Her2 + Breast Cancer
Where are we today ?

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August 27, 2022

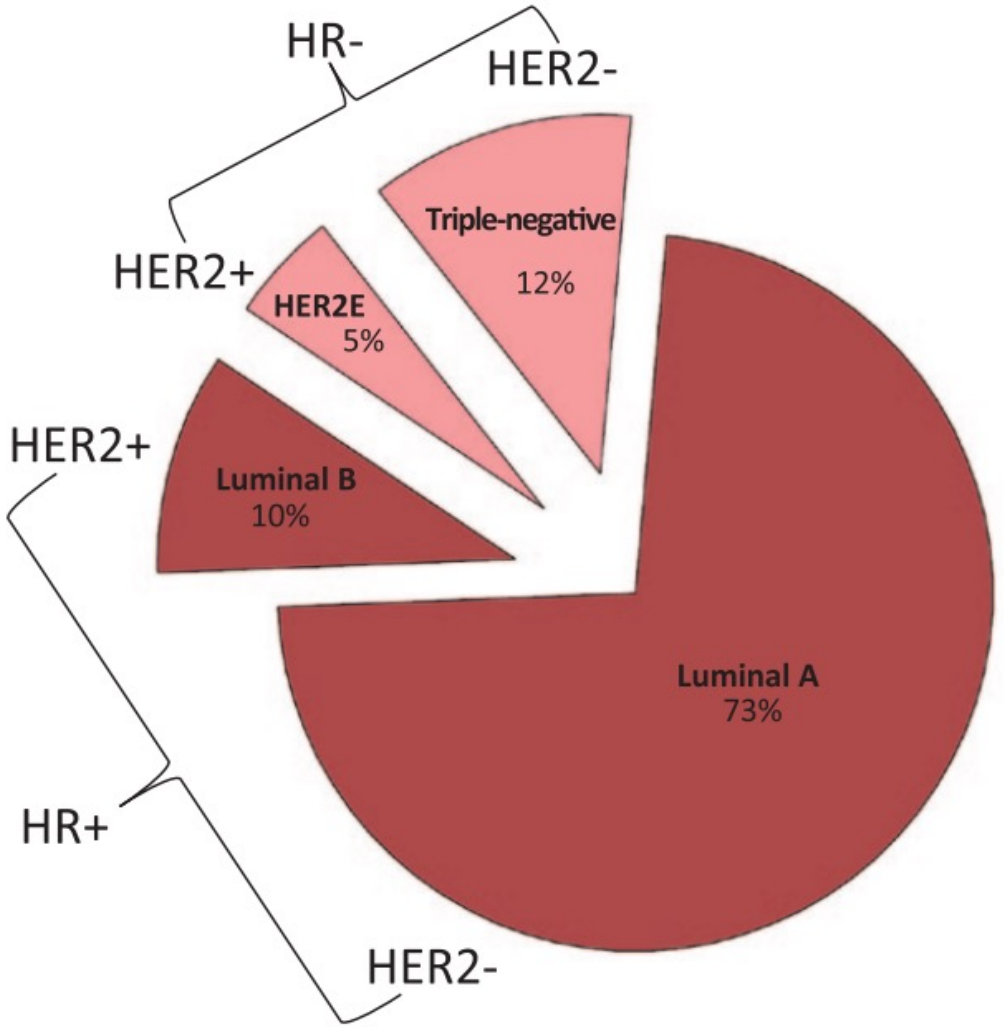
Objectives

- Current status of breast cancer subtypes
- Therapeutic advances in HER2 +
- Therapeutic advances in HER2 low
- Future direction

Subtypes of Breast Cancer

Her2 low?

Intrinsic Breast Cancer Subtypes

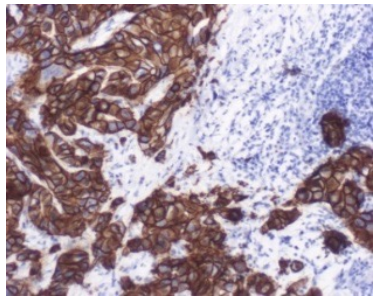


Anderson et al, JNCI 2014

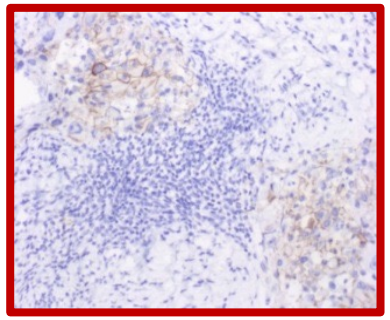
Prevalence of HER2-low by HR-status

HER2 IHC examples

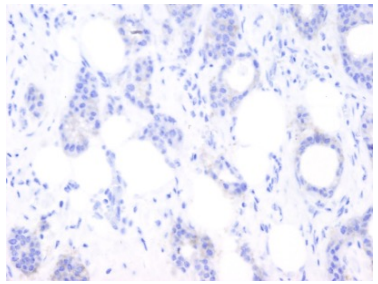
HER2+

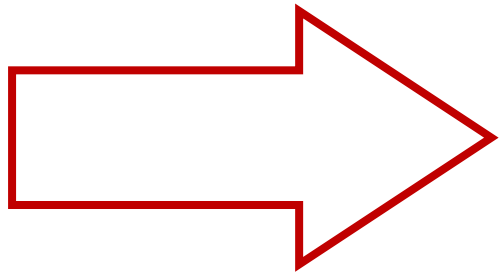


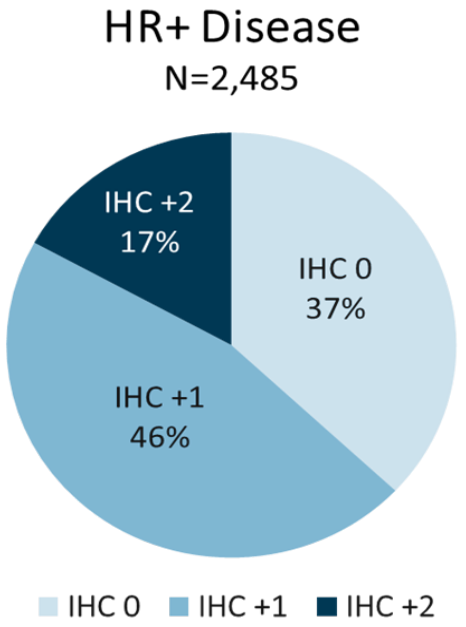
HER2-low



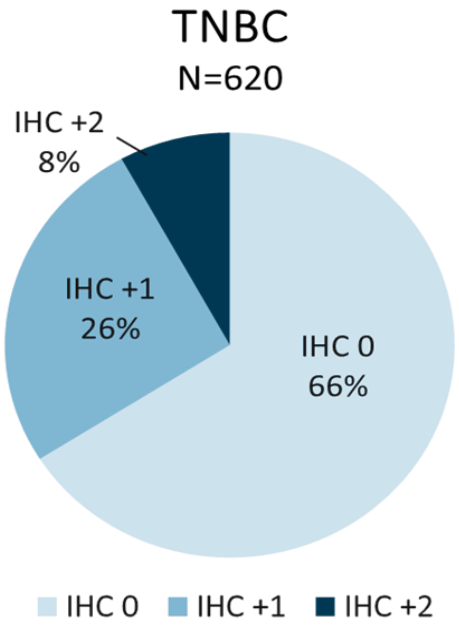
HER2-







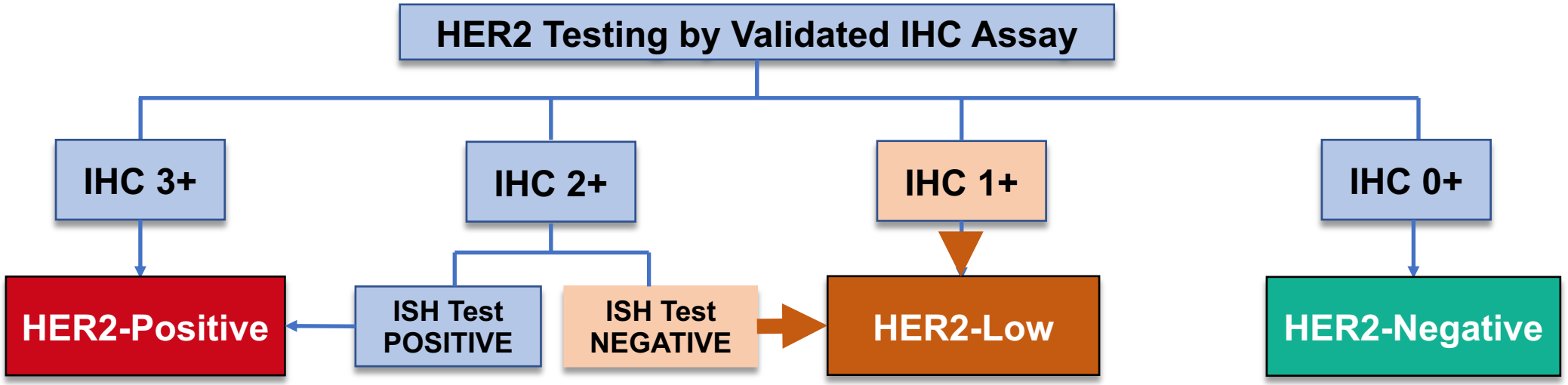
63% HER2 Low

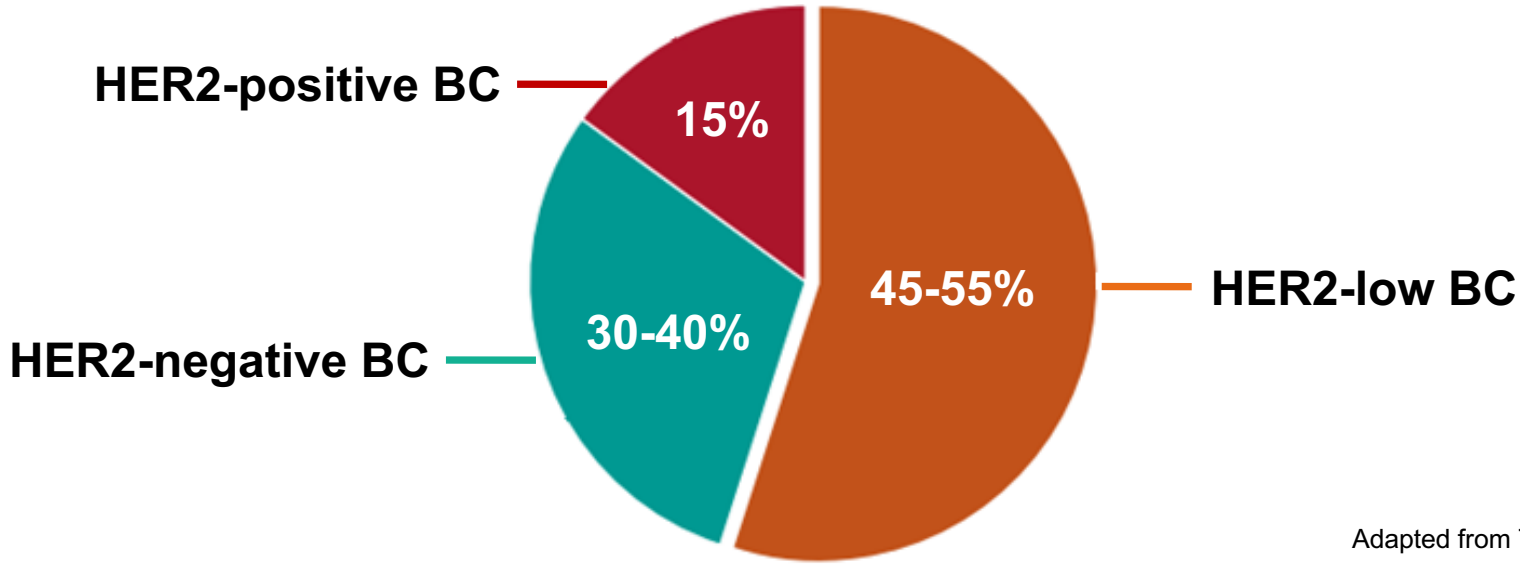


34% HER2 Low

Schettini. ESMO Breast Cancer Virtual Meeting 2020. Abstr 23P. Slide courtesy of Aleix Prat.

Defining HER2-low BC: Is it a New Subtype





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

Do HER2 Low Tumors Have Worse Prognosis?

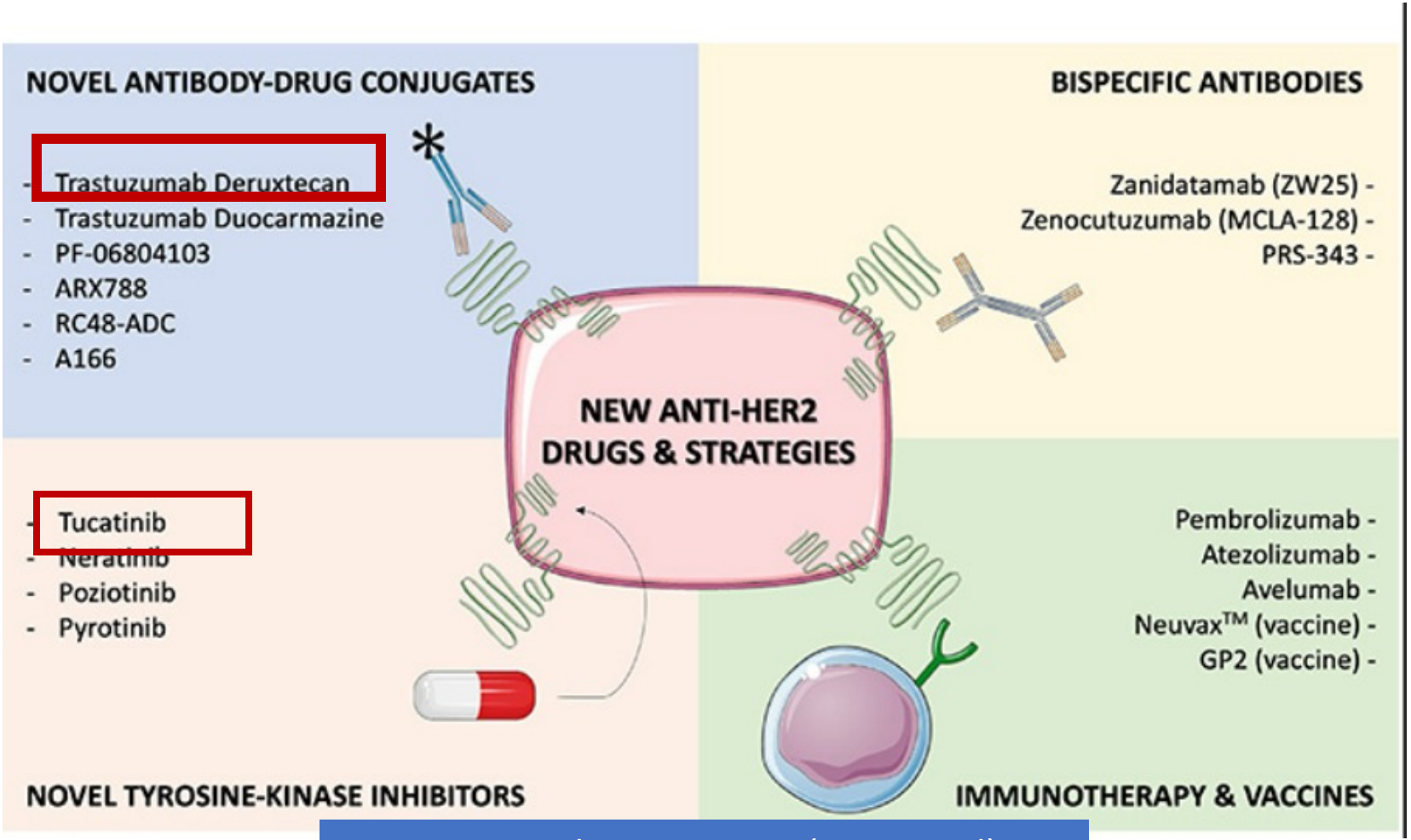
- Prognostic significance of HER2 expression in HER2 low tumors has been evaluated retrospectively in different patient groups, with conflicting results.
- Prognostic significance may vary among HR positive and Her2 negative tumors
- Data are limited by lack of prospective data

Take Home Points for Breast Cancer Subtypes

- HER2 positivity has been a defining criteria for distinguishing various breast cancers with prognostic and predictive implications
- Although we may disagree on whether HER2 low is an independent subtype, very clear therapeutic implications as we will discuss today.
- Expansion of therapeutic options for both previously identified HR positive and TNBC tumors.

Therapeutic Advances HER2 +

Evolving Therapeutic Strategies for HER2 positive MBC



Patritumab Deruxtecan (HER3-DXd)

Tarantino P et al Exp Target Antitumor, 2021

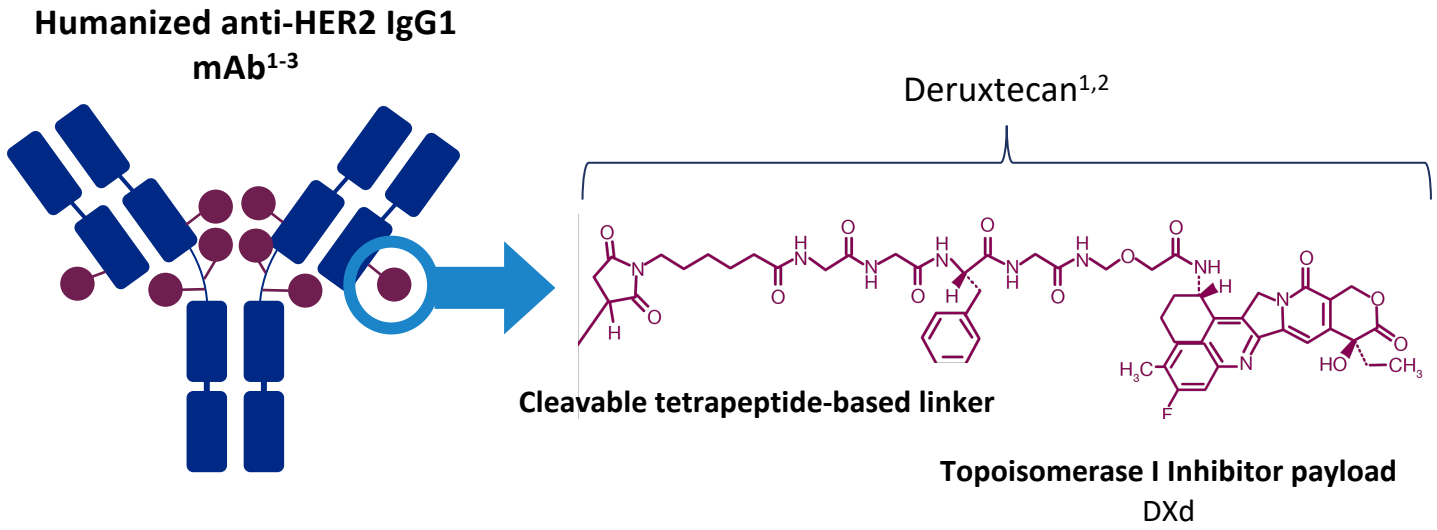
T-DXD

T-DXd is an ADC composed of 3 components[1,2]

A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab, covalently linked to:

A topoisomerase I inhibitor payload, an exatecan derivative, via

A tetrapeptide-based cleavable linker



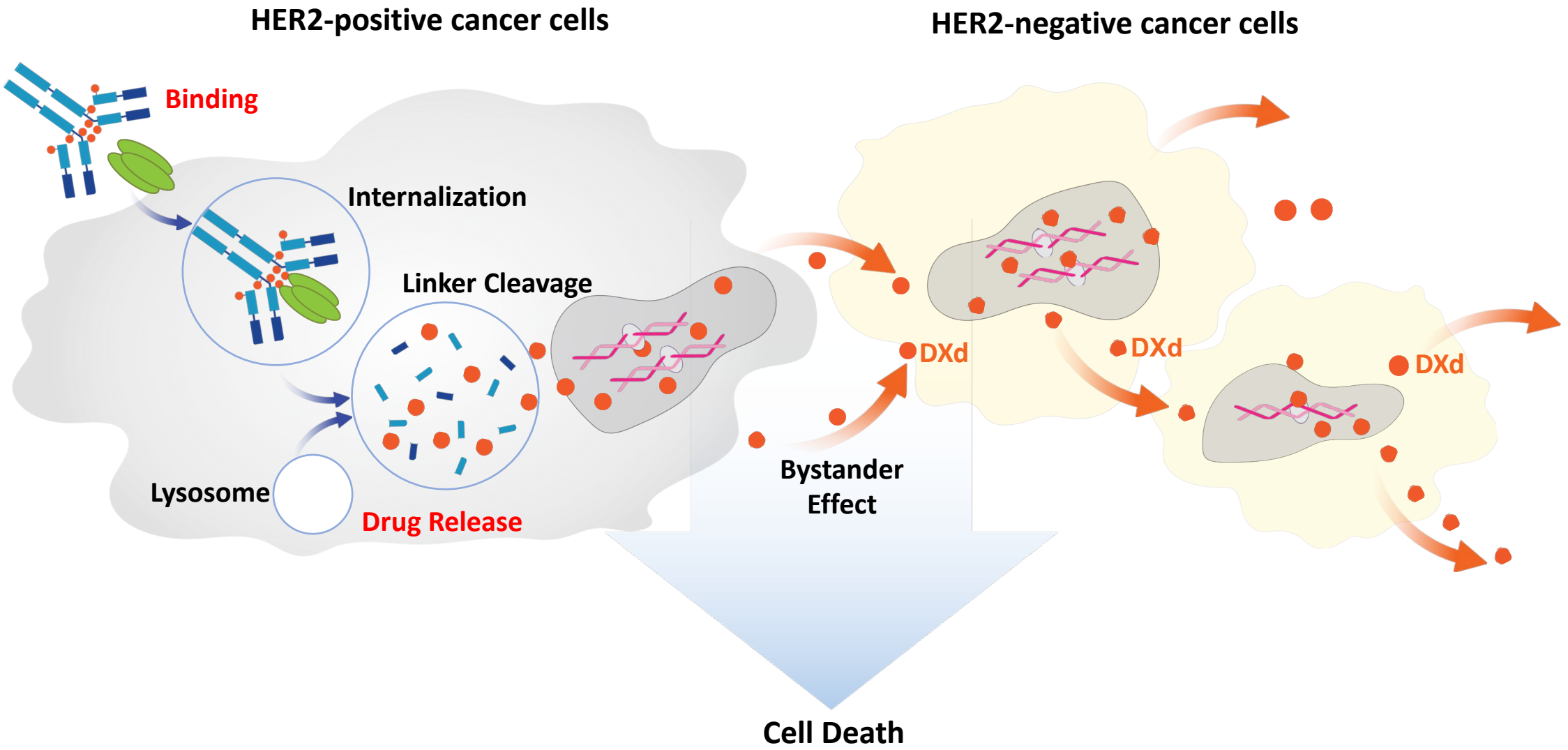
- Payload mechanism of action: topoisomerase I inhibitor[a,1,2]
- High potency of payload[a,1,2]
- High drug-to-antibody ratio, ≈8[a,1,2]
- Payload with short systemic half-life[a,1,2]
- Stable linker-payload[a,1,2]
- Tumor-selective cleavable linker[a,1,2]
- Bystander antitumor effect[a,1,4]

ADC, antibody-drug conjugate; DXd, DX-8951f derivative; HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; mAB, monoclonal antibody; T-DXd, trastuzumab deruxtecan.

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

1. Nakada T et al. *Chem Pharm Bull (Tokyo).* 2019;67:173-185. 2. Ogitani Y et al. *Clin Cancer Res.* 2016;22:5097-5108. 3. Trail PA et al. *Pharmacol Ther.* 2018;181:126-142. 4. Ogitani Y et al. *Cancer Sci.* 2016;107:1039-1046.

T-DXd Mechanism of Action



Adapted from: Mosele, MF. Presented at ESMO Breast Cancer Congress. May 4, 2022. Abstract LBA1

15:05 - 16:35 Presidential symposium 1

CHAIRS : ANDRÉS CERVANTES, SOLANGE PETERS

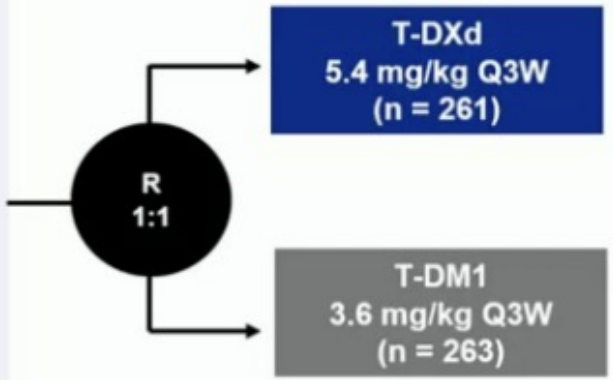
DESTINY-Breast03

DESTINY-Breast03: First Randomized Ph3 Study of T-DXd

An open-label, multicenter study (NCT03529110)

Patients
- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

Stratification factors
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Interim analysis for PFS (data cutoff: May 21, 2021)
- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

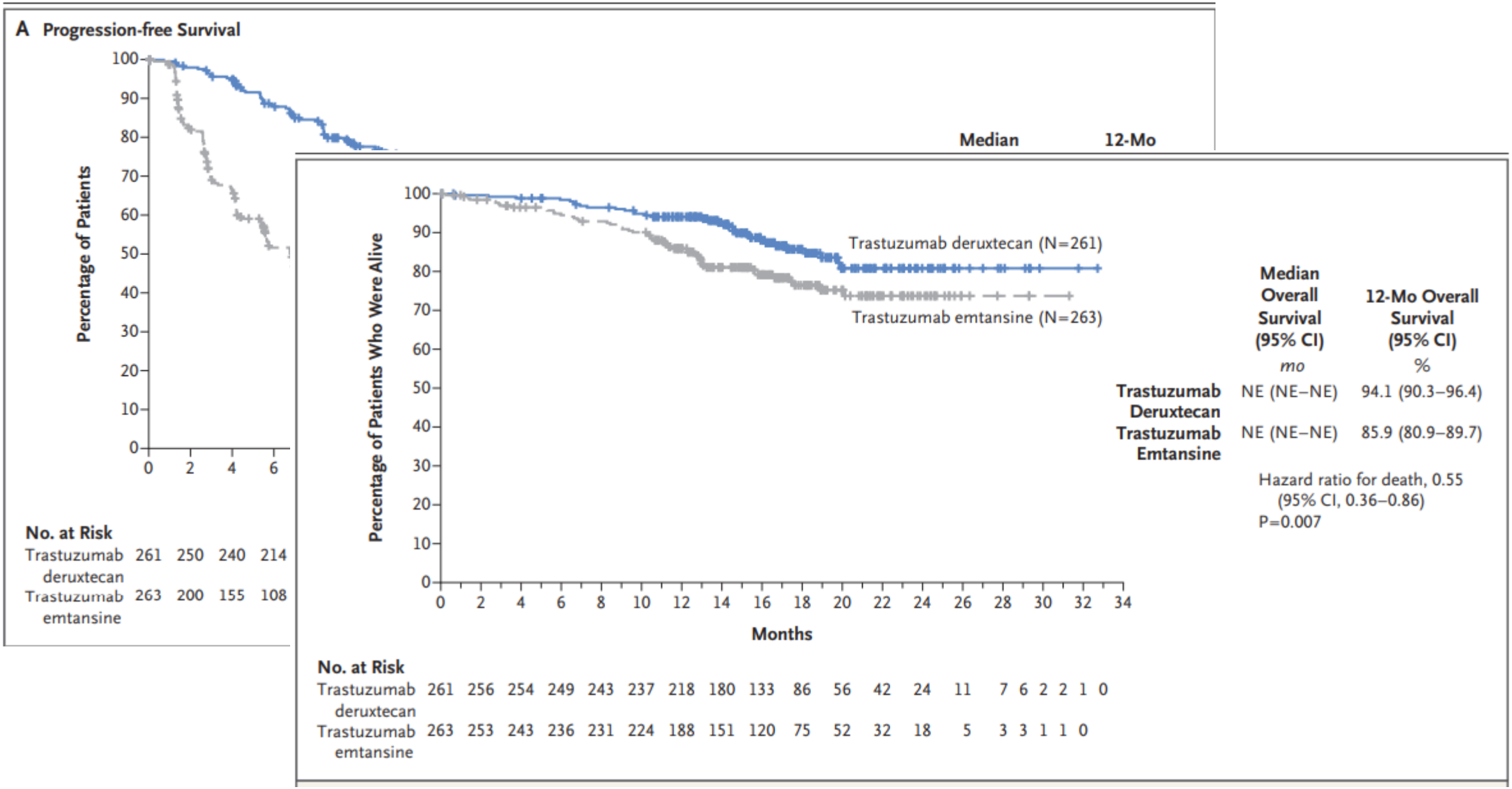
Key secondary endpoint, OS: boundary for efficacy: $P < 0.000265$ (based on 86 events)

2021 ESMO congress

BICR, blinded independent central review; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Ph3, phase 3; Q3W, every 3 weeks.
[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane

Javier Cortés

Trastuzumab Deruxtecan (T-DXd) vs Trastuzumab Emtansine (T-DM1) in Patients (Pts) With HER2+ Metastatic Breast Cancer (mBC): Results of the Randomized Phase 3 DESTINY-Breast03 Study



Cortes, et al NEJM, 2022

2022 ASCO ANNUAL MEETING

Trastuzumab Deruxtecan vs Trastuzumab Emtansine in Patients With HER2-Positive Unresectable and/or Metastatic Breast Cancer: Safety Follow-up of the Randomized, Phase 3 Study DESTINY-Breast03

Erika Hamilton, MD,[a] Vanessa Petry, Winnie Yeo, Sung-Bae Kim, Giampaolo Bianchini, Toshinari Yamashita, Kan Yonemori, Kenichi Inoue, Giuseppe Curigliano, Sara A. Hurvitz, Javier Cortés, Hiroji Iwata, Jillian Cathcart, Yali Liu, Caleb Lee, Emarjola Bako, Rachel Kim, Seock-Ah Im
On behalf of the DESTINY-Breast03 investigators

[a]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA

Safety Update Overview (September 7, 2021)

n (%)	T-DXd n = 257	T-DM1 n = 261
Patients discontinued from study treatment	141 (54.9)	222 (85.1)
Any grade TEAE	256 (99.6)	249 (95.4)
Grade ≥3 TEAE	137 (53.3)	130 (49.8)
Any grade serious TEAE	54 (21.0)	50 (19.2)
Grade ≥3 serious TEAE	39 (15.2)	38 (14.6)
TEAE associated with drug discontinuation	38 (14.8)	19 (7.3)
TEAE associated with dose reduction	59 (23.0)	36 (13.8)

- Rates of TEAEs (any grade and grade ≥3) and serious TEAEs were similar between the T-DXd and T-DM1 arms
- TEAEs associated with drug discontinuation occurred in 38 patients (14.8%) in the T-DXd arm and 19 patients (7.3%) in the T-DM1 arm

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

Drug-Related TEAEs[a] Reported in ≥20% of Patients in Either Treatment Arm

	T-DXd n = 257		T-DM1 n = 261	
n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Nausea	189 (73.5)	17 (6.6)	72 (27.6)	1 (0.4)
Fatigue	118 (45.9)	16 (6.2)	76 (29.1)	2 (0.8)
Vomiting	114 (44.4)	4 (1.6)	15 (5.7)	1 (0.4)
Neutropenia	111 (43.2)	51 (19.8)	30 (11.5)	8 (3.1)
Alopecia	97 (37.7)	1 (0.4)	7 (2.7)	0
Anemia	82 (31.9)	16 (6.2)	37 (14.2)	11 (4.2)
Leukopenia	79 (30.7)	17 (6.6)	21 (8.0)	2 (0.8)
Decreased appetite	68 (26.5)	3 (1.2)	34 (13.0)	0
Thrombocytopenia	65 (25.3)	19 (7.4)	137 (52.5)	65 (24.9)
Diarrhea	61 (23.7)	1 (0.4)	11 (4.2)	2 (0.8)
Constipation	60 (23.3)	0	25 (9.6)	0

- Most of the selected drug-related TEAEs in either treatment arm were hematologic or gastrointestinal

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse events.
Selected TEAEs (and preferred terms included): anemia (hemoglobin decreased, red blood cell count decreased, anemia, hematocrit decreased); neutropenia (neutrophil count decreased, neutropenia); thrombocytopenia (platelet count decreased, thrombocytopenia); fatigue (fatigue, asthenia, malaise).
[a]Based on nonclinical data, clinical data, epidemiology data, and reported data from drugs in a similar class (anti-HER2 therapies), selected TEAEs for T-DXd were reviewed for additional characterization.

Adjudicated Drug-Related ILD/Pneumonitis

	T-DXd n = 257	T-DM1 n = 261
Any grade, n (%)	28 (10.9)	5 (1.9)
Grade 1	7 (2.7)	4 (1.5)
Grade 2	19 (7.4)	1 (0.4)
Grade 3	2 (0.8)	0
Grade 4	0	0
Grade 5	0	0
Time to first onset, median (range), days	181 (33-507)	289 (80-499)
Outcome of worst event, n (%)		
Fatal	0	1 (20.0)[a]
Not recovered/not resolved	8 (28.6)	0
Ongoing	0	0
Recovering/resolving	2 (7.1)	0
Recovered/resolved with sequelae	2 (7.1)	0
Recovered/resolved	16 (57.1)	4 (80.0)

For this safety update:

- Majority of adjudicated ILD/pneumonitis cases were low grade and no new grade 4 or 5 events occurred in either treatment arm
- One additional grade 2 adjudicated drug-related ILD/pneumonitis occurred
- The majority of events resolved with ongoing follow-up

ILD, interstitial lung disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Patient had an event of pulmonary embolism that the investigator considered to be grade 5. This was initially reported as respiratory failure but subsequently updated to pulmonary embolism. The ILD adjudication committee adjudicated this event as drug-related grade 1 ILD/pneumonitis. The death was not evaluable for adjudication. The investigator recorded disease progression as the primary cause of death.[1]

1. Cortés J et al. *N Engl J Med.* 2022;386:1143-1154 (supplementary appendix).

Conclusions

- **No new safety signals were observed for T-DXd in patients with HER2+ mBC in this safety update,[1-3] and in-depth analysis demonstrated that:**
  - Most TEAEs were grade 1 or 2, and exposure-adjusted incidence rates of grade ≥3 TEAEs and serious TEAEs were lower with T-DXd than T-DM1
  - Risk of nausea, vomiting, fatigue, and alopecia was higher for T-DXd in the initial treatment cycles
  - Prevalence of nausea and vomiting was higher for T-DXd in the initial treatment cycles and was consistent over time for alopecia and fatigue
    - In the T-DXd arm, the increased risk and higher prevalence of these events that persisted throughout treatment duration necessitates ongoing supportive care
  - There were no additional grade 3 adjudicated ILD/pneumonitis events with T-DXd (overall rate = 0.8%), and no grade 4 or 5 events overall

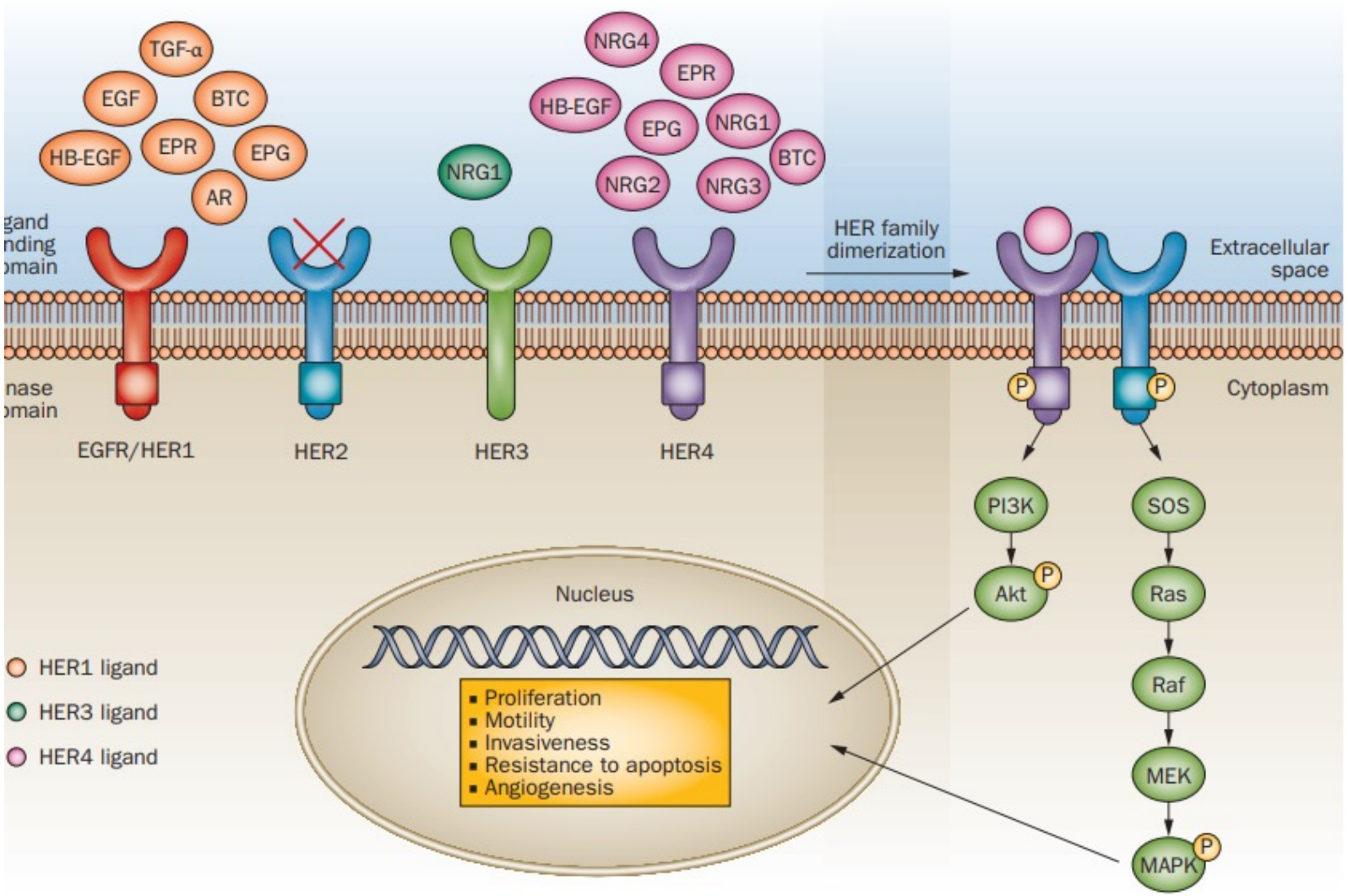
These data reinforce the established favorable benefit/risk profile of T-DXd over T-DM1 in HER2+ mBC

HER2, human epidermal growth factor receptor-2; ILD, interstitial lung disease; mBC, metastatic breast cancer; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

1. Modi S et al. *J Clin Oncol*. 2020;38:1887-1896. 2. Modi S et al. *N Engl J Med*. 2020;382:610-621. 3. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154.

OTHER EMERGING HER2/HER3 DIRECTED THERAPIES

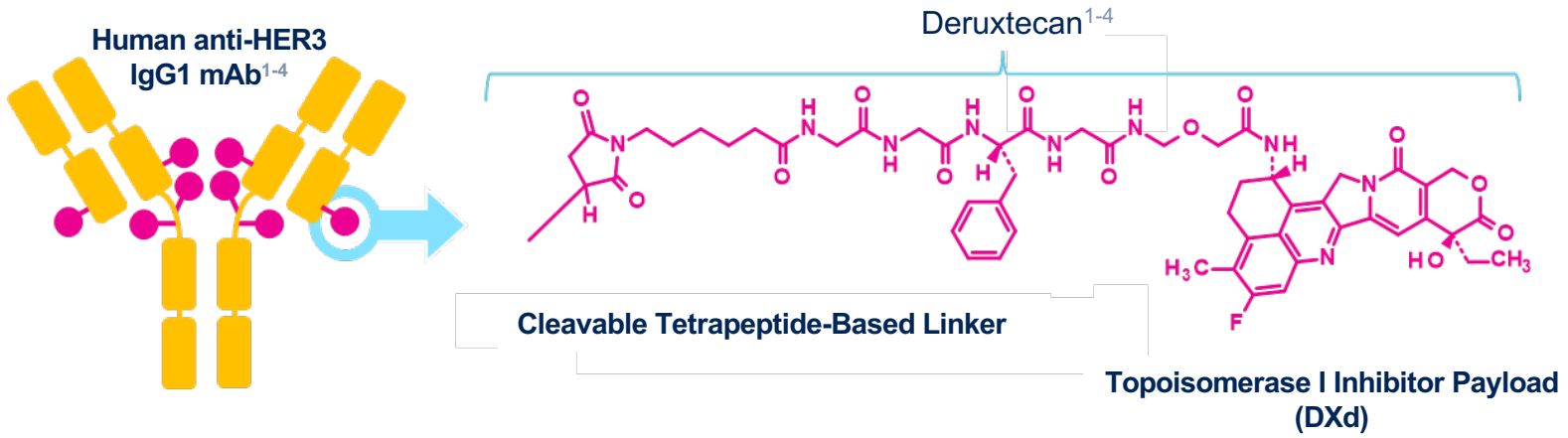
HER Family Signaling Cascades



Arteaga et al. Nature Reviews, 2012

Patritumab Deruxtecan (HER3-DXd)

- HER3-DXd is an ADC with 3 components[1-6]:
  - A fully human anti-HER3 IgG1 mAb (patritumab), covalently linked to
  - A topoisomerase I inhibitor payload, an exatecan derivative, via
  - A tetrapeptide-based cleavable linker



7 Key Attributes of HER3-DXd

- Payload mechanism of action: topoisomerase I inhibitor [a,1-4]
- High potency of payload [a,1-4]
- High drug to antibody ratio ≈ 8 [a,1,2]
- Payload with short systemic half-life [a,b,2,3]
- Stable linker-payload [a,2-4]
- Tumor-selective cleavable linker [a,1-5]
- Bystander antitumor effect [a,2,6]

HER, human epidermal growth factor receptor; IgG1, immunoglobulin G1; mAb, monoclonal antibody.
[a] The clinical relevance of these features is under investigation. [b] Based on animal data.
1. Hashimoto Y, et al. *Clin Cancer Res.* 2019;25:7151-7161. 2. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. 3. Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097-5108. 4. Koganemaru S, et al. *Mol Cancer Ther.* 2019;18:2043-2050. 5. Haratani K, et al. *J Clin Invest.* 2020;130(1):374-388. 6. Ogitani Y, et al. *Cancer Sci.* 2016;107(7):1039-1046.

Study Design

KEY ELIGIBILITY CRITERIA

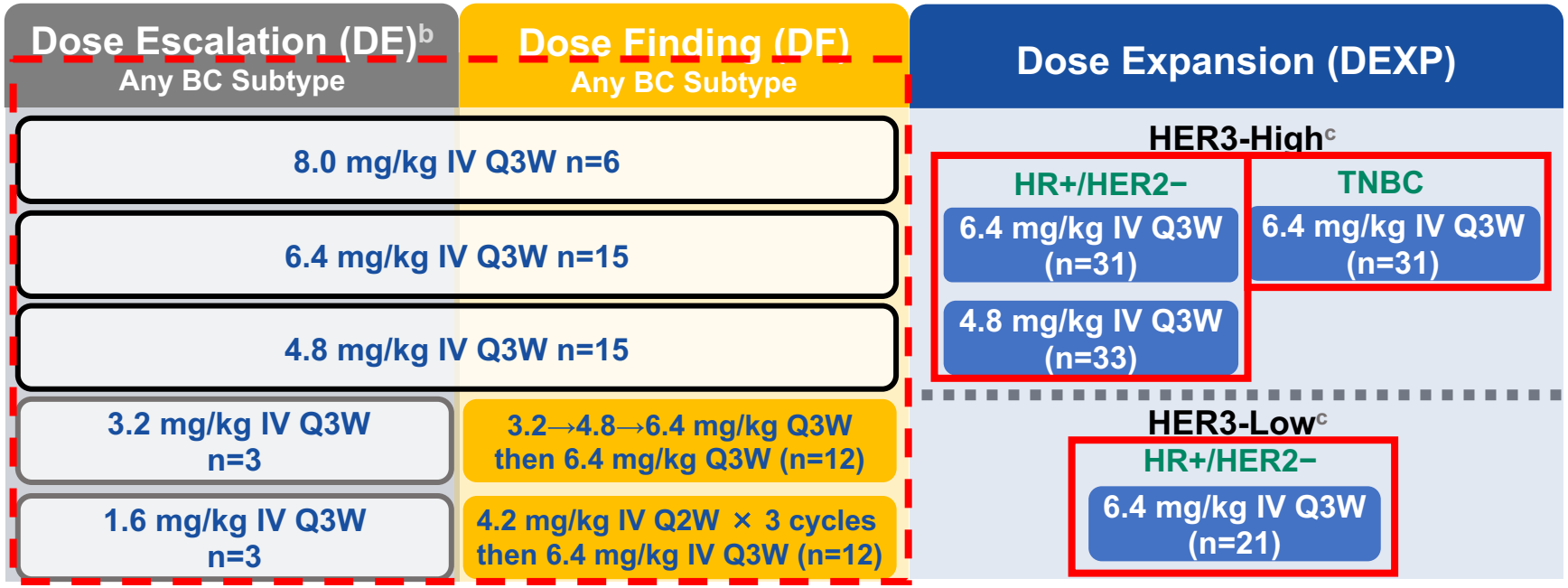
- Advanced/unresectable or metastatic breast cancer
- HER3-positive[a]

DF & DEXP (HR+/HER2−)

- ≥2 and ≤6 lines of prior chemotherapy; ≥2 for advanced disease

DEXP (TNBC)

- 1 to 2 prior chemotherapy regimens for advanced disease



Data for all 3 phases were pooled

- **Efficacy** is reported by BC subtype: HR+/HER2− (n=113), TNBC (n=53), and HER2+ (n=14)
- **Safety** is reported for patients who received HER3-DXd 4.8 mg/kg (n=48), 6.4 mg/kg (n=98), and all patients (N=182[d])

DE, dose escalation; DEXP, dose expansion; DF, dose finding; EWOC, escalation with overdose control; HR, hormone receptor; IHC, immunohistochemistry; mCRM, modified continuous reassessment method; Q2W, once every 2 weeks; Q3W, once every 3 weeks; TNBC, triple-negative breast cancer.

[a] HER3 status was determined by IHC in archival tumor tissue (pre-treatment samples [<6 months prior to HER3-DXd treatment] were used for screening when archival tissue was not available); HER3-positive was defined as IHC 2+ and IHC 3+ for DE/DF cohorts and as ≥25% membrane positivity at 10x for DEXP cohorts. [b] Guided by mCRM with EWOC. [c] HER3-high was defined as ≥75% membrane positivity at 10x; HER3-low was defined as ≥25% and <75% membrane positivity at 10x. [d] Includes two patients with unknown BC subtype.

Baseline Characteristics

		HR+/HER2− (n=113) HER3-High and -Low[a]	TNBC (n=53) HER3-High[a]	HER2+ (n=14) HER3-High[a]
Median age (range), years		55.0 (30-83)	59.0 (30-81)	58.0 (37-70)
Country, %	Japan	70.8	86.8	100.0
	USA	29.2	13.2	0.0
ECOG PS, %	0	75.4	62.3	85.7
	1	24.6	37.7	14.3
HER2 status, %[b]	HER2-zero	34.5	35.8	0.0
	HER2-low	51.3	54.7	0.0
	HER2+	0.0	0.0	100.0
	HER2 IHC 2+ (ISH unknown)	11.5	9.4	0.0
	Unknown	2.7	0.0	0.0
Presence of metastasis (BICR), %	Lung and/or Liver	90.3	64.2	85.7
	Lung	43.4	47.2	42.9
	Liver	75.2	34.0	57.1
	Brain[c]	10.6	9.4	28.6
	Bone	60.2	35.8	50.0
Median sum of diameters (BICR; range), mm		54.0 (10, 182)	44.4 (11, 186)	44.6 (17, 85)
Median number of prior cancer regimens (range), n	All regimens	7.0 (2-14)	3.0 (1-13)	6.5 (2-11)
	In advanced setting	6.0 (2-13)	2.0 (1-13)	5.5 (2-11)
	CT in advanced setting	3.0 (1-7)	2.0 (1-6)	4.0 (2-8)

Patients with HER3-expressing metastatic BC with poor prognostic characteristics were heavily pretreated.

BICR, blinded independent central review; CT, chemotherapy; DE/DF, dose escalation/dose finding; ECOG PS, Eastern Cooperative Oncology Group performance status; ISH, in situ hybridization.
[a] HER3-high was defined as ≥75% membrane positivity at 10x; HER3-low was defined as ≥25% and <75% membrane positivity at 10x. In DE/DF cohorts, IHC 2+ and 3+ were considered HER3-high. [b] HER2 status (based on medical records) was defined as: HER2-zero, IHC 0; HER2-low, IHC 1+ or 2+ (ISH−); HER2+, IHC 2+ (ISH+), IHC 3+. [c] Patients with clinically active brain metastases were excluded.

Clinical Activity of HER3-DXd Across BC Subtypes

Outcomes (BICR per RECIST 1.1)	HR+/HER2– (n=113) HER3-High and -Low	TNBC (n=53) HER3-High	HER2+ (n=14) HER3-High
Confirmed ORR, % (95% CI[a])	30.1 (21.8-39.4)	22.6 (12.3-36.2)	42.9 (17.7-71.1)
Best overall response, %[b]			
PR	30.1	22.6	42.9
SD	50.4	56.6	50.0
PD	11.5	17.0	7.1
NE	8.0	3.8	0.0
DOR, median (95% CI), mo	7.2 (5.3-NE)	5.9 (3.0-8.4)	8.3 (2.8-26.4)
PFS, median (95% CI), mo	7.4 (4.7-8.4)	5.5 (3.9-6.8)	11.0 (4.4-16.4)
6-month PFS rate, % (95% CI)	53.5 (43.4-62.6)	38.2 (24.2-52.0)	51.6 (22.1-74.8)
OS, median (95% CI), mo	14.6 (11.3-19.5)	14.6 (11.2-17.2)	19.5 (12.2-NE)

HER3-DXd demonstrated durable antitumor activity across BC subtypes

- Confirmed ORR for all patients (N=182), 28.6% (95% CI, 22.1%-35.7%); median DOR, 7.0 mo (95% CI, 5.5-8.5 months)

CR, complete response; DOR, duration of response; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.
[a] 95% exact binomial confidence interval (by Clopper-Pearson method).
[b] No patients had a CR.

TEAEs in Patients Treated with 4.8 mg/kg and 6.4 mg/kg

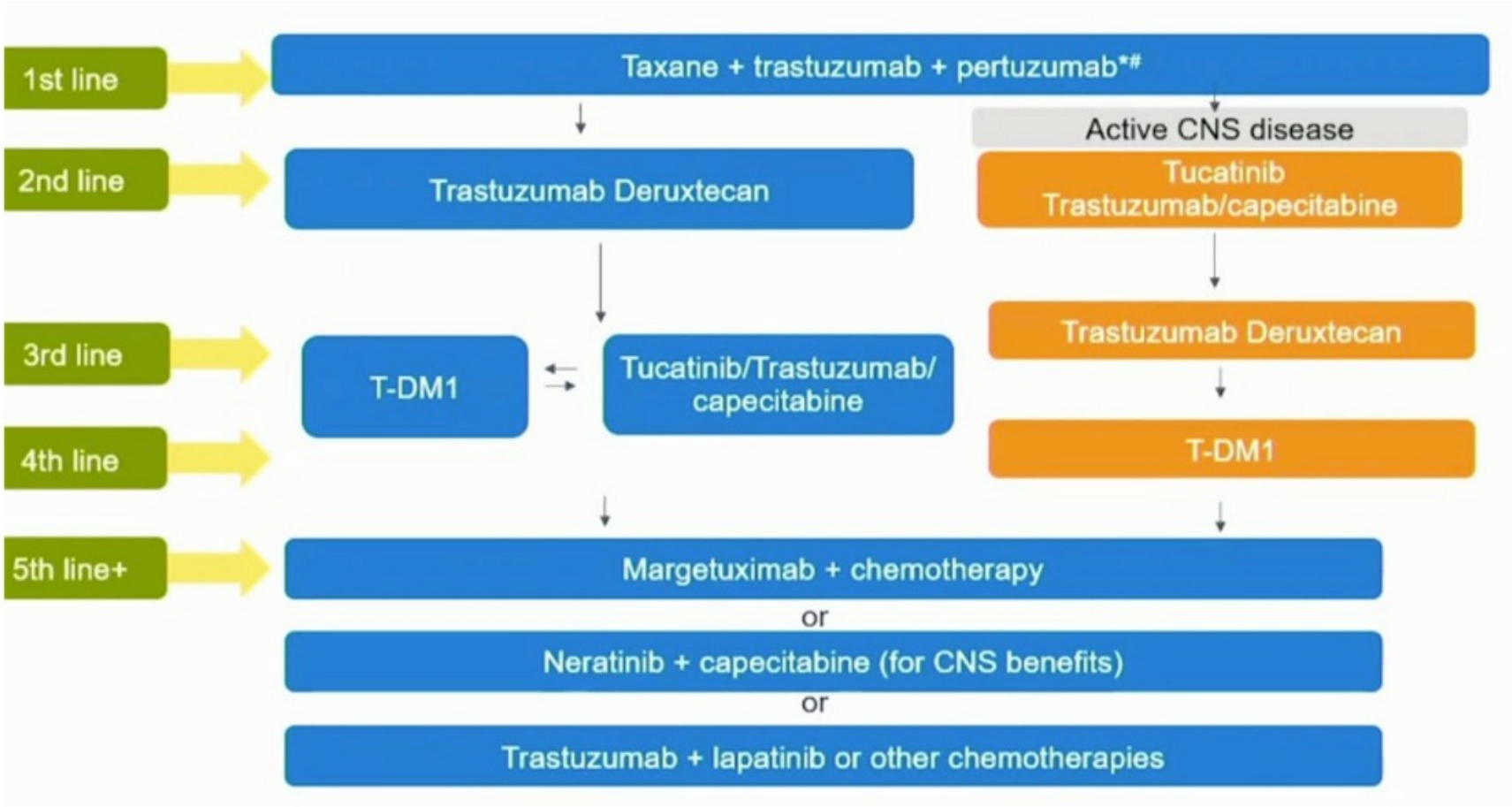
- GI and hematologic toxicity were the most common TEAEs
- Rates of non-hematologic toxicity were similar at both doses and generally low grade
- Rates of grade ≥3 neutropenia, thrombocytopenia and leukopenia were numerically higher at 6.4 mg/kg vs 4.8 mg/kg
  - All events were managed by dose delay or reduction and were not associated with treatment discontinuation
  - No grade ≥3 TEAE of thrombocytopenia resulted in a grade ≥3 bleeding event

ILD rate: 6.6% (0.5% Grade 5)

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

GI, gastrointestinal; NA, not applicable.
[a] Grouped terms: platelet count decreased (platelet count decreased, thrombocytopenia); neutrophil count decreased (neutrophil count decreased, neutropenia); white blood cell count decreased (leukopenia, white blood cell decreased); anemia (hemoglobin decreased, red blood cell count decreased, anemia, hematocrit decreased).

Current Treatment Paradigm for Her2 Positive Metastatic Breast Cancer



Modi ESMO 21

THERAPEUTIC ADVANCES IN HER2 LOW (1+ 2+ IHC FISH NEGATIVE)

2022 ASCO ANNUAL MEETING

DESTINY-Breast04

Trastuzumab deruxtecan (T-DXd) vs treatment of physician's choice in patients with HER2-low unresectable and/or metastatic breast cancer: Results of DESTINY-Breast04, a randomized, phase 3 study

Shanu Modi Memorial Sloan Kettering Cancer Center, Memorial Hospital, New York, USA

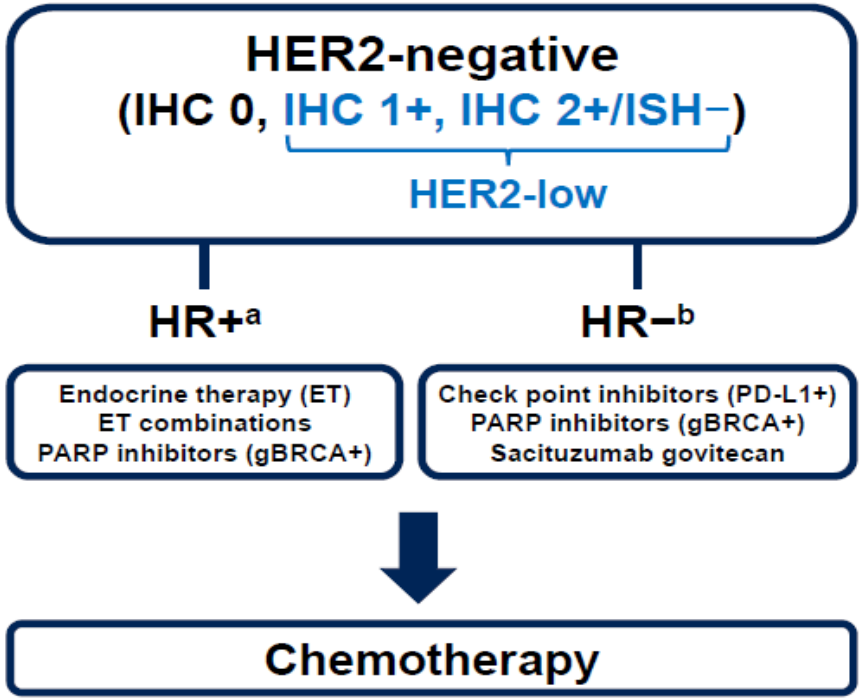
June 5, 2022

Additional authors: William Jacot, Toshinari Yamashita, Joo Hyuk Sohn, Maria Vidal, Eriko Tokunaga, Junji Tsurutani, Naoto Ueno, Yee Soo Chae, Keun Seok Lee, Naoki Niikura, Yeon Hee Park, Xiaojia Wang, Binghe Xu, Dhiraj Gambhire, Lotus Yung, Gerold Meinhardt, Yibin Wang, Nadia Harbeck, David Cameron

On behalf of the DESTINY-Breast04 investigators

HER2-low mBC: Unmet Clinical Need

Current Standard of Care



- **HER2-low mBC is defined by IHC scores of 1+ or 2+/ISH−**
  - This is a heterogenous population with a high prevalence of HR co-expression, and without a distinct biology
- **HER2-low mBC is treated as HER2− mBC with limited options for later lines of therapy[1-4]**
  - Current HER2-targeted therapies are not effective for patients with tumors that express lower levels of HER2
- **Therapeutic options for patients with HR+/HER2− mBC post-CDK4/6i progression have limited efficacy**
  - Real-world studies suggest a PFS of <4 months after progressive disease with CDK4/6i[5]
- **Limited benefit exists for patients who progress after multiple lines of chemotherapy**
  - In a pooled analysis of patients with HER2− mBC, eribulin and capecitabine provide minimal benefit with a mPFS of ~4 months and mOS of ~15 months[6]

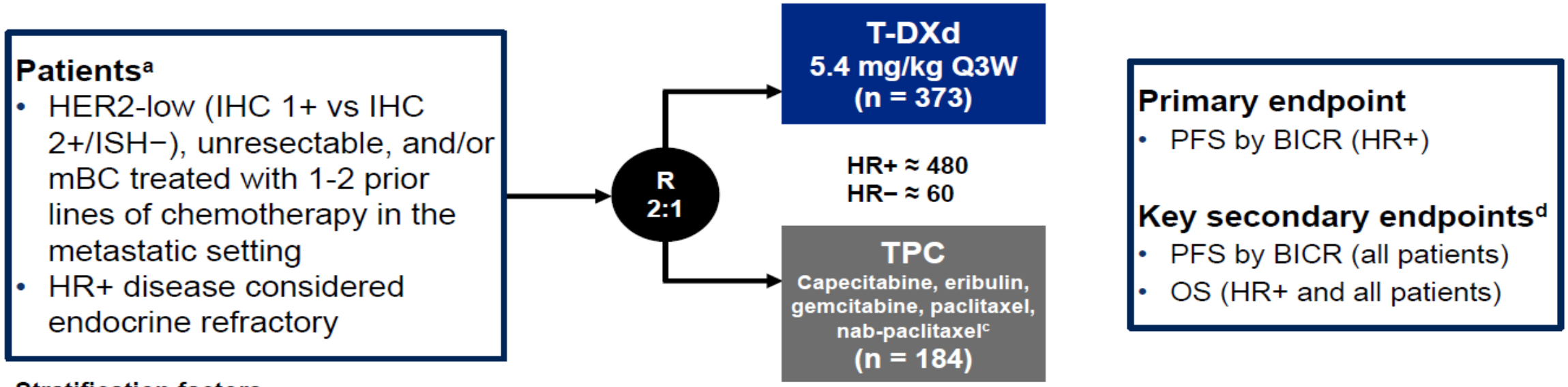
CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; bBRCA+, germline breast cancer gene positive; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PD-1, programmed cell death protein 1; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.

[a]Immunoreactive for estrogen or progesterone receptor in ≥1% tumor cell nuclei. [b]Immunoreactive for estrogen or progesterone receptor in <1% tumor cell nuclei.

1. Tarantino P, et al. *J Clin Oncol*. 2020;38(17):1951-19622. 2. Aogi K, et al. *Ann Oncol*. 2012;23:1441-8. 3. Eiger D, et al. *Cancers (Basel)*. 2021;13(5):1015. 4. Fehrenbacher L, et al. *J Clin Oncol*. 2019;38(5):444-453. 5. Mo H, et al. *Clin Breast Cancer*. 2022;22:143-8. 6. Kaufman et al. *J Clin Oncol*. 2015;33:594-601.

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

An open-label, multicenter study (NCT03734029)



Stratification factors

- Centrally assessed HER2 status[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.

PRESENTED BY:
Shanu Modi, MD

Baseline Characteristics

	Hormone receptor-positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Age, median (range), years	57 (32-80)	56 (28-80)	58 (32, 80)	56 (28, 80)
Female, n (%)	329 (99)	163 (100)	371 (99)	184 (100)
Region, n (%)				
Europe + Israel	149 (45)	73 (45)	166 (45)	85 (46)
Asia	128 (39)	60 (37)	147 (39)	66 (36)
North America	54 (16)	30 (18)	60 (16)	33 (18)
HER2 status (IHC), n (%)				
1+	193 (58)	95 (58)	215 (58)	106 (58)
2+/ISH−	138 (42)	68 (42)	158 (42)	78 (42)
ECOG performance status, %				
0	187 (56)	95 (58)	200 (54)	105 (57)
1	144 (44)	68 (42)	173 (46)	79 (43)
Hormone receptor[a], n (%)				
Positive	328 (99)	162 (99)	333 (89)	166 (90)
Negative	3 (1)	1 (1)	40 (11)	18 (10)
Brain metastases at baseline, n (%)	18 (5)	7 (4)	24 (6)	8 (4)
Liver metastases at baseline, n (%)	247 (75)	116 (71)	266 (71)	123 (67)
Lung metastases at baseline, n (%)	98 (30)	58 (36)	120 (32)	63 (34)

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Hormone receptor status is based on data collected using the interactive web/voice response system at the time of randomization, which includes mis-stratified patients.

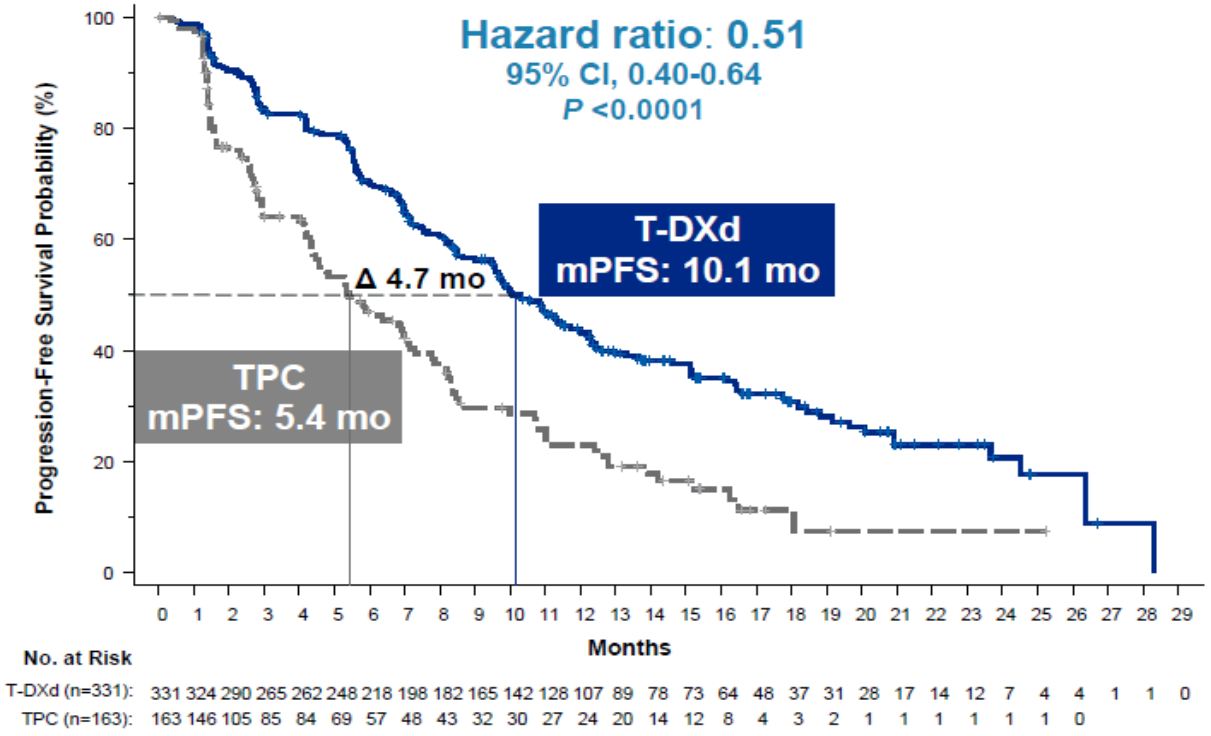
Prior Therapies

	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)				
Median number of lines (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)				
Median number of lines (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)				
Median number of lines (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)

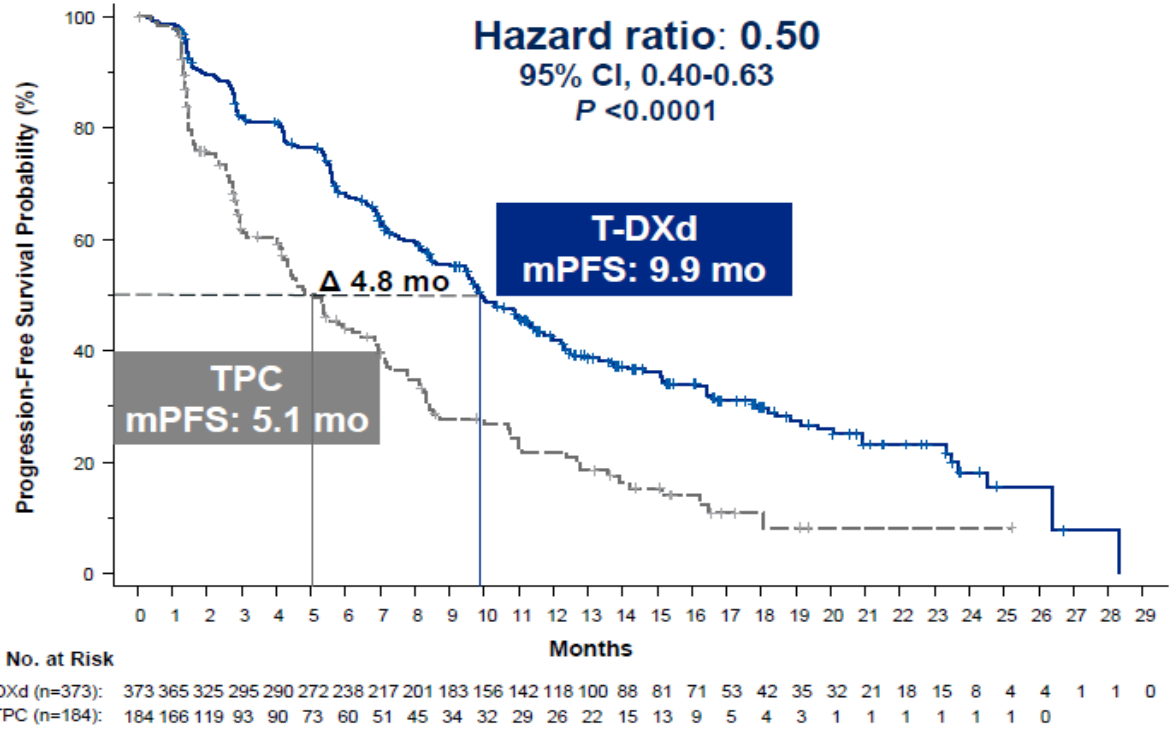
Based on derived data, which includes protocol deviations. CDK, cyclin-dependent kinase; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PFS in HR+ and All Patients

Hormone receptor-positive



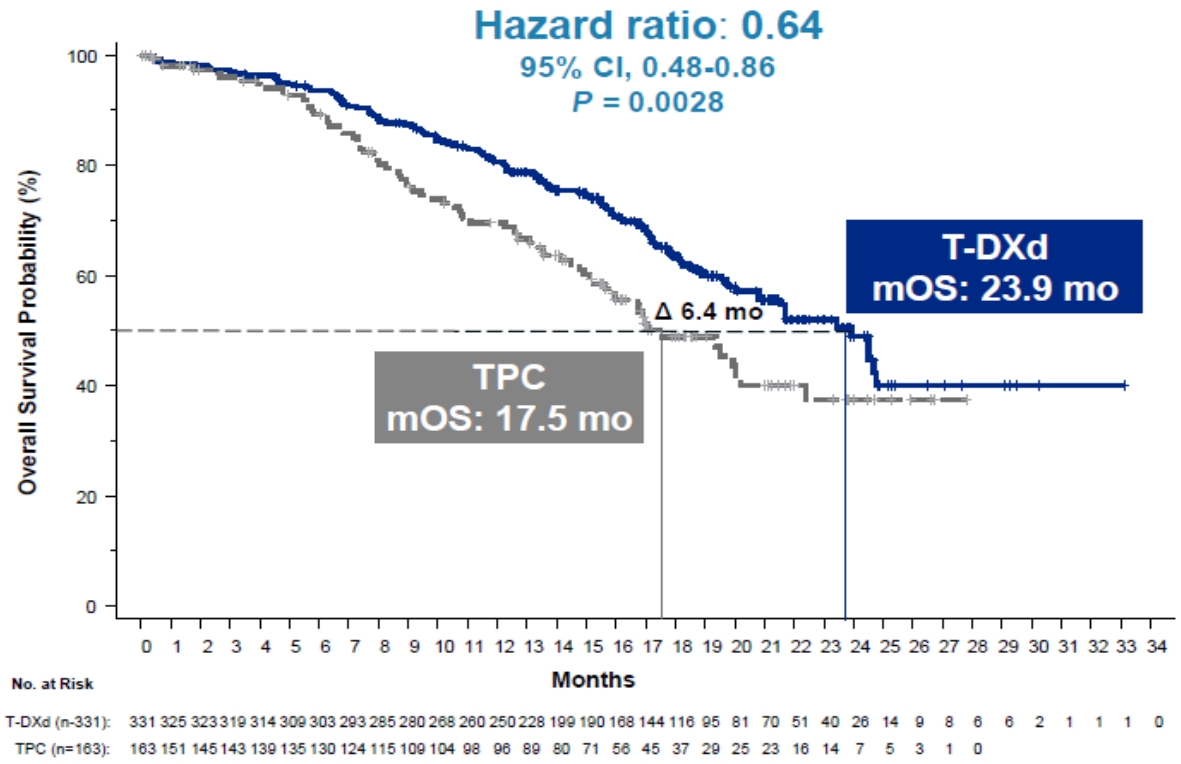
All patients



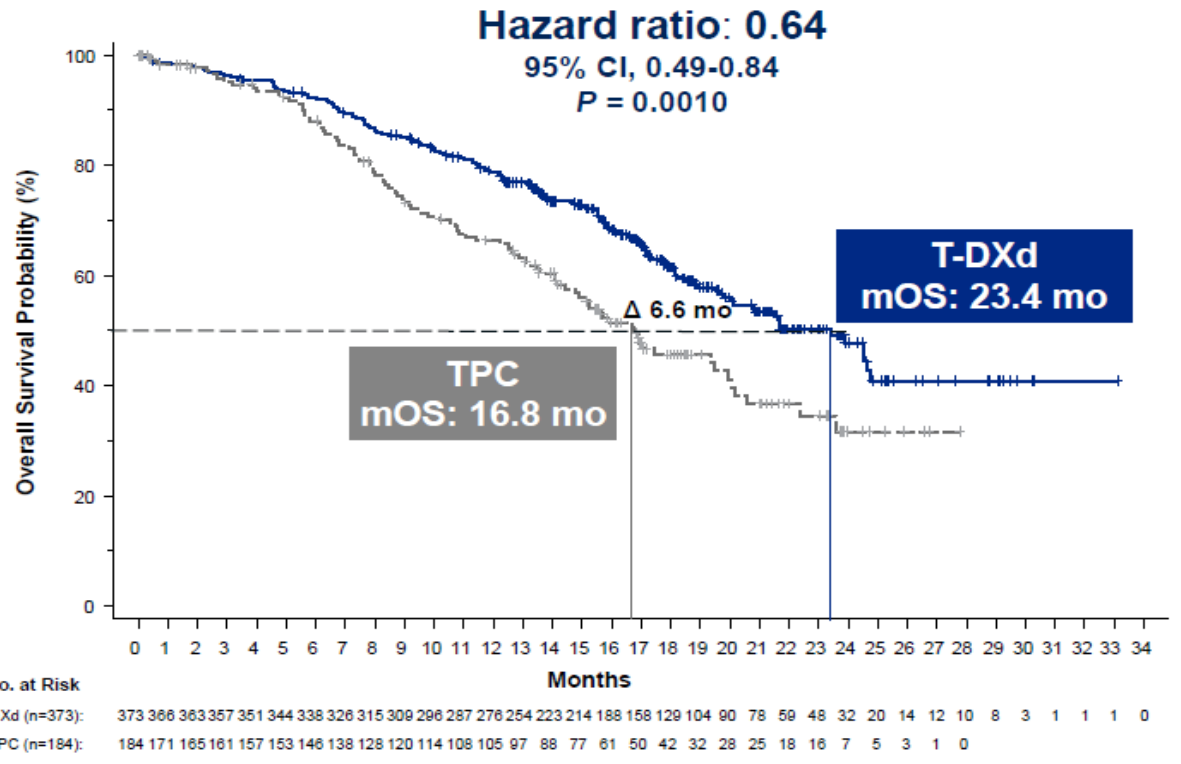
PFS by blinded independent central review.
HR, hormone receptor; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

OS in HR+ and All Patients

Hormone receptor-positive



All patients

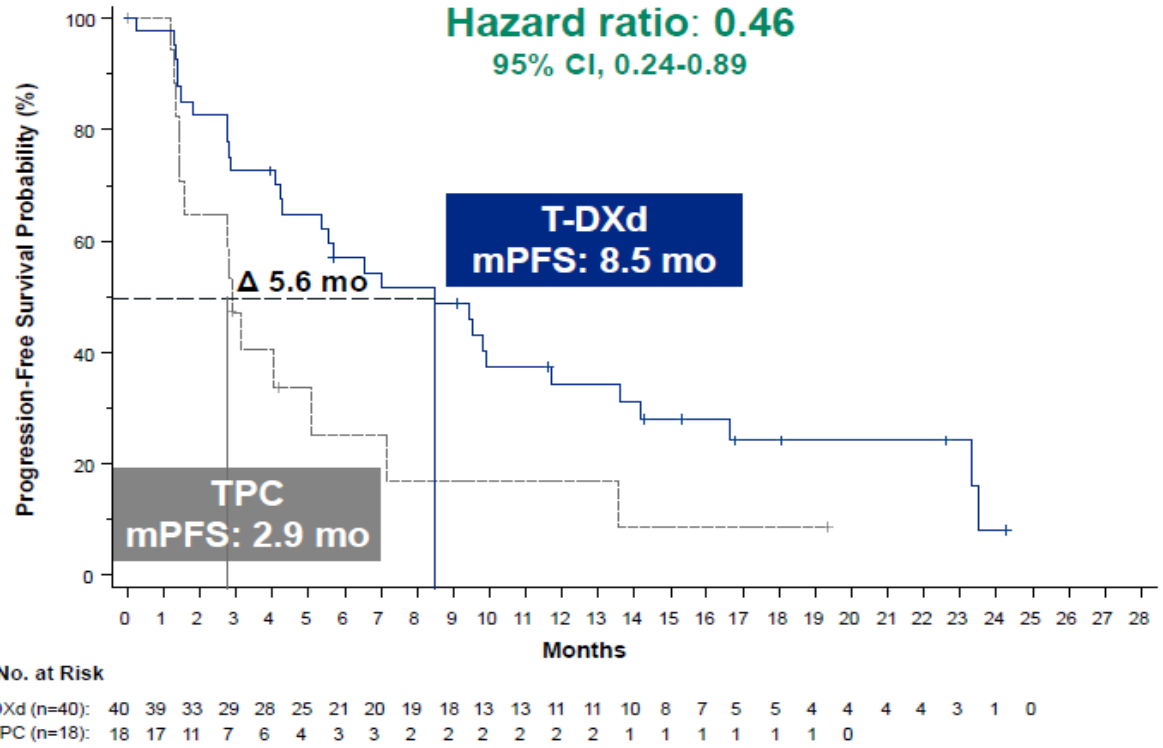


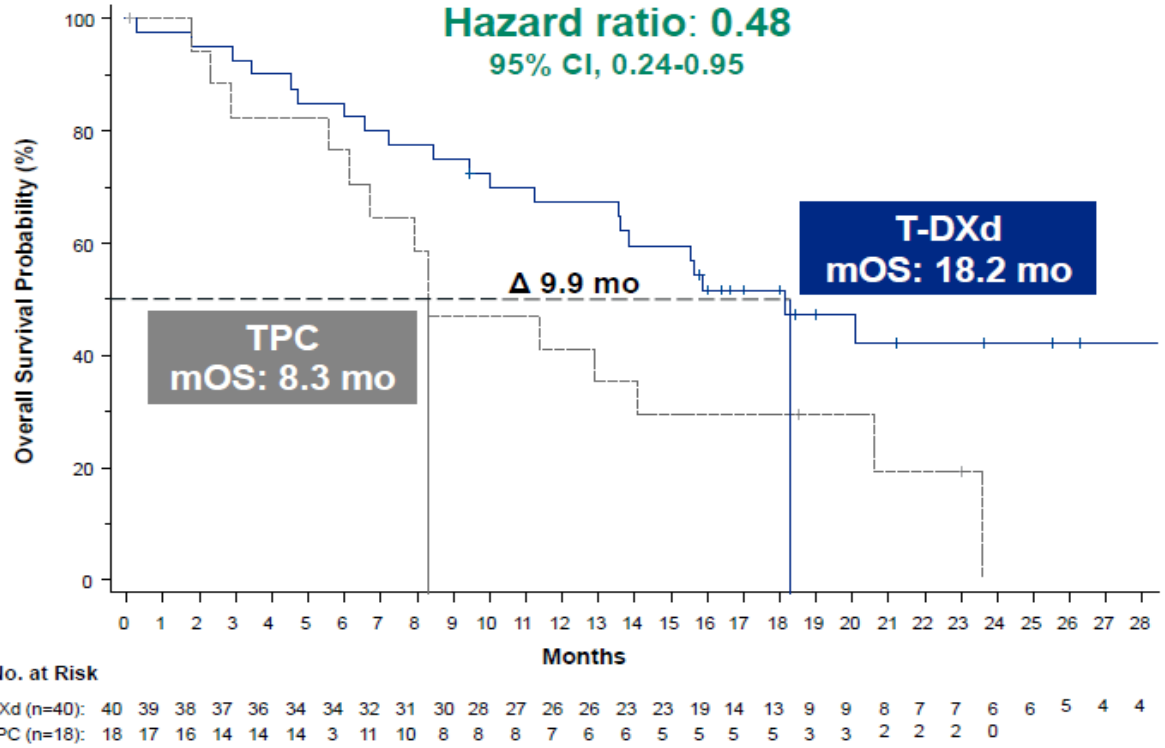
HR, hormone receptor; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PRESENTED BY:
Shanu Modi, MD

Exploratory Endpoints: PFS and OS in HR–

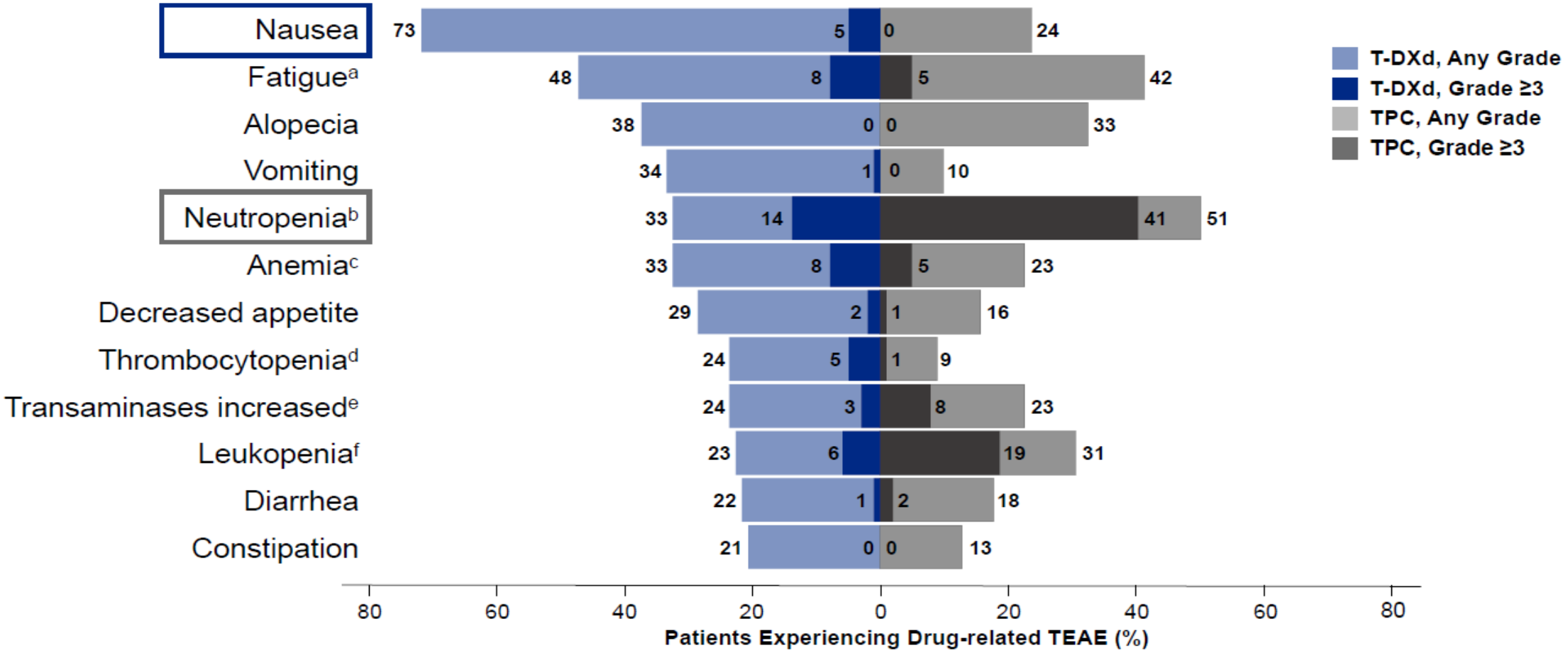
Hormone receptor-negative





HR, hormone receptor; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
For efficacy in the hormone receptor negative cohort, hormone receptor status is based on data from the electronic data capture corrected for mis-stratification.

Drug-Related TEAEs in ≥20% of Patients (Safety Analysis Set)



T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment with physician's choice.
[a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms neutrophil count decreased and neutropenia. [c]This category includes the preferred terms hemoglobin decreased, red-cell count decreased, anemia, and hematocrit decreased. [d]This category includes the preferred terms platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal. [f]This category includes the preferred terms white-cell count decreased and leukopenia.

Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis[a]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 371)	13 (3.5)	24 (6.5)	5 (1.3)	0	3 (0.8)	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)

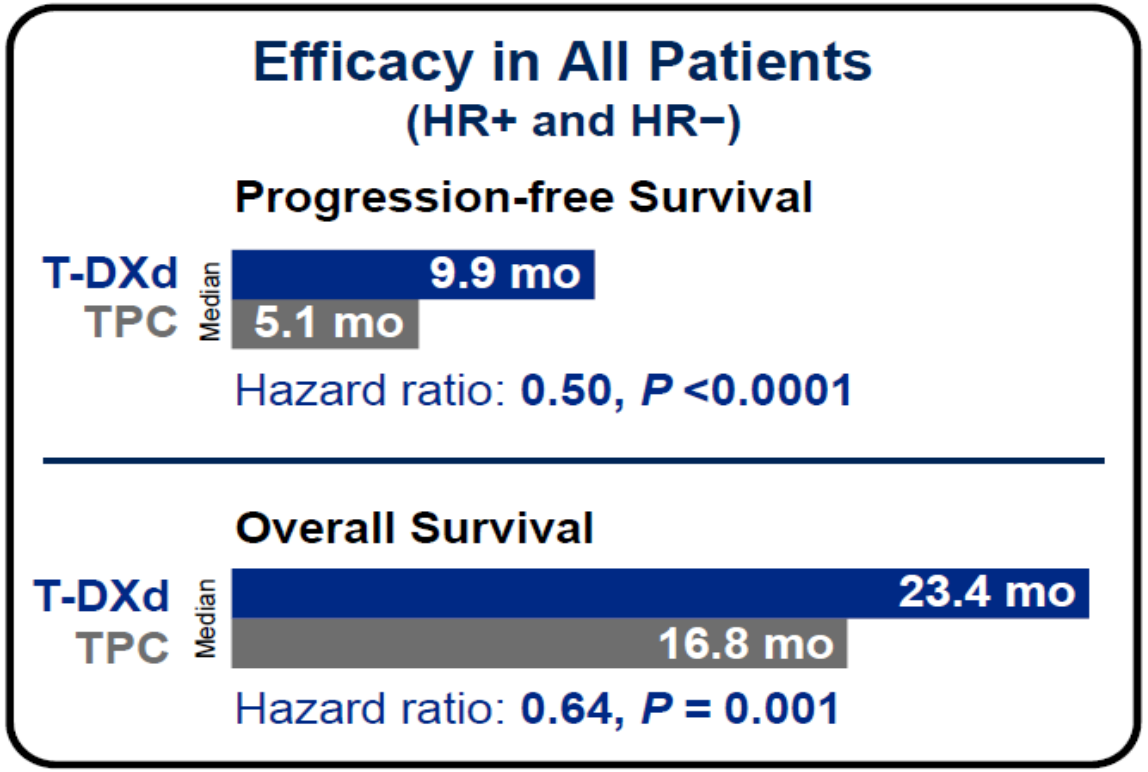
Left ventricular dysfunction[b]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
Ejection fraction decreased						
T-DXd (n = 371)	1 (0.3)	14 (3.8)	1 (0.3)	0	0	16 (4.3)
TPC (n = 172)	0	0	0	0	0	0
Cardiac failure[c]						
T-DXd (n = 371)	0	1 (0.3)	1 (0.3)	0	0	2 (0.5)
TPC (n = 172)	0	0	0	0	0	0

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TPC, treatment with physician's choice.
[a]Median time to onset of ILD/pneumonitis for patients with T-DXd was 129.0 days (range, 26-710). [b]Left ventricular dysfunction was reported in a total of 17 (4.6%) patients in the T-DXd arm. One patient initially experienced ejection fraction decrease, then later developed cardiac failure. [c]Both patients with cardiac failure were reported to have recovered.

DESTINY-Breast04 establishes T-DXd as the new standard of care in HER2-low, HR+/HR− mBC

- T-DXd is the first HER2-targeted therapy to demonstrate unprecedented statistically significant and clinically meaningful improvement in PFS and OS versus TPC
- Similar magnitude of benefit across all subgroups, including HER2 IHC status and prior CDK4/6i use
- Safety is consistent with the known safety profile and showed an overall positive benefit-risk
- DESTINY-Breast04 establishes HER2-low (IHC 1+, IHC 2+/ISH−) mBC as a new targetable patient population with T-DXd as a new standard of care



CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment with physician's choice.

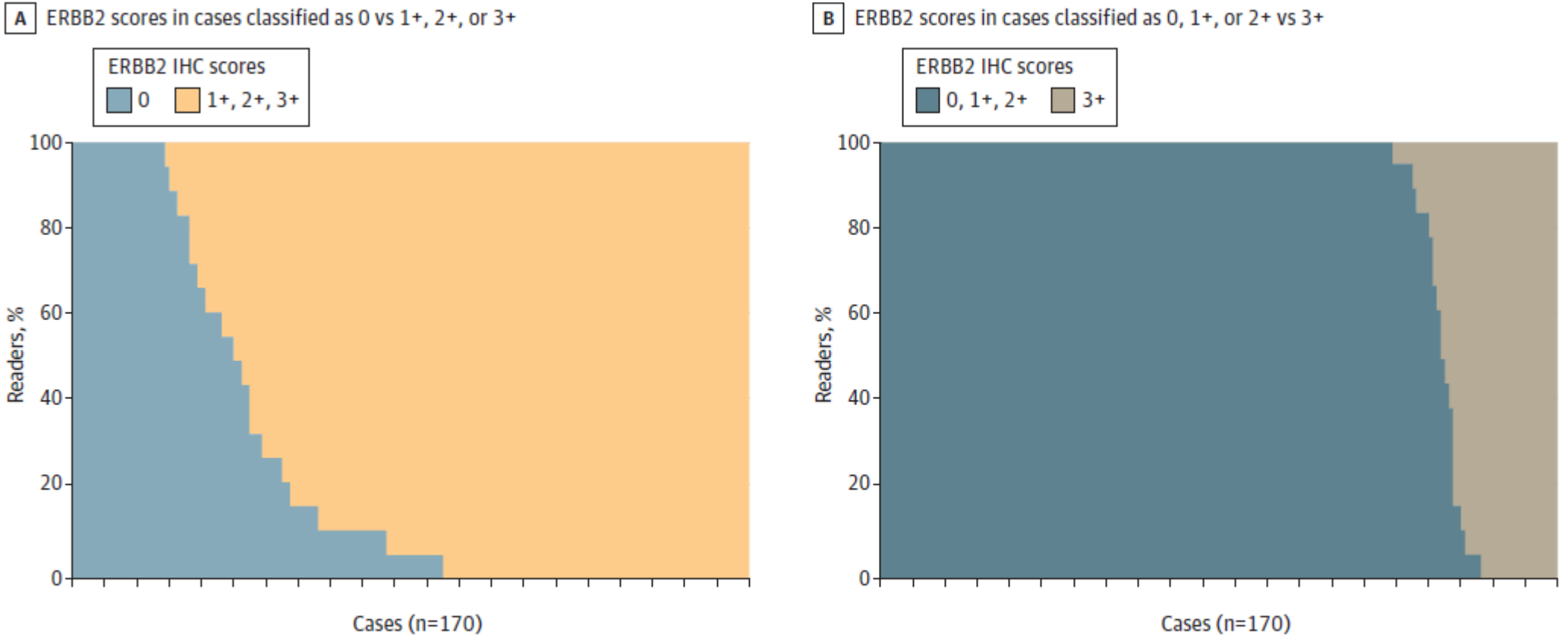
NEXT STEPS/FUTURE DIRECTIONS

With this new class of anti-cancer agents, more accurate and sensitive ways of assessing Her2 status are needed.

JAMA Oncology | Brief Report

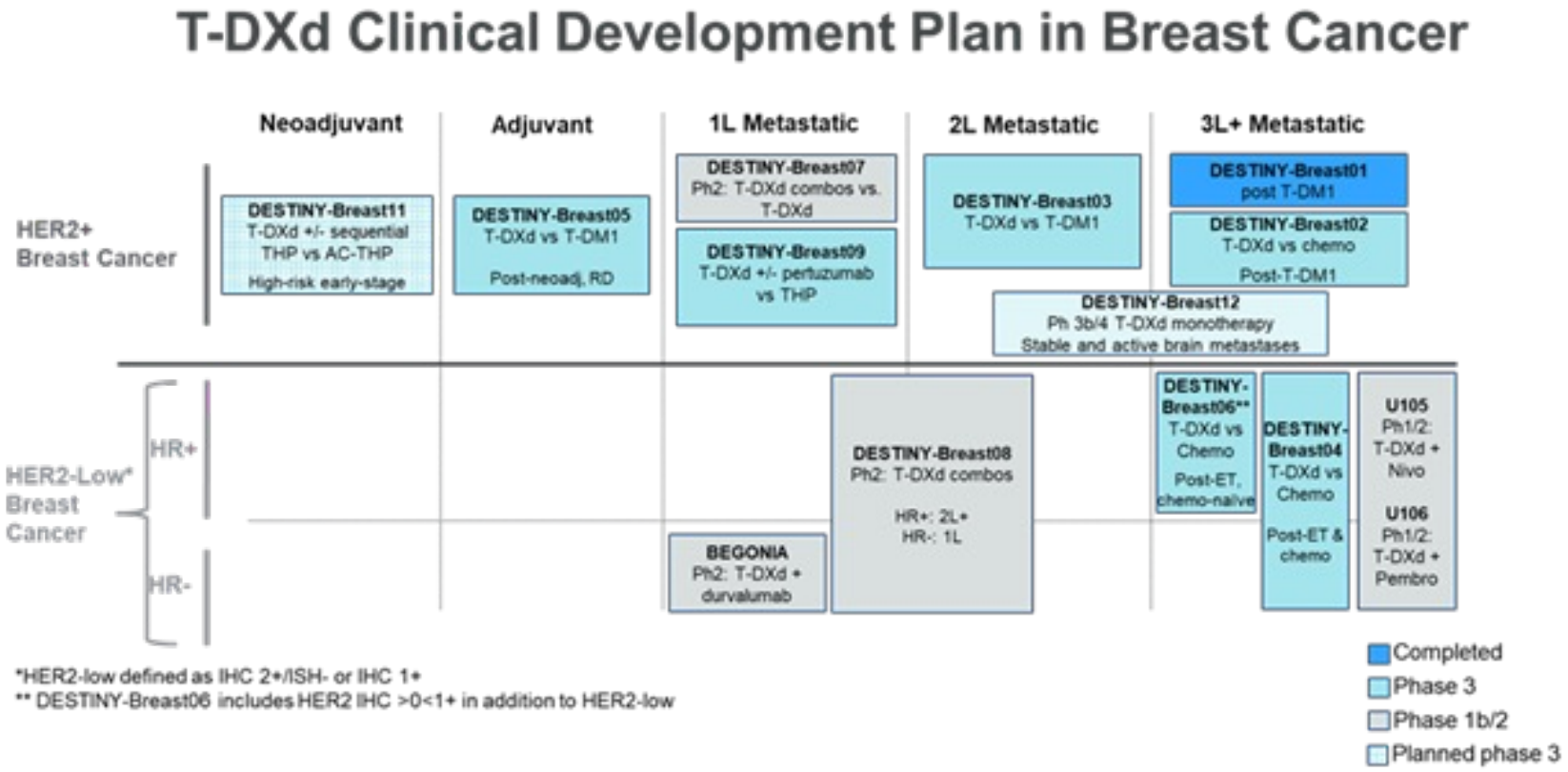
Examination of Low ERBB2 Protein Expression in Breast Cancer Tissue

Aileen I. Fernandez, PhD; Matthew Liu; Andrew Bellizzi, MD; Jane Brock, MD; Oluwole Fadare, MD; Krisztina Hanley, MD; Malini Harigopal, MD; Julie M. Jorns, MD; M. Gabriela Kuba, MD; Amy Ly, MD; Mirna Podoll, MD; Kimmie Rabe, MD; Mary Ann Sanders, MD; Kamaljeet Singh, MD; Olivia L. Snir, MD; T. Rinda Soong, MD, PhD; Shi Wei, MD; Hannah Wen, MD; Serena Wong, MD; Esther Yoon, MD; Lajos Pusztai, MD, DPhil; Emily Reisenbichler, MD; David L. Rimm, MD, PhD



A, Each case (on the x-axis) is shown as the percentage of observers who called the case ERBB2 0 vs ERBB2 1+, 2+, or 3+. B, Each case (on the x-axis) is shown as the percentage of observers who called the case ERBB2 3+ vs ERBB2 0, 1+, or 2+.

What is the Future of Her2 positive/Her2 low breast cancer



Conclusions

- The HER2 oncogene has proven to be one of the most druggable targets in oncology.
- Expect continued transformation of the traditional chemotherapy space expanded uses of ADCs.
- Better biomarker assessment for response and reliable predictors of toxicity are needed.
- Patient outcomes are improving but more is needed still and we as a community are working toward for more personalized treatment and symptom management strategies.

Thank You

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