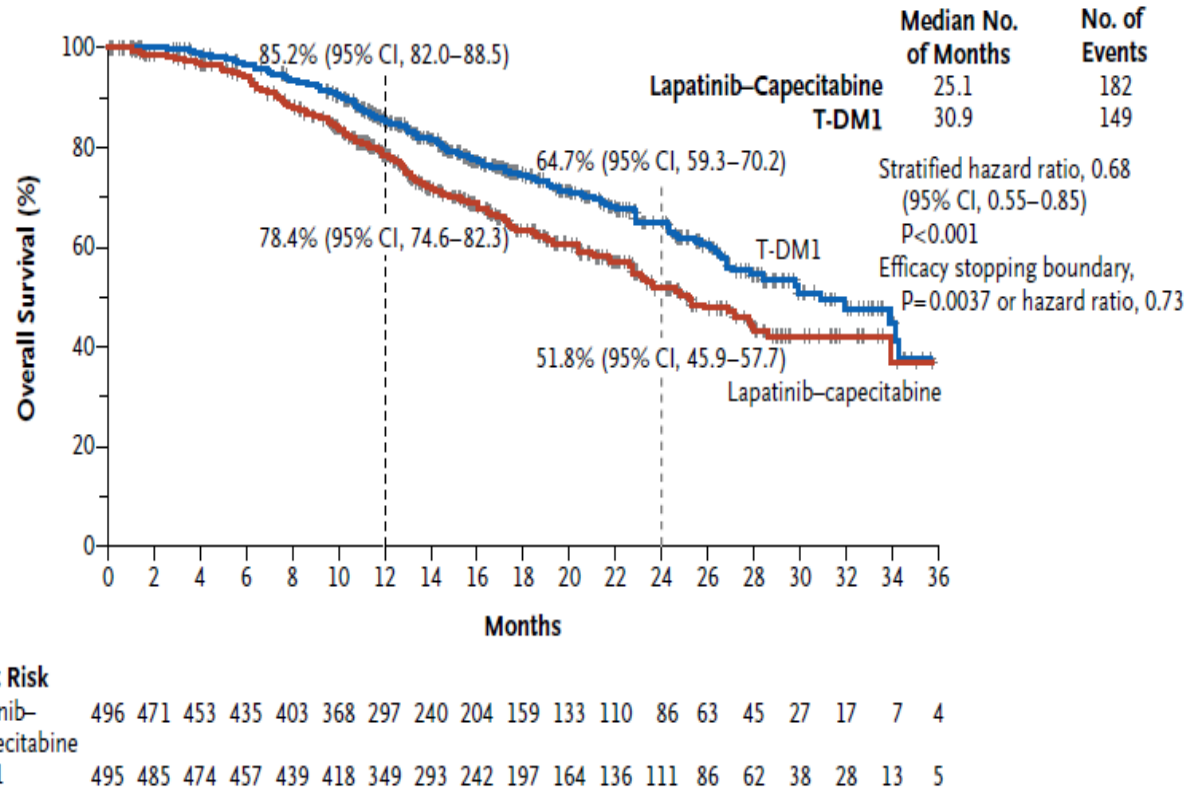
HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; OS, overall survival; TP, trastuzumab and pertuzumab.

Swain SM, et al. *Lancet Oncol*. 2020;21(4):519-530.

EMILIA TRIAL: T-DM1 Superior to Capecitabine + Lapatinib in Patients With HER2-Positive Advanced Breast Cancer





HER2, human epidermal growth factor receptor 2; T-DM1, ado-trastuzumab emtansine.

Verma S, et al. *N Engl J Med*. 2012;367(19):1783-1791.

HER2CLIMB-02 Study Design

- HER2+ LA/MBC with progression after trastuzumab and taxane in any setting[a]
- ECOG PS ≤1
- Previously treated stable, progressing, or untreated brain metastases not requiring immediate local therapy

N≈460

R 1:1

Stratification factors:
- Line of treatment for metastatic disease (1L vs other)
- Hormone receptor status (positive vs negative)
- Presence or history of brain metastases (yes vs no)
- ECOG PS (0 vs 1)

Tucatinib (TUC) + T-DM1

Tucatinib 300 mg PO BID and T-DM1 3.6 mg/kg IV

Placebo (PBO) + T-DM1

Placebo PO BID and T-DM1 3.6 mg/kg IV

Outcomes

Primary
- PFS by investigator assessment per RECIST v1.1

Key Secondary (hierarchical)
- OS
- PFS in patients with brain metastases
- cORR per RECIST v1.1
- OS in patients with brain metastases

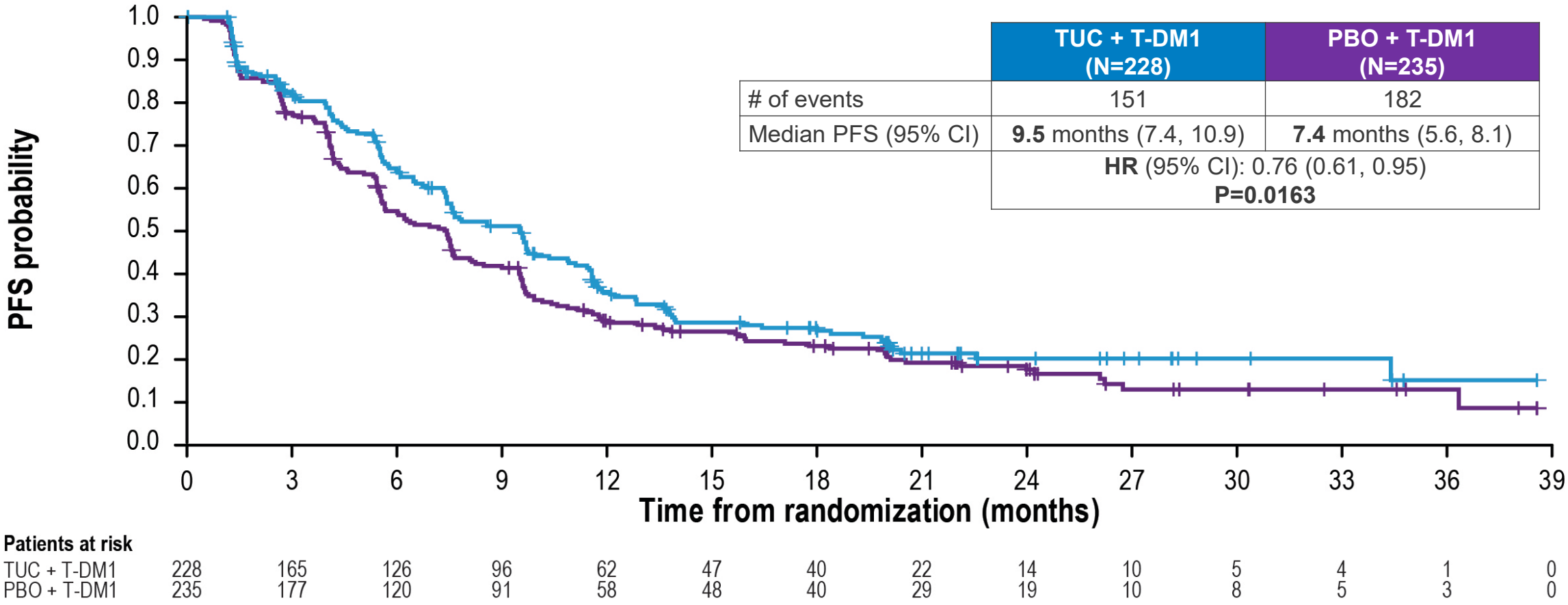
The primary analysis for PFS was planned after ≈331 PFS events to provide 90% power for hazard ratio of 0.7.
The first of two interim analysis for OS was planned at the time of the primary PFS analysis, if the PFS result was significantly positive.[b]

Date of data cutoff: Jun 29, 2023. Patients were enrolled from Oct 8, 2019, to Jun 16, 2022.
[a]Patients who received prior tucatinib, afatinib, T-DXd, or any investigational anti-HER2, anti-EGFR, or HER2 TKIs were not eligible. Patients who received lapatinib and neratinib were ineligible if the drugs were received within 12 months of starting study treatment, and patients who received pyrotinib for recurrent or metastatic breast cancer were not eligible. These patients were eligible if the drugs were given for ≤21 days and were discontinued for reasons other than disease progression or severe toxicity.
[b]Subsequent OS analyses are planned upon 80% and 100% of events.

1L, first-line; BID, twice daily; cORR, confirmed objective response rate; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; IV, intravenously; LA/MBC, locally advanced or metastatic breast cancer; OS, overall survival; PBO, placebo; PFS, progression-free survival; PO, orally; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKIs, tyrosine kinase inhibitors; TUC, tucatinib.

ClinicalTrials.gov. NCT03975647. https://www.clinicaltrials.gov/study/NCT03975647. Hurvitz S, et al. SABCS 2023. Abstract GS01-10.

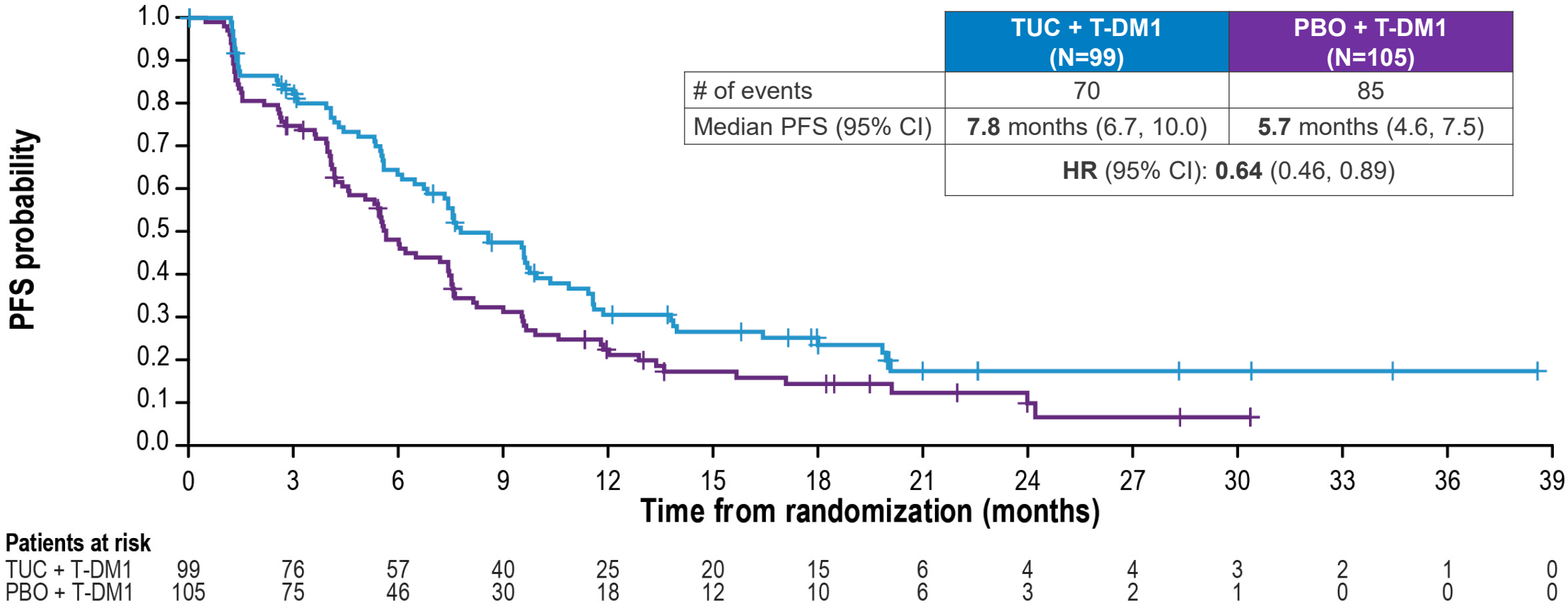
HER2CLIMB-02: Progression-Free Survival



	TUC + T-DM1 (N=228)	PBO + T-DM1 (N=235)
# of events	151	182
Median PFS (95% CI)	**9.5** months (7.4, 10.9)	**7.4** months (5.6, 8.1)
	HR (95% CI): 0.76 (0.61, 0.95) **P=0.0163**	

Date of data cutoff: June 29, 2023.
HR, hazard ratio; PBO, placebo; PFS, progression-free survival; T-DM1, trastuzumab emtansine; TUC, tucatinib.
ClinicalTrials.gov. NCT03975647. https://www.clinicaltrials.gov/study/NCT03975647. Hurvitz S, et al. SABCS 2023. Abstract GS01-10.

HER2CLIMB-02: PFS in Patients with Brain Metastases[a]

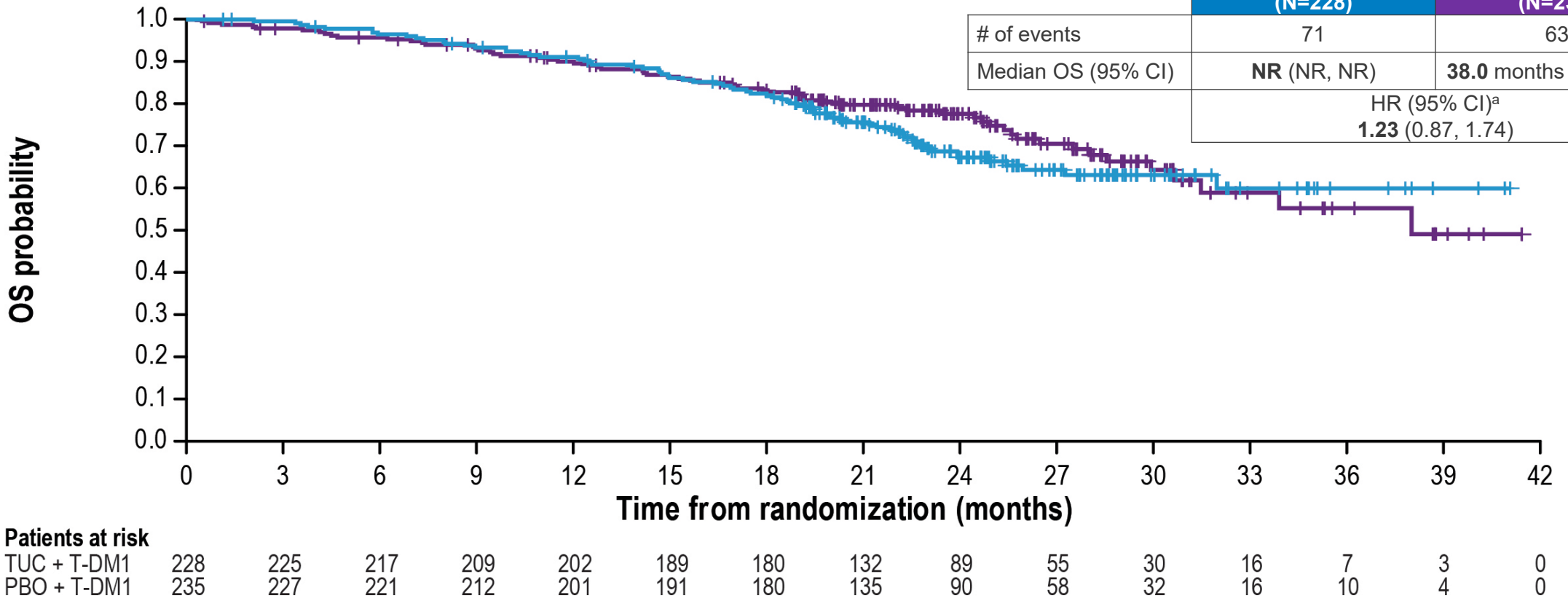


	TUC + T-DM1 (N=99)	PBO + T-DM1 (N=105)
# of events	70	85
Median PFS (95% CI)	**7.8** months (6.7, 10.0)	**5.7** months (4.6, 7.5)
	HR (95% CI): **0.64** (0.46, 0.89)	

Date of data cutoff: June 29, 2023.
[a]The outcome was not formally tested.
HR, hazard ratio; PBO, placebo; PFS, progression-free survival; T-DM1, trastuzumab emtansine; TUC, tucatinib.
ClinicalTrials.gov. NCT03975647. https://www.clinicaltrials.gov/study/NCT03975647. Hurvitz S, et al. SABCS 2023. Abstract GS01-10.

HER2CLIMB-02: Overall Survival

	TUC + T-DM1 (N=228)	PBO + T-DM1 (N=235)
# of events	71	63
Median OS (95% CI)	**NR** (NR, NR)	**38.0** months (31.5, NR)
HR (95% CI)[a]	**1.23** (0.87, 1.74)	



Patients at risk

TUC + T-DM1	228	225	217	209	202	189	180	132	89	55	30	16	7	3	0
PBO + T-DM1	235	227	221	212	201	191	180	135	90	58	32	16	10	4	0

Median follow-up was 24.4 months. As of data cutoff, 134 out of 253 (53%) prespecified events for the OS final analysis were observed. Interim OS results did not meet the prespecified crossing boundary of $P = 0.0041$.

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Date of data cutoff: June 29, 2023.

[a]The proportional hazard assumption was not maintained post-18 months, with heavy censoring on both arms.

HRs, hazard ratios; NR, not reached; OS, overall survival; PBO, placebo; T-DM1, trastuzumab emtansine; TUC, tucatinib.

ClinicalTrials.gov. NCT03975647. https://www.clinicaltrials.gov/study/NCT03975647. Hurvitz S, et al. SABCS 2023. Abstract GS01-10.

HER2CLIMB-02: Adverse Events of Interest

Hepatic TEAEs

- Grade ≥3 hepatic TEAEs greater in TUC + T-DM1 arm (28.6% vs 7.3%), primarily due to AST/ALT elevations
- No Hy's law cases were identified
- 85% of all-grade hepatic TEAEs in TUC + T-DM1 arm resolved or returned to grade 1, with median of 22 days to resolution[a]

Diarrhea

- Grade ≥3 events reported in 4.8% of TUC + T-DM1 arm and 0.9% of PBO + T-DM1 arm

Dose modifications Due to Hepatic TEAEs

	TUC + T-DM1 (N=231) n (%)	PBO + T-DM1 (N=233) n (%)
TUC/PBO dose holds	76 (32.9)	26 (11.2)
TUC/PBO dose reductions	46 (19.9)	12 (5.2)
Treatment discontinuation		
TUC/PBO	16 (6.9)	5 (2.1)
T-DM1	18 (7.8)	5 (2.1)

Dose modifications Due to Diarrhea

	TUC + T-DM1 (N=231) n (%)	PBO + T-DM1 (N=233) n (%)
TUC/PBO dose holds	9 (3.9)	2 (0.9)
TUC/PBO dose reductions	9 (3.9)	1 (0.4)
Treatment discontinuation		
TUC/PBO	1 (0.4)	0
T-DM1	0	0

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Date of data cutoff: June 29, 2023.

[a]For PBO + T-DM1 arm, 75% of all-grade hepatic TEAEs resolved or returned to grade 1, with median of 22 days to resolution.

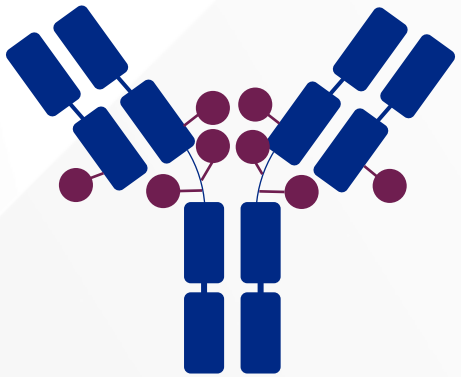
ALT, alanine aminotransferase; AST, aspartate aminotransferase; PBO, placebo; T-DM1, trastuzumab emtansine; TEAEs, treatment-emergent adverse events; TUC, tucatinib.

ClinicalTrials.gov. NCT03975647. https://www.clinicaltrials.gov/study/NCT03975647. Hurvitz S, et al. SABCS 2023. Abstract GS01-10.

Characteristic Differences Between T-DXd and T-DM1

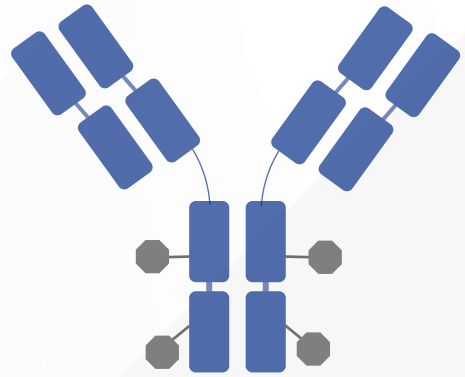
HER2 Targeting ADCs with similar mAB Backbone

Trastuzumab deruxtecan (T-DXd)[1]



T-DXd[1-4,a]	ADC Attributes	T-DM1[3-5]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

Trastuzumab emtansine (T-DM1)[5]

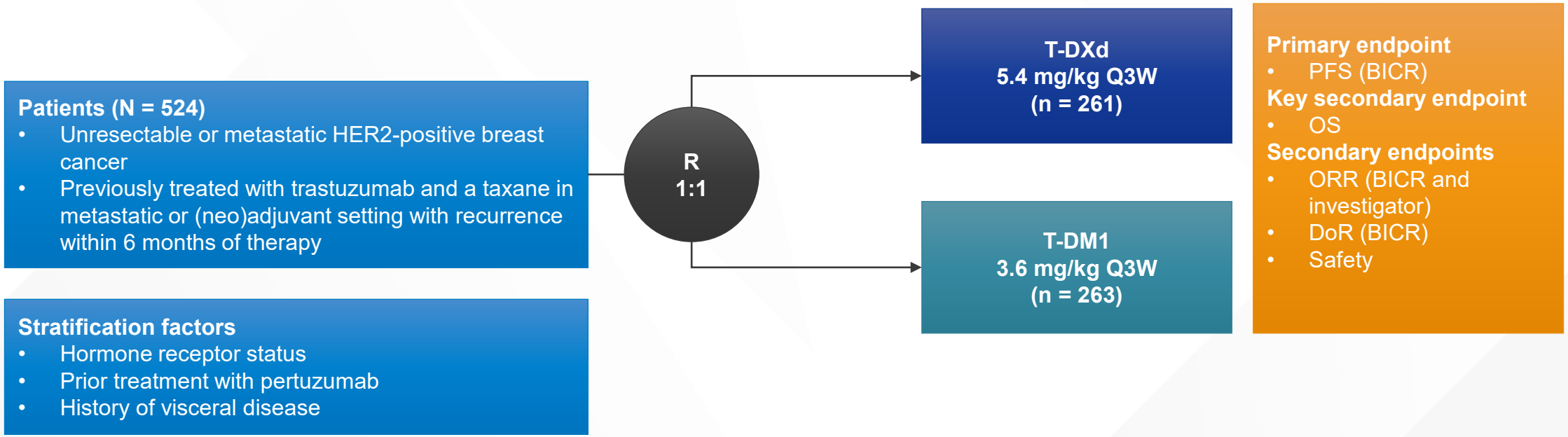


[a]The clinical relevance of these features is under investigation.

ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; mAB, monoclonal antibody; MoA, mechanism of action; T-DM1, ado-trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Cortés J, et al. ESMO 2021. Abstract LBA1.
1. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. 2. Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097-5108. 3. Trail PA, et al. *Pharmacol Ther.* 2018;181:126-142. 4. Ogitani Y, et al. *Cancer Sci.* 2016;107(7):1039-1046. 5. LoRusso PM, et al. *Clin Cancer Res.* 2011;17(20):6437-6447.

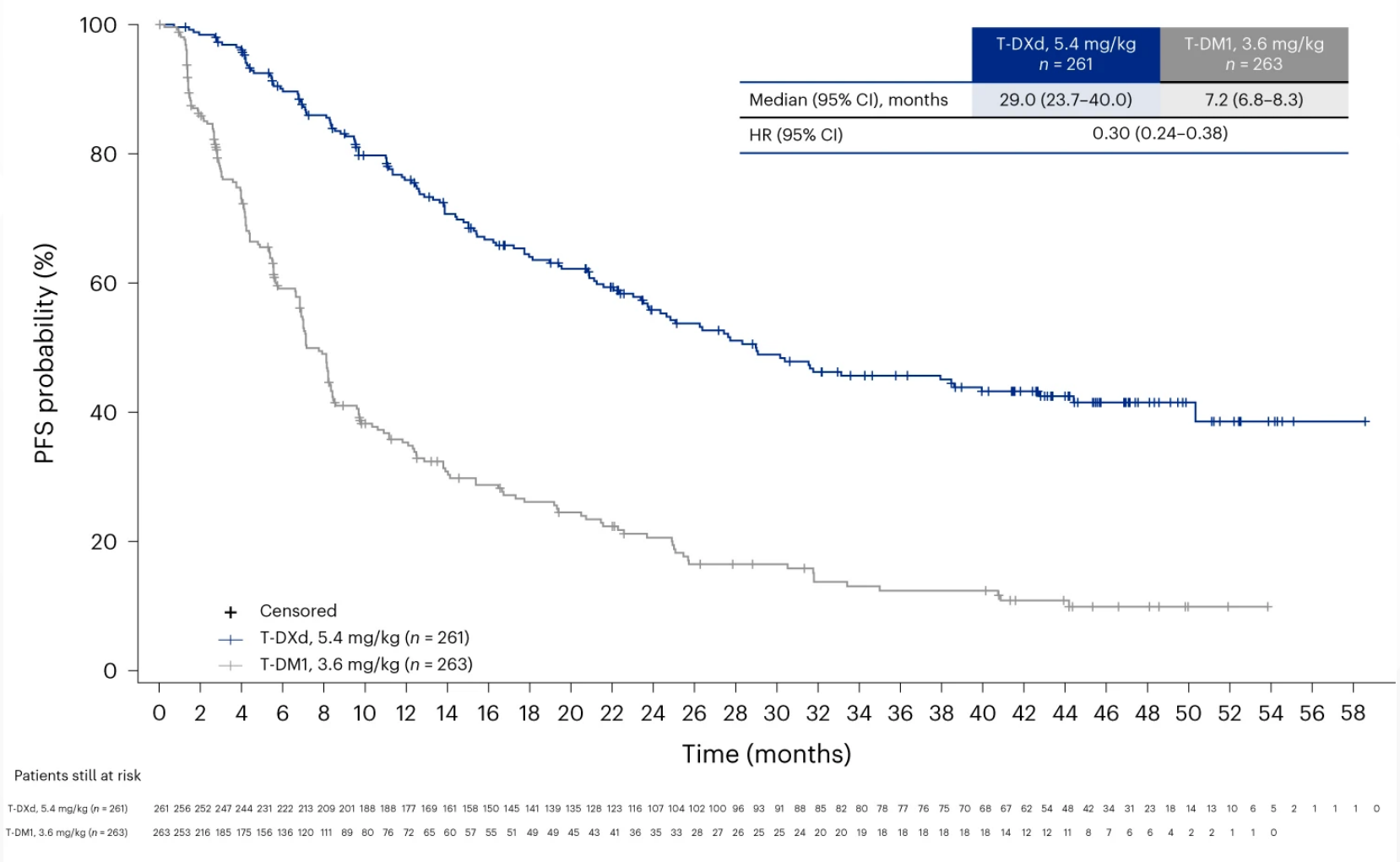
Updated OS Analysis of DESTINY-Breast03 Randomized, Open-Label, Multicenter Study (NCT03529110)



BICR, blinded independent central review; DoR, duration of response; HER2, human epidermal growth factor receptor 2; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; T-DM1, ado-trastuzumab emtansine; T-DXd, fam-trastuzumab deruxtecan-nxki.

Cortés J, et al. *Nat Med.* 2024;30:2208-2215.

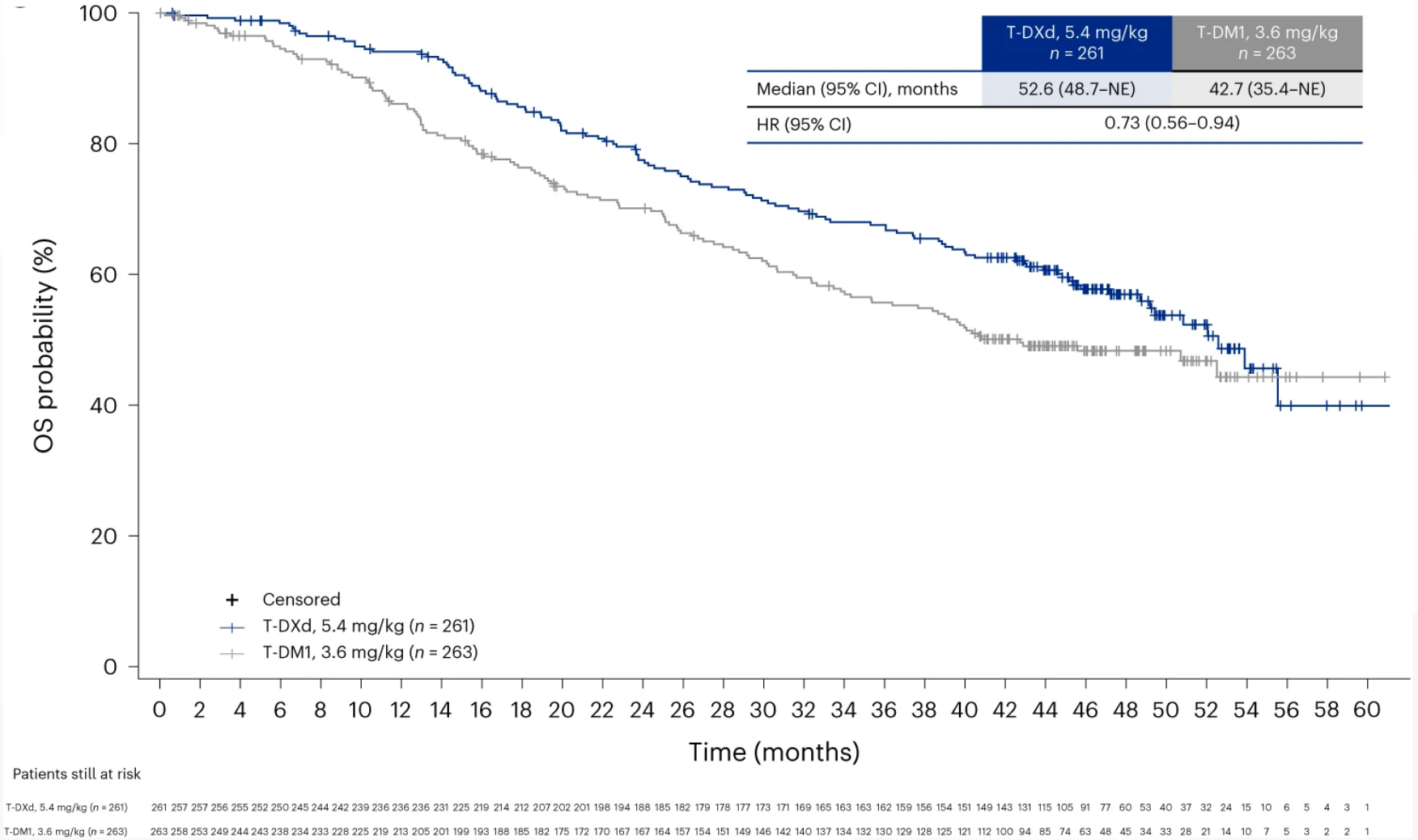
Updated Primary Endpoint: PFS by BICR



BICR, blinded independent central review; HR, hazard ratio; PFS, progression-free survival; T-DM1, ado-trastuzumab emtansine; T-DXd, fam-trastuzumab deruxtecan-nxki.

Cortés J, et al. *Nat Med.* 2024;30:2208-2215.

Key Secondary Endpoint: Overall Survival



HR, hazard ratio; NE, not estimable; T-DM1, ado-trastuzumab emtansine; T-DXd, fam-trastuzumab deruxtecan-nxki.

Cortés J, et al. *Nat Med.* 2024;30:2208-2215.

Adjudicated Drug-Related Interstitial Lung Disease/Pneumonitis

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	11 (4.3)	30 (11.7)	2 (0.8)	0	0	43 (16.7)
T-DM1 (n = 261)	5 (1.9)	3 (1.1)	1 (0.4)	0	0	9 (3.4)

- Adjudicated drug-related ILD/pneumonitis rates were similar to other mBC trials with T-DXd
- With longer treatment exposure and follow-up, the ILD/pneumonitis rate increased from 10.5% in the PFS interim analysis to 16.7%
- The overall incidence of grade 3 events (0.8%) was the same as in the PFS interim analysis
- There were no adjudicated drug-related grade 4 or 5 events

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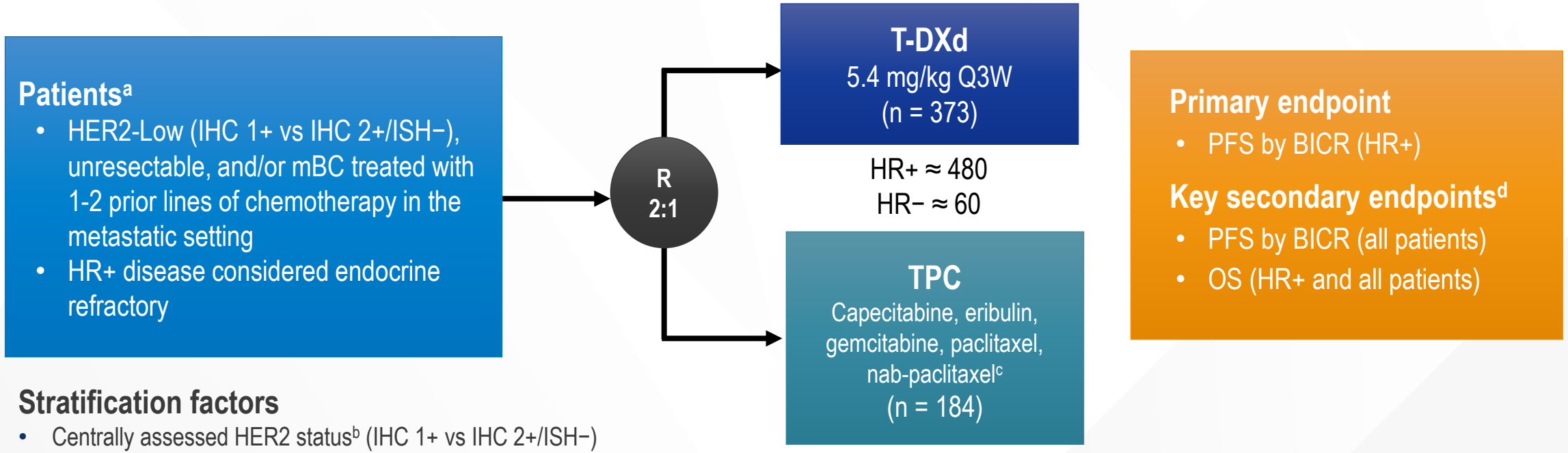
ILD, interstitial lung disease; mBC, metastatic breast cancer; PFS, progression-free survival; T-DM1, ado-trastuzumab emtansine; T-DXd, fam-trastuzumab deruxtecan-nxki.

Cortés J, et al. *Nat Med.* 2024;30:2208-2215.

DESTINY-Breast04: Study Design

An Open-Label, Multicenter, Phase 3 Study (NCT03734029)



Stratification factors

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

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

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; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every three weeks; R, randomized; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Modi S, et al. *N Engl J Med*. 2022;387(1):9-20.

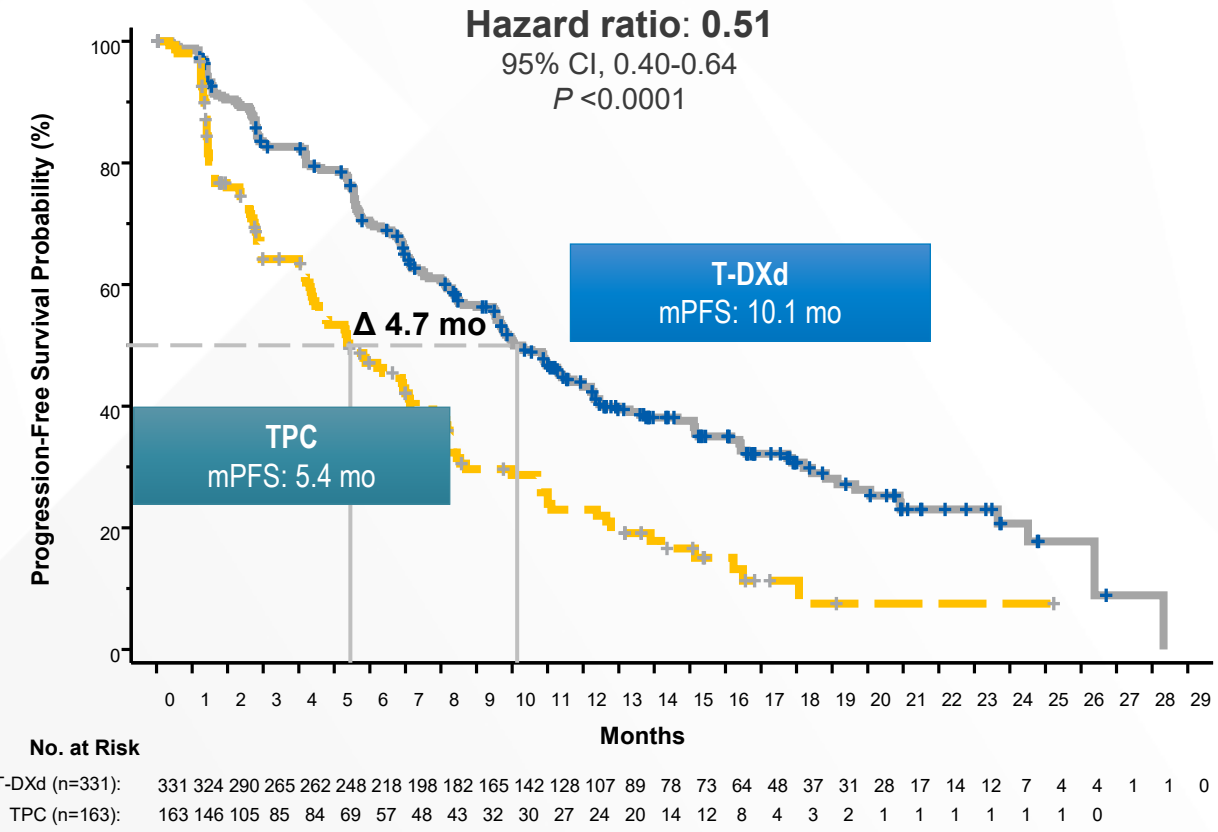
DESTINY-Breast04: Prior Therapies

	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)

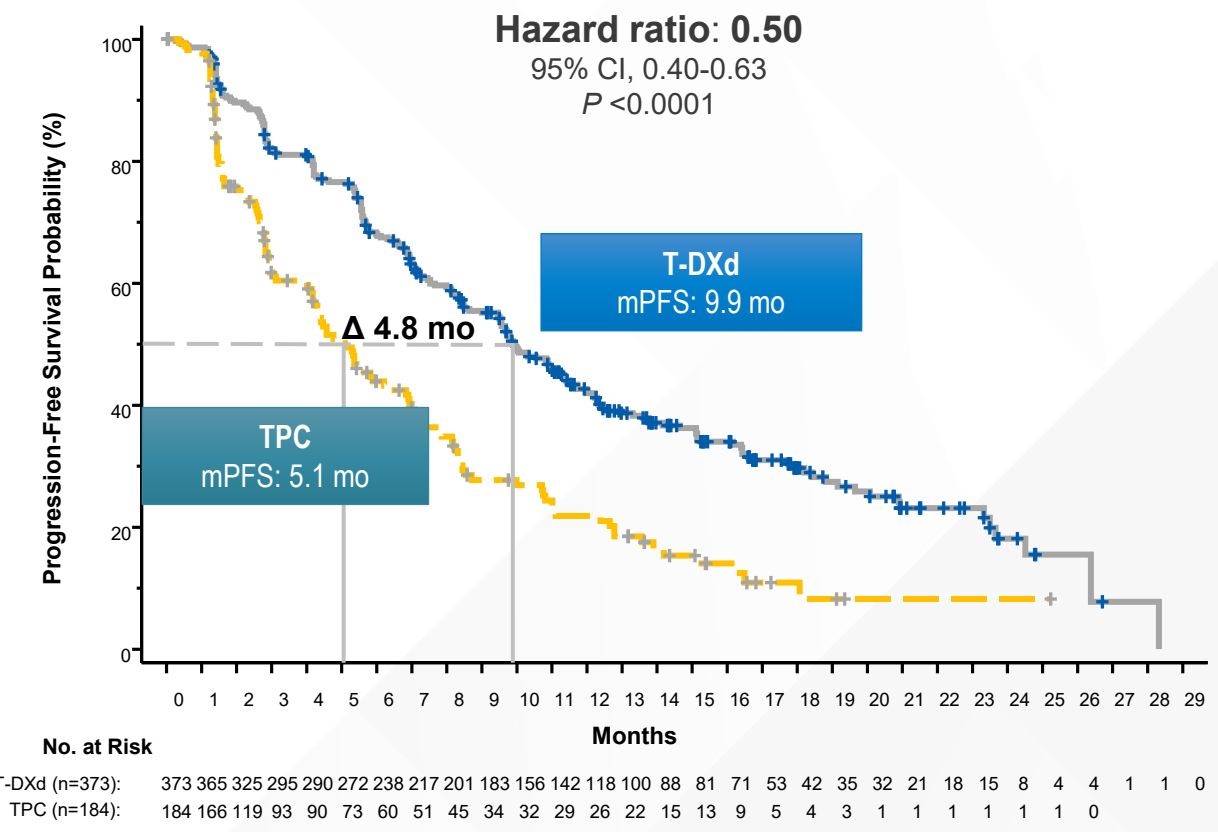
Based on derived data, which includes protocol deviations.
CDK, cyclin-dependent kinase; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Modi S, et al. *N Engl J Med*. 2022;387(1):9-20.

DESTINY-Breast04: PFS in HR+ and All Patients

Hormone receptor-positive



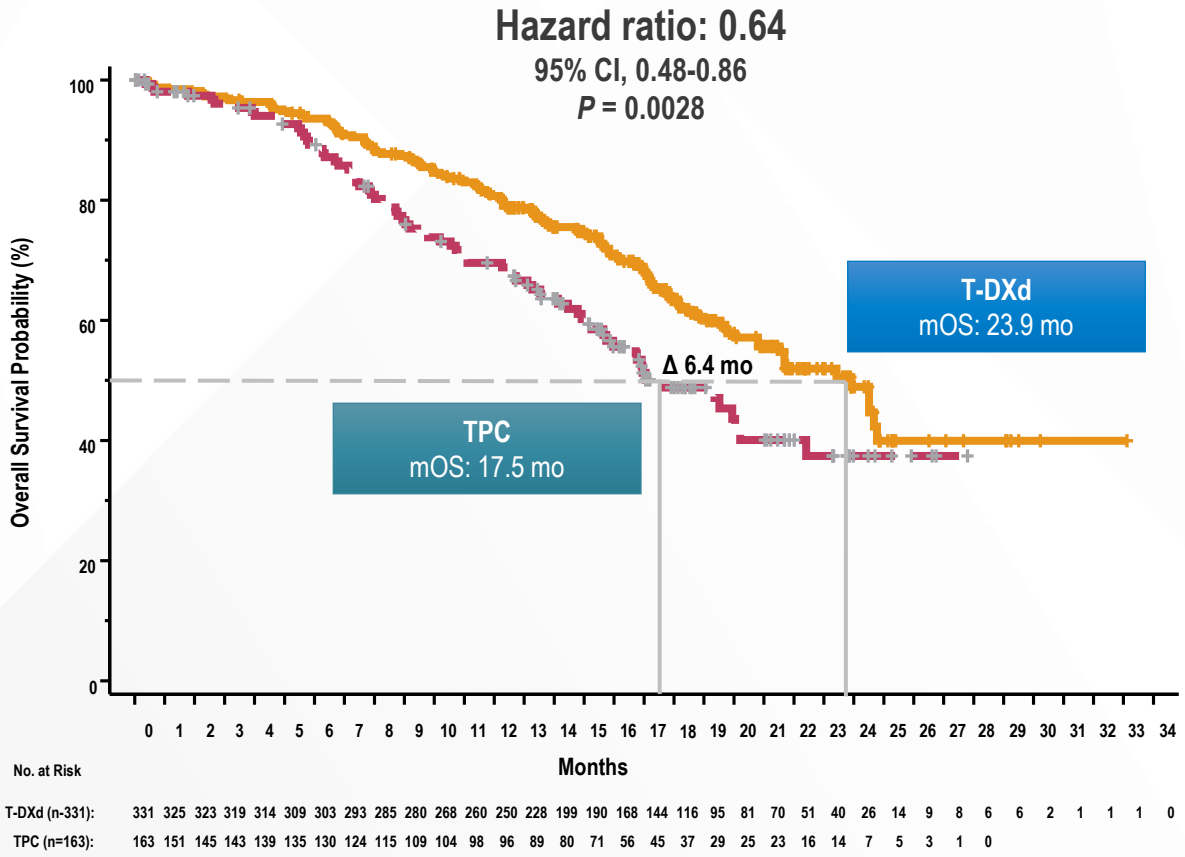
All patients



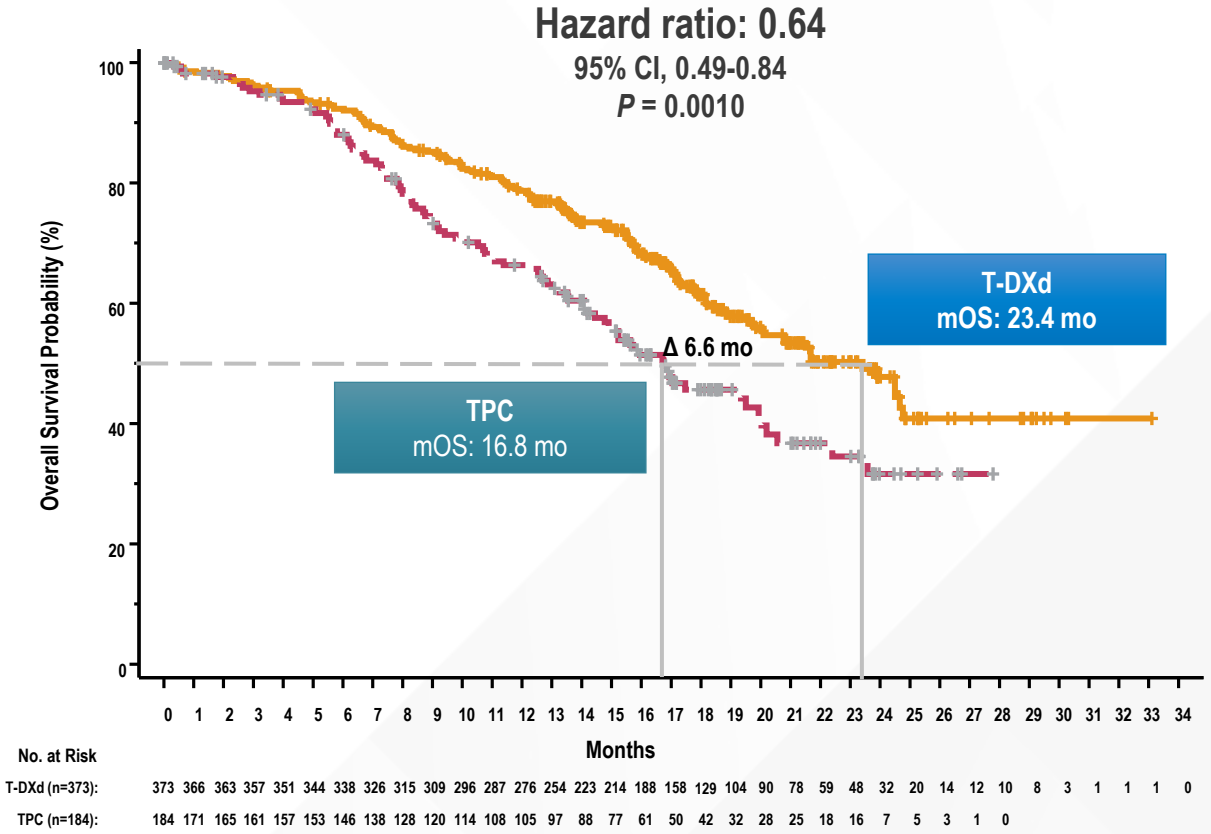
PFS by blinded independent central review.
HR, hormone receptor; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Modi S, et al. *N Engl J Med*. 2022;387(1):9-20.

DESTINY-Breast04: OS in HR+ and All Patients

Hormone receptor-positive



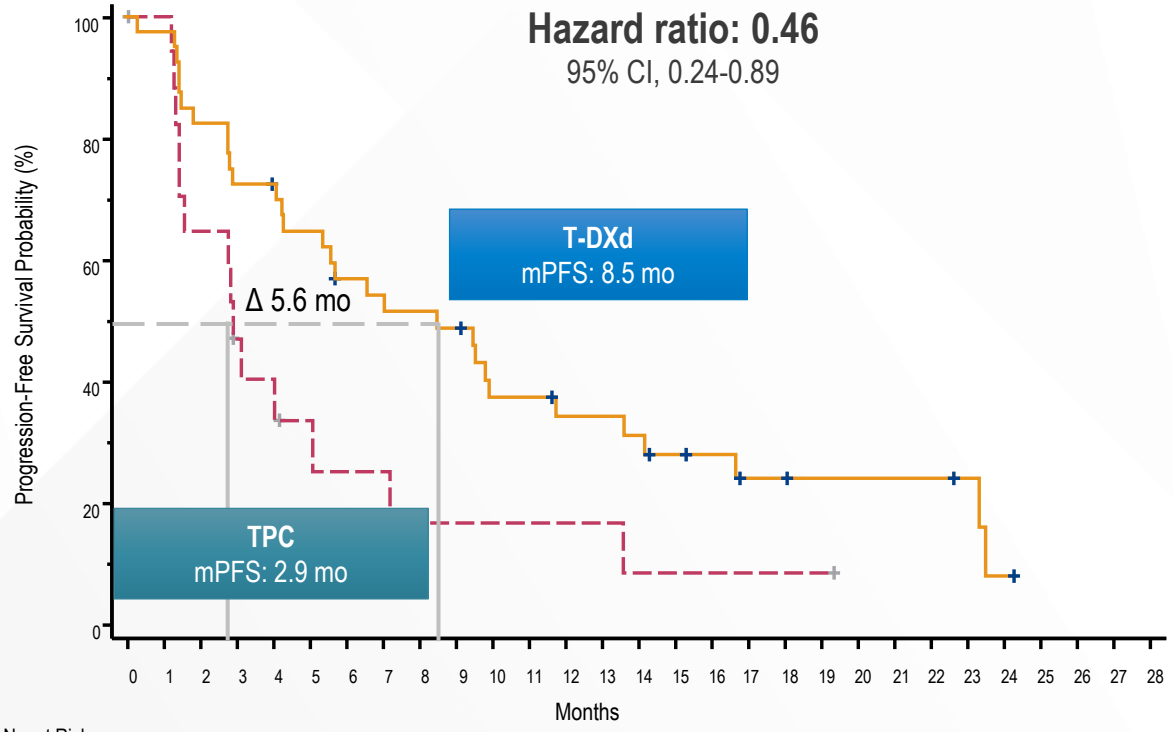
All patients

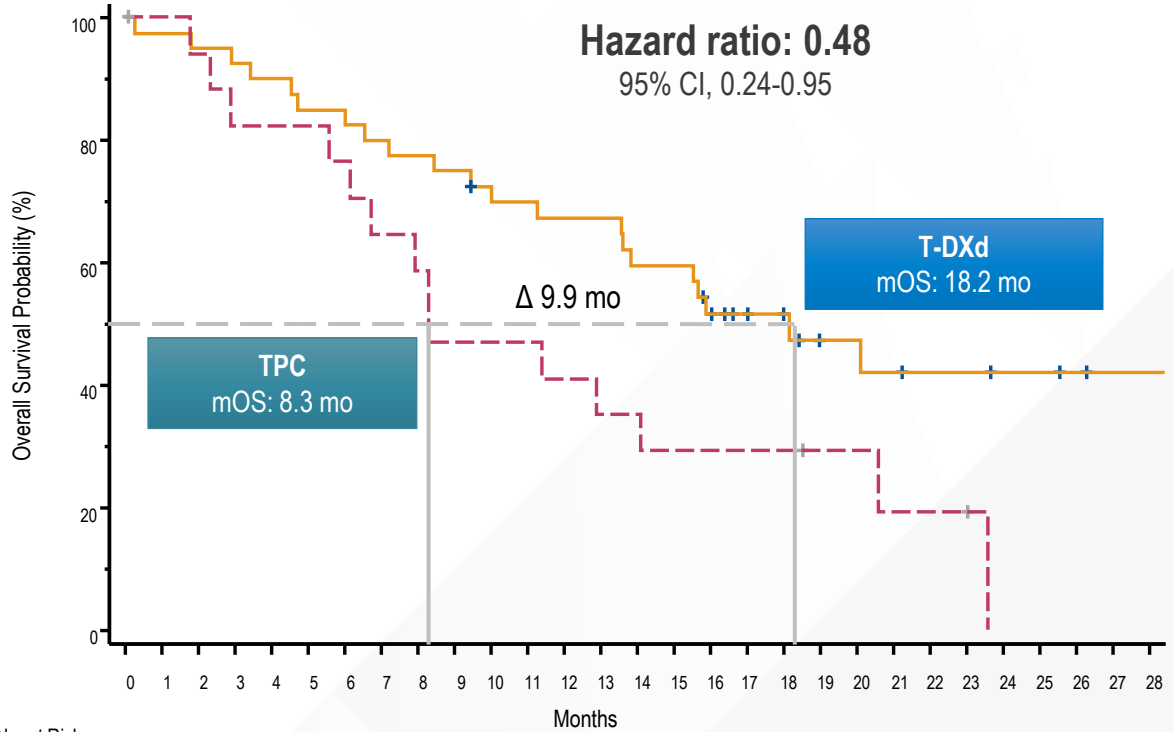


PFS by blinded independent central review.
HR, hormone receptor; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Modi S, et al. *N Engl J Med*. 2022;387(1):9-20.

DESTINY-Breast04: PFS and OS in HR− (Exploratory Endpoints)

Hormone receptor-negative





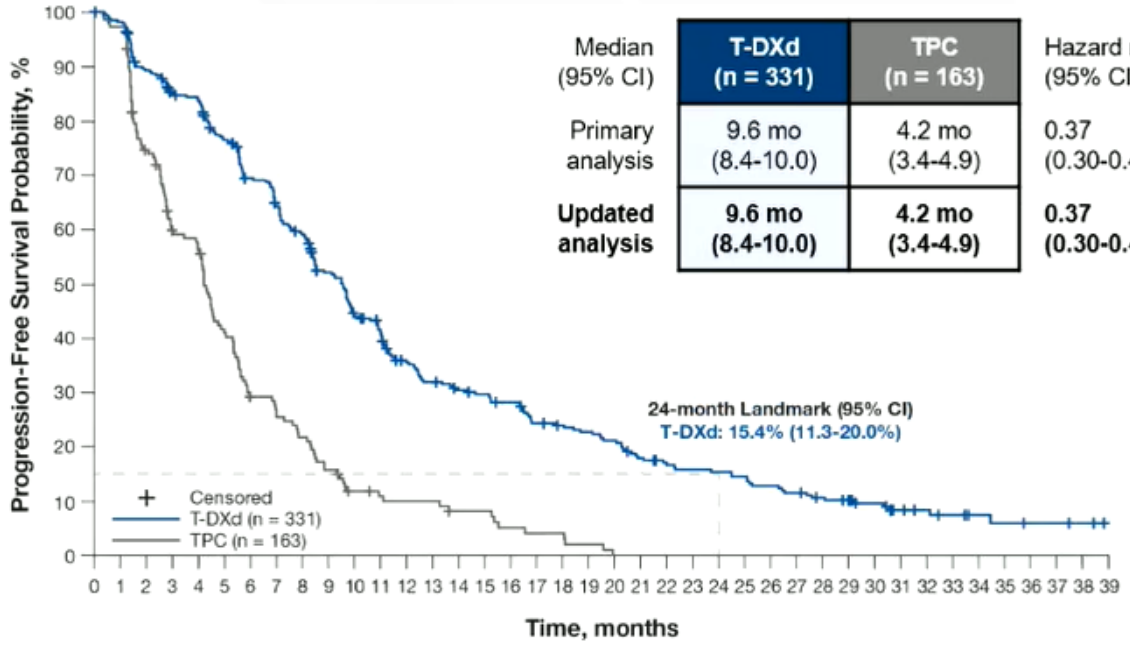
For efficacy in the hormone receptor negative cohort, hormone receptor status is based on data from the electronic data capture corrected for mis-stratification.
HR, hormone receptor; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Modi S, et al. *N Engl J Med*. 2022;387(1):9-20.

DESTINY-Breast04: Updated PFS Analysis

Median of 2 prior lines of ET and **1 prior line of chemo**

HR+ Cohort

Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis	9.6 mo (8.4-10.0)	4.2 mo (3.4-4.9)	0.37 (0.30-0.47)
Updated analysis	**9.6 mo (8.4-10.0)**	**4.2 mo (3.4-4.9)**	**0.37 (0.30-0.46)**



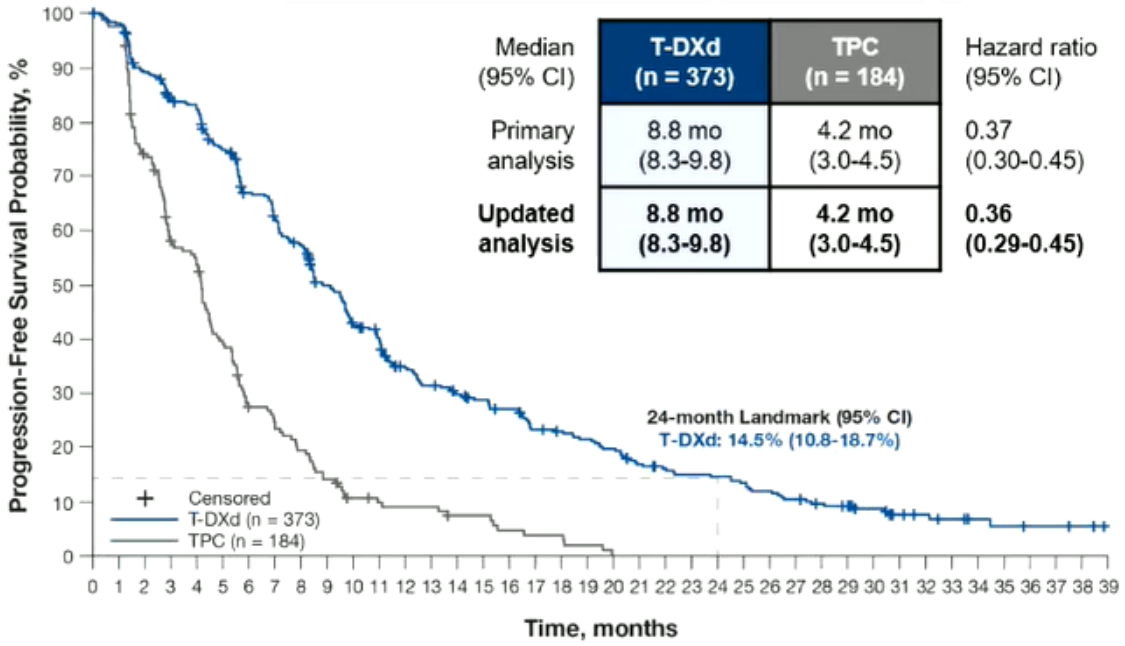
Patients still at risk:

T-DXd (n = 331) 331 323 290 272 267 241 215 198 181 154 129 119 98 88 82 79 74 63 60 57 53 44 40 37 36 34 30 27 23 21 16 11 9 7 5 4 3 3 2 0

TPC (n = 163) 163 143 107 83 78 66 39 34 29 21 14 12 11 11 8 6 5 4 4 2 0

All Patients

Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis	8.8 mo (8.3-9.8)	4.2 mo (3.0-4.5)	0.37 (0.30-0.45)
Updated analysis	**8.8 mo (8.3-9.8)**	**4.2 mo (3.0-4.5)**	**0.36 (0.29-0.45)**



Patients still at risk:

T-DXd (n = 373) 373 364 327 304 297 267 234 216 198 166 140 130 107 97 90 85 79 67 64 60 55 46 42 39 38 35 31 27 23 21 16 11 9 7 5 4 3 3 2 0

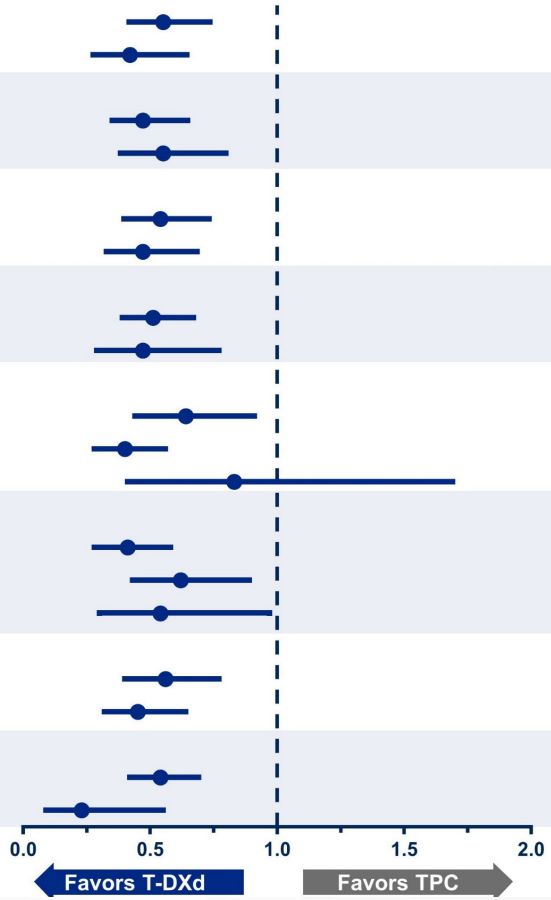
TPC (n = 184) 184 160 121 92 85 61 41 35 29 21 14 12 11 11 8 6 5 4 4 2 0

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

Modi S, et al. ESMO 2023. Abstract 376O.

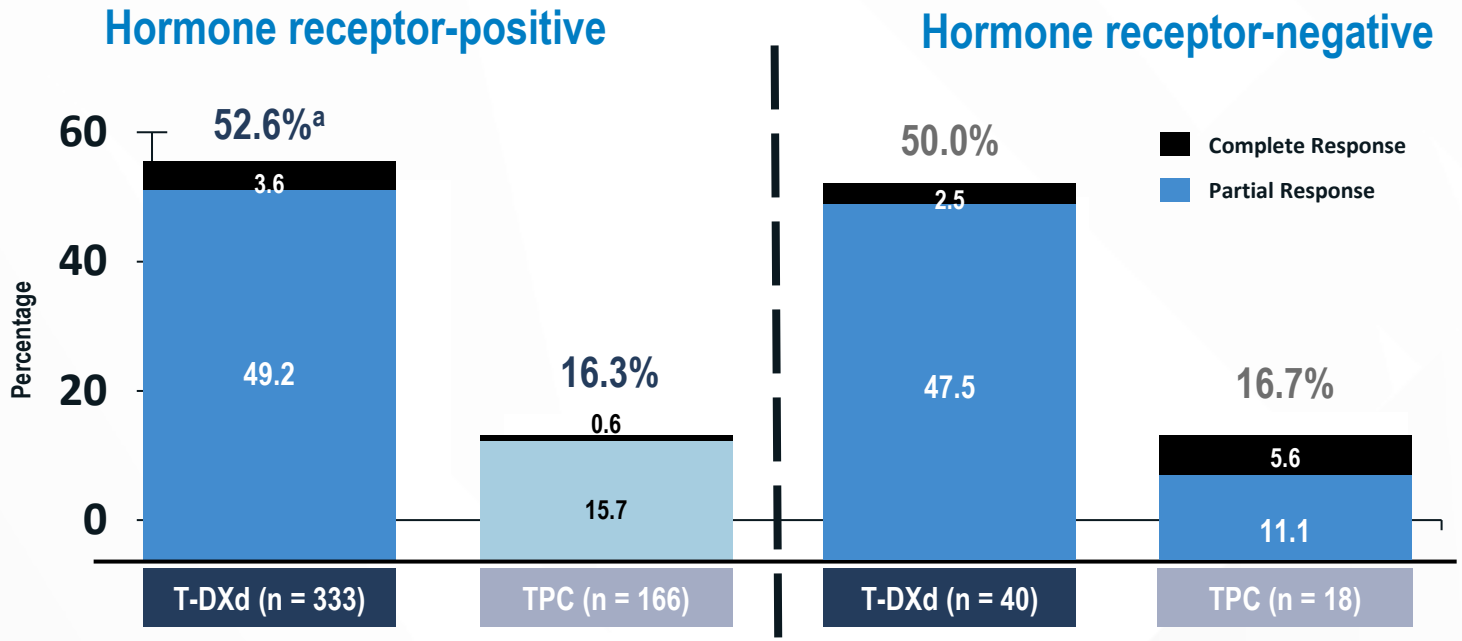
DESTINY-Breast04: Subgroup Analysis: PFS in HR+

	No. of Events/No. of Patients		PFS, median (95% CI), mo		Hazard Ratio for Disease Progression or Death (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6 inhibitors					
Yes	149/233	74/115	10.0 (8.3-11.4)	5.4 (4.0-7.8)	0.55 (0.42-0.73)
No	60/96	35/47	11.7 (9.5-17.7)	5.9 (4.3-8.2)	0.42 (0.28-0.64)
IHC status					
IHC 1+	119/192	66/96	10.3 (8.6-12.3)	5.3 (4.1-7.8)	0.48 (0.35-0.65)
IHC 2+/ISH−	92/139	44/67	10.1 (8.2-12.2)	5.9 (4.3-7.9)	0.55 (0.38-0.80)
Prior lines of chemotherapy					
1	129/203	63/93	10.9 (8.5-12.3)	6.8 (4.5-8.2)	0.54 (0.40-0.73)
≥2	81/127	47/69	9.9 (8.3-11.7)	4.6 (2.8-6.2)	0.47 (0.33-0.68)
Age					
<65 years	170/260	79/120	9.8 (8.4-11.3)	5.4 (4.1-7.8)	0.51 (0.39-0.67)
≥65 years	41/71	31/43	12.0 (9.5-14.7)	5.6 (4.3-10.8)	0.47 (0.29-0.77)
Race					
White	100/156	43/78	10.0 (8.5-12.2)	7.1 (4.0-10.0)	0.64 (0.44-0.91)
Asian	83/131	54/66	11.0 (8.4-13.8)	4.8 (4.2-6.4)	0.40 (0.28-0.56)
Other	25/37	11/16	6.0 (5.4-10.5)	7.0 (1.4-11.0)	0.83 (0.41-1.69)
Region					
Asia	81/128	48/60	10.9 (8.4-14.7)	5.3 (4.2-6.8)	0.41 (0.28-0.58)
Europe and Israel	90/149	44/73	10.8 (8.5-13.0)	7.1 (3.0-10.7)	0.62 (0.43-0.89)
North America	40/54	18/30	8.5 (6.3-11.3)	4.5 (2.9-8.2)	0.54 (0.30-0.97)
ECOG performance status					
0	116/187	55/95	10.9 (9.5-13.0)	7.0 (4.2-8.5)	0.56 (0.40-0.77)
1	95/144	55/68	9.7 (7.3-11.5)	4.6 (2.9-6.2)	0.45 (0.32-0.64)
Visceral disease at baseline					
Yes	196/298	100/146	9.8 (8.5-11.1)	5.8 (4.4-7.1)	0.54 (0.42-0.69)
No	15/33	10/17	17.9 (10.9-26.4)	4.5 (1.6-12.4)	0.23 (0.09-0.55)



PFS by blinded independent central review. Based on derived data, which include protocol deviations.
CDK, cyclin-dependent kinase; ECOG, Eastern Cooperative Oncology Group; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Modi S, et al. ESMO 2023. Abstract 376O.

DESTINY-Breast04: Confirmed Objective Response Rate



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 mis-stratification.
[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.
T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
Modi S, et al. ESMO 2023. Abstract 376O.

DESTINY-Breast04: Safety

- Grade ≥3 AEs occurred in 52.6% of patients receiving T-DXd vs. 67.4% physician's choice of chemotherapy
- ILD/pneumonitis occurred in 12.1% of patient receiving T-DXd (0.8% Grade 5)
- LV dysfunction reported in 17 patients receiving T-DXd (4.6%)
  - Grade 3 events reported in 1.5% of patients

Most Common Drug-Related Adverse Events (in ≥20% of Patients) in the Safety Analysis Set

Event	Trastuzumab Deruxtecan (N=371)		Physician's Choice of Chemotherapy (N=172)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Blood and lymphatic system disorders				
Neutropenia†	123 (33.2)	51 (13.7)	88 (51.2)	70 (40.7)
Anemia‡	123 (33.2)	30 (8.1)	39 (22.7)	8 (4.7)
Thrombocytopenia§	88 (23.7)	19 (5.1)	16 (9.3)	1 (0.6)
Leukopenia¶	86 (23.2)	24 (6.5)	54 (31.4)	33 (19.2)
Gastrointestinal disorders				
Nausea	271 (73.0)	17 (4.6)	41 (23.8)	0
Vomiting	126 (34.0)	5 (1.3)	17 (9.9)	0
Diarrhea	83 (22.4)	4 (1.1)	31 (18.0)	3 (1.7)
Constipation	79 (21.3)	0	22 (12.8)	0
Investigations: increased aminotransferase levels‖	87 (23.5)	12 (3.2)	39 (22.7)	14 (8.1)
General disorders: fatigue**	177 (47.7)	28 (7.5)	73 (42.4)	8 (4.7)
Metabolism and nutrition disorders: decreased appetite	106 (28.6)	9 (2.4)	28 (16.3)	2 (1.2)
Skin and subcutaneous tissue disorders: alopecia	140 (37.7)	0	56 (32.6)	0

* Shown are adverse events that emerged or worsened after initiation of a trial drug until 47 days after the last dose of the trial drug and that were adjudicated as being related to a trial drug by an independent committee.
† This category includes the preferred terms neutrophil count decreased and neutropenia.
‡ This category includes the preferred terms hemoglobin decreased, red-cell count decreased, anemia, and hematocrit decreased.
§ This category includes the preferred terms platelet count decreased and thrombocytopenia.
¶ This category includes the preferred terms white-cell count decreased and leukopenia.
‖ This category includes the preferred terms aminotransferase levels increased, aspartate aminotransferase increased, alanine aminotransferase increased, γ-glutamyltransferase increased, liver function test abnormal, and hepatic function abnormal.
** This category includes the preferred terms fatigue, asthenia, and malaise.

AXIS Medical Education

AE, adverse event; ILD, interstitial lung disease; LV, left ventricular; T-DXd, fam-trastuzumab deruxtecan-nxki.
Modi S, et al. *N Engl J Med*. 2022;387(1):9-20.

DESTINY-Breast06: Study Design

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

PATIENT POPULATION

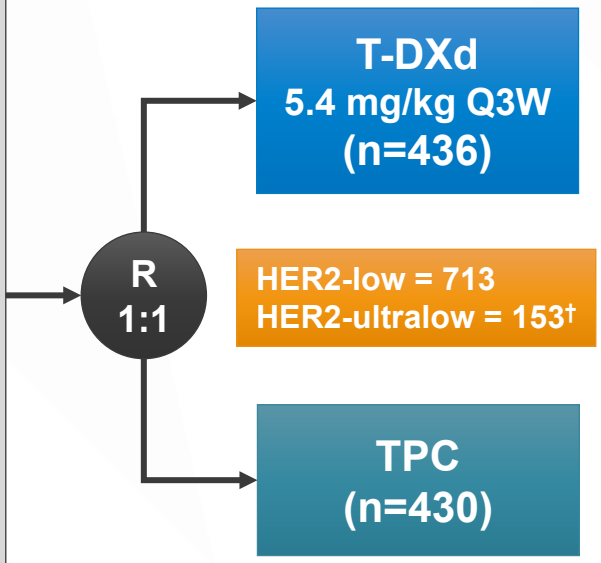
- HR+ mBC
- HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining)*
- **Chemotherapy naïve in the mBC setting**

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)



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)

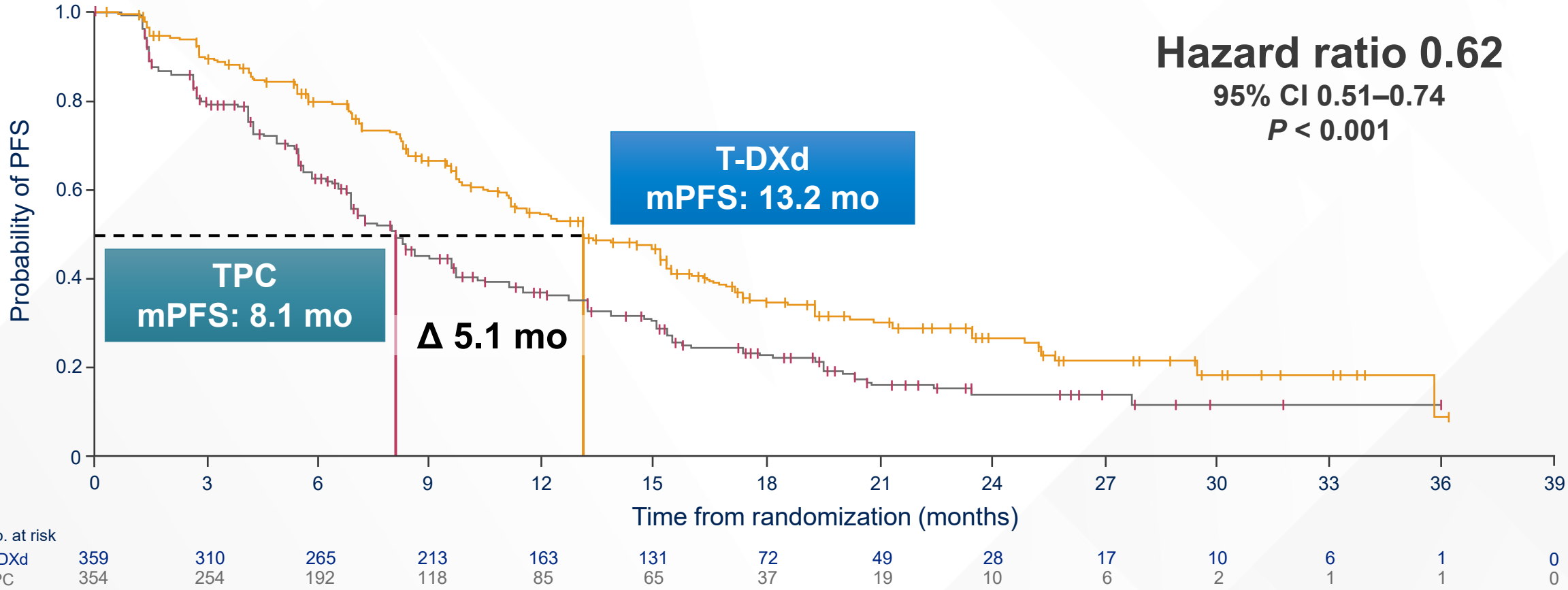
Other secondary

- PFS (INV) in HER2-low
- ORR (BICR/INV) and DOR (BICR/INV) in HER2-low and ITT (HER2-low + ultralow)
- Safety and tolerability
- Patient-reported outcomes‡

*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; PFS, progression-free survival; Q3W, every 3 weeks; R, randomized; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice.
ClinicalTrials.gov identifier: NCT04494425.
Curigliano G, et al. ASCO 2024. Abstract LBA1000. Bardia A, et al. *N Engl J Med.* Published online September 14, 2024. doi:10.1056/NEJMoa2407086

PFS (BICR) in HER2-Low: Primary Endpoint

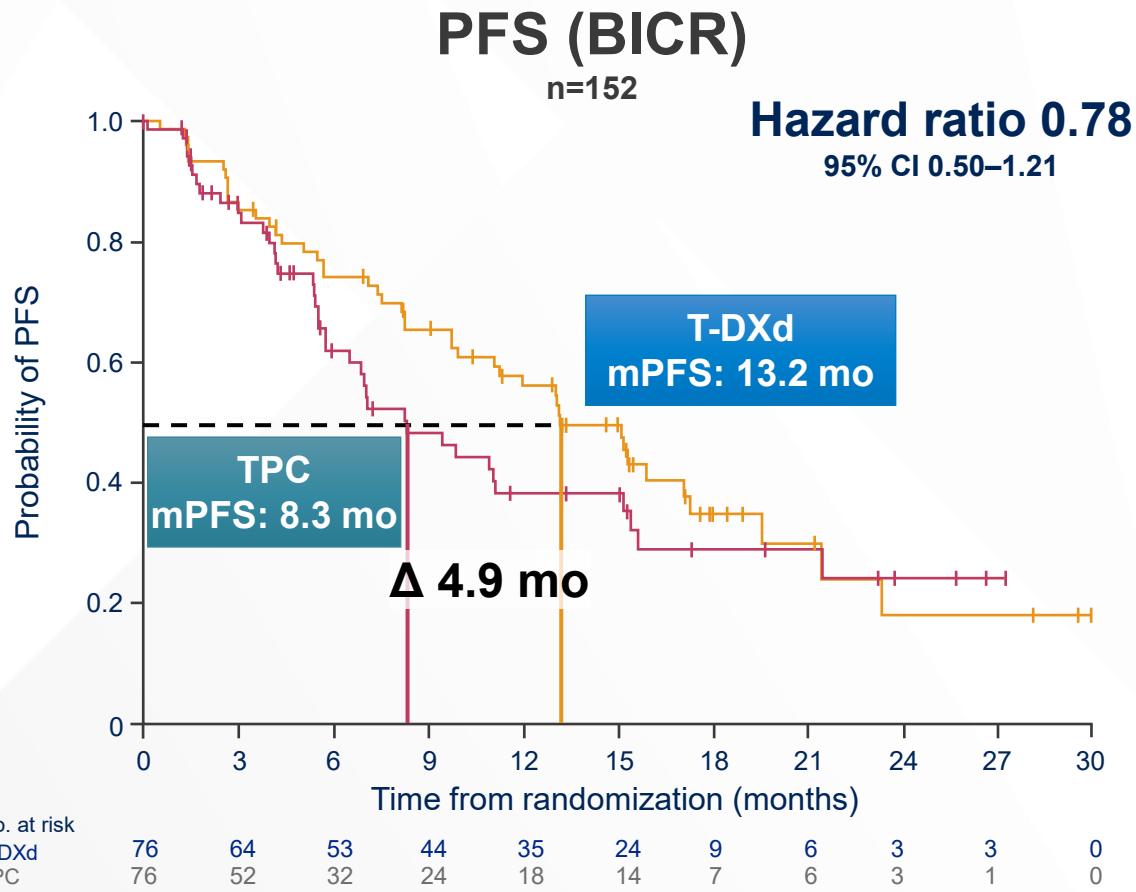
Median of 2 prior lines of ET, 90% with prior CDK4/6i, **no prior chemo**, 85% had visceral disease, 70% relapsed

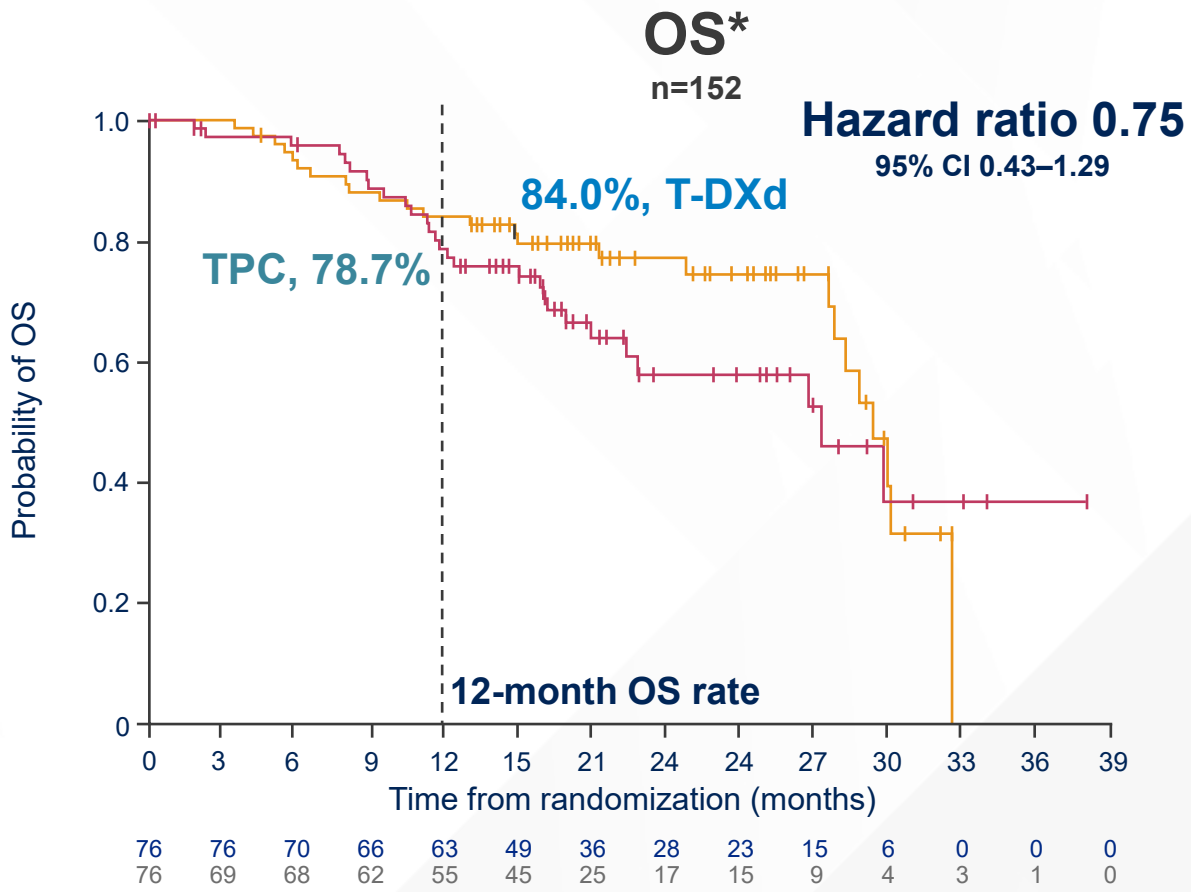


BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Curigliano G, et al. ASCO 2024. Abstract LBA1000. Bardia A, et al. *N Engl J Med.* Published online September 14, 2024. doi:10.1056/NEJMoa2407086

PFS and OS in HER2-Ultralow: Prespecified Exploratory Analyses





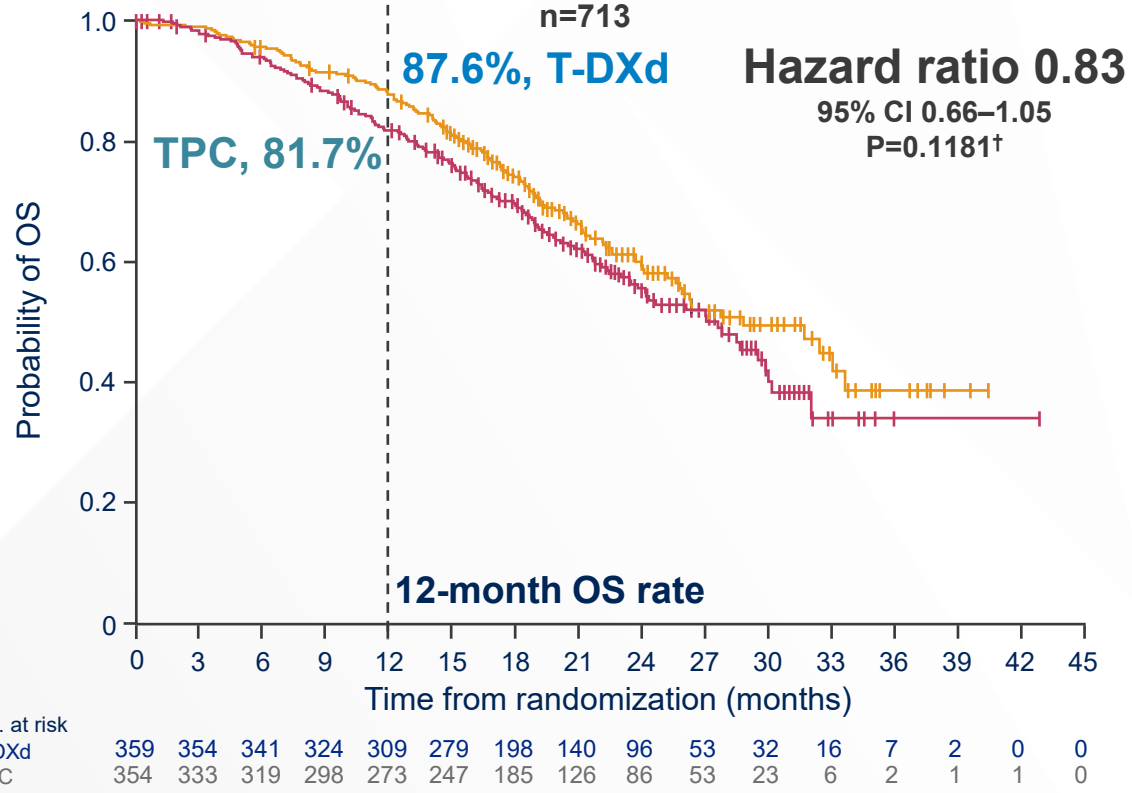
PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

*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; mPFS, (median) progression-free survival; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice.

Curigliano G, et al. ASCO 2024. Abstract LBA1000. Bardia A, et al. *N Engl J Med.* Published online September 14, 2024. doi:10.1056/NEJMoa2407086

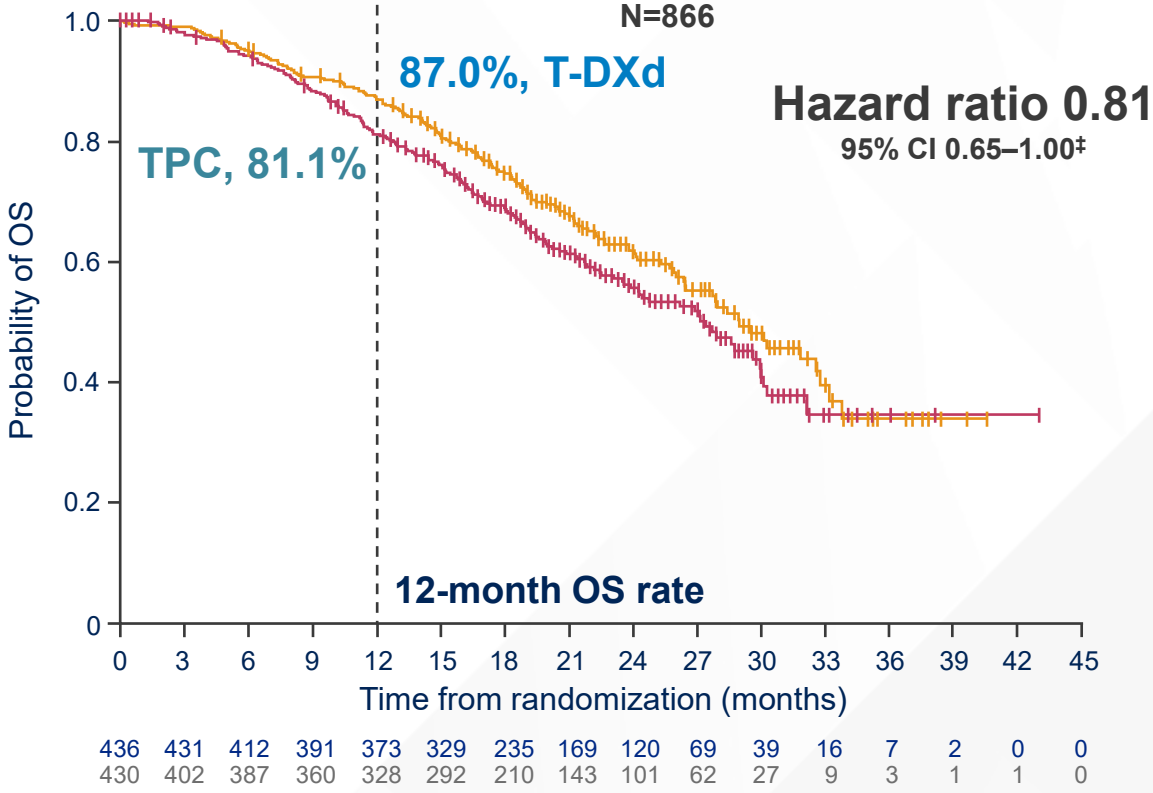
OS in HER2-Low and ITT: Key Secondary Endpoints (~40% Maturity)

HER2-low*



20.1% of patients in the TPC group received T-DXd post treatment discontinuation (HER2-low)

ITT (HER2-low + HER2-ultralow)



17.9% of patients in the TPC group received T-DXd post treatment discontinuation (ITT)

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*39.6% maturity (of total N for population) at this first interim analysis; median duration of follow up was 18.6 months (HER2-low). †P-value of <0.0046 required for statistical significance.
‡No test of significance was performed in line with the multiple testing procedure; median duration of follow up was 18.2 months (ITT).
CI, confidence interval; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice.

Curigliano G, et al. ASCO 2024. Abstract LBA1000. Bardia A, et al. *N Engl J Med.* Published online September 14, 2024. doi:10.1056/NEJMoa2407086

Adverse Events of Special Interest

Adjudicated as drug-related interstitial lung disease / pneumonitis

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n=434)	7 (1.6)	36 (8.3)	3 (0.7)	0	3 (0.7)	49 (11.3)
TPC (n=417)	0	1 (0.2)	0	0	0	1 (0.2)

Left ventricular dysfunction

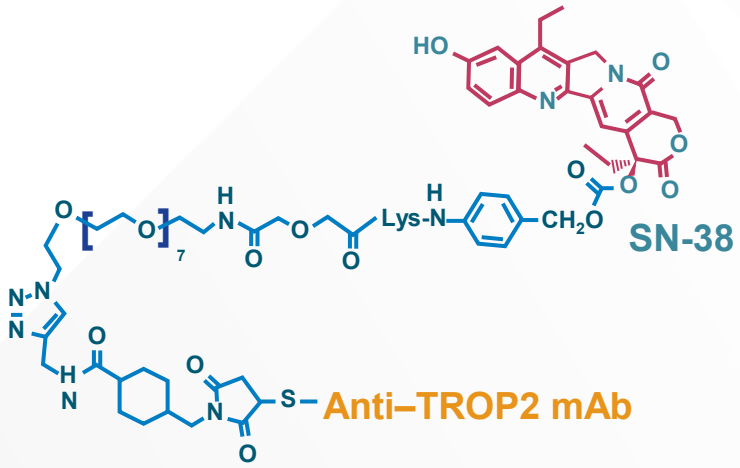
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
Ejection fraction decreased						
T-DXd (n=434)	1 (0.2)	31 (7.1)	3 (0.7)	0	0	35 (8.1)
TPC (n=417)	0	11 (2.6)	1 (0.2)	0	0	16 (3.8)
Cardiac failure						
T-DXd (n=434)	0	0	0	0	0	0
TPC (n=417)	0	1 (0.2)	1 (0.2)	1 (0.2)	0	3 (0.7)

On January 27, 2025, T-DXd was approved by the FDA for patients with HR+, HER2-low or HER2-ultralow MBC who have progressed on ≥1 line of endocrine therapy.

FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice.

Curigliano G, et al. ASCO 2024. Abstract LBA1000. Bardia A, et al. *N Engl J Med.* Published online September 14, 2024. doi:10.1056/NEJMoa2407086

Sacituzumab Govitecan

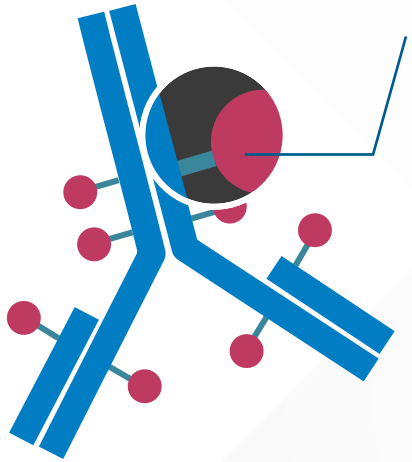


Humanized Anti-TROP2 Antibody

- Targets TROP2, an antigen expressed in many epithelial cancers
- Antibody type: hRS7 IgG1κ

SN-38 Payload (Topoisomerase I Inhibitor)

- Delivers up to 136-fold more SN-38 to tumors than parent compound irinotecan
- Unique chemistry improves solubility, selectively delivers SN-38 to tumor



Linker for SN-38

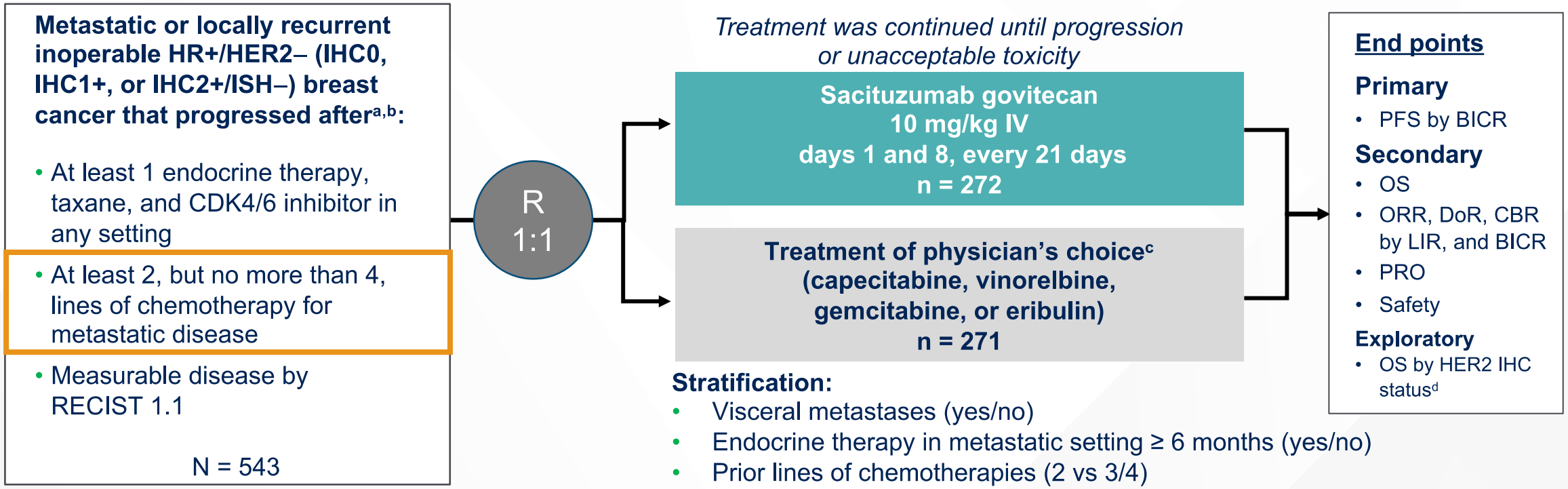
- High drug-to-antibody ratio (7.6:1)
- pH-sensitive linker for rapid release of payload at or inside tumor

Bystander effect: In acidic tumor microenvironment, SN-38 is released from anti-TROP2 antibody, diffuses into neighboring cells

mAB, monoclonal antibody.

Goldenberg DM, Sharkey RM. *MAbs.* 2019;11(6):987. Goldenberg DM, et al. *Oncotarget.* 2015;6(26):22496-22512. TRODELVY (sacituzumab govitecan-hziy). Prescribing information. Gilead Sciences; 2023. Kopp A, et al. *Mol Cancer Ther.* 2023;22(1):102-111.

TROPiCS-02 Phase 3 trial: Expanding the Benefit of Sacituzumab Govitecan to HR+ Disease



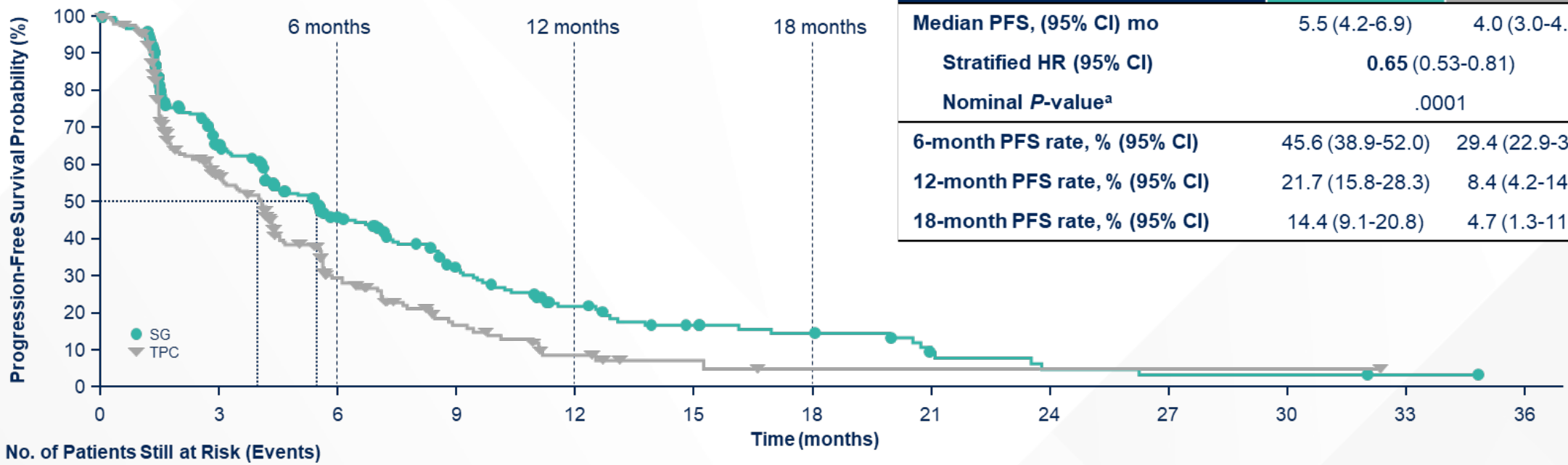
[a]ClinicalTrials.gov. NCT03901339. [b]Disease histology based on the ASCO/CAP criteria. [c]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator. [d]HER2-low was defined as ICH score of 1+, or score of 2+ with negative ISH result; HER2 IHC0 was defined as IHC score of 0.

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; DoR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenously; LIR, local investigator review; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcomes; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

Tolaney SM, et al. ASCO 2023. Abstract 1003. Rugo HS, et al. *Lancet*. 2023;402(10411):1423-1433.

TROPiCS-02: PFS

Median of 3 prior lines of chemotherapy, 100% had received prior CDK4/6 inhibitors, 95% had visceral disease



BICR analysis	SG (n = 272)	TPC (n = 271)
Median PFS, (95% CI) mo	5.5 (4.2-6.9)	4.0 (3.0-4.4)
Stratified HR (95% CI)	**0.65** (0.53-0.81)	
Nominal *P*-value[a]	.0001	
6-month PFS rate, % (95% CI)	45.6 (38.9-52.0)	29.4 (22.9-36.2)
12-month PFS rate, % (95% CI)	21.7 (15.8-28.3)	8.4 (4.2-14.5)
18-month PFS rate, % (95% CI)	14.4 (9.1-20.8)	4.7 (1.3-11.6)

No. of Patients Still at Risk (Events)

SG	272 (0)	148 (86)	82 (127)	48 (149)	27 (164)	17 (170)	13 (172)	6 (176)	3 (179)	2 (180)	2 (180)	1 (180)	0 (180)
TPC	271 (0)	109 (96)	42 (144)	18 (160)	7 (168)	3 (169)	1 (170)	1 (170)	1 (170)	1 (170)	1 (170)	0 (170)	

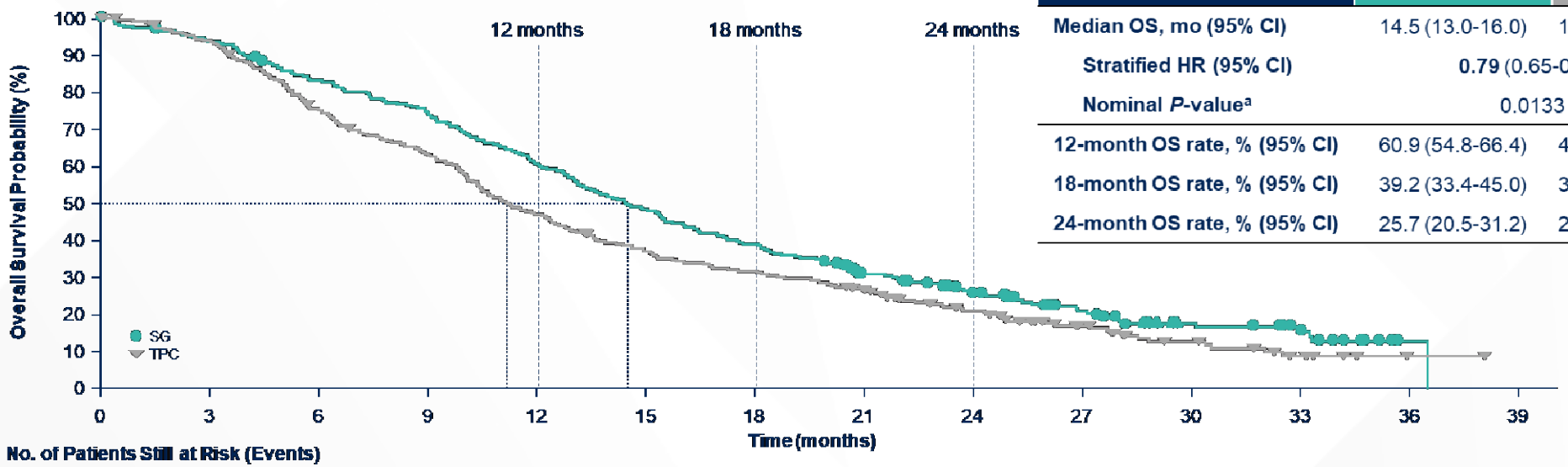
AXIS Medical Education

BICR, blinded independent central review; CDK, cyclin-dependent kinase; HR, hazard ratio; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Tolaney SM, et al. ASCO 2023. Abstract 1003. Rugo HS, et al. *Lancet*. 2023;402(10411):1423-1433.

TROPiCS-02: OS

Median of 3 prior lines of chemo



	SG (n = 272)	TPC (n = 271)
Median OS, mo (95% CI)	14.5 (13.0-16.0)	11.2 (10.2-12.6)
Stratified HR (95% CI)	**0.79** (0.65-0.95)	
Nominal *P*-value[a]	0.0133	
12-month OS rate, % (95% CI)	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-month OS rate, % (95% CI)	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-month OS rate, % (95% CI)	25.7 (20.5-31.2)	21.1 (16.3-26.3)

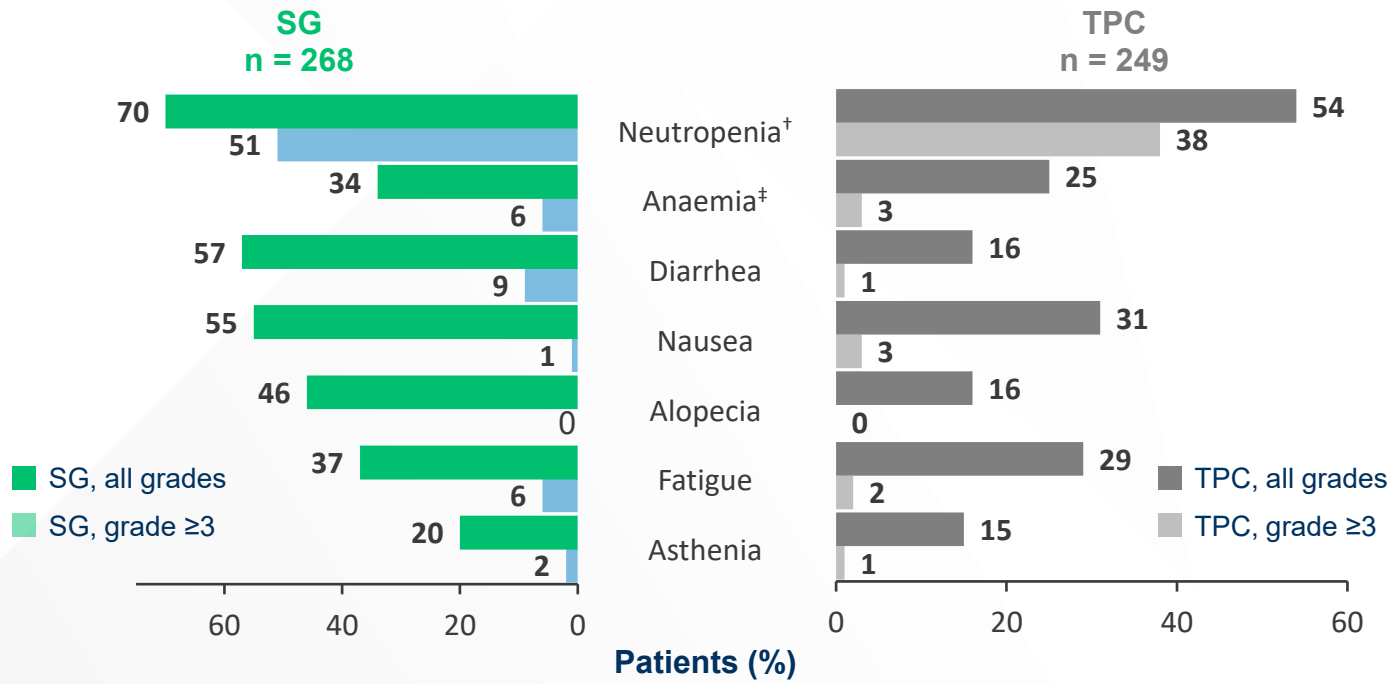
SG continued to demonstrate improvement in OS vs TPC at longer follow-up, with 21% reduction in risk of death and a higher proportion of patients remaining alive at each landmark

HR, hazard ratio; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Tolaney SM, et al. ASCO 2023. Abstract 1003. Rugo HS, et al. *Lancet*. 2023;402(10411):1423-1433.

TROPiCS-02: Safety

Drug-Related TEAEs in ≥20% of Patients[1]



TEAEs Associated With/Leading to[2]:

n (%)	SG (n = 268)	TPC (n = 249)
Treatment discontinuation	17 (6)	11 (4)
Dose reductions	90 (34)	82 (33)
Treatment-related death§	1 (<1)	0

- No events of ILD in the SG arm (vs 1% in the TPC arm)[1]
- No TRAEs of cardiac failure or left ventricular dysfunction in either arm[1,2]

Neutropenia and diarrhea were the most common TRAEs*

Assessed in the safety population of patients who received ≥1 dose of study treatment. Patients may report more than 1 event per preferred term.
*Key all grade and grade ≥3 TRAEs defined as those occurring in ≥10% and ≥5% of patients in 1 arm, respectively. †Combined preferred terms of neutropenia and neutrophil count decreased. ‡Combined preferred terms of anaemia, haemoglobin decreased, and red blood cell count decreased. §Of 6 TEAEs leading to death, only 1 was considered by the investigator as treatment related (septic shock due to neutropenic colitis). The other 5 were: COVID-19 pneumonia, pulmonary embolism, pneumonia, nervous system disorder, and arrhythmia. Upon detailed review of the TEAEs leading to death, there were no patterns identified.
ILD, interstitial lung disease; SG, sacituzumab govitecan; TPC, treatment of physician's choice (capecitabine, vinorelbine, gemcitabine or eribulin); TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
1. Rugo HS, et al. *J Clin Oncol*. 2022;40(29):3365-3376. 2. Rugo HS, et al. *Lancet*. 2023;402(10411):1423-1433.

TROPION-Breast01 Phase 3 Trial

Key inclusion criteria:

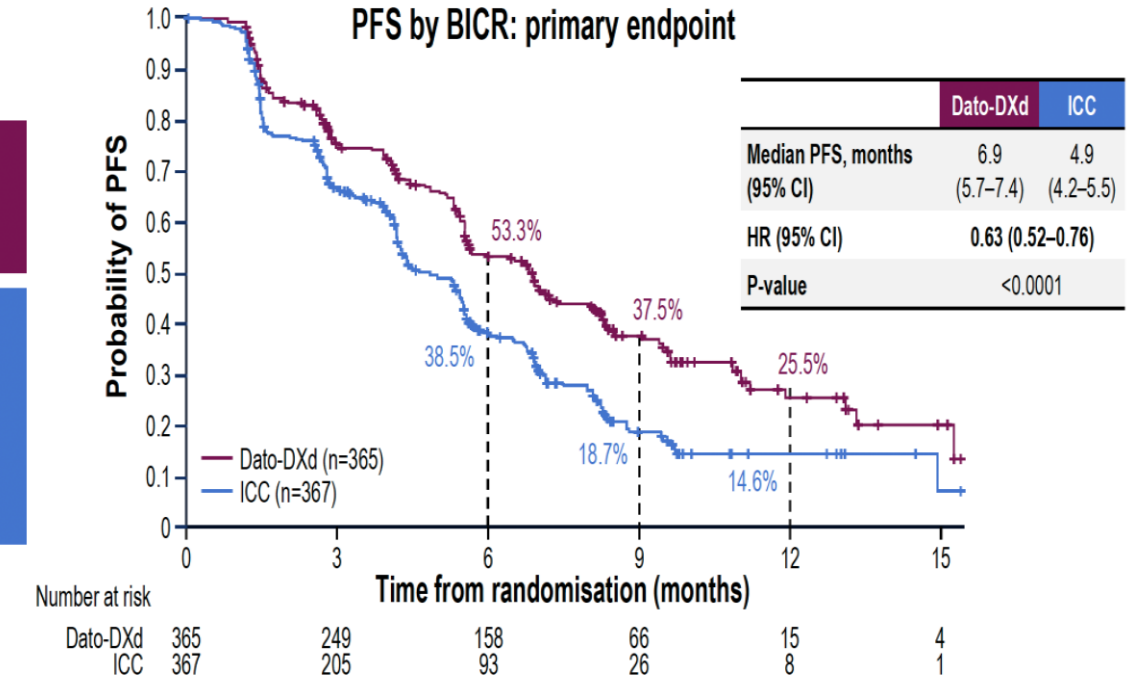
- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

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)

Randomisation stratified by:
- **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
- **Geographic location** (US/Canada/Europe vs ROW)
- **Previous CDK4/6 inhibitor** (yes vs no)



	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	

On January 17, 2025, Dato-DXd was approved by the FDA for patients with HR+/HER2- MBC who have received prior endocrine therapy and chemotherapy.

ADC, antibody-drug conjugate; BICR, blinded independent central review; CDK, cyclin-dependent kinase; Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ET, endocrine therapy; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenous; MBC, metastatic breast cancer; PFS, progression-free survival; ROW, rest of world.

Bardia A, et al. ESMO 2023. Abstract LBA11. Bardia A, et al. *J Clin Oncol.* Published online September 12, 2024. doi.org/10.1200/JCO.24.00920

Sequencing Strategies in HR+ Metastatic Breast Cancer: *Leveraging ADCs Across the HER2 Continuum*

AXIS Medical Education

Impact of DESTINY-Breast06 on Treatment Sequencing

- 1L T-DXd preferred for patients with:
  - Symptomatic disease
  - Extensive visceral disease burden
  - Short PFS on AI+CDK4/6i
  - Relapse within 2 years on adjuvant endocrine therapy

AXIS Medical Education

1L, first line; AI, aromatase inhibitor; CDK, cyclin-dependent kinase; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; PFS, progression-free survival; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan.

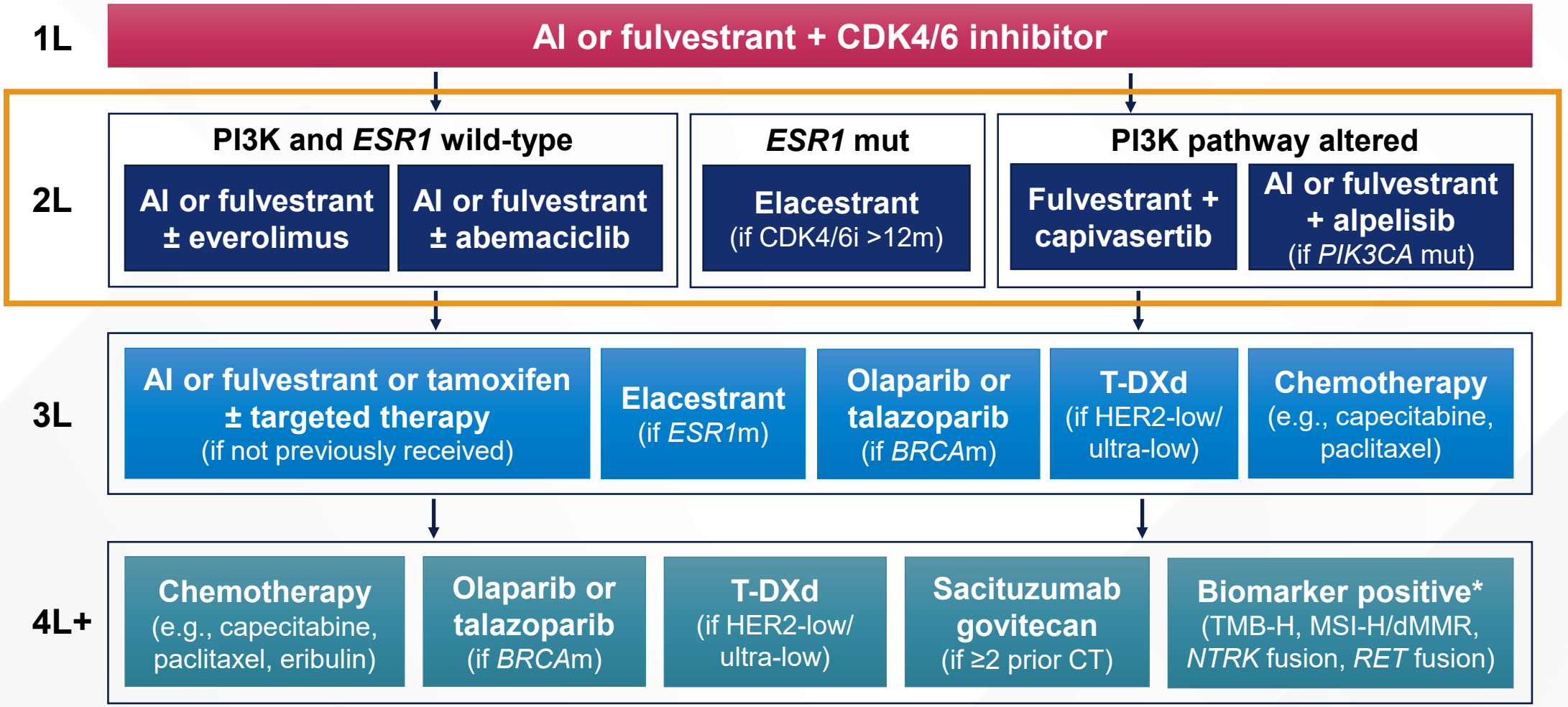
Landscape of ADCs in HER2-Negative MBC: ASCO 2024

	HR+/HER2- BC				TNBC	
ADC trials in MBC	**DESTINY-Breast06**	**DESTINY-Breast04**	**TROPION-Breast01**	**TROPiCS-02**	**DESTINY-Breast04**	**ASCENT**
Treatment arms	T-DXd (HER2) vs TPC	T-DXd (HER2) vs TPC	Dato-DXd (TROP2) vs TPC	SG (TROP2) vs TPC	T-DXd (HER2) vs. TPC	SG (TROP2) vs. TPC
HER2 status	>0 <1+, 1+, 2+/ISH-	1+, 2+/ISH-	0, 1+, 2+/ISH-	0, 1+, 2+/ISH-	1+, 2+/ISH-	0, 1+, 2+/ISH-
Prior chemotherapy for MBC	**0**	**1-2**	**1-2**	**2-4**	**1-2**	**≥1**
Median PFS HR (95% CI)	13.2 vs 8.1 mo. HR 0.63 (0.53-0.75)	9.6 vs 4.2 mo. HR 0.37 (0.30-0.56)	6.9 vs 4.9 mo. HR 0.63 (0.52-0.76)	5.5 vs 4.0 mo. HR 0.65 (0.53-0.81)	6.3 vs 2.9 mo. HR 0.29 (0.15-0.57)	5.6 vs 1.7 mo. HR: 0.41 (0.32-0.52)
Median OS HR (95% CI)	N/A HR 0.81 (0.65-1.00)	23.9 vs 17.6 mo. HR 0.69 (0.55-0.87)	N/A HR 0.84 (0.62–1.14)	14.5 vs 11.2 mo. HR 0.79 (0.65-0.95)	17.1 vs 8.3 mo. HR 0.58 (0.31-1.08)	12.1 vs 6.7 mo. 0.48 (0.38-0.59)
ORR	57.3% vs 31.2%	52.6% vs 16.3%	36.4% vs 22.9%	21% vs 14%	50.0% vs 16.7%	35% vs 5%

ADC, antibody-drug conjugate; BC, breast cancer; Dato-DXd, datopotamab deruxtecan; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor positive; HR, hazard ratio; ISH, in situ hybridization; MBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice.

Garrido-Castro A, et al. SABCS 2023. Abstract PO3-03-05. Curigliano G, et al. ASCO 2024. Abstract LBA1000. Bardia A, et al. *N Engl J Med.* Published online September 14, 2024. doi:10.1056/NEJMoa2407086. Modi S, et al. ESMO 2023. Abstract 376O. Bardia A, et al. ESMO 2023. Abstract LBA11. Rugo HS, et al. *Lancet.* 2023;402(10411):1423-1433. Tolaney SM, et al. ASCO 2023. Bardia A, et al. *N Engl J Med.* 2021;384(16):1529-1541.

Treatment Algorithm for HR+/HER2- MBC



*TMB-H: Pembrolizumab; MSI-H: Pembrolizumab, Dostarlimab; NTRK fusion: Larotrectinib, Entrectinib; RET fusion: Selpercatinib

1L/2L/3L/4L, 1st line, 2nd line, 3rd line, 4th line; AI, aromatase inhibitor; *BRCA*m, breast cancer gene mutation; CDK, cyclin-dependent kinase; CT, chemotherapy; ESR1, estrogen receptor 1; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; mut, mutated; MSI-H/dMMR, microsatellite instability-high/mismatch repair deficient; *NTRK*, neurotrophic tyrosine receptor kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PI3K, phosphoinositide 3-kinase; RET, rearranged during transfection; T-DXd, trastuzumab deruxtecan; TMB-H, tumor mutational burden-high.

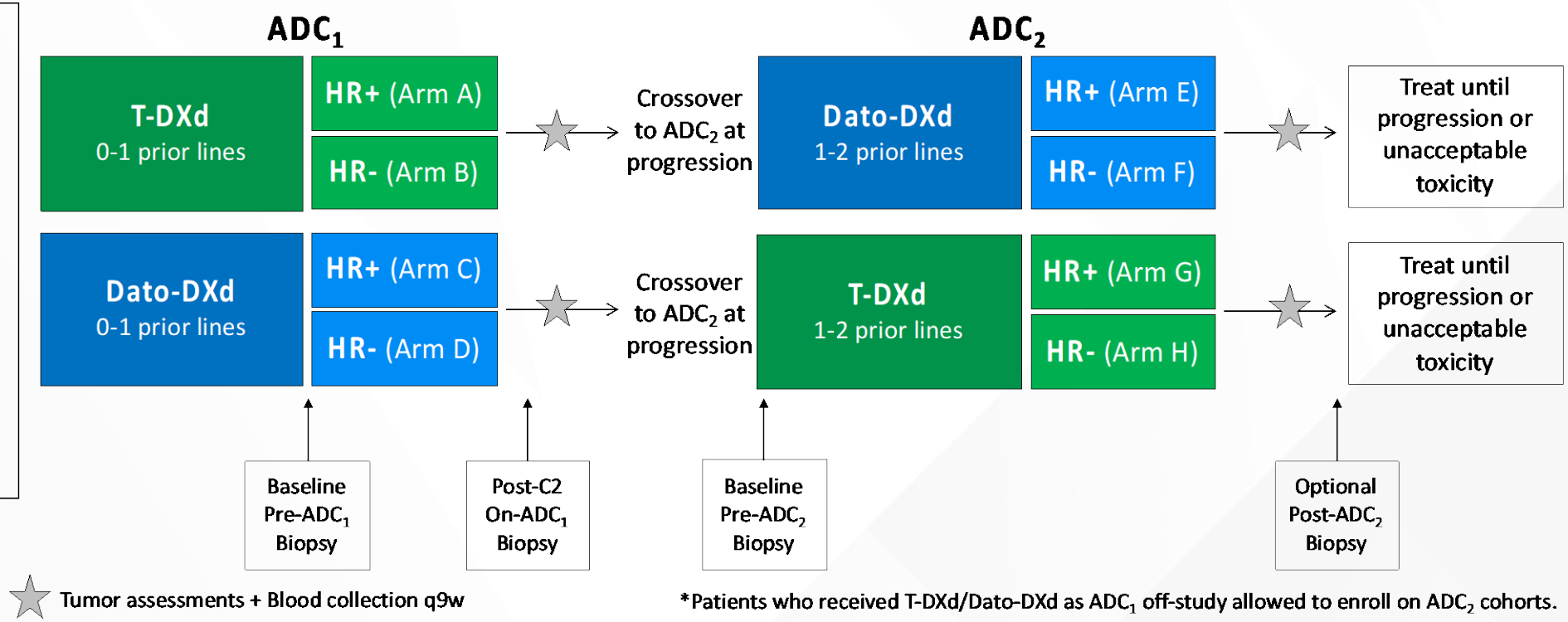
TBCRC 064: TReatment of ADC-Refractory Breast CancEr with Dato-DXd or T-DXd (TRADE-DXd)

Primary endpoint (ADC_1, ADC_2): ORR
Secondary endpoints: PFS, OS, CBR, TTOR, DOR

Eligibility:

- Confirmed unresectable locally advanced or metastatic disease
- History of HER2-low breast cancer (any prior primary or metastatic tumor) defined as IHC 1+ or 2+/ISH non-amplified
- Most recent pathology: HER2 IHC 0 or HER2-low
- Measurable disease
- No prior topo-I inhibitor-based therapy

Allocation 1:1 to T-DXd or Dato-DXd as ADC_1



*Patients who received T-DXd/Dato-DXd as ADC_1 off-study allowed to enroll on ADC_2 cohorts.

PI: A. Garrido-Castro.

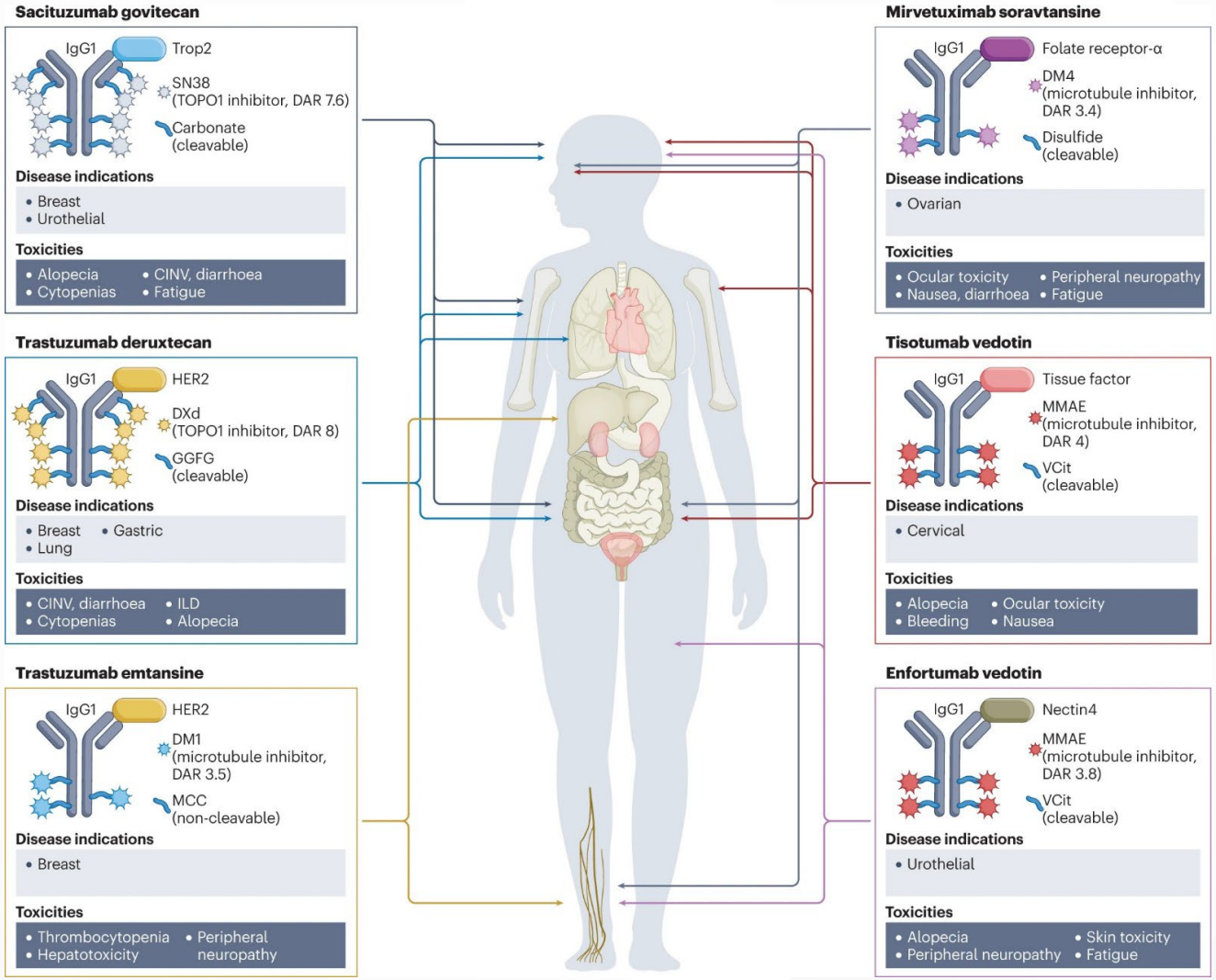
ADC, antibody-drug conjugate; CBR, clinical benefit rate; Dato-DXd, datopotamab deruxtecan; DOR, duration of response; DMI, ; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PI, principal investigator; q9w, every 9 weeks; TBCRC, Translational Breast Cancer Research Consortium; T-DXd, trastuzumab deruxtecan; TTOR, time to objective response.

Monitoring and Managing Adverse Events:

Navigating ADCs in Breast Cancer Treatment

AXIS Medical Education

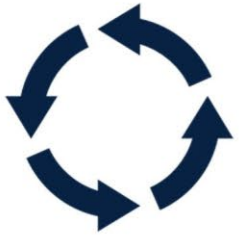
Toxicities of ADCs Can Resemble Their Chemotherapy Payload



ADC, antibody-drug conjugate; CINV, chemotherapy-induced nausea and vomiting; DM, derivative of maytansine; DXd, deruxtecan; HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; ILD, interstitial lung disease; MCC, 4-maleimidomethyl cyclohexane-1-carboxylate; MMAE, monomethyl auristatin E; TOPO1, topoisomerase I; VCit, valine-citrulline.
Tarantino P, et al. *Nat Rev Clin Oncol.* 2023;20(8):558–576.

AXIS Medical Education

Management of ILD: The 5 “S” Rules

1	2	3	4	5
				
Screen	**Scan**	**Synergy**	**Suspend Treatment**	**Steroids**
• Careful patient selection is warranted before initiating T-DXd to optimize the monitoring strategies based on the baseline risk • Screening continues during treatment, with regular clinical assessments to exclude signs/symptoms of ILD	• The fundamental diagnostic tools for ILD remain radiological scans, with preference for high-resolution CT scans of the chest • A baseline scan is recommended, with repeat scans to be performed every 6-12 weeks	• Minimizing the risk of ILD involves teamwork, which includes educating patients and all the care team, as well as multidisciplinary management once ILD is suspected	• T-DXd should always be interrupted if ILD is suspected; it can only be restarted in the case of asymptomatic ILD that fully resolves	• The mainstay for treating T-DXd–induced ILD remains corticosteroids, with the dose to be adapted to the toxicity grade

AXIS Medical Education

CT, computed tomography; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.

Tarantino P, Tolaney SM. *JCO Oncol Pract.* 2023;19(8):526-527.

Management Strategies for ILD/Pneumonitis With T-DXd

Monitoring[1]

- Patients should be advised to report cough, dyspnea, fever, and/or any new or worsening respiratory symptoms immediately
- Promptly investigate evidence of ILD
- Evaluate patients with suspected ILD by radiographic imaging
- Consider consultation with a pulmonologist

Confirm[2]

Evaluations may include:

- High-resolution CT
- Pulmonologist consultation
- Blood culture and CBC
- Consider bronchoscopy
- PFTs and pulse oximetry

Dose Interruptions[1]

For Grade 1 (asymptomatic):

- Interrupt dose until recovery (Grade 0)

For Grade ≥2 (symptomatic):

- Permanently discontinue

Corticosteroid Treatment[1]

For Grade 1 (asymptomatic):

- Consider corticosteroid treatment as soon as ILD is suspected
- (eg, ≥0.5 mg/kg prednisolone or equivalent)

For Grade ≥2 (symptomatic):

- Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is suspected
- (eg, ≥1 mg/kg prednisolone or equivalent)

Upon improvement, follow by gradual taper (eg, 4 weeks).

Resume Therapy (Grade 1 only)[1]

If resolved in ≤28 days from date of onset:

Maintain dose

If resolved in >28 days from date of onset:

Reduce dose 1 level

Do not re-escalate the T-DXd dose after a dose reduction is made[2]

Initial dose reduction	4.4 mg/kg
Final dose reduction	3.2 mg/kg
Requirement for further dose reduction	Discontinue treatment

AXIS Medical Education

CBC, complete blood count; CT, computed tomography; ILD, interstitial lung disease; PFT, pulmonary function test; T-DXd, trastuzumab deruxtecan.

1. ENHERTU (fam-trastuzumab deruxtecan-nxki). Prescribing information. Daiichi Sankyo, Inc.; 2024. 2. Meyer KC. *Transl Respir Med.* 2014;2:4.

Managing Nausea With T-DXd

- With T-DXd, consider 3 drug prophylaxis:
  - Dexamethasone
  - 5HT3 receptor antagonist (ondansetron)
  - NK1 receptor antagonist (aprepitant)
- For delayed nausea:
  - Ondansetron prn

    or
  - Olanzapine prn

NK1, neurokinin-1; prn, pro re nata (as needed); T-DXd, trastuzumab deruxtecan.

Stankowicz M, et al. *Breast Care (Basel)*. 2021;16(4):408-411.

Management of LV Dysfunction With T-DXd

LV Dysfunction Severity	Treatment Approach
LVEF >45%, absolute decrease from baseline 10-20%	Continue T-DXd
LVEF 40-45%, absolute decrease from baseline <10%	• Continue T-DXd • Repeat LVEF assessment within 3 weeks
LVEF 40-45%, absolute decrease from baseline 10-20%	• Interrupt T-DXd • Repeat LVEF assessment within 3 weeks • If LVEF has not recovered to within 10% from baseline, permanently discontinue T-DXd • If LVEF recovers to within 10% from baseline, resume T-DXd treatment at same dose
LVEF <40% or absolute decrease from baseline is >20%	• Interrupt T-DXd • Repeat LVEF assessment within 3 weeks • If LVEF of <40% or absolute decrease from baseline of >20% is confirmed, permanently discontinue T-DXd
Symptomatic congestive heart failure	• Permanently discontinue T-DXd

AXIS Medical Education

LV, left ventricular; LVEF, left ventricular ejection fraction; T-DXd, trastuzumab deruxtecan.

ENHERTU (fam-trastuzumab deruxtecan-nxki). Prescribing information. Daiichi Sankyo, Inc.; 2024.

Adverse Events Associated With SG

- Neutropenia and diarrhea were the most reported AEs associated with SG in TROPiCS-02 and ASCENT
  - May be prevented and managed with guideline-established management protocols
  - Treatment discontinuation due to AEs occurred in 6% of patients receiving SG in TROPiCS-02, 5% in ASCENT

AXIS Medical Education

AE, adverse event; SG, sacituzumab govitecan.

Rugo HS, et al. *J Clin Oncol*. 2022;40(29):3365-3376. Bardia A, et al. *N Engl J Med*. 2021;384(16):1529-1541.

Potential Management Approaches for Neutropenia and Diarrhea With SG

- Neutropenia
  - Withhold SG for ANC < 1500/mm^3 or neutropenic fever
  - Monitor blood counts periodically during treatment
  - Consider G-CSF for secondary prophylaxis
  - Begin anti-infective treatment in patients with febrile neutropenia immediately
- Diarrhea
  - Monitor patients and give fluids/electrolytes as needed
  - Evaluate for infectious causes and if negative, begin loperamide
  - For severe diarrhea, withhold SG until diarrhea is ≤ grade 1 and reduce subsequent doses

AXIS Medical Education

ANC, absolute neutrophil count; G-CSF, granulocyte colony stimulating factor; SG, sacituzumab govitecan.

TRODELVY (sacituzumab govitecan-hziy). Prescribing information. Gilead Sciences; 2023.

Case-Based Learning Lab

Case Study Patient Presentation and History

Presentation

- 72-year-old female presented with 2-year history of neglected breast mass
- Staging workup identified multiple abnormal-appearing axillary, supraclavicular, and mediastinal nodes along with bone metastases without evidence of impending fracture
- Biopsy of breast mass: IDC, ER+/HER2 1+
- Treated with AI + CDK4/6i and has a response for 13 mo
- Then develops new liver metastases
- Tumor is *ESR1*m and *PI3K* wild-type
- Receives fulvestrant + everolimus, and progresses after 4 months

Medical History

- Diabetes
- Hypertension
- Hyperlipidemia
- Obesity
- Baseline mild neuropathy

Social History

- Works as a piano teacher

Family History

- No family history

AXIS Medical Education

AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; *ESR1*m, estrogen receptor 1 gene mutation; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; *PI3K*, phosphoinositide 3-kinase.

Case Study Clinical Course

- CT scan identifies multiple new lung nodules, worsening bone lesions, and a new 2-cm lesion in the liver. LFTs are normal.

CT, computed tomography; LFT, liver function test.

Case Study Audience Question

What would be the next step in management?

a) Eribulin
b) Capecitabine
c) Sacituzumab govitecan
d) Trastuzumab deruxtecan
e) Unsure

Case Study Clinical Course

- The patient started therapy with trastuzumab deruxtecan
- 3 months after starting, she develops cough
- Imaging reveals bilateral ground glass changes
- Work-up reveals no infectious etiology

Case Study Audience Question

What would be the next step in management?

a) Continue treatment with trastuzumab deruxtecan
b) Continue treatment with trastuzumab deruxtecan and start steroids
c) Dose reduce trastuzumab deruxtecan and continue therapy
d) Discontinue trastuzumab deruxtecan and start steroids
e) Hold therapy with trastuzumab deruxtecan

Key Takeaways

- The definition of HER2 status in mBC is evolving and HER2 heterogeneity is commonly observed
- Antibody-drug conjugates have changed the treatment landscape for metastatic HR+/HER2-expressing mBC
- We will need to better understand how to optimally select patients for ADC therapy, and in whom these agents can be effectively sequenced
- Monitoring and managing adverse events associated with ADCs are critical to achieving optimal patient outcomes

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ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mBC, metastatic breast cancer.

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Redefining Treatment Across the Spectrum of HR+/HER2-Expressing Metastatic Breast Cancer