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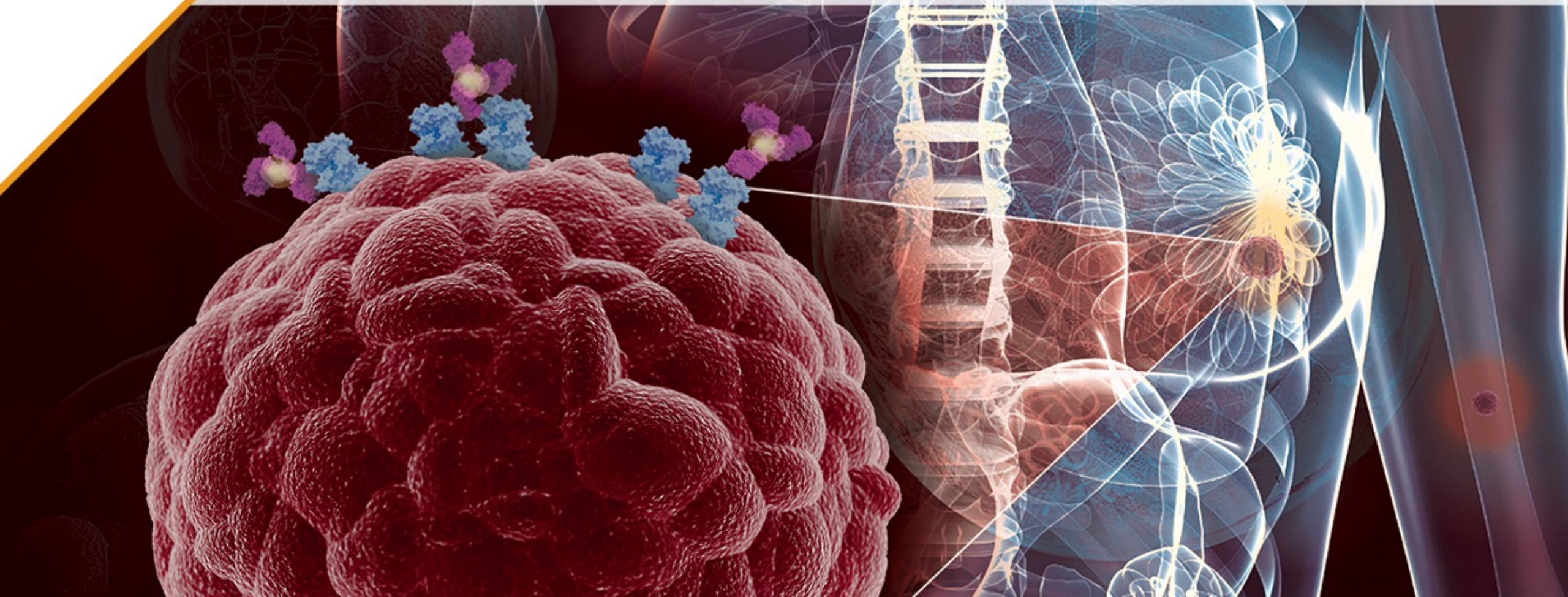
Tailoring ADC Therapies Across the HER2 Spectrum in Metastatic Breast Cancer



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Activity Agenda

- Emerging landscape of HER2-low BC: Clinical value and implications for HER2 testing
- Treatment options: Clinical decision-making and ADC therapies
- Anticipating potential treatment-related adverse events and treatment resistance
- Case study and key takeaways

Learning Objectives

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

- Apply new strategies based on available detection methods and guideline recommendations to account for disease heterogeneity and properly assess HER2 status.
- Incorporate the accumulating body of evidence from current clinical trials and real-world data on ADCs and their implications in HER2-positive and HER2-low breast cancer into personalized patient treatment planning.
- Employ strategies to identify, mitigate, and manage potential treatment-related adverse events in patients receiving HER2-directed ADC therapies.

ADC, antibody-drug conjugates; HER, human epidermal growth factor receptor.

Emerging Landscape of HER2-Low BC

Clinical Value and Implications for HER2 Testing

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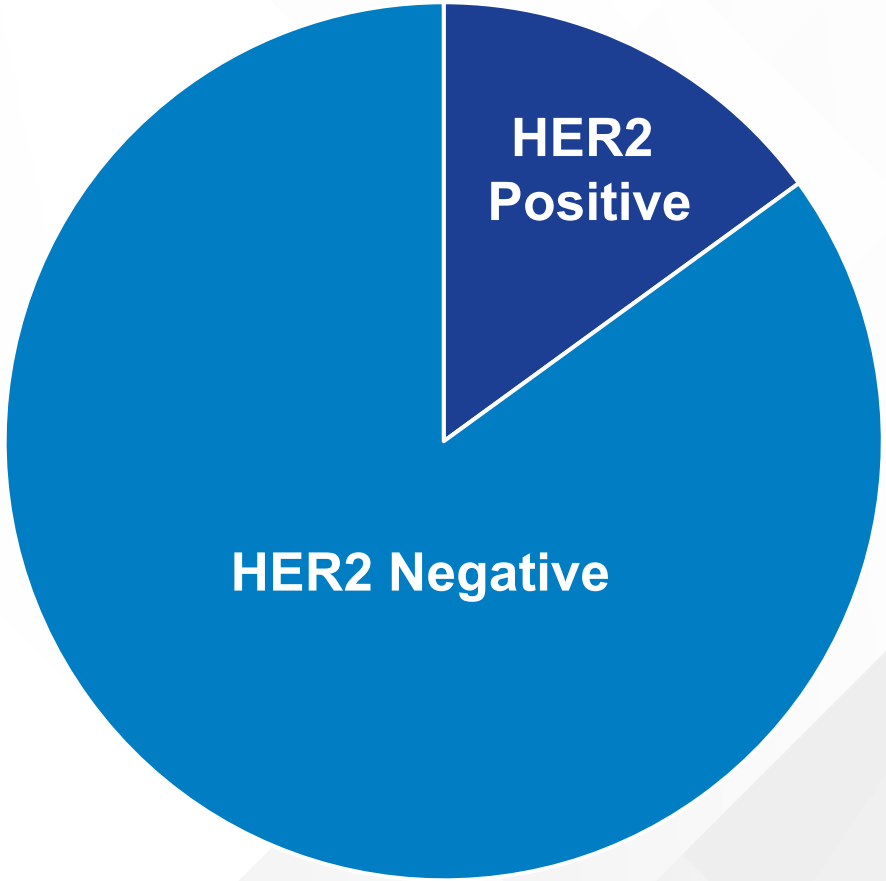
Traditional View of HER2-Positive Breast Cancer

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



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

HER2-Low mBC Has Been Explored as an Actionable Population Within the HER2 Expression Spectrum

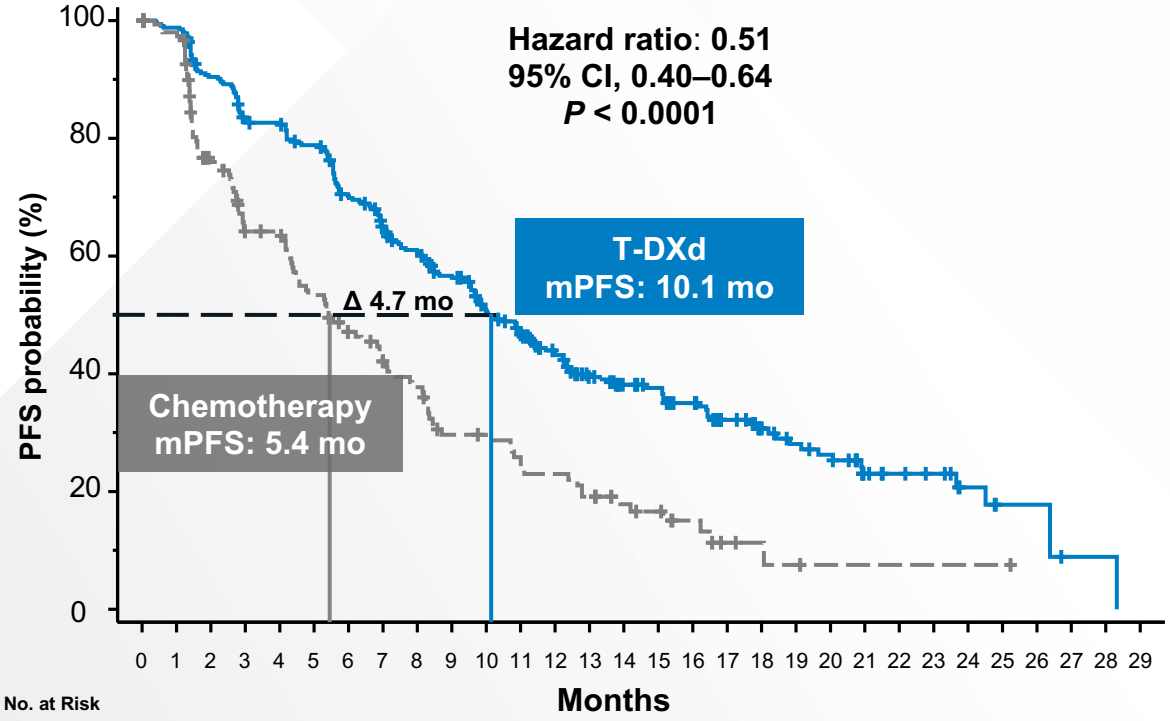
Historical binary HER2 scoring paradigm[1]	HER2-negative			HER2-positive	
	IHC 0	IHC 1+	IHC 2+/ISH-	IHC 2+/ISH+	IHC 3+

Modified HER2 scoring scale[2,3]	HER2-null	HER2-low		HER2-positive	
	IHC 0	IHC 1+	IHC 2+/ISH-	IHC 2+/ISH+	IHC3+

1. Wolff AC, et al. *J Clin Oncol*. 2018;36(20):2105-2122. 2. Modi S, et al. *N Engl J Med*. 2022;387(1):9-20. 3. Franchet C, et al. *Ann Pathol*. 2021;41(6):507-520.
HER, human epidermal growth factor receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer.

T-DXd Improved mPFS and Extended mOS vs. Chemotherapy in Patients With HR-positive HER2-Low (IHC 1+, 2+/ISH–) mBC

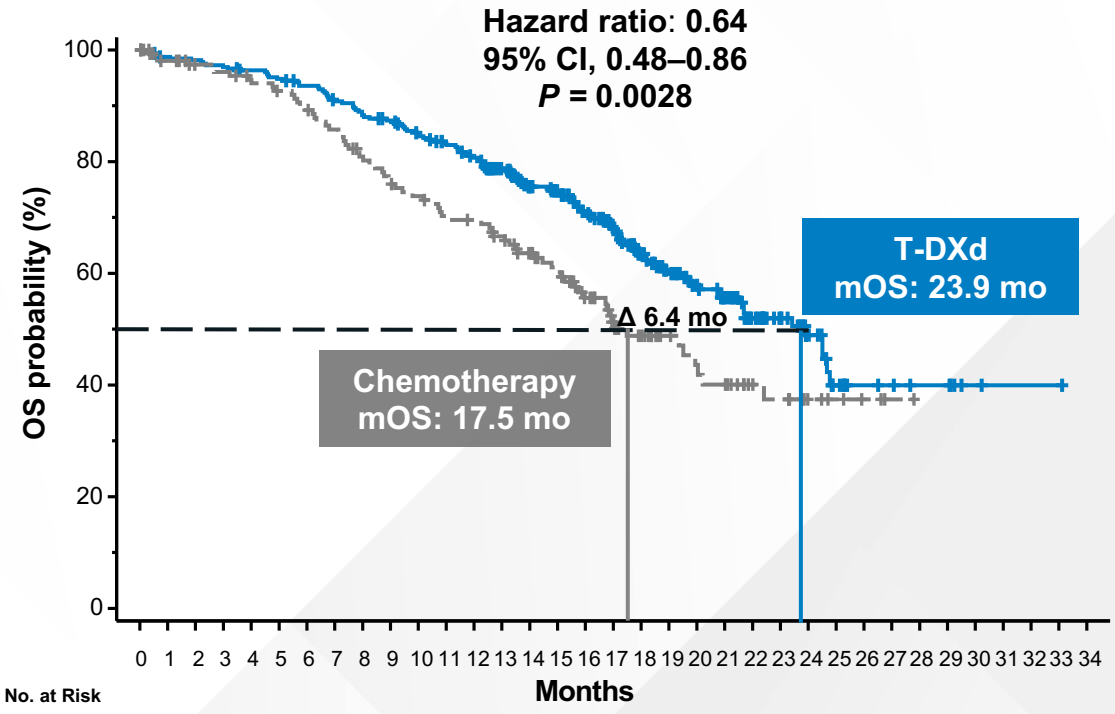
Primary endpoint: HR-positive PFS



No. at Risk

T-DXd (n=331):	331	324	290	265	262	248	218	198	182	165	142	128	107	89	78	73	64	48	37	31	28	17	14	12	7	4	4	1	1	0
Chemotherapy (n=163):	163	146	105	85	84	69	57	48	43	32	30	27	24	20	14	12	8	4	3	2	1	1	1	1	1	1	0			

Key secondary endpoint: HR-positive OS



No. at Risk

T-DXd (n=331):	331	325	323	319	314	309	303	293	285	280	268	260	250	228	199	190	168	144	116	95	81	70	51	40	26	14	9	8	6	6	2	1	1	1	0
Chemotherapy (n=163):	163	151	145	143	139	135	130	124	115	109	104	98	96	89	80	71	56	45	37	29	25	23	16	14	7	5	3	1	0						

Based on derived data, which includes protocol deviations.
Modi S, et al. ASCO 2022. Abstract LBA3.
2L, second-line; CI, confidence interval; ET, endocrine therapy; HER, human epidermal growth factor receptor; HR, hormone receptor; IHC, immunohistochemistry; ISH, *in situ* hybridization; mBC, metastatic breast cancer; mo, months; mOS, median overall survival; mPFS, median progression-free survival; T-DXd, trastuzumab deruxtecan.

Recent Developments in Diagnostic Testing for HER2-Low Assessment

- IHC/ISH combination remains gold standard for HER2 assessment, but is susceptible to challenges with disease heterogeneity and observer variability[1]
- Anti-HER2/neu (4B5) assay employed in DESTINY-Breast04[1*]
- Novel methodologies being investigated
  - Quantitative immunofluorescence/mass spectrometry HER2 array[2]
  - Immunoaffinity enrichment paired with multiple reaction-monitoring mass spectrometry[3]
  - AI and mRNA-focused methods being explored as a means of guiding HER2-low identification[1,4]

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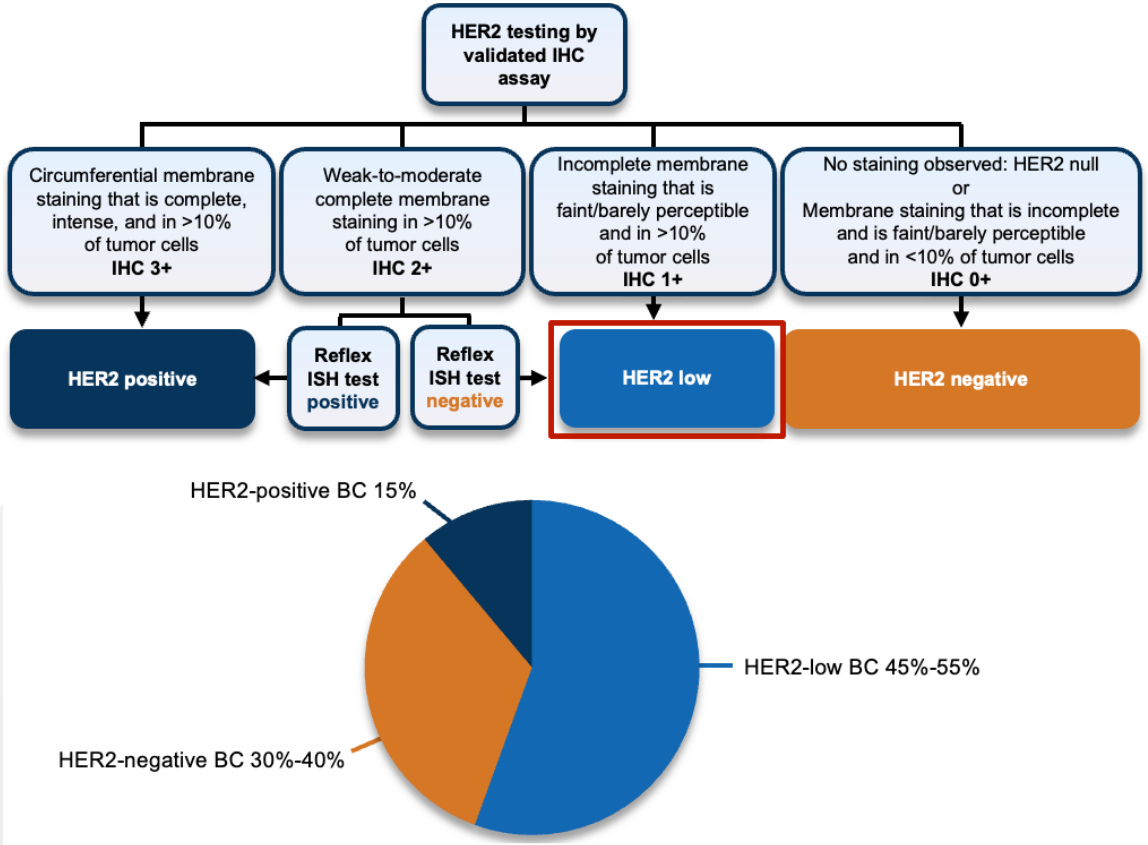
*Approved by FDA as companion diagnostic test

1. Zhang H, Peng Y. *Cancers (Basel).* 2023;15(1):126. 2. Moutafi M, et al. *Lab Invest.* 2022;102(10):1101-1108. 3. Kennedy JJ, et al. *Clin Chem.* 2021;67(7):1008-1018. 4. Xu K, et al. *J Mol Diagn.* 2022;24(7):775-783.

AI, artificial intelligence; FDA, Food and Drug Administration; HER, human epidermal growth factor receptor; mRNA, messenger ribonucleic acid.

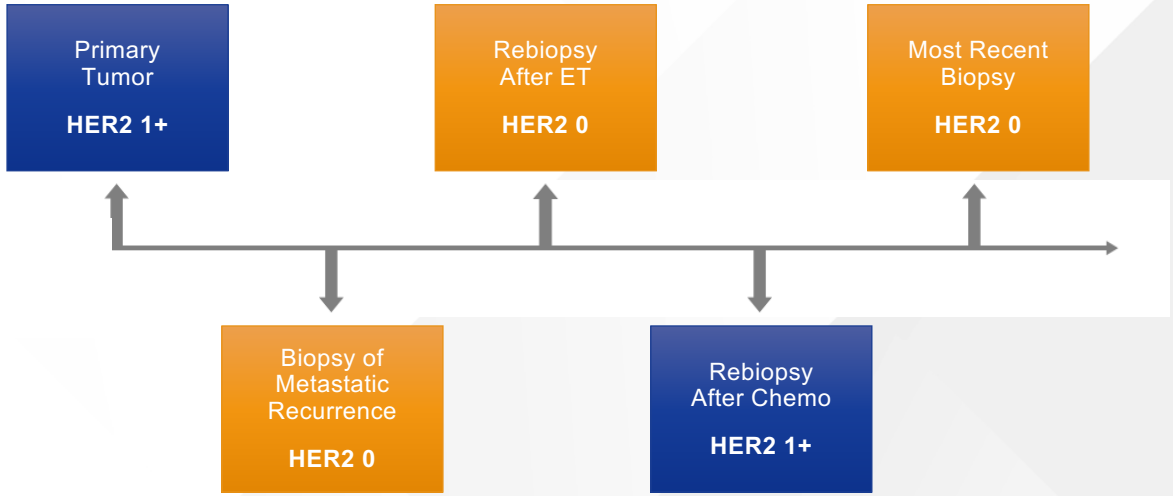
How to Define HER2-Low Breast Cancer?

Static Definition



Dynamic Definition (Real Life)

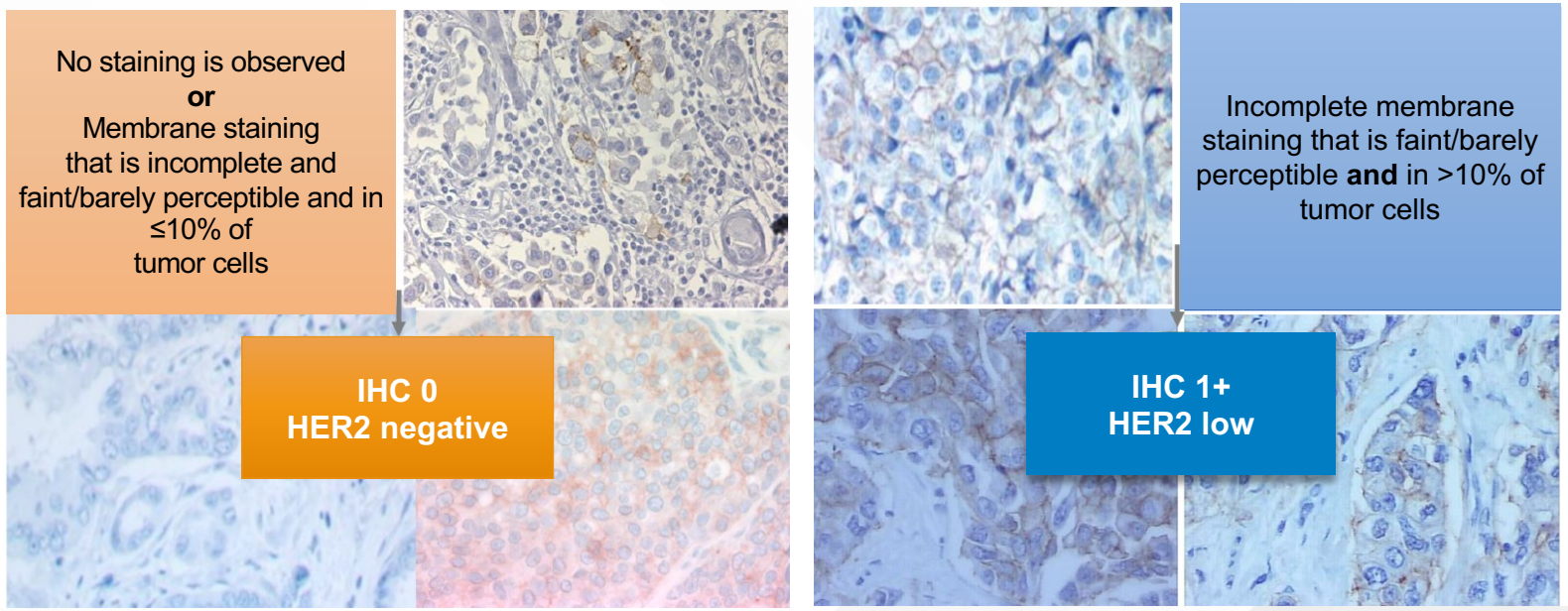
- HER2-low status changes over time
- Which timepoint to use to define a tumor as HER2 low?



Tarantino P, et al. *J Clin Oncol*. 2020;38(17):1951-1962.
BC, breast cancer; ET, endocrine therapy; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; ISH, in situ hybridization.

Low Concordance Among Pathologists Between HER2 0 & HER2 1+

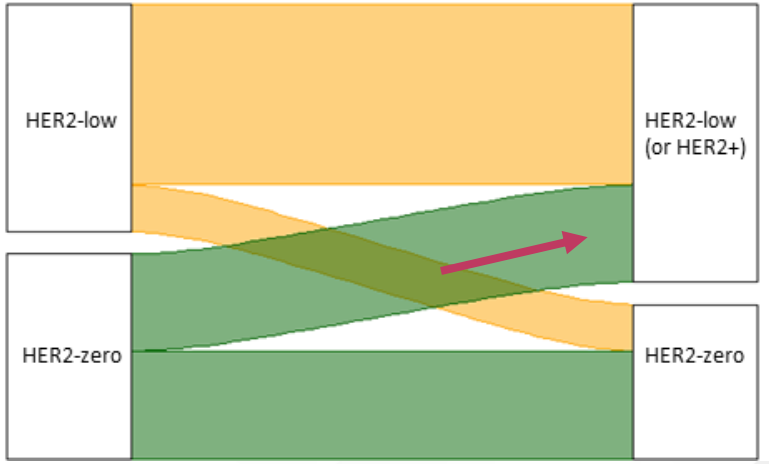
- In a recent study among 18 experienced pathologists, there was **only 26% concordance** between the diagnoses of HER2 0 and HER2 1+
- Importantly, HER2 0 does not mean absence of HER2, as it also includes tumors with **“ultralow”** expression



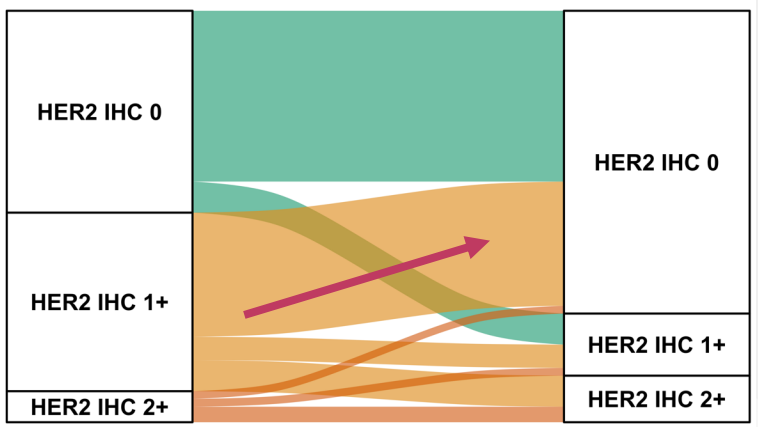
Fernandez AI, et al. *JAMA Oncol.* 2022;8(4):1-4.
HER, human epidermal growth factor receptor; IHC, immunohistochemistry.

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



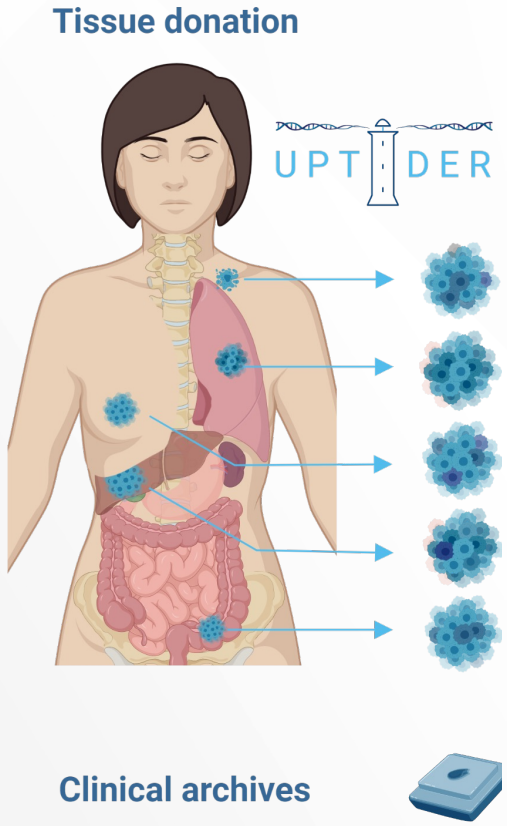
Matched paired primary-met TNBC

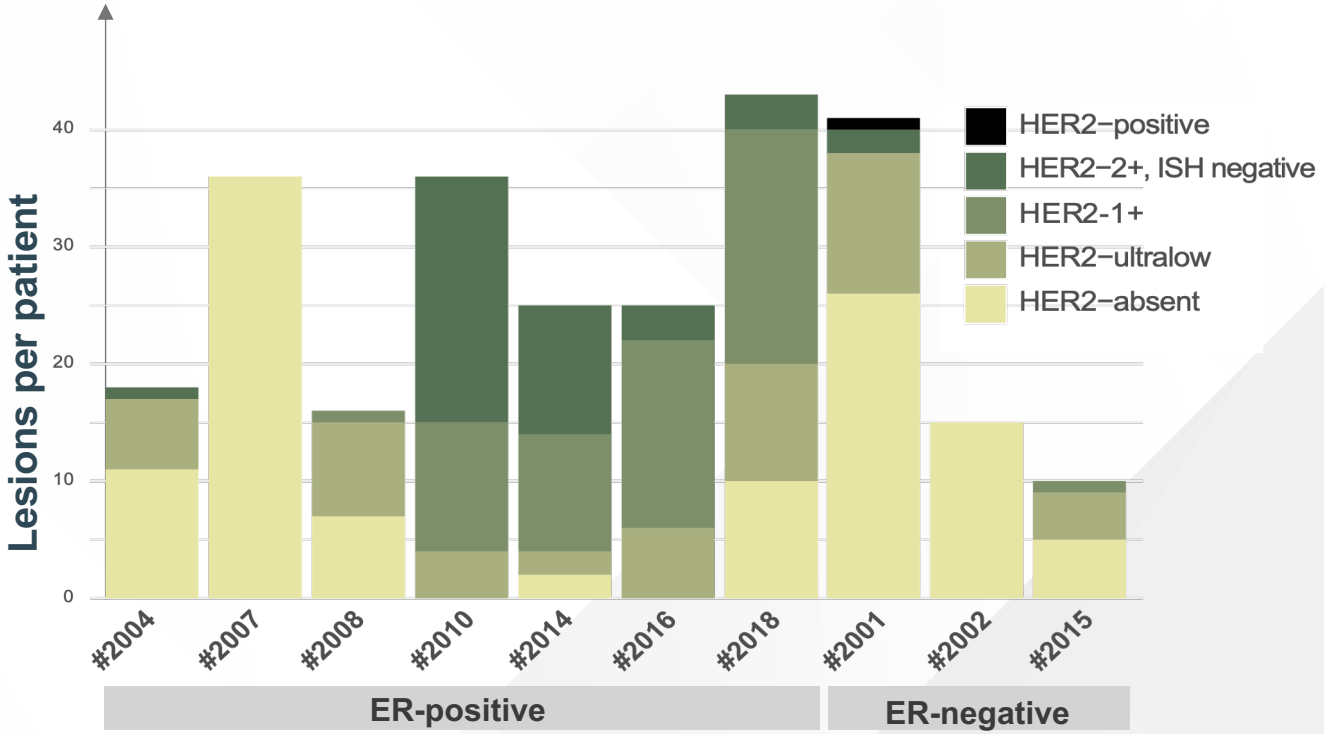


1. Tarantino P, et al *Eur J Cancer.* 2022;163:35-43. 2. Miglietta F, et al. *NPJ Breast Cancer.* 2021;7(1):137. 3. Garrido-Castro A, et al. SABCS 2022. Abstract HER2-10.
HER, human epidermal growth factor receptor; IHC, immunohistochemistry; TNBC, triple-negative breast cancer.

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

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





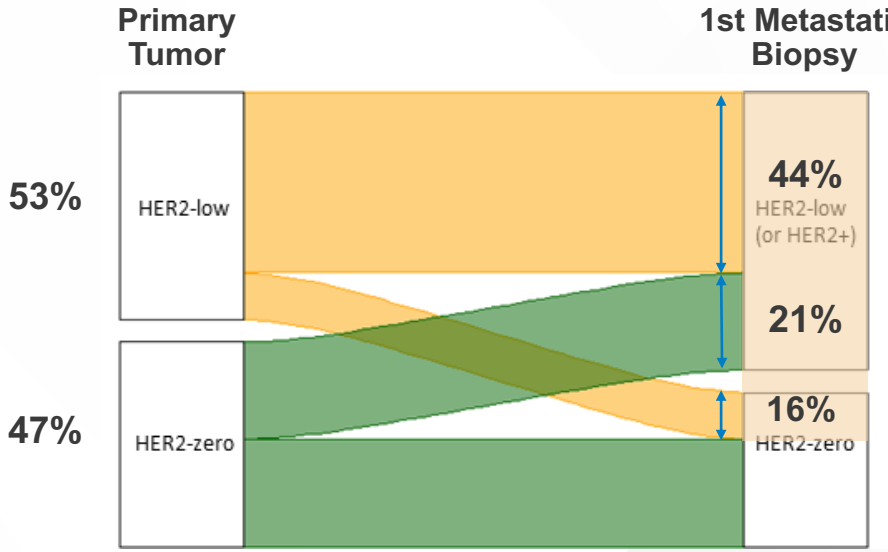
HER2-status of different metastases was highly variable within one patient, with HER2-low and zero lesions in 8/10 patients

Geukens T, et al. SABCS 2022. Abstract HER2-16.
ER, estrogen receptor; HER, human epidermal growth factor receptor; ISH, in situ hybridization.

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

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

Next Challenge: How LOW can we go?

DAISY

	Total	Cohort 1 (HER2 over-expressing)	Cohort 2 (HER2 Low-expressing)	Cohort 3 (HER2 non-detected)
BOR confirmed n/N [95%CI]	86/177 (48.6%) [41.0; 56.2]	48/68 (70.6%) [58.3; 81.0]	27/72 (37.5%) [26.4; 49.7]	11/37 (29.7%) [15.9; 47.0]
Median DOR (months) [95%CI]	8.5 [6.5; 9.8]	9.7 [6.8; 13]	7.6 [4.2; 9.2]	6.8 [2.8; Not reached]
Median PFS (months) [95%CI]	7.0 [6.0; 8.7]	11.1 [8.5; 14.4]	6.7 [4.4; 8.3]	4.2 [2.0; 5.7]

IHC 3+ IHC 1+ or 2+ IHC 0

Decreasing ORR by degree of HER2 expression

Dieras V, et al. SABCS 2021. Abstract PD8-02.
BOR, best objective response; DOR, duration of response; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; ORR, objective response rate; PFS, progression-free survival.

In the Future, the HER2 Spectrum May Evolve Further, With The Identification of IHC >0<1[1-4]

- With these emerging classifications of HER2 expression at the low end of the spectrum, strategies for identification of patients will require further optimization.

Historical binary HER2 scoring paradigm[1]	HER2-negative			HER2-positive	
	IHC 0	IHC 1+	IHC 2+/ISH-	IHC 2+/ISH+	IHC 3+

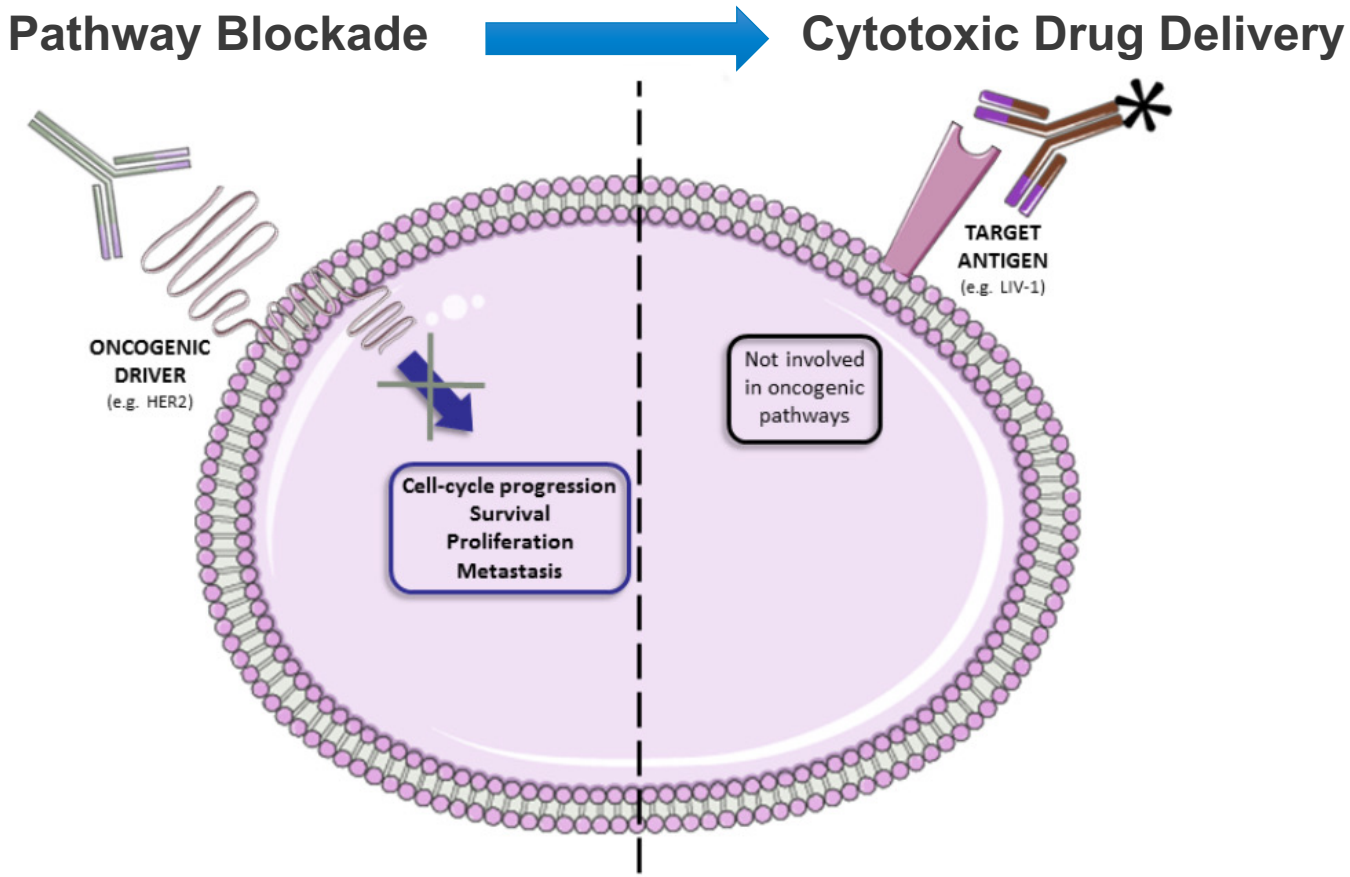
Modified HER2 scoring scale[2,3]	HER2-null	HER2-low		HER2-positive	
	IHC 0	IHC 1+	IHC 2+/ISH-	IHC 2+/ISH+	IHC3+

1. Wolff AC, et al. J Clin Oncol. 2018;36(20):2105-2122. 2. Modi S, et al. *N Engl J Med*. 2022;387(1):9-20. 3. Franchet C, et al. *Ann Pathol*. 2021;41(6):507-520. 4. ClinicalTrials.gov. NCT04494425. https://clinicaltrials.gov/ct2/show/NCT04494425

HER, human epidermal growth factor receptor; IHC, immunohistochemistry; ISH, in situ hybridization.

HER2 Low: Activity of HER2-directed ADCs not likely related to blockade of an oncogenic driver

- No benefit with HER2-blockade
- Activity is not likely related to the blockade of an oncogenic pathway, but rather to the targeted delivery of a highly potent payload
- HER2-low is not a new subtype characterized by an oncogenic driver, but is rather a biomarker for benefit to ADCs targeting HER2



1. Tarantino P, et al. *Expert Opin Biol Ther.* 2020;20(9):1009-1024.
ADC, antibody-drug conjugate; HER, human epidermal growth factor receptor.

Treatment Options

Clinical Decision-Making and ADC Therapies

NCCN Guidelines for Recurrent Unresectable or Stage IV (M1) Disease

HR-Positive or -Negative and HER2-Positive	
Setting	**Regimen**
First line	• Pertuzumab + trastuzumab + docetaxel (Category 1, preferred) • Pertuzumab + trastuzumab + paclitaxel (preferred)
Second line	• Fam-trastuzumab deruxtecan-nxki (Category 1, preferred)
Third line	• Tucatinib + trastuzumab + capecitabine (Category 1, preferred) • Ado-trastuzumab emtansine (T-DM1)
Fourth line and beyond (optimal sequence unknown)	• Trastuzumab + docetaxel or vinorelbine • Trastuzumab + paclitaxel ± carboplatin • Capecitabine + trastuzumab or lapatinib • Trastuzumab + lapatinib (without cytotoxic therapy) • Trastuzumab + other chemotherapy agents • Neratinib + capecitabine • Margetuximab-cmkb + chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) • Additional Targeted Therapy Options

Gradishar WJ, et al. NCCN Guidelines: Breast Cancer. Version 4.2023.
HER, human epidermal growth factor receptor; HR, hormone receptor; M1, metastatic; NCCN, National Comprehensive Cancer Network.

NCCN Guidelines for Recurrent Unresectable or Stage IV (M1) Disease

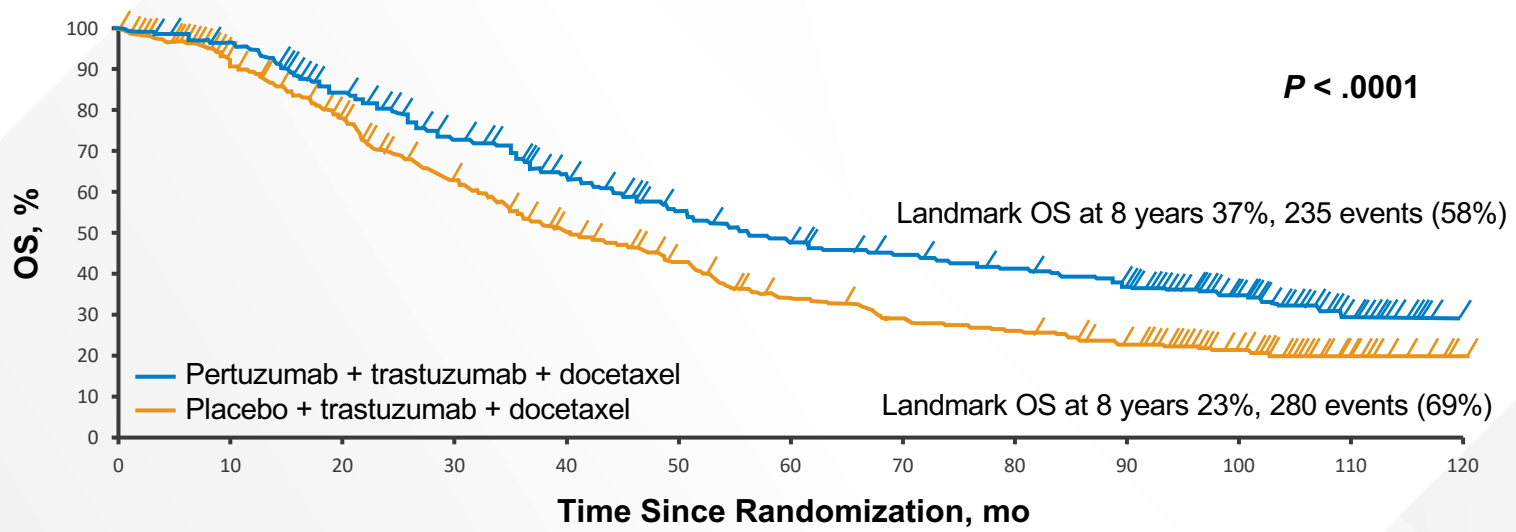
HR-Negative and HER2-Negative (Triple-Negative Breast Cancer; TNBC)		
Setting	**Subtype/Biomarker**	**Regimen**
Second line	Germline BRCA1/2 mutation	PARPi (olaparib, talazoparib) (Category 1, preferred)
	Any	Sacituzumab govitecan (Category 1, preferred)
		Systemic chemotherapy
	No germline BRCA1/2 mutation and HER2 IHC 1+ or 2+/ISH negative	Fam-trastuzumab deruxtecan-nxki (Category 1, preferred)

Gradishar WJ, et al. NCCN Guidelines: Breast Cancer. Version 4.2023.

HER, human epidermal growth factor receptor; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; M1, metastatic; NCCN, National Comprehensive Cancer Network.

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**

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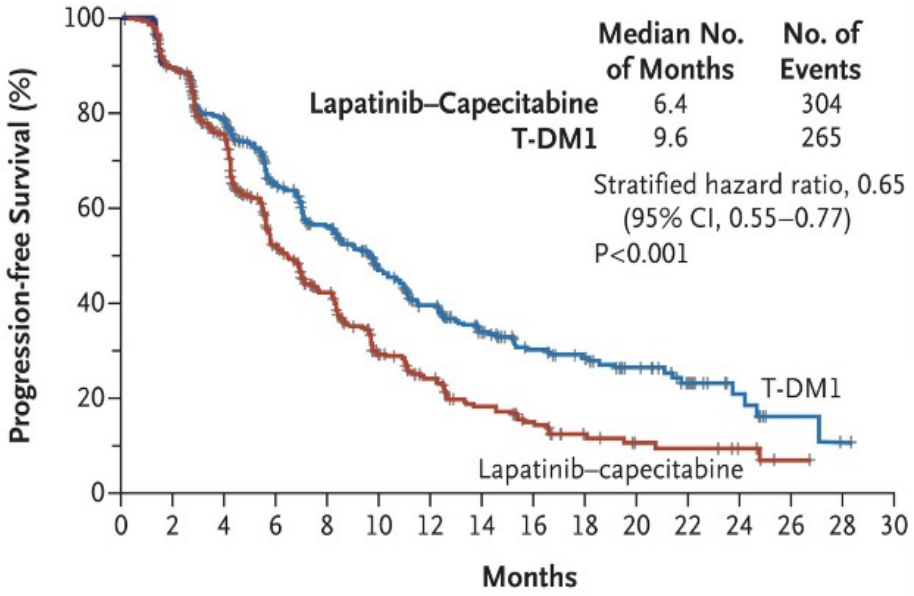
Swain SM, et al. *Lancet Oncol*. 2020;21(4):519-530.

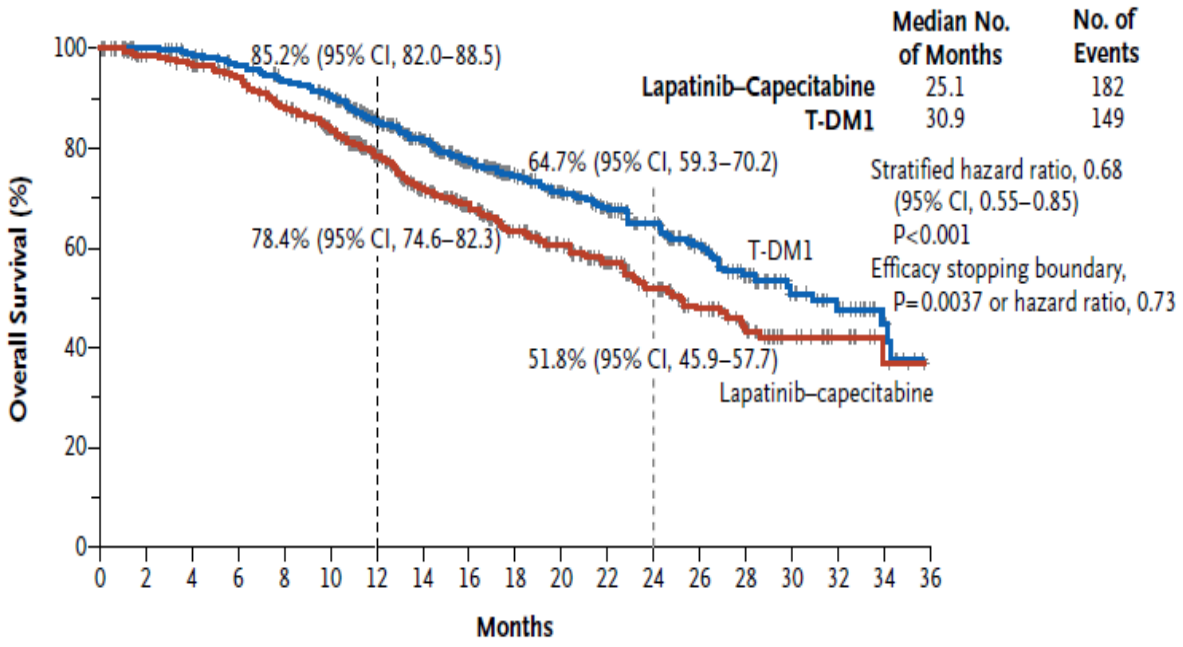
HER, human epidermal growth factor receptor; mBC, metastatic breast cancer; OS, overall survival; TP, trastuzumab and pertuzumab.

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



No. at Risk

Lapatinib–capecitabine	496	404	310	176	129	73	53	35	25	14	9	8	5	1	0	0
T-DM1	495	419	341	236	183	130	101	72	54	44	30	18	9	3	1	0



No. at Risk

Lapatinib–capecitabine	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

Verma S, et al. N Engl J Med. 2012;367(19):1783-1791.
HER, human epidermal growth factor receptor; T-DM1, ado-trastuzumab emtansine.

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.

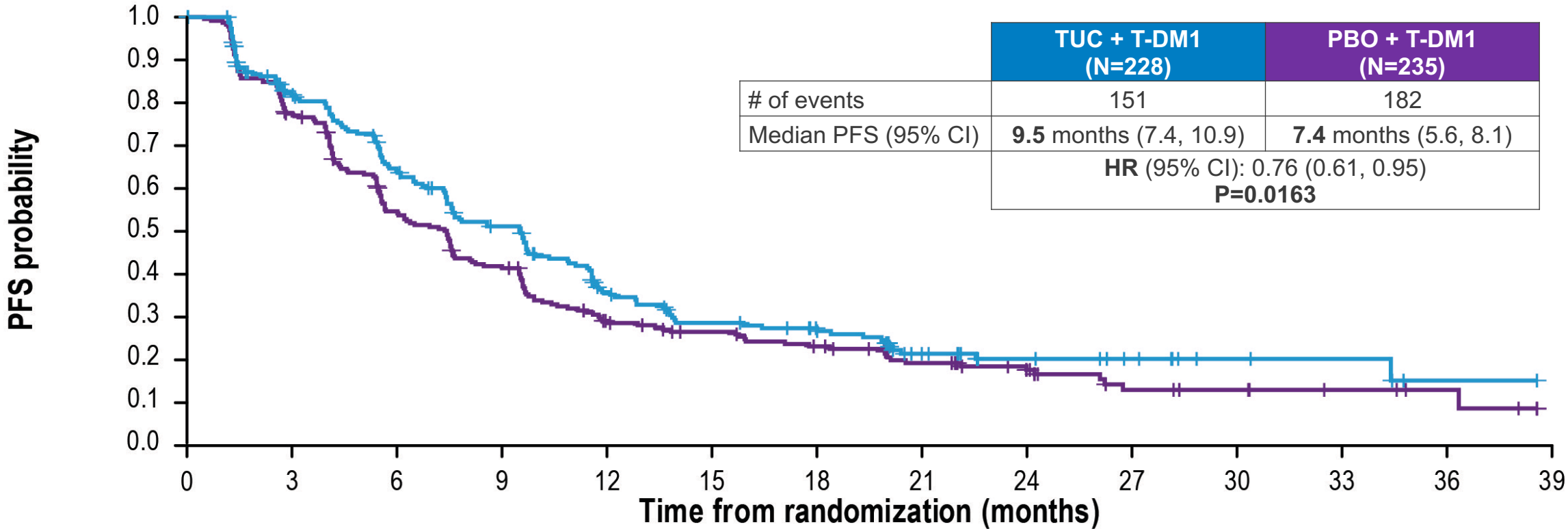
[b]Subsequent OS analyses are planned upon 80% and 100% of events.

ClinicalTrials.gov. NCT03975647. https://www.clinicaltrials.gov/study/NCT03975647

1L, first-line; BID, twice daily; cORR, confirmed objective response rate; ECOG PS, Eastern Cooperative Oncology Group performance status; 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.

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**	



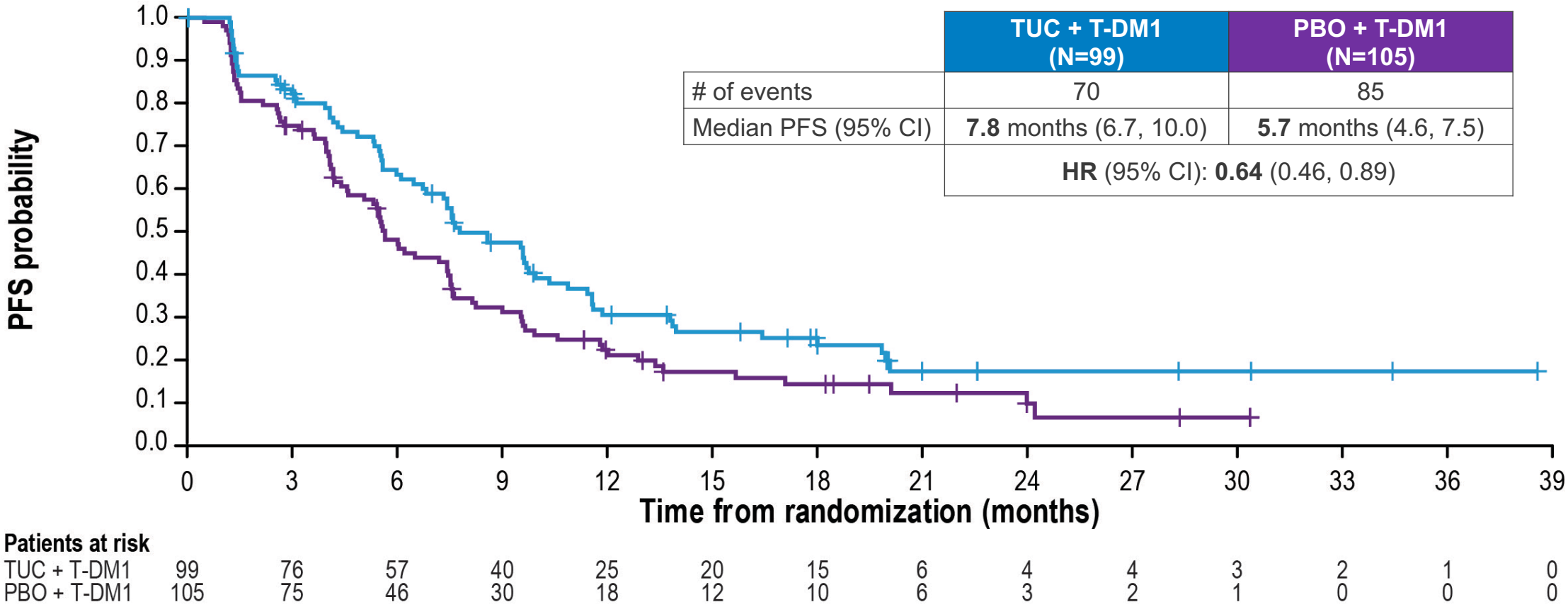
Patients at risk

TUC + T-DM1	228	165	126	96	62	47	40	22	14	10	5	4	1	0
PBO + T-DM1	235	177	120	91	58	48	40	29	19	10	8	5	3	0

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

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

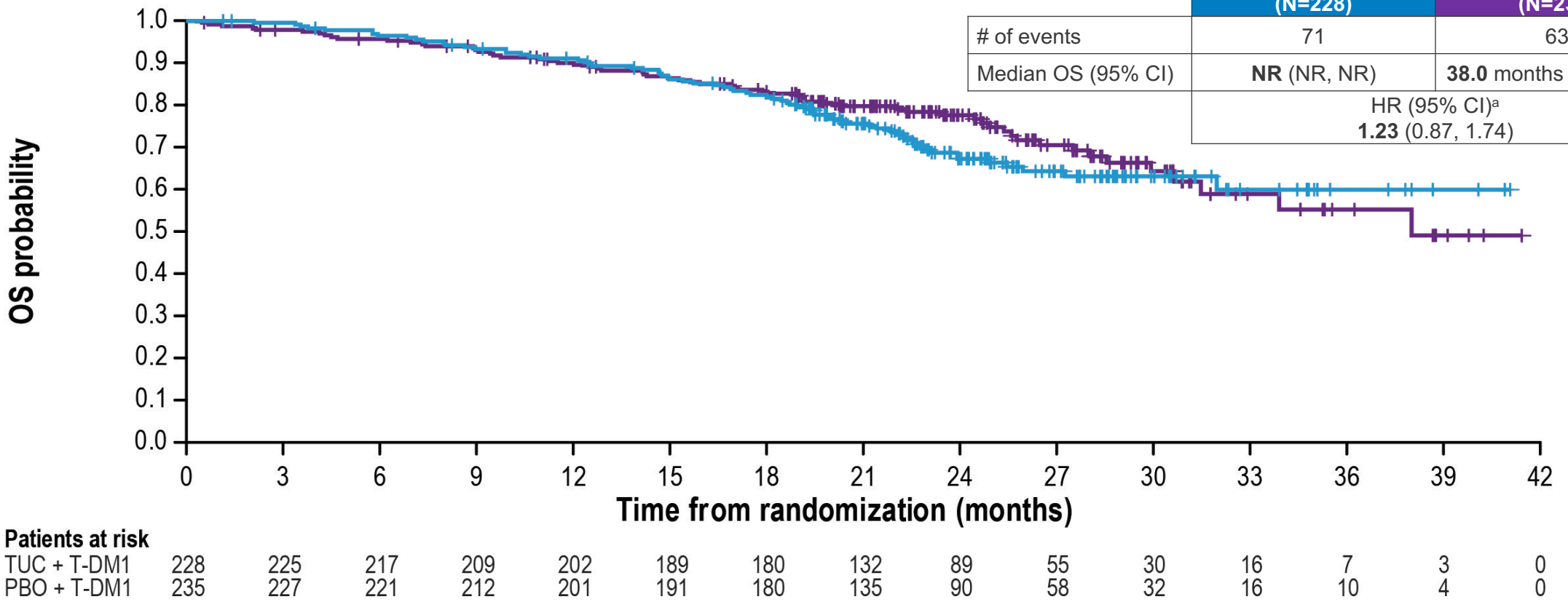
	TUC + T-DM1 (N=99)	PBO + T-DM1 (N=105)
# of events	70	85
Median PFS (95% CI)	**7.8** months (6.7, 10.0)	**5.7** months (4.6, 7.5)
	HR (95% CI): **0.64** (0.46, 0.89)	



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

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.

Date of data cutoff: June 29, 2023.

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

ClinicalTrials.gov. NCT03975647. https://www.clinicaltrials.gov/study/NCT03975647

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

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

AXIS Medical Education

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.

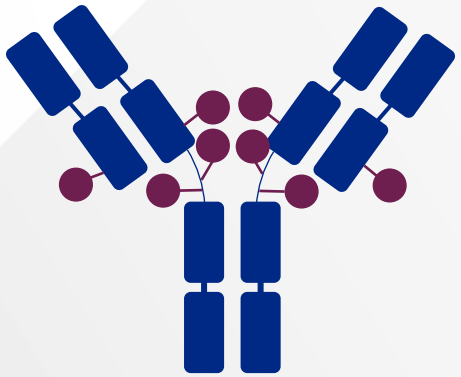
ClinicalTrials.gov. NCT03975647. https://www.clinicaltrials.gov/study/NCT03975647

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

Characteristic Differences Between T-DXd and T-DM1

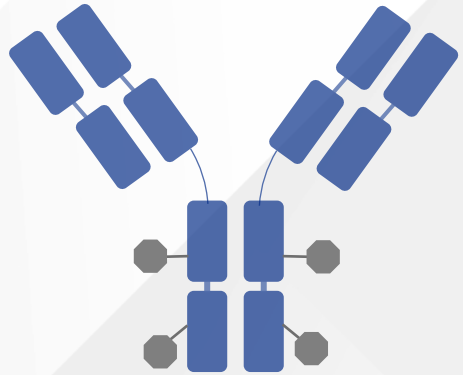
HER2 Targeting ADCs with similar mAB Backbone

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.

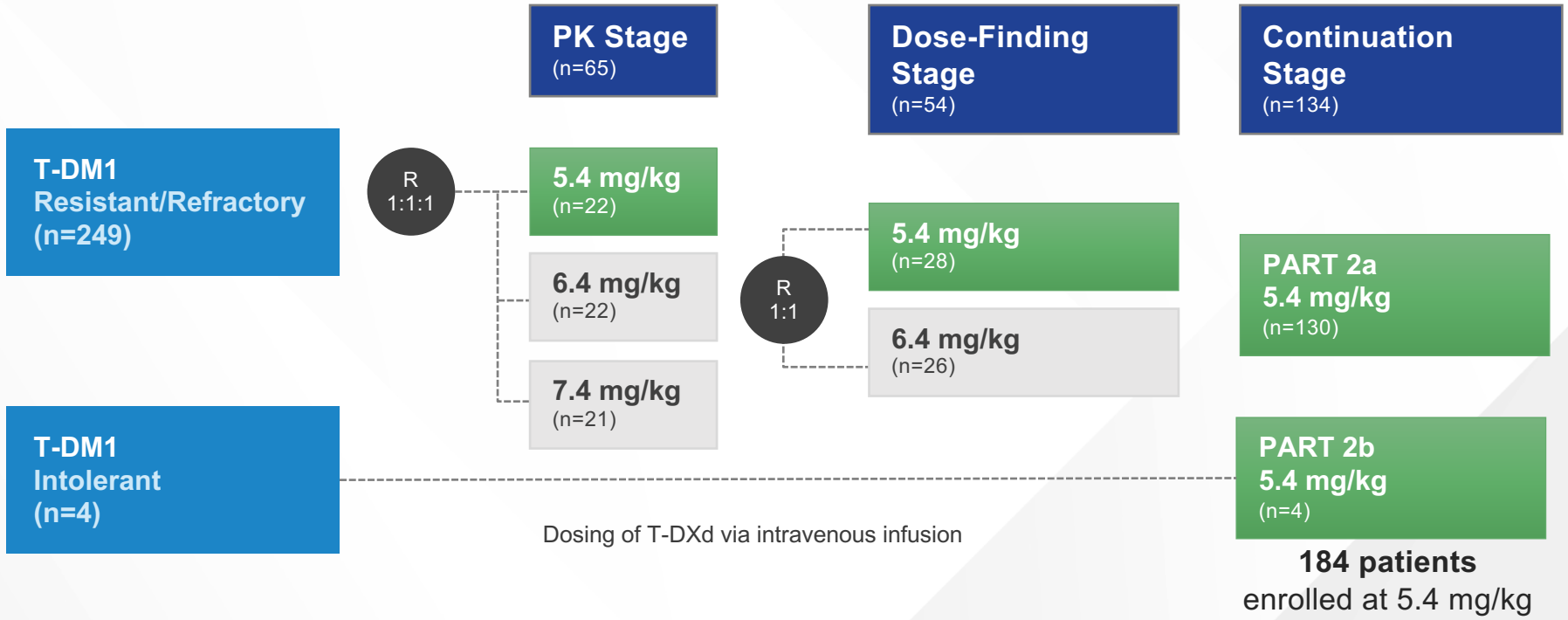
Cortés J, et al. ESMO 2021. Abstract LBA1.
1. Nakada T et al. Chem Pharm Bull (Tokyo). 2019;67(3):173-185. 2. Ogitani Y et al. Clin Cancer Res. 2016;22(20):5097-5108. 3. Trail PA et al. Pharmacol Ther. 2018;181:126-142. 4. Ogitani Y et al. Cancer Sci. 2016;107(7):1039-1046. 5. LoRusso PM et al. Clin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

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

DESTINY-Breast01: An Open-Label Multicenter Phase 2 Study of T-DXd1-3

Population

- ≥18 years of age
- Unresectable and/or metastatic BC
- HER2 positive (centrally confirmed in archival tissue)
- Prior T-DM1
- Excluded patients with history of significant ILD
- Pretreated and stable brain metastases were allowed



Endpoints

- **Primary:** confirmed ORR by independent central imaging facility review per RECIST v1.1
- **Secondary:** investigator-assessed ORR, DCR, DOR, CBR, PFS, OS, PK and safety

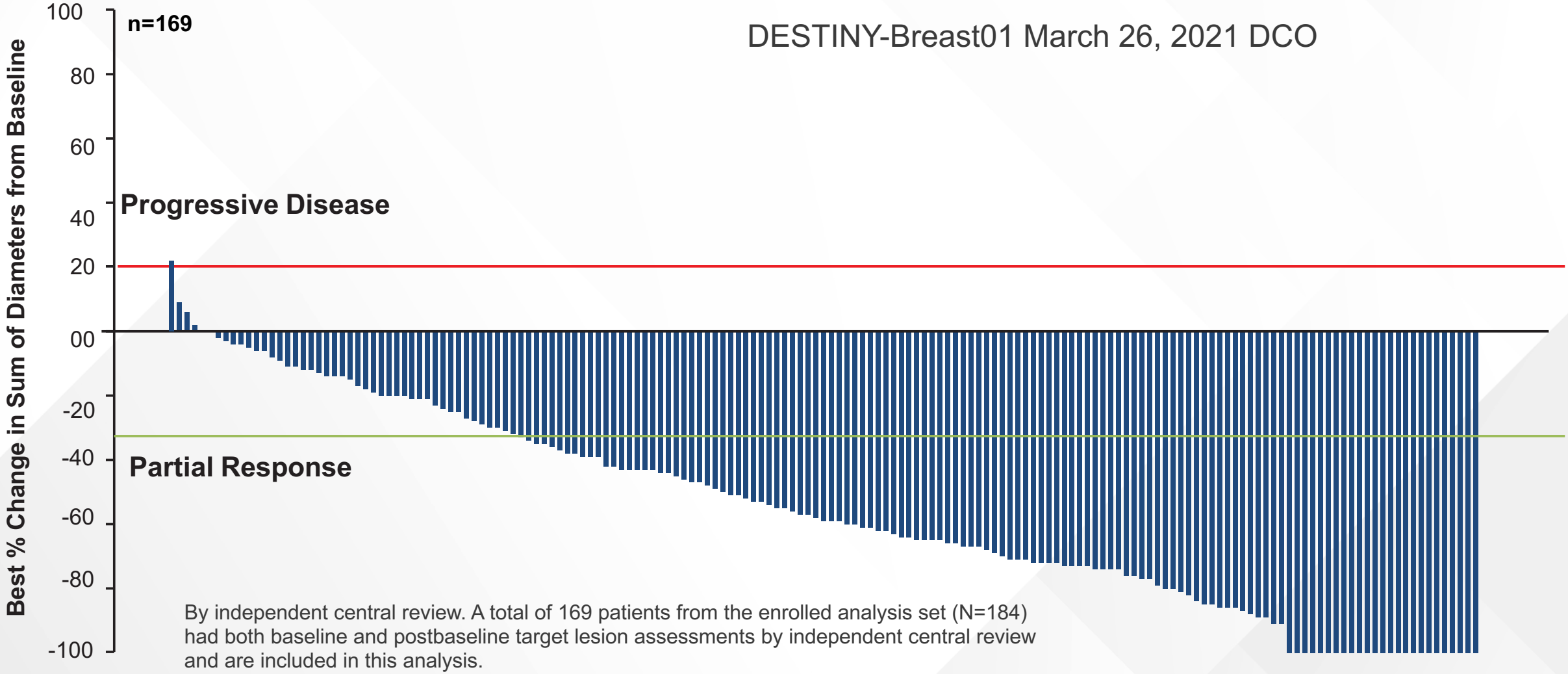
Median Duration of Follow-Up

- **August 1, 2019 data cutoff:** 11.1 months (range, 0.7-19.9 months)[1]
- **June 8, 2020 data cutoff:** 20.5 months (range, 0.7-31.4 months)[2]
- **March 26, 2021 data cutoff**: 26.5 months (range, 0.7-39.1 months)[3]

AXIS Medical Education

1. Modi S, et al. N Engl J Med. 2020; 382(7):610-621. 2. Modi S, et al. SABCS 2020. Poster PD3-06. 3. Saura C, et al. ESMO 2021. Poster 279P.
BC, breast cancer; CBR, clinical benefit rate; DCR, disease control rate; DoR, duration of response; HER, human epidermal growth factor receptor; ILD, interstitial lung disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors; T-DM1, ado-trastuzumab deruxtecan; T-DXd, fam-trastuzumab deruxtecan-nxki.

Best Percent Change From Baseline in Target Lesions



By independent central review. A total of 169 patients from the enrolled analysis set (N=184) had both baseline and postbaseline target lesion assessments by independent central review and are included in this analysis.

Saura C, et al. ESMO 2021. Poster 279P.
DCO, data cutoff.

DESTINY-Breast01: Progression-Free Survival and Overall Survival

Progression-Free Survival

- Median progression-free survival was 19.4 months (95% CI, 14.1-25.0 months) with a median follow-up of 26.5 months
- N=184
- Data from 108 patients (58.7%) were censored
- 76 PFS events reported 41.3%)

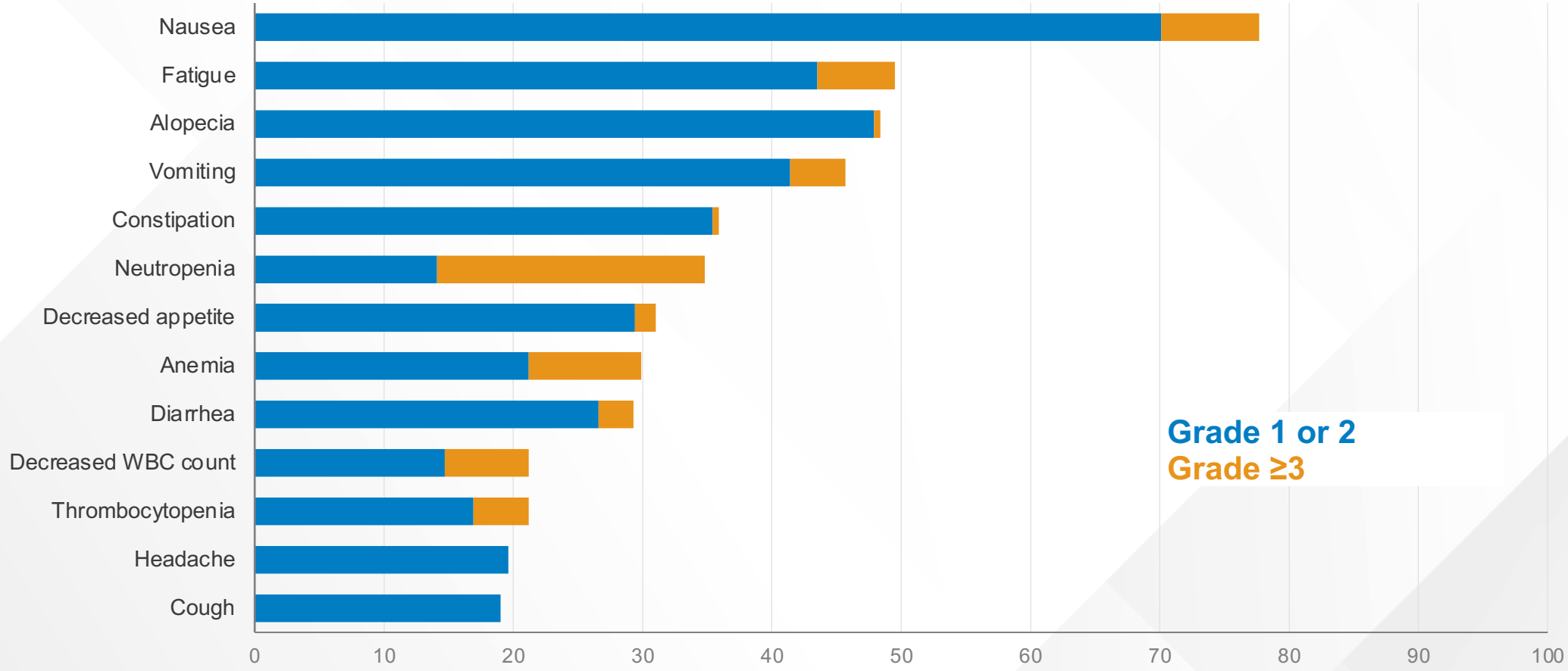
Overall Survival

- As of March 26, 2021, median duration of OS follow-up was 31.1 months (95% CI, 30.7-32.0)
- The updated median OS was 29.1 months (95% CI, 24.6-36.1), and with greater data maturity, more than half of the patients had OS events (95/184, 51.6%)

Estimated OS, % (95% CI)	
12-month	85 (79-90)
18-month	75 (67-80)
24-month	58 (51-65)

Saura C, et al. ESMO 2021. Poster 279P.
OS, overall survival; PFS, progression-free survival.

Treatment-Emergent Adverse Events in >15% of Patients*



Patients who received T-DXd 5.4 mg/kg.

*Reduction in LVEF observed in 2.2% of patients (4/184, Ref. 2), with 1 case grade ≥3.

1. Saura C, et al. ESMO 2021. Poster 279P. 2. Modi S, et al. SABCS 2020. Poster PD3-06.

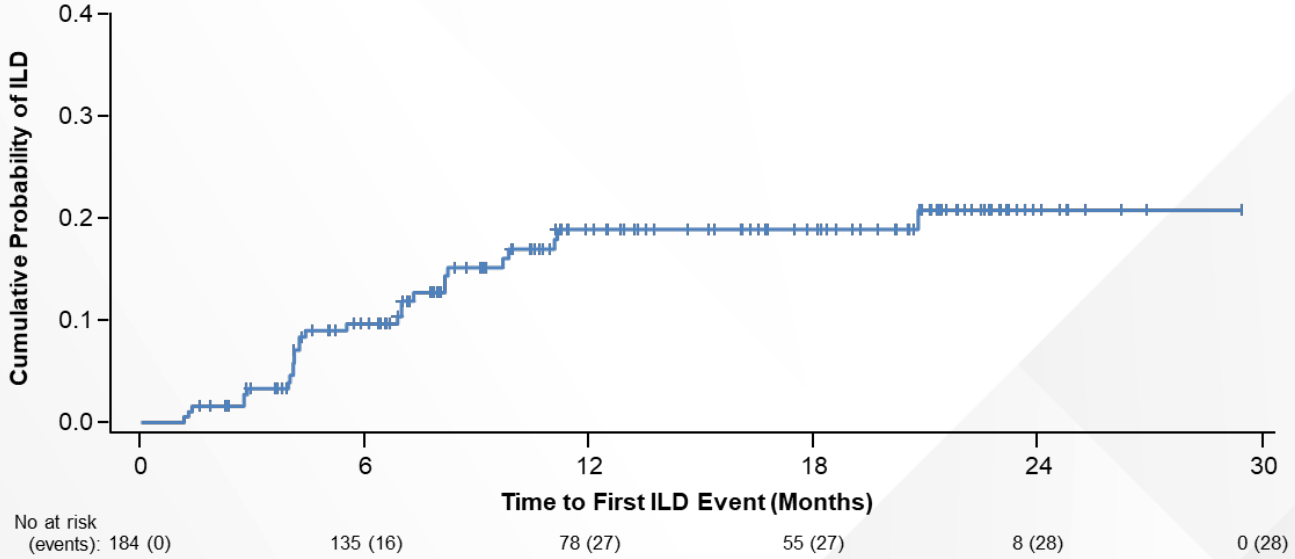
T-DXd, fam-trastuzumab deruxtecan-nxki.

DESTINY-Breast01 Results: Safety

Drug-related ILD/Pneumonitis[a] [Table 4]

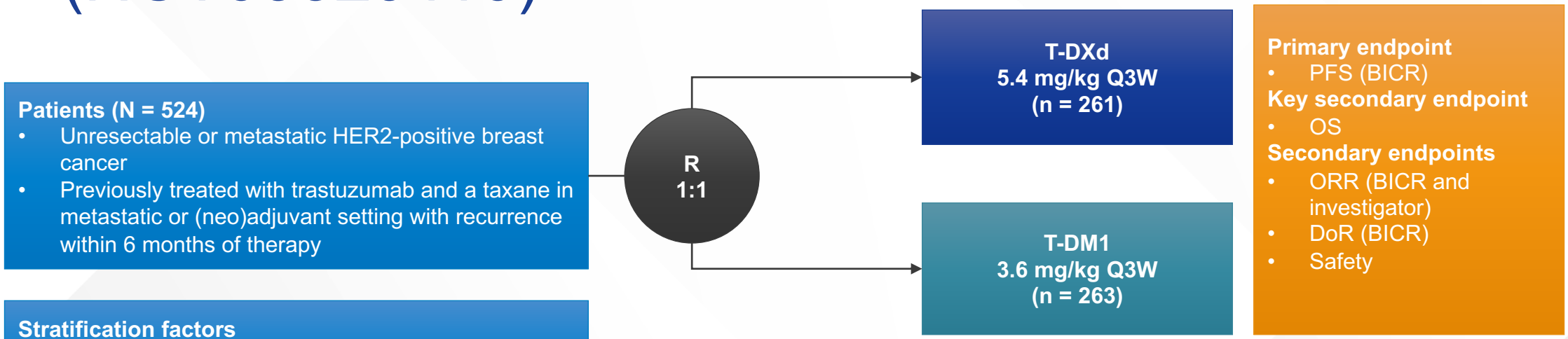
Interstitial lung disease, n (%)	T-DXd 5.4 mg/kg (N=184)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade/ Total
Aug 2019 data cutoff	5 (2.7)	15 (8.2)	1 (0.5)	0	4 (2.2)	**25 (13.6)**
June 2020 data cutoff	6 (3.3)	16 (8.7)	1 (0.5)	0	5 (2.7)	**28 (15.2)**

Cumulative Probability of Adjudicated Drug-related Any-grade ILD[b] [Figure 6]



[a]As determined by an independent interstitial lung disease adjudication committee. At data cutoff, 1 grade 1 event and 1 grade 3 event were pending adjudication.
[b]In patients with HER2-positive breast cancer (T-DXd 5.4 mg/kg).
ILD, interstitial lung disease; T-DXd, fam-trastuzumab deruxtecan-nxki.

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



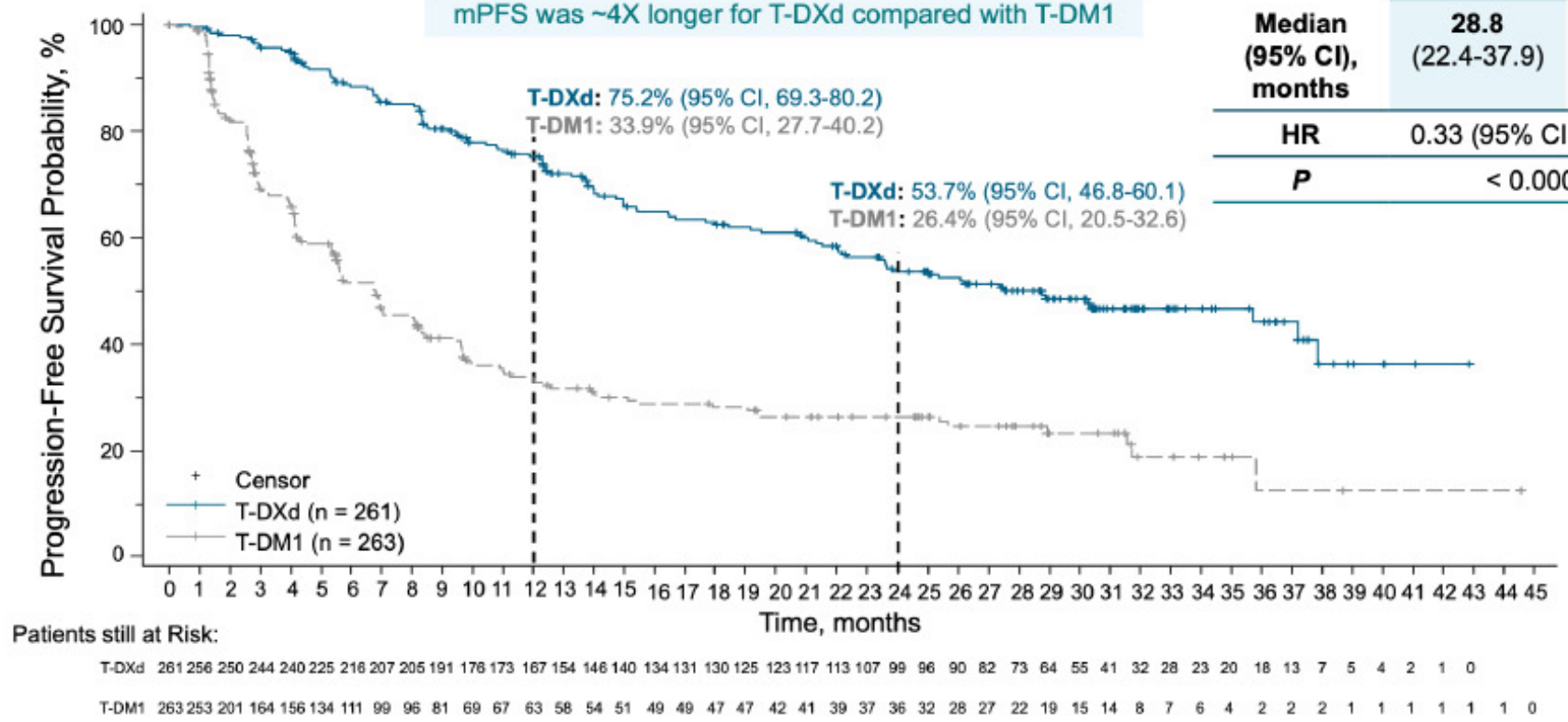
At data cutoff (June 30, 2022), the median duration of follow-up was:
- **21.5 months** (range, 0.1-45.6 months) in the T-DXd arm
- **18.6 months** (range, 0-45.7 months) in the TPC arm

Dosing of T-DXd, T-DM1 via intravenous infusion

The prespecified OS interim analysis was planned with 153 events. At the time of data cutoff (July 25, 2022), 169 OS events were observed and the *P* value to achieve statistical significance was 0.013

Hurvitz S, et al. SABCS 2022. Abstract GS2-02.
BICR, blinded independent central review; DoR, duration of response; HER, human epidermal growth factor receptor; OS, overall survival; PFS, progression-free survival; T-DM1, ado-trastuzumab emtansine; T-DXd, fam-trastuzumab deruxtecan-nxki.

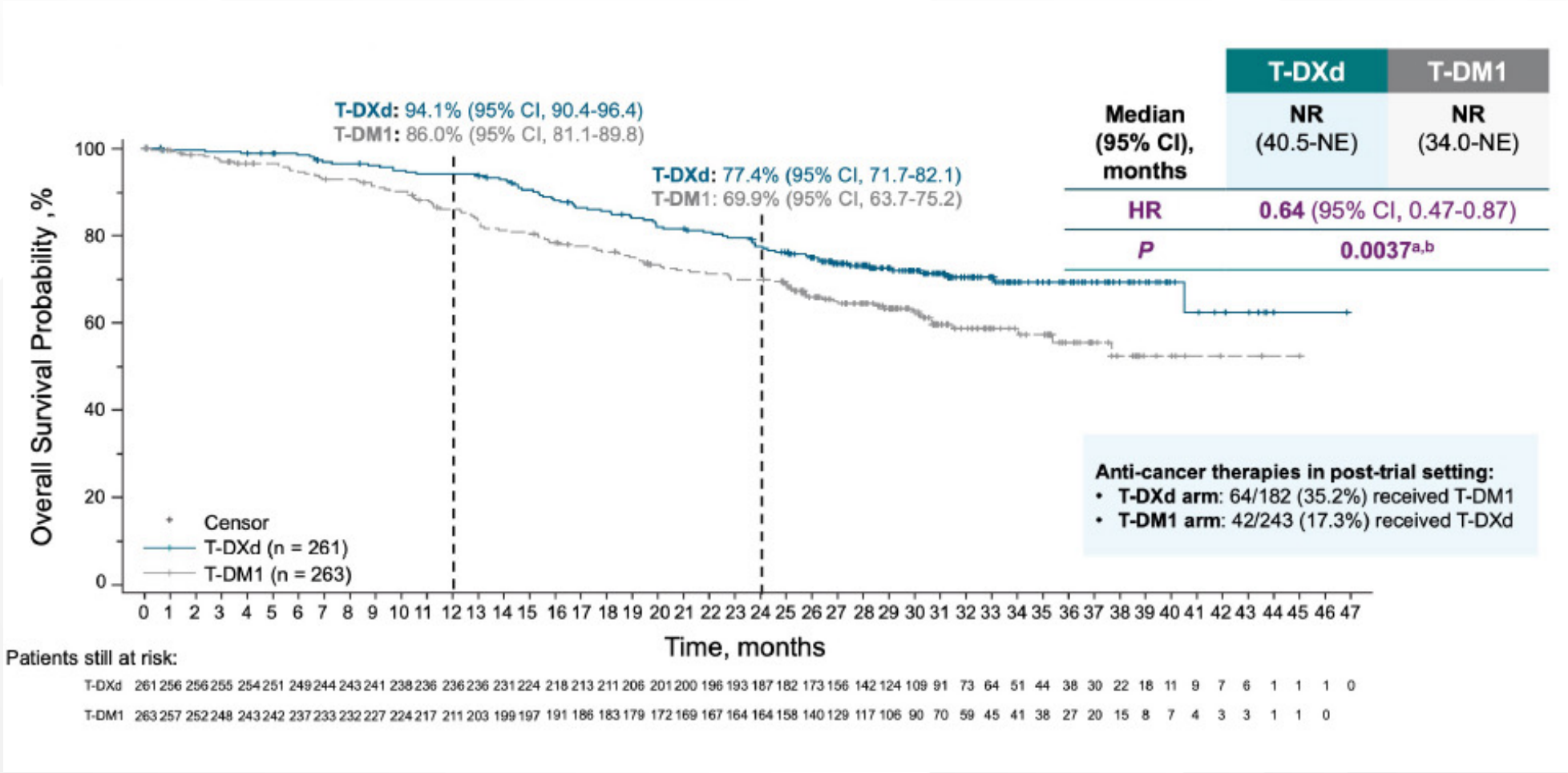
Updated Primary Endpoint: PFS by BICR



	T-DXd	T-DM1
Median (95% CI), months	**28.8** (22.4-37.9)	**6.8** (5.6-8.2)
HR	0.33 (95% CI, 0.26-0.43)	
P	< 0.000001[a,b]	

Hurvitz S, et al. SABCS 2022. Abstract GS2-02.
BICR, blinded independent central review; HR, hazard ratio; mPFS, median progression-free survival; T-DM1, ado-trastuzumab emtansine; T-DXd, fam-trastuzumab deruxtecan-nxki.

Key Secondary Endpoint: Overall Survival



	T-DXd	T-DM1
Median (95% CI), months	NR (40.5-NE)	NR (34.0-NE)
HR	0.64 (95% CI, 0.47-0.87)	
P	0.0037[a,b]	

Anti-cancer therapies in post-trial setting:
- **T-DXd arm**: 64/182 (35.2%) received T-DM1
- **T-DM1 arm**: 42/243 (17.3%) received T-DXd

Hurvitz S, et al. SABCS 2022. Abstract GS2-02.
HR, hazard ratio; NE, not estimable; NR, not reached; T-DM1, ado-trastuzumab emtansine; T-DXd, fam-trastuzumab deruxtecan-nxki.

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)	26 (10.1)	2 (0.8)	0	0	39 (15.2)
T-DM1 (n = 261)	4 (1.5)	3 (1.1)	1 (0.4)	0	0	8 (3.1)

- 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 15.2%
  - There were 4 additional grade 1, 8 additional grade 2, and no additional grade 3 events
- 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

Hurvitz S, et al. SABCS 2022. Abstract GS2-02.
ILD, interstitial lung disease; mBC, metastatic breast cancer; PFS, progression-free survival; T-DM1, ado-trastuzumab emtansine; T-DXd, fam-trastuzumab deruxtecan-nxki.

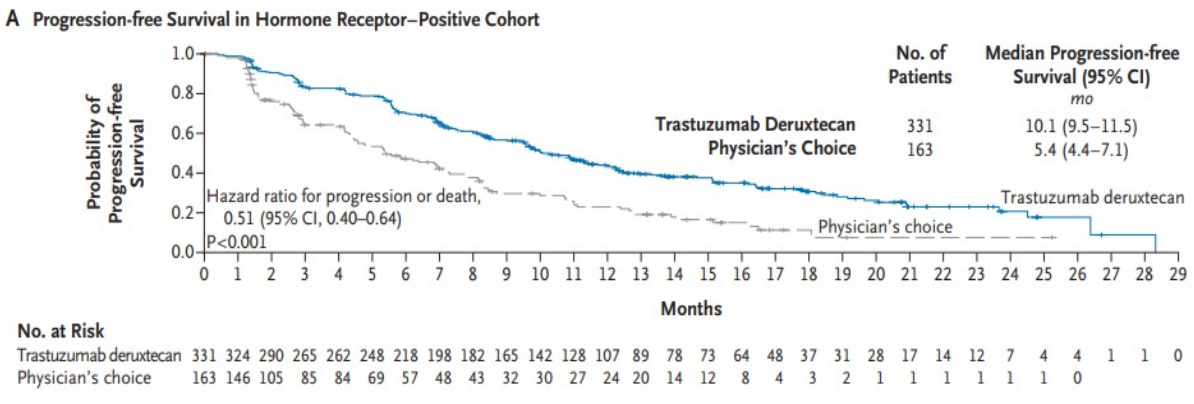
DESTINY-Breast04:T-DXd in Previously Treated HER2-Low MBC (NCT03734029)

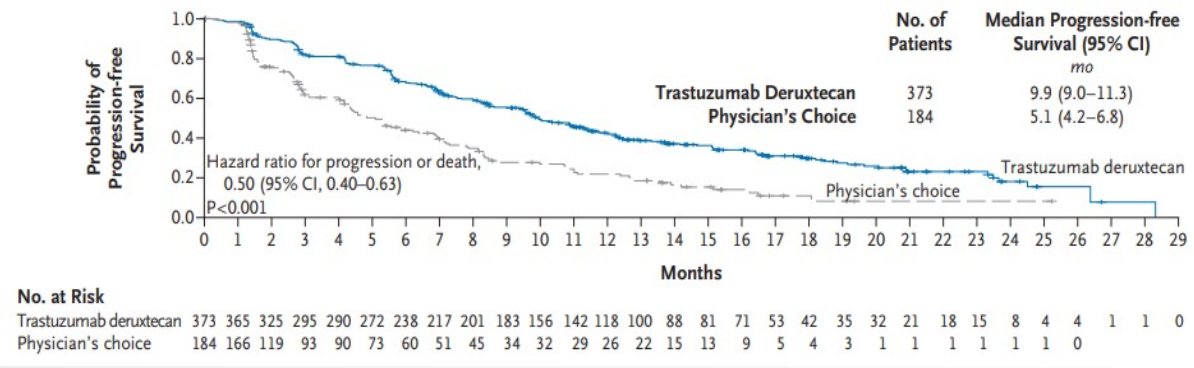
- Phase 3 study of patients with HER2-low MBC who had received 1 or 2 lines of chemotherapy
- HER2-low defined as IHC1+ or IHC2+/ISH-
- 557 patients randomized 2:1 to receive T-DXd or physician's choice of chemotherapy
  - Primary endpoint: PFS in HR+ cohort
  - Secondary endpoints: PFS in all patients, OS in HR+ cohort, OS in all patients

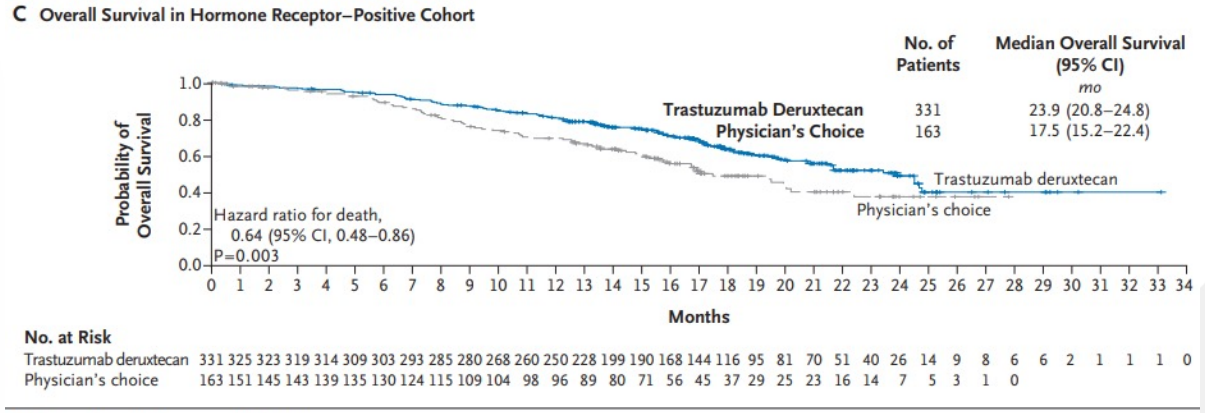
Modi S, et al. *N Engl J Med*. 2022;387(1):9-20.

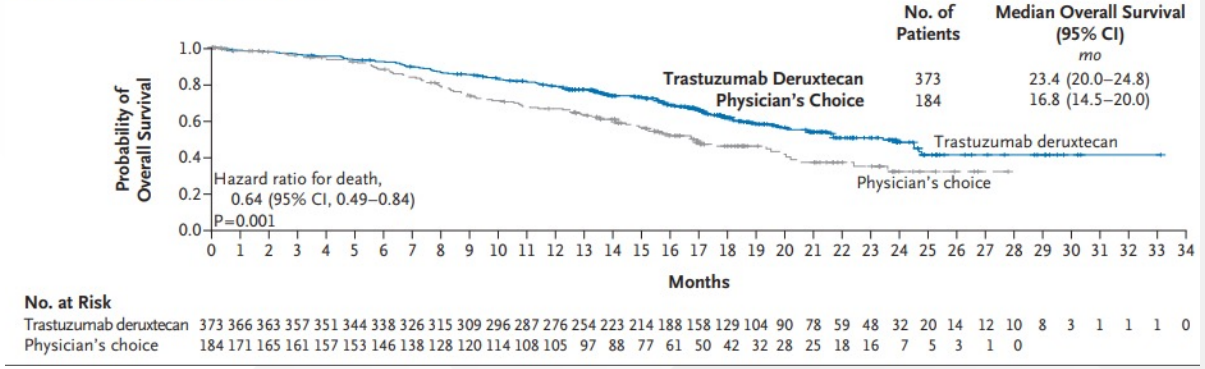
HER, human epidermal growth factor receptor; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; MBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; T-DXd, fam-trastuzumab deruxtecan-nxki.

DESTINY-Breast04: PFS and OS Outcomes







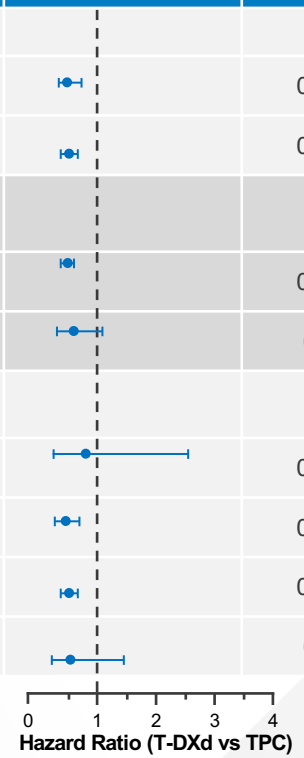


Modi S, et al. *N Engl J Med*. 2022;387(1):9-20.
HER, human epidermal growth factor receptor; OS, overall survival; PFS, progression-free survival.

For Patients Enrolled in DESTINY-Breast04, Efficacy of T-DXd Compared with TPC Was Consistent Regardless of Tumor Sample Characteristics

mPFS by tumor sample characteristic (DESTINY-Breast04)

N=557	Number of Events		mPFS Months (95% CI)		Hazard Ratio (95% CI)
Subgroup (N, %)	T-DXd	TPC	T-DXd	TPC	
Tumor location					
Primary (196, 35.2)	96/136	43/60	9.6 (7.1–11.3)	4.2 (1.6–6.4)	0.47 (0.32–0.70)
Metastases (359, 64.5))	145/235	84/124	10.9 (9.5–12.3)	5.4 (4.3–7.1)	0.50 (0.38–0.66)
Collection Type					
Archival tissue (482, 86.5)	203/324	109/158	10.3 (8.6–12.0)	5.3 (4.2–7.0)	0.48 (0.37–0.61)
Newly obtained tissue (75, 13.5)	40/49	18/26	9.7 (5.6–10.9)	4.8 (2.8–6.9)	0.57 (0.30–1.1)
Tumor specimen collection date					
2013 and earlier (29, 5.2)	11/19	9/10	7.0 (2.8–NE)	6.8 (1.4–11.1)	0.78 (0.24–2.54)
2014–2018 (175, 31.4)	76/126	33/49	11.4 (9.5–15.1)	4.3 (1.6–7.0)	0.44 (0.28–0.70)
2019 or later (310, 55.7)	137/203	75/107	9.8 (8.4–11.3)	5.1 (4.1–7.1)	0.49 (0.37–0.66)
Missing (n = 43)	19/25	10/18	6.6 (2.8–10.8)	2.8 (1.2–8.3)	0.54 (0.20–1.4)



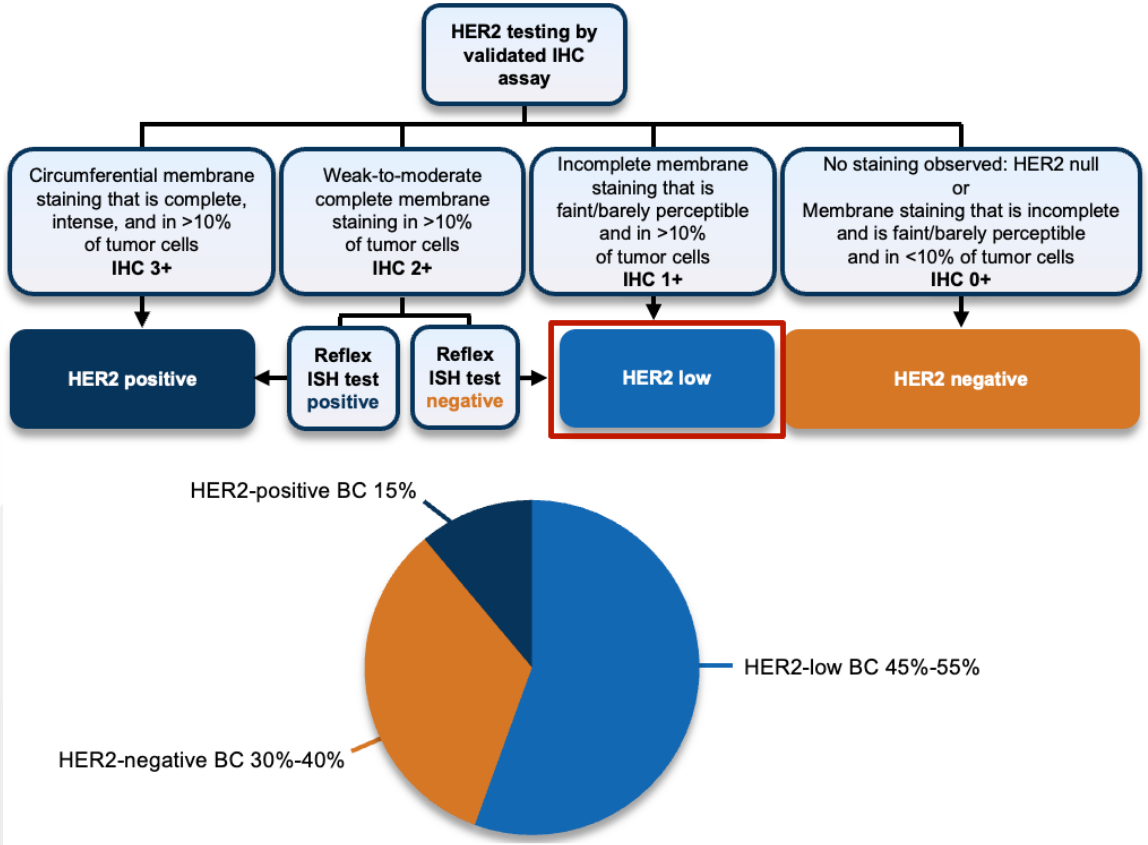
Benefit was observed in patients with a HER2-low classification, regardless of tumor location, collection type, and tumor specimen collection date

Prat A, et al. SABCS 2022. Abstract HER2-18.

CI, confidence interval; HER, human epidermal growth factor receptor; mPFS, median progression-free survival; NE, not estimable; T-DXd, fam-trastuzumab deruxtecan-nxki; TPC, treatment of physician's choice.

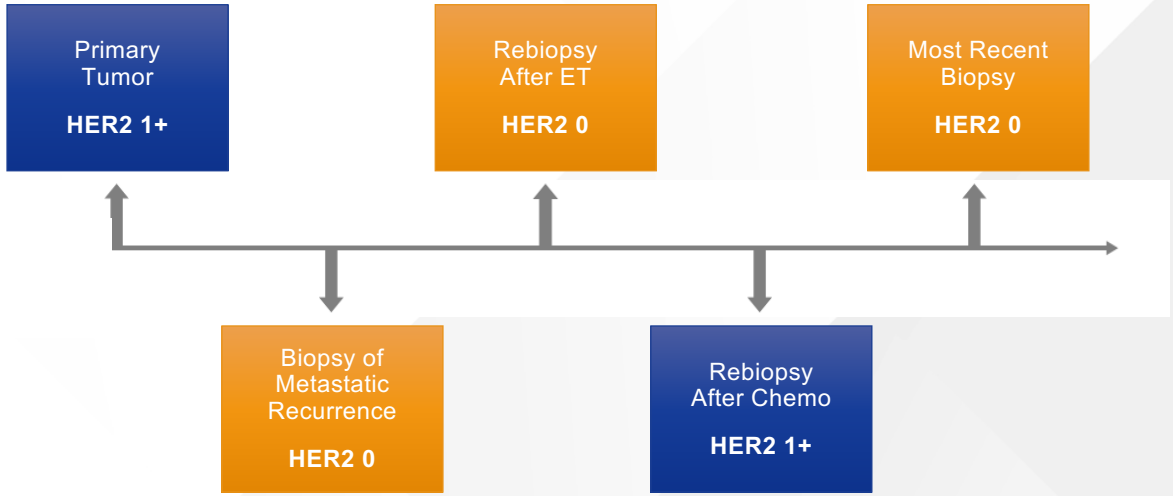
How to Define HER2-Low Breast Cancer?

Static Definition



Dynamic Definition (Real Life)

- HER2-low status changes over time
- Which timepoint to use to define a tumor as HER2 low?



Tarantino P, et al. *J Clin Oncol*. 2020;38(17):1951-1962.
BC, breast cancer; ET, endocrine therapy; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; ISH, in situ hybridization.

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.

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

In the Future, the HER2 Spectrum May Evolve Further, With The Identification of IHC >0<1[1-4]

- With these emerging classifications of HER2 expression at the low end of the spectrum, strategies for identification of patients will require further optimization.

Historical binary HER2 scoring paradigm[1]	HER2-negative			HER2-positive	
	IHC 0	IHC 1+	IHC 2+/ISH-	IHC 2+/ISH+	IHC 3+

Modified HER2 scoring scale[2,3]	HER2-null	HER2-low		HER2-positive	
	IHC 0	IHC 1+	IHC 2+/ISH-	IHC 2+/ISH+	IHC3+

1. Wolff AC, et al. J Clin Oncol. 2018;36(20):2105-2122. 2. Modi S, et al. *N Engl J Med*. 2022;387(1):9-20. 3. Franchet C, et al. *Ann Pathol*. 2021;41(6):507-520. 4. ClinicalTrials.gov. NCT04494425. https://clinicaltrials.gov/ct2/show/NCT04494425

HER, human epidermal growth factor receptor; IHC, immunohistochemistry; ISH, in situ hybridization.

Next Challenge: How LOW can we go?

DAISY

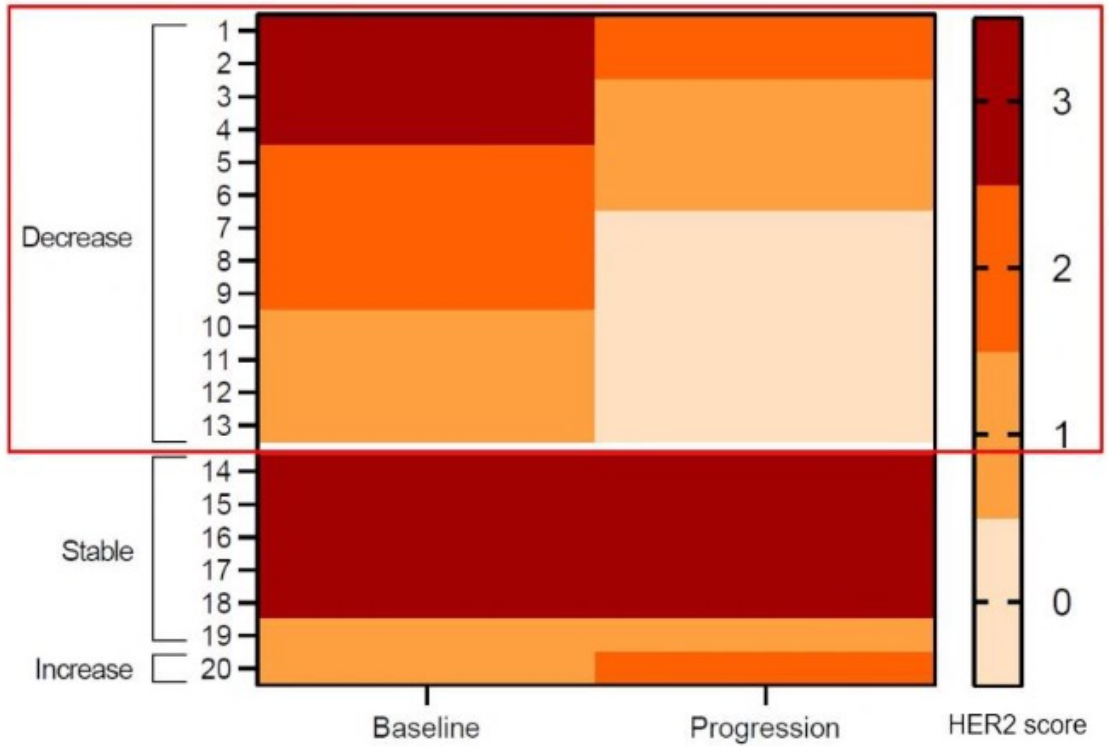
	Total	Cohort 1 (HER2 over-expressing)	Cohort 2 (HER2 Low-expressing)	Cohort 3 (HER2 non-detected)
BOR confirmed n/N [95%CI]	86/177 (48.6%) [41.0; 56.2]	48/68 (70.6%) [58.3; 81.0]	27/72 (37.5%) [26.4; 49.7]	11/37 (29.7%) [15.9; 47.0]
Median DOR (months) [95%CI]	8.5 [6.5; 9.8]	9.7 [6.8; 13]	7.6 [4.2; 9.2]	6.8 [2.8; Not reached]
Median PFS (months) [95%CI]	7.0 [6.0; 8.7]	11.1 [8.5; 14.4]	6.7 [4.4; 8.3]	4.2 [2.0; 5.7]

IHC 3+ IHC 1+ or 2+ IHC 0

Decreasing ORR by degree of HER2 expression

Dieras V, et al. SABCS 2021. Abstract PD8-02.
BOR, best objective response; DOR, duration of response; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; ORR, objective response rate; PFS, progression-free survival.

Exploratory Endpoint: In DAISY, 65% (13/20) Patients Presented a Decrease of HER2 Expression at Progression



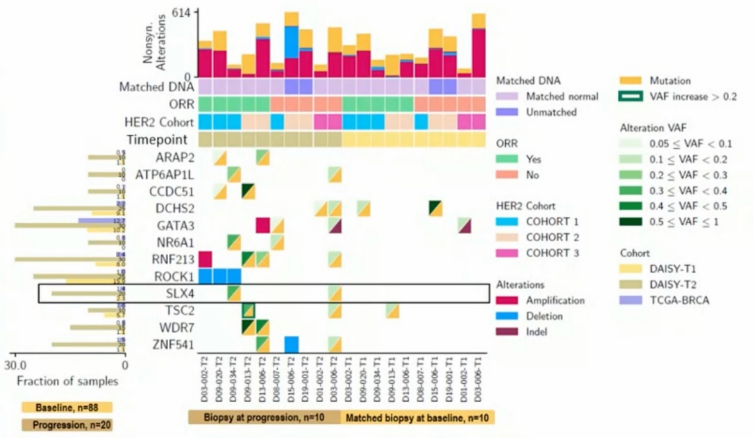
13/20 (65%)
95% CI [40.8-84.6]

- 25 FFPE samples at baseline and progression:
- 9 HER2 IHC 3+ or IHC 2+/ISH+
- 11 HER2 IHC 2+/ISH– or IHC 1+
- 5 IHC 0
  - HER2 status by standard IHC

5 patients HER2 IHC 0: 4 stable and 1 to IHC.
Mosele F, et al. ESMO 2022. Abstract LBA1.
CI, confidence interval; FFPE, formalin-fixed paraffin-embedded; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; ISH, in situ hybridization.

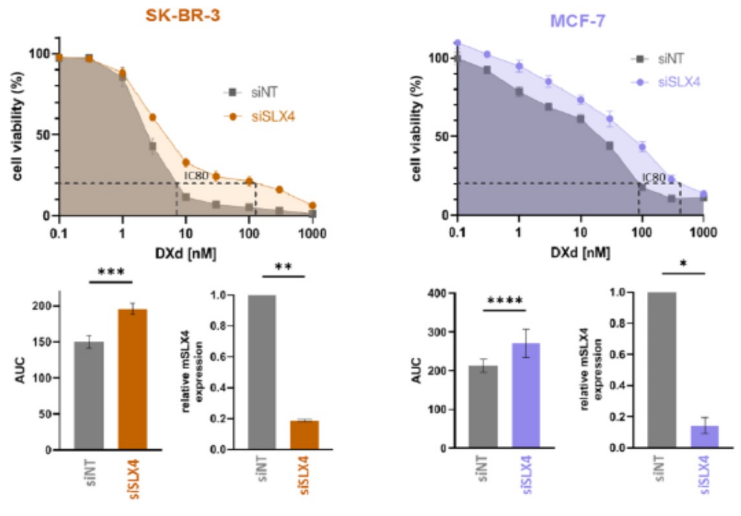
Exploratory Endpoint: SLX4 Mutations Could Induce DXd Resistance However, Further Research Is Required to Confirm This Finding

20 tumor biopsies at progression with 10 baseline matched samples



- The SLX4 gene encodes for a DNA repair protein that regulates endonuclease
- SLX4's role in camptothecin resistance is unclear
- Two of the mutations were acquired (ie, not detectable in baseline samples)
- Matched baseline biopsies were not available for the remaining two patients

SK-BR3 and MCF-7 BC cell lines treated with DXd for 5 days



	SK-BR-3	MCF-7
$IC80_{siNT}$	8.18nM	95.10nM
$IC80_{siSLX4}$	167.27nM	502.40nM

- SLX4 depleted SK-BR3 and MCF-7 BC cell lines required a higher quantity of DXd for cell death
- SLX4 mutations could mediate DXd resistance

BC, breast cancer; BRCA, breast cancer gene; DNA, deoxyribonucleic acid; DXd, deruxtecan; HER, human epidermal growth factor receptor; ORR, objective response rate.

Mosele MF, et al. ESMO 2022. Abstract LBA72.

Sacituzumab Govitecan

- Phase III TROPiCS-02 study[1]
  - 543 patients with HR positive, locally recurrent inoperable or metastatic breast cancer
  - Heavily pretreated cohort (median 3 previous lines of chemotherapy)
  - Patients randomized to sacituzumab govitecan (TROP-2 directed ADC) or chemotherapy of physician's choice
    - > Median PFS: 5.5 months with SG vs. 4.0 months with chemotherapy (HR 0.66, 95% CI 0.53-0.83, *P* = 0.0003)
    - > Median OS: 14.4 months with SG vs. 11.2 months with chemotherapy (HR 0.79, 95% CI 0.65-0.96, *P* = 0.02)[2]
    - > Objective response rates: 21% with SG, 14% with chemotherapy

AXIS Medical Education

HR, hormone receptor; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan.

1. Rugo HS, et al. *J Clin Oncol.* 2022;40(29):3365-3376. 2. Rugo HS, et al. ESMO Congress 2022. Abstract LBA76.

TROPiCS-02 Exploratory Analysis

- Exploratory analysis of OS from TROPiCS-02 (longer median follow-up of 12 .75 months)
  - Median overall survival: 14.5 months with SG vs. 11.2 months with TPC
  - OS rates:
    - 12 months: 60.9% vs. 47.1%
    - 18 months: 39.2% vs. 31. 7%
    - 24 months: 25.6% vs. 21.1%
  - Median OS in HER-low cohort: 15.4 vs. 11.5 months, HR 0.74 (95% CI 0.57-0.97)

HER, human epidermal growth factor receptor; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Tolaney SM, et al. *J Clin Oncol.* 2023;41(Suppl 16):1003.

ASCENT

- Phase III study of patients with relapsed/refractory metastatic TNBC
- Randomized patients to receive SG or physician's choice of chemotherapy (eribulin, vinorelbine, capecitabine, or gemcitabine)
  - Median PFS 4.8 months with SG vs. 1.7 months with chemotherapy (HR 0.43; 95% CI 0.35-0.54)
  - Median OS was 11.8 months with SG vs. 6.9 months with chemo (HR 0.51; 95% CI 0.41-0.62)
  - Objective response rates: 31% with SG, 4% with chemotherapy

HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer.
Bardia A, et al. *N Engl J Med.* 2021;384(16):1529-1541.

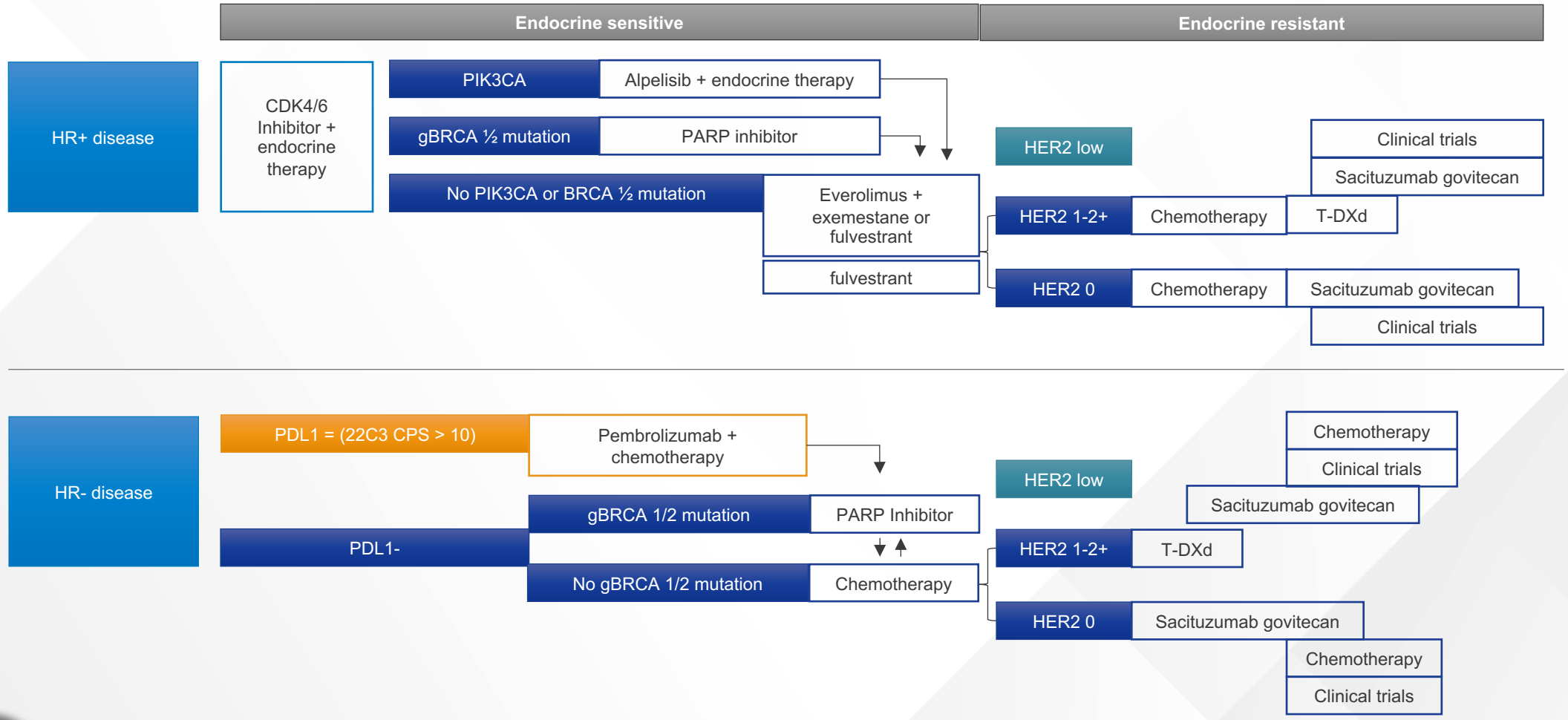
Post-Hoc Analysis of ASCENT

- Among 123 patients with HER2-low disease in ASCENT:
  - Objective response rate was 32% with SG vs. 8% with chemotherapy
  - Median OS was 14.0 months with SG vs. 8.7 months with chemotherapy (HR 0.43; 95% CI 0.28-0.67 [*P* < 0.001])
  - Median PFS was 6.2 months with SG vs. 2.9 months with chemotherapy (HR 0.44; 95% CI 0.27-0.72 [*P* = 0.002])

HER, human epidermal growth factor receptor; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan.

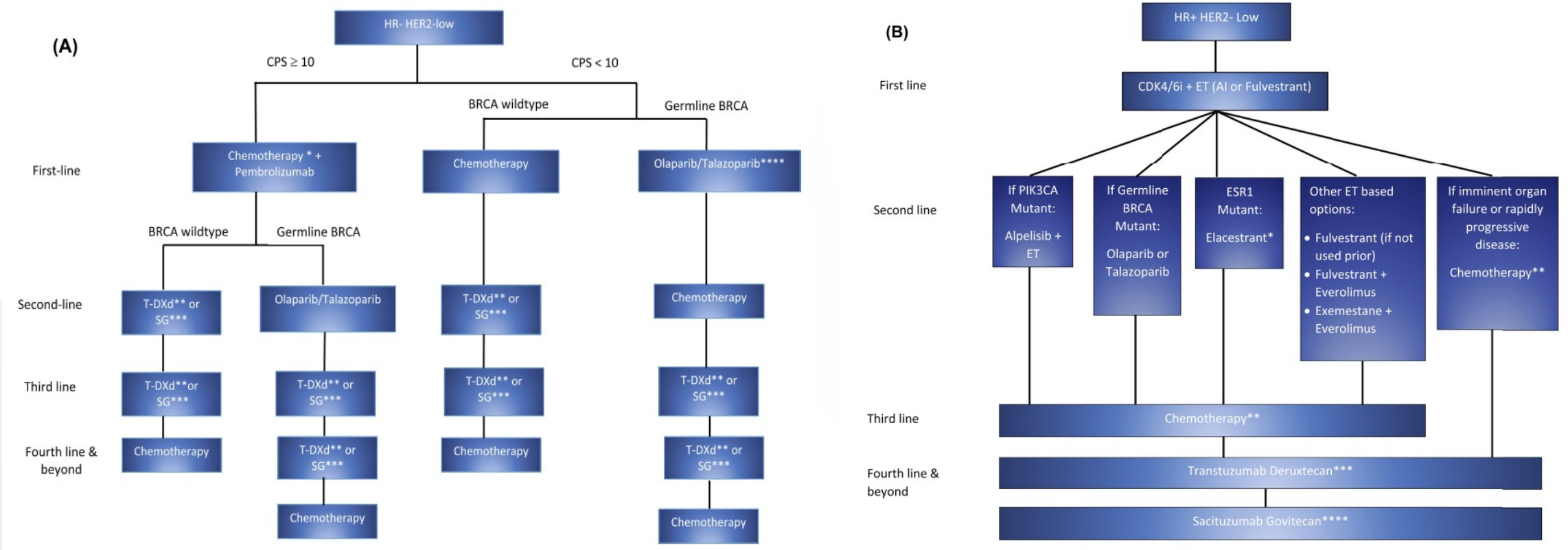
Hurvitz SA, et al. *Ann Oncol.* 2022;33:S194-S223.

Proposed Sequencing Approaches to HER2-Low BC



Schlam I, et al. *Breast.* 2023;67:116-123.
BC, breast cancer; HER, human epidermal growth factor receptor; HR, hormone receptor; T-DXd, fam-trastuzumab deruxtecan-nxki.

Proposed Sequencing Approaches to HER2-Low BC (Cont.)



Roy AM, et al. *Cancer*. 2023;129(18):2773-2788.
BC, breast cancer; CPS, combined positive score; ET, endocrine therapy; HER, human epidermal growth factor receptor; SG, sacituzumab govitecan; T-DXd, fam-trastuzumab deruxtecan-nxki.

Other Select ADCs in Development for HER2+ Breast Cancer

ADC	Target	Antibody	Payload	DAR	Clinical Program
MRG002[1]	HER2	Anti-HER2 IgG1	MMAE	3.8	Phase 3
RC48 (disitamab)[2,3]	HER2	Hertuzumab	MMAE	4	Phase 3
FS-1502[4]	HER2	Trastuzumab	MMAF	Not available	Phase 3
ARX788[5]	HER2	Modified heavy chain Ala114 of anti-HER2 mAb	Dolastatin MMAF	1.9	Phase 2

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04924699. 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04400695. 3. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT05904964. 4. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT05755048. 5. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04829604.

ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio; HER, human epidermal growth factor receptor; IgG1, immunoglobulin G1; mAb, monoclonal antibody; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F.

Anticipating Potential Treatment-Related Adverse Events and Treatment Resistance

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
- 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

1. ENHERTU [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc.; 2022. 2. Meyer KC. *Transl Respir Med.* 2014;2:4.

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

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

prn, pro re nata (as needed); T-DXd, fam-trastuzumab deruxtecan-nxki.

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

1. ENHERTU [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc.; 2022.
LV, left ventricular ejection fraction; T-DXd, fam-trastuzumab deruxtecan-nxki.

Adverse Events Associated With SG in TROPiCS-02

Treatment-Related AE	All Grade (n=268)	Grade 2 (n=268)	Grade ≥3 (n=268)
Neutropenia	188 (70)	45 (17)	136 (51)
Anemia	91 (34)	44 (16)	17 (6)
Leukopenia	37 (14)	7 (3)	23 (9)
Lymphopenia	31 (12)	11 (4)	10 (4)
Febrile neutropenia	14 (5)	0	14 (5)
Diarrhea	152 (57)	56 (21)	25 (9)
Nausea	148 (55)	56(21)	3 (1)
Vomiting	50 (19)	12 (4)	1 (<1)
Constipation	49 (18)	8 (3)	0
Abdominal pain	34 (13)	12 (4)	2 (1)
Alopecia	123 (46)	105 (39)	0
Fatigue	100 (37)	37 (14)	15 (6)
Asthenia	53 (20)	26 (10)	5 (2)
Decreased appetite	41 (15)	9 (3)	1 (<1)
Neuropathy	23 (9)	8 (3)	3 (1)

Rugo HS, et al. *J Clin Oncol.* 2022;40(29):3365-3376.
AE, adverse event; SG, sacituzumab govitecan.

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

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.
AE, adverse event; SG, sacituzumab govitecan.

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

TRODELVY (Sacituzumab govitecan). Prescribing Information. Foster City, CA: Gilead Sciences; 2023.
ANC, absolute neutrophil count; G-CSF, granulocyte colony stimulating factor; SG, sacituzumab govitecan.

Potential Mechanisms of Resistance to ADC in Breast Cancer

- Many tumors develop resistance to ADC therapies
- Potential mechanisms
  - Reduced antigen expression
  - Lower ADC trafficking and processing
  - Resistance to the cytotoxic component of the ADC
  - Increased efflux of ADC payload from cell

Occhiogrosso Abelman R, et al. *Cancers (Basel)*. 2023;15(4):1278.
ADC, antibody-drug conjugate.

Case Study

Case: Patient Presentation and Medical 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 2 yrs
- Then develops new liver metastases
- Has an *ESR1*m and *PI3K* wild-type
- Receives fulvestrant + everolimus, and progresses after 4 months
- Receive capecitabine for 6 months

Medical History

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

Social History

- Works as a piano teacher

Family History

- No family history

AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER, estrogen receptor; ESR1m, estrogen receptor 1 gene mutation; HER, human epidermal growth factor receptor; IDC, invasive ductal carcinoma; PI3K, phosphoinositide 3-kinase.

Case: 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.

Question Management

What would be the next step in management?

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

Case: 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

Question Management

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

Question

For this patient with HR+, HER2 low (1+) breast cancer, which pharmacologic option might be appropriate?

a) Pembrolizumab
b) Olaparib
c) Everolimus + exemestane
d) Sacituzumab govitecan
e) Unsure

HER, human epidermal growth factor receptor; HR, hormone receptor.

AXIS Medical Education

Tailoring ADC Therapies Across the HER2 Spectrum in Metastatic Breast Cancer