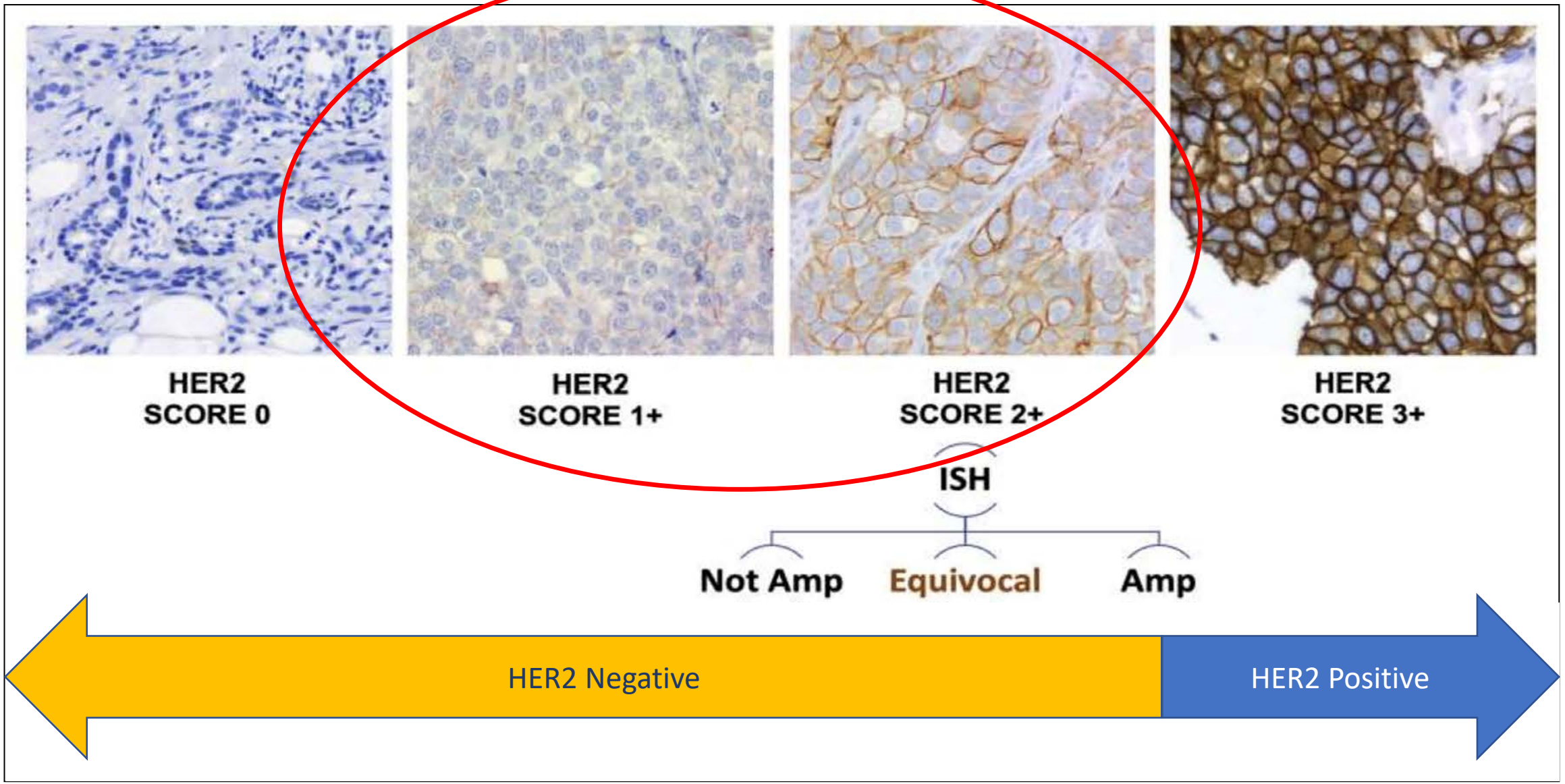
From HER2-Positive to HER2-Low Breast Cancer

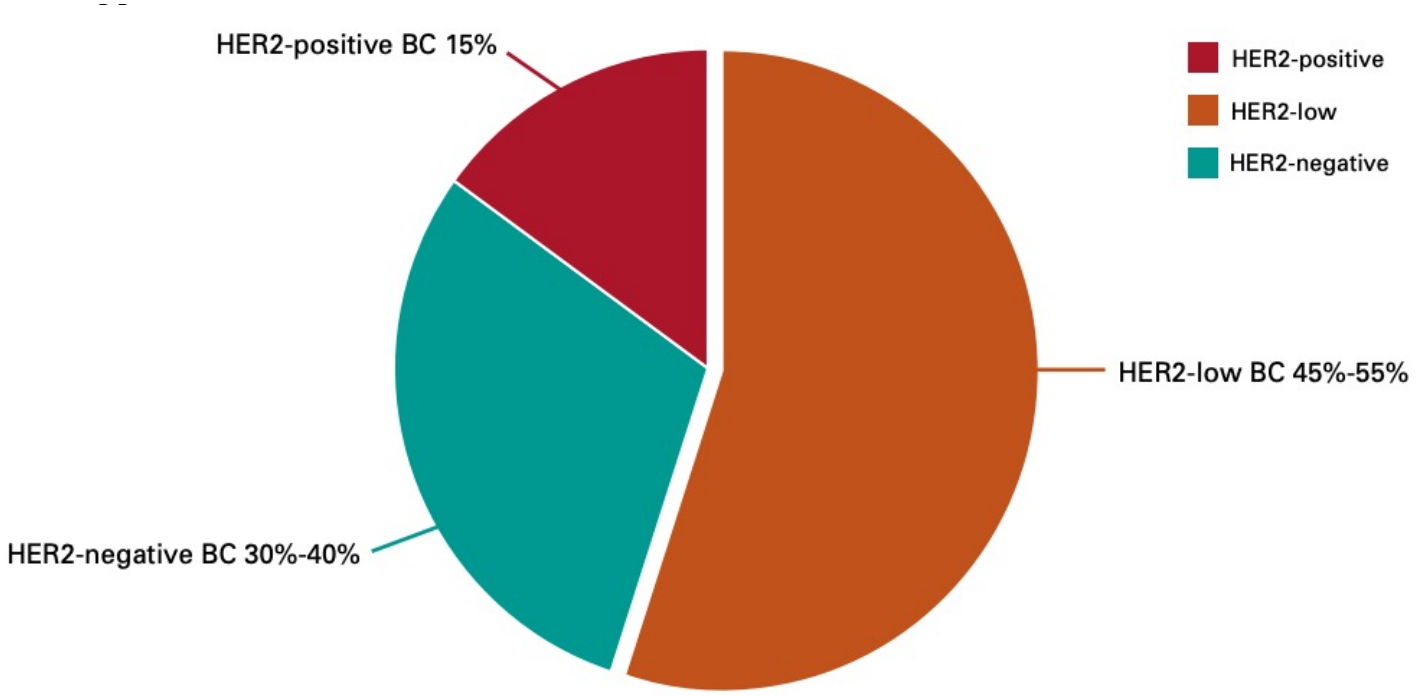
Shanu Modi, MD
Attending, Breast Medicine Service
Memorial Sloan Kettering Cancer Center
New York, New York

Current Binary Classification of HER2 in Breast Cancer



Modified from Marcio C, et al – Seminars in Cancer Biology 2021

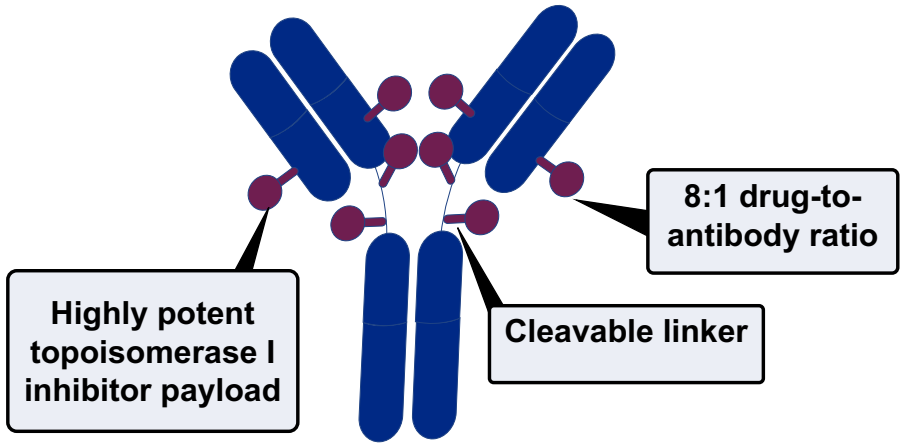
HER2-low Breast Cancer (IHC 1+ or 2+/ISH negative)



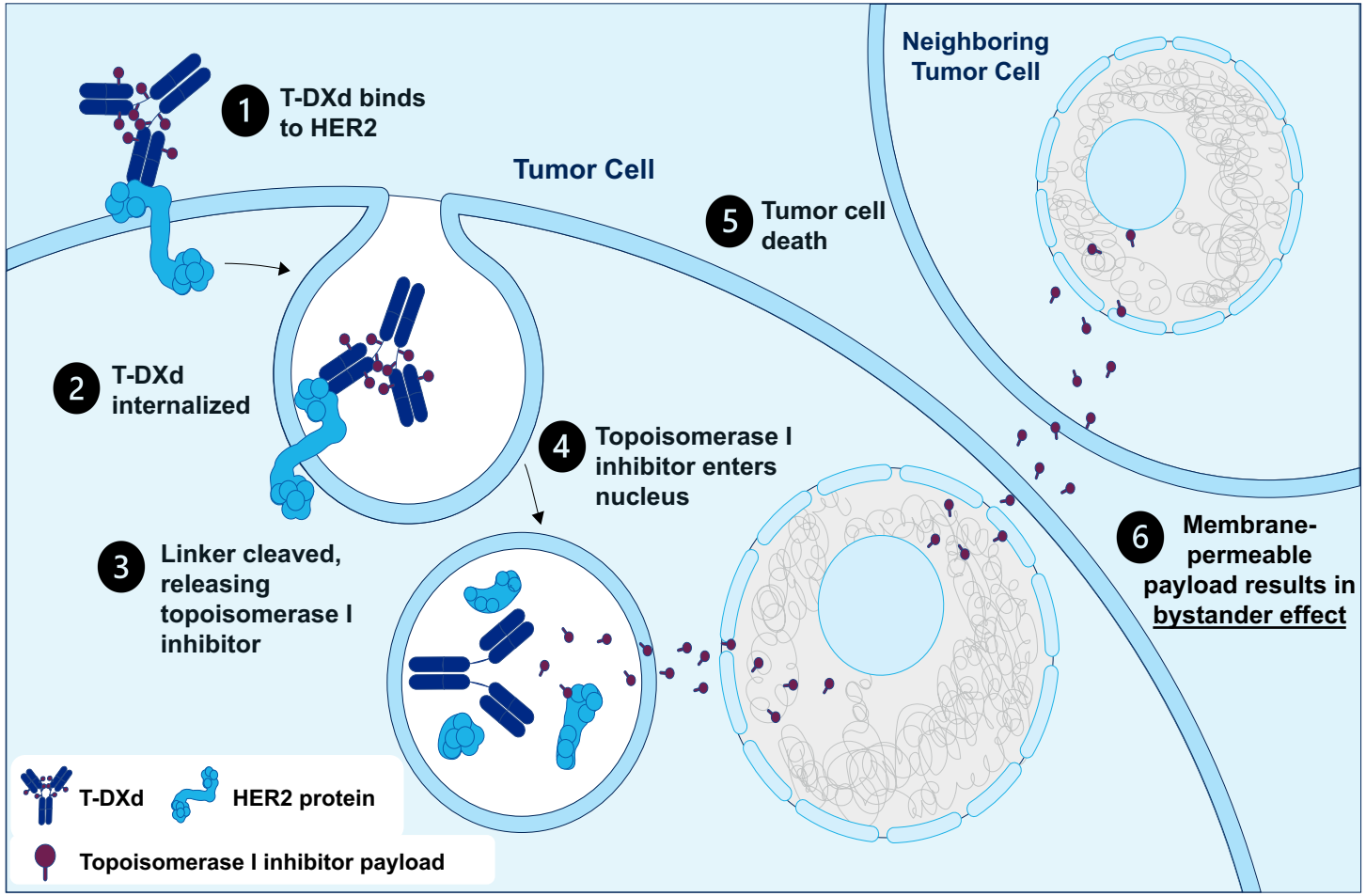
- Predominantly HR+
- Prognostically and biologically indistinct from HER2 IHC 0 BC
- Not a unique subtype
- Targetable by new generation antibody drug conjugates

Tarantino, et al. J Clin Oncol. 2020.

Trastuzumab Deruxtecan (T-DXd): MOA, Bystander Effect, and Rationale for Targeting HER2-low MBC



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



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

HER2, human epidermal growth factor receptor 2; MOA, mechanism of action; mBC, metastatic breast cancer; mPFS, median progression-free survival; ORR, objective response rate; T-DXd, trastuzumab deruxtecan.

1. Nakada T, et al. *Chem Pharm Bull*. 2019;67:173-85. 2. Ogitani Y, et al. *Clin Cancer Res.* 2016;22:5097-108. 3. Modi S, et al. *J Clin Oncol* 2020;38:1887-96.

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd versus Treatment of Physicians Choice for HER2-low mBC

An open-label, multicenter study (NCT03734029)

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

R 2:1

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

HR+ ≈ 480
HR− ≈ 60

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

Primary endpoint
- PFS by BICR (HR+)

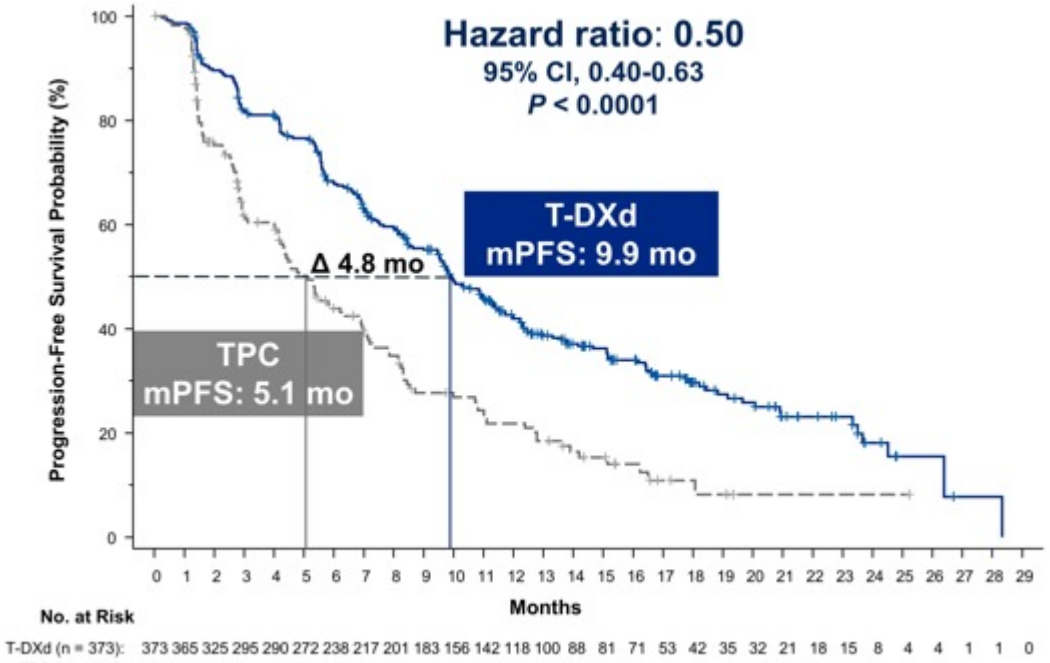
Key secondary endpoints[d]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

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−

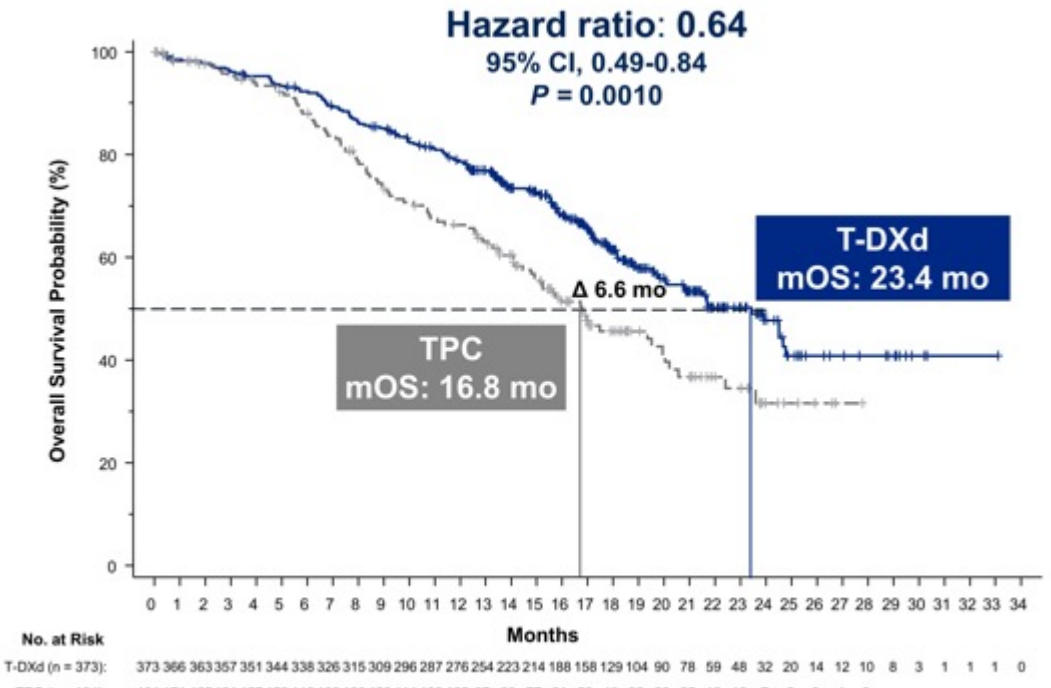
BICR, blinded independent central review; CDK, cyclin-dependent kinase; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every three weeks; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[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 accordingly 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.

DESTINY-Breast04: Results

PFS in all patients



OS in all patients



2022 FDA Approved T-DXd as the new SOC For HER2 Low (1+ or 2+/ISH-) MBC

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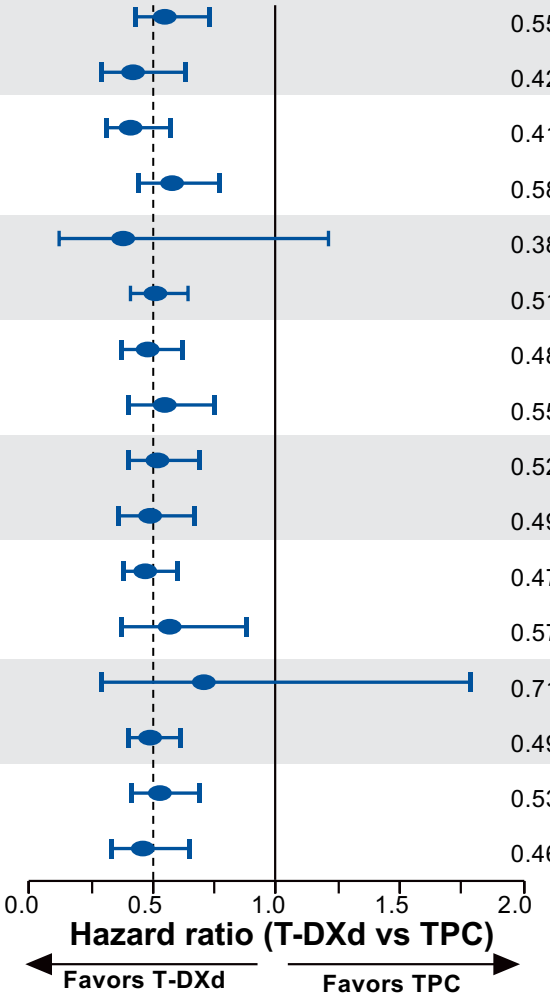
Modi S, et al. Presented at: ASCO 2022 Annual Meeting; June 3-June 7, 2022; Chicago, IL; Modi S et al, NEJM 2022.

DESTINY-Breast04: Updated Subgroup Analyses

Progression-free survival[a] (all patients)

		No. of Events/No. of Patients		Median PFS (mo, 95% CI)[a]		Hazard Ratio (95% CI)[b]
		T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6i use (HR+ cohort)	Yes (n = 348)	149/233	74/115	10.0 (8.3-11.4)	5.4 (4.0-7.8)	0.55 (0.42-0.74)
	No (n = 143)	60/96	35/47	11.7 (9.5-17.7)	5.9 (4.3-8.2)	0.42 (0.28-0.64)
Disease burden[c]	Low (n = 235)	88/150	60/85	11.4 (9.8-16.2)	5.1 (3.1-7.3)	0.41 (0.30-0.58)
	High (n = 322)	155/223	67/99	9.5 (7.5-10.1)	4.8 (2.9-6.9)	0.58 (0.43-0.78)
Rapid progression[d]	Yes (n = 22)	9/14	6/8	8.2 (1.4-NE)	2.2 (0.6-NE)	0.38 (0.12-1.21)
	No (n = 535)	234/359	121/176	9.9 (9.0-11.3)	5.3 (4.2-6.9)	0.51 (0.41-0.64)
HER2 IHC status	IHC 1+ (n = 321)	134/214	75/107	10.0 (8.6-12.3)	4.8 (3.0-7.0)	0.48 (0.36-0.63)
	IHC 2+/ISH− (n = 236)	109/159	52/77	9.9 (8.0-11.5)	5.1 (2.9-7.1)	0.55 (0.39-0.76)
Prior lines of chemotherapy	1 (n = 321)	141/221	68/100	10.1 (8.4-12.2)	6.4 (4.3-7.8)	0.52 (0.39-0.70)
	2 (n = 234)	101/151	59/83	9.7 (8.1-11.4)	4.2 (3.0-5.4)	0.49 (0.35-0.68)
Age	<65 years (n = 426)	191/290	93/136	9.8 (8.4-11.1)	4.6 (2.9-5.9)	0.47 (0.37-0.61)
	≥65 years (n = 131)	52/83	34/48	11.4 (8.3-13.3)	6.2 (4.3-10.8)	0.57 (0.36-0.89)
Baseline CNS metastases	Yes (n = 32)	18/24	6/8	8.1 (4.0-11.3)	4.8 (0.6-11.0)	0.71 (0.28-1.80)
	No (n = 525)	225/349	121/176	10.1 (9.5-11.5)	5.1 (4.2-6.8)	0.49 (0.39-0.62)
Prior anthracycline treatment[e]	Yes (n = 342)	155/239	81/113	9.8 (8.5-11.7)	5.3 (3.0-7.9	0.53 (0.40-0.70)
	No (n = 205)	88/134	46/71	10.0 (7.2-12.5)	4.6 (3.0-6.8)	0.46 (0.32-0.66)

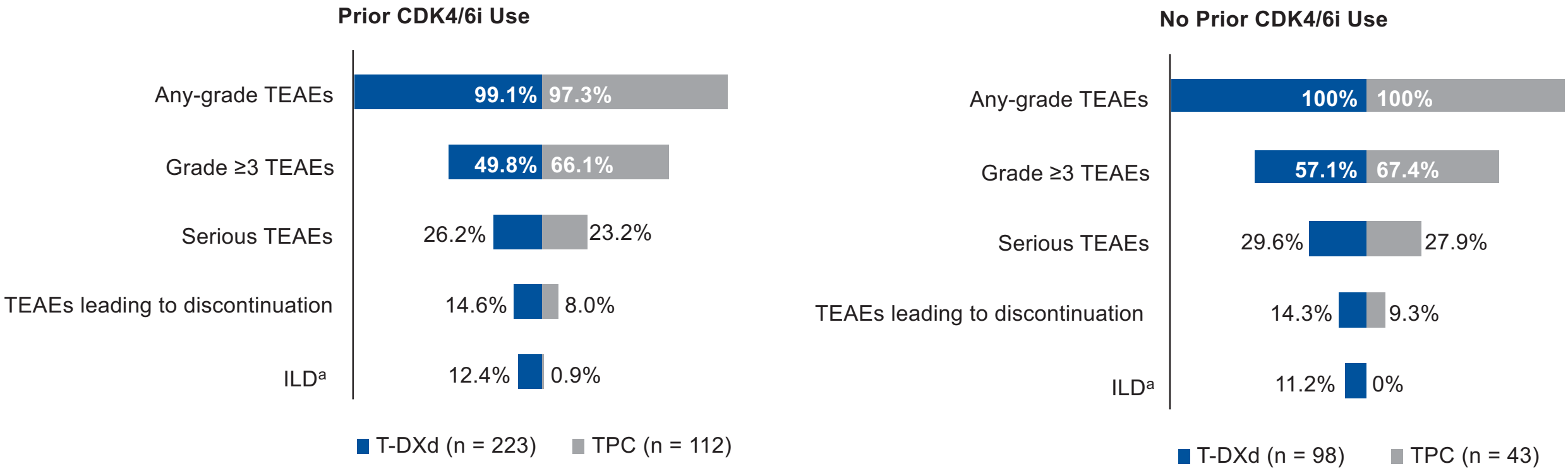


Dashed line at 0.50 represents median PFS for all patients (Modi S et al. *N Engl J Med*. 2022;387(1):9-20).

[a]Median PFS is from Kaplan-Meier analysis. CI for median was computed using the Brookmeyer-Crowley method. [b]Hazard ratio is from unstratified Cox proportional hazards model with treatment as the only covariate. [c]Disease burden was defined by the number of metastatic disease sites at baseline (low = 0-2; high = 3+). At baseline, 69.8% of patients had liver metastases. [d]Rapid progressor status was defined as disease progression within 6 months of concluding a prior course of chemotherapy in early breast cancer.

Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0.

DB04: Safety by CDK4/6i use (all patients)

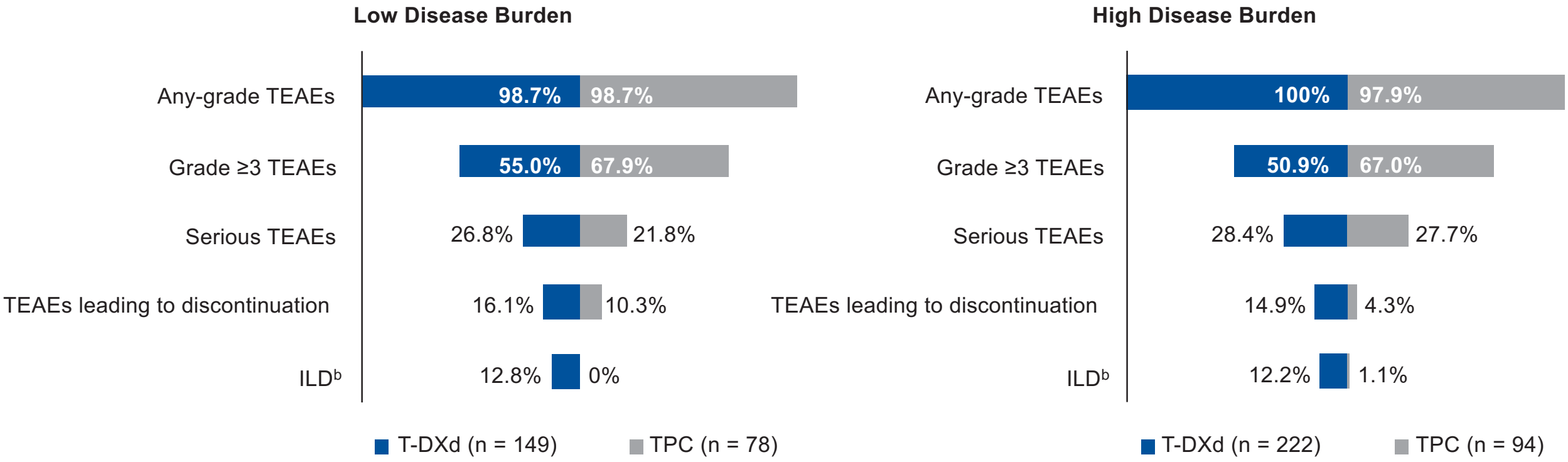


CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.

[a]Adjudicated ILD events per the ILD Adjudication Committee.

Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0.

DB04: Safety by disease burden[a] (all patients)



HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]Disease burden was defined by the number of metastatic disease sites at baseline (low = 0-2; high = 3+). At baseline, 69.8% of patients had liver metastases.
[b]Adjudicated ILD events per the ILD Adjudication Committee.
Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0.

DESTINY-Breast04: Determination of HER2 Low Status

N=1340
samples submitted

↓

N=1060
HER2 Low locally &
Centrally testable

↓

N=823
Centrally confirmed HER2 Low

↓

N=557
Eligible for Trial

Concordance Between Historical and Central HER2 IHC Results[a]

HER2 Status by Central Testing, n	HER2 Status by Historical Result, n				Total
	IHC 0	IHC 1+	IHC 2+/ISH−	IHC 2+/ISH+	
IHC 0	18	157	51	2	228
IHC 1+	18	**344**	**126**	3	491
IHC 2+/ISH−	5	**122**	**231**	0	358
IHC 2+/ISH+	0	9	11	1	21
IHC 3+	1	2	7	0	10
Total	42	634	426	6	1108

- central testing using the PATHWAY HER2 4B5 assay (and INFORM HER2 Dual ISH DNA Probe Cocktail when applicable)

- 78% (823/1060) of samples centrally confirmed HER2 low
- Among discordant samples: 208/237 (88%) were centrally scored IHC 0, and 29/237 (12%) were scored IHC 2+/ISH+ or IHC 3+

Prat A et al, SABCS 2022

Factors Associated With Scoring Agreement

Feature	Patients With Historical and Valid Central HER2 Results (n = 1108), n (%)	Overall Percentage Agreement (95% CI)
Region of origin		
North America	252 (22.7)	0.85 (0.81-0.90)
Europe and Israel	461 (41.6)	0.70 (0.66-0.74)
Asia, excluding China	287 (25.9)	0.82 (0.77-0.86)
China	108 (9.7)	0.68 (0.59-0.76)
Specimen collection time (relative to study screening)		
2013 or earlier	94 (8.5)	0.64 (0.54-0.74)
2014-2018	421 (38.0)	0.75 (0.71-0.79)
2019 or later	555 (50.1)	0.79 (0.75-0.82)
Missing	38 (3.4)	0.89 (0.80-0.99)

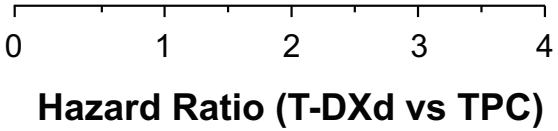
- Scoring agreement of HER2 tumor samples varied by region and collection date

HER2, human epidermal growth factor receptor 2.

Prat A et al. San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18.

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

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

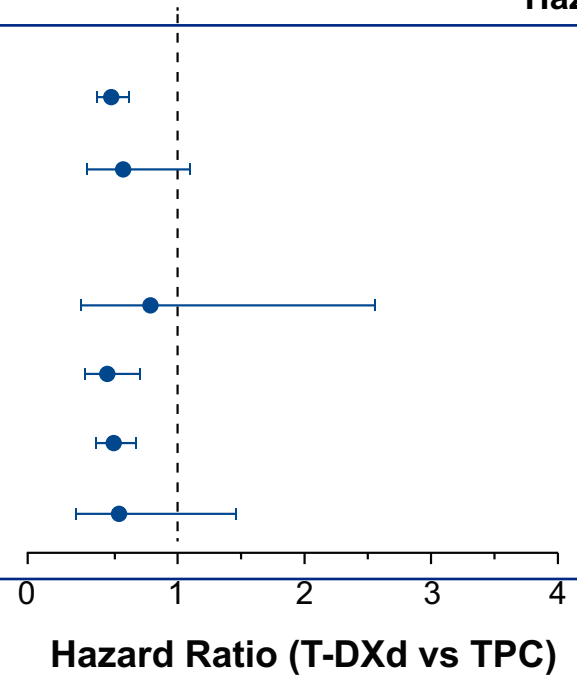


PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Prat A et al. San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18.

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

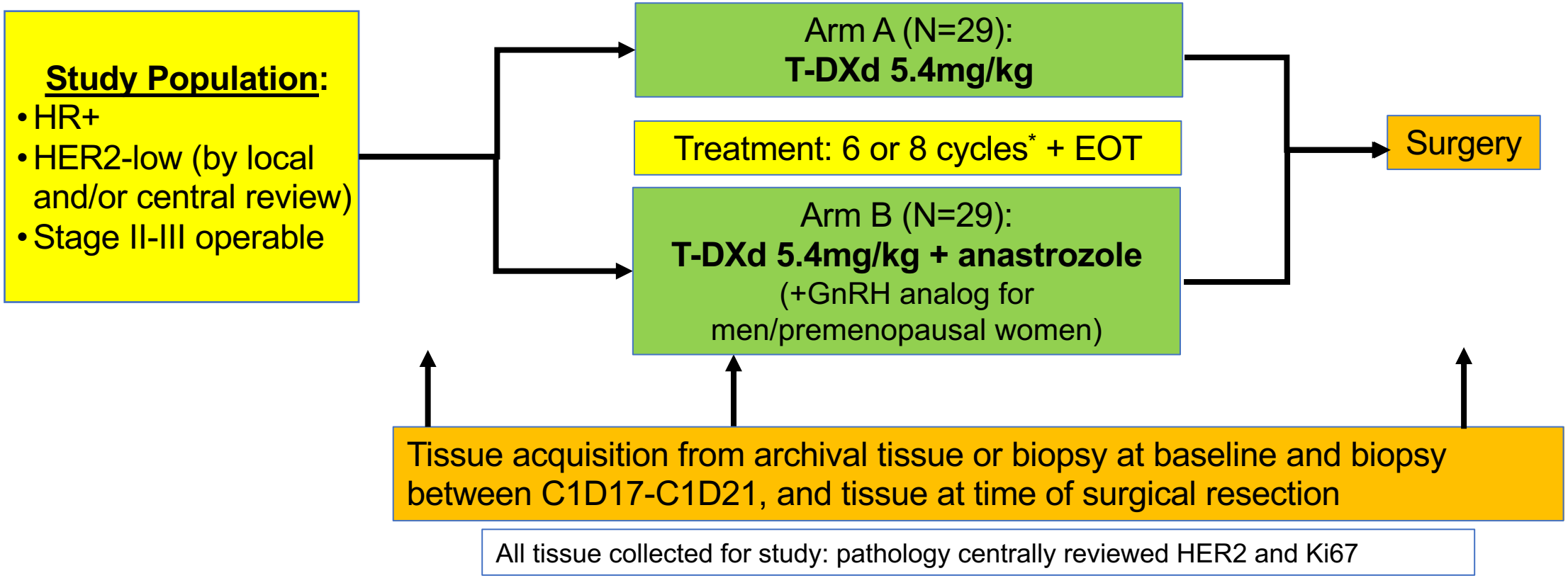
	Number of Events		Median PFS, Months (95% CI)		
Subgroup	**T-DXd**	**TPC**	**T-DXd**	**TPC**	**Hazard Ratio (95% CI)**
Collection type					
Archival tissue (n = 482)	203/324	109/158	10.3 (8.6-12.0)	5.3 (4.2-7.0)	0.48 (0.37-0.61)
Newly obtained tissue (n = 75)	40/49	18/26	9.7 (5.6-10.9)	4.8 (2.8-6.9)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



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

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

TRIO-US B-12 (TALENT): Neoadjuvant HER2 Low Trial



* Originally, 6 cycles of treatment were given but in 02/2022, an amendment increased the number of treatment cycles from 6 to 8 for newly enrolled participants, or those who had not yet had surgery.

Presented by Bardia A, Hurvitz S; SABCS 2022

RCB Results by Arm, Number of Cycles and Stage

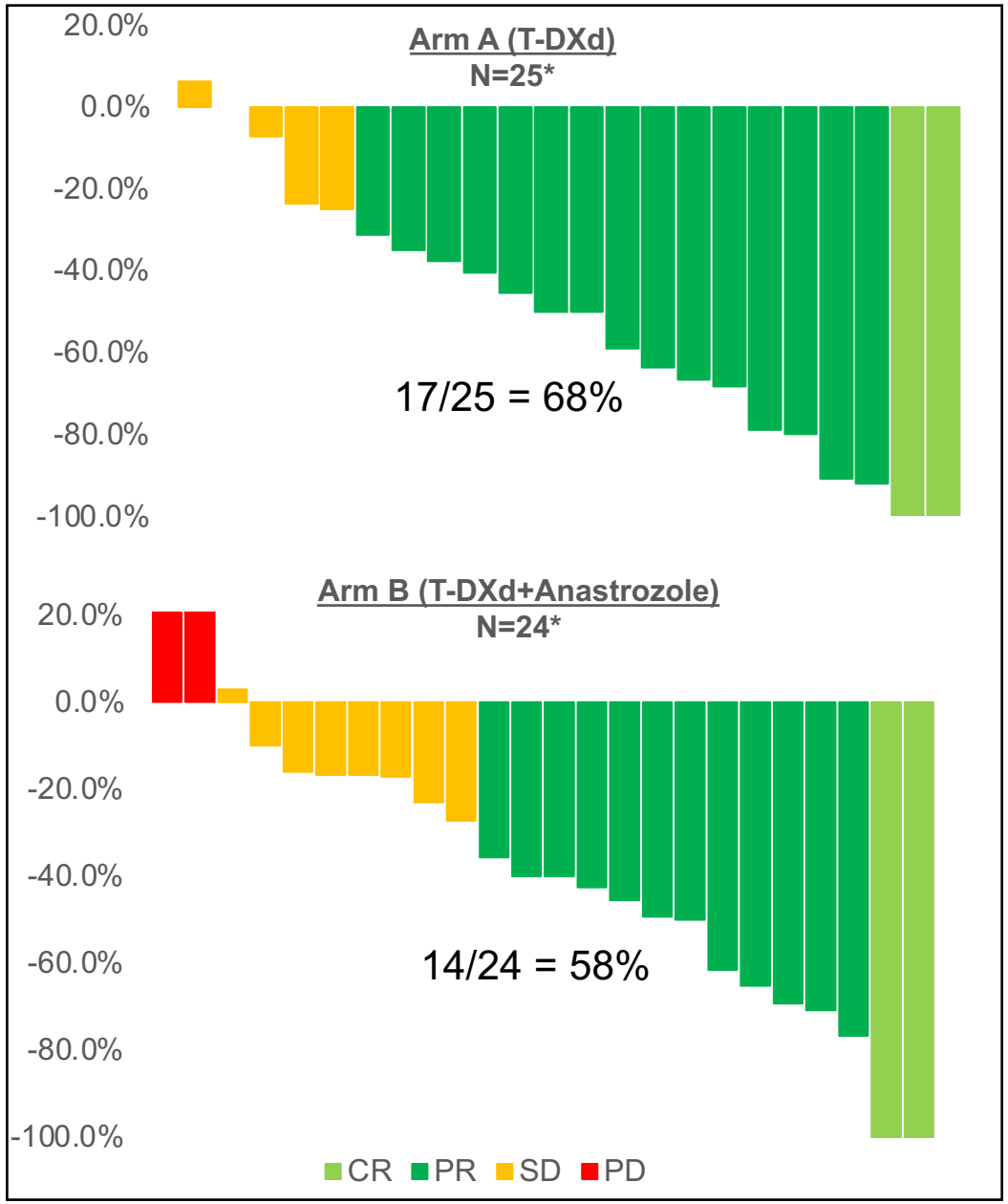
Cycles	Stage at Baseline	Arm A (T-DXd) N=22*				Arm B (T-DXd+Anastrozole) N=20**			
		RCB-0	RCB-I	RCB-II	RCB-III	RCB-0	RCB-I	RCB-II	RCB-III
6 Cycles	Stage IIA	0	1 (5%)	2 (9%)	0	0	1 (5%)	6 (30%)	0
	Stage IIB	0	1 (5%)	4 (18%)	2 (9%)	0	0	3 (15%)	1 (5%)
	Stage IIIA	0	0	1 (5%)	2 (9%)	0	0	1 (5%)	1 (5%)
	Stage IIIB	0	0	1 (5%)	0	0	0	0	0
8 Cycles	Stage IIA	0	0	2 (9%)	0	0	1 (5%)	1 (5%)	0
	Stage IIB	0	0	1 (5%)	1 (5%)	0	0	2 (10%)	0
	Stage IIIA	1 (5%)	0	0	0	0	1 (5%)	0	0
	Stage IIIB	0	0	0	0	0	0	0	0

RCBi = Residual cancer burden index; RCB 0 = pCR

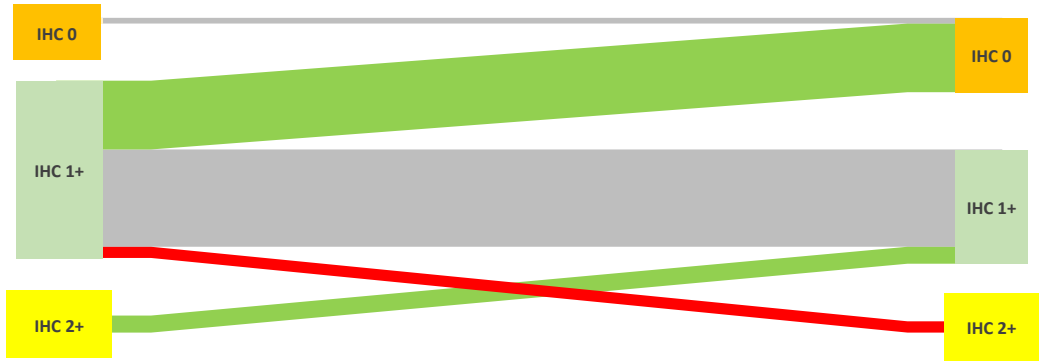
- As of data cutoff 11/25/2022, denominator excludes pts currently awaiting surgery or actively on treatment (3 pts in Arm A and 4 pts in Arm B pending surgical data, 4 active pts in Arm A and 5 active pts in Arm B).
- *4 pts discontinued early **3 pts discontinued early
- IHC Status did not appear to be associated with RCB

Presented by Bardia A, Hurvitz S; SABCS 2022

Objective Response Rate (based on local imaging)

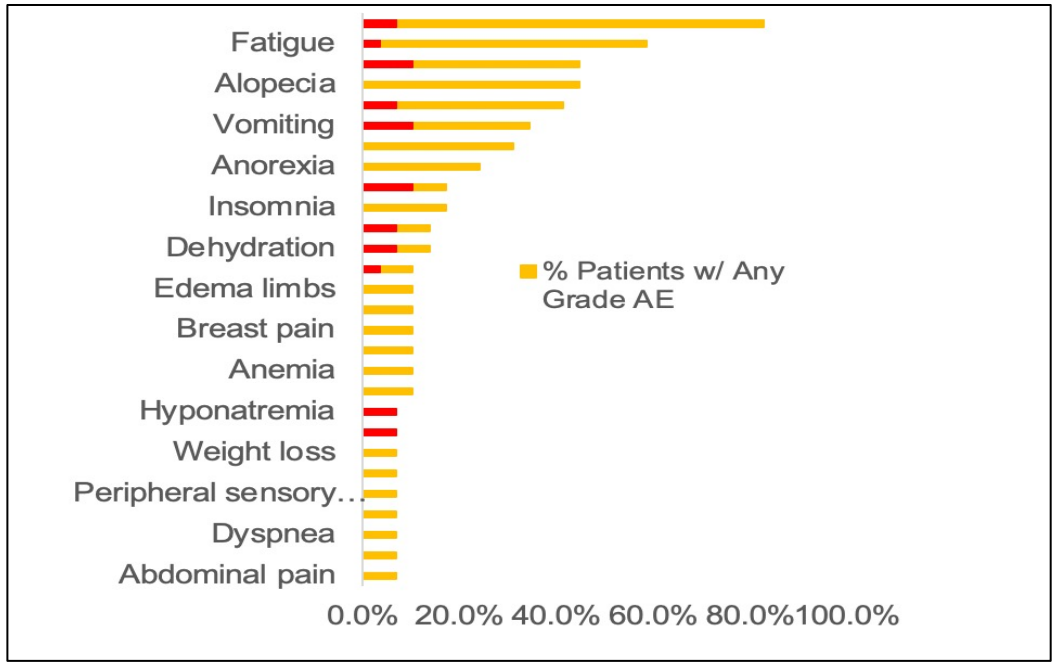


HER2 Change from Baseline to Surgery (by Central Review)



- 48.6% (17/35) had change in HER2 IHC
- Of those, majority (88.2%) had decrease in HER2

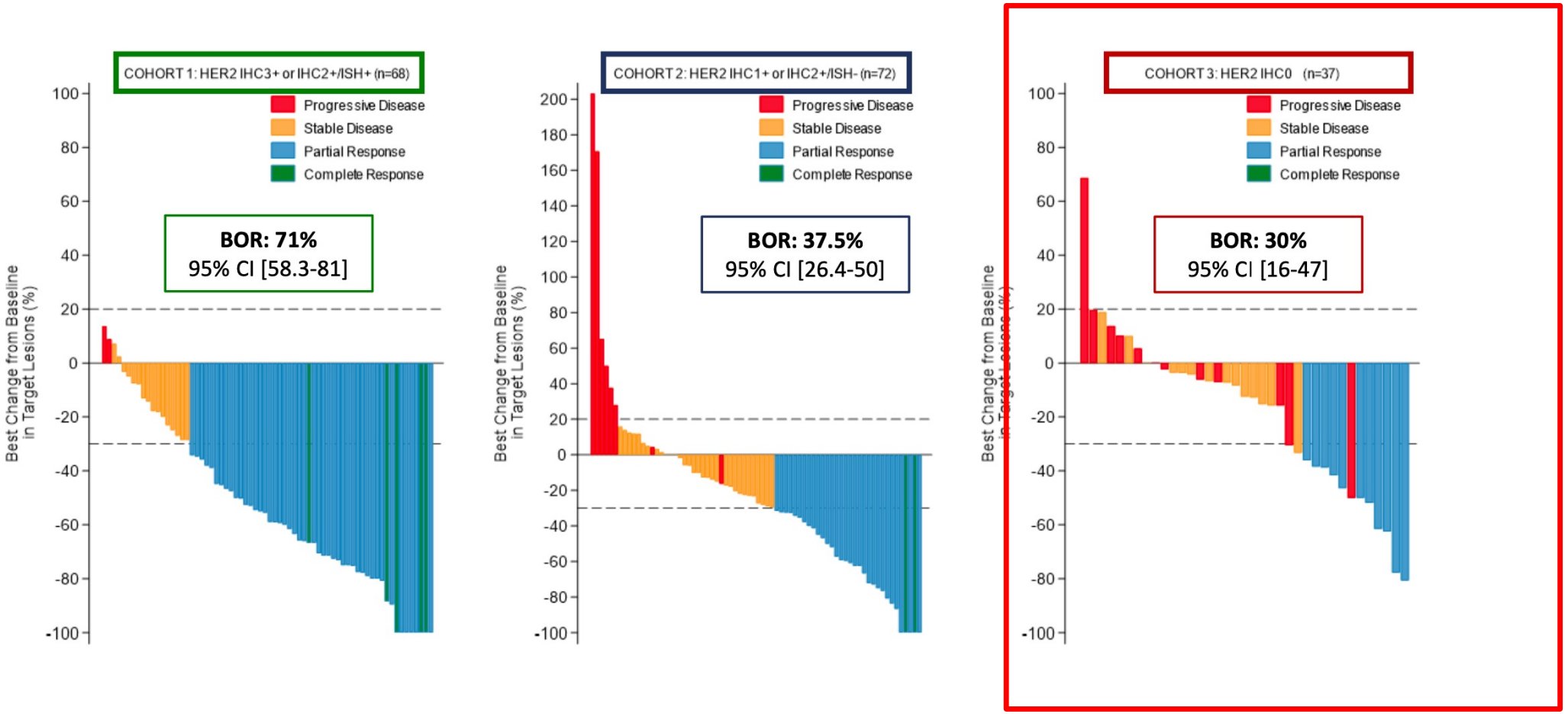
Arm A T-DXd Related AEs (N=29)



HER2 LOW: Challenges

What is the Threshold Level of HER2 Expression to activate T-DXd?

DAISY, Phase 2 Trial of T-DXd: Activity seen in HER2 IHC 0 Cohort

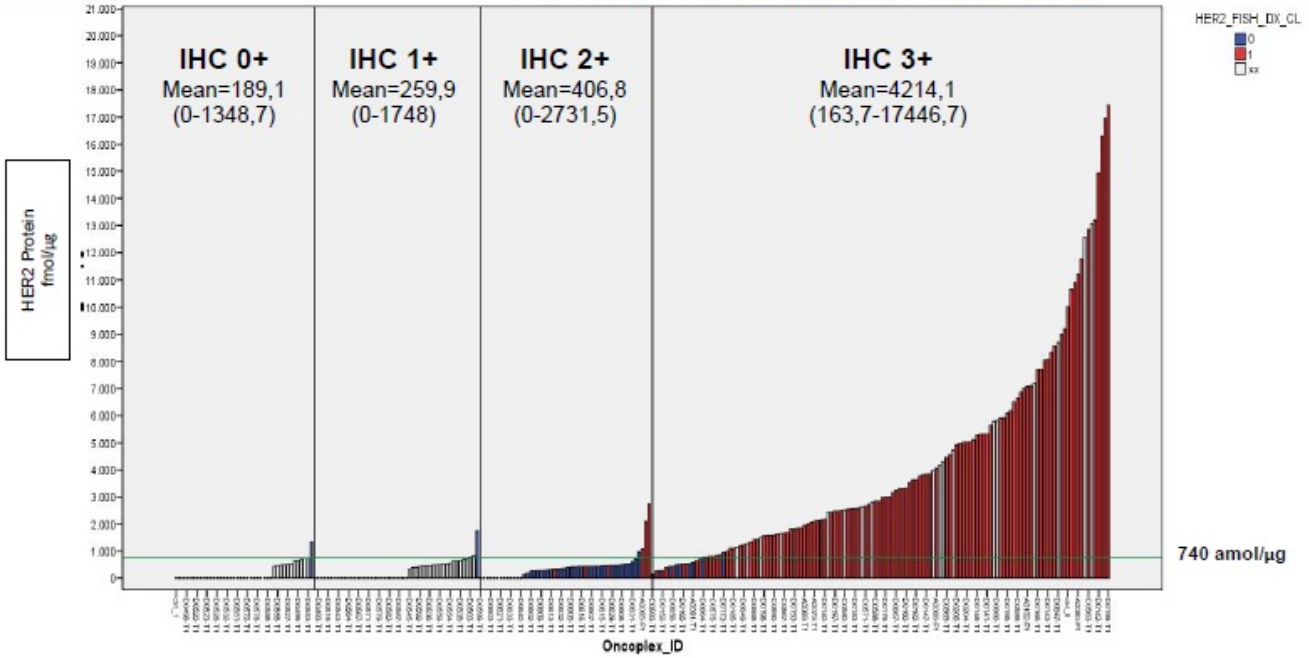


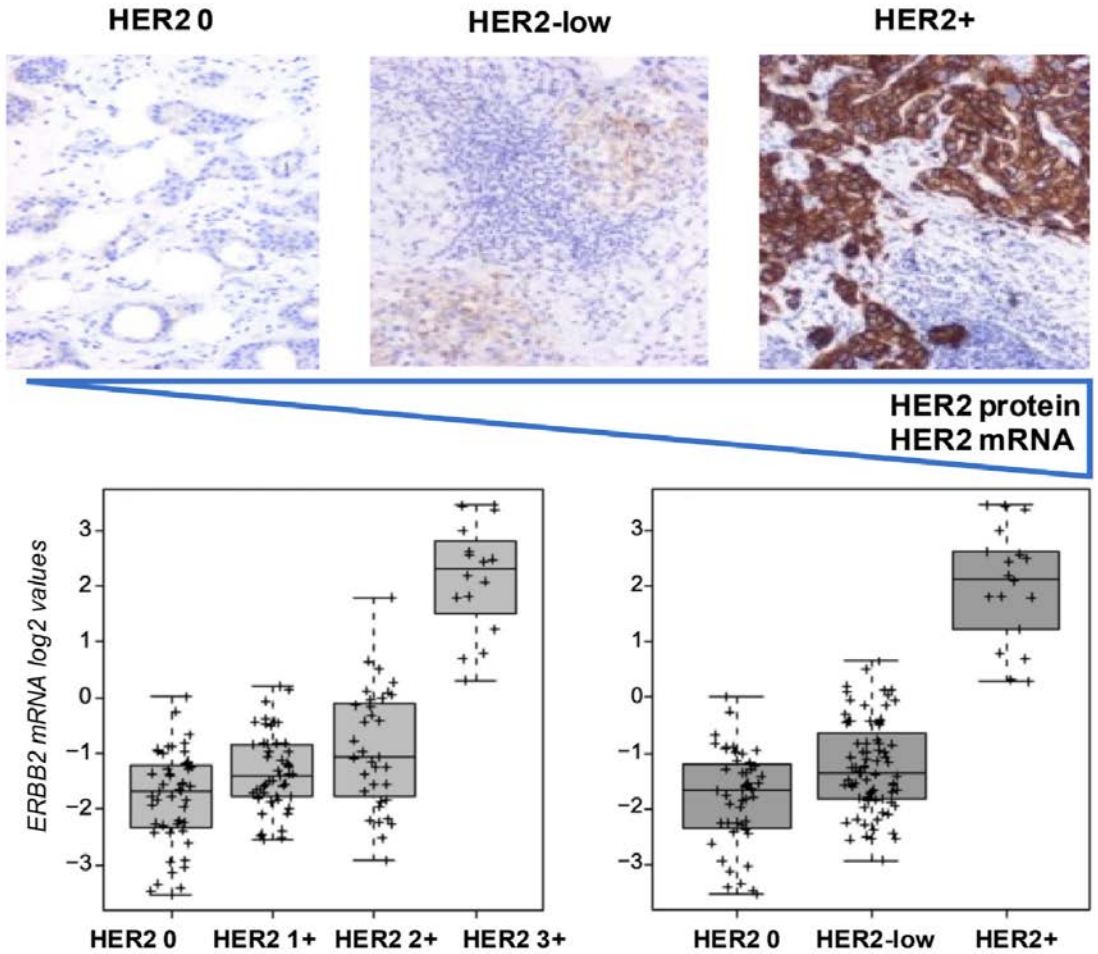
IHC 0 Cohort med DoR: 6.8mo (CI: 2.8; NR) ; med PFS: 4.2mo (CI: 2.0; 5.7)

Dieras, V et a; SABCS 2021

Are There Alternate Methods of Measuring HER2 Expression?

Quantitative Measurement of HER2 levels by Multiplexed Mass Spectrometry from FFPE tissue

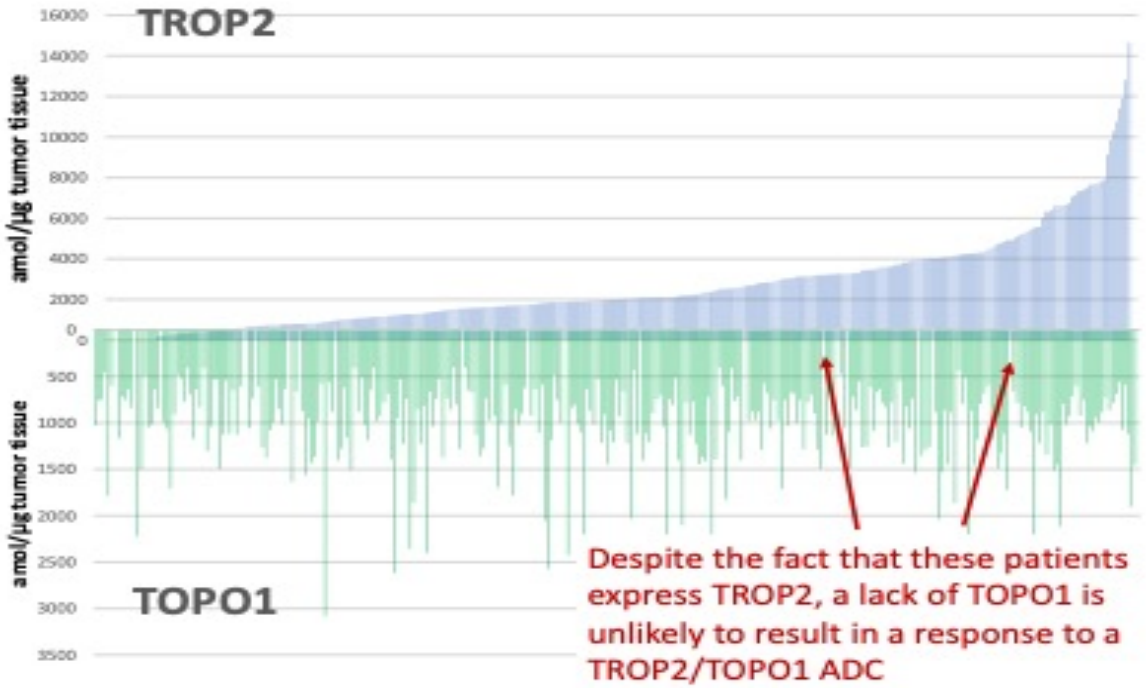




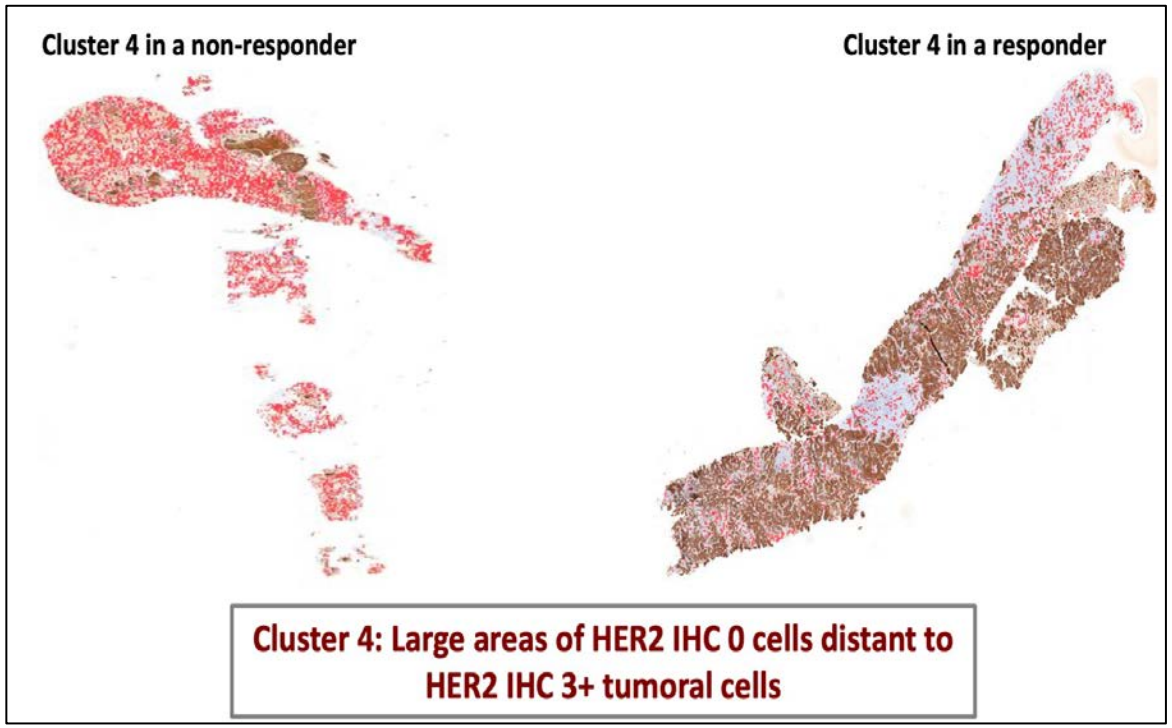
Nuciforo P et al, Mol Oncol 2016; Schettini P et al, The Breast 2021

Novel Biomarkers of Response: Payload Markers and Spatial Heterogeneity

Clinical Survey of TROP2 antibody-drug conjugate target and payload biomarkers in multiple cancer indications using multiplex mass spectrometry



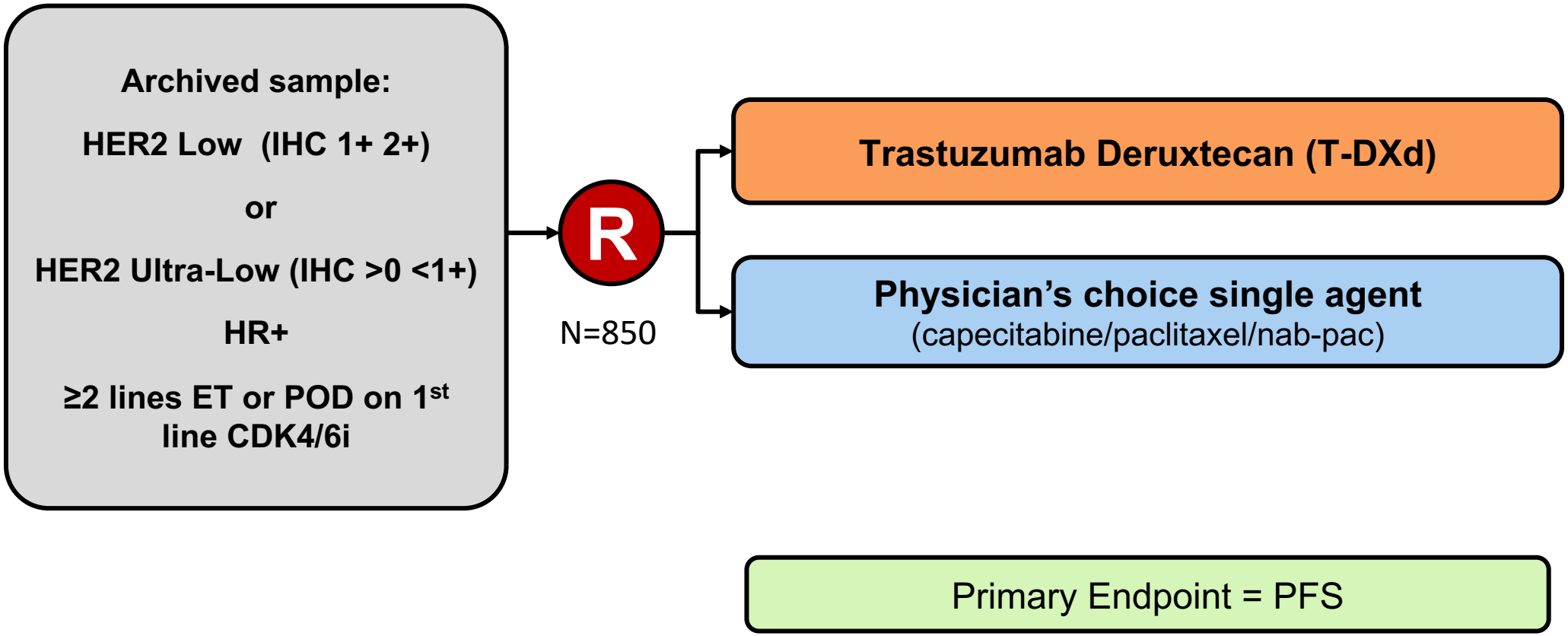
Spatial heterogeneity of target antigen as a predictor of response to T-DXd in HER2+ MBC



Biomarkers of Toxicity?

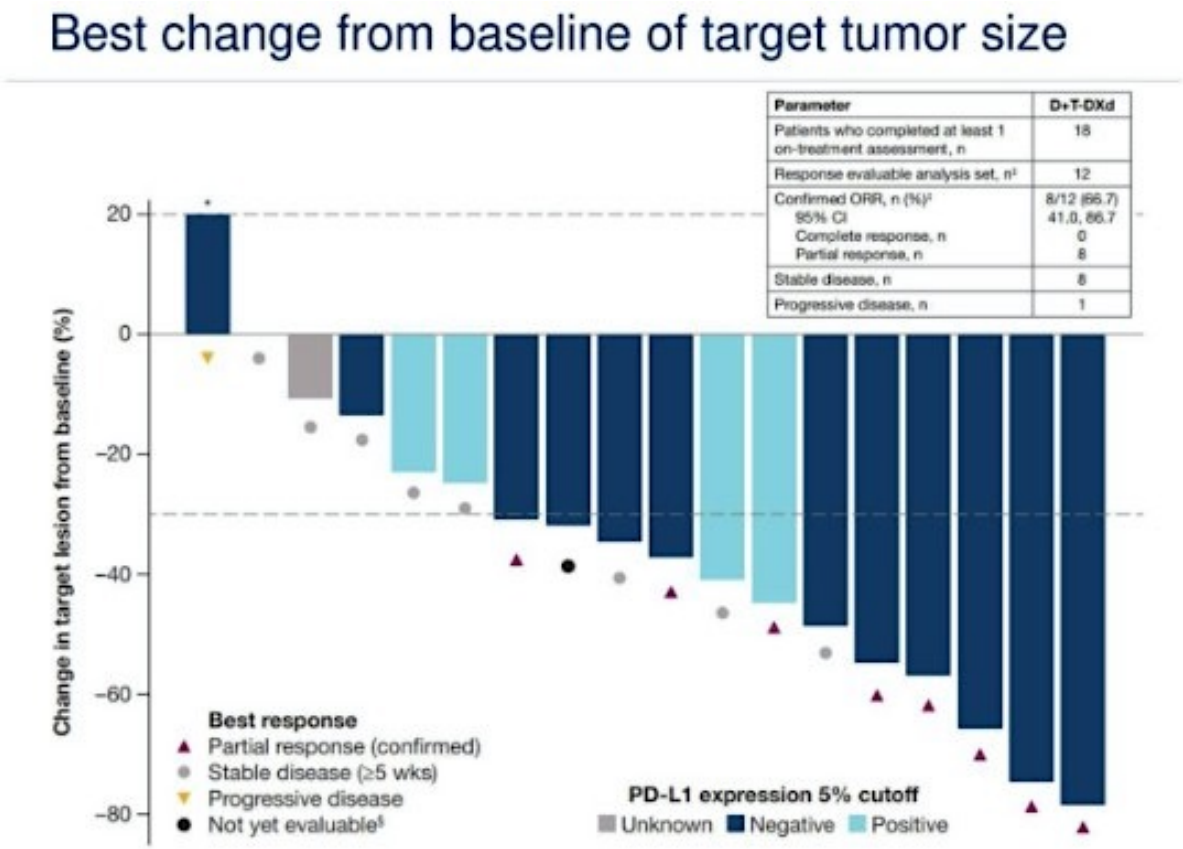
Thyparambil S et al, AACR 2022; Dieras, V et al, SABCS 2021

DESTINY Breast-06: Chemotherapy-naïve, HR+, HER2 LOW or HER2 Ultra-Low MBC



ClinicalTrials.gov Identifier: NCT04494425

HER2 LOW TNBC:
BEGONIA Phase 1b/2 Platform Study of durvalumab (D) combinations in TNBC
Preliminary Results for Arm 6: D+T-DXd in HR- HER2 LOW MBC (TNBC)



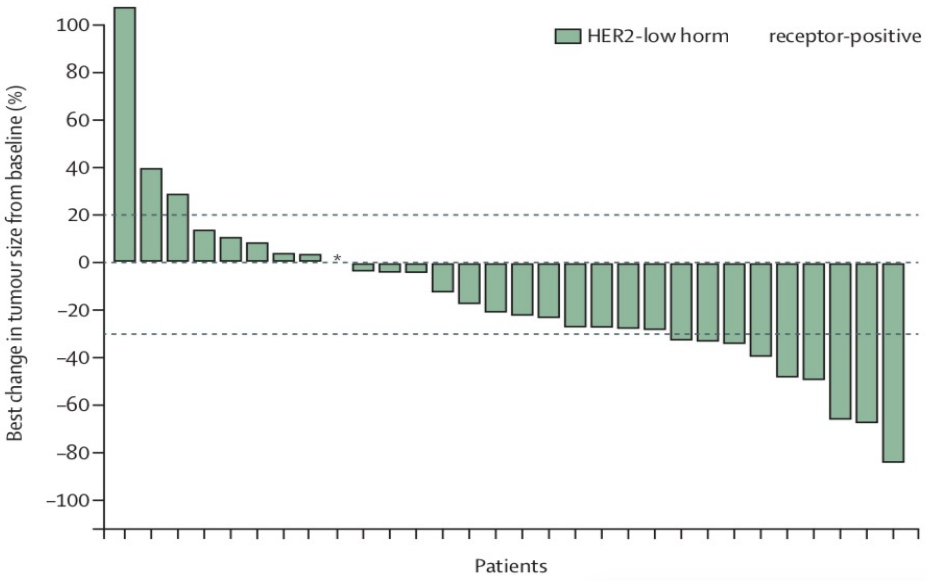
Local testing of HER2 expression successfully identified patients with HER2 IHC1+ and HER2 IHC2+/ISH– tumors, who benefit from this treatment combination.

In this small group of patients, responses were observed in both PD-L1–positive (confirmed ORR 1/1 [100%]) and –negative (confirmed ORR 7/10 [70.0%]) groups (5% cutoff).

Schmid P et al ASCO 2021

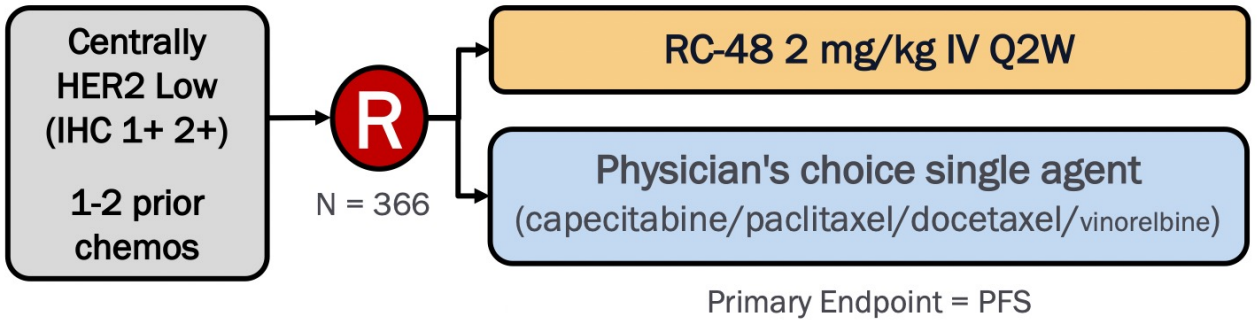
Novel ADCs for HER2-low in Development

Trastuzumab duocarmazine (SYD985)[1]



49 HER2-low mBC patients: ORR 32%, mPFS 4 mo

Randomized Phase 3 Study: RC48-ADC vs TPC for HER2-Low MBC



- Banerji U, et al. *Lancet Oncol.* 2019;20(8):1124–1135; Wang J, et al. Presented at ASCO 2021.

Can we Maximize the potential of T-DXd via Combinations?

DESTINY Breast 08: Study Schema

Part 1: Dose Finding

Patient population

- HR+ or HR−, HER2-low (IHC 1+ or IHC 2+/ISH−) metastatic breast cancer
  - HR+ patients: ≥1 prior line of ET and ≥1 prior line of CTX for metastatic disease
  - HR− patients: ≥1 prior line of CTX for metastatic disease

Centrally assigned

- Module 1: T-DXd + capecitabine (HR+ or HR−)
- Module 2: T-DXd + durvalumab + paclitaxel (HR+ or HR-)
- Module 3: T-DXd + capivasertib (HR+ or HR-)
- Module 4: T-DXd + anastrozole (HR+ patients only)
- Module 5: T-DXd + fulvestrant (HR+ patients only)

CTX, chemotherapy; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan.

Part 2: Dose Expansion Based on RP2D From Part 1

Patient population

- **Module 1** (HR+ or HR−)
  - HR+: only 1 prior line of ET but no prior CTX for mBC
  - HR−: only 1 prior line of CTX for mBC
- **Module 2** (HR−): no prior CTX for mBC[a]
- **Module 3** (HR−): only 1 prior line of CTX for mBC
- **Modules 4 and 5** (HR+): only 1 prior line of ET but no prior CTX for mBC

Allocation to open modules (dependent on available RP2D)

A

- Module 1: T-DXd + capecitabine (HR+ or HR−) (n=20)
- Module 2: T-DXd + durvalumab + paclitaxel (HR−)
- Module 3: T-DXd + capivasertib (HR−) (n=40)[c]
- Module 4: T-DXd + anastrozole (HR+)
- Module 5: T-DXd + fulvestrant (HR+)

[a] Patients who have received CTX in the neoadjuvant or adjuvant setting are eligible, as long as they have had a disease-free interval of >12 months.
[b] Molecularly defined subgroup of special interest, PD-L1(+).
[c] Molecularly defined subgroup of special interest, AKT/PTEN/PIK3CA altered

Clinicaltrials.gov Identifier: NCT04556773

DESTINY-Breast09 Phase III Trial Design

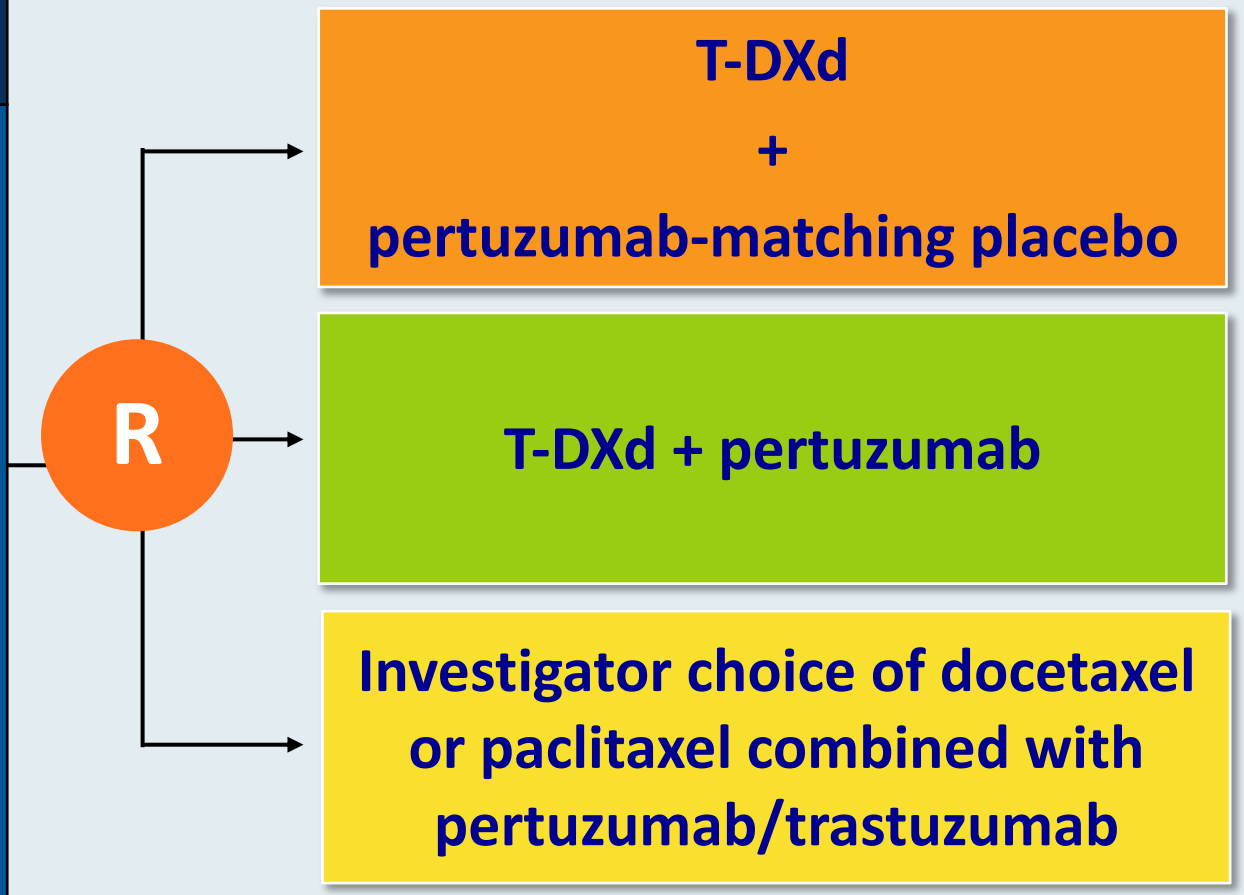
Estimated enrollment: N = 1,134

Pathologically documented breast cancer:

- Advanced or metastatic
- Locally assessed and prospectively centrally confirmed as IHC 3+ or ISH+
- Documented by local testing as HR-positive or negative in the metastatic setting

No prior chemotherapy or HER2-targeted therapy for advanced or metastatic disease or only 1 previous line of ET in the metastatic setting

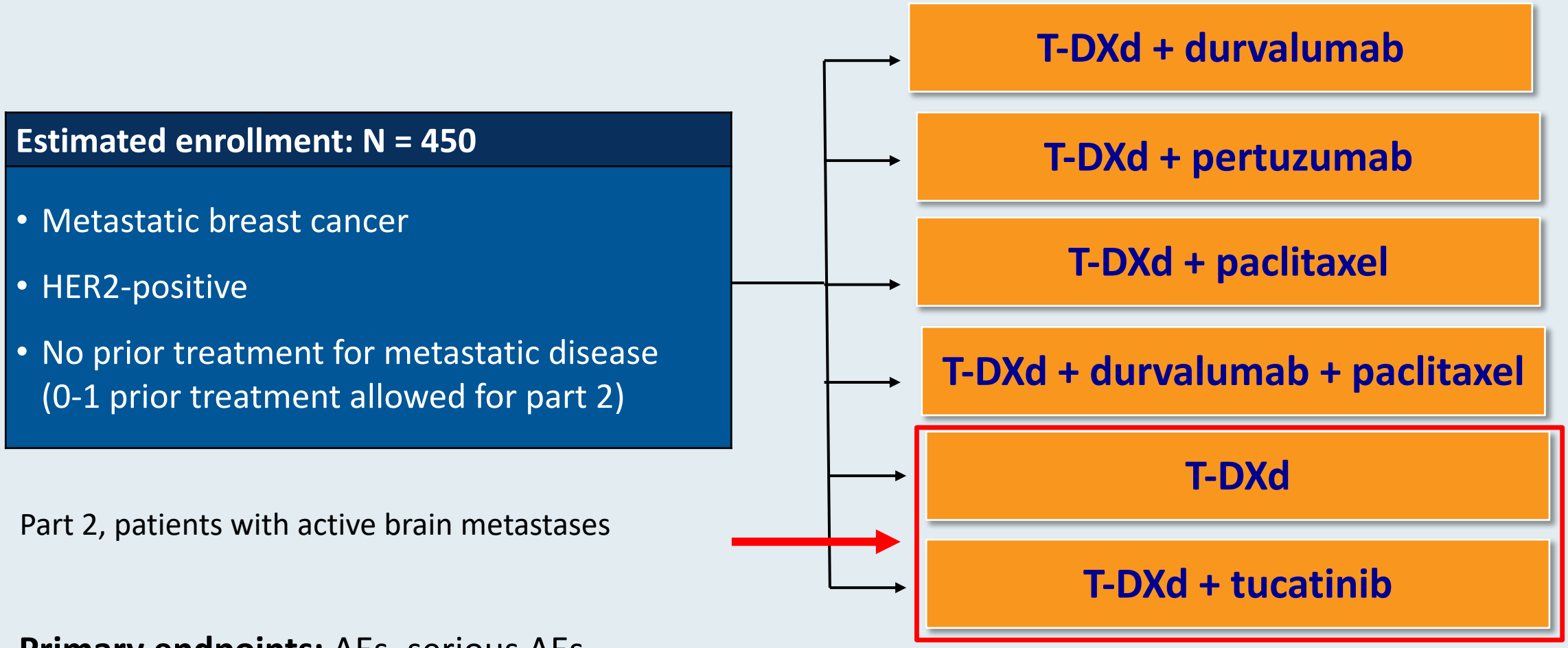
Prior (neo)adjuvant chemotherapy or HER2-targeted therapy allowed if >6 months from treatment to diagnosis of metastasis



Primary endpoint: Progression-free survival

www.clinicaltrials.gov. NCT04784715. Accessed December 2022.

DESTINY-Breast07 Phase I/II Trial Design



Part 2, patients with active brain metastases

Primary endpoints: AEs, serious AEs

Secondary endpoints include objective response rate, PFS, PFS2, duration of response, overall survival

www.clinicaltrials.gov. NCT04538742. Accessed December 2022.

Select Ongoing Trials Evaluating Tucatinib for HER2-Positive Metastatic Breast Cancer

Trial identifier	Phase (N)	Setting	Regimens	Estimated completion date
HER2CLIMB-02 (NCT03975647)	III (N = 565)	Unresectable, locally advanced or metastatic disease Prior treatment with a taxane and trastuzumab in any setting	• T-DM1 + placebo • T-DM1 + tucatinib	2024
HER2CLIMB-05 (NCT05132582)	III (N = 650)	Unresectable, locally advanced or metastatic disease No evidence of PD after 1L taxane and HP for advanced disease	*As maintenance after 1L therapy* • HP + placebo • HP + tucatinib	2027
HER2CLIMB-04 (NCT04539938)	II (N = 70)	Unresectable, locally advanced or metastatic disease Prior treatment with a taxane and trastuzumab	• Tucatinib + trastuzumab deruxtecan	2025

HP = trastuzumab and pertuzumab

www.clinicaltrials.gov. Accessed December 2022.

Summary: Beyond HER2+ BC

- Next generation ADCs with advanced pharmaceutical properties have not only improved outcomes in HER2+ BC and have allowed us to move into new populations
- HER2 Low breast cancer is today a targetable new subgroup
  - T-DXd is the first approved HER2 targeted therapy for this population
  - But this is still a new and evolving space and we may need better quantitative biomarker assays to optimize patient selection for these new HER2 ADC therapies
  - And we remain excited about the potential to have other agents in the future for this pop of pts
- Clearly Understanding Mechanisms of Resistance, identifying novel biomarkers and Sequencing studies will be key to optimizing and personalizing ADC therapy in the future

THANK YOU