ASCO/ESMO BC Presentation Materials

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1. **DESTINY-Breast04 data**
   - Modi S et al., ASCO 2022 #LBA3 Plenary Session
2. **Retrospective study to estimate the prevalence of HER2 low BC**
   - Viale G et al., ASCO 2022 #1087 Poster
3. **DESTINY-Breast03 safety follow up**
   - Hamilton E et al., ASCO 2022 #1000 Oral
4. **DESTINY-Breast03 patient-reported outcomes**
   - Curigliano G et al., ESMO BC 2022 #1630 Oral
5. **TUXEDO-1 primary analysis**
   - Bartsch R et al., ESMO BC 2022 #165 Mini Oral
6. **Primary analysis of Ph1b study in combination with nivolumab**
   - Hamilton E et al., ESMO BC 2022 #1620 Oral
7. **Preliminary results from DESTINY-Breast07 & 08 studies**
   - Andre F et al., ASCO 2022 #3025 Poster

ASCO/ESMO BC Presentation Materials

Dato-DXd

- **Initial results of BEGONIA study**
  – Schmid P et al., ESMO BC 2022 #166 Mini Oral

HER3-DXd

- **Results from Ph1/2 study in patients with HER3 expressing mBC**
  – Krop I et al., ASCO 2022 #1002 Oral
- **Results from Ph1 dose expansion study in patients with NSCLC without EGFR activating mutations**
  – Steuer C et al., ASCO 2022 #9017 Poster

DS-6000

- **Initial results from Ph1 study**
  – Hamilton E et al., ASCO 2022 #3002 Oral

DS-6157

- **Results from Ph1 study**
  – George S et al., ASCO 2022 #11512 Poster

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

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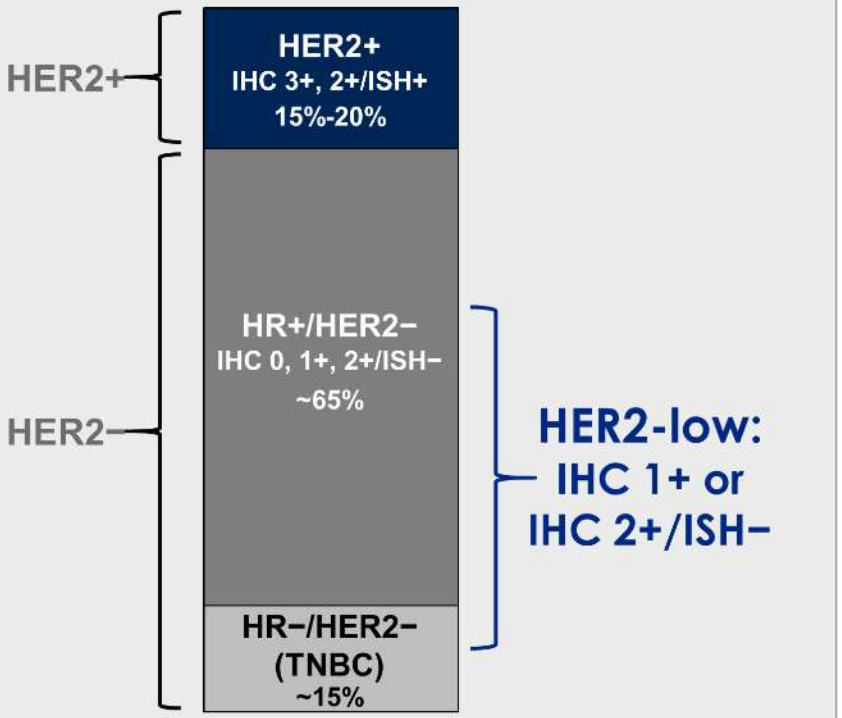
DESTINY-Breast04 Summary and Impact

DESTINY-Breast04

Daiichi-Sankyo

T-DXd treatment showed unprecedented improvement in efficacy for patients with HER2-low mBC

Current mBC paradigm[1,2]



The new mBC paradigm

- T-DXd is the first HER2-targeted therapy to demonstrate improved efficacy in HER2-low mBC
- DESTINY-Breast04 establishes T-DXd as the new standard of care for HER2-low mBC
- Potential improvement for ~50% of all mBC patients

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice.

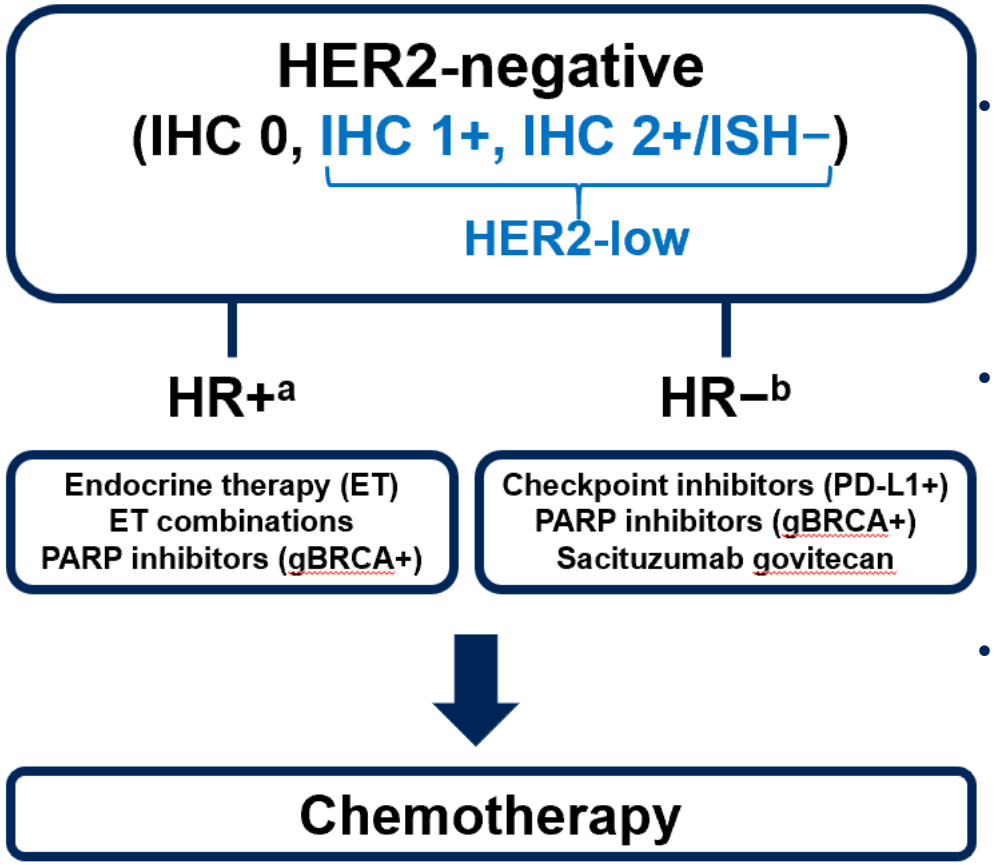
1. Schettini F, et al. *NPJ Breast Cancer*. 2021;7(1):1. 2. Tarantino P, et al. *J Clin Oncol*. 2020;38(17):1951-1962.

HER2-low mBC: Unmet Clinical Need

DESTINY-Breast04

Daiichi-Sankyo

Current Standard of Care



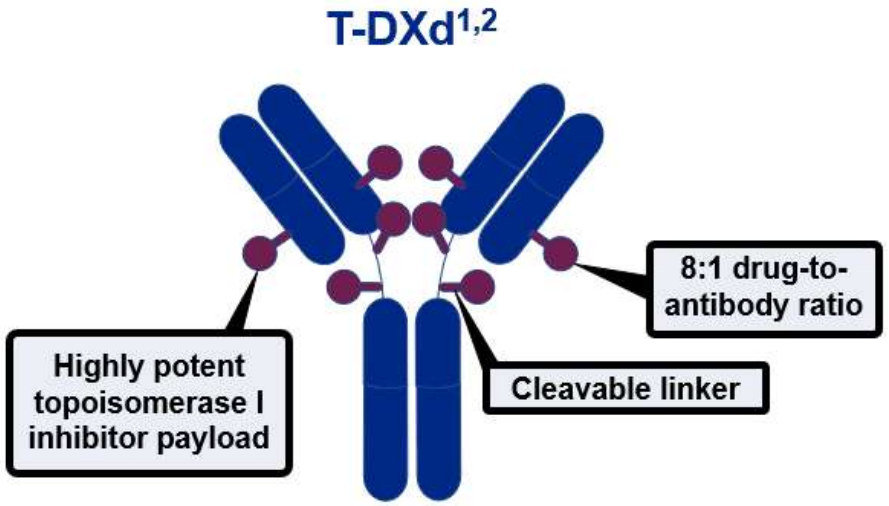
- **HER2-low mBC is defined by IHC scores of 1+ or 2+/ISH−**
  - This is a heterogenous population with a high prevalence of HR coexpression and without a distinct biology
- **HER2-low mBC is treated as HER2− mBC, with limited options for later lines of therapy[1-4]**
  - Current HER2-targeted therapies are not effective for patients with tumors that express lower levels of HER2
- **Therapeutic options for patients with HR+/HER2− mBC after 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; gBRCA+, 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; mOS, median overall survival; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed death ligand 1; mPFS, median progression-free survival; T-DXd, trastuzumab deruxtecan.

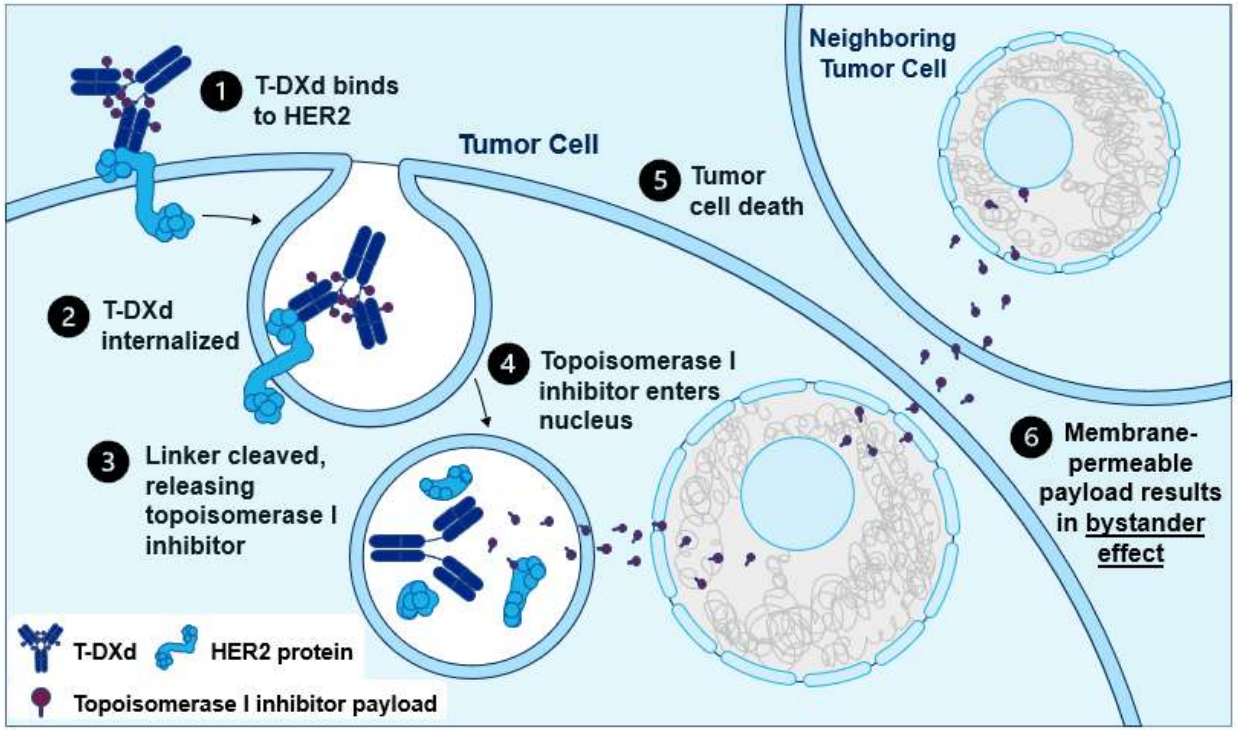
[a]Immunoreactive for estrogen or progesterone receptor in ≥1% tumor cell nuclei. [b]Immunoreactive for estrogen or progesterone receptor in <1% tumor cell nuclei.

1. Tarantino P, et al. *J Clin Oncol*. 2020;38(17):1951-1962. 2. Aogi K, et al. *Ann Oncol.* 2012;23:1441-1448. 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;22:143-148. 6. Kaufman PA, et al. *J Clin Oncol.* 2015;33:594-601.

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[1,2]



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

- **Results from a phase 1b study have reported efficacy of T-DXd in heavily pretreated patients (N = 54) with HER2-low mBC, with a mPFS of 11.1 months and an ORR of 37.0%[3]**

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;67:173-185. 2. Ogitani Y, et al. *Clin Cancer Res.* 2016;22:5097-5108. 3. Modi S, et al. *J Clin Oncol.* 2020;38:1887-1896.

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

DESTINY-Breast04

Daiichi-Sankyo

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

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

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

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

DESTINY-Breast04: Statistical Analysis and Hierarchical Testing

DESTINY-Breast04

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Hierarchical testing

PFS in HR+

⬇

PFS in all patients

⬇

OS in HR+

⬇

OS in all patients

Primary analysis for PFS by BICR (planned after at least 318 events)

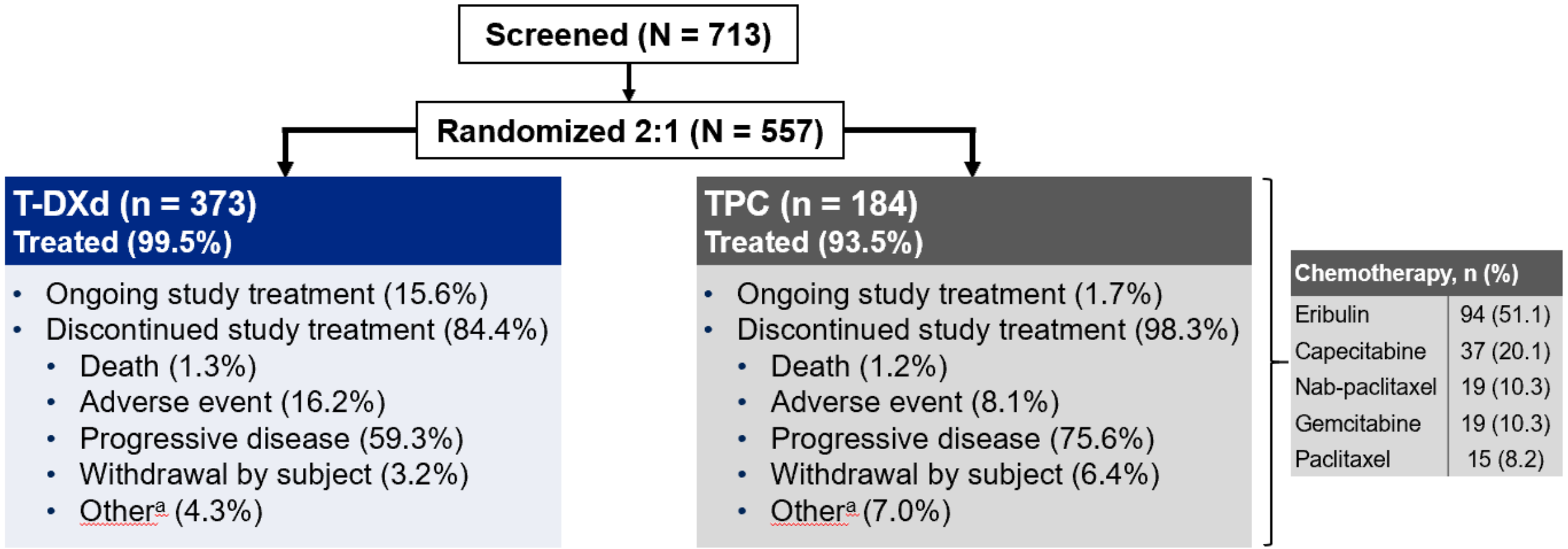
- At data cutoff (January 11, 2022), there were 321 and 370 BICR-assessed PFS events in the HR+ cohort and in all patients, respectively
- At data cutoff, 61 patients remained on treatment (58 on T-DXd and 3 on TPC), and median follow-up was 18.4 months

OS analysis

- 199 events in the HR+ cohort and 239 events in all patients
- Stopping boundary for first interim OS analysis:
  - Efficacy boundary for superiority: $P < 0.0075$

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

Patient Disposition



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

T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Other includes clinical progression, physician decision, lost to follow-up, and other unknown reasons.

Baseline Characteristics

DESTINY-Breast04

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	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 misstratified patients.

Prior Therapies

DESTINY-Breast04

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

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

PFS in HR+ and All Patients

DESTINY-Breast04

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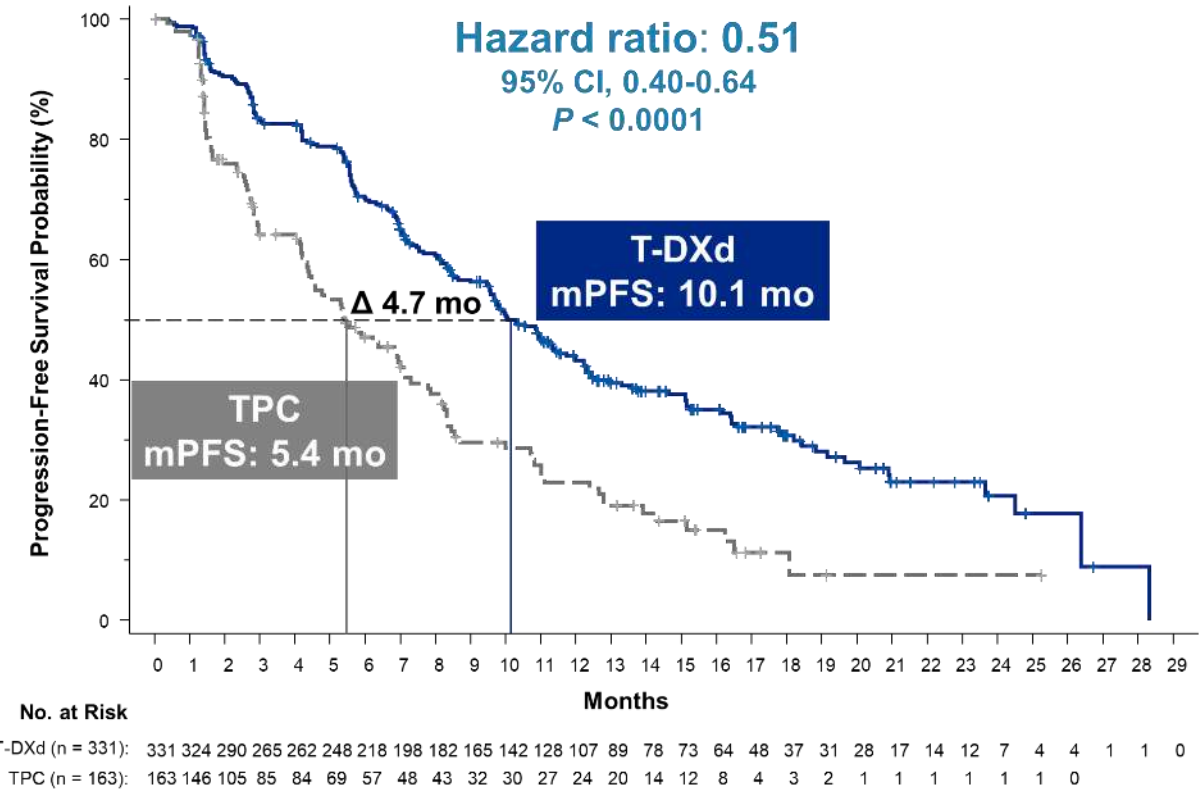
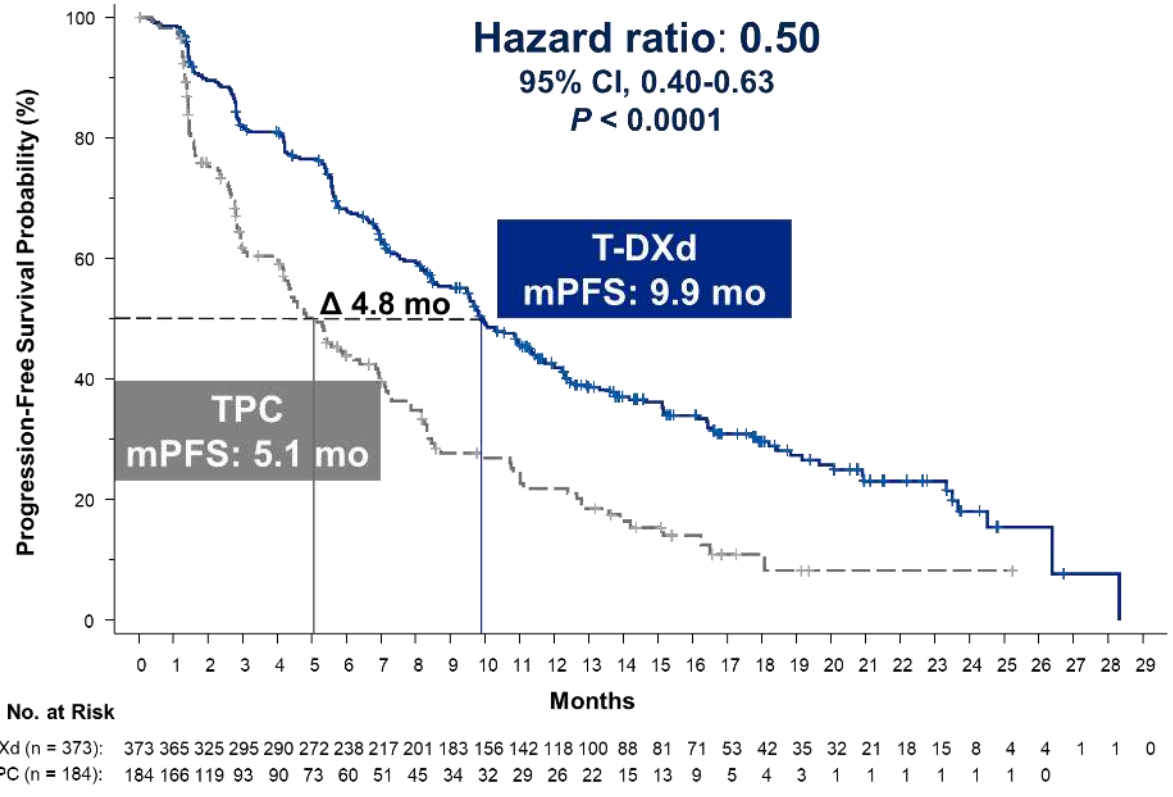
Hormone receptor–positive



All patients



PFS by blinded independent central review.

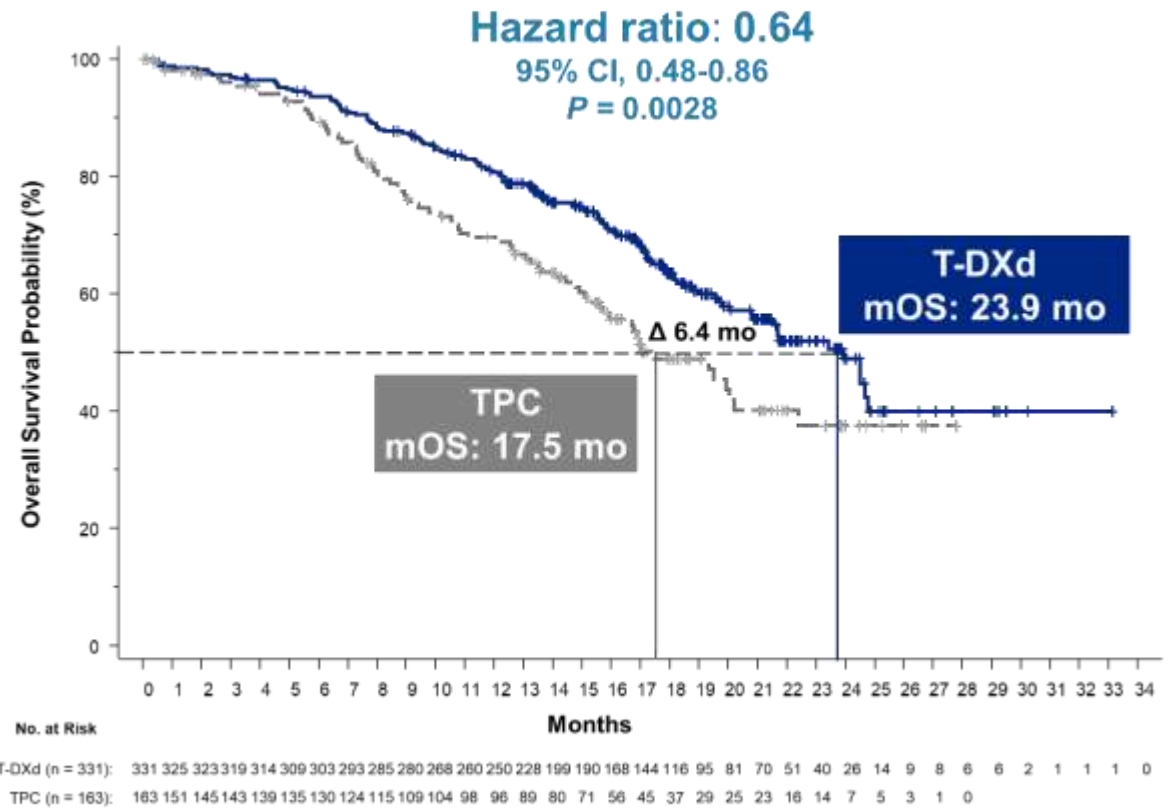
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

OS in HR+ and All Patients

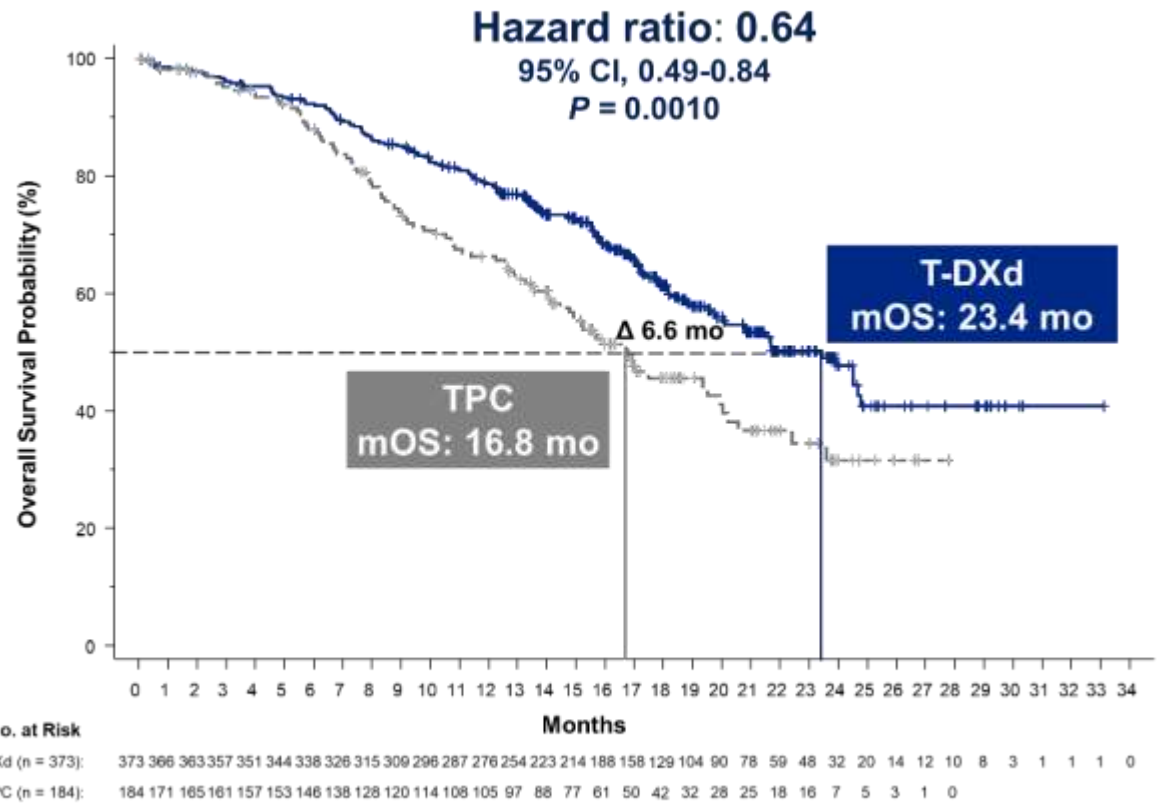
DESTINY-Breast04

Daiichi-Sankyo

Hormone receptor–positive



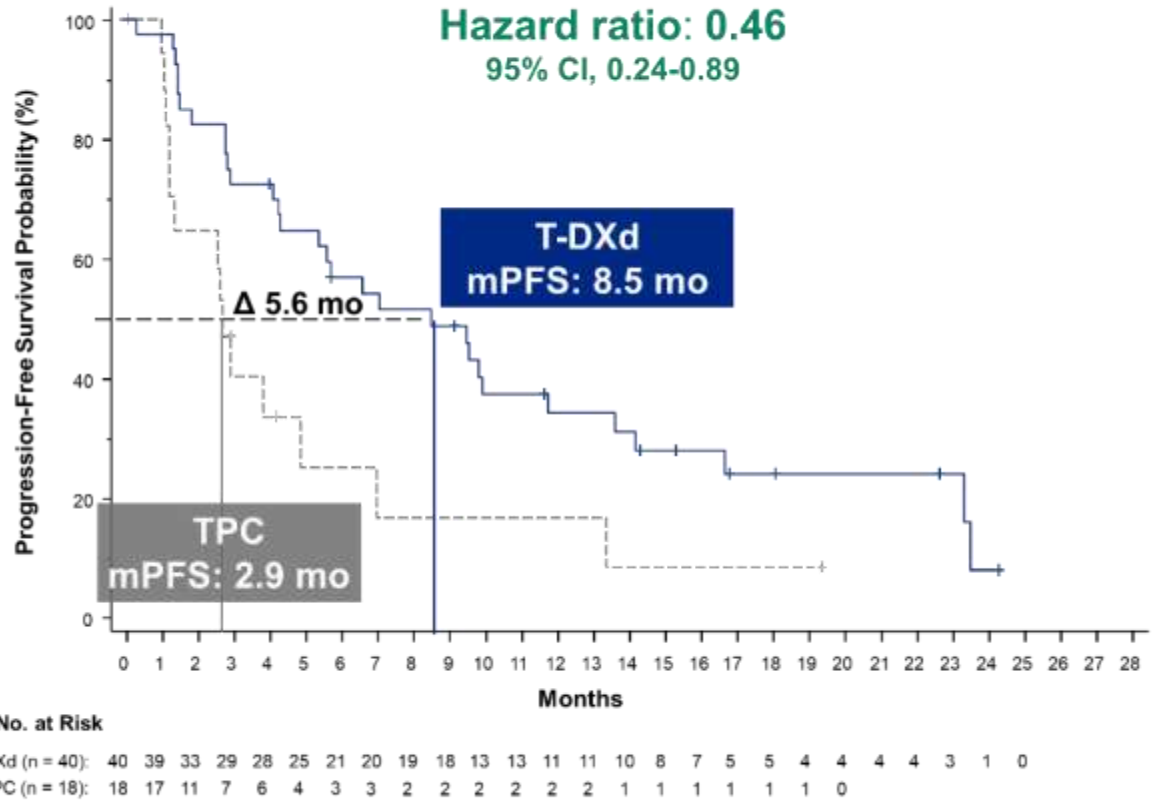
All patients



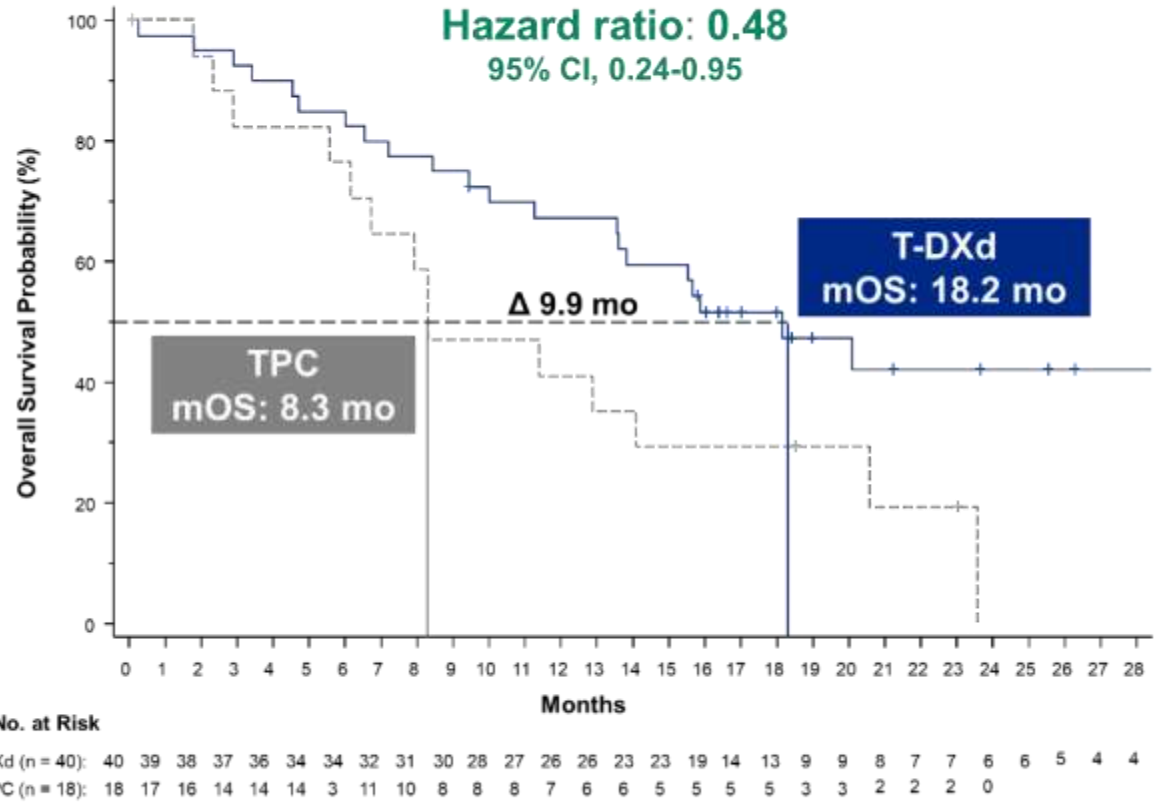
HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PFS and OS in HR− (Exploratory Endpoints)

PFS



OS



HR, hormone receptor; mOS, median overall survival; mPFS, median progression-free survival; 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 misstratification.

Subgroup Analysis: PFS in HR+

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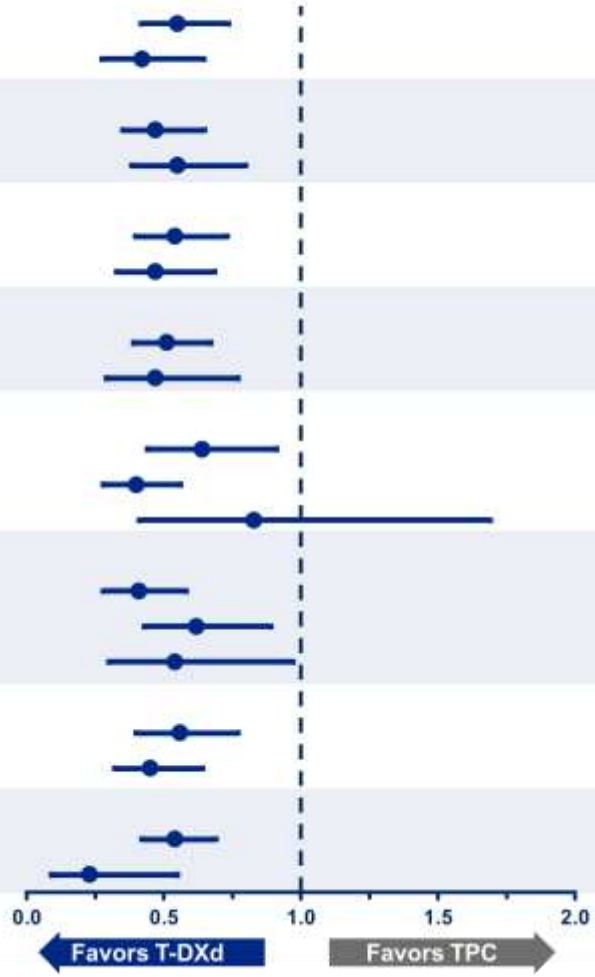
	No. of Events/No. of Patients T-DXd	TPC	PFS, median (95% CI), mo T-DXd	TPC	Hazard Ratio for Disease Progression or Death (95% CI)
Prior CDK4/6 inhibitors					
Yes	149/233	74/115	10.0 (8.3-11.4)	5.4 (4.0-7.8)	0.55 (0.42-0.73)
No	60/96	35/47	11.7 (9.5-17.7)	5.9 (4.3-8.2)	0.42 (0.28-0.64)
IHC status			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

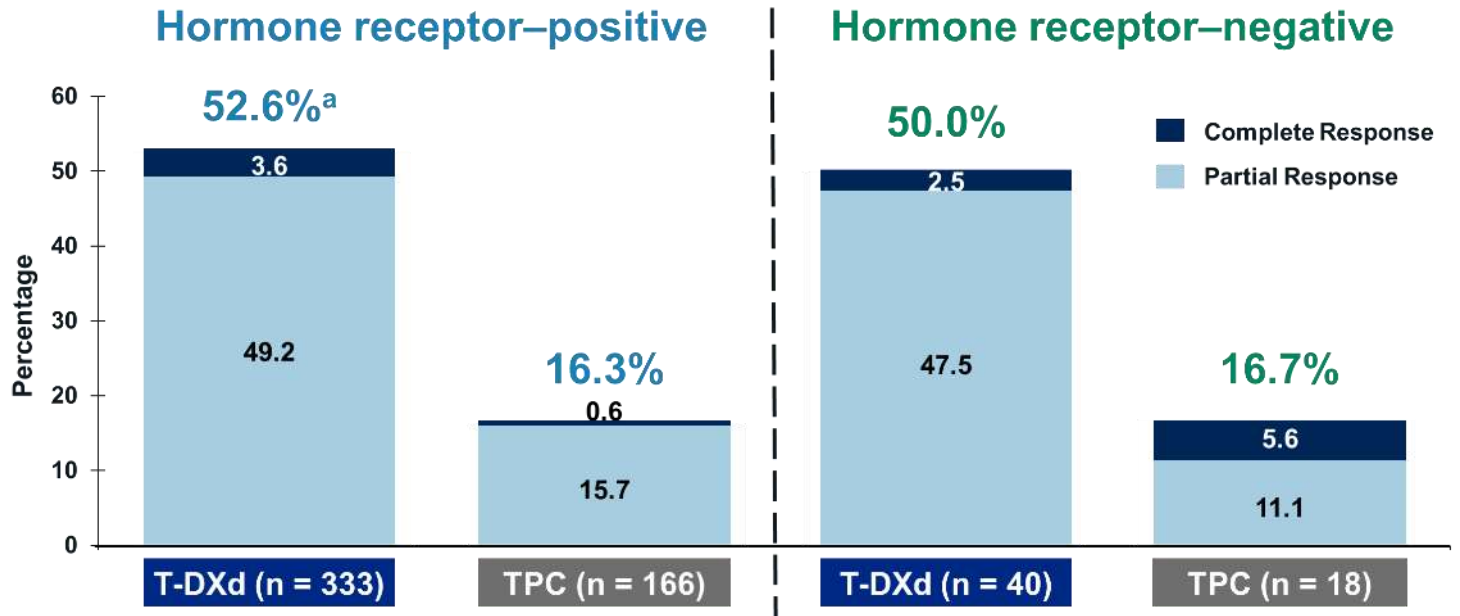


PFS by blinded independent central review. Based on derived data, which include protocol deviations.

CDK, cyclin-dependent kinase; ECOG, Eastern Cooperative Oncology Group; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Confirmed ORR

Confirmed Objective Response Rate



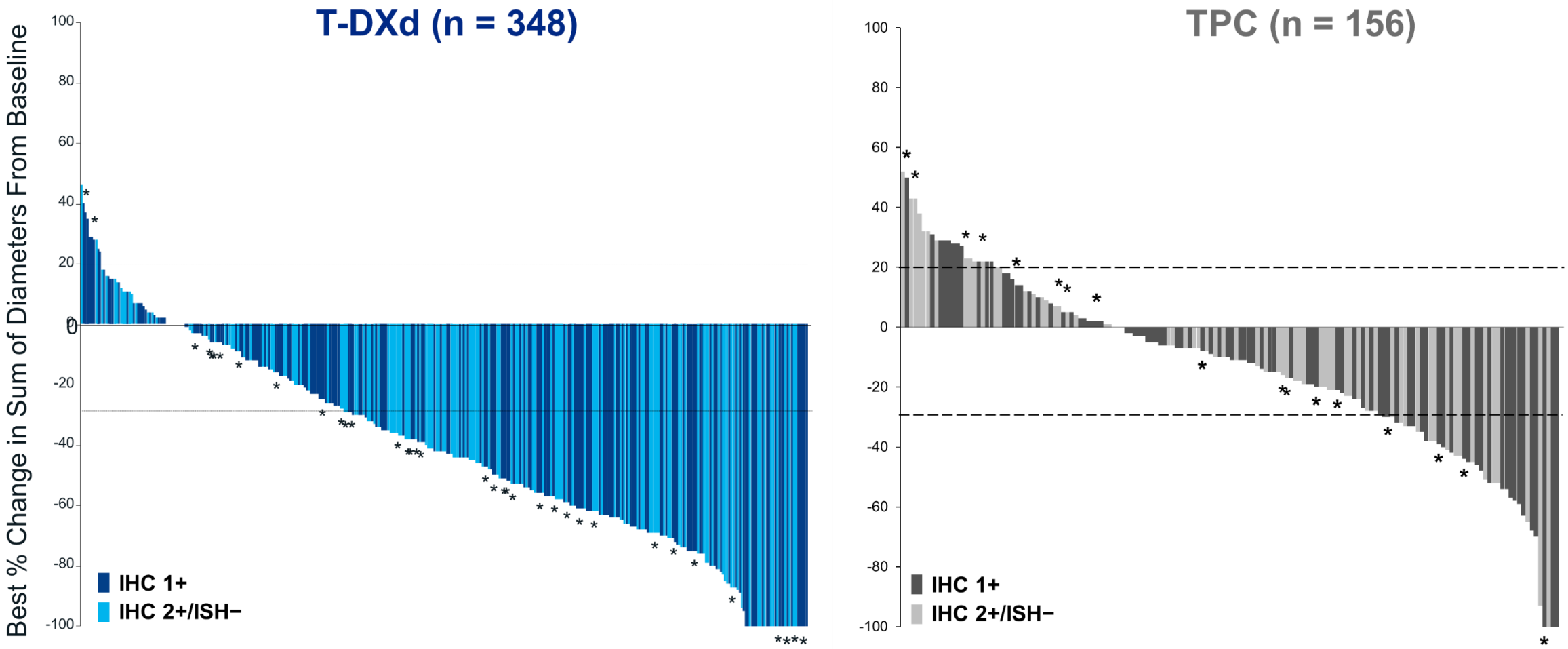
	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

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

Best Change in Target Lesions (All Patients)

DESTINY-Breast04

Daiichi-Sankyo



*Patients with HR− disease

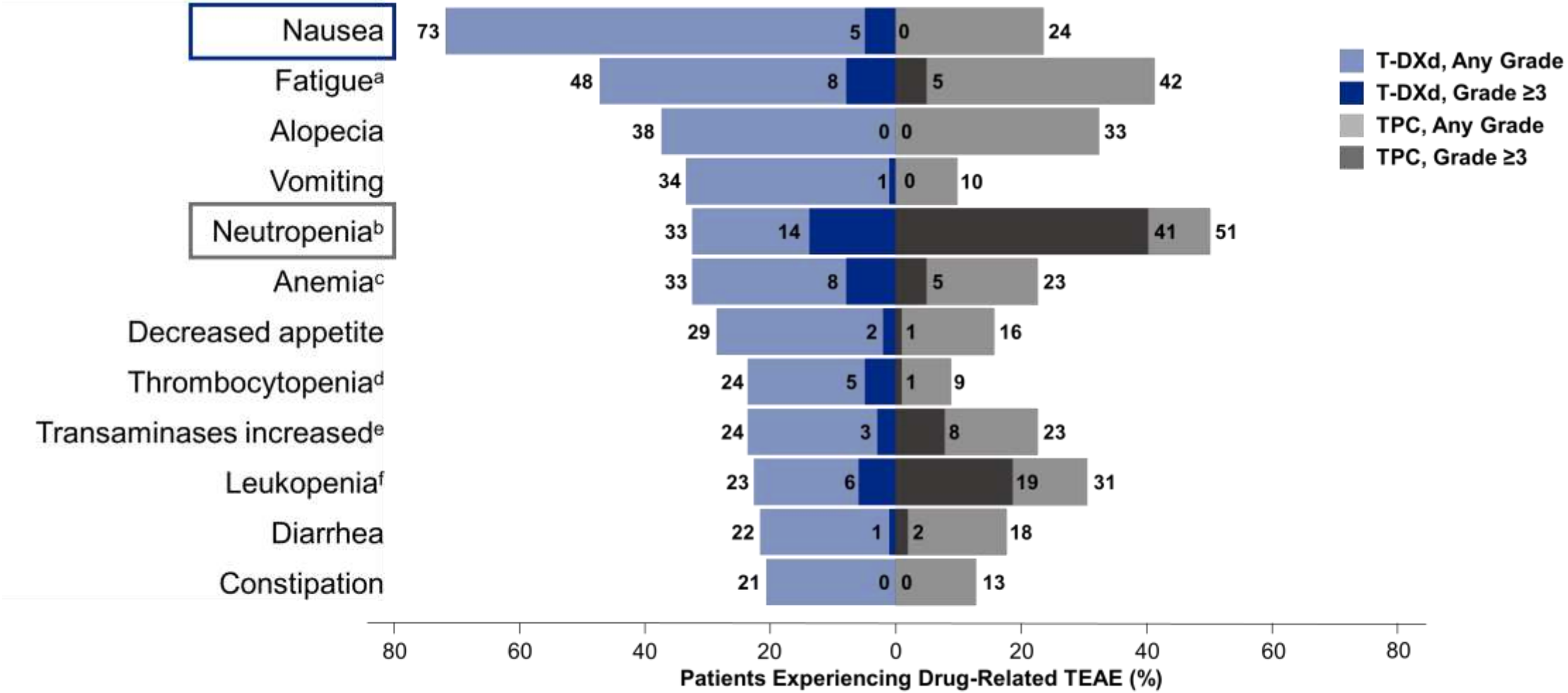
Shown are the best percentage changes from baseline in the sum of the largest diameters of measurable tumors in patients for whom data from both baseline and postbaseline assessments of target lesions by independent central review were available. The upper dashed horizontal line indicates a 20% increase in tumor size in the patients who had disease progression, and the lower dashed line indicates a 30% decrease in tumor size (partial response).

HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Drug-Related TEAEs in ≥20% of Patients

DESTINY-Breast04

Daiichi-Sankyo



T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms neutrophil count decreased and neutropenia. [c]This category includes the preferred terms hemoglobin decreased, red-cell 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.

Overall Safety Summary

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

- **Median treatment duration**
  - **T-DXd: 8.2 months (range, 0.2-33.3)**
  - **TPC: 3.5 months (range, 0.3-17.6)**
- Most common TEAE associated with treatment discontinuation
  - T-DXd: 8.2%, ILD/pneumonitis[c]
  - TPC: 2.3%, peripheral sensory neuropathy
- Most common TEAE associated with dose reduction
  - T-DXd: 4.6%, nausea and fatigue[d]
  - TPC: 14.0%, neutropenia[d]
- Total on-treatment deaths[e]
  - T-DXd: 3.8%
  - TPC: 4.7%

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]Safety analyses were performed in patients who received ≥1 dose of a study regimen. [b]Patient-years of exposure are the treatment duration with year as unit. [c]Grouped term. [d]Fatigue includes the preferred terms fatigue, malaise, and asthenia; neutropenia included the preferred terms of neutropenia and neutrophil count decreased. [e]On-treatment death was defined as any death that occurred from the date of the first dose to 47 days after the last dose of study drug irrespective of the cause; the TEAEs associated with deaths represent a subset of on-treatment deaths reported by the investigators as adverse events.

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

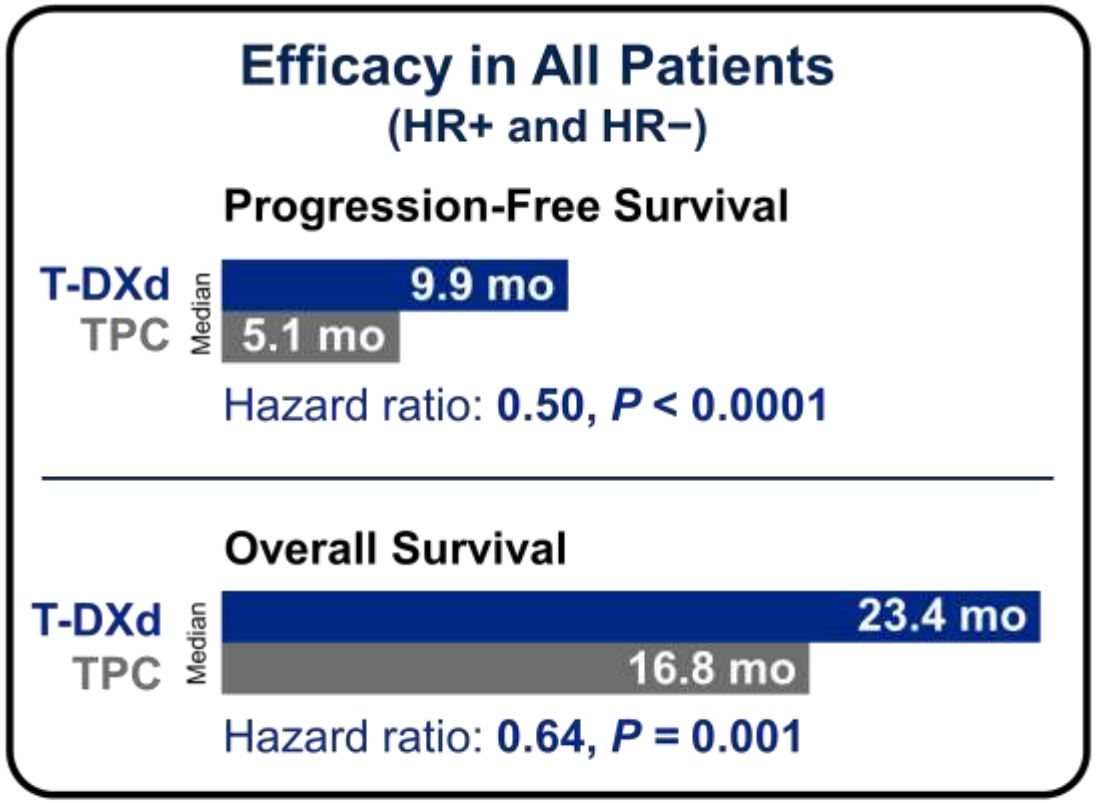
ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Median time to onset of ILD/pneumonitis for patients with T-DXd was 129.0 days (range, 26-710). [b]Left ventricular dysfunction was reported in a total of 17 (4.6%) patients in the T-DXd arm. One patient 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

DESTINY-Breast04

Daiichi-Sankyo

- 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; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

Poster 465

Retrospective study to estimate the prevalence of HER2-low breast cancer (BC) and describe its clinicopathological characteristics

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Objectives

- The objectives were to (1) assess the prevalence of human epidermal growth factor receptor 2 (HER2)–low expression (immunohistochemistry [IHC] 1+ or IHC 2+/in situ hybridization [ISH]−; ie, HER2-low BC) among patients with unresectable/metastatic BC (mBC) originally scored as HER2 negative based on rescored HER2 IHC slides after training on low-end expression scoring; (2) describe characteristics, clinical presentation, treatment patterns, and clinical outcomes of patients with HER2-low vs HER2 IHC 0 mBC; and (3) characterize the concordance between HER2 IHC rescores and historical scores
  - Here we report interim analysis data with an expanded data set (392 of 800 planned patients) from that previously reported in the abstract (233 patients)

Conclusions

- In this study of mBC samples previously categorized as HER2-negative, the prevalence of HER2-low status was 61.2%
  - HER2-low prevalence was numerically higher among patients with hormone receptor (HR)–positive mBC compared with HR-negative mBC (66.4% and 46.0%, respectively)
  - Data on HER2-low prevalence in BC are limited, but this estimated prevalence is similar to that in a previous study of HER2-negative BC samples (≈60%)[1]
- The overall concordance rate for HER2 status classification between historical and rescored slides was 79.1% (κ [95% CI], 0.554 [0.468-0.640]) indicating that historical scores were relatively accurate in identifying patients with HER2-low BC
  - Overall concordance was similar in the Ventana 4B5 and non-Ventana 4B5 cohorts (79.5% and 78.7%, respectively)
- HER2-low and HER2 IHC 0 groups had similar demographic and baseline disease characteristics
- As HER2-targeted therapies such as trastuzumab deruxtecan (T-DXd) for the treatment of patients with HER2-low BC are emerging,[2-6] a greater understanding of patients with HER2-low expression who could benefit from these therapies is important

Plain language summary

Why did we perform this research?
Breast cancers can have high levels of the HER2 protein (HER2-positive breast cancer), low levels of the HER2 protein (HER2-low breast cancer), or no HER2 protein (HER2-negative breast cancer). About 60% of breast cancers historically classified as HER2 negative are HER2-low breast cancers.[1] Some anticancer drugs, like trastuzumab deruxtecan (T-DXd), are designed to target and kill cancer cells that express HER2.[2,3] T-DXd may be able to treat HER2-low breast cancer, but the tests to detect HER2 are not sensitive for low amounts of HER2.[4-7] We wanted to find out how many patients who were historically categorized as having HER2-negative breast cancer should actually be considered as having HER2-low breast cancer. We also wanted to describe the differences between characteristics of patients with breast cancer that was identified as HER2-low and characteristics of patients with breast cancer that had no HER2 expression detected (immunohistochemistry [IHC] score of 0).

How did we perform this research?
Patients who were diagnosed with HER2-negative unresectable or metastatic breast cancer from 2014 through 2017 were included. Staff at local laboratories, who did not know how the tissue biopsies were scored when the patients were diagnosed, reevaluated the tissue samples after being trained. The samples were then categorized as either HER2-low or HER2 IHC 0. The number of patients who were recategorized as HER2-low among all patients reevaluated was calculated, and information about the patients (such as age, race, and aspects of disease and treatment) was examined. We also looked at how well the new HER2 category matched with the first category the patients were given.

What were the findings of this research and what are the implications?
We found that 61.2% of patients with HER2-negative breast cancer were actually HER2-low. We did not see notable differences in the characteristics of patients with HER2-low and patients with HER2 IHC 0 breast cancer. The majority (79.1%) of HER2 tests that were rescored as HER2-low matched historical HER2 results. This research helps us understand how many patients have HER2-low breast cancer and differences between patients with HER2-low and HER2 IHC 0 breast cancer.

Where can I access more information?
ClinicalTrials.gov. Estimation of the prevalence of HER2-low and describe the standard of care, treatment patterns, and outcome in real-world practice among unresectable and/or metastatic breast cancer patients with HER2-low status. https://clinicaltrials.gov/ct2/show/NCT04807595

This study is sponsored by AstraZeneca Pharmaceuticals and Daiichi Sankyo Inc. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).

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Poster

Plain language summary

Supplementary material (HER2-low prevalence by country, overall reported treatments in the metastatic setting, time to treatment failure)

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Poster presented at ASCO Annual Meeting, June 3-7, 2022; Chicago, IL and online by Dr Giuseppe Viale.

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Introduction

- HER2-negative BC (IHC 0, 1+, or IHC 2+/ISH−) comprises ≈80% of all BCs[7]; however, ≈60% of BCs traditionally categorized as HER2 negative express low levels of HER2 (IHC 1+ or IHC 2+/ISH−)[1]
- HER2-targeted therapies for HER2-low mBC are under investigation (eg, T-DXd in the phase 3 DESTINY-Breast04 study [NCT03734029] and the phase 2 DAISY trial [NCT04132960]).[2-6] In DESTINY-Breast04, T-DXd demonstrated superior progression-free survival in previously treated patients with HER2-low mBC vs the standard of care; the safety profile of T-DXd was consistent with previous trials[2]
- As patients with HER2-low BC become a clinically relevant population and the HER2 paradigm shifts from binary categorization to more nuanced recognition of the continuum of HER2 expression, accurate identification of patients with HER2-low BC is important
  - HER2 assays currently used to select patients for approved anti-HER2 therapies are optimized for high HER2 expression and are not validated for HER2-low detection.[8] A recent study found relatively poor concordance (19% of cases had <70% interrater agreement) in evaluation of IHC scores of 0 and 1+ using current HER2 assays, which underscores the need to understand the performance of HER2 assays for detection of HER2-low BC[9]
- Here we report the overall prevalence of HER2-low status among patients with unresectable/mBC identified as HER2 negative based on rescoring of historical HER2 IHC slides. We also describe patient characteristics, treatment patterns, and outcomes in HER2-low and HER2 IHC 0 mBC and the concordance between HER2 IHC rescores and historical scores

Methods

Study design

- This global, multicenter, retrospective study (NCT04807595) included patients with confirmed HER2-negative (HER2 IHC 0, 1+, or 2+/ISH−) unresectable/mBC diagnosed from 2014 through 2017 (date of mBC diagnosis was the index date)
  - Patients from Australia, Canada, France, Italy, Japan, Korea, and United Kingdom were included
- Staff at local laboratories, blinded to historical HER2 scores, rescored HER2 IHC–stained slides
  - HER2 was assessed using Ventana 4B5 and other assays (eg, HercepTest™ [DAKO] or Bond Oracle™ [Leica])
- BCs were categorized as HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2 IHC 0

Outcomes

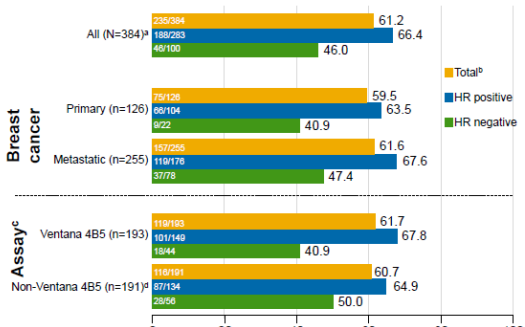
- The prevalence of HER2-low BC among patients originally scored as HER2 negative was measured
- Demographics, clinicopathological characteristics, treatment patterns, and outcomes were examined via medical charts/electronic health records
  - Data cutoff was December 31, 2020 (ie, ≥3 years of follow-up post index date)
- Concordance between historical HER2 scores and rescores was also assessed using Cohen's kappa (κ), with κ describing the relative strength of agreement using the following scale:[10]
  - κ>0.8, almost perfect; 0.6<κ≤0.8, substantial; 0.4<κ≤0.6, moderate; 0.2<κ≤0.4, fair; 0≤κ≤0.2, slight; κ<0, poor
- Time-to-event outcomes were estimated using Kaplan-Meier method and reported as medians and 95% CI

Results and interpretation

HER2-low prevalence within the HER2-negative population

- HER2 rescores were available for 384 of 392 patients
- HER2-low prevalence was 61.2% overall and numerically greater in the HR-positive subgroup vs HR-negative subgroup (66.4% vs 46.0%; **Figure 1**)
  - No notable differences in prevalence were seen when rescores were assessed using the Ventana 4B5 and other assays (*P*=.8524)

Figure 1. HER2-low prevalence in the HER2-negative mBC population

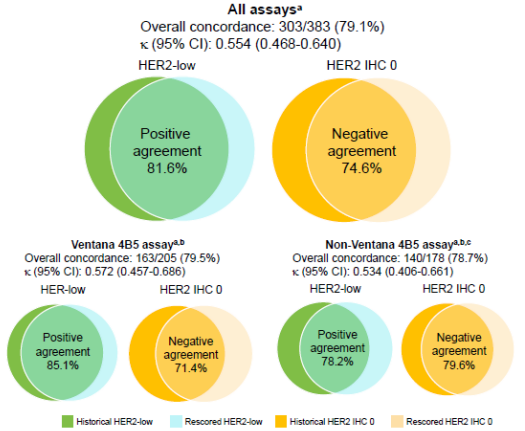


[a] Only patients with available HER2 score (HER2-low or HER2 IHC 0) contributed to prevalence calculations. [b] Patients with presently unknown HR status included in total category only. [c] Ventana and non-Ventana groups based on the rescore results. [d] Includes HercepTest, Bond Oracle, or unknown.

HER2 testing concordance

- The concordance rate between historical and rescored slides for HER2 status classification was 79.1% (**Figure 2**)
  - Overall, positive agreement was 81.6% and negative agreement was 74.6%
  - Overall concordance was similar in the Ventana 4B5 and non-Ventana 4B5 cohorts (79.5% and 78.7%, respectively)

Figure 2. Concordance between rescores and historical scores



[a] Only patients with available historical scores were included. [b] Ventana and non-Ventana groups based on the historical score. [c] Includes HercepTest, Bond Oracle, or unknown.

Patient demographics and clinicopathological characteristics

- No notable differences in demographic or baseline disease characteristics between the HER2-low and HER2 IHC 0 groups were seen (**Tables 1** and **2**)
  - At index date, most patients (291/392; 74.2%) were HR positive, most (75.3%) were ≥45 years of age, and most (79.6%) were Asian or White
  - Visceral (58.9%) and bone (45.2%) metastases were commonly observed among reported metastatic sites; most patients (55.4%) reported 1 metastatic site

Table 1. Patient demographics

	HR positive			HR negative			
	HER2-low (N=188)	HER2 IHC 0 (N=95)	Total[a] (N=291)	HER2-low (N=46)	HER2 IHC 0 (N=54)	Total[a] (N=100)	Total[b] (N=392)
Female, n (%)	187 (99.5)	94 (98.9)	288 (99.0)	46 (100.0)	54 (100.0)	100 (100.0)	389 (99.2)
Median age at index date, median (range), years[c]	60 (27-93)	56 (28-90)	59 (27-93)	57 (31-80)	51 (35-92)	53 (31-92)	57 (27-93)
Age group at index date, n (%)[c]							
18 to 44 years	23 (12.2)	11 (11.6)	36 (12.4)	9 (19.6)	16 (29.6)	25 (25.0)	61 (15.6)
45 to 64 years	82 (43.6)	46 (50.5)	134 (46.0)	23 (50.0)	20 (37.0)	43 (43.0)	177 (45.2)
≥65 years	66 (35.1)	27 (28.4)	93 (32.0)	12 (26.1)	13 (24.1)	25 (25.0)	118 (30.1)
Not reported/missing	1 (0.5)	0	2 (0.7)	0	0	0	2 (0.5)
Smoking status of "never," n (%)	110 (58.5)	61 (64.2)	178 (61.2)	30 (65.2)	34 (63.0)	64 (64.0)	242 (61.7)
Race, n (%)							
Asian	82 (43.6)	38 (40.0)	126 (43.3)	14 (30.4)	23 (42.6)	37 (37.0)	163 (41.6)
White	67 (35.6)	34 (35.8)	101 (34.7)	23 (50.0)	25 (46.3)	48 (48.0)	149 (38.0)
Black or African American	1 (0.5)	1 (1.1)	2 (0.7)	1 (2.2)	0	1 (1.0)	3 (0.8)
Other	2 (1.1)	0	2 (0.7)	0	0	0	2 (0.5)
Not reported/missing	36 (19.1)	22 (23.2)	60 (20.6)	8 (17.4)	6 (11.1)	14 (14.0)	75 (19.1)

[a] Includes patients with missing HER2 category. [b] Includes patients with missing HR status. [c] Index date was the date of mBC diagnosis.

Table 2. Patient clinical characteristics

	HR positive			HR negative			
	HER2-low (N=188)	HER2 IHC 0 (N=95)	Total[a] (N=291)	HER2-low (N=46)	HER2 IHC 0 (N=54)	Total[a] (N=100)	Total[b] (N=392)
Time from initial BC diagnosis to mBC diagnosis, n (%)							
<2 years	76 (40.4)	35 (36.8)	116 (39.9)	21 (45.7)	28 (51.9)	49 (49.0)	165 (42.1)
2 to 5 years	39 (20.7)	22 (23.2)	63 (21.6)	14 (30.4)	10 (18.5)	24 (24.0)	87 (22.2)
>5 years	57 (30.3)	28 (29.5)	85 (29.2)	9 (19.6)	11 (20.4)	20 (20.0)	105 (26.8)
Not reported/missing	16 (8.5)	10 (10.5)	27 (9.3)	2 (4.3)	5 (9.3)	7 (7.0)	35 (8.9)
Location of metastasis/metastases, n (%)[c]							
Bone	96 (51.1)	47 (49.5)	150 (51.5)	13 (28.3)	13 (24.1)	26 (26.0)	177 (45.2)
Brain	7 (3.7)	5 (5.3)	13 (4.5)	6 (13.0)	4 (7.4)	10 (10.0)	23 (5.9)
Liver	48 (25.5)	30 (31.6)	81 (27.8)	16 (39.1)	14 (25.9)	32 (32.0)	113 (28.8)
Lung	46 (24.5)	23 (24.2)	73 (25.1)	10 (21.7)	17 (31.5)	27 (27.0)	101 (25.8)
Visceral	103 (54.8)	61 (64.2)	171 (58.8)	29 (63.0)	30 (55.6)	59 (59.0)	231 (58.9)
Number of metastatic locations, n (%)[c]							
1	113 (60.1)	49 (51.6)	162 (55.7)	26 (56.5)	29 (53.7)	55 (55.0)	217 (55.4)
2	36 (19.1)	18 (18.9)	56 (19.2)	7 (15.2)	14 (25.9)	21 (21.0)	77 (19.6)
≥3	39 (20.7)	28 (29.5)	73 (25.1)	13 (28.3)	11 (20.4)	24 (24.0)	98 (25.0)
Metastatic or locally advanced at index date, n (%)[d]							
Metastatic	169 (89.9)	85 (89.5)	261 (89.7)	43 (93.5)	47 (87.0)	90 (90.0)	351 (89.5)
Locally advanced	1 (0.5)	0	1 (0.3)	0	2 (3.7)	2 (2.0)	3 (0.8)
Both	3 (1.6)	1 (1.1)	4 (1.4)	1 (2.2)	2 (3.7)	3 (3.0)	7 (1.8)
Not reported/missing	15 (8.0)	9 (9.5)	25 (8.6)	2 (4.3)	3 (5.6)	5 (5.0)	31 (7.9)
Stage at initial BC diagnosis, n (%)							
I	14 (7.4)	6 (6.3)	20 (6.9)	7 (15.2)	7 (13.0)	14 (14.0)	34 (8.7)
II	62 (33.0)	34 (35.8)	97 (33.3)	11 (23.9)	17 (31.5)	28 (28.0)	125 (31.9)
III	30 (16.0)	20 (21.1)	52 (17.9)	13 (28.3)	13 (24.1)	26 (26.0)	78 (19.9)
IV	27 (14.4)	14 (14.7)	44 (15.1)	1 (2.2)	9 (16.7)	10 (10.0)	54 (13.8)
Other/not reported/missing	55 (29.3)	21 (22.1)	78 (26.8)	14 (30.4)	8 (14.8)	22 (22.0)	101 (25.8)

[a] Includes patients with missing HER2 category. [b] Includes patients with missing HR status. [c] Reported over the course of patients' metastatic disease. [d] Index date was the date of mBC diagnosis.

Discussion and limitations

- These data are from a retrospective study, and findings may be impacted by the inherent limitations associated with this type of data (eg, missing/inaccurate data from health/medical records); as such, these data should be interpreted carefully
  - Furthermore, this data set may not have been optimal for robust analyses of treatment patterns and outcomes because of the relatively short window of follow-up
- Our data from an unresectable/mBC population have shown a similar HER2-low prevalence (61.2%) in a HER2-negative cohort as that found in a previous study of a HER2-negative BC population (≈60%)[1]
- Treatment findings are in line with the typical standard of care for HR-positive and HR-negative subgroups, with endocrine therapy being the most common for HR-positive mBC and chemotherapy being the most common for HR-negative mBC[11]
- Survival outcomes are also consistent with previous reports, with no overall difference in OS observed between HER2-low and HER2 IHC 0 BC,[1,12,13] although other studies have shown differing results[14,15]
- Future analyses will investigate stratification of HER2-low status by IHC 1+ vs 2+, which may impact outcomes[12]

Treatment patterns and outcomes

- Most patients (50.0%-78.2%) received monotherapy as their first treatment in the metastatic setting; 21.8%-50.0% had combination therapy, of whom ≈15% received CDK4/6 inhibitors (**Figure 3**)
- Median time to first subsequent treatment and overall survival (OS) were numerically greater for HER2-low than for HER2 IHC 0 with 1 exception (OS in patients who were HR positive and did not receive CDK4/6 inhibitors; **Figures 4** and **5**)
- The magnitude of the differences in median OS between HER2-low and HER2 IHC 0 was generally larger among HR-negative than HR-positive groups

Figure 3. First treatment received in the metastatic setting

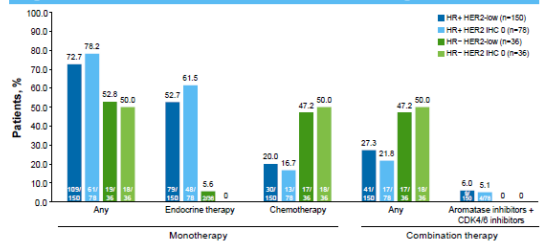
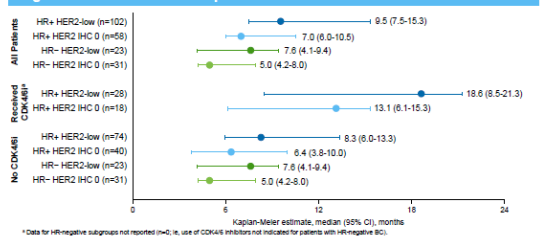
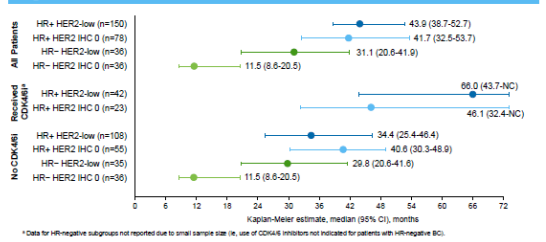


Figure 4. Time to first subsequent treatment



[a] Data for HR-negative subgroups not reported (n=0; ie, use of CDK4/6 inhibitors not indicated for patients with HR-negative BC).

Figure 5. Overall survival



[a] Data for HR-negative subgroups not reported due to small sample size (ie, use of CDK4/6 inhibitors not indicated for patients with HR-negative BC).

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Abbreviations

BC, breast cancer; CDK4/6, cyclin-dependent kinase 4/6; CDK4/6i, CDK4/6 inhibitor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic BC; NC, not calculable; OS, overall survival; T-DXd, trastuzumab deruxtecan.

Acknowledgments

We thank Olga Kovbasnjuk (Jewish General Hospital, McGill University) for her contributions to this work. We thank the patients who are participating in this study as well as their families and caregivers. This study is sponsored by AstraZeneca Pharmaceuticals and Daiichi Sankyo Inc. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201). Medical writing support was provided by JoAnna Anderson, PhD, CMPP (ArticulateScience, LLC), and was funded by AstraZeneca.

Daiichi-Sankyo

DESTINY-Breast03

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

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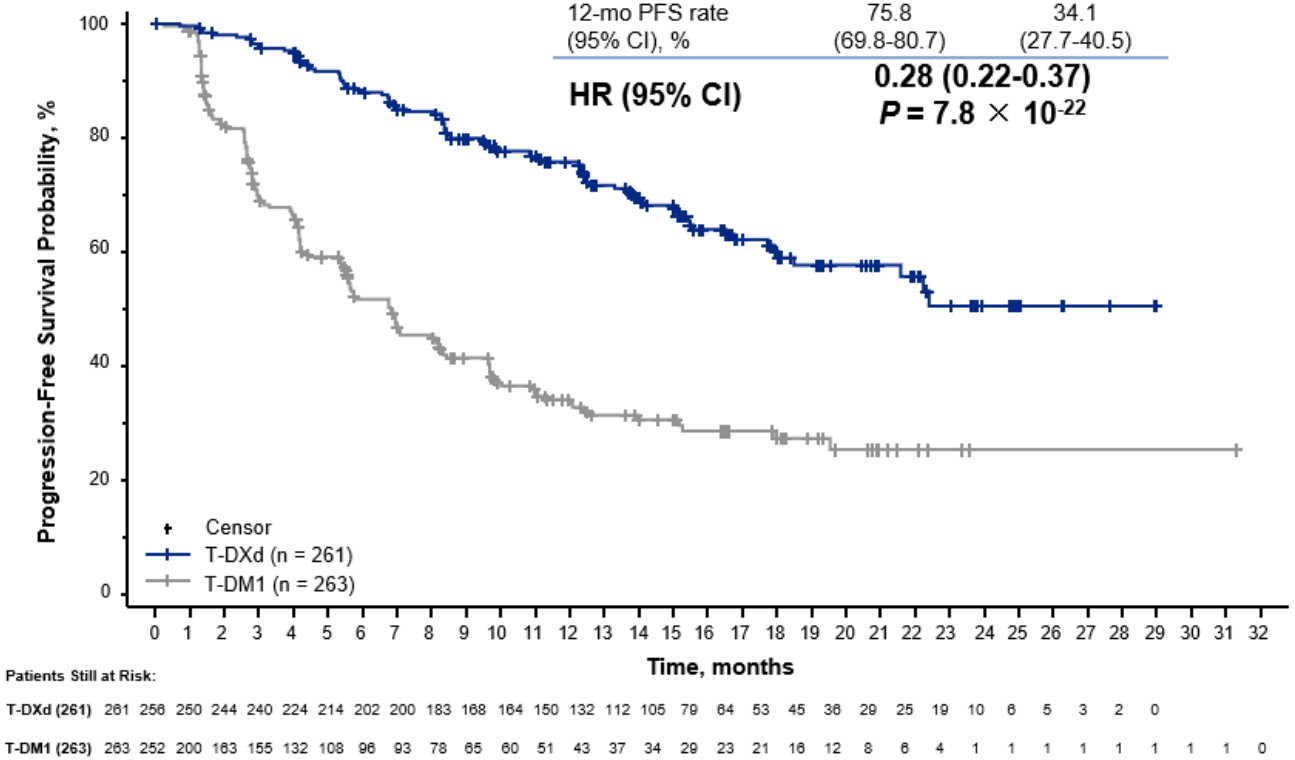
Background

PFS by BICR[1,a]

	T-DXd	T-DM1
mPFS (95% CI), mo	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate (95% CI), %	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	

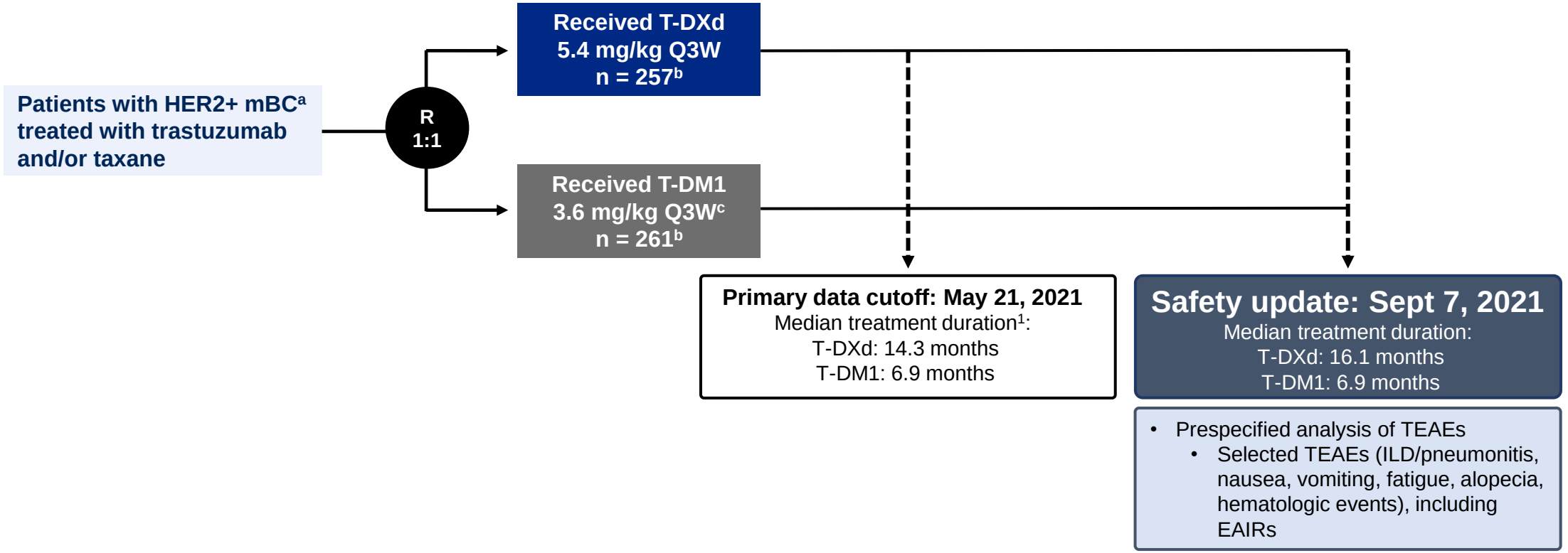


- T-DXd, a HER2-targeted ADC, was approved for the treatment of patients with HER2+ unresectable or mBC who have received a prior anti-HER2 therapy in the metastatic or neoadjuvant/adjuvant setting and had recurrence during or within 6 months after therapy[2]
- DESTINY-Breast03 (NCT03529110) investigated T-DXd vs T-DM1 in patients with HER2+ unresectable or mBC
  - In the primary analysis (May 21, 2021), T-DXd was superior to T-DM1 for PFS by BICR (primary endpoint)[1]
  - Overall health status and QoL was maintained with T-DXd and numerically favored T-DXd over T-DM1[3]

ADC, antibody-drug conjugate; BICR, blinded independent central review; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mBC, metastatic breast cancer; mPFS, median progression-free survival; PFS, progression-free survival; QoL, quality of life; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan. 1. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154. 2. Enhertu (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use. Daiichi Sankyo, Inc; 2022. 3. Curigliano G et al. Presented at ESMO Breast Cancer meeting; May 3-5, 2022; Berlin, Germany. Presentation 1630. [a]From *New England Journal of Medicine*, Cortés J et al, Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer, Vol. 386, Pages 1143-1154.

DESTINY-Breast03 Study Design

DESTINY-Breast03



Objective of the study was to provide updated safety data with additional analyses in patients with HER2+ mBC treated with T-DXd or T-DM1 in DESTINY-Breast03

EAIRs, exposure-adjusted incidence rates; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; mBC, metastatic breast cancer; Q3W, every 3 weeks; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

[a]Central testing of archived sample for HER2 status. [b]Number of treated patients (not the randomized number of patients). [c]Or in accordance with the local label.

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

Safety Update Overview (September 7, 2021)

DESTINY-Breast03

Daiichi-Sankyo

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.

Safety update: Sept 7, 2021

Exposure-Adjusted Incidence Rates (EAIRs)[a]

DESTINY-Breast03

Daiichi-Sankyo

	Exposure-adjusted incidence per total patient-years of exposure	
	T-DXd n = 257	**T-DM1 n = 261**
Patients remaining on treatment, n (%)	116 (45.1)	39 (14.9)
Treatment duration, median (range), months	**16.1 (0.7-33.0)**	**6.9 (0.7-28.5)**
Exposure, patient-years[b]	327.2	186.3
EAIR, grade ≥3 TEAE	0.42	0.70
EAIR, any grade serious TEAE	0.17	0.27
EAIR, grade ≥3 serious TEAE	0.12	0.20
EAIR, TEAE associated with drug discontinuation	0.12	0.10
EAIR, TEAE associated with dose reduction	0.18	0.19

- EAIRs were measured to account for differences in treatment duration exposure between T-DXd and T-DM1 and provide a more meaningful comparison
- EAIRs per patient-year were lower in the T-DXd arm than the T-DM1 arm except for TEAEs associated with drug discontinuation, which were primarily associated with ILD/pneumonitis in the T-DXd arm
  - EAIR for grade ≥3 TEAEs was 0.42 for T-DXd and 0.70 for T-DM1
  - EAIR for any grade serious TEAEs was 0.17 for T-DXd and 0.27 for T-DM1

EAIRs, exposure-adjusted incidence rates; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]EAIR was the number of patients with at least 1 event incidence divided by the sum of patient-years of exposure over patients in the safety analysis set (total patient-years of exposure). [b]Patient years of exposure were the treatment duration with year as unit.

Safety update: Sept 7, 2021

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

DESTINY-Breast03

Daiichi-Sankyo

n (%)	T-DXd n = 257		T-DM1 n = 261	
	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.

Safety update: Sept 7, 2021

Time to First Onset of TEAEs

DESTINY-Breast03

Median time to event, days	T-DXd n = 257	T-DM1 n = 261
TEAE associated with treatment discontinuation	224	147
TEAE associated with first dose reduction	96	19
Selected TEAEs		
Anemia	70.0	42.0
Lymphopenia	196.0	168.0
Thrombocytopenia	132.0	8.0
Fatigue	22.0	24.0
Leukopenia	74.5	92.0
Neutropenia[a]	64.0	105.0
Nausea	2.0	3.0
Vomiting	10.0	6.0
Alopecia	27.0	43.0

- TEAEs associated with first drug discontinuation or first dose reduction occurred later with T-DXd treatment than with T-DM1 treatment
- Median time to any TEAE associated with first dose reduction was longer in the T-DXd arm at 96 days compared with the T-DM1 arm at 19 days

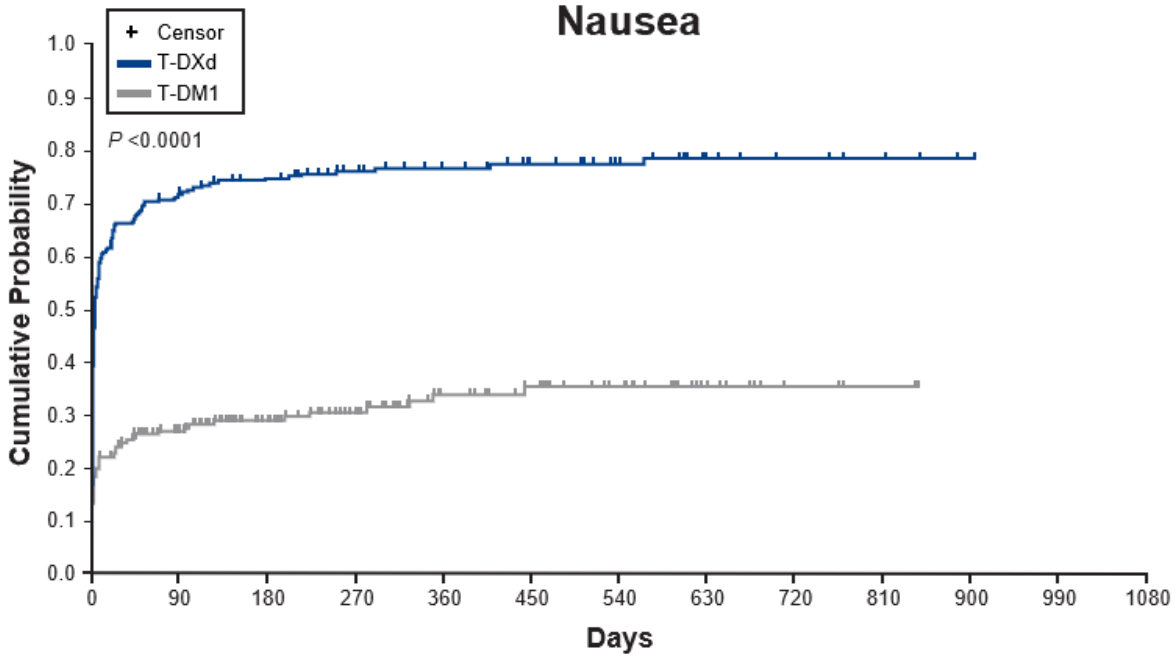
T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
Selected TEAEs (and preferred terms included): anemia (hemoglobin decreased, red blood cell count decreased, anemia, hematocrit decreased); lymphopenia (lymphocyte count decreased, lymphopenia); neutropenia (neutrophil count decreased, neutropenia); thrombocytopenia (platelet count decreased, thrombocytopenia); leukopenia (white blood cell count decreased, leukopenia); fatigue (fatigue, asthenia, malaise).
[a]11.7% of patients in the T-DXd group and 2.3% of patients in the T-DM1 group were treated with G-CSF within 28 days after onset of neutropenia, including febrile neutropenia.

Safety update: Sept 7, 2021

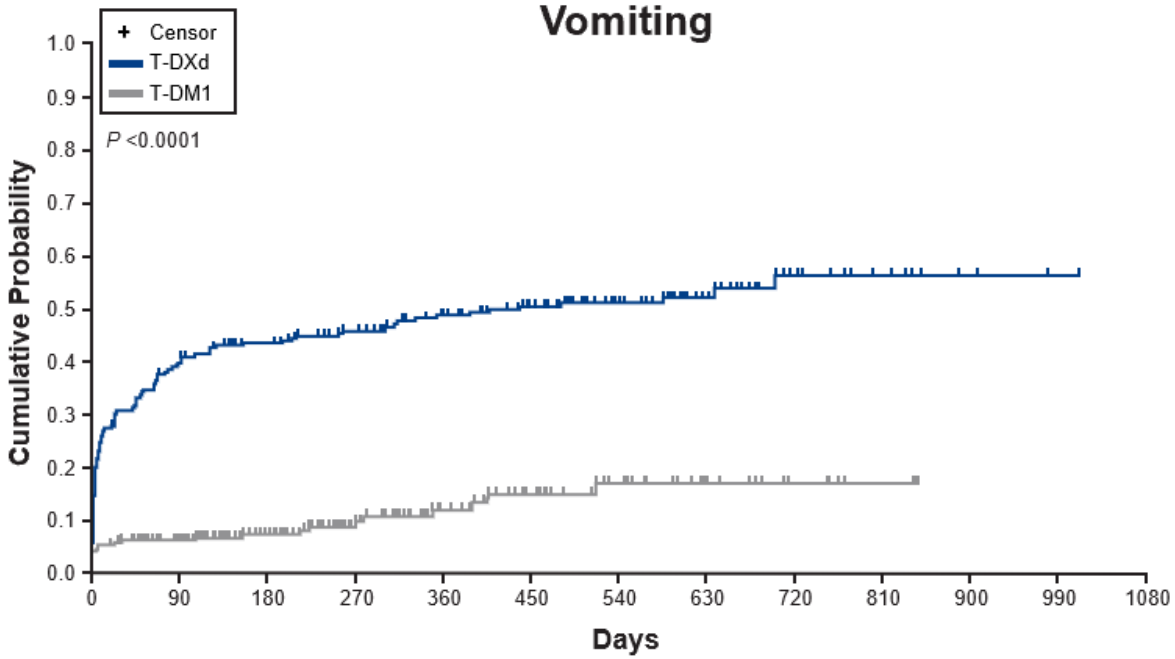
Time to First Occurrence of Nausea and Vomiting

DESTINY-Breast03

Daiichi-Sankyo



T-DXd	257	71	59	46	37	27	20	9	6	4	1	0
T-DM1	261	150	100	74	50	39	29	15	4	2	0	



T-DXd	257	153	133	115	95	79	55	29	14	8	3	1	0
T-DM1	261	202	141	95	66	47	34	19	7	3	0		

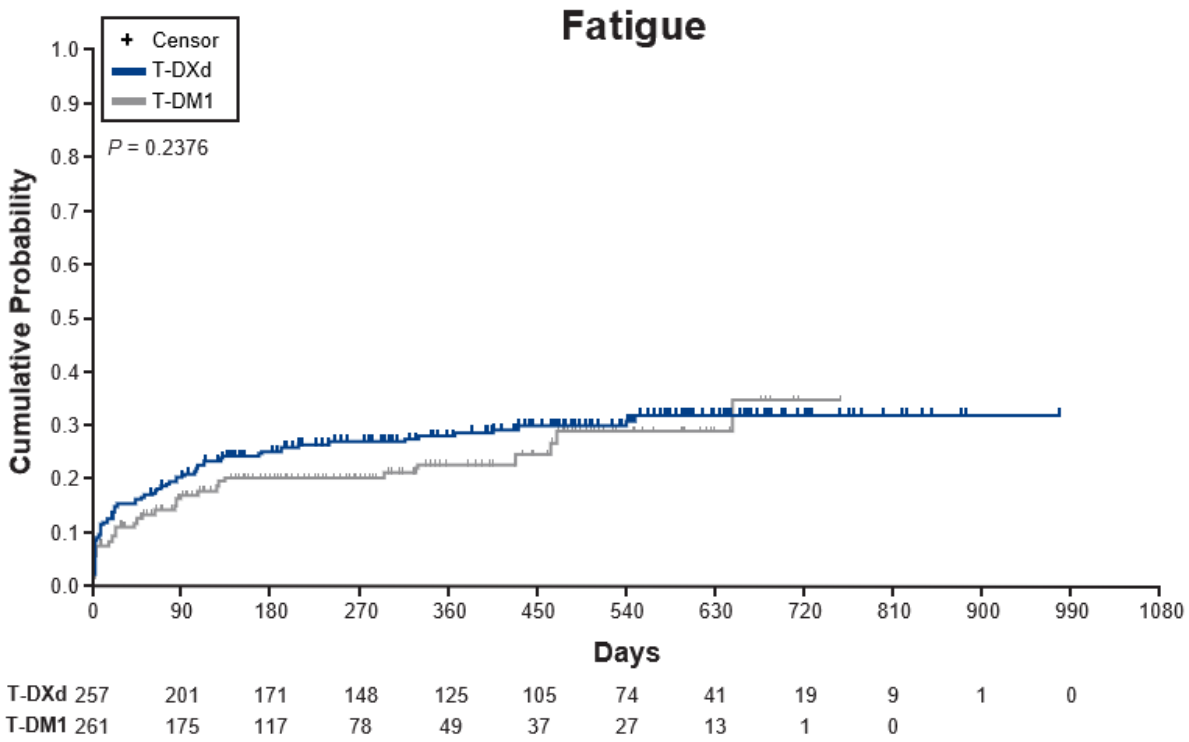
- Risk of first event of nausea and vomiting was higher with T-DXd in earlier cycles

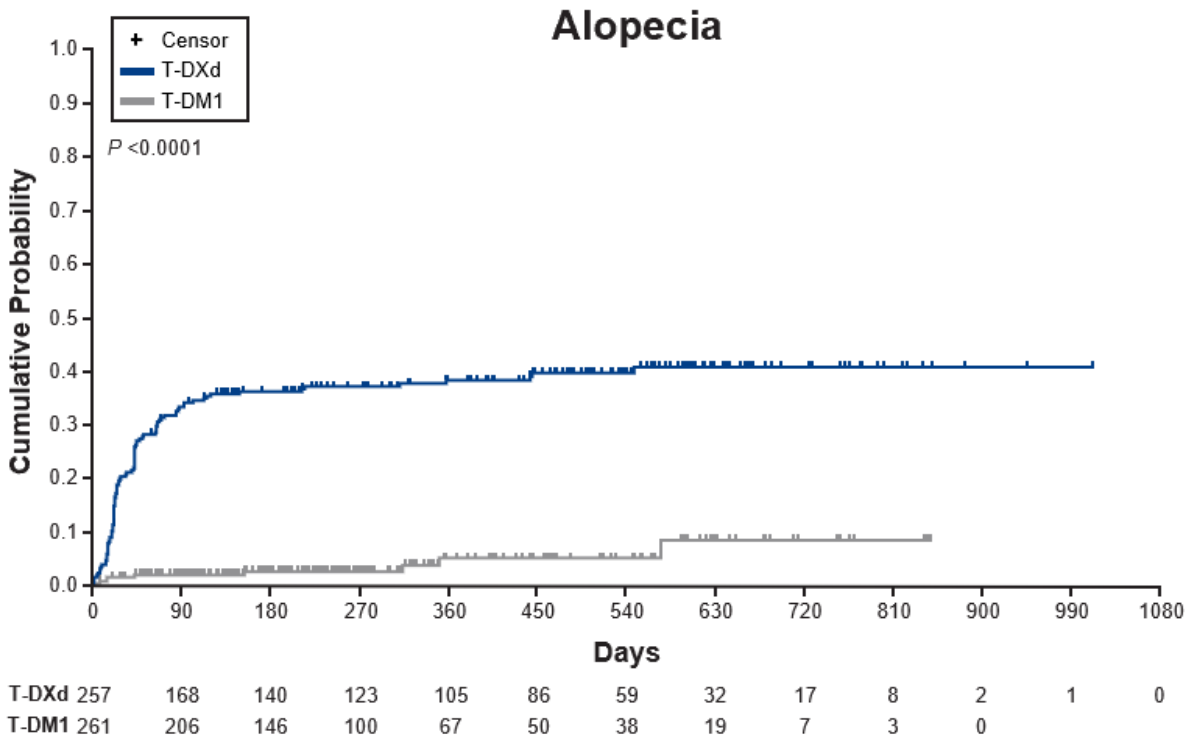
T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
Time to first occurrence of the TEAE was defined as the date of the first occurrence of the TEAE minus the date of first study drug plus 1. Patients that did not experience the TEAE were censored at min (treatment end date + 47 days, new treatment start date, death date, date last known alive) minus first study drug date plus 1. P value was from the unstratified log rank test and was for descriptive purposes only.

Time to First Occurrence of Fatigue and Alopecia

DESTINY-Breast03

Daiichi-Sankyo



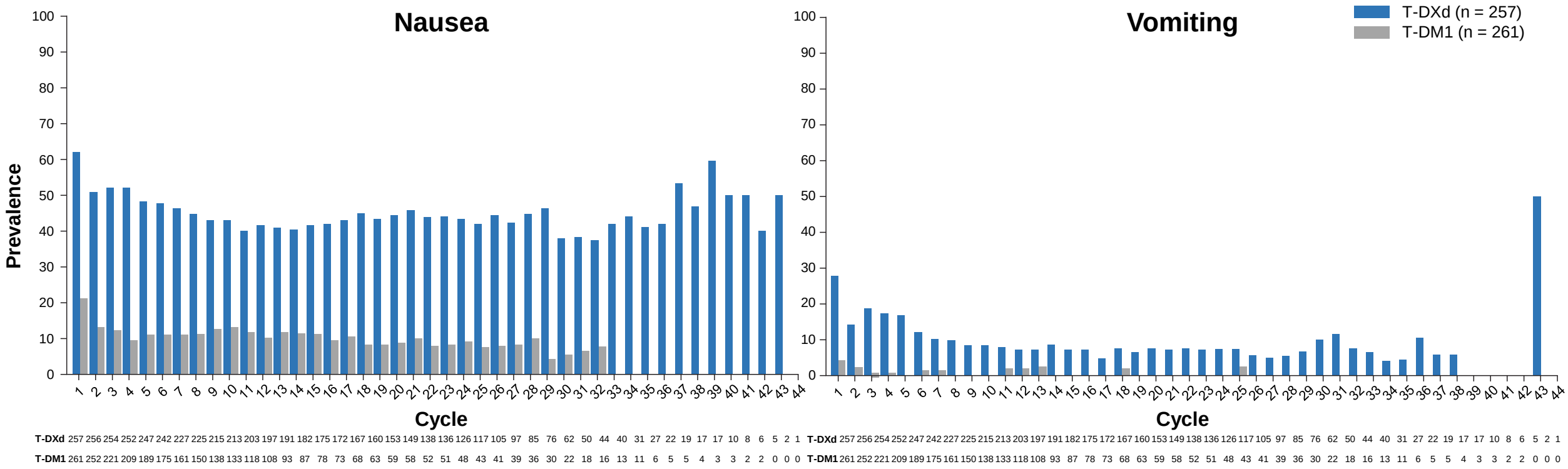


- The cumulative incidence and trend of fatigue over time was similar between T-DXd and T-DM1
- Risk of first event of alopecia was higher with T-DXd in earlier cycles

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
Time to first occurrence of the TEAE was defined as the date of the first occurrence of the TEAE minus the date of first study drug plus 1. Patients that did not experience the TEAE were censored at min (treatment end date + 47 days, new treatment start date, death date, date last known alive) minus first study drug date plus 1. P value was from the unstratified log rank test and was for descriptive purposes only.

Prevalence of Nausea and Vomiting

DESTINY-Breast03



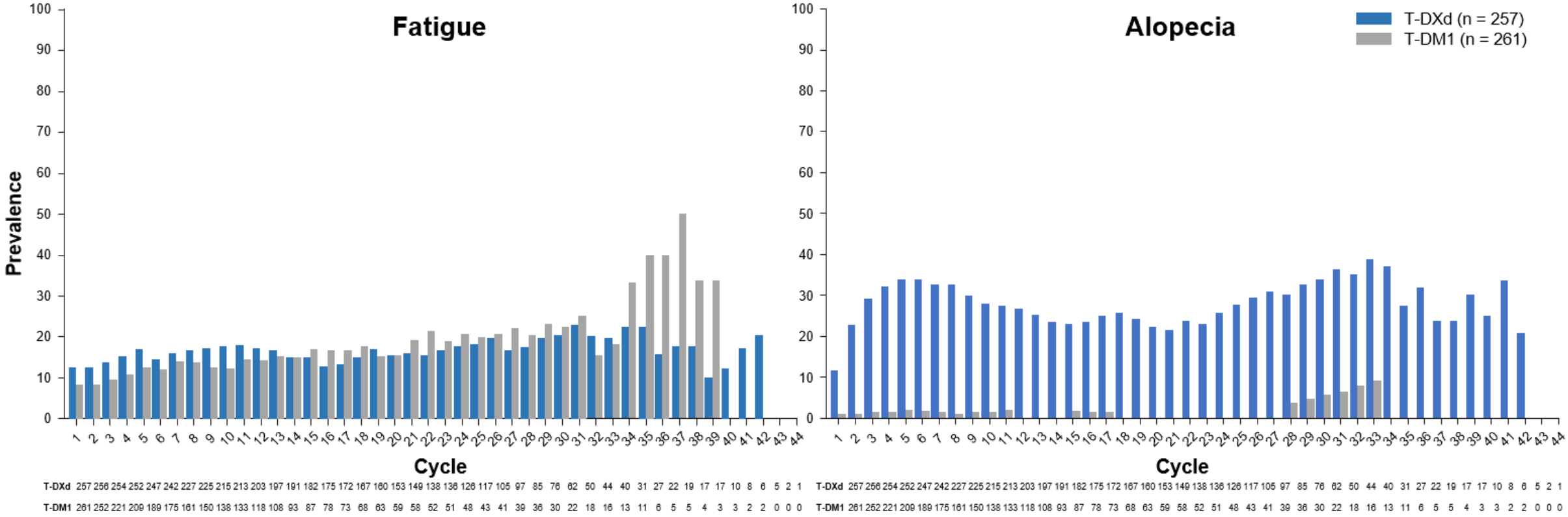
- The prevalence of nausea and vomiting was higher with T-DXd than with T-DM1 and was relatively consistent over time
- Majority of events with T-DXd were grade 1 and 2 and resolved, and one patient discontinued study drug due to vomiting
  - Antiemetic prophylaxis recommendations were updated during the study based on emerging data supporting the moderately emetogenic potential of T-DXd[1,2]

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Prevalence was defined as the number of patients who had the event starting at a particular cycle or still ongoing at that cycle divided by the number of patients on treatment at that cycle.
1. Hesketh PJ et al. *J Clin Oncol*. 2020;38(24):2782-2797. 2. Modi S et al. *N Engl J Med*. 2020;382:610-621.

Safety update: Sept 7, 2021

Prevalence of Fatigue and Alopecia

DESTINY-Breast03



- The prevalence of fatigue and alopecia was relatively consistent over time

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Prevalence was defined as the number of patients who had the event starting at a particular cycle or still ongoing at that cycle divided by the number of patients on treatment at that cycle.

Adjudicated Drug-Related ILD/Pneumonitis

DESTINY-Breast03

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	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).

Safety update: Sept 7, 2021

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.

Safety update: Sept 7, 2021

PATIENT-REPORTED OUTCOMES FROM DESTINY-Breast03, A RANDOMIZED PHASE 3 STUDY OF TRASTUZUMAB DERUXTECAN (T-DXd) VS TRASTUZUMAB EMTANSINE (T-DM1) IN PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER

GIUSEPPE CURIGLIANO, KYLE DUNTON, MATS ROSENLUND, MARTIN JANEK, JILLIAN CATHCART, YALI LIU, PETER A. FASCHING, HIROJI IWATA

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Milan, Italy

ESMO BC 2022 #1630 Oral

On behalf of the investigators

DESTINY-Breast03 Study Design

DESTINY-Breast03

Daiichi-Sankyo

Patients (N = 524)
- Unresectable or metastatic HER2-positive[a] breast cancer that has been previously treated with trastuzumab and a taxane[b]

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

R 1:1

T-DXd
5.4 mg/kg Q3W
(n = 261)[c]

(open-label)

T-DM1
3.6 mg/kg Q3W
(n = 263)[d]

Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety
- **HEOR outcomes (PROs and hospitalization rates)**

PRO endpoint assessment schedule[e]

Cycle 1	Cycle 2	Cycle 3	Every 2 cycles (cycle 5, 7, 9, etc)	EOT	40-day follow-up visit	3-month follow-up visit

BICR, blinded independent central review; DOR, duration of response; EOT, end of treatment; HEOR, health economics outcomes research; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; Q3W, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and a taxane. [c]4 patients were randomly assigned but not treated. [d]2 patients were randomly assigned but not treated. [e]1 cycle = 21 days; T-DXd or T-DM1 administered on day 1 of each cycle; questionnaires completed before treatment on day 1 of cycles indicated.

Demographics and Baseline Clinical Characteristics

DESTINY-Breast03

Daiichi-Sankyo

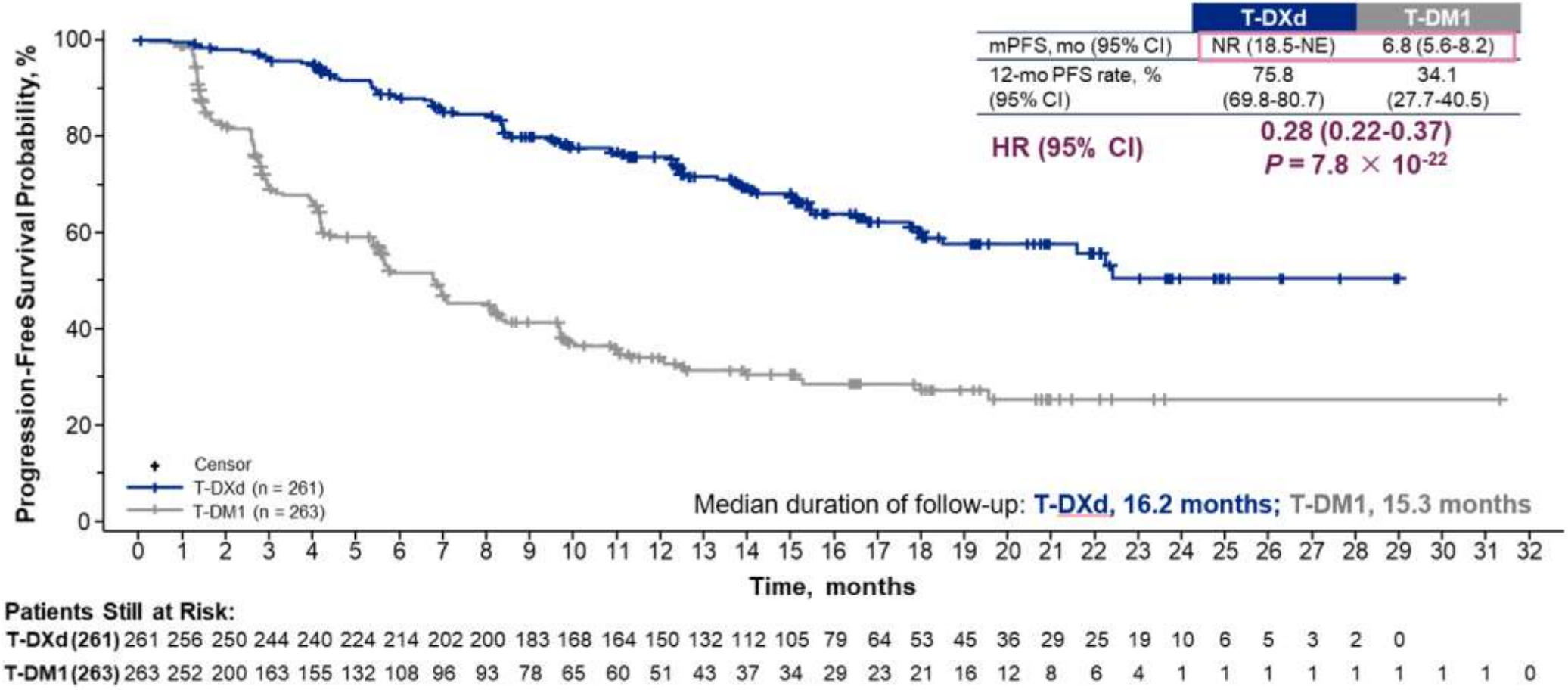
Baseline Characteristics	T-DXd n = 261	T-DM1 n = 263
Age, median (range), years	54.3 (27.9-83.1)	54.2 (20.2-83.0)
Region, n (%)		
Asia	149 (57.1)	160 (60.8)
North America	17 (6.5)	17 (6.5)
Europe	54 (20.7)	50 (19.0)
Rest of World	41 (15.7)	36 (13.7)
Hormone-receptor status, n (%)		
Positive	131 (50.2)	134 (51.0)
Negative	130 (49.8)	129 (49.0)
HER2 status,[a] n (%)		
3+	234 (89.7)	232 (88.2)
2+ with HER2 ISH+	25 (9.6)	30 (11.4)
1+	1 (0.4)	0
Visceral disease, n (%)		
Yes | No	184 (70.5) | 77 (29.5)	185 (70.3) | 78 (29.7)
Prior treatment for mBC,[b] n (%)	240 (92.0)	234 (89.0)
Pertuzumab	162 (62.1)	158 (60.1)
Prior lines of therapy for metastatic disease,[c] n (%)		
0-1	132 (50.6)	126 (47.9)
2+	129 (49.4)	137 (52.1)

HER2, human epidermal growth factor receptor 2; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]HER2 status was evaluated by immunohistochemical analysis at a central laboratory. HER2 ISH-positive refers to positive results on in situ hybridization. HER2 status could not be evaluated for 1 patient in each treatment group. [b]Excluding hormone therapy. [c]Patients who had had rapid progression (i.e., progression that had occurred within 6 months after receipt of neoadjuvant or adjuvant therapy or within 12 months after receipt of a neoadjuvant or adjuvant pertuzumab-containing regimen) were considered to have had one line of previous therapy. Lines of previous therapy did not include endocrine therapy.
1. Cortés J et al. *N Engl J Med*. 2022:386:1143-1154.

DESTINY-Breast03: PFS by BICR[1-3]

DESTINY-Breast03

Daiichi-Sankyo



BICR, blinded independent central review; HR, hazard ratio; mPFS, median progression-free survival; NE, not estimable; NR, not reached; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

1. Cortés J et al. *N Engl J Med.* 2022;386:1143-1154. 2. Cortés J et al. *N Engl J Med.* 2022; 2022;386(supplement). 3. Hurvitz SA et al. Presented at: San Antonio Breast Cancer Symposium 2021; December 7-10, 2021. Presentation GS3-01.

DESTINY-Breast03: Safety Summary

DESTINY-Breast03

Daiichi-Sankyo

n (%)[1]	T-DXd (n = 257)	T-DM1 (n = 261)
Any drug-related TEAE	252 (98.1)	226 (86.6)
Drug-related TEAE grade ≥3	116 (45.1)	104 (39.8)
Serious drug-related TEAE	28 (10.9)	16 (6.1)
Drug-related TEAE associated with discontinuation	33 (12.8)	13 (5.0)
Drug-related TEAE associated with dose interruption	91 (35.4)	34 (13.0)
Drug-related TEAE associated with dose reduction	55 (21.4)	33 (12.6)
Drug-related TEAE associated with an outcome of death	0	0

- Median (range) treatment duration[2]:
  - **T-DXd: 14.3 (0.7-29.8) months**
  - T-DM1: 6.9 (0.7-25.1) months
- Most common TEAE associated with treatment discontinuation[3]:
  - **T-DXd: ILD/pneumonitis[a] (8.2%)**
  - T-DM1: thrombocytopenia[b] (2.7%)
- Most common TEAEs associated with dose reduction[3]:
  - **T-DXd: nausea (6.2%), neutropenia[c] (3.5%)**
  - T-DM1: thrombocytopenia[b] (4.2%), ALT and AST increased (2.7% each)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ILD, interstitial lung disease; PTs, preferred terms; SMQ, standardized MedDRA query; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
Relationship to study drug was determined by the treating investigator. [a]Interstitial lung disease includes events that were adjudicated as ILD and related to use of T-DXd or T-DM1 (includes cases of potential ILD/pneumonitis, based on MedDRA v23.0 for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure). [b]This category includes the PTs platelet count decreased and thrombocytopenia. [c]This category includes the PTs neutrophil count decreased and neutropenia.
1. Cortés J et al. *N Engl J Med.* 2022;386(supplement). 2. Cortés J et al. *N Engl J Med.* 2022;386:1143-1154. 3. Cortés J et al. Presented at: ESMO Virtual Congress 2021; September 16-21, 2021. Presentation 2525.

DESTINY-Breast03 PRO & Hospitalization Endpoints & Analyses

DESTINY-Breast03

Daiichi-Sankyo

Endpoint	Description	Measures of interest	Main analyses
EORTC QLQ-C30	Oncology-specific questionnaire	• Global health status (GHS)/QoL[a] • Functioning scales: physical, role, emotional, cognitive, and social • Symptom scales: pain	• Change from baseline • Time to definitive deterioration (TDD)[b,c]
EORTC QLQ-BR45	Breast cancer-specific questionnaire	• Symptom scales: arm and breast	• TDD[b,c]
EQ-5D-5L	Generic questionnaire	• Self-rated health status (visual analog scale [VAS])	• TDD[c]
Hospitalization	Records assessment	• Date of admission to hospital • Status/date of discharge	• Time to first hospitalization • Length of stay

- Completion compliance for HRQoL patient questionnaires was high in both treatment groups, with **>97% completion at baseline** and **>82% completion from cycles 3-27** in both arms

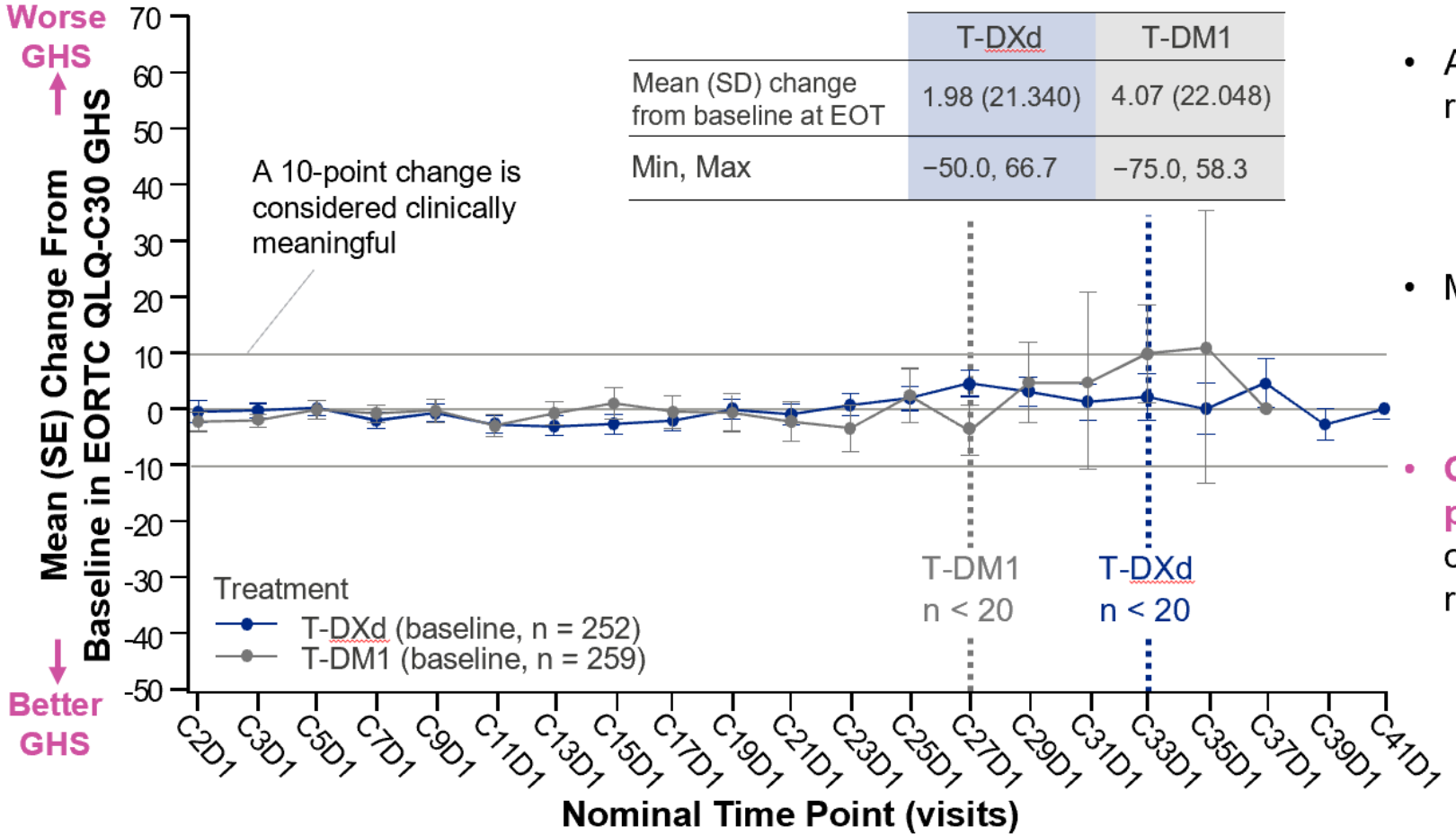
EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire; GHS, global health status; HRQoL, health-related quality of life; PRO, patient-reported outcome; QLQ-BR45, Quality of Life Breast cancer questionnaire; QLQ-C30, Quality of Life Core 30 questionnaire; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a]Primary PRO variable of interest. [b]Clinically meaningful deterioration defined as a change of 10 points or more in the GHS and subscale scores. [c]Not all variables measured were assessed for TDD.

Overall Health Status and QOL on Treatment

DESTINY-Breast03

Daiichi-Sankyo



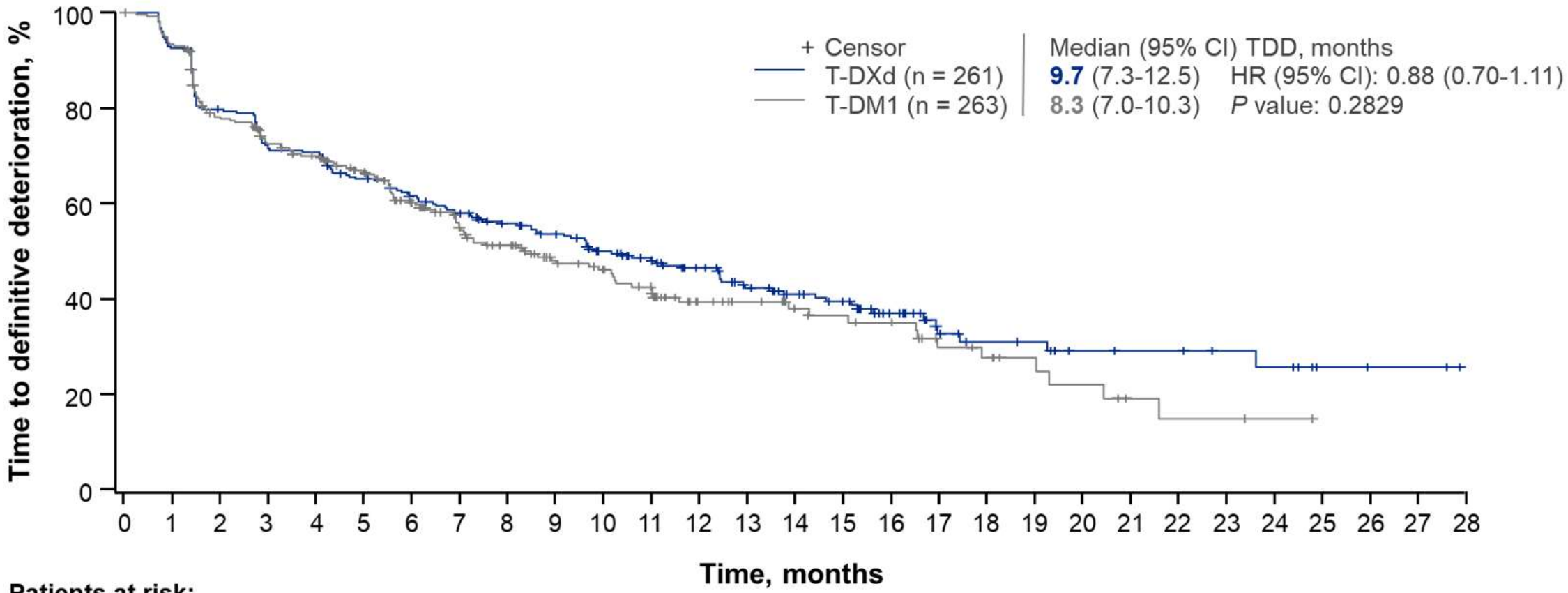
	T-DXd	T-DM1
Mean (SD) change from baseline at EOT	1.98 (21.340)	4.07 (22.048)
Min, Max	−50.0, 66.7	−75.0, 58.3

- As of May 21, 2021, patients still receiving study drug included:[1]
  - **T-DXd: 132 (51.4%)**
  - **T-DM1: 47 (18.0%)**
- Median (range) treatment duration:[2]
  - **T-DXd: 14.3 (0.7-29.8) months**
  - **T-DM1: 6.9 (0.7-25.1) months**
- **Global health was maintained in patients treated with T-DXd** while on treatment (until n < 20 when results are no longer informative)

C, cycle; D, day; EORTC, European Organization for Research and Treatment of Cancer; EOT, end of treatment; GHS, global health scale; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Scores range from 0 to 100; a linear transformation was applied to the raw GHS score, thus a higher score represents lower ("worse") GHS/overall QoL

1. Cortés J et al. Presented at: ESMO Virtual Congress 2021; September 16-21, 2021. Presentation 2525. 2. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154. `

Time to Definitive Deterioration (TDD) of QLQ-C30 GHS



Patients at risk:

T-DXd	261	232	198	179	175	158	146	136	125	116	101	92	79	66	55	50	34	23	16	15	11	10	10	8	7	4	3	2	0
T-DM1	263	237	191	171	162	146	121	102	86	70	64	56	37	32	26	23	21	16	12	9	7	4	3	3	1	0			

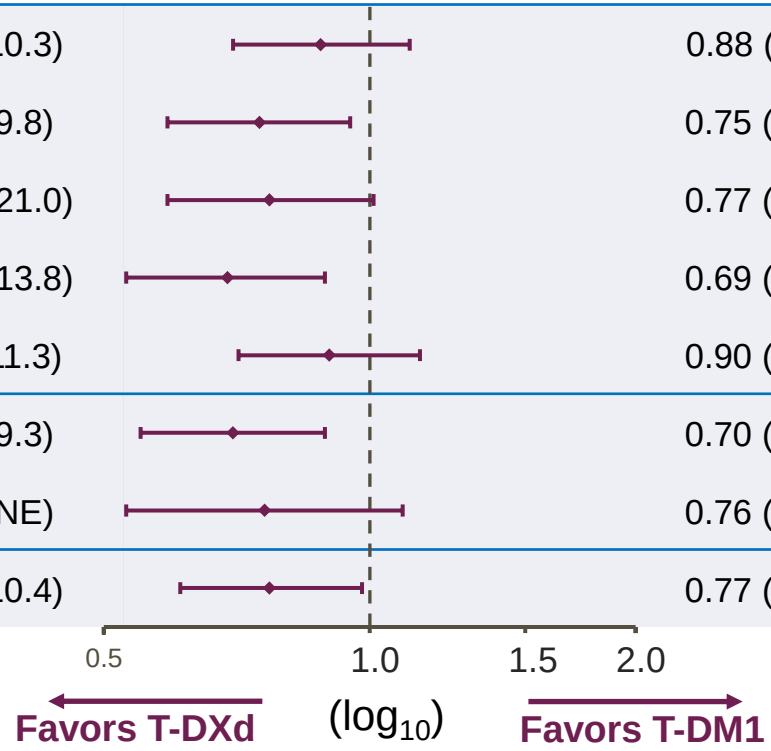
EORTC, European Organization for Research and Treatment of Cancer; GHS, global health status; HR, hazard ratio; QLQ-C30, Quality of Life Core 30 questionnaire; TDD, time to definitive deterioration; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
P values are not adjusted for multiple testing. TDD is defined as a >10-point change from baseline.

TDD in PRO Measures of Interest

DESTINY-Breast03

Daiichi-Sankyo

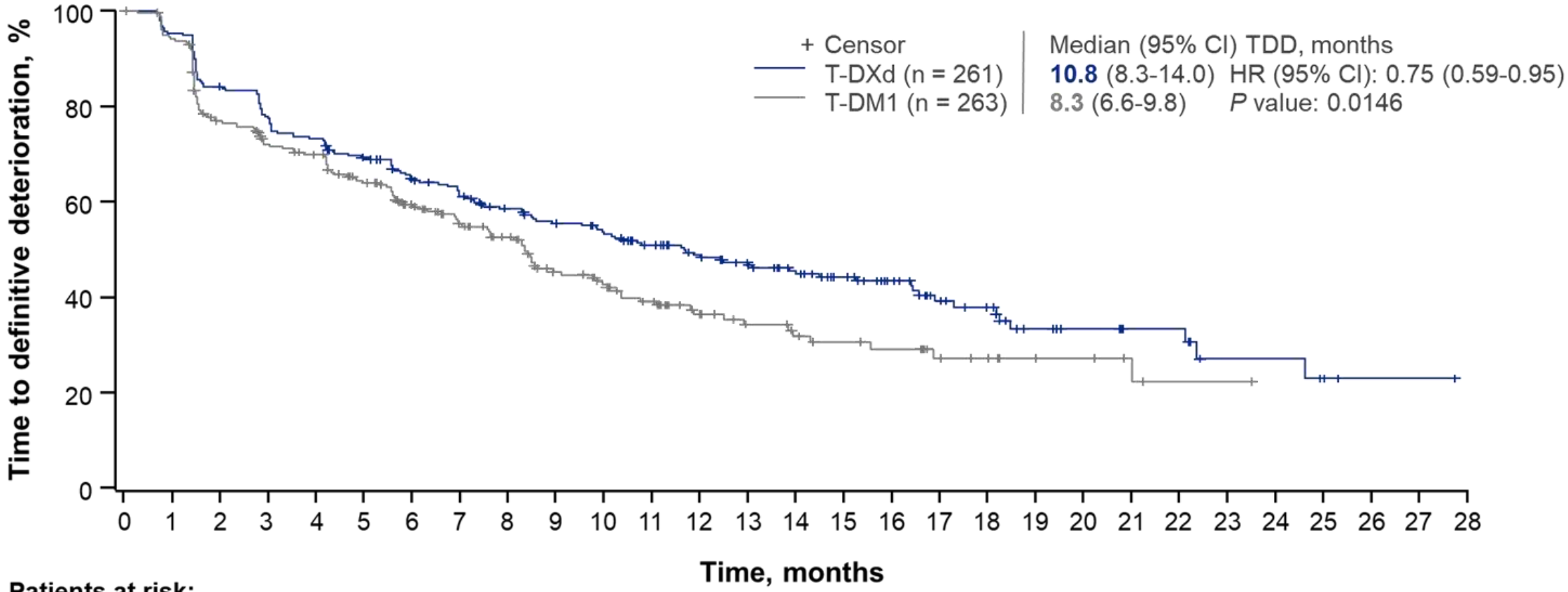
		Median (95% CI) TDD, months		HR (95% CI)	Nominal *P* value
		T-DXd (n = 261)	T-DM1 (n = 263)		
EORTC QLQ-C30	Global health status/QoL[a]	9.7 (7.3-12.5)	8.3 (7.0-10.3)	0.88 (0.70-1.11)	0.2829
	Pain symptoms[b]	10.8 (8.3-14.0)	8.3 (6.6-9.8)	0.75 (0.59-0.95)	0.0146
	Physical functioning[b]	16.7 (14.5-NE)	10.3 (8.3-21.0)	0.77 (0.59-1.01)	0.0529
	Emotional functioning[b]	16.4 (14.1-19.9)	10.5 (9.0-13.8)	0.69 (0.53-0.89)	0.0049
	Social functioning[b]	11.1 (7.3-13.4)	9.0 (7.1-11.3)	0.90 (0.71-1.14)	0.3577
EORTC QLQ-BR45	Arm symptoms[b]	11.1 (8.5-14.8)	7.0 (5.6-9.3)	0.70 (0.55-0.89)	0.0033
	Breast symptoms[b]	26.4 (26.4-NE)	NE (NE-NE)	0.76 (0.53-1.09)	0.1329
EQ-5D-5L	VAS[b]	13.2 (10.1-15.3)	8.5 (7.3-10.4)	0.77 (0.61-0.98)	0.0354



EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire; GHS, global health status; HR, hazard ratio; PRO, patient-reported outcome; QLQ-BR45, Quality of Life Breast cancer questionnaire; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; TDD, time to definitive deterioration; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; VAS, visual analog scale.
P values are not adjusted for multiple testing. TDD is defined as a >10-point change from baseline. [a]Primary PRO variable of interest. [b]Secondary PRO variable of interest.

TDD of QLQ-C30 Pain Symptoms

DESTINY-Breast03



Patients at risk:

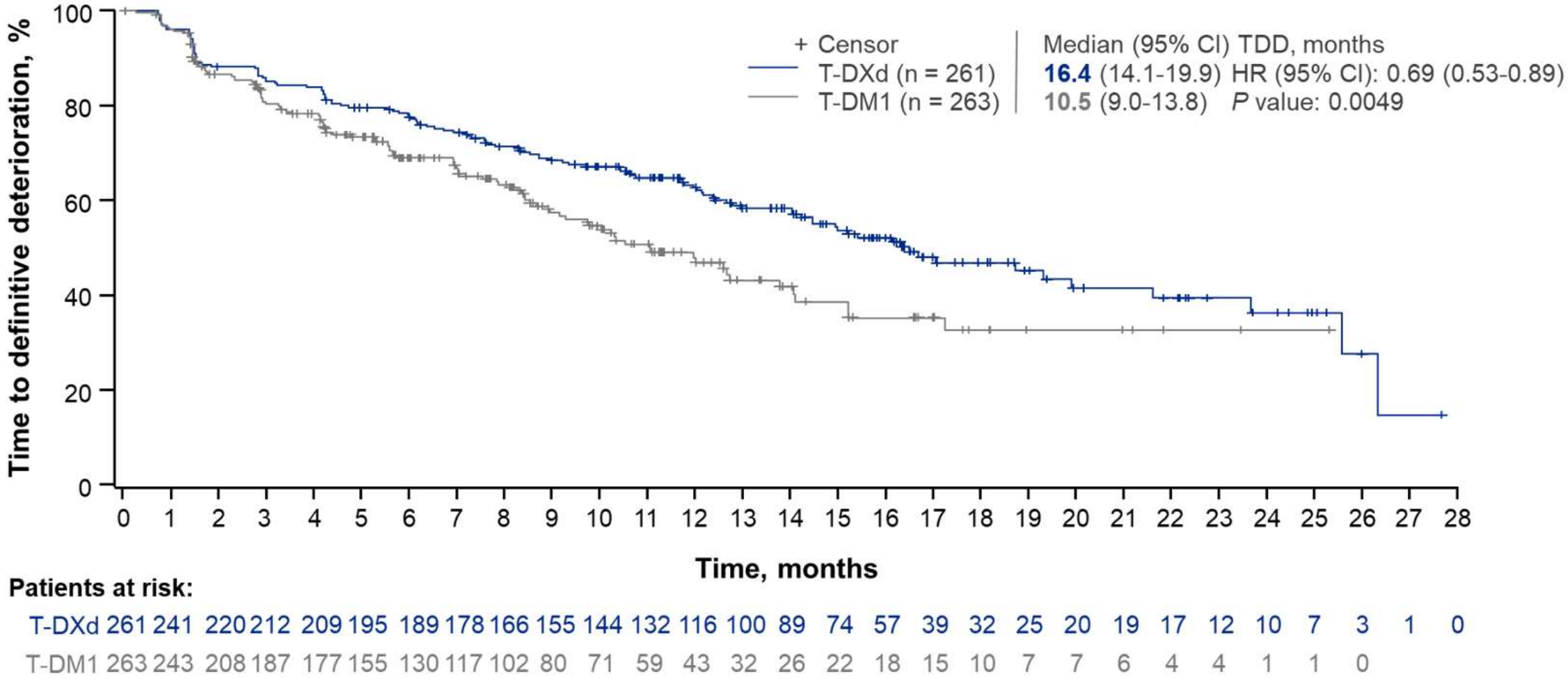
T-DXd	261	240	210	193	182	168	152	141	129	120	111	100	89	80	68	58	44	31	26	17	14	11	11	6	6	3	1	1	0
T-DM1	263	237	185	169	161	141	118	100	87	67	59	49	34	28	24	20	18	13	11	7	7	4	3	3	0				

EORTC, European Organization for Research and Treatment of Cancer; HR, hazard ratio; QLQ-C30, Quality of Life Core 30 questionnaire; TDD, time to definitive deterioration; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
P values are not adjusted for multiple testing. TDD is defined as a >10-point change from baseline.

TDD of QLQ-C30 Emotional Functioning

DESTINY-Breast03

Daiichi-Sankyo



EORTC, European Organization for Research and Treatment of Cancer; HR, hazard ratio; QLQ-C30, Quality of Life Core 30 questionnaire; TDD, time to definitive deterioration; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
P values are not adjusted for multiple testing. TDD is defined as a >10-point change from baseline.

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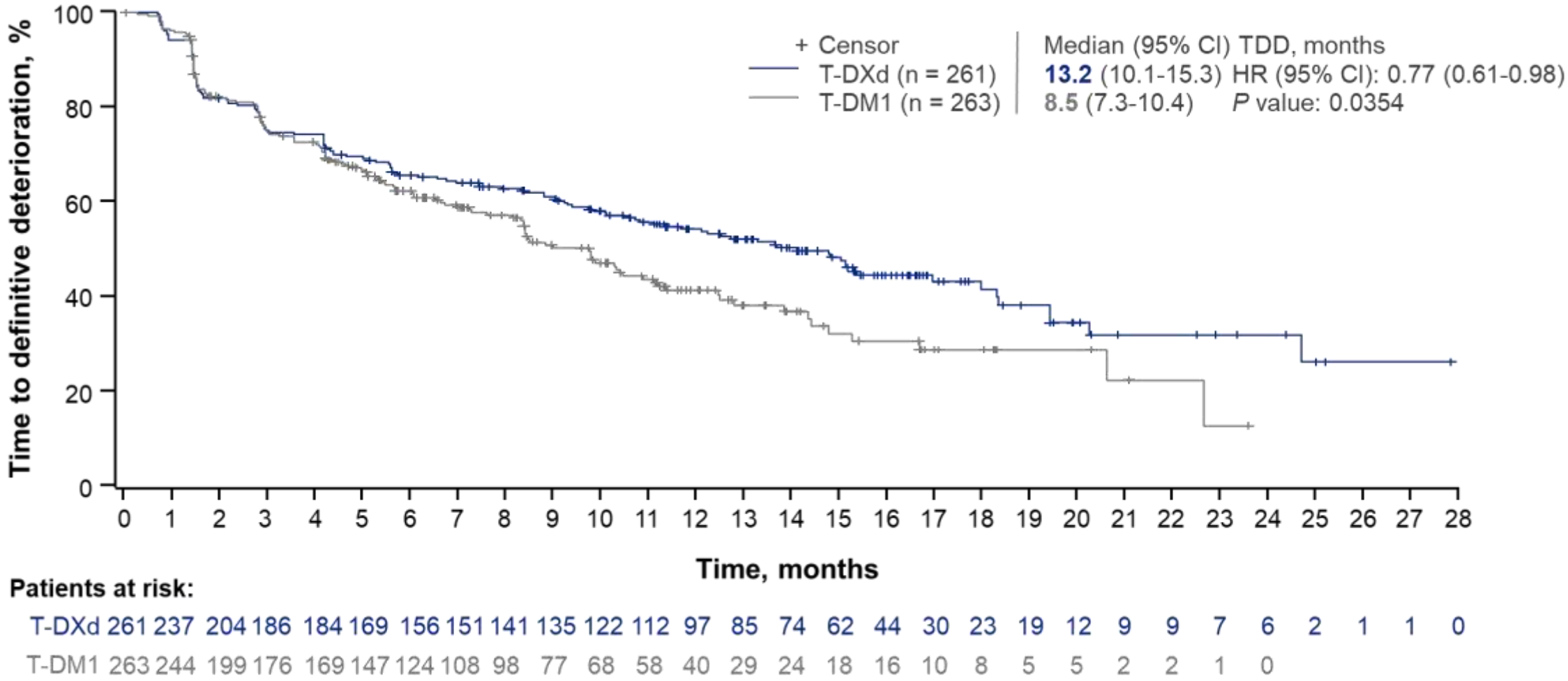
TDD of EQ-5D-5L VAS[a]



EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire; HR, hazard ratio; TDD, time to definitive deterioration; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; VAS, visual analog scale.

P values are not adjusted for multiple testing. TDD is defined as a >10-point change from baseline. [a]VAS of self-rated overall health and quality of life, measured on a scale from 0 to 100.

Hospitalization-Related Endpoints

DESTINY-Breast03

Parameter	T-DXd (n = 261)	T-DM1 (n = 263)
Subjects with hospitalization, n (%)	18 (6.9)	19 (7.2)
Median (range) time to first hospitalization,[a] days	219.5 (0-723)	60.0 (0-399)
Median (range) length of hospital stay, days	10.5 (1-181)	9.0 (2-25)
Died, n (%)	2 (0.8)	1 (0.4)
Discharged home, n (%)	15 (5.7)	16 (6.1)
Discharged to home health care, n (%)	1 (0.4)	1 (0.4)

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Time to first hospitalization is defined as the time from the date of randomization to the date of the first hospitalization during the study treatment (from date of first dose to 47 days after last dose). Time for subjects whose first hospitalization date was prior to treatment start date was calculated as 0.

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Conclusions

- **Overall health status and QoL was maintained with T-DXd,** based on mean change from baseline of EORTC QLQ-C30 GHS scale (primary PRO variable of interest) and other specified subscales of interest
- Median (range) treatment duration was longer in the T-DXd arm (14.3 [0.7-29.8] months) than in the T-DM1 arm (6.9 [0.7-25.1] months)[1]
- For all prespecified PRO variables of interest, the HR for TDD numerically favored T-DXd over T-DM1 (HR range, 0.69-0.90), indicating **T-DXd treatment delays the deterioration of QoL in patients with mBC**
  - **Delayed TDD of pain symptoms with T-DXd** (HR, 0.75) is particularly salient, given its profound impact on QoL[2,3]
- Time to **first hospitalization was delayed with T-DXd** versus T-DM1: median 219.5 days versus 60.0 days, respectively (interpretation limited by low rates of hospitalization in both arms)
- This evidence of **maintained QoL while on treatment with T-DXd and delayed definitive deterioration across prespecified scales versus T-DM1** further supports the improved efficacy (including superior PFS) and manageable safety profile of T-DXd versus T-DM1,[1] thus supporting **T-DXd as a standard of care for patients with HER2+ mBC**

EORTC, European Organization for Research and Treatment of Cancer; GHS, global health status; HR, hazard ratio; mBC, metastatic breast cancer; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; TDD, time to definitive deterioration; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

1. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154. 2. Dueñas M, et al. *J Pain Res.* 2016;9:457–467. 3. Dams L et al. *Supportive Care Cancer.* 2022;doi: 10.1007/s00520-022-06805-0.

Trastuzumab-deruxtecan (T-DXd) in HER2-positive breast cancer patients with active brain metastases: Primary outcome analysis from the TUXEDO-1 trial

Rupert Bartsch[1], Anna Sophie Berghoff[1], Julia Furtner[2], Maximilian Marhold[1], Elisabeth Sophie Bergen[1], Sophie Roider-Schur[3], Angelika Martina Starzer[1], Heidrun Forstner[1], Beate Rottenmanner[1], Karin Dieckmann[4], Zsuzsanna Bago-Horvath[5], Georg Widhalm[6], Aysegül Ilhan-Mutlu[1], Christoph Minichsdorfer[1], Thorsten Fuereder[1], Christian Singer[7], Ansgar Weltermann[8], Rainer Puhr[1], Matthias Preusser[1]

[1] Department of Medicine 1, Division of Oncology, Medical University of Vienna; [2] Department of Radiology, Medical University of Vienna, Vienna, Austria; [3] Department Oncology, St. Joseph's Hospital, Vienna, Austria; [4] Department of Radio-Oncology, Medical University of Vienna, Vienna, Austria; [5] Department of Pathology, Medical University of Vienna, Vienna, Austria; [6] Department of Neurosurgery, Medical University of Vienna, Vienna, Austria; [7] Department of Gynaecology, Medical University of Vienna, Vienna, Austria; [8] Department of Medicine 1, Elisabethinen Hospital Linz, Ordensklinkum Linz, Linz, Austria

Investigator-Initiated Study

Background

- Breast cancer is the second most common cause of brain metastases among solid cancers[1]
- Growing interest in systemic treatment to improve disease control
- HER2 tyrosine-kinase inhibitors in combination with capecitabine yielded clinically relevant activity in BM progressing after prior local therapy[2,3]
- Upfront therapy with lapatinib and capecitabine delayed WBRT[4]
- HER2Climb[5]
  - Tucatinib + trastuzumab +capecitabine *vs*. placebo + trastuzumab + capecitabine
  - Largest population of patients with active BM in a randomized study
  - Intracranial response rate (active BM): 47.3%
  - PFS in patients with active BM 9.5 months (95% CI 7.5-11.1)
  - ESMO guidelines: standard-of-care for active BM if no immediate local therapy is required
- Role of antibody drug-conjugates is less well established[6,7]
  - DEBBRAH: RR (T-DXd) in progressive BM 44.4% (4/9 pts.)[8]

1 Weil RJ et al. Am J Pathol 2005;167:913-920.; 2 Lin NU et al. Clin Cancer Res 2009;15:1452-1459.; 3 Freedman RA et al. J Clin Oncol 2019;37:1081-1089.; 4 Bachelot T et al. Lancet Oncol 2013;14:64-71.; 5 Lin NU et al. J Clin Oncol 2020;38:2610-2619.; 6 Montemurro F et al. Ann Oncol 2020;31:1350-1358.; 7 Hurvitz S et al. GS3-01; SABCS 2021.; 8 Vaz Batista M et al. PF4-06; SABCS 2021.

Study Design

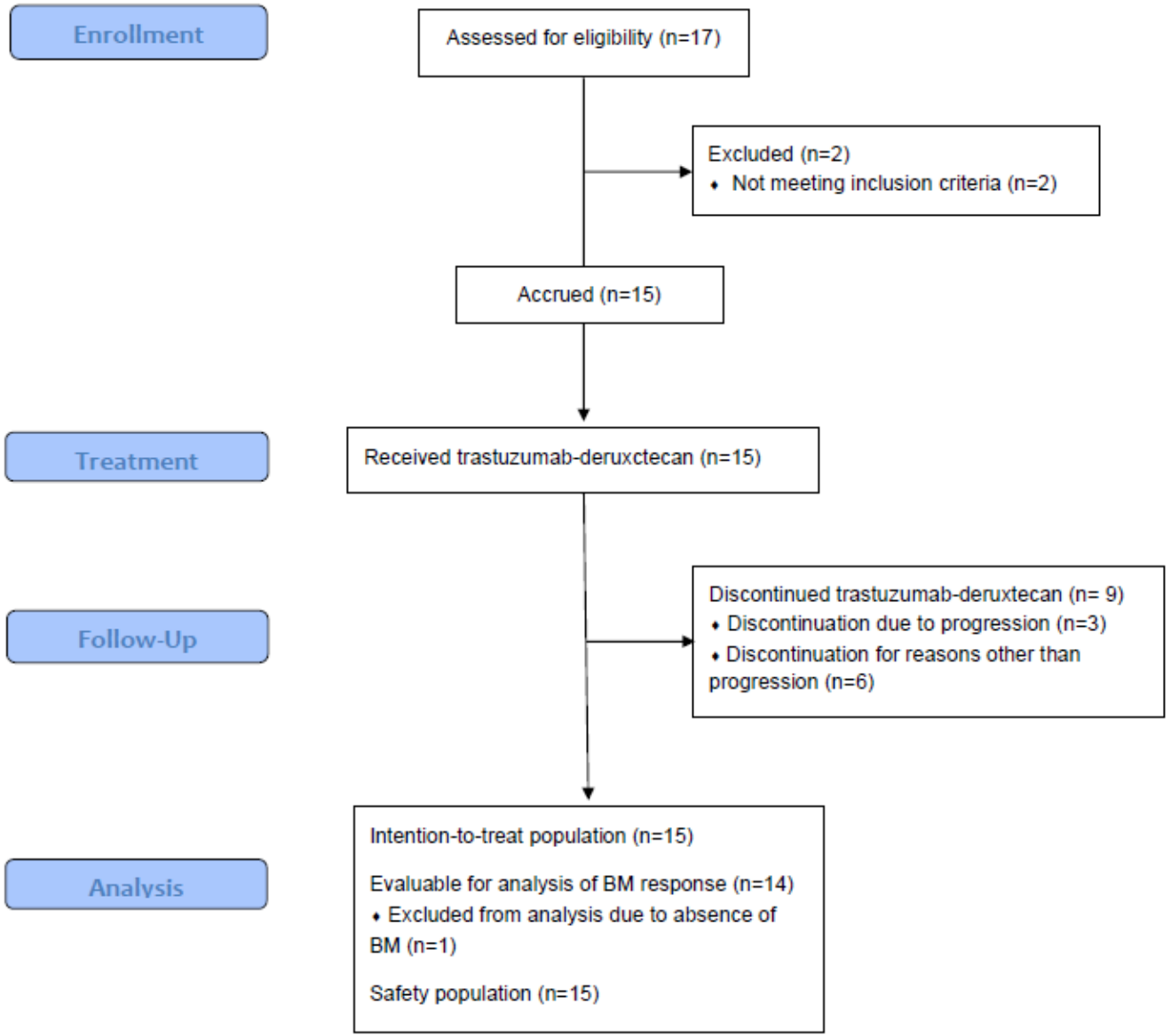
Primary Endpoint: ORR (CNS) by RANO-BM criteria
Secondary Endpoints:
- Clinical Benefit Rate (CR+PR+SD ≥6 months)
- Extracranial Response rate
- PFS
- OS
- Safety
- Ouality of Life

TUXEDO-1 (NCT04752059)

BM, brain metastasis; BW, body weight; CNS, central nervous system; D1, day 1; EOT, end of treatment; FU, follow up; IV, intravenous; KPS, Karnofsky performance; LVEF, left ventricular ejection fraction; q3w, once every 3 weeks; RANO, response assessment in neuro-oncology; T-DXd, trastuzumab deruxtecan.
EudraCT: 2020-000981-41.

Simon Two Stage Design
- RR (CNS) >60% suggests clinically relevant activity
- RR (CNS) <26% suggests no benefit compared to previous systemic treatment options
- Stage 1: 6 pts. (at least three responses); Stage 2: 9 pts; overall 15 pts. (at least 7 responses)
- Type 1 error rate 5%; power 80%

Patient Populations and Disposition



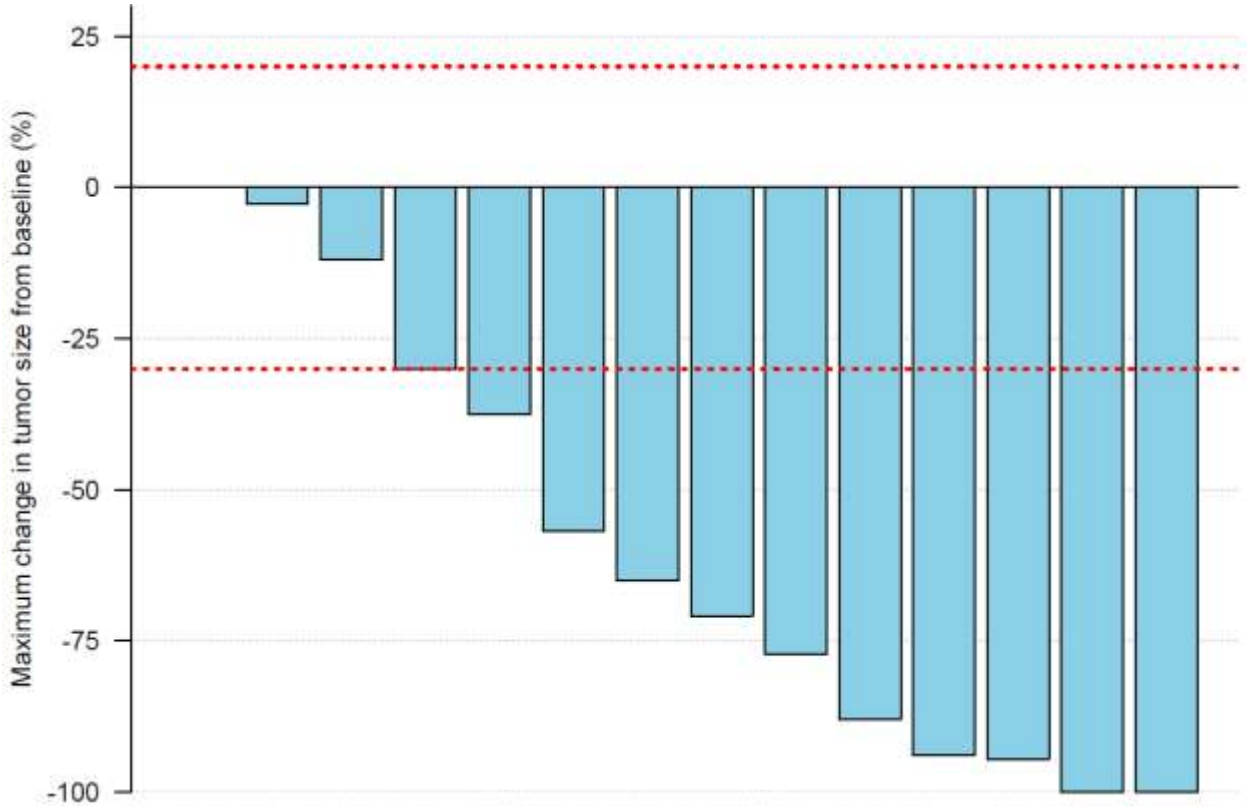
Patient Characteristics

Patient Characteristcs	N=15
Sex; n (%)	
Female	14 (93.3%)
Male	1 (6.7%)
Age; median (range)	
Age at Baseline	69 (30-76)
ECOG Performance Status; n (%)	
ECOG 0	9 (60%)
ECOG 1	6 (40%)
Presence of Neurologic Symptoms at Baseline; n (%)	
Yes	6 (40%)
No	9 (60%)
Disease Subtype; n (%)	
HER2-positive/Luminal B	12(80%)
HER2-positive/non-luminal	3 (20%)
Brain Metastases Free Survival (BMFS); median (range)	
BMFS from Diagnosis of Metastatic Disease (months)	17 (0-48)
Visceral Metastases; n (%)	
Yes	12 (80%)
No	3 (20%)
Prior HER2-directed Therapy; n (%)	
Trastuzumab+Pertuzumab	15 (100%)
T-DM1	9 (60%)
Lapatinib	4 (26.7%)
Other	1 (6.7%)
Status of Brain Metastases; n (%)	
Untreated	6 (40%)
Progressive BM after prior Local Therapy	9 (60%)
Prior Lines of Treatment for mBC; median (range)	
Prior Lines of Treatment before T-DXd	2 (1-5)

Primary Endpoint

Objective Response Rate (RANO-BM criteria)

ORR (intention-to-treat population; *n*=15): 73.3% (95% CI 48.1-89.1)



One patient with dural metastases

RR (per-protocol-population; *n*=14): 78.6%

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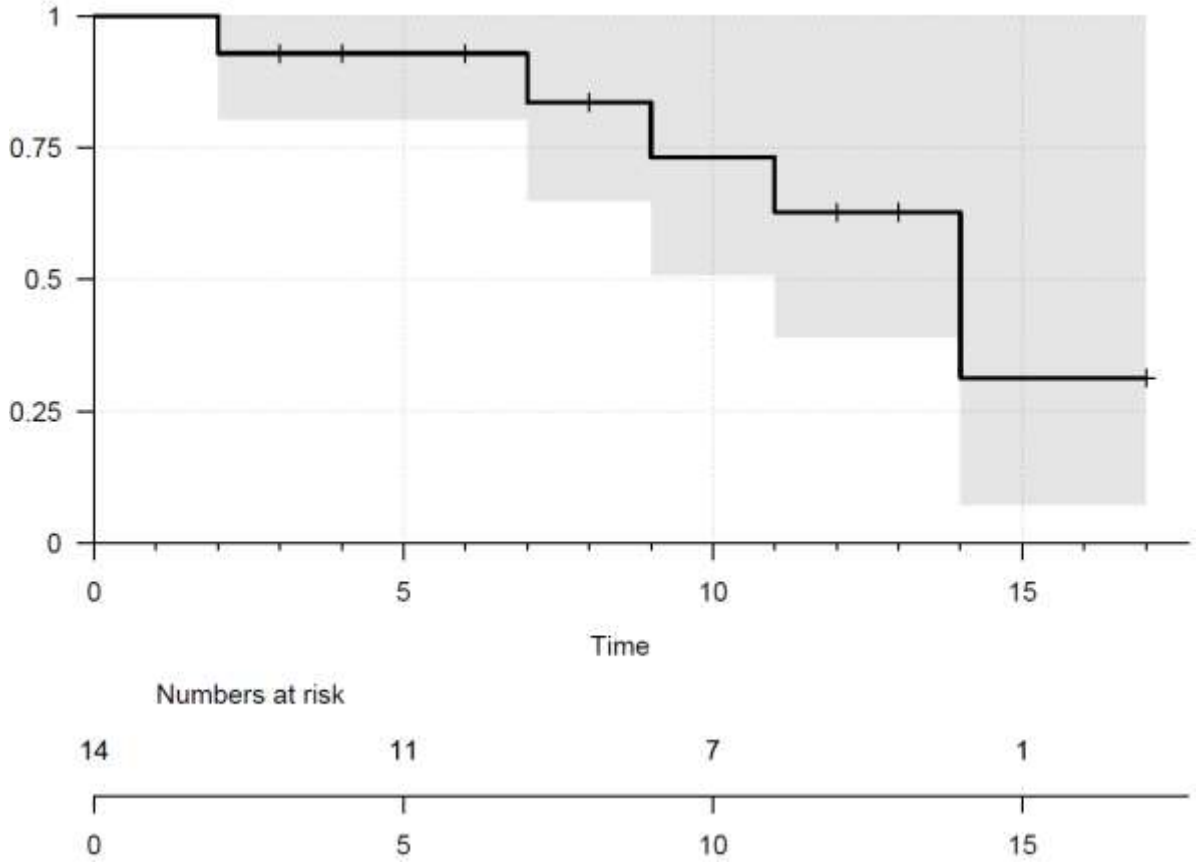
Secondary Endpoints



- PFS: 14 months (95% CI 11.0-n.r.)
- Median follow-up 11 months (range 3 – 17 months)

- Clinical Benefit Rate (CR+PR+SD ≥6 months): 13/15 (86.7%) in the ITT population and 13/14 (92.9%) in the PP population
- Median OS not reached
- Extracranial Response Rate:
- Pts. with extracranial metastases at baseline (*n*=13): PR 5/13 (27.8%)
- Pts with measurable extracranial disease at baseline (*n*=8): PR 5/8 (62.5%)

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Safety

Safety population n=15			
Any adverse event 15 pts. (100%)			
Haematological adverse events			
	Grade 1/2	Grade 3	Grade 4
Anaemia	46.6%	6.7%	
Neutropenia	46.6%		
Non-haematologic adverse events >2 patients			
	Grade 1/2	Grade 3	Grade 4
Fatigue	66.7%	15.3%	
Nausea	46.7%		
Constipation	40%		
Hypokalaemia	40%		
Diarrhoea	33.4%	6.7%	
Bone pain	26.6%		
Dyspnoea	26.6%	6.7%	
Fall	20%		
Urinary tract infection	20%	6.7%	
Vomiting	20%		

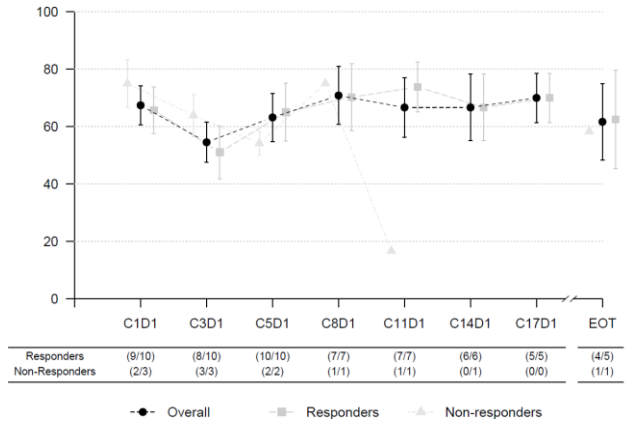
AEs of special interest:
- Ejection fraction decrease grade 3: 1 pt.,
- ILD grade 2 1 pt.

6 SAEs in a total of 4 patients

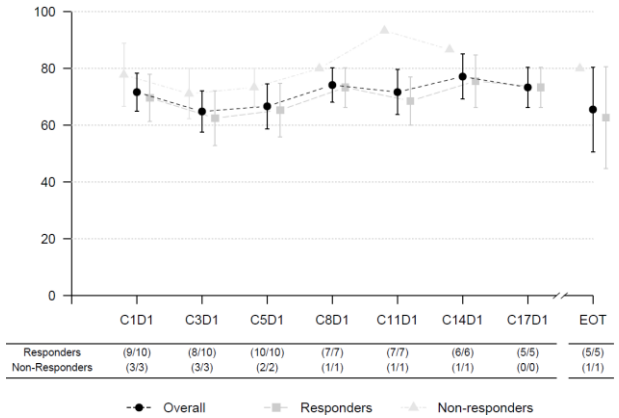
1 Pt. grade 5 urosepsis (not related to IMP)

Quality-of-Life

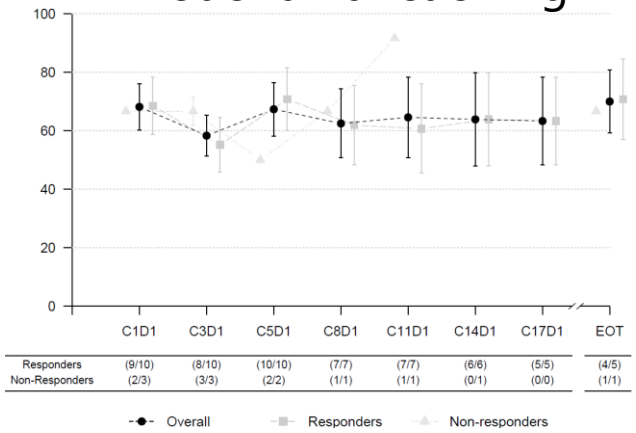
Global health status



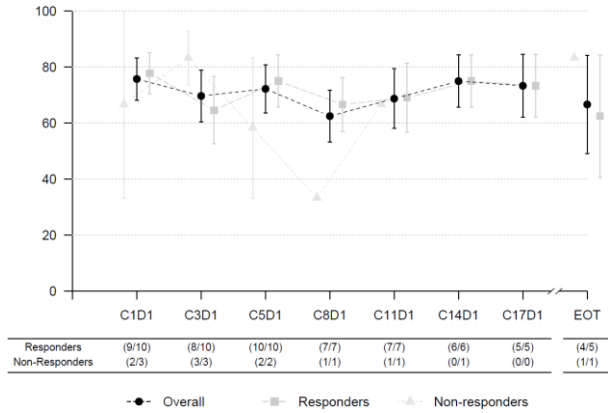
Physical functioning



Emotional functioning



Cognitive functioning



QoL was maintained over the treatment period

Conclusions

- Trastuzumab-deruxtecan was active in patients with HER2-positive breast cancer brain metastases
  - TUXEDO-1 met its primary endpoint
  - Response rate (intention-to-treat population) 73.3%
  - Comparable extra- and intracranial response rates
  - Prolonged disease control
- No new safety signals were observed
- Quality-of-life was maintained over the treatment period
- Adds to the growing body of evidence that systemic therapy is feasible in HER2-positive breast cancer with CNS metastasis
- Supports further investigation of ADCs in the context of secondary CNS malignancies

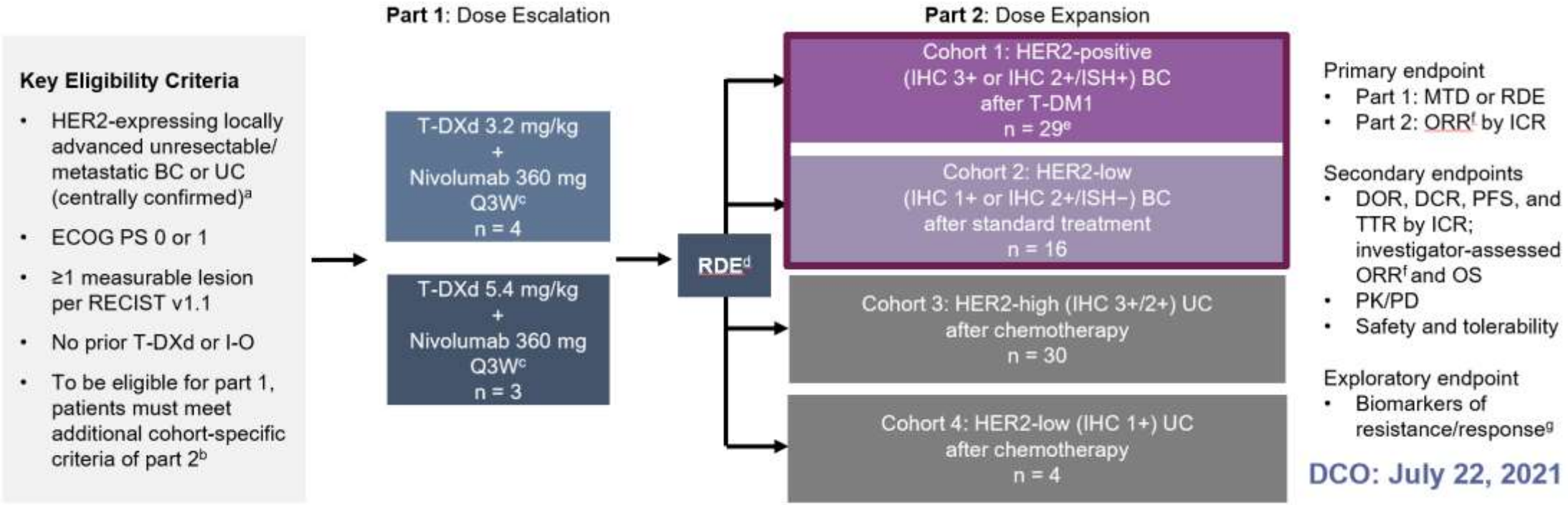
Primary Analysis from DS8201-A-U105: A 2-part, Open-label, Phase 1b Trial Assessing Trastuzumab Deruxtecan (T-DXd) with Nivolumab in Patients with HER2-expressing Advanced Breast Cancer

Erika Hamilton, Charles L. Shapiro, Valentina Boni, Miguel Martin, Gianluca Del Conte, Javier Cortes, Laila Agrawal, Hendrik-Tobias Arkenau, Antoinette R. Tan, Philip Debruyne, Anna Minchom, Annemie Rutten, Frances Valdes-Albini, Evan Y. Yu, Fumitaka Suto, Fu-Chih Cheng, Bincy Augustine, Ben Cheng, Daniel Barrios, Sara A. Hurvitz

Erika Hamilton, MD

Sarah Cannon Research Institute/Tennessee Oncology,
Nashville, TN, USA

DS8201-A-U105 Study Design



BC, breast cancer; DCO, data cutoff; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; I-O, immuno-oncology; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; MTD, maximum tolerated dose; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PK/PD, pharmacokinetics/pharmacodynamics; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; RDE, recommended dose for expansion; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TTR, time to response; UC, urothelial carcinoma.

[a]By IHC (BC and UC) and ISH (BC) before enrollment. [b]Includes all inclusion criteria listed and cohort descriptions in Part 2. Other inclusion criteria were: cohort 1 patients had prior T-DM1 therapy with documented progression; cohort 2 patients should have exhausted treatments that could confer any clinically meaningful benefit; cohorts 3 and 4 patients had prior platinum-based combination chemotherapy with documented progression.

[c]Nivolumab 360 mg Q3W is an approved dose in the United States for certain indications in combination with ipilimumab or fluoropyrimidine- and platinum-containing chemotherapy (Opdivo [nivolumab] prescribing information) and is currently under investigation in monotherapy oncology studies. [d]The RDE for T-DXd was 5.4 mg/kg. [e]Data from 3 patients treated with the RDE of 5.4 kg/mg in part 1 were pooled with data from cohort 1 for part 2. [f]ORR was based on RECIST v1.1. [g]Biomarker data (PD-L1 expression by IHC) were assessed from baseline archival or new tumor tissue biopsies.

Baseline Demographics and Clinical Characteristics in BC Cohorts

Baseline Characteristics	Cohort 1 HER2+ n = 32[a]	Cohort 2 HER2-low n = 16	Overall N = 48
Median age[b], years (range)	55.5 (36.3-76.2)	47.3 (34.4-64.7)	53.6 (34.4-76.2)
Female, n (%)	32 (100)	16 (100)	48 (100)
Region, n (%)			
Europe	12 (37.5)	9 (56.3)	21 (43.8)
United States	20 (62.5)	7 (43.8)	27 (56.3)
ECOG PS[c], n (%)			
0	20 (62.5)	8 (50.0)	28 (58.3)
1	12 (37.5)	8 (50.0)	20 (41.7)
HER2 expression[d], n (%)			
IHC 1+	0	6 (37.5)	6 (12.5)
IHC 2+	5 (15.6)	10 (62.5)	15 (31.3)
ISH+	5 (100)	0	5 (33.3)
ISH equivocal	0	1 (10.0)	1 (6.7)
ISH−	0	9 (90.0)	9 (60.0)
IHC 3+	27 (84.4)	0	27 (56.3)
HR status, n (%)			
Positive	20 (62.5)	13 (81.3)	33 (68.8)
Negative	12 (37.5)	3 (18.8)	15 (31.3)

Treatment History	Cohort 1 HER2+ n = 32[a]	Cohort 2 HER2-low n = 16	Overall N = 48
Number of lines of unique regimens for metastatic/locally advanced unresectable setting, n (%)			
0	1 (3.1)	2 (12.5)	3 (6.3)
1	0	1 (6.3)	1 (2.1)
2	3 (9.4)	1 (6.3)	4 (8.3)
3	5 (15.6)	1 (6.3)	6 (12.5)
≥4	23 (71.9)	11 (68.8)	34 (70.8)
Lines of unique regimens for metastatic/locally advanced unresectable setting, median (range)	5 (0-14.0)	4 (0-10.0)	4.5 (0-14.0)
History of brain metastasis, n (%)	7 (21.9)	3 (18.8)	10 (20.8)

ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; RDE, recommended dose for expansion.
[a]Includes 3 patients treated at T-DXd 5.4 mg/kg RDE in combination with nivolumab 360 mg during part 1. [b]Median age at informed consent. [c]Performance status on the ECOG scale ranges from 0 to 5, with higher scores indicating greater disability. [d]HER2 expression was centrally confirmed prospectively by analysis of archival tissue (most recent tumor tissue preferred) according to the guidelines from the American Society of Clinical Oncology/College of American Pathologists. According to these guidelines, HER2 positivity was defined as HER2 IHC 3+ or IHC 2+/ISH+.

Patient Disposition

	Cohort 1 HER2+ n = 32[a]	Cohort 2 HER2-low n = 16	Overall N = 48
T-DXd treatment status, n (%)			
Ongoing	7 (21.9)	1 (6.3)	8 (16.7)
Discontinued	25 (78.1)	15 (93.8)	40 (83.3)
Primary reason for discontinuing T-DXd, n (%)			
Progressive disease	9 (28.1)	11 (68.8)	20 (41.7)
Clinical progression	3 (9.4)	2 (12.5)	5 (10.4)
Adverse event	10 (31.3)[b]	1 (6.3)[c]	11 (22.9)
Patient withdrawal	1 (3.1)	1 (6.3)	2 (4.2)
Physician decision	1 (3.1)	0	1 (2.1)
Other[d]	1 (3.1)	0	1 (2.1)
Nivolumab treatment status, n (%)			
Ongoing	6 (18.8)	0	6 (12.5)
Discontinued	26 (81.3)	16 (100)	42 (87.5)
Primary reason for discontinuing nivolumab, n (%)			
Progressive disease	8 (25.0)	11 (68.8)	19 (39.6)
Clinical progression	2 (6.3)	2 (12.5)	4 (8.3)
Adverse event	13 (40.6)[e]	2 (12.5)[f]	15 (31.3)
Patient withdrawal	1 (3.1)	1 (6.3)	2 (4.2)
Physician decision	2 (6.3)	0	2 (4.2)
Duration of follow-up, median (range), months	18.7 (1.7-26.9)	12.7 (1.7-21.4)	18.2 (1.7-26.9)

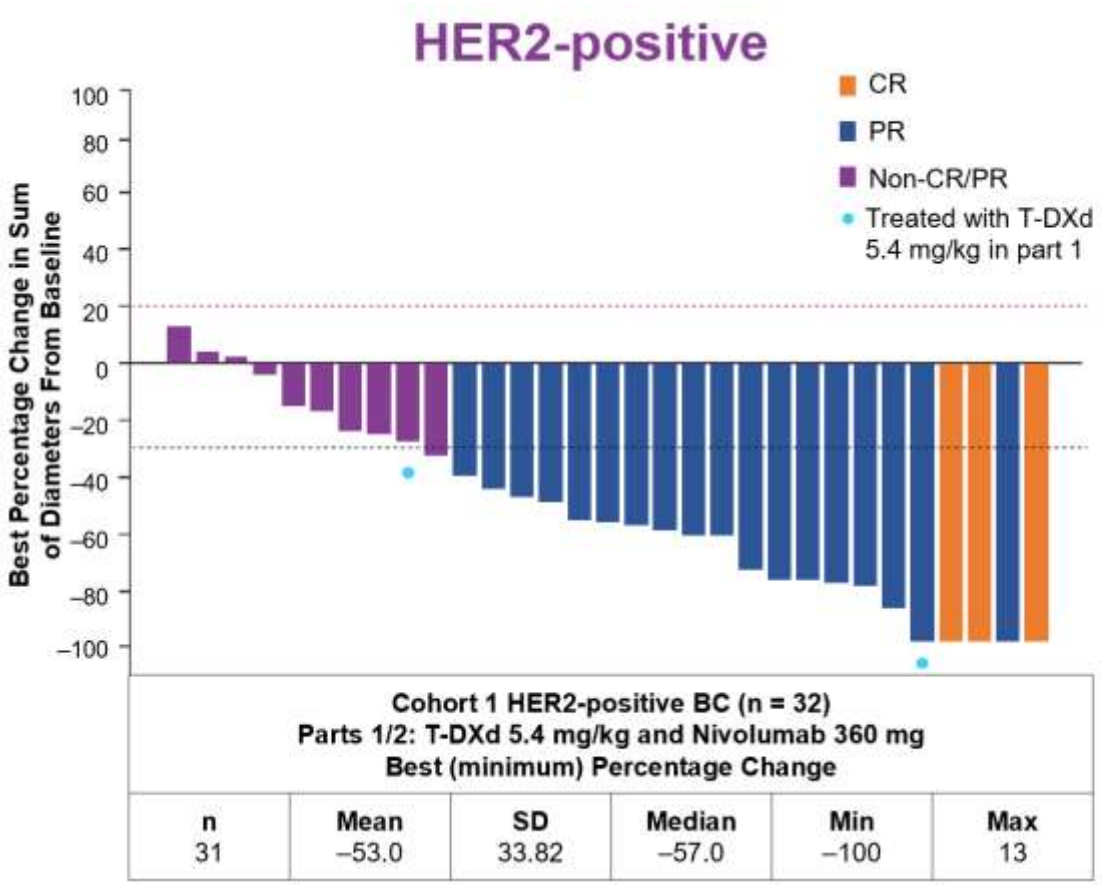
HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; RDE, recommended dose for expansion; T-DXd, trastuzumab deruxtecan.
[a]Includes 3 patients treated at T-DXd 5.4 mg/kg RDE in combination with nivolumab 360 mg during part 1. [b]1 troponin T increase (grade 3); 2 ILD (1 grade 1 and 1 grade 2); 4 pneumonitis (1 grade 1, 2 grade 2, and 1 grade 5); 1 amylase increase (grade 3); 1 femur fracture (grade 3); and 1 anemia (grade 3). [c]1 pneumonitis (grade 1). [d]Patient decision. [e]1 anemia (grade 3); 1 aspartate aminotransferase increase (grade 2); 1 vision blurred (grade 3); 1 troponin T increase (grade 3); 2 ILD (1 grade 1 and 1 grade 2); 1 femur fracture (grade 3); 1 lymphocyte count decreased (grade 3); 4 pneumonitis (1 grade 1, 2 grade 2, and 1 grade 5); 1 amylase increase (grade 3). [f]1 neutropenia (grade 3); 1 aspartate aminotransferase increase (grade 3).

Summary of Efficacy Results in BC Cohorts

	Cohort 1 HER2+ n = 32[a]	Cohort 2 HER2-low n = 16
Confirmed ORR by ICR (ORR, CR + PR)		
n (%)	**21 (65.6)**	**8 (50.0)**
95% CI	46.8-81.4	24.7-75.3
Best overall response, n (%)		
CR	3 (9.4)	0
PR	18 (56.3)	8 (50.0)
SD	9 (28.1)	4 (25.0)
PD	2 (6.3)	2 (12.5)
NE	0	2 (12.5)
Median DOR[b], months (95% CI)	NE (7.9-NE)	5.5 (2.8-8.0)
Median PFS, months (95% CI)	11.6 (6.9-NE)	7.0 (2.3-10.8)
Median TTR, months (range)	1.6 (1.2-5.5)	3.7 (2.6-9.8)
Median OS, months (95% CI)	NE (20.8-NE)	19.5 (2.7-NE)
Median treatment duration, months (range)		
T-DXd	8.9 (1-23)[c]	6.9 (1-21)
Nivolumab	5.5 (1-23)[c]	5.9 (1-14)

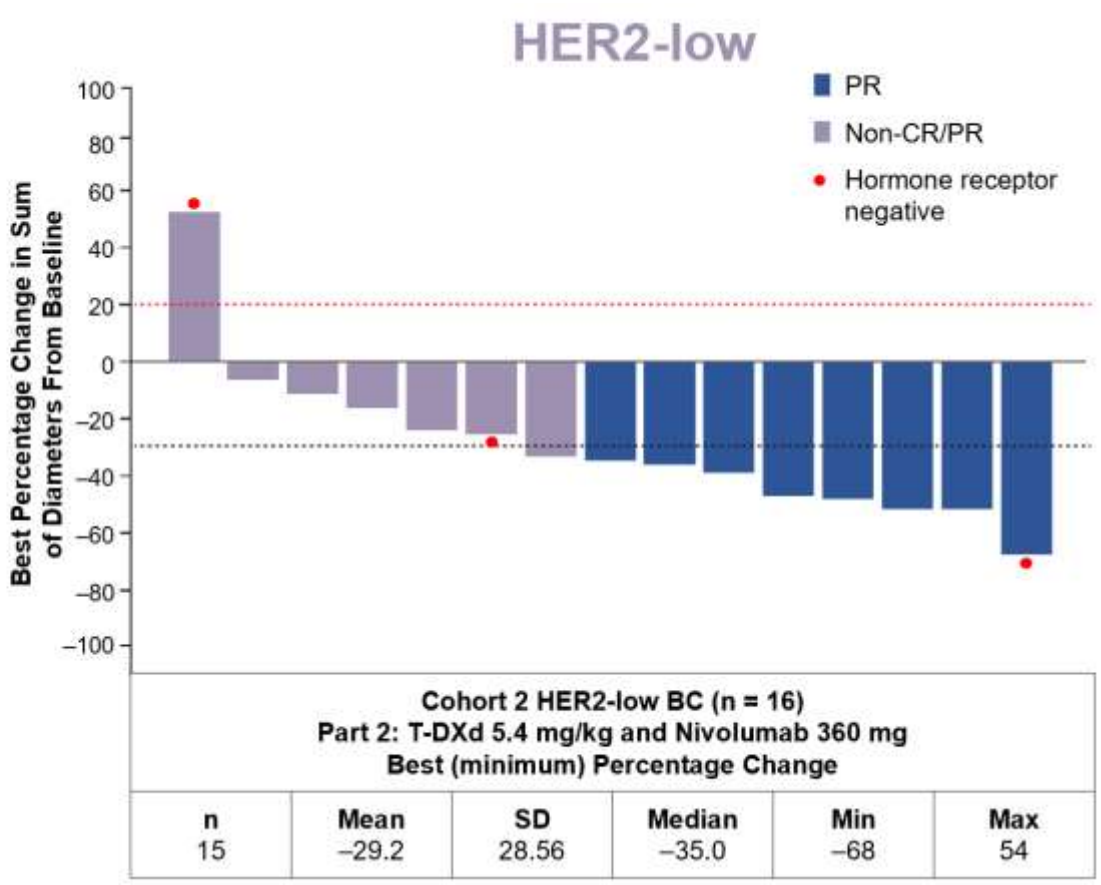
CR, complete response; DOR, duration of response; HER2, human epidermal growth factor receptor 2; ICR, independent central review; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan; RDE, recommended dose for expansion.
[a]Includes 3 patients treated at T-DXd 5.4 mg/kg RDE in combination with nivolumab 360 mg during part 1. [b]Among patients with confirmed CR or PR. [c]Only includes the 29 patients treated at T-DXd 5.4 mg/kg RDE in combination with nivolumab 360 mg during part 2.

Best Percentage Change in Tumor Size by ICR in BC Cohorts



Cohort 1 HER2-positive BC (n = 32)
Parts 1/2: T-DXd 5.4 mg/kg and Nivolumab 360 mg
Best (minimum) Percentage Change

n	Mean	SD	Median	Min	Max
31	−53.0	33.82	−57.0	−100	13



Cohort 2 HER2-low BC (n = 16)
Part 2: T-DXd 5.4 mg/kg and Nivolumab 360 mg
Best (minimum) Percentage Change

n	Mean	SD	Median	Min	Max
15	−29.2	28.56	−35.0	−68	54

BC, breast cancer; CR, complete response; HER2, human epidermal growth factor receptor 2; ICR, independent central review; PR, partial response; RDE, recommended dose for expansion; SD, standard deviation; T-DXd, trastuzumab deruxtecan.
2 of 3 patients with HER2-positive BC treated at T-DXd 5.4 mg/kg RDE in combination with nivolumab 360 mg in part 1 are shown. In cohort 2, 1 of 3 patients who were hormone receptor negative had a confirmed PR. The line at 20% indicates progressive disease, and the line at −30% indicates a PR.

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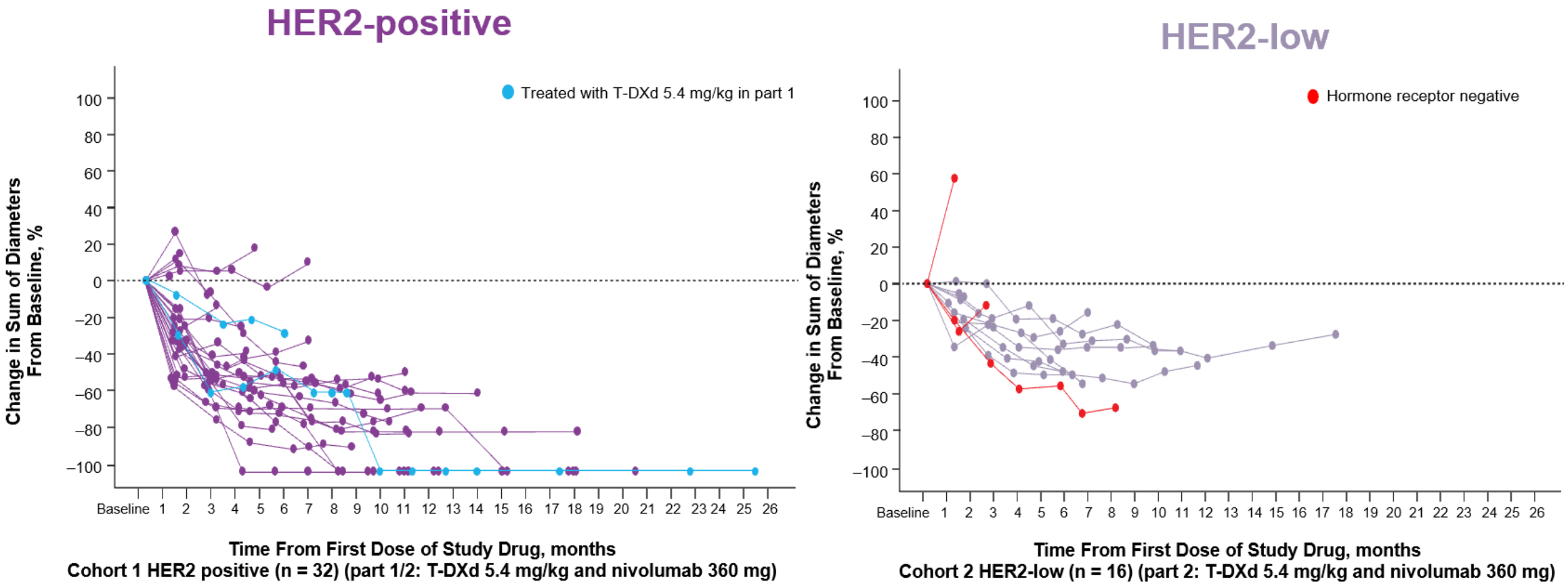
Change in Tumor Size over Time in BC Cohorts



BC, breast cancer; HER2, human epidermal growth factor receptor 2; T-DXd, trastuzumab deruxtecan.
2 out of 3 patients with HER2-positive BC treated with T-DXd 5.4 mg/kg RDE in combination with nivolumab 360 mg in Part 1 are shown. 2 out of 3 patients with HER2-low hormone receptor negative BC shown.

Overall Safety Summary

n (%)	Cohort 1 HER2+ n = 29	Cohort 2 HER2-low n = 16	Overall N = 48[a]
TEAEs	**29 (100)**	**16 (100)**	**48 (100)**
Related to T-DXd	26 (89.7)	13 (81.3)	42 (87.5)
Related to nivolumab	24 (82.8)	13 (81.3)	40 (83.3)
Grade ≥3 TEAEs	**15 (51.7)**	**7 (43.8)**	**24 (50.0)**
Related to T-DXd	10 (34.5)	1 (6.3)	11 (22.9)
Related to nivolumab	8 (27.6)	3 (18.8)	11 (22.9)
Serious TEAEs	**12 (41.4)**	**4 (25.0)**	**18 (37.5)**
Related to T-DXd	1 (3.4)	0	1 (2.1)
Related to nivolumab	2 (6.9)	1 (6.3)	3 (6.3)
TEAEs leading to any study drug discontinuation[b]	**14 (48.3)**	**3 (18.8)**	**18 (37.5)**
Related to T-DXd	9 (31.0)	2 (12.5)	12 (25.0)
Related to nivolumab	7 (24.1)	3 (18.8)	10 (20.8)
TEAEs leading to T-DXd discontinuation[b]	**12 (41.4)[c]**	**1 (6.3)**	**13 (27.1)**
Related to and leading to T-DXd discontinuation	9 (31.0)[d]	1 (6.3)[e]	10 (20.8)
TEAEs leading to nivolumab discontinuation[b]	**14 (48.3)[f]**	**2 (12.5)**	**17 (35.4)**
Related to and leading to nivolumab discontinuation	7 (24.1)[g]	2 (12.5)[h]	9 (18.8)
TEAEs leading to T-DXd dose reduction and related to T-DXd	**3 (10.3)**	**0**	**4 (8.3)**
TEAEs leading to any study drug interruption	**14 (48.3)**	**8 (50.0)**	**23 (47.9)**
Related to T-DXd	8 (27.6)	3 (18.8)	12 (25.0)
Related to nivolumab	5 (17.2)	7 (43.8)	13 (27.1)
TEAEs associated with death	**2 (6.9)**	**2 (12.5)**	**5 (10.4)[j]**
Drug-related[i]	1 (3.4)	0	1 (2.1)

HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event. [a]Includes 3 patients treated at T-DXd 5.4 mg/kg RDE in combination with nivolumab 360 mg during part 1. [b]Investigator assessed. [c]Unrelated to T-DXd: 1 troponin T increase (grade 3); 1 blood bilirubin increase (grade 3); 1 femur fracture (grade 3). [d]1 amylase increase (grade 3); 1 anemia (grade 3); 2 ILD (1 grade 1, 1 grade 2); 4 pneumonitis (1 grade 1, 2 grade 2, and 1 grade 5); 1 lichenoid keratosis (grade 3). [e]1 pneumonitis (grade 1). [f]Unrelated to nivolumab: 1 blood bilirubin increase (grade 3); 1 ILD (grade 1); 1 pneumonitis (grade 2); 1 amylase increased (grade 3); 1 femur fracture (grade 3); 1 anemia (grade 3); 1 aspartate aminotransferase increased (grade 2). [g]1 troponin T increase (grade 3); 1 lymphocyte count decrease (grade 3); 1 vision blurred (grade 3); 2 pneumonitis (1 grade 1, 1 grade 5); 1 ILD (grade 2); 1 lichenoid keratosis (grade 3). [h]1 neutropenia (grade 3), 1 aspartate aminotransferase increased (grade 3). [i]Drug-related grade 5 ILD/pneumonitis. [j]3 disease progression; 1 malignant neoplasm progression; 1 ILD/pneumonitis.

Adverse Events of Special Interest: ILD/Pneumonitis and LV Dysfunction

Adjudicated as Drug-related ILD/Pneumonitis[a,b]						
Overall N = 48[c]	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/Total
n (%)	0	6 (12.5)[d]	0	0	1 (2.1)	7 (14.6)

- Median time to adjudicated onset was 168 days (range, 40-250 days)
- A grade 3 adjudicated drug-related ILD/pneumonitis event also occurred in 1 patient (25.0%) with BC who received 3.2 mg/kg T-DXd in combination with nivolumab in part 1

LV Dysfunction

- In cohort 1, 2 patients (6.9%) experienced an LV dysfunction event[e,f]
  - No patients in cohort 2 experienced LV dysfunction

BC, breast cancer; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; LV, left ventricular; RDE, recommended dose for expansion; T-DXd, trastuzumab deruxtecan. [a]Cases of potential ILD or pneumonitis were evaluated by an independent adjudication committee that was separate from the response assessment committee. Data shown here are for cases that were deemed drug-related by the adjudication committee. [b]The adjudication committee did not discriminate between T-DXd and nivolumab-related ILD/pneumonitis. [c]Includes all patients with BC who received T-DXd 5.4 mg/kg RDE in combination with nivolumab 360 mg in parts 1 and 2. [d]2 grade 1 ILD events by the principal investigator were adjudicated as grade 2. [e]Per Standardized Medical Dictionary of Regulatory Activities Query of Cardiac Failure and of Myocardial Infarction. [f]1 asymptomatic ejection fraction decreased (grade 2) and 1 troponin T increased (grade 3). Neither events recovered and 1 patient discontinued treatment.

Exploratory Biomarker Analysis in BC Cohorts

	Cohort 1 HER2+		Cohort 2 HER2-low	
Biomarker[a]	**N**	**ORR, % (n, 95% CI)**	**N**	**ORR, % (n, 95% CI)**
PD-L1 TC ≥ 1%	Low: 28	64.3% (18, 44.1-81.4)	Low: 13	46.2% (6, 19.2-74.9)
	High: 3	100% (3, 29.2-100)	High: 2	50.0% (1, 1.3-98.7)
PD-L1 IC+ ≥ 5%	Low: 17	64.7 % (11, 38.3-85.8)	Low: 9	44.4 % (4, 13.7-78.8)
	High: 14	71.4 % (10, 41.9-91.6)	High: 6	50.0 % (3, 11.8-88.2)
PD-L1 IC+ ≥ 1%	Low: 12	66.7 % (8, 34.9-90.1)	Low: 6	33.3 % (2, 4.3-77.7)
	High: 19	68.4 % (13, 43.4-87.4)	High: 9	55.6 % (5, 21.1-86.3)

- Biomarker analyses for cohorts 1 and 2 were performed on baseline new or archival tumor biopsy tissue
- Antitumor activity with T-DXd plus nivolumab was observed regardless of PD-L1 IHC status

BC, breast cancer; HER2, human epidermal growth factor receptor 2; IC, immune cell; IHC, immunohistochemistry; ORR, objective response rate; PD-L1, programmed death ligand 1; TC, tumor cell; T-DXd, trastuzumab deruxtecan.
[a]VENTANA PD-L1 (SP263) assay.

Conclusions

- T-DXd 5.4 mg/kg IV Q3W in combination with nivolumab 360 mg Q3W showed **antitumor activity** consistent with previously reported data for T-DXd monotherapy in patients with HER2-positive BC
  - The addition of nivolumab to T-DXd in the late-line setting, however, showed no discernible benefit
  - The data from the small HER2-low BC cohort are insufficient to determine the effects of anti–PD-1/PD-L1 therapy combined with T-DXd in the late-line setting
- The overall safety profile was generally **consistent with previous studies for T-DXd** monotherapy in patients with BC, and the addition of nivolumab did not appear to cause any overall increased toxicity
  - The incidence of adjudicated ILD/pneumonitis across both cohorts was 14.6%
  - All but 1 ILD/pneumonitis events were low grade (grade 2)
- An exploratory biomarker analysis showed that patients with HER2-positive and HER2-low BC responded to treatment with T-DXd plus nivolumab regardless of PD-L1 IHC status
  - However, results should be interpreted with caution given the small sample size

BC, breast cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ILD, interstitial lung disease; IV, intravenous; ORR, objective response rate; PD-1, PD-L1, programmed death 1; PD-L1, programmed death ligand 1; Q3W, every 3 weeks; TC, tumor cell; T-DXd, trastuzumab deruxtecan.

Poster 17

Dose-finding and -expansion studies of trastuzumab deruxtecan in combination with other anticancer agents in patients with advanced/metastatic HER2+ (DESTINY-Breast07) and HER2-low (DESTINY-Breast08) breast cancer

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Objective

- The primary objective of part 1 of the ongoing DESTINY-Breast07 (DB-07) and DESTINY-Breast08 (DB-08) clinical trials is to investigate the safety and tolerability and determine the recommended phase 2 dose (RP2D; DB-07) and recommended doses for expansion (DB-08) of combinations of T-DXd with anticancer therapies in patients with HER2+ breast cancer (DB-07) or HER2-low–expressing breast cancer (DB-08)

Conclusions

- For the following T-DXd combination therapies, the RP2D (DB-07) and recommended doses for expansion (DB-08) were the standard doses for breast cancer for each individual drug:
  - DB-07: T-DXd 5.4 mg/kg Q3W + pertuzumab 420 mg Q3W (pertuzumab loading dose: 840 mg)
  - DB-08: T-DXd 5.4 mg/kg Q3W + anastrozole 1 mg daily
  - DB-08: T-DXd 5.4 mg/kg Q3W + fulvestrant 500 mg Q4W (fulvestrant loading dose: 500 mg on C1D15)
- These doses of these T-DXd combination regimens were well tolerated and will serve as the doses for further evaluation in part 2
- DB-07 (NCT04538742) and DB-08 (NCT04556773) are ongoing, with additional T-DXd combinations being evaluated and further follow-up underway

Plain language summary

Why did we perform this research?
Some breast cancers have high levels of the HER2 protein (HER2+) and some have lower levels (HER2 low). T-DXd is an anticancer drug designed to target and kill cancer cells that express HER2.[1,2] It is being studied for the treatment of HER2+ breast cancer[3] and HER2-low–expressing breast cancer.[4,5] We wanted to find out if T-DXd can be used to treat HER2+ and HER2-low–expressing breast cancer in combination with other drugs that are already used to treat breast cancer and experimental drugs that could potentially be used to treat breast cancer.

How did we perform this research?
In the ongoing DESTINY-Breast07 and DESTINY-Breast08 trials, we are assessing T-DXd by itself and in combination with other anticancer drugs in patients with HER2+ (IHC 3+ or IHC 2+/ISH+) and HER2-low–expressing (IHC 1+ or IHC 2+/ISH−) breast cancer, respectively. In part 1 of both trials, we are assessing the safety of different doses of each combination treatment; results will be used to decide what dose to use for each combination in part 2. In part 2, we will further assess how safe and effective these drug combinations are for treating patients with HER2+ or HER2-low–expressing breast cancer.

What were the findings of this research and what are the implications?
In part 1 of DESTINY-Breast07, 7 patients were treated with T-DXd 5.4 mg/kg Q3W + pertuzumab 420 mg Q3W (pertuzumab loading dose: 840 mg). In part 1 of DESTINY-Breast08, 6 patients each were treated with T-DXd 5.4 mg/kg Q3W combined with either anastrozole 1 mg daily or fulvestrant 500 mg Q4W (fulvestrant loading dose: 500 mg on day 15 of cycle 1). These preliminary results show that T-DXd can be combined with pertuzumab, anastrozole, or fulvestrant. These doses were determined to be the recommended doses to use in part 2 of these trials, where their safety and efficacy (antitumor activity) will be evaluated further. T-DXd combined with other anticancer drugs is also being assessed in both trials.

Where can I access more information?
DESTINY-Breast07: ClinicalTrials.gov. A Phase 1b/2 Study of T-DXd Combinations in HER2-positive Metastatic Breast Cancer (DB-07). https://clinicaltrials.gov/ct2/show/NCT04538742
DESTINY-Breast08: ClinicalTrials.gov. A Phase 1b Study of T-DXd Combinations in HER2-low Advanced or Metastatic Breast Cancer (DB-08). https://clinicaltrials.gov/ct2/show/NCT04556773

These studies were funded by AstraZeneca. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for T-DXd (DS-8201).

References: 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. Cortés J, et al. *N Engl J Med.* 2022;386(12):1143-1154. 4. Modi S, et al. *J Clin Oncol.* 2020;38(17):1887-1896. 5. AstraZeneca. News release. Accessed March 31, 2022. https://www.astrazeneca.com/media-centre/press-releases/2022/enhertu-improves-pfs-and-os-in-her2-low-bc.html#:~:text=Positive%20high%20level%20results%20from

Poster | Plain language summary | Supplementary material (Study design details, parts 1 and 2)

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Poster presented at ASCO Annual Meeting; June 3-7, 2022; Chicago, IL, and virtual.

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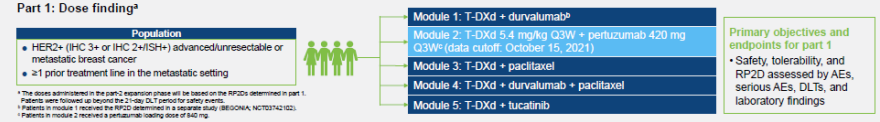
Introduction

- T-DXd is an antibody-drug conjugate composed of a humanized anti-HER2 monoclonal antibody and a topoisomerase I inhibitor payload[1,2]
- T-DXd is approved in the US for patients with unresectable or metastatic HER2+ breast cancer who have received a prior anti-HER2–based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing therapy[3]
  - T-DXd is also approved in multiple countries for patients with unresectable or metastatic HER2+ breast cancer with ≥2 prior anti-HER2–based therapies[4]
- In the phase 3 DESTINY-Breast03 trial, T-DXd has shown lower risk of disease progression or death vs T-DM1 in patients with HER2+ metastatic breast cancer previously treated with trastuzumab and a taxane[5]
- T-DXd demonstrated preliminary antitumor activity in patients with HER2-low advanced/metastatic breast cancer in a phase 1 trial[6] and improved PFS and OS vs physician's choice of chemotherapy in patients with HER2-low unresectable and/or metastatic breast cancer in the phase 3 DESTINY-Breast04 trial[7]
- Combinations of T-DXd with anticancer therapies are being assessed in 2 ongoing, open-label, multicenter, modular clinical trials in patients with advanced/metastatic HER2+ breast cancer (DB-07) or HER2-low-expressing breast cancer (DB-08)
  - Each trial has a dose-finding phase (part 1) and a dose-expansion phase (part 2)
  - Here we report preliminary results from the dose-finding phase of DB-07 (module 2: T-DXd + pertuzumab) and DB-08 (module 4: T-DXd + anastrozole; module 5: T-DXd + fulvestrant), including safety and RP2D (DB-07)/ recommended doses for expansion (DB-08)

Methods

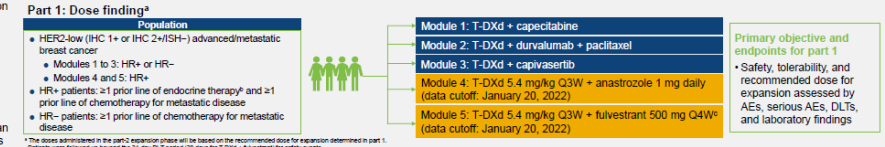
- Data are reported for the following part 1 modules of DB-07 (phase 1b/2; NCT04538742) and DB-08 (phase 1b; NCT04556773; **Figures 1** and **2**)
  - DB-07 module 2: T-DXd 5.4 mg/kg Q3W + pertuzumab 420 mg Q3W (pertuzumab loading dose: 840 mg)
  - DB-08 module 4: T-DXd 5.4 mg/kg Q3W + anastrozole 1 mg daily
  - DB-08 module 5: T-DXd 5.4 mg/kg Q3W + fulvestrant 500 mg Q4W (fulvestrant loading dose: 500 mg on C1D15)
- The part 1 primary objective was to assess safety and tolerability and determine the RP2D/recommended doses for expansion according to the modified toxicity probability interval–2 algorithm[8]
- Study design details (parts 1 and 2) can be found in the supplemental materials using the QR code

Figure 1. DB-07 study design (part 1)



[a] The doses administered in the part-2 expansion phase will be based on the RP2Ds determined in part 1. Patients were followed up beyond the 21-day DLT period for safety events. [b] Patients in module 1 received the RP2D determined in a separate study (BEGONIA; NCT03742102). [c] Patients in module 2 received a pertuzumab loading dose of 840 mg.

Figure 2. DB-08 study design (part 1)



[a] The doses administered in the part-2 expansion phase will be based on the recommended dose for expansion determined in part 1. Patients were followed up beyond the 21-day DLT period (28 days for T-DXd + fulvestrant) for safety events. [b] With or without a targeted therapy (such as CDK4/6, mTOR, or PI3K inhibitors). [c] Patients in module 5 received a fulvestrant loading dose of 500 mg on C1D15.

Results and interpretation

DB-07 part 1: T-DXd + pertuzumab

Patients

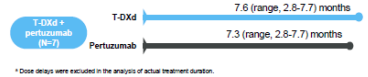
- As of the data cutoff, 7 patients were assigned to the T-DXd + pertuzumab module and received the initial dose level (**Table 1**)
  - Treatment ongoing: n=5 (71.4%)
  - Treatment discontinued: n=2 (28.6%; discontinued both T-DXd and pertuzumab)
    - Withdrawal by patient: n=1 (14.3%)
    - AE: n=1 (14.3%; ejection fraction decreased)
- Treatment duration is reported in **Figure 3**

Table 1. Patient demographics and disease characteristics

	N=7
Age, mean (range), years	54.3 (38-66)
Female, n (%)	7 (100.0)
Race, n (%)	
Asian	6 (85.7)
White	1 (14.3)
Primary tumor location at diagnosis, n (%)	
Breast	7 (100.0)
HER2 status, n (%)	
IHC 3+	5 (71.4)
IHC 2+/ISH+	1 (14.3)
Missing	1 (14.3)[a]
ECOG performance status, n (%)	
0	4 (57.1)
1	3 (42.9)

[a] The HER2 status for this patient was missing at the time of the data cutoff and was later confirmed to be IHC 3+.

Figure 3. Median actual treatment duration[a]



[a] Dose delays were excluded in the analysis of actual treatment duration.

Dose modifications: T-DXd + pertuzumab

Patients with:

	≥1 dose delay	≥1 dose reduction	≥1 dose interruption
T-DXd	1 (14.3%) Reason: other[a]	1 (14.3%) Reason: AE[b]	0
Pertuzumab	0	Dose modifications not allowed per protocol	0

[a] Evaluation for potential pneumonitis. [b] Grade 3 platelet count decreased.

Safety

- Six patients were evaluable for DLTs (1 was not evaluable for DLTs due to using G-CSF for grade 3 neutropenia); no DLTs were reported
- The combination treatment was generally well tolerated (**Table 2**)
- There were no deaths; no patients experienced ILD/pneumonitis

Table 2. Safety with RP2D

Patients, n (%)	N=7
Any AE	7 (100.0)
Any grade ≥3 AE	3 (42.9)
Hematologic	
Neutrophil count decreased	2 (28.6)
White blood cell count decreased	2 (28.6)
Anemia	1 (14.3)
Febrile neutropenia	1 (14.3)
Platelet count decreased	1 (14.3)
Non-hematologic	
Ejection fraction decreased	1 (14.3)
Hypokalemia	1 (14.3)
Serious AEs	1 (14.3)[a]
AEs leading to treatment discontinuation	1 (14.3)[b]
AEs of special interest	
ILD/pneumonitis	0
Left ventricular ejection fraction decreased	1 (14.3)[b]
Deaths	0

[a] Febrile neutropenia. [b] One patient (14.3%) experienced a nonserious AE of grade 3 ejection fraction decreased; it was considered related to T-DXd but not to pertuzumab, led to discontinuation of T-DXd and pertuzumab, and was not resolved by the data cutoff.

RP2D was
T-DXd 5.4 mg/kg Q3W + pertuzumab 420 mg Q3W (pertuzumab loading dose: 840 mg)

Acknowledgments

We thank the patients who are participating in these studies as well as their families and caregivers.

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The authors thank Tinghui Yu, PhD (formerly an employee of AstraZeneca) and Canon Lloyd (AstraZeneca) for their contributions to this work. Medical writing support was provided by Christopher Edwards, PhD, CMPP (ArticulateScience, LLC), and was funded by AstraZeneca.

Abbreviations

AE, adverse event; C, cycle; CDK, cyclin-dependent kinase; D, day; DB-07, DESTINY-Breast07; DB-08, DESTINY-Breast08; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; G-CSF, granulocyte-colony stimulating factor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ILD, interstitial lung disease; ISH, in situ hybridization; mTOR, mechanistic target of rapamycin kinase; OS, overall survival; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; Q3W, every 3 weeks; Q4W, every 4 weeks; RP2D, recommended phase 2 dose; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Disclosures

Fabrice André reports travel, accommodations, and/or expenses from Novartis, Roche, GSK, and AstraZeneca; stock and other ownership interests in Pegascy; and research funding from Novartis, Roche, AstraZeneca, Pfizer, Lilly, and Daiichi Sankyo.

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DB-08 part 1: T-DXd + anastrozole and T-DXd + fulvestrant

Patients

T-DXd + anastrozole

- As of the data cutoff, 6 patients were assigned to the T-DXd + anastrozole module and received the initial dose level (**Table 3**)
  - Treatment ongoing: n=3 (50.0%)
  - Treatment discontinued: n=3 (50.0%; discontinued both T-DXd and anastrozole)
    - Objective disease progression: n=2 (33.3%)
    - Clinical disease progression: n=1 (16.7%)

T-DXd + fulvestrant

- As of the data cutoff, 6 patients were assigned to the T-DXd + fulvestrant module and received the initial dose level
  - Treatment ongoing: n=5 (83.3%)
  - Treatment discontinued: n=1 (16.7%; discontinued T-DXd due to AE [pneumonitis] and fulvestrant due to objective disease progression)
- Treatment duration is reported in **Figure 4**

Table 3. Patient demographics and disease characteristics

	T-DXd + anastrozole N=6	T-DXd + fulvestrant N=6
Age, mean (range), years	57.7 (47-71)	59.0 (46-74)
Female, n (%)	6 (100.0)	6 (100.0)
Race, n (%)		
Asian	6 (100.0)	4 (66.7)
White	0	2 (33.3)
Primary tumor location, n (%)		
Breast	6 (100.0)	6 (100.0)
HER2 status, n (%)		
IHC 2+/ISH−	3 (50.0)	4 (66.7)
IHC 1+	3 (50.0)	2 (33.3)
ECOG performance status, n (%)		
0	5 (83.3)	4 (66.7)
1	1 (16.7)	2 (33.3)

Figure 4. Median actual treatment duration[a]

[a] Dose delays and interruptions were excluded in the analysis of actual treatment duration.

Dose modifications: T-DXd + anastrozole

Patients with:

	≥1 dose delay[a]	≥1 dose reduction	≥1 dose interruption
T-DXd	4 (66.7%) Reasons: AE (n=3);[b] other (n=1)[c]	0	0
Anastrozole	2 (33.3%) Reason: AE (n=2)[d]	Dose modifications not allowed per protocol	1 (16.7%) Reason: AE[e]

[a] Reasons for dose delays were not mutually exclusive in patients who had multiple dose delays; patients were counted only once per category. [b] Anemia (n=1), femoral neck fracture (n=1), and vomiting and pneumonitis (n=1). [c] Medication error (n=1). [d] Vomiting and pneumonitis (n=1) and nasopharyngitis (n=1). [e] Nasopharyngitis.

Dose modifications: T-DXd + fulvestrant

Patients with:

	≥1 dose delay[a]	≥1 dose reduction	≥1 dose interruption
T-DXd	2 (33.3) Reason: AE (n=1)[b] other (n=2)[c]	3 (50.0%) Reason: AE (n=3)[d]	0
Fulvestrant	0	Dose modifications not allowed per protocol	1 (16.7%) Reason: other[e]

[a] Reasons for dose delays were not mutually exclusive; patients with multiple dose delays were counted only once per category. [b] Nausea (was updated from a dose interruption after the data cutoff). [c] Public holiday (n=1) and assessment of possible disease progression (n=1; was updated from a dose interruption after the data cutoff). [d] Nausea (n=2) and platelet count decreased (n=1). [e] Assessment of possible disease progression.

Safety

- All patients were evaluable for DLTs; no DLTs were reported in either module
- Both combination treatments were generally well tolerated (**Table 4**)

T-DXd + anastrozole

- One patient (16.7%) died 226 days after the first dose due to disease progression; no patients had ILD/pneumonitis

T-DXd + fulvestrant

- No patients died; 1 patient (16.7%) experienced drug-related ILD/pneumonitis outside the 28-day DLT cycle

Table 4. Safety with recommended doses for expansion

Patients, n (%)	T-DXd + anastrozole N=6	T-DXd + fulvestrant N=6
Any AE	6 (100.0)	6 (100.0)
Any grade ≥3 AE	2 (33.3)	3 (50.0)
Hematologic		
Anemia	2 (33.3)	1 (16.7)
Platelet count decreased	0	1 (16.7)
Non-hematologic		
Femoral neck fracture	1 (16.7)	0
Hypokalemia	1 (16.7)	1 (16.7)
Nausea	0	1 (16.7)
Serious AEs	2 (33.3)[a]	1 (16.7)[b]
AEs leading to treatment discontinuation	0	1 (16.7)[c]
AEs of special interest		
ILD/pneumonitis	0	1 (16.7)[d]
Deaths	1 (16.7)[e]	0

[a] One patient (16.7%) experienced 2 serious AEs, vomiting and anemia; neither were considered related to study drugs; the patient delayed T-DXd and anastrozole treatment due to the vomiting; the patient recovered from the vomiting but the anemia had not resolved by the data cutoff. One (16.7%) patient experienced a serious AE of femoral neck fracture that was not considered related to study drugs; the patient delayed T-DXd treatment and the event was not resolved by the data cutoff. [b] One patient (16.7%) experienced a serious AE of seizure that was not considered related to study drugs; the seizure had resolved by the data cutoff. [c] Pneumonitis. [d] Occurred outside 28-day DLT period. [e] Due to disease progression, 226 days after first dose.

Recommended doses for expansion were
T-DXd 5.4 mg/kg Q3W + anastrozole 1 mg daily and T-DXd 5.4 mg/kg Q3W + fulvestrant 500 mg Q4W (fulvestrant loading dose: 500 mg on C1D15)

Datopotamab deruxtecan + durvalumab as first-line treatment for unresectable locally advanced/metastatic triple-negative breast cancer

Initial results from BEGONIA, a phase 1b/2 study

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Background

- Combining immune checkpoint inhibitors with 1st-line chemotherapy improves outcomes in patients with advanced/metastatic triple-negative breast cancer (a/mTNBC), but only in PD-L1–positive disease[1,2]
- Datopotamab deruxtecan (Dato-DXd), a TROP2-directed antibody-drug conjugate (ADC) with topoisomerase I inhibitor payload, demonstrated promising antitumor activity as monotherapy in heavily pretreated patients with recurrent a/mTNBC[3]
- BEGONIA is an ongoing 2-part, open-label platform study evaluating durvalumab, an anti–PD-L1 antibody, combined with other therapies, including ADCs, as 1st-line treatment of a/mTNBC in a biomarker unselected population
  - In the paclitaxel + durvalumab arm, a confirmed ORR of 58.3% was demonstrated and responses were durable (median PFS: 7.3 mos., 95% CI 5.4-13.8)[4], consistent with reported response rates for immune checkpoint inhibitors in first-line mTNBC and independent of PD-L1 status.
  - In the trastuzumab deruxtecan + durvalumab arm, a confirmed ORR of 66.7% was demonstrated, with 87.5% of patients remaining in response at time of data cutoff[5]
- We report preliminary results with Dato-DXd + durvalumab in BEGONIA, the first data with this novel combination in patients with newly diagnosed a/mTNBC

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PD-L1, programmed cell death ligand-1; TROP2, trophoblast cell-surface antigen 2.

BEGONIA (NCT03742102) Study Design

- Females aged ≥18 years
- Unresectable a/mTNBC
- No prior treatment for Stage IV TNBC
- ≥12 months since prior taxane therapy
- ECOG PS 0-1
- Adequate organ function
- Measurable disease per RECIST v1.1
- No prior treatment with checkpoint inhibitor or TOPO I-based ADC[a]

Part 1 (this presentation includes results from part 1)

First 20 patients:
- Paclitaxel + Durvalumab (P + D) (N=20)
- **Dato-DXd + D[c]** (N=30) Q3W until PD

All others randomized to an open cohort:
- Capivasertib + P + D (N=30)
- Oleclumab + P + D (N=30)
- T-DXd + D (N=30)

Each novel combination cohort

Primary endpoint:
Safety and tolerability
Secondary endpoints:
ORR, PFS, DoR, OS

Simon 2-stage futility analysis for Part 2 expansion[c]

Part 2 expansion (currently active/ongoing)

Randomized if multiple cohorts open:
- **Dato-DXd + D[b]** Q3W until PD
- T-DXd + D

Enroll additional 27 patients in each arm

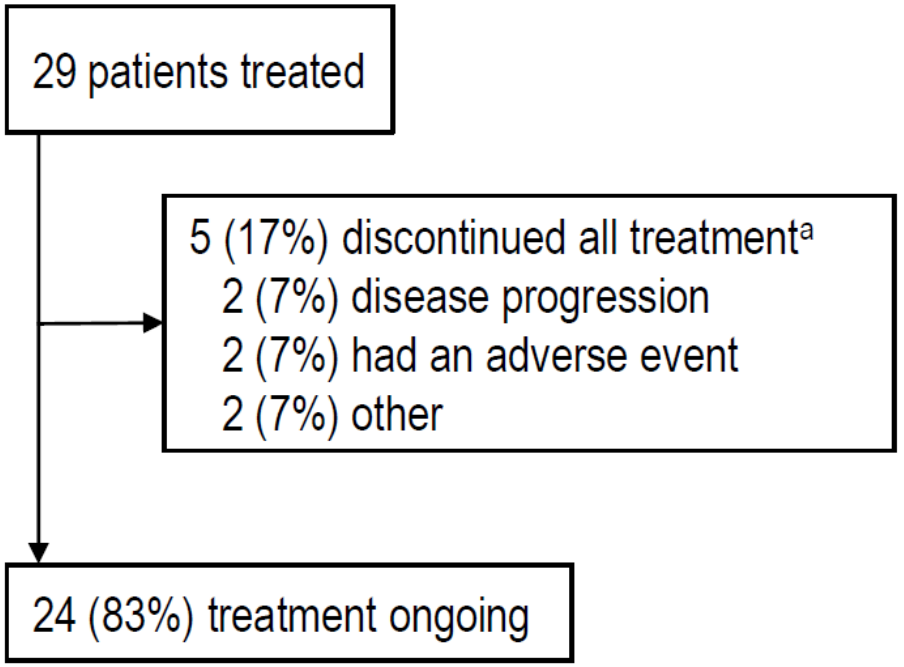
Primary endpoint:
ORR
Secondary endpoints:
PFS, DoR, PFS6, OS

[a]ADC-cohort-specific criteria. [b]Dato-DXd 6 mg/kg + D 1120 mg. [c]Novel treatment combinations may enter Part 2 expansion if confirmed ORR is at least 57%.

ADC, antibody-drug conjugate; a/mTNBC, locally advanced/metastatic triple negative breast cancer; DLT, dose-limiting toxicity; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance scale; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PD, progressive disease; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors; T-DXd, trastusumab deruxtecan; TOPO I, topoisomerase I.

Data cutoff: November 15, 2021

Disposition and Baseline Characteristics



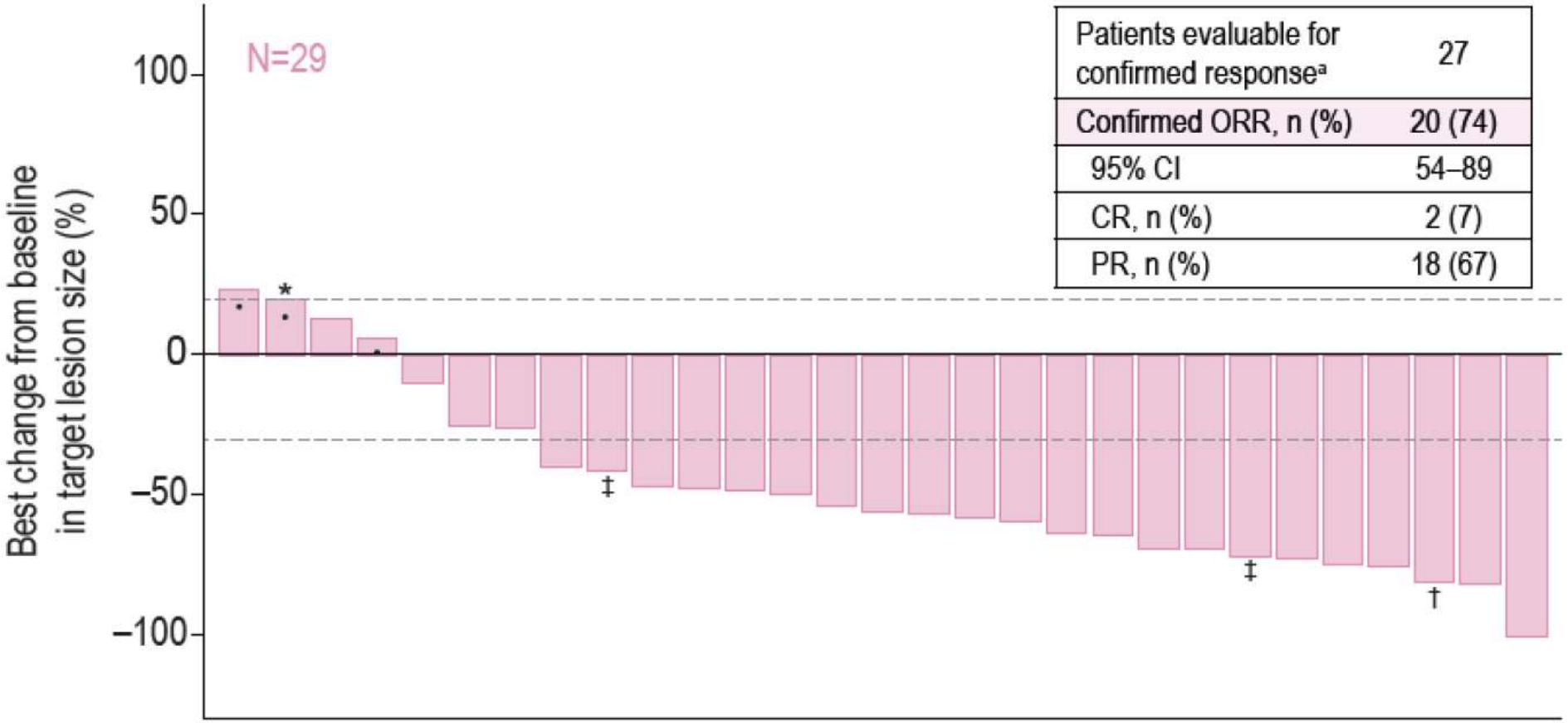
Median follow-up: 3.9 (range, 2–6) months

Characteristic	Dato-DXd + D N=29
Age, median (range), years	51 (33–72)
No prior treatment, n (%)	9 (31)
Prior treatments for early-stage disease, n (%)	
Radiotherapy	17 (59)
Cytotoxic chemotherapy	19 (66)
Taxane	14 (48)
Anthracycline	16 (55)
Platinum compound	5 (17)
Hormonal therapy	6 (21)
Targeted therapy	2 (7)
Visceral metastases,[b] n (%)	20 (69)
Lymph node metastasis, n (%)	22 (76)
PD-L1 expression[c], **n (%)**	
High (≥5%)	5 (17.2%)
Low (<5%)	21 (72.4%)
Unknown Missing	3 (10.3%)

Data cutoff: November 15, 2021

[a]Patients may have discontinued for more than 1 reason. [b]Defined as liver/hepatic and/or respiratory metastases. [c]PD-L1 expression was assessed by immunohistochemistry using the VENTANA PD-L1 (SP263) Assay. PD-L1 expression was defined as "high" if ≥5% of the tumor area was populated by PD-L1 expressing tumor or immune cells, otherwise it was defined as "low".
a/mTNBC, locally advanced/metastatic triple negative breast cancer; PD-L1, programmed cell death ligand-1; TROP2, trophoblast cell-surface antigen 2.

Antitumor Responses



Patients evaluable for confirmed response[a]	27
Confirmed ORR, n (%)	20 (74)
95% CI	54–89
CR, n (%)	2 (7)
PR, n (%)	18 (67)

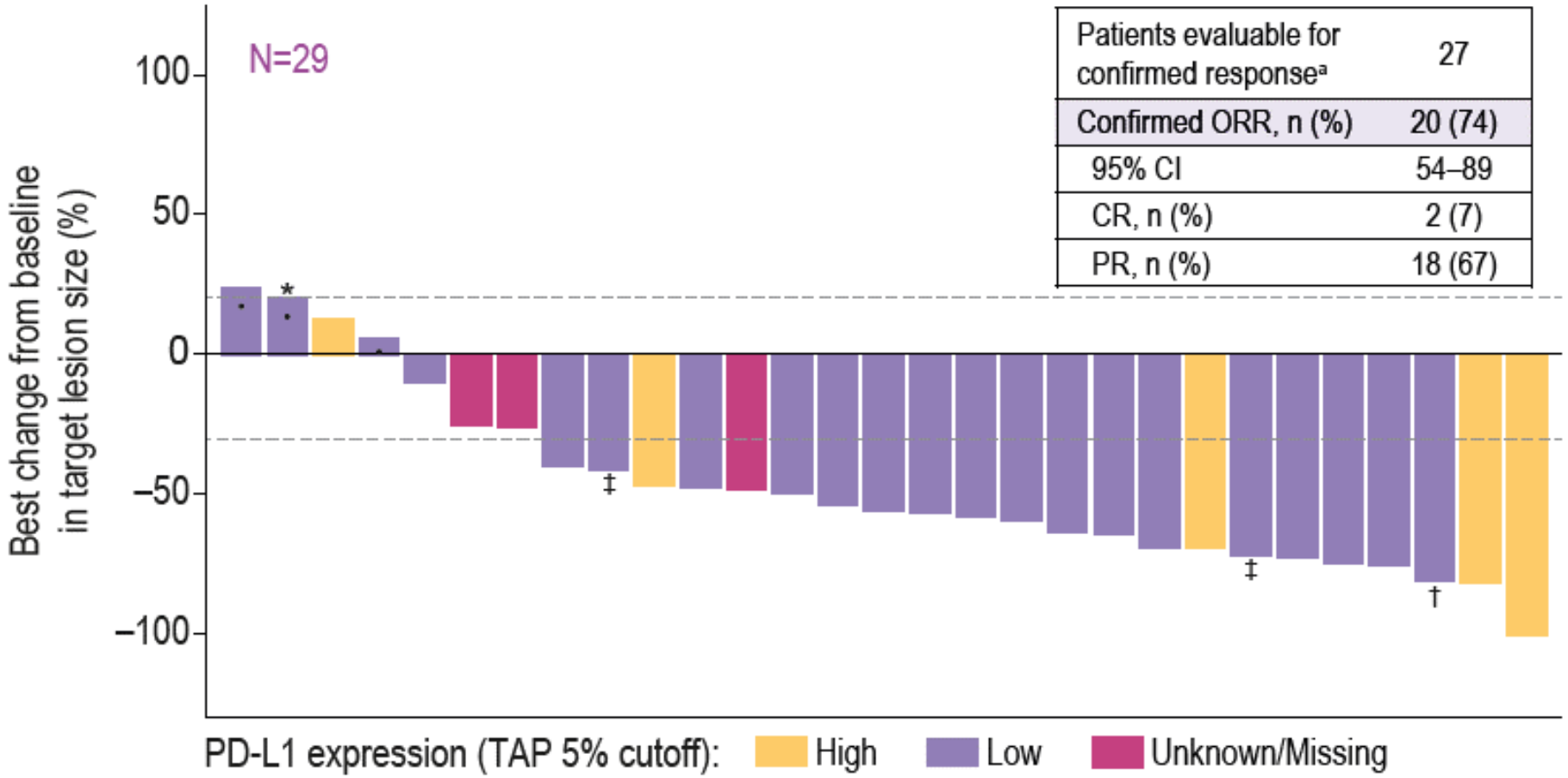
- Confirmed ORR was observed in 20/27 (74%) patients

[a]Had the opportunity to have 2 postbaseline scans.
Dotted lines indicate thresholds for partial response (−30%) and progressive disease (20%).
*If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal, or death, the value is imputed at +20%.
"•" Patients with PD as best overall response. †CR with lymph node disease (CR per RECIST in lymph nodes, is <10mm). ‡ Unconfirmed response.
CR, complete response; ORR, objective response rate; PR, partial response.

Data cutoff: November 15, 2021

Antitumor Responses

Responses observed regardless of PD-L1 expression



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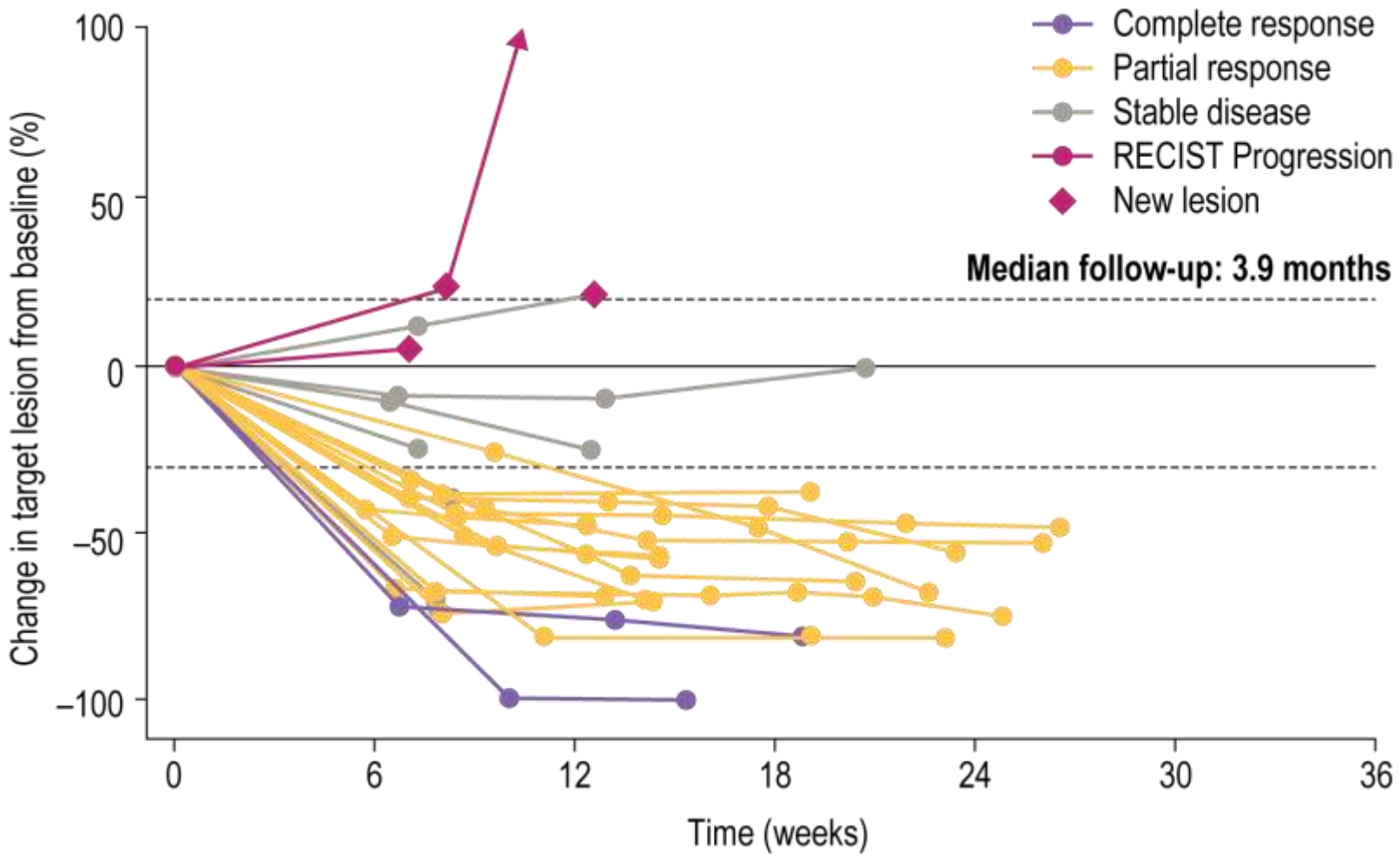
*If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal, or death, the value is imputed at +20%.
"•" Patients with PD as best overall response. †CR with lymph node disease (CR per RECIST in lymph nodes, is <10mm). ‡ Unconfirmed response.
CR, complete response; ORR, objective response rate; PR, partial response.

Data cutoff: November 15, 2021

Antitumor Responses



- Median time to response was 1.4 mos. (95% CI, 1.35–1.58)
- All patients with a response had an ongoing response at data cutoff
- Median duration of response was not reached

Data cutoff: November 15, 2021

Dotted lines indicate thresholds for partial response (−30%) and progressive disease (20%).

Safety Summary

No dose limiting toxicities	
Patients, n (%)	**Dato-DXd + D N=29**
Any grade AEs	29 (100)
Grade 3/4	8 (28)
Any grade treatment-related AEs	27 (93)
Grade 3/4	8 (28)
Dose adjustments	
Dato-DXd dose reduction[a]	4 (14)
Dato-DXd dose delay	1 (3)
Durvalumab dose delay	4 (14)
Serious AEs	5 (17)
AEs leading to death	1 (3)[b]
AEs leading to discontinuation of all treatments[c]	2 (7)

[a] All 4 Dato-DXd dose reductions were due to stomatitis.
[b] One patient died due to hypotension unrelated to treatment.
[c] Includes 1 case of anaphylactic reaction and 1 case of troponin increase.

Data cutoff: November 15, 2021

Most Reported Adverse Events (≥15% all grades)

Preferred term, n (%) AEs all causes	Dato-DXd + D N=29			
	All Grades, ≥15% of patients	Grade 1	Grade 2	Grade 3
Stomatitis	20 (69)	8 (28)	8 (28)	4 (14)
Alopecia	19 (66)	13 (45)	6 (21)	0
Nausea	19 (66)	13 (45)	6 (21)	0
Constipation	11 (38)	8 (28)	3 (10)	0
Fatigue	11 (38)	9 (31)	2 (6.9)	0
Rash	9 (31)	8 (28)	1 (3)	0
Vomiting	5 (17)	3 (10)	2 (6.9)	0

- Low rates of diarrhea reported (4 [14%]; all Grade 1)
- No cases of ILD/pneumonitis or neutropenic events were reported
- 13.7% of patients required dose reduction due to stomatitis
- Updated TMGs and prophylaxis for stomatitis are being implemented

Data cutoff: November 15, 2021

ILD, interstitial lung disease; TMG, trial management guide.

Conclusions

- Preliminary results of BEGONIA show that Dato-DXd + durvalumab demonstrated a robust response rate in first line a/mTNBC in a biomarker-unselected population
  - Confirmed ORR was 74%, with all patients ongoing response at the time of data cut-off
  - Responses were observed regardless of PD-L1 expression
- The combination of Dato-DXd + durvalumab had a manageable safety profile consistent with the known profile of the individual agents, with no new safety signals
  - No dose-limiting toxicities
  - Stomatitis and low-grade nausea and alopecia were the most frequent AEs
  - Low rates of diarrhea, and no cases of ILD/pneumonitis or neutropenic events, were reported
- Enrollment to Part 2 Dato-DXd + durvalumab arm is currently ongoing; follow-up continues in order to determine duration of response and PFS/OS

a/mTNBC, locally advanced/metastatic triple negative breast cancer; Dato-DXd, datopotamab deruxtecan; ORR, objective response rate.

Results From the Phase 1/2 Study of Patritumab Deruxtecan, a HER3-Directed Antibody-Drug Conjugate (ADC), in Patients With HER3-Expressing Metastatic Breast Cancer

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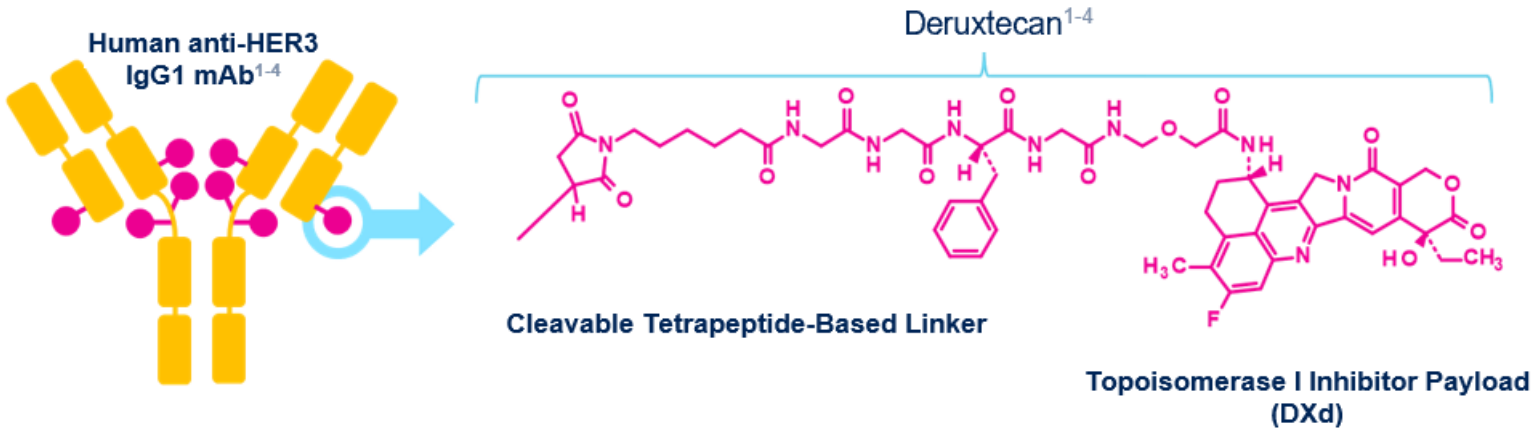
ASCO 2022 #1002 Oral

On behalf of the investigators

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.

Background

- HER3 is overexpressed in many types of cancer, including 30% to 50% of breast cancers[1-3]
  - Overexpression of HER3 in breast cancer is associated with poor prognosis[4,5]
  - No HER3-directed therapies have been approved for the treatment of any cancer

- U31402-A-J101 (NCT02980341/JapicCTI-163401) is an ongoing phase 1/2 study of HER3-DXd in patients with HER3-expressing metastatic breast cancer
  - Early data from the dose escalation, dose finding,[6] and dose expansion[7] parts showed promising antitumor activity and a manageable safety profile in heavily pretreated patients

- Here we report mature data across all study cohorts, providing consolidated data among patients with a range of breast cancer subtypes
  - As of the August 16, 2021, data cutoff, the median follow-up for all patients was 31.9 months (range,15-56 months)

BC, breast cancer.

1. Naidu R, et al. *Br J Cancer.* 1998;78(10):1385-1390. 2. Travis A, et al. *Br J Cancer.* 1996;74(2):229-233. 3. Kogawa T, et al. ASCO 2018. Poster 2512. 4. Witton CJ, et al. *J Pathol.* 2003;200(3): 290-297.
5. Ocana A, et al. *J Natl Cancer Inst.* 2013;105(4):266-273. 6. Masuda N, et al. SABCS 2018. Poster PD1-03. 7. Krop IE, et al. SABCS 2020. Poster PD1-09.

Study Design

Patritumab Deruxtecan : U31402-A-J101

KEY ELIGIBILITY CRITERIA

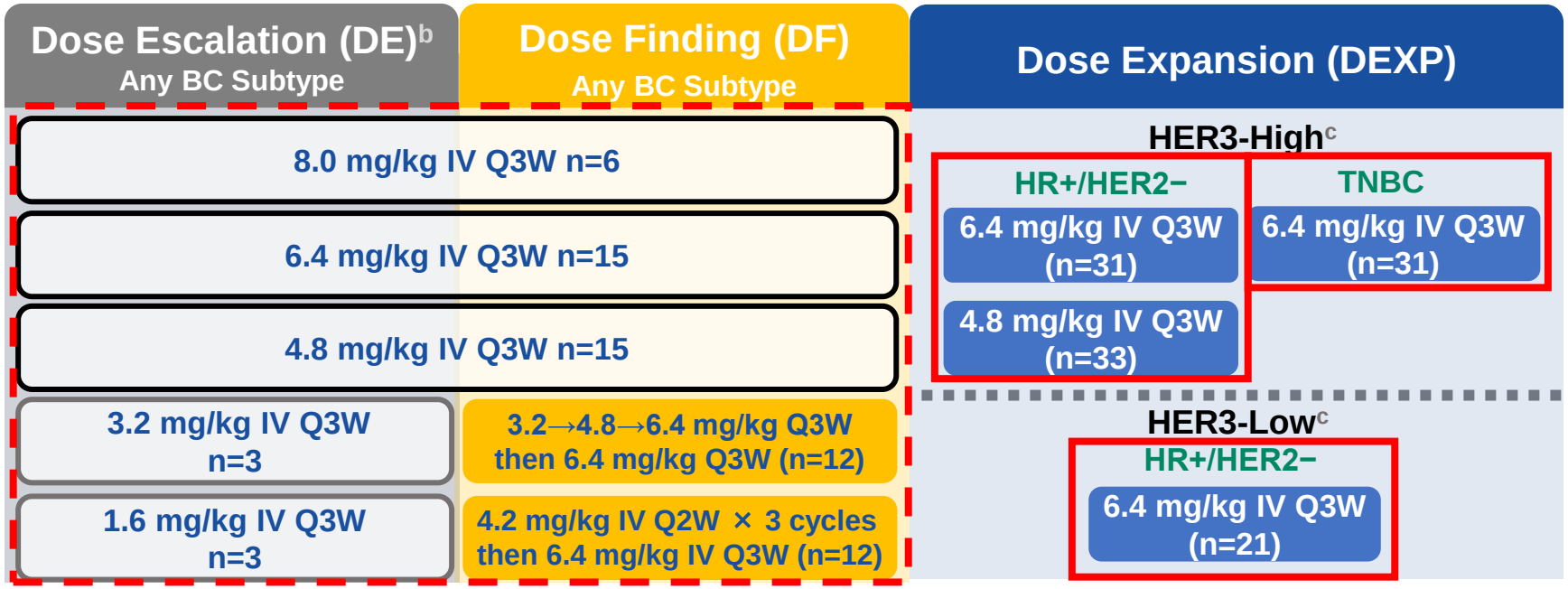
- Advanced/unresectable or metastatic breast cancer
- HER3-positive[a]

DE/DF & HR+/HER2− DEXP

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

Dose expansion: 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; R, randomized; TNBC, triple-negative breast cancer.

[a] HER3 status was determined by IHC; 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 High	0.0	0.0	100.0
	HER2+ 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

ASCO-CAP, American Society of Clinical Oncology-College of American Pathologists; 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 definitions: HER2 zero, IHC 0; HER2 low, IHC 1+ or 2+ (ISH−); HER2 high, IHC 2+ (ISH+), IHC 3+. [c] Patients with clinically active brain metastases were excluded.

Disposition, Follow-Up, and Treatment Duration

	All Patients (N=182[a])
Discontinued from treatment, n (%)	178 (97.8)
PD (RECIST version 1.1)	133 (73.1)
Clinical progression	15 (8.2)
AE	15 (8.2)
Death	3 (1.6)
Withdrawal by patient	6 (3.3)
Other	6 (3.3)
Ongoing on study treatment, n (%)	4 (2.2)
Median follow-up (range), months	31.9 (15-56)
Median treatment duration (range), months	5.9 (0.7-30.6)

Data cutoff: August 16, 2021
AE, adverse event; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors.
[a] All patients received ≥1 dose.

Clinical Activity of HER3-DXd Across BC Subtypes

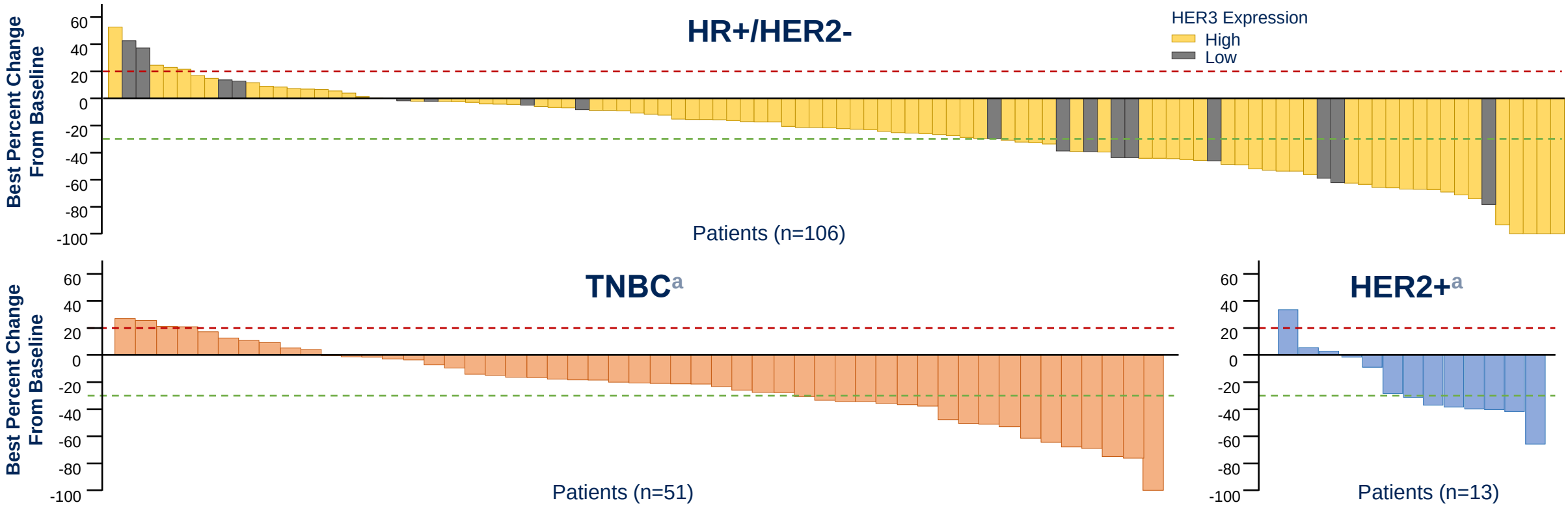
Outcomes (BICR per RECIST 1.1)	HR+/HER2− (n=113) HER3-High and -Low	TNBC (n=53) HER3-High	HER2+ (n=14) HER3-High
Confirmed ORR, % (95% CI[a])	30.1 (21.8-39.4)	22.6 (12.3-36.2)	42.9 (17.7-71.1)
Best overall response, %[b]			
PR	30.1	22.6	42.9
SD	50.4	56.6	50.0
PD	11.5	17.0	7.1
NE	8.0	3.8	0.0
DOR, median (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, confirmed 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.

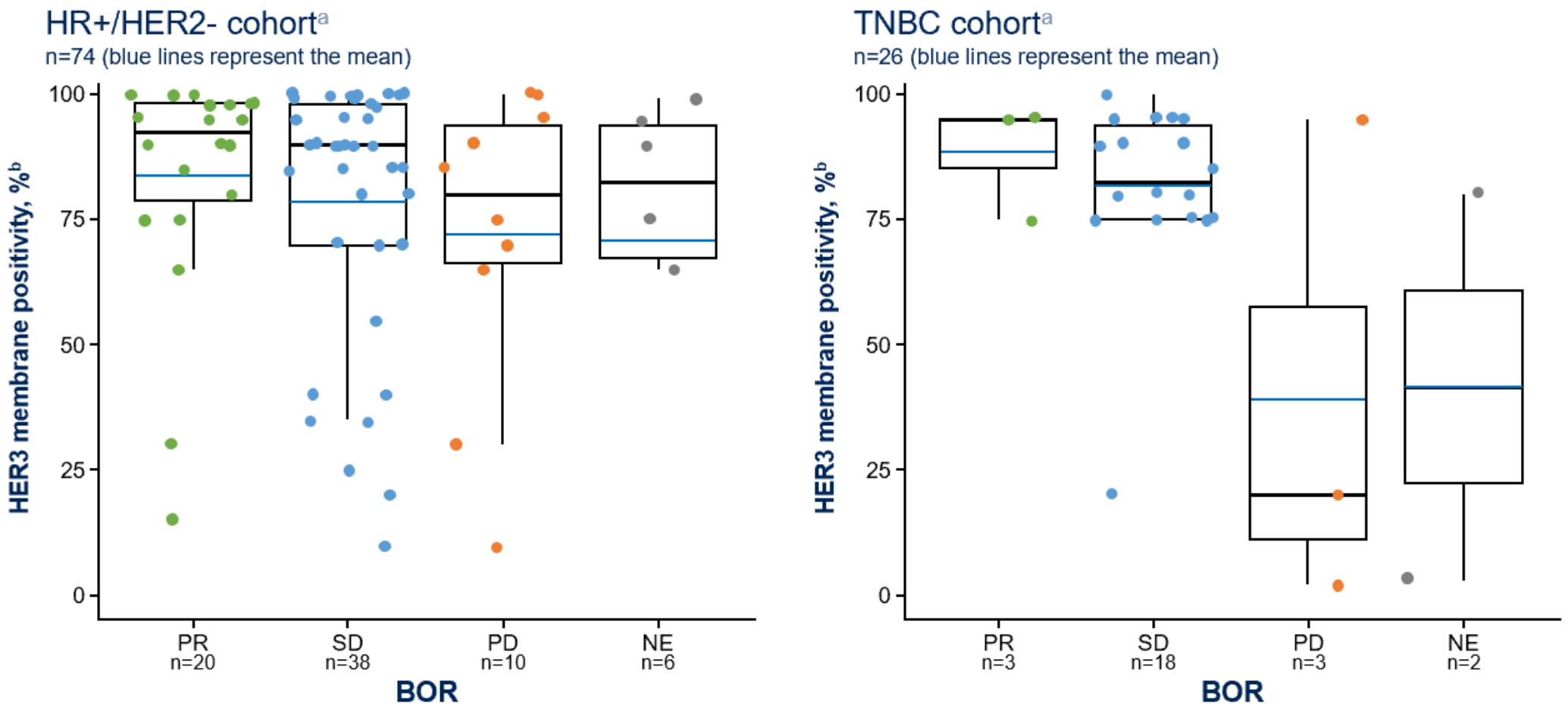
Change in Tumor Size From Baseline



HER3-DXd induced a clinically meaningful decrease in tumor size by BICR in most patients across BC subtypes[b]

[a] Patients with TNBC and HER2+ were all HER3-high.
[b] Best percentage change from baseline in sum of diameters based on BICR for all target lesions identified is represented by patient. If any lesion measurement is missing at a post-baseline tumor assessment visit, that visit is not taken into consideration for best percent change from baseline in sum of diameters.

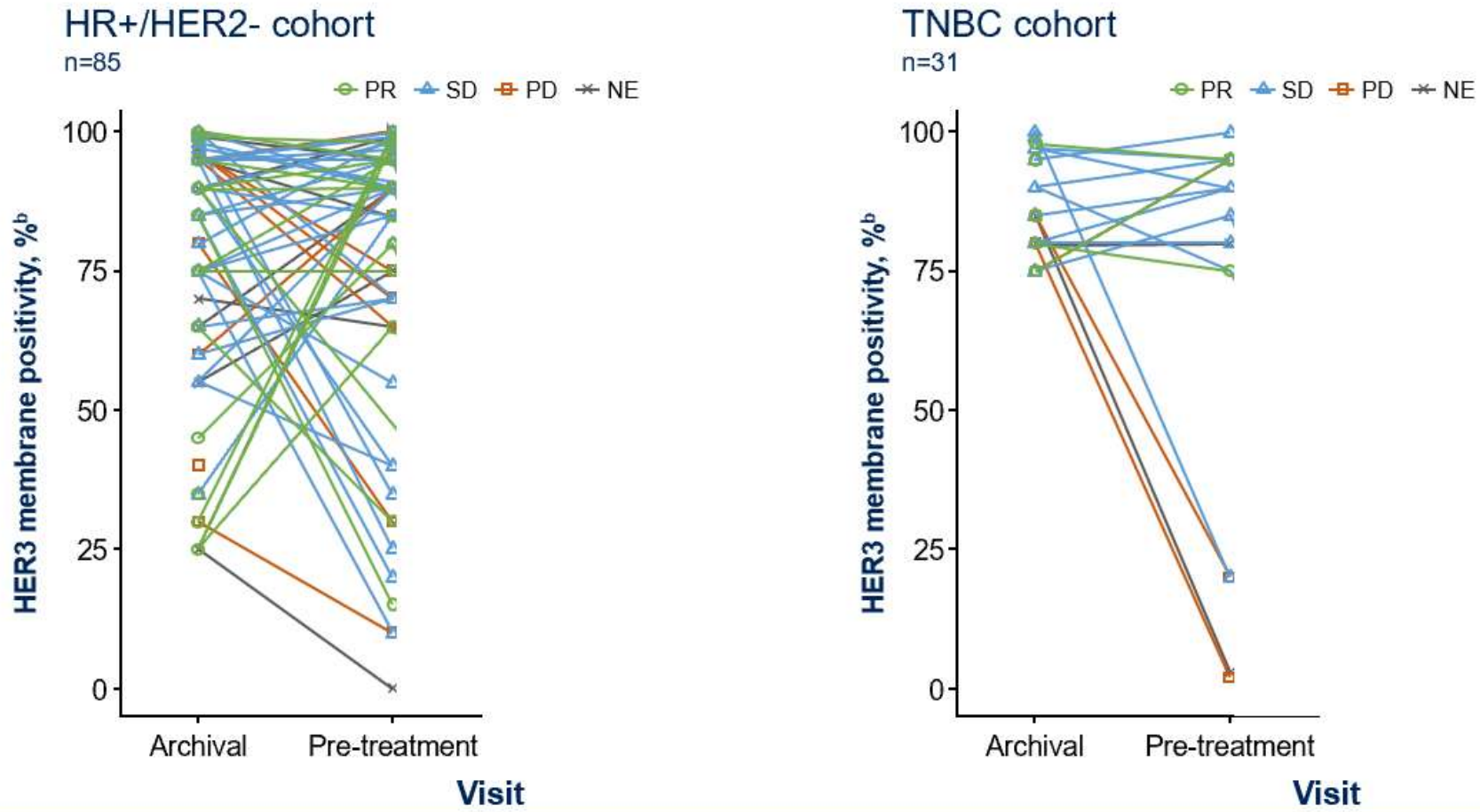
Baseline HER3 Membrane Expression by BOR



Antitumor responses across a broad range of baseline HER3 membrane expression

BOR, best overall response.
[a] Pre-treatment HER3 positivity from patients in the dose expansion cohorts. [b] Percent HER3 membrane positivity was centrally assessed by HER3 IHC.

HER3 Membrane Expression Over Time



HER3 membrane expression changed dynamically, but this was not associated with clinical activity

EOT, end of treatment.

[a] On-treatment biopsy taken at cycle 2 day 3 or cycle 3 day 3. [b] Percent HER3 membrane positivity was centrally assessed by HER3 IHC.

Overall Safety Profile of HER3-DXd

- HER3-DXd was associated with a manageable safety profile
- There was a low rate of TEAEs associated with treatment discontinuation (9.9%)
  - 18 patients had TEAEs associated with treatment discontinuation across all doses: pneumonitis (n=6), disease progression (n=2), ejection fraction decreased (n=2), ILD, malaise, peripheral edema, hepatotoxicity, gastric cancer, mental status changes, extradural hematoma, and general physical health deterioration (all n=1)
- 6.6% of patients had treatment-related ILD events[a]
  - Most were grade 1 and 2 (4.4%)
  - There was one grade 5 ILD event (0.5%)

Patients, n (%) **Median treatment duration: 5.9 mo (range 0.7-30.6 mo)**	**4.8 mg/kg n=48**	**6.4 mg/kg n=98**	**All Doses N=182**
Any TEAE	47 (97.9)	98 (100)	181 (99.5)
Associated with discontinuation	5 (10.4)	8 (8.2)	18 (9.9)
Associated with dose reduction	6 (12.5)	22 (22.4)	35 (19.2)
Associated with drug interruption	23 (47.9)	57 (58.2)	100 (54.9)
Associated with death	1 (2.1)[b]	6 (6.1)[b]	7 (3.8)[b]
Grade ≥3 TEAE	31 (64.6)	80 (81.6)	130 (71.4)
Treatment-related TEAE	47 (97.9)	97 (99.0)	180 (98.9)
Associated with death	0	1 (1.0)[c]	1 (0.5)[c]
Grade ≥3	27 (56.3)	76 (77.6)	120 (65.9)
Serious TEAE	7 (14.6)	23 (23.5)	38 (20.9)
Adjudicated treatment-related ILD[d]			
Grade 1	0	2 (2.0)	3 (1.6)
Grade 2	1 (2.1)	2 (2.0)	5 (2.7)
Grade 3	0	2 (2.0)	3 (1.6)
Grade 4	0	0	0
Grade 5	0	1 (1.0)	1 (0.5)
Total	**1 (2.1)**	**7 (7.1)**	**12 (6.6)**

ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.
[a] As determined by an independent adjudication committee. [b] TEAEs associated with death included disease progression (n=4), neutropenic sepsis (n=1), extradural hematoma (n=1), and choking (n=1). [c] Treatment-related TEAE associated with death was neutropenic sepsis (n=1). [d] Median time to onset, 141.5 days (95% CI; 36-584 days).

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

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).

Conclusions

- HER3-DXd demonstrated clinically meaningful and durable antitumor activity in a heavily pretreated population of patients with HER3-expressing BC
  - Durable antitumor activity was demonstrated across BC subtypes: HR+/HER2− (ORR, 30%; median DOR, 7.2 months), TNBC (ORR, 23%; median DOR, 5.9 months), and HER2+ (ORR, 43%; median DOR, 8.3 months)
  - Antitumor activity was also demonstrated across the range of HER3 expression
- The safety profile was manageable with a low rate of discontinuation due to TEAEs (10%)
  - The rate of adjudicated treatment-related ILD was 7%; most cases were grade 1 and 2
  - Grade ≥3 hematological toxicities were manageable; no grade ≥3 thrombocytopenia resulted in treatment discontinuation nor in a grade ≥3 bleeding event
- As a similar safety profile was seen with 4.8 mg/kg and 6.4 mg/kg, a 5.6 mg/kg dose, currently used in NSCLC, is being evaluated in BC to refine dose optimization
- These data provide encouraging evidence of antitumor efficacy with a manageable safety profile and warrant further evaluation of HER3-DXd across clinical and histopathological BC subtypes

Abstract 9017

Efficacy and safety of patritumab deruxtecan (HER3-DXd) in advanced/metastatic non-small cell lung cancer (NSCLC) without *EGFR*-activating mutations

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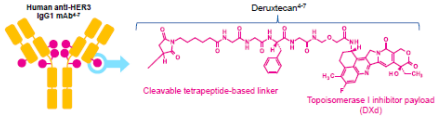
Background

- Human epidermal growth factor receptor 3 (HER3) is expressed in 83% of NSCLC tumors[1]
  - Overexpression of HER3 in NSCLC has been associated with poor clinical outcomes[1]
- Patients with advanced NSCLC without *EGFR*-activating mutations (*EGFR*m) have limited treatment options after failure of molecularly targeted therapies or platinum-based chemotherapy (PBC) with or without immunotherapy (IO)[2,3]
- Patritumab deruxtecan (HER3-DXd) is an antibody-drug conjugate (**Figure 1**)

Figure 1. HER3-DXd Structure and Attributes

HER3-DXd is an antibody drug conjugate with 3 components[1-4]

- 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



The 7 Key Attributes of HER3-DXd

Payload mechanism of action: topoisomerase I inhibitor[4-7,a]
High potency of payload[4-7,a]
High drug-to-antibody ratio ≈8[4,5,a]
Payload with short systemic half-life[5,6,a,b]
Stable linker-payload[5-7,a]
Tumor-selective cleavable linker[4-8,a]
Bystander antitumor effect[5,8,a]

[a] The clinical relevance of these features is under investigation. [b] Based on animal data.

- We previously reported efficacy and safety data for HER3-DXd in heavily pretreated patients with *EGFR*m NSCLC (all had prior EGFR TKI therapy and 80% had prior PBC)[10]
  - In 57 patients receiving HER3-DXd 5.6 mg/kg IV every 3 weeks (Q3W), the confirmed objective response rate (ORR) by blinded independent central review (BICR; Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) was 39% (95% CI, 26.0%-52.4%), and median progression-free survival (PFS) was 8.2 months (95% CI, 4.4-8.3 months)
  - Clinical activity was observed across a broad range of HER3 membrane expression levels and mechanisms of EGFR TKI resistance
- Here we describe the efficacy and safety results of HER3-DXd in patients with advanced NSCLC without common *EGFR*m whose disease progressed after treatment with PBC ± IO

Conclusions

- Similar to the previously reported observations in patients with *EGFR*m NSCLC, HER3-DXd showed promising clinical activity in heavily pretreated patients with advanced NSCLC with or without identified variant genomic alterations
  - Durable antitumor activity was seen in patients with variant identified driver genomic alterations and patients without such genomic alterations
- The overall safety profile of HER3-DXd was manageable and similar to that previously reported in patients with *EGFR*m NSCLC
- These results demonstrate the promising clinical activity of HER3-DXd in patients with NSCLC harboring a broad range of genomic alterations or without identified driver genomic alterations, and they warrant further clinical evaluation

Poster presented at: 2022 ASCO Annual Meeting; June 3-7, 2022; Chicago, IL, and virtual.

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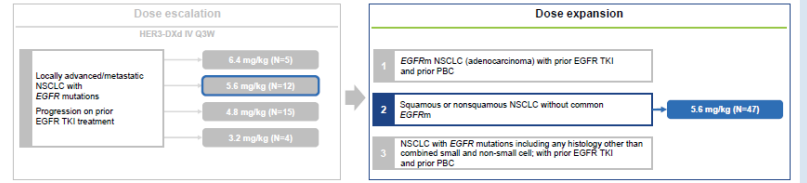
Methods

- U31402-A-U102 is an ongoing phase 1 dose-escalation and dose-expansion study in patients with NSCLC (**Figure 2**; ClinicalTrials.gov, NCT03260491; EudraCT, 2017-000543-41; JapicCTI, 194868)
  - Here we report data from the dose-expansion part, cohort 2; all patients had squamous or nonsquamous NSCLC without the common Ex19del, L858R, L861Q, or G719X mutations
  - Patients with stable brain metastases were eligible
  - Patients with non-*EGFR* oncogenic alterations were eligible provided that they had prior treatment with ≥1 targeted therapy, if available
  - All patients received HER3-DXd 5.6 mg/kg IV Q3W
- The primary endpoint was confirmed ORR by BICR per RECIST 1.1
- Secondary endpoints included disease control rate, time to response, duration of response, PFS, and safety

Figure 2. Study Design (This Poster Presents Cohort 2)



Results

- At the January 28, 2022, data cutoff, 47 patients in cohort 2 had been treated with HER3-DXd 5.6 mg/kg IV Q3W (**Tables 1** and **2**)
  - In this heavily pretreated cohort, all patients had prior PBC and 45 of 47 had prior IO (**Table 1**)
  - Most patients had adenocarcinoma (74%; **Figure 3**)
  - 21 patients had identified driver genomic alterations (**Figure 3**)
- Median follow-up was 19.7 months (range, 13.8-29.2 months)
- Confirmed responses by BICR were observed in patients with NSCLC harboring a range of driver genomic alterations and also with NSCLC without such genomic alterations (**Figures 4** and **5**)

Table 1. Patient Characteristics and Treatment History

	HER3-DXd 5.6 mg/kg (N=47)
Age, median (range), years	62 (29-79)
Female, n (%)	25 (53.2)
ECOG performance status 0/1, n (%)	16 (34.0)/31 (66.0)
Sum of diameters at baseline, median (range), mm[a]	67 (18-205)
History of CNS metastases, n (%)	15 (31.9)
Patients with identified driver genomic alterations, n (%)	21 (44.7)
Patients without identified driver genomic alterations, n (%)	26 (55.3)
Prior lines of systemic therapy, median (range)[b]	3 (1-8)
Prior cancer regimens, n (%)	
PBC	47 (100)
IO	45 (95.7)
Anti–PD-1/anti–PD-L1	45 (95.7)
Anti–CTLA-4	1 (2.1)
Genomic-directed therapy	9 (19.1)

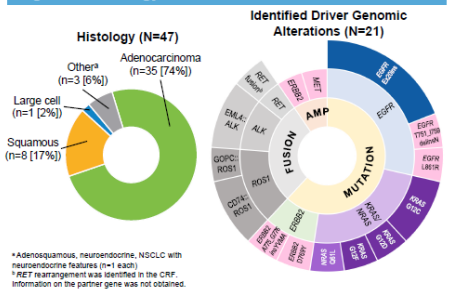
Data cutoff: January 28, 2022.
[a] By BICR per RECIST 1.1. [b] In the locally advanced or metastatic setting.

Table 2. Disposition

Patients, n (%) Median (range) follow-up: 19.7 mo (13.8-29.2 mo)	HER3-DXd 5.6 mg/kg (N=47)
Treated	47 (100)
Ongoing study treatment	5 (10.6)
Discontinued from study treatment	42 (89.4)
Primary reason for discontinuation	
PD	24 (51.1)
Clinical progression	6 (12.8)
Adverse event	5 (10.6)
Withdrawal of consent by patient	4 (8.5)
Death	3 (6.4)

Data cutoff: January 28, 2022.

Figure 3. Histology and Driver Genomic Alterations



[a] Adenosquamous, neuroendocrine, NSCLC with neuroendocrine features (n=1 each). [b] *RET* rearrangement was identified in the CRF. Information on the partner gene was not obtained.

Figure 4. Clinical Activity With Durable Responses Observed in Patients With Variant Genomic Alterations or Without Identified Driver Genomic Alterations

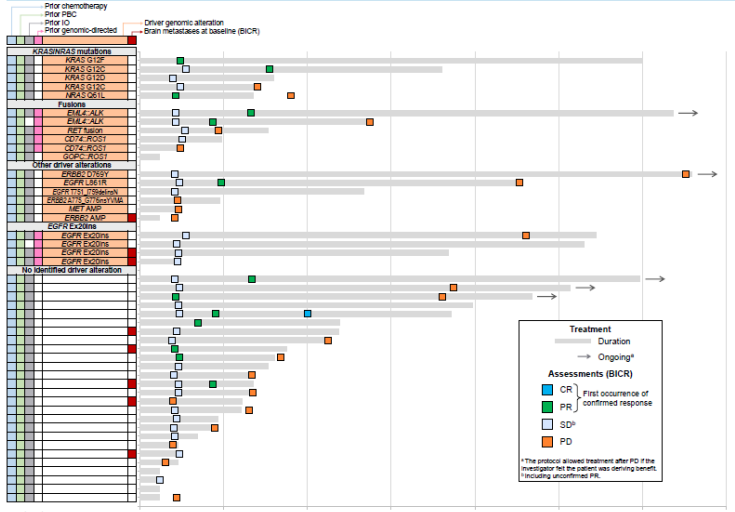
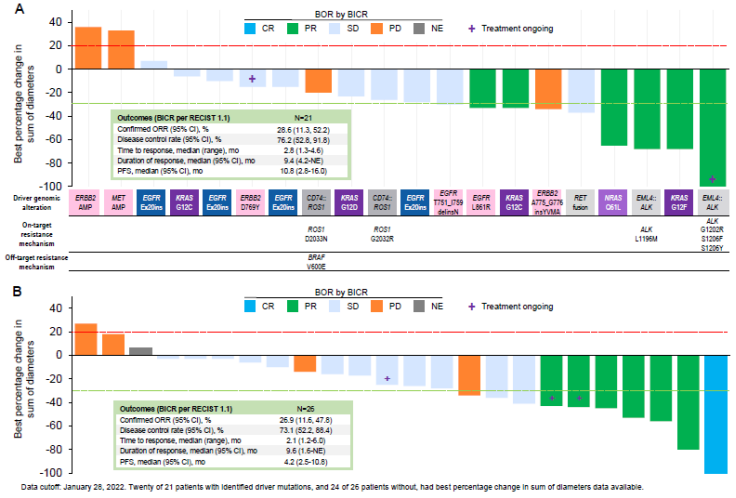


Figure 5. Antitumor Activity in Patients With (A) or Without (B) Identified Driver Genomic Alterations



Data cutoff: January 28, 2022. Twenty of 21 patients with identified driver mutations, and 24 of 26 patients without, had best percentage change in sum of diameters data available.

Safety

- The overall safety profile was manageable (**Table 3**), and similar to that in patients with *EGFR*m NSCLC[10]
  - 5 patients (11%) had TEAEs associated with treatment discontinuation
  - The most common grade ≥3 TEAEs were neutropenia (26%), fatigue (17%), thrombocytopenia (15%), hypokalemia (13%), anemia (11%), leukopenia (11%), and pneumonia (11%)
  - Drug-related interstitial lung disease by central adjudication occurred in 5 patients (11%; all grade 1 or 2; median time to onset, 140 days [range, 43-331 days])
  - No drug-related deaths occurred in this cohort

Table 3. Manageable Safety Profile

TEAEs by patient, n (%) Median (range) treatment duration: 4.2 mo (0.7-19.8 mo)	5.6 mg/kg (N=47)
Any TEAE	47(100)
Associated with treatment discontinuation[a]	5 (10.6)
Associated with treatment dose reduction	11 (23.4)
Associated with treatment dose interruption	24 (51.1)
Associated with death[b]	7 (14.9)
Grade ≥3	34 (72.3)
Serious AE	19 (40.4)
Treatment-related TEAE	47(100)
Associated with death	0
Grade ≥3	24 (51.1)
Serious AE	6 (12.8)
Adjudicated treatment-related interstitial lung disease	5 (10.6)
Grade 1	1 (2.1)
Grade 2	4 (8.5)
Grade ≥3	0

Data cutoff: January 28, 2022.
[a] TEAEs associated with treatment discontinuation were pneumonitis (n=2) and pneumonia, platelet count decreased, red blood cell count decreased, and pericardial effusion (n=1 each). [b] TEAEs associated with death were disease progression (n=2); pneumonia (n=2); and COVID-19, malignant neoplasm progression, physical deconditioning, and white blood cell count decreased (n=1 each).

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10. Jänne PA, et al. *Cancer Disc*. 2022;12(1):74-89.

Abbreviations

BICR, blinded independent central review; BOR, best overall response; CNS, central nervous system; CR, complete response; CRF, case report form; ECOG, Eastern Cooperative Oncology Group; *EGFR*m, *EGFR*-activating mutations; HER3, human epidermal growth factor receptor 3; IO, immunotherapy; IV, intravenous; mAb, monoclonal antibody; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PBC, platinum-based chemotherapy; PD, progressive disease; PR, partial response; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TEAE, treatment-emergent adverse event.

Funding

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Acknowledgments

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Phase I, Two-Part, Multi-Center, First-in-Human Study of DS-6000a in Subjects with Advanced Renal Cell Carcinoma and Ovarian Cancer

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Background

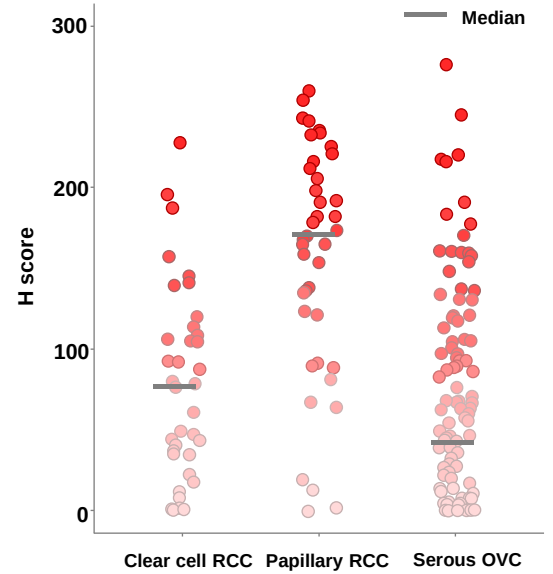
Cadherin 6 (CDH6) is part of the cadherin family, which is involved with cell-cell adhesion, organ development, and epithelial-mesenchymal transition

CDH6 is found to be overexpressed in various cancers, particularly ovarian cancer (OVC) and renal cell carcinoma (RCC)[1]

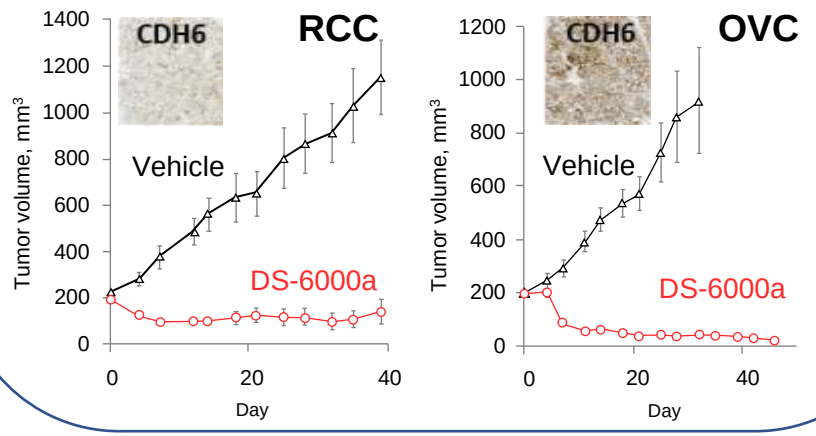
In preclinical studies, DS-6000a inhibited tumor growth and induced tumor regression in CDH6-expressing OVC and RCC[1]

Here, we report initial results from the dose-escalation portion of a first-in-human trial in patients with advanced OVC and RCC (NCT04707248)

CDH6 Expression in RCC/Serous OVC[1]



Antitumor Activity of DS-6000a in RCC and OVC PDX Model[1]



PDX, patient-derived xenograft.

1. Hirokazu S, et al. ESMO 2021. Abstract 10P.

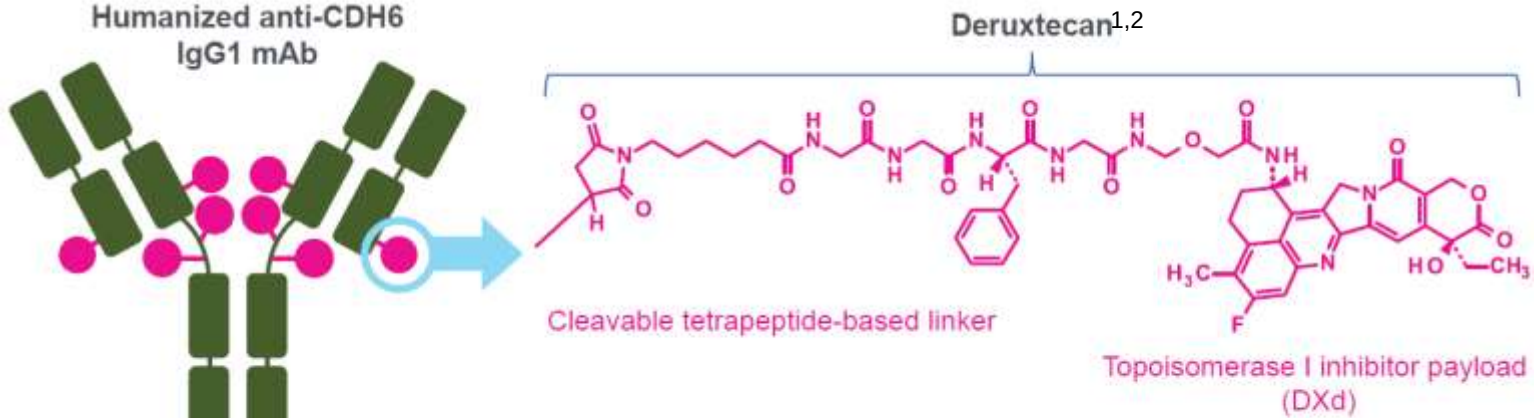
DS-6000a Was Designed With 7 Key Attributes

DS-6000a is a cadherin 6 (CDH6) directed ADC composed of 3 components:[1-3]

A humanized anti-CDH6 IgG1 monoclonal antibody covalently linked to:

A topoisomerase I inhibitor payload, an exatecan derivative, via

A tetrapeptide-based cleavable linker

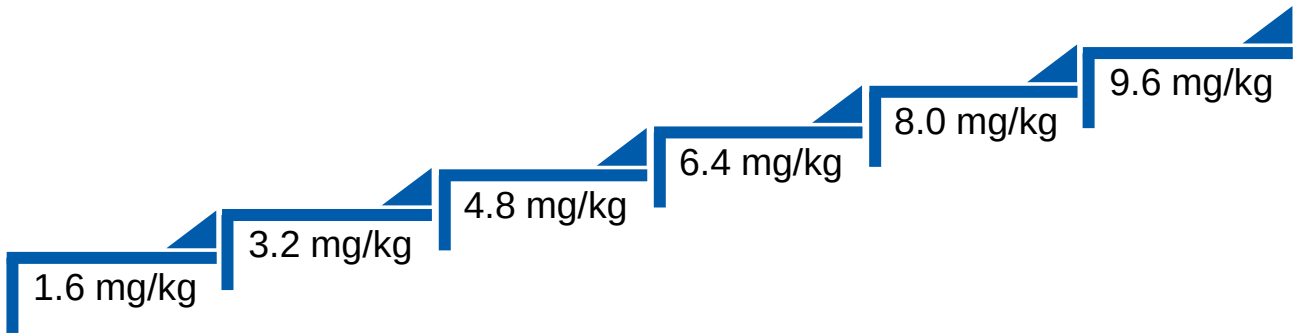


- Payload mechanism of action: topoisomerase I inhibitor [a,1,2]
- High potency of payload [a,1,2]
- High drug-to-antibody ratio ≈8 [a,1,2]
- Payload with short systemic half-life [a,b,1,2]
- Stable linker-payload [a,1,2]
- Tumor-selective cleavable linker [a,1,2]
- Bystander antitumor effect [a,1,2]

ADC, antibody-drug conjugate; DXd, a novel topoisomerase 1 inhibitor that is a derivative of exatecan; IgG1, immunoglobulin G1; mAb, monoclonal antibody.
[a] The clinical relevance of these features is under investigation. [b] Based on animal data.
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.** Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

Study Design

Dose Escalation (Part A)
DS-6000a IV q3w
RCC and serous OVC



RDE

Dose Expansion (Part B)
DS-6000a IV q3w at RDE

- Cohort B-1 → RCC
- Cohort B-2 → Serous OVC

Enrollment criteria

- Advanced/metastatic RCC or OVC not amenable to SOC therapy[a]
- ECOG PS 0 to 1
- Ability to provide archived tissue for correlative testing
- No previous treatment with CDH6-targeting agents or ADCs with a linked topoisomerase I inhibitor

Primary objectives

- Safety and tolerability
- Determine MTD and RDE

Secondary objectives

- PK of DS-6000a, total anti-CDH6 antibody, and the DXd payload
- Antitumor activity per RECIST 1.1
- Immunogenicity

ADC, antibody drug conjugate; CDH6, cadherin 6; DXd, topoisomerase I inhibitor payload; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MTD, maximum tolerated dose; OVC, ovarian cancer; PK, pharmacokinetics; q3w, every 3 weeks; RCC, renal cell carcinoma, RDE, recommended dose for expansion; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SOC, standard of care.
[a] Patients with OVC must have also had prior treatment with platinum and taxane therapy.

Baseline Patient and Disease Characteristics

DS-6000a Dose Escalation	OVC (N=20)	RCC (N=9)	Total (N=30)[a]
Age, median (range), years	65.5 (51-78)	60.0 (41-72)	64.5 (41-78)
Sex, n (%)			
Female	20 (100)	4 (44.4)	25 (83.3)
Male	0	5 (55.6)	5 (16.7)
Baseline ECOG PS, n (%)			
0	10 (50)	6 (66.7)	16 (53.3)
1	10 (50)	3 (33.3)	14 (46.7)
Tumor type, n (%)			
Renal cell carcinoma			
Clear cell RCC	–	8 (88.9)	8 (26.7)
Non–clear cell RCC	–	1 (11.1)	1 (3.3)
Serous ovarian cancer	20 (100)	–	20 (66.7)
Platinum-resistant disease	17 (85)	–	17 (56.7)
No. of prior systemic regimens			
Median (range)	4.0 (1-12)	2.0 (1-6)	3.0 (1-12)
Baseline CDH6 expression H score, range	0-250	17-218	0-250[b]

Data cutoff: February 25, 2022.
CDH6, cadherin 6; ECOG PS, Eastern Cooperative Oncology Group performance status; OVC, ovarian cancer; RCC, renal cell carcinoma.
[a] One missing primary diagnosis of OVC.
[b] Membrane CDH6 expression of 23 evaluable archival tissues.

Patient and Treatment Summary

- As of data cutoff, 30 patients enrolled in part A (dose escalation) had received DS-6000a (OVC, n=21; RCC, n=9)
  - 17 patients (56.7%) were receiving ongoing treatment with DS-6000a (OVC, n=12; RCC, n=5)
  - 13 patients (43.3%) discontinued treatment
    - 9 of 13 patients discontinued due to disease progression
    - 1 patient (3.3%) discontinued due to TEAE
- Median treatment duration was 12.1 weeks (range, 3.0-54.1 weeks)

- Data cutoff: February 25, 2022.
- OVC, ovarian cancer; RCC, renal cell carcinoma; TEAE, treatment-emergent adverse event.

Treatment Related TEAEs (Any Grade) Occurring in ≥10% of Patients

	1.6 mg/kg (n=1)	3.2 mg/kg (n=6)	4.8 mg/kg (n=6)	6.4 mg/kg (n=8)	8.0 mg/kg (n=6)	9.6 mg/kg (n=3)	Total (N=30)
Any treatment-related TEAE, n (%)	1 (100)	4 (66.7)	4 (66.7)	7 (87.5)	6 (100.0)	3 (100.0)	25 (83.3)
Nausea	0	3 (50.0)	3 (50.0)	5 (62.5)	5 (83.3)	2 (66.7)	18 (60.0)
Fatigue	0	2 (33.3)	3 (50.0)	4 (50.0)	6 (100.0)	2 (66.7)	17 (56.7)
Vomiting	0	2 (33.3)	1 (16.7)	2 (25.0)	2 (33.3)	2 (66.7)	9 (30.0)
Neutrophil count decreased	0	0	0	1 (12.5)	3 (50.0)	3 (100.0)	7 (23.3)
Decreased appetite	1 (100)	0	0	4 (50.0)	1 (16.7)	0	6 (20.0)
Diarrhea	0	0	0	2 (25.0)	1 (16.7)	1 (33.3)	4 (13.3)

- Treatment-related TEAEs occurred in 25 patients (83.3%)
- The most common treatment-related TEAEs of any grade were nausea, fatigue, and vomiting
- One patient in the 9.6-mg/kg arm experienced grade 2 pneumonitis, which led to treatment discontinuation

Data cutoff: February 25, 2022.
TEAE, treatment-emergent adverse event.

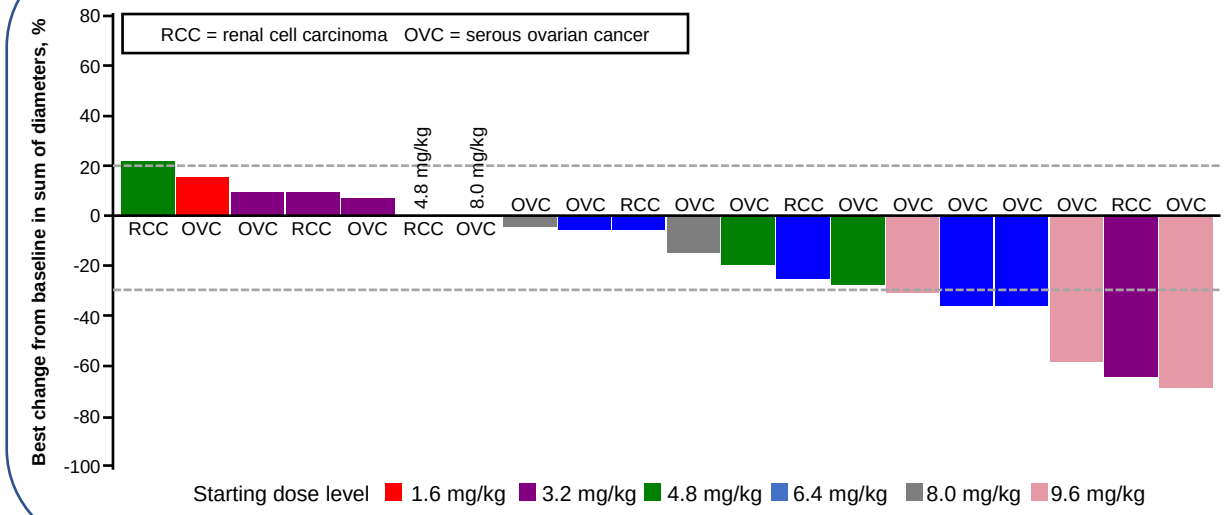
Treatment-Related TEAEs (Grade ≥3)

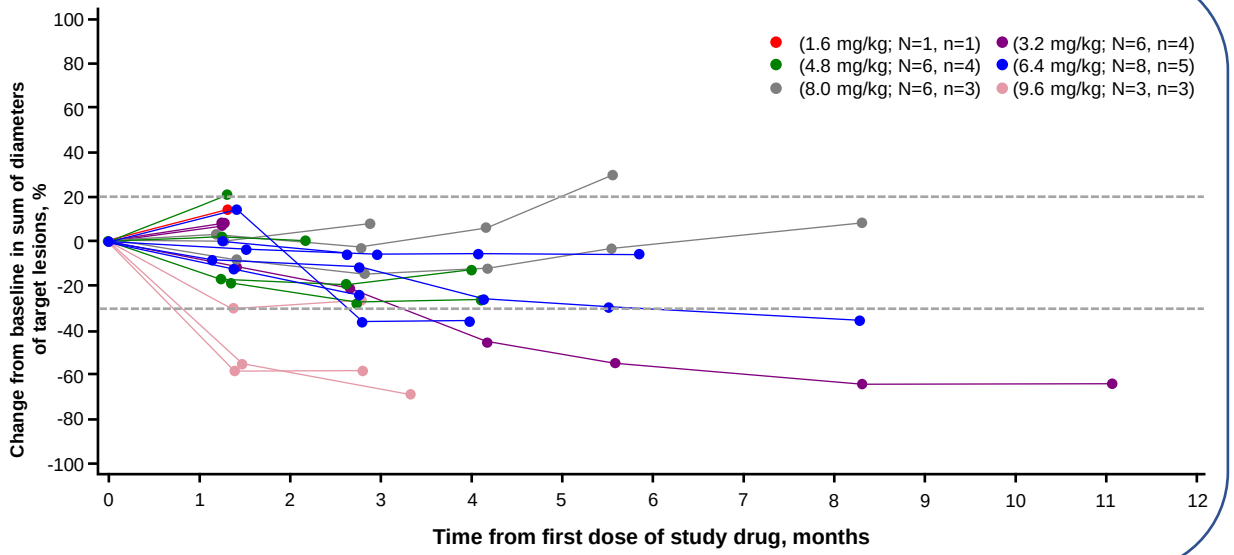
	1.6 mg/kg (n=1)	3.2 mg/kg (n=6)	4.8 mg/kg (n=6)	6.4 mg/kg (n=8)	8.0 mg/kg (n=6)	9.6 mg/kg (n=3)	Total (N=30)
Any grade ≥3 treatment-related TEAE, n (%)	0	0	0	2 (25.0)	2 (33.3)	3 (100)	7 (23.3)
Neutrophil count decreased	0	0	0	0	2 (33.3)	3 (100)	5 (16.7)
Anemia	0	0	0	1 (12.5)	0	1 (33.3)	2 (6.7)
Febrile neutropenia	0	0	0	1 (12.5)	0	1 (33.3)	2 (6.7)
Decreased appetite	0	0	0	0	1 (16.7)	0	1 (3.3)
Platelet count decreased	0	0	0	0	0	1 (33.3)	1 (3.3)

- Grade ≥3 treatment-related TEAEs occurred in 7 patients (23.3%)
- The most common treatment-related TEAEs (nausea, fatigue, and vomiting) had no grade ≥3 events
- Two patients experienced DLTs in the 9.6-mg/kg arm (grade 3 febrile neutropenia and grade 4 platelet count decreased)
- Two patients experienced grade 3 treatment-related SAEs (anemia and febrile neutropenia)

Data cutoff: February 25, 2022.
DLT, dose-limiting toxicity; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Change From Baseline in Target Lesions: OVC and RCC Evaluable Population[a]



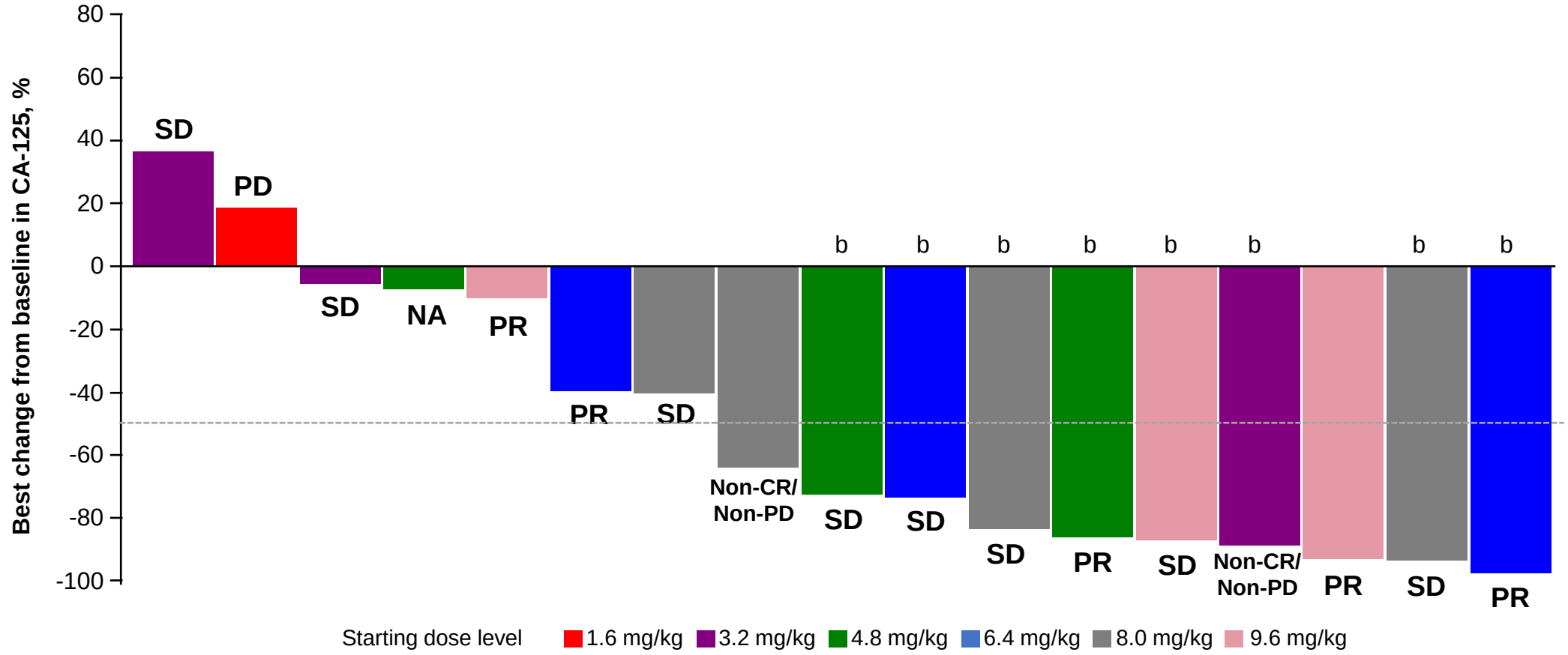


- Among 20 evaluable patients with measurable disease, there were 6 PRs (platinum-resistant OVC, n=5; RCC, n=1)
  - 4 confirmed PRs (platinum-resistant OVC, n=3; RCC, n=1)
  - 2 unconfirmed PRs (1 patient still in the trial)
- 12 patients had stable disease

Data cutoff: February 25, 2022.
OVC, ovarian cancer; PR, partial response; RCC, renal cell carcinoma.
[a] Patients who received ≥1 dose of study treatment and have completed ≥1 postbaseline tumor assessment or discontinued treatment for any reason.

Change From Baseline in CA-125 Levels

- Among 17 evaluable patients with OVC,[a] 8 CA-125 responses[b] were observed



Data cutoff: February 25, 2022.

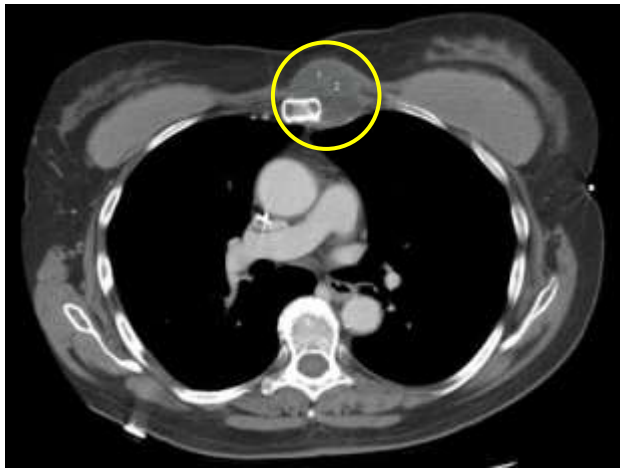
CA-125, cancer antigen 125; CR, complete response; GCIG, Gynecologic Cancer InterGroup; NA, not available; OVC, ovarian cancer; PD, progressive disease; PR, partial response; SD, stable disease.

[a] Patients with baseline CA-125 value and ≥1 postbaseline CA-125 value were included.

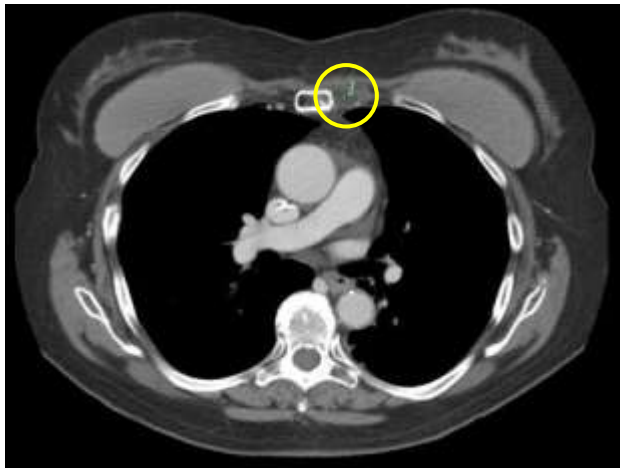
[b] According to the GCIG criteria, patients can be evaluated for response only if they have a baseline sample that is ≥2 × the upper limit of normal obtained within 2 weeks prior to starting treatment. CA-125 response is defined as a ≥50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for ≥28 days.

Case Summary: Patient With Serous OVC

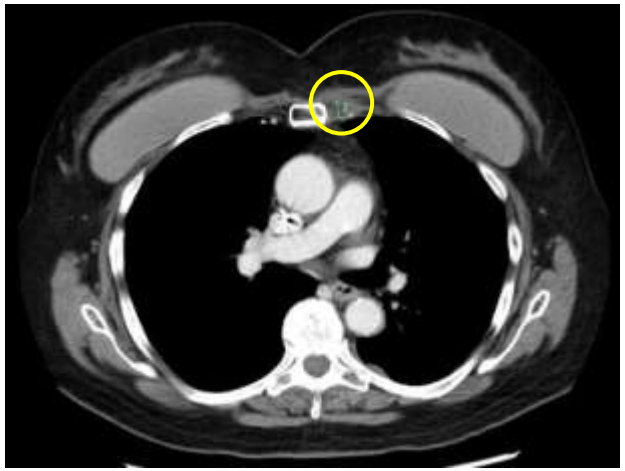
- 67-year-old woman with stage IV platinum-resistant OVC
- Treated with DS-6000a 6.4 mg/kg intravenously q3w
- 3 prior therapies
  - Paclitaxel + carboplatin with olaparib maintenance
  - Carboplatin + gemcitabine + bevacizumab
  - Pegylated liposomal doxorubicin
- Cycle 14 treatment ongoing



Baseline



18 weeks
Overall SD (−26.2%)

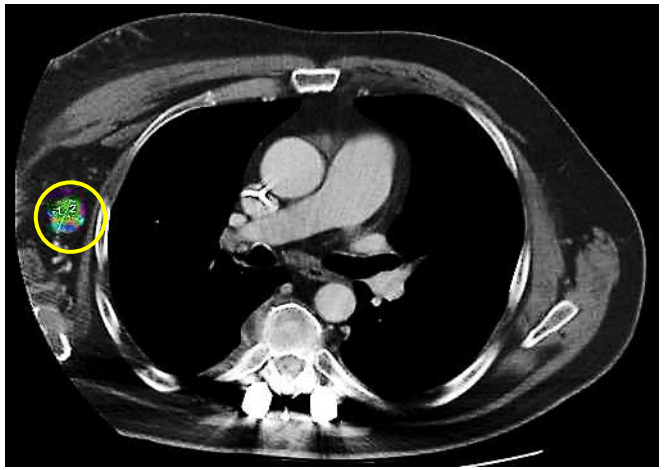


36 weeks
Overall PR (−35.7%)

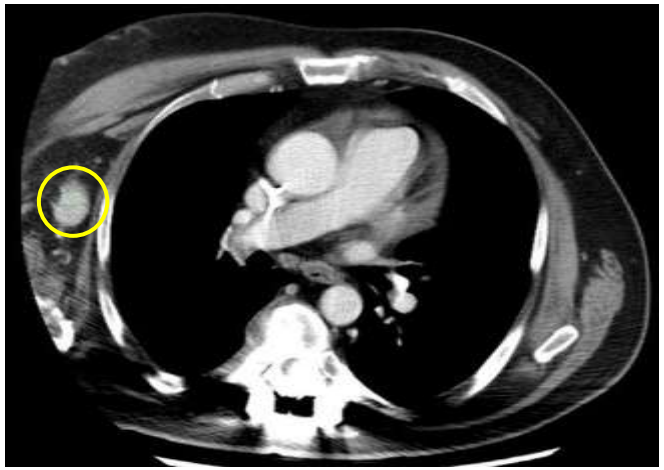
OVC, ovarian cancer; PR, partial response; q3w, every 3 weeks; SD, stable disease.

Case Summary: Patient With Clear Cell RCC

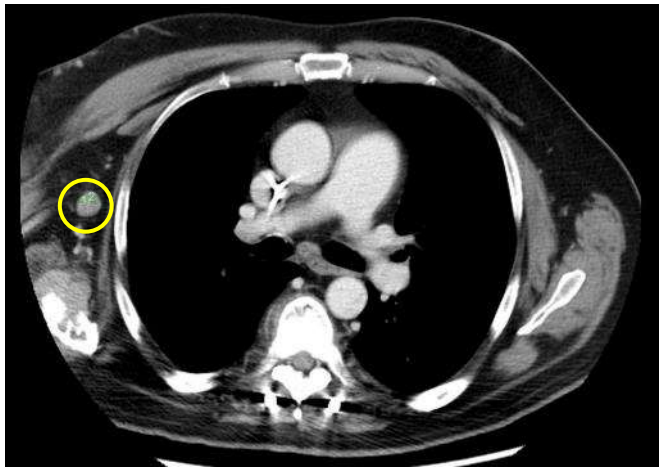
- 60-year-old man with stage IV RCC
- Treated with DS-6000a 3.2 mg/kg intravenously q3w
- 3 prior therapies
  - Sorafenib
  - Nivolumab
  - Telaglenastat + cabozantinib
- Cycle 18 treatment ongoing



Baseline



19 weeks
Overall PR (−45.2%)



48 weeks
Overall PR (−64.3%)

PR, partial response; q3w, every 3 weeks; RCC, renal cell carcinoma.

Conclusions

- DS-6000a was generally well tolerated, and the recommended dose for expansion (RDE) was declared 8.0 mg/kg
- DS-6000a demonstrated early clinical signals (RECIST and CA-125 responses) in heavily pretreated patients with advanced platinum-resistant OVC and RCC
- Expansion cohorts (part B) opened at 8.0 mg/kg are enrolling patients with OVC and RCC

Phase I, Multicenter, Open-Label, First-in-Human Study of DS-6157a in Patients with Advanced Gastrointestinal Stromal Tumor

Suzanne George, MD[1], Michael Heinrich, MD[2], Neeta Somaiah, MD[3], Brian A Van Tine, MD, PhD[4], Robert McLeod, MD[5], Abderrahmane Laadem, MD, PhD[5], Ben Cheng, MD[5], Satoshi Nishioka[6], Madan G Kundu, PhD[5], Xiaozhong Qian, PhD[5], Yvonne Lau, PhD[5], Brittany Tran, PharmD[5], Prasanna Kumar, PhD[5], Ololade Dosunmu, MD[7], Julia Shi[7], Yoichi Naito, MD[8]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]OHSU Knight Cancer Institute, Portland, OR; [3]The University of Texas MD Anderson Cancer Center, Houston TX; [4] Washington University in Saint Louis, St. Louis, MO; [5]Daiichi Sankyo, Inc., Basking Ridge, NJ; [6]Daiichi Sankyo Co., Ltd, Tokyo, Japan; [7]Sarah Cannon Research Institute, Nashville, TN; [8]National Cancer Center Hospital East, Kashiwa, Japan

BACKGROUND

- GPR20 is selectively and abundantly expressed in gastrointestinal stromal tumors (GISTs), the most common sarcoma of the digestive tract.
- DS-6157a is an anti-GPR20 antibody-drug conjugate with a novel tetrapeptide-based linker and DNA topoisomerase I inhibitor exatecan derivative (DXd) which target the drug-to-antibody ratio (DAR) of ~8.
- In nonclinical pharmacology studies, DS-6157a inhibited the growth of GPR20-expressing GIST xenografted mouse models[1].
- Here, we report the results from a Phase I trial of DS-6157a in patients (pts) with advanced GIST (NCT04276415).

STUDY OBJECTIVES

Primary

- Dose Escalation (Part 1): Investigate the safety and tolerability of the DS-6157a, and determine the maximum tolerated dose (MTD) and/or the recommended dose for expansion (RDE)

Secondary

- Characterize the pharmacokinetic (PK) properties of DS-6157a, total anti-GPR20 antibody, and the drug component (MAAA-1181a)
- Investigate the efficacy of DS-6157a (Part 1 only)

STUDY DESIGN

- The dose-escalation portion of this study (Part 1) enrolled pts with advanced GIST. DS-6157a was administered IV as monotherapy on Day 1 of 21-day cycles.
- Part 1 assessed safety, tolerability, and MTD or RDE using Bayesian logistic regression model (BLRM), with at least 3 dose-limiting toxicity (DLT)-evaluable pts per dose level.

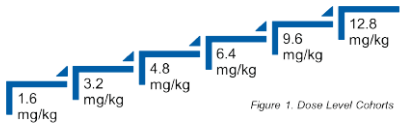


Figure 1. Dose Level Cohorts

KEY INCLUSION CRITERIA

- Histopathologically-documented unresectable and/or metastatic GIST, Part 1
- Enrollment in Part 1 was allowed regardless of GPR20 expression
- At least one measurable lesion per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Adequate organ function
- Consent to provide fresh tumor biopsy tissue samples before and on DS-6157a treatment for correlative testing

DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS

Table 1. Demographics and Baseline Disease Status

Total Number of Patients	34	Primary Site Location n(%)	
		Stomach	13 (38.2)
Age (years)		Small Intestine Jejunum	5 (14.7)
Median	60.5	Small Intestine Ileum	3 (8.8)
		Small Intestine Duodenum	2 (5.9)
Sex n(%)		Rectum	2 (5.9)
Male	19 (55.9)	Other	9 (26.5)
Female	15 (44.1)		
		Metastatic Site at Study Entry n(%)	
Country of Enrollment n(%)		Liver	24 (70.6)
US	18 (52.9)	Peritoneum	22 (64.7)
Japan	16 (47.1)	Bone	3 (8.8)
		Lung	8 (23.5)
Race n(%)		Other	13 (38.2)
Asian	16 (47.1)		
Black or African American	1 (2.9)	GPR20 H-score at screening	
White	16 (47.1)	Median	168.0
Other	1 (2.9)	Min, Max	12, 273
ECOG Performance Status n(%)		GPR20 H-score values n(%)	
0 - Normal activity	18 (52.9)	0 to <100	5 (14.7)
1 - Symptoms, but ambulatory	16 (47.1)	>100 to <200	14 (41.2)
		>200 to <300	11 (32.4)
Number of Prior Systemic Regimens		Missing	4 (11.8)
Median	5.0		

PATIENT DISPOSITION SUMMARY

Table 2. Patient Disposition

Parameter	DS-6157a dose, mg/kg 1.6 (n=4)	3.2 (n=4)	4.8 (n=5)	6.4 (n=13)	9.6 (n=6)	12.8 (n=2)	Total (n=34)
Treatment Status							
Ongoing on the Study Treatment	0	0	2 (40.0)	0	0	0	2 (5.9)
Discontinued from Study Treatment	4 (100)	4 (100)	3 (60.0)	13 (100)	6 (100)	2 (100)	32 (94.1)
Primary Reason for discontinuation from Study Treatment							
Adverse Event	0	0	0	3 (23.1)	0	0	3 (8.8)
Clinical Progression	1 (25.0)	1 (25.0)	0	0	1 (16.7)	0	3 (8.8)
Other*	0	0	0	1 (7.7)	0	0	1 (2.9)
Physician Decision	0	0	0	2 (15.4)	1 (16.7)	0	3 (8.8)
Progressive Disease	3 (75.0)	3 (75.0)	3 (60.0)	6 (46.2)	2 (33.3)	2 (100)	19 (55.9)
Withdrawal by Subject	0	0	0	1 (7.7)	2 (33.3)	0	3 (8.8)

*Other, finished per patient request

- At time of data cut-off, 34 pts were exposed to a median of 3.0 treatment cycles (range 1-18) with DS-6157a. The median treatment duration was 9.9 weeks (wks) (range 3-56 wks). Two pts (5.9%) continued to receive study treatment, having completed 17 and 18 cycles, respectively.
- There were 2 on-treatment deaths. A TEAE of hepatic function abnormality was the primary cause of death in 1 pt at 6.4 mg/kg and progressive disease in a second pt at 9.6 mg/kg, respectively.

ADVERSE EVENTS

Table 3. Adverse Events Summary

Parameter	DS-6157a dose, mg/kg 1.6 (n=4)	3.2 (n=4)	4.8 (n=5)	6.4 (n=13)	9.6 (n=6)	12.8 (n=2)	Total (n=34)
Treatment-Emergent Adverse Events (TEAE)	4 (100)	4 (100)	5 (100)	13 (100)	6 (100)	2 (100)	34 (100)
TEAE associated with Drug Discontinuation[a]	0	0	0	3 (23.1)	1 (16.7)	0	4 (11.8)
TEAE associated with Dose Interruption	0	0	0	0	1 (16.7)	2 (100)	3 (8.8)
TEAE associated with Dose Reduction	0	0	0	0	0	1 (50.0)	1 (2.9)
TEAE associated with Death as Outcome[b]	0	0	0	1 (7.7)	0	0	1 (2.9)
Related Treatment-Emergent Serious Adverse Event (TESAE)	0	0	0	1 (7.7)	2 (33.3)	1 (50.0)	4 (11.8)
Adverse Events of Special Interest (AESI)[c]	0	0	0	4 (30.8)	1 (16.7)	0	5 (14.7)
Interstitial lung disease (ILD)/Pneumonitis	0	0	0	1 (7.7)	0	0	1 (2.9)
Infusion-related reactions (IRR)	0	0	0	3 (23.1)	1 (16.7)	0	4 (11.8)
Dose-Limiting Toxicities (Any Grade by Patient)[d]	0	0	0	1 (8.1)	1 (16.7)	2 (100)	4 (12.9)

a Four pts (11.8%) experienced a TEAE leading to drug discontinuation. Three pts at 6.4 mg/kg discontinued; 1 each for interstitial lung disease, infusion-related reaction, and hepatic function abnormality, while 1 pt discontinued at 9.6 mg/kg for white blood cell count reduction.

b One pt death was related to an adverse event of hepatic function abnormality.

c One IRR event at 6.4 mg/kg was Grade 3, while the others were Grade 1. One ILD event at 6.4 mg/kg was Grade 1, which occurred after Cycle 6 and the pt recovered in 1 month.

d Four pts experienced 1 or more DLTs during Cycle 1 at dose levels 6.4 mg/kg and above as follows: a pt receiving 6.4 mg/kg experienced Grade 3 anemia, Grade 4 hepatic function abnormality, Grade 4 platelet decrease and Grade 5 hepatic function death, a pt at the 9.6 mg/kg dose experienced Grade 3 anemia, Grade 3 febrile neutropenia, Grade 4 hepatic function abnormality, and Grade 4 platelet decrease and recovered, a pt at the 12.8 mg/kg dose experienced Grade 3 neutropenic fever and recovered, and a second pt at the 12.8 mg/kg dose experienced Grade 2 dehydration, diarrhea, nausea and vomiting and recovered. The MTD for DS6157a was determined to be 6.4 mg/kg, per the DLT information.

TEAEs

Table 4. TEAEs in ≥10% of Patients

Parameter	DS-6157a dose, mg/kg 1.6 (n=4)	3.2 (n=4)	4.8 (n=5)	6.4 (n=13)	9.6 (n=6)	12.8 (n=2)	Total (n=34)
Any Adverse Events n(%)	4 (100)	4 (100)	5 (100)	13 (100)	6 (100)	2 (100)	34 (100)
Nausea	3 (75.0)	3 (75.0)	3 (60.0)	11 (84.6)	6 (100)	2 (100)	28 (82.4)
Decreased appetite	3 (75.0)	2 (50.0)	3 (60.0)	6 (46.2)	4 (66.7)	2 (100)	20 (58.8)
Anaemia	3 (75.0)	2 (50.0)	3 (60.0)	6 (46.2)	3 (50.0)	0	17 (50.0)
Fatigue	3 (75.0)	1 (25.0)	2 (40.0)	6 (46.2)	1 (16.7)	2 (100)	15 (44.1)
Constipation	1 (25.0)	2 (50.0)	2 (40.0)	5 (38.5)	2 (33.3)	2 (100)	14 (41.2)
Platelet count decreased	0	1 (25.0)	2 (40.0)	4 (30.8)	5 (83.3)	1 (50.0)	13 (38.2)
Vomiting	1 (25.0)	2 (50.0)	2 (40.0)	4 (30.8)	1 (16.7)	2 (100)	12 (35.3)
Abdominal pain	1 (25.0)	2 (50.0)	1 (20.0)	2 (15.4)	1 (16.7)	2 (100)	9 (26.5)
Neutrophil count decreased	0	0	0	5 (38.5)	4 (66.7)	0	9 (26.5)
White blood cell count decreased	0	0	0	3 (23.1)	5 (83.3)	1 (50.0)	9 (26.5)
Alanine aminotransferase increased	2 (50.0)	1 (25.0)	1 (20.0)	3 (23.1)	1 (16.7)	0	8 (23.5)
Aspartate aminotransferase increased	1 (25.0)	1 (25.0)	1 (20.0)	3 (23.1)	1 (16.7)	1 (50.0)	8 (23.5)
Dizziness	1 (25.0)	0	0	4 (30.8)	1 (16.7)	2 (100)	8 (23.5)
Insomnia	1 (25.0)	2 (50.0)	1 (20.0)	2 (15.4)	2 (33.3)	0	8 (23.5)
Oedema peripheral	1 (25.0)	1 (25.0)	2 (40.0)	1 (7.7)	0	2 (100)	7 (20.6)
Dry skin	1 (25.0)	2 (50.0)	2 (40.0)	0	0	1 (50.0)	6 (17.6)
Headache	1 (25.0)	1 (25.0)	0	4 (30.8)	0	0	6 (17.6)
Dehydration	1 (25.0)	0	0	1 (7.7)	1 (16.7)	2 (100)	5 (14.7)
Hypertension	1 (25.0)	1 (25.0)	0	2 (15.4)	0	1 (50.0)	5 (14.7)
Hypercalcaemia	0	1 (25.0)	1 (20.0)	1 (7.7)	2 (33.3)	0	5 (14.7)
Hypokalaemia	0	1 (25.0)	0	2 (15.4)	1 (16.7)	1 (50.0)	5 (14.7)
Pyrexia	1 (25.0)	0	1 (20.0)	3 (23.1)	0	0	5 (14.7)
Cough	1 (25.0)	0	0	3 (23.1)	0	0	4 (11.8)
Diarrhoea	0	0	0	3 (23.1)	0	1 (50.0)	4 (11.8)
Dysgeusia	0	1 (25.0)	1 (20.0)	2 (15.4)	0	0	4 (11.8)
Dyspnoea	0	0	0	3 (23.1)	1 (16.7)	0	4 (11.8)
Hypoalbuminaemia	0	1 (25.0)	1 (20.0)	2 (15.4)	0	0	4 (11.8)
Infusion related reaction	0	0	0	3 (23.1)	1 (16.7)	0	4 (11.8)
Lymphocyte count decreased	0	0	1 (20.0)	1 (7.7)	1 (16.7)	1 (50.0)	4 (11.8)
Rash maculo-papular	1 (25.0)	1 (25.0)	1 (20.0)	0	1 (16.7)	0	4 (11.8)

The most common (≥35%) of all AEs were nausea (82%), decreased appetite (59%), anemia (50%), fatigue (44%), constipation (41%), decreased platelets (38%), and vomiting (35%).

CTCAE GRADE ≥3 TREATMENT RELATED TEAE

Table 5. CTCAE Grade ≥3 Treatment Related TEAE

Parameter	DS-6167a dose, mg/kg 1.6 (n=4)	3.2 (n=4)	4.8 (n=5)	6.4 (n=13)	9.6 (n=6)	12.8 (n=2)	Total (n=34)
Maximum CTCAE Grade >=3 Treatment-Related TEAE	0	1 (25.0)	1 (20.0)	8 (61.5)	5 (83.3)	1 (50.0)	16 (47.1)
Blood and lymphatic system disorders	0	1 (25.0)	1 (20.0)	3 (23.1)	1 (16.7)	1 (50.0)	7 (20.6)
Anaemia	0	1 (25.0)	1 (20.0)	3 (23.1)	1 (16.7)	0	6 (17.6)
Febrile neutropenia	0	0	0	0	1 (16.7)	1 (50.0)	2 (5.9)
Gastrointestinal disorders	0	0	0	0	0	1 (50.0)	1 (2.9)
Vomiting	0	0	0	0	0	1 (50.0)	1 (2.9)
General disorders and administration site conditions	0	0	0	1 (7.7)	0	1 (50.0)	2 (5.9)
Fatigue	0	0	0	1 (7.7)	0	1 (50.0)	2 (5.9)
Oedema peripheral	0	0	0	0	0	1 (50.0)	1 (2.9)
Hepatobiliary disorders	0	0	0	1 (7.7)	1 (16.7)	0	2 (5.9)
Hepatic function abnormal	0	0	0	1 (7.7)	1 (16.7)	0	2 (5.9)
Infections and infestations	0	0	0	0	0	1 (50.0)	1 (2.9)
Pneumonia	0	0	0	0	0	1 (50.0)	1 (2.9)
Injury, poisoning and procedural complications	0	0	0	1 (7.7)	0	0	1 (2.9)
Infusion related reaction	0	0	0	1 (7.7)	0	0	1 (2.9)
Investigations	0	0	0	5 (38.5)	5 (83.3)	1 (50.0)	11 (32.4)
Lymphocyte count decreased	0	0	0	1 (7.7)	0	0	1 (2.9)
Neutrophil count decreased	0	0	0	2 (15.4)	3 (50.0)	0	5 (14.7)
Platelet count decreased	0	0	0	3 (23.1)	4 (66.7)	1 (50.0)	8 (23.5)
White blood cell count decreased	0	0	0	1 (7.7)	4 (66.7)	0	5 (14.7)
Musculoskeletal and connective tissue disorders	0	0	0	1 (7.7)	0	0	1 (2.9)
Muscular weakness	0	0	0	1 (7.7)	0	0	1 (2.9)
Renal and urinary disorders	0	0	0	0	1 (16.7)	0	1 (2.9)
Renal disorder	0	0	0	0	1 (16.7)	0	1 (2.9)

REFERENCES

1. Ilida K, et al. Poster presented at: Annual American Association for Cancer Research Meeting; June 22-24, 2020. Abstract 5181.

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PHARMACOKINETIC RESULTS

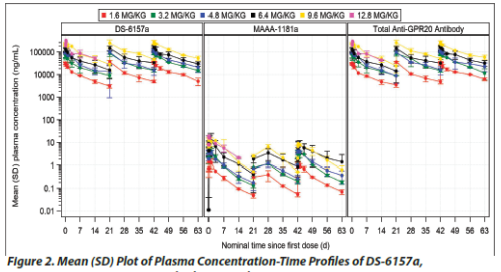

Figure 2. Mean (SD) Plot of Plasma Concentration-Time Profiles of DS-6157a, MAAA-1181a, anti-GPR20 Antibody, PK Analysis Set

- PK results from 34 patients indicate that intact DS-6157a, total anti-GPR20 antibody, and cytotoxic payload (MAAA-1181a) plasma concentrations increased in a dose dependent manner.
- Mild accumulation for AUC_{21d} between Cycle 3 (at steady state) and Cycle 1 (after a single dose) at 1.6 mg/kg and 6.4 mg/kg doses was observed for both intact DS-6157a (1.3 and 1.6, respectively) and MAAA-1181a (1.1 and 1.5, respectively).
- On a molar basis, MAAA-1181a C_{max} in Cycle 1 across 1.6 mg/kg to 9.6 mg/kg dose range were approximately 42-fold to 83-fold lower than those for intact DS-6157a.
- Total anti-GPR20 antibody and intact DS-6157a have a similar PK profile, indicating DS-6157a is stable in circulation.
- Preliminary immunogenicity results showed no treatment-emergent ADA.

RESPONSE PER RECIST v1.1

Table 6. Best Overall Response (BOR) per RECIST v1.1

Parameter	DS-6157a dose, mg/kg 1.6 (n=4)	3.2 (n=4)	4.8 (n=5)	6.4 (n=13)	9.6 (n=6)	12.8 (n=2)	Total (n=34)
BOR, n (%)							
CR	0	0	0	0	0	0	0
PR	0	0	0	1 (7.7)	0	0	1 (2.9)
SD[a]	2 (50.0)	3 (75.0)	3 (60.0)	7 (53.8)	2 (33.3)	0	17 (50.0)
PD	2 (50.0)	0	2 (40.0)	3 (23.1)	1 (16.7)	2 (100)	10 (29.4)
NE	0	1 (25.0)	0	2 (15.4)	3 (50.0)	0	6 (17.6)

[a]SD† for 23 is considered confirmed response when assessment occurred ≥ 6 weeks from start/re-treatment.

Tumor shrinkage was observed in 4 pts with KIT/PDGFRA wild-type GIST who had at least one restaging scan, and were treated at different doses. These included a confirmed PR at the MTD of 6.4 mg/kg in a patient with SDH-deficient GIST with both SDH B and NF1 mutations (See Figure 5).

RESPONSE

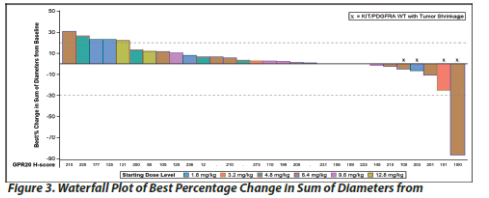

Figure 3. Waterfall Plot of Best Percentage Change in Sum of Diameters from Baseline in Target Lesions

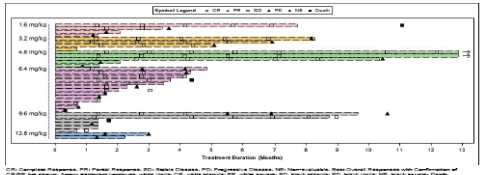

Figure 4. A Swimmer Plot of Tumor Response over Time

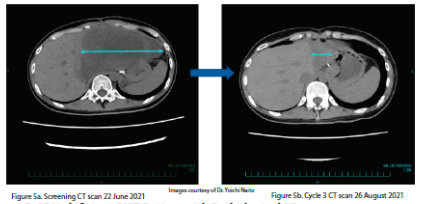

Figure 5a. Screening CT scan 22 June 2021 — Figure 5b. Cycle 3 CT scan 26 August 2021

Images courtesy of Dr. Yoichi Naito

Figure 5. SDH-deficient GIST Patient with Pathological PR

- A 29 y/o female pt with SDH-deficient GIST diagnosed in 2020 without any prior cancer systemic therapies, demonstrated a maximum 87% decrease in tumor size, following treatment with DS-6157a, at the MTD confirmed dose of 6.4 mg/kg.
- The target lesion, an abdominal mass, was 150 mm at baseline (Figure 5a) which decreased to 33 mm in Cycle 3, and decreased further to 20 mm 4 weeks later (Figure 5b).
- The pt discontinued from study to undergo a surgical resection of the remaining small lesion to become tumor-free. The resected tumor showed a pathological CR per the Investigator's assessment.

CONCLUSIONS

DS-6157a was generally well-tolerated with early signs of moderate clinical activity. Tumor shrinkage was observed in only 4 pts with KIT/PDGFRA wild-type GIST treated at different doses. One pt with SDH-deficient GIST with both SDH-B and NF1 mutations achieved a PR per CT scan, and then complete pathological response after surgical resection.

The study did not proceed to the Part 2 expansion phase, because the efficacy targets were not met in Part 1.