DESTINY-Breast04 (DS8201-A-U303)

Trastuzumab Deruxtecan (T-DXd) vs Treatment of Physician's Choice (TPC) in Patients With HER2-Low Unresectable and/or Metastatic Breast Cancer

October 2023

DESTINY-Breast04

DXd ADC TECHNOLOGY™

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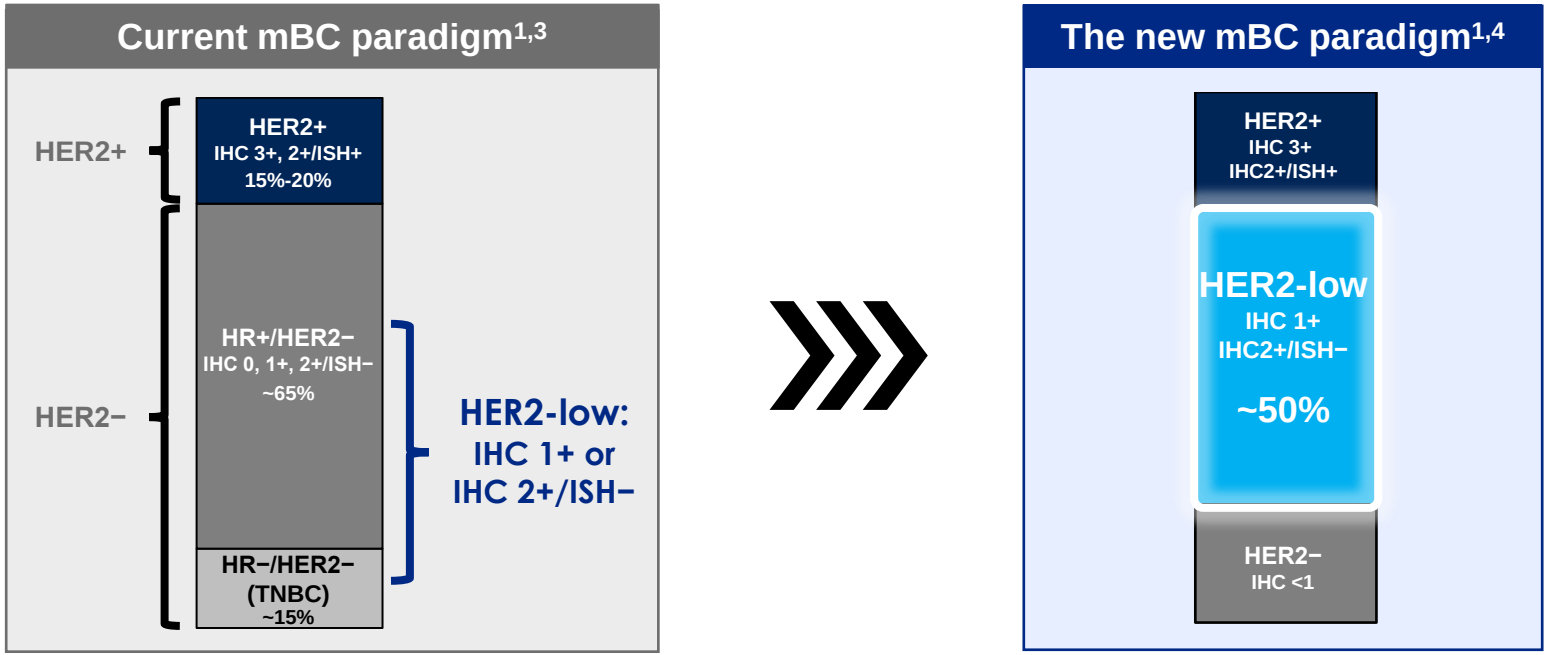
DESTINY-Breast04: Introduction

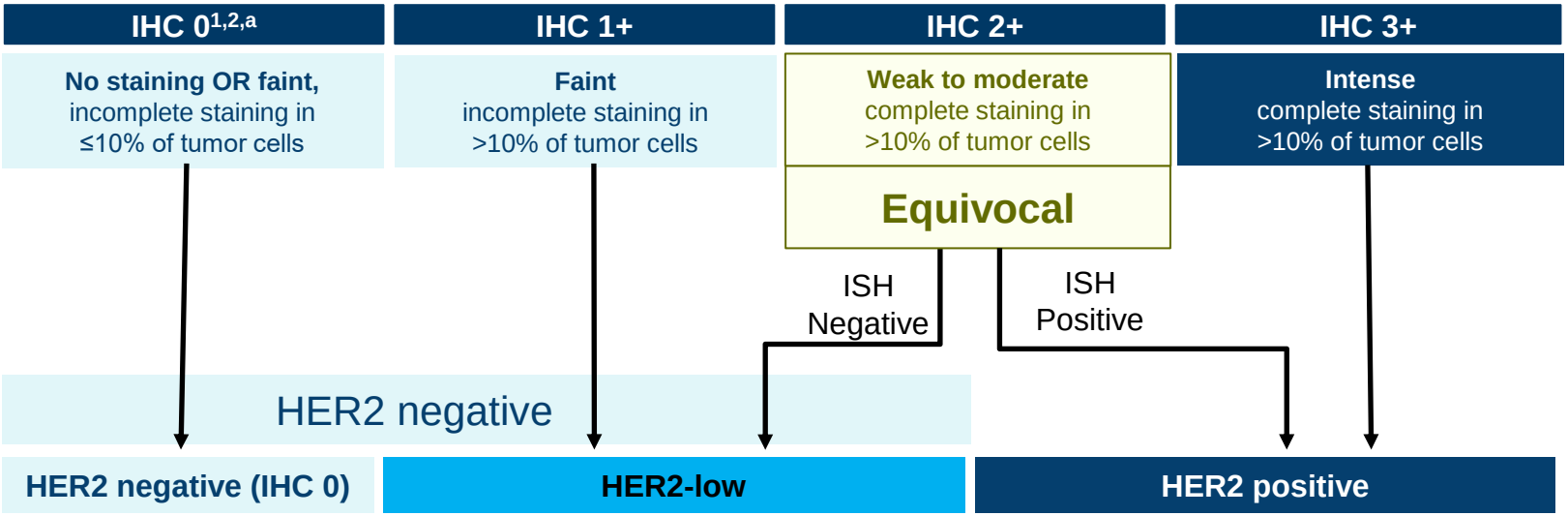
Around 60% of metastatic breast cancers categorized as HER2 negative express low levels of HER2 (HER2-low), which is clinically meaningful[1]

Guidelines recommend assessment of HER2 status in all newly diagnosed patients with BC and those patients who develop metastatic disease[2]



1. Schettini F et al. *NPJ Breast Cancer*. 2021;7(1):1. 2. Wolff AC et al. *J Clin Oncol.* 2018;36(20):2105-2122. 3. Tarantino P et al. *J Clin Oncol.* 2020;38(17):1951-1962. 4. Modi S et al. *N Engl J Med*. 2022; 387:9-20.

Proposed paradigm of identifying HER2-low BC



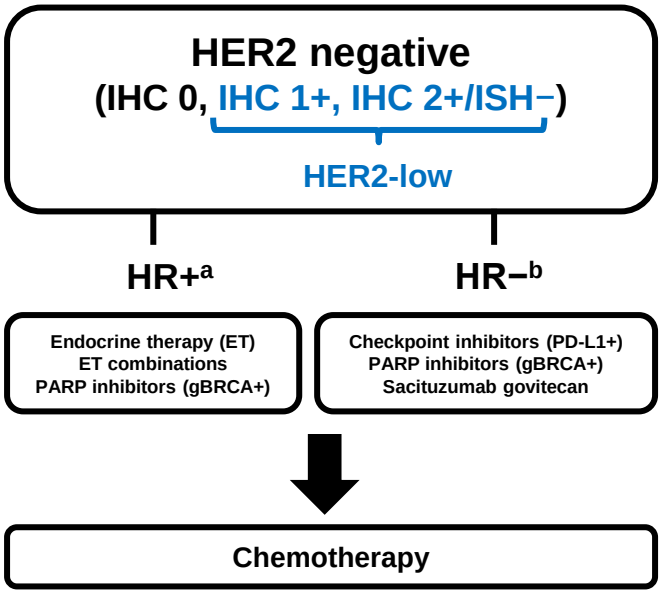
- HER2-low is defined as a HER2 IHC score of 1+ or 2+/ISH negative[2]
- As per the latest ASCO/CAP guidelines in HER2 testing for BC, it is currently best practice to distinguish IHC 0 from IHC 1+ to identify patients who may be eligible for treatment that targets nonamplified HER2 expression levels[2]

[a]An IHC score of 0 may reflect an artifactual limitation of the technique rather than the total absence of HER2 protein on the membrane, which could be defined as low HER2 expression.

1. Wolff AC et al. *J Clin Oncol.* 2018;36(20):2105-2122. 2. Wolff AC et al. *Arch Pathol Lab Med.* 2023;147(9):993-1000.

HER2-low mBC: Unmet clinical need

Standard of Care Prior to DESTINY-Breast04



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

Prior to DESTINY-Breast04, HER2-low mBC was treated as HER2− mBC, with limited options for later lines of therapy[1-4]

– Prior HER2 targeted therapies were 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]

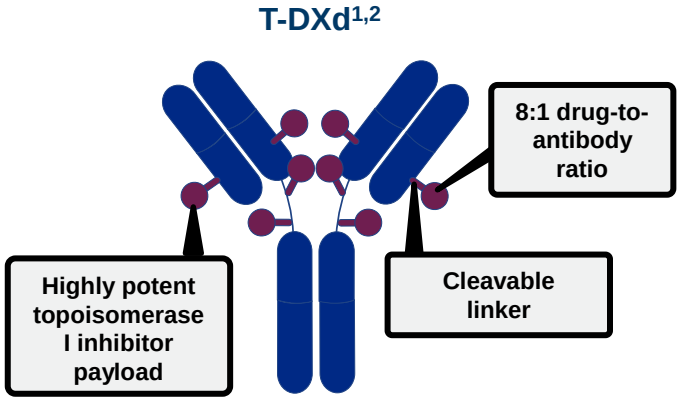
Limited benefit exists for patients who progress after multiple lines of chemotherapy

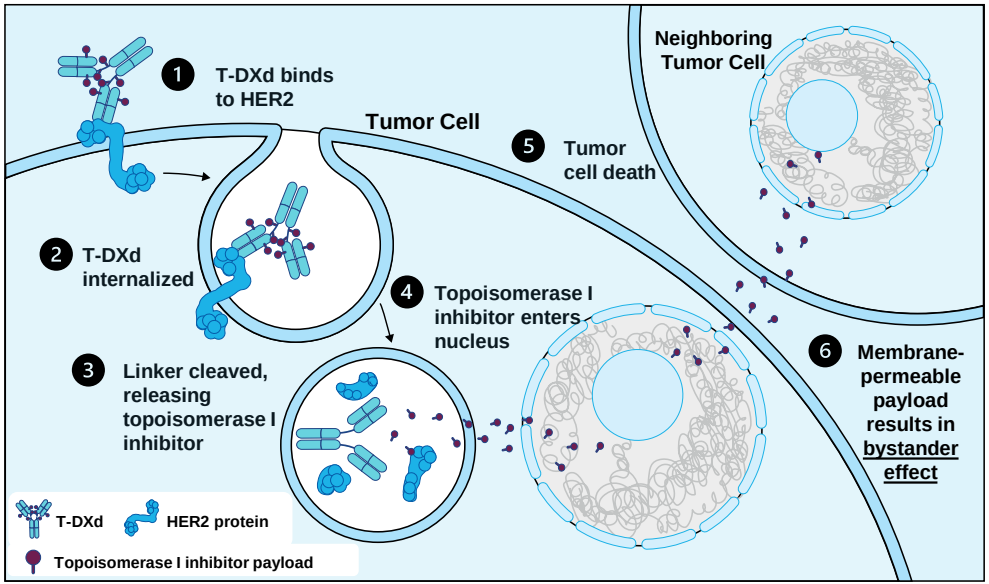
– In a pooled analysis of patients with HER2− mBC, eribulin and capecitabine provide minimal benefit, with a mPFS of ~4 months and mOS of ~15 months[6]

[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.* 2021;22:143-148. 6. Kaufman PA et al. *J Clin Oncol.* 2015;33:594-601.

T-DXd MOA, bystander antitumor effect, and rationale for targeting HER2-low mBC





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

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]

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

Guideline recommendations of T-DXd in patients with HER2-low mBC

ESMO Guidelines[1]

The ESMO metastatic breast cancer living guideline for ER-positive HER2-negative breast cancer recommends considering T-DXd for patients with HER2-low mBC after at least 1 line of chemotherapy

NCCN Guidelines[2]

The NCCN Guidelines for breast cancer recommend fam-trastuzumab deruxtecan-nxki (T-DXd) as a second line, NCCN Category 1, preferred regimen for HER2 IHC 1+ or 2+/ISH negative (HR+ with visceral crisis or endocrine refractory or HR-negative with no germline *BRCA1/2* mutation) recurrent unresectable (local or regional) or metastatic breast cancer

- **Based on the strength of the DESTINY-Breast04 trial efficacy and safety data reported at ASCO 2022, the NCCN Guidelines for breast cancer were updated to recommend fam-trastuzumab deruxtecan-nxki as a Category 1 preferred second line treatment option for HER2 IHC 1+ or 2+/ISH− mBC**
- **Based on the primary results from DESTINY-Breast04,[3] the ESMO metastatic breast cancer living guideline recommends considering T-DXd for patients with HER2-low mBC after at least 1 line of chemotherapy**
- **Based on the primary results from DESTINY-Breast04, T-DXd was approved for patients with HER2-IHC 1+ or 2+/ISH− unresectable and/or metastatic breast cancer[3,4]**

1. Gennari A et al. *Ann Oncol*. 2021;32:1475-1495 ESMO Metastatic Breast Cancer Living Guidelines, v1.1, May 2023. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.4.2023. ©National Comprehensive Cancer Network, Inc, 2023. All rights reserved. Accessed April 13, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 3. Modi S et al. *N Engl J Med*. 2022; 387:9-20. 4. Enhertu® (fam-trastuzumab deruxtecan-nxki) for injection, for intravenous use. Prescribing Information. Daiichi Sankyo; Basking Ridge, NJ, USA, 2022.

DESTINY-Breast04: Study Design

An open-label, multicenter, phase 3 study (NCT03734029)[1-4]

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

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

R 2:1

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

HR+ = 494
HR− = 63

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

Primary endpoint
- PFS by BICR (HR+)

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

Secondary endpoints[d]
- PFS (investigator)
- ORR (BICR and investigator)
- DOR (BICR)
- Safety
- Patient-reported outcomes (HR+)[e]

Exploratory analysis subgroups

All Patients (HR+/−)
- Disease burden (low = 0-2, high = 3+ sites)
- Rapid progression (disease progression ≤6 months of neo/adjuvant therapy)
- HER2 status (IHC 1+, IHC 2+/ISH−)
- Number of prior lines of chemotherapy (1, 2)
- Age (<65, ≥65 years)
- Baseline CNS metastases (yes, no)
- Prior anthracycline treatment (yes, no)
- ER expression (ER-negative [IHC 0%], ER-low [IHC 1%-10%])

HR+ cohort
- Prior CDK4/6i use (yes, no)

[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational-use-only [IUO] assay system, at the time of study. [c]TPC was administered according to the label. [d]Efficacy in the HR− cohort was an exploratory endpoint. [e]The patient-reported outcomes analysis was conducted in the HR+ cohort (per the statistical analysis plan) since the primary efficacy endpoint was evaluated in the HR+ cohort.

1. Modi S et al. *N Engl J Med*. 2022;387(1):9-20. 2. Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0. 3. Prat A et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster HER2-18. 4. Cameron DA et al. Presented at: ESMO Breast Cancer 2023; May 11-13, 2023; Berlin, Germany. Presentation 192MO. 5. Modi S et al. Presented at: European Society for Medical Oncology 2023; October 20-24, 2023; Madrid, Spain. Presentation 376O

Key eligibility criteria[1,2]

Inclusion Criteria

- Age of majority in respective countries
- Pathologically documented breast cancer that is unresectable or metastatic, has HER2-low expression (IHC 2+/ISH− or IHC 1+), and was previously treated with 1-2 lines of chemotherapy/adjuvant in the metastatic setting[a]
- Never previously HER2+ (IHC 3+ or IHC 2+/ISH+) on prior pathology testing or was historically HER2 IHC 0 only
- Never previously treated with anti-HER2 therapy
- Documented radiologic progression of disease
- Protocol-defined adequate cardiac, bone marrow, renal, hepatic, and blood clotting functions

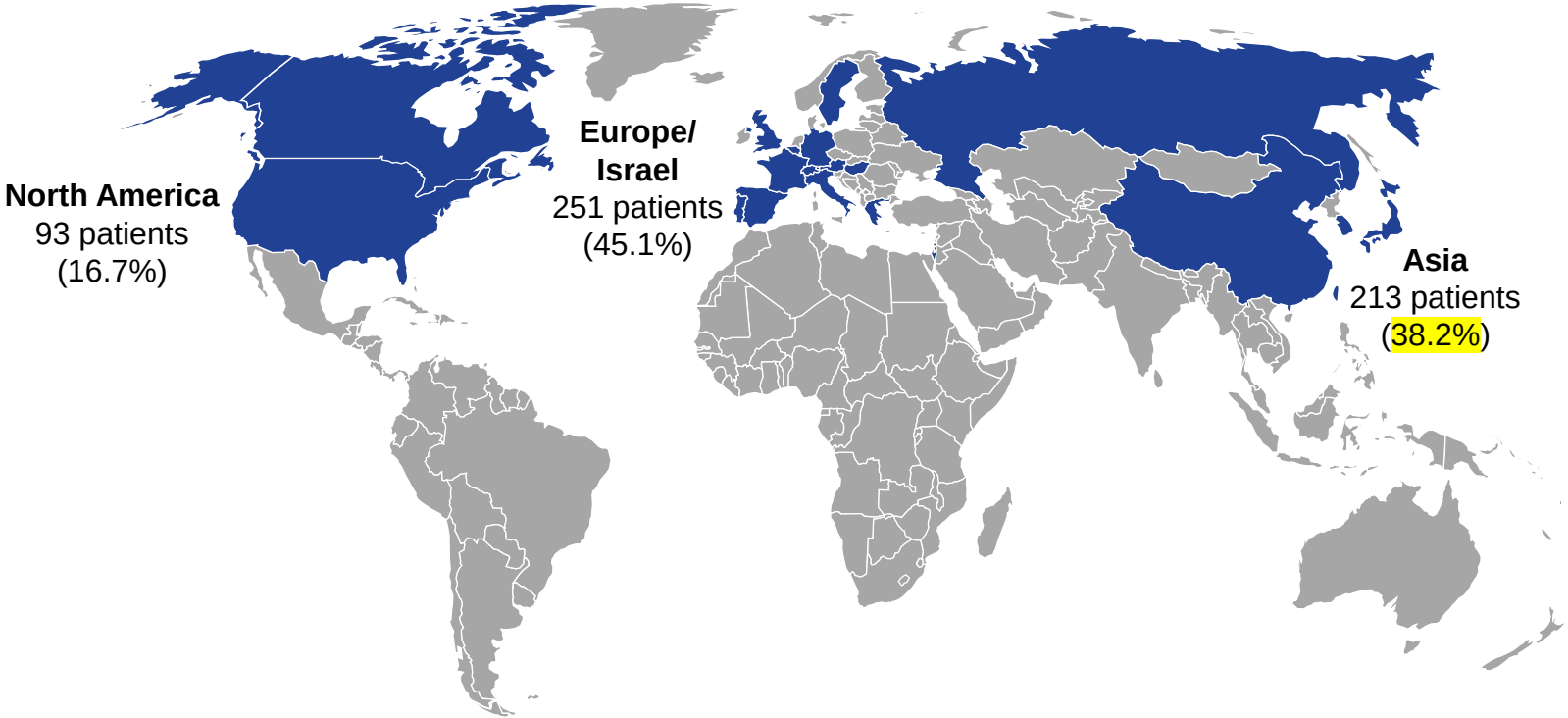
Exclusion Criteria

- Ineligible for any physician's treatment of choice options
- Prior treatment with an anti-HER2 therapy or an ADC that consist of a topoisomerase I inhibitor
- Uncontrolled or significant CVD
- Medical history of (non-infectious) ILD/pneumonitis that required steroids or active or suspected ILD/pneumonitis
- Spinal cord compression or active CNS metastases that are untreated and symptomatic, or require therapy to control symptoms

[a]Eligible patients must have received chemotherapy in the metastatic setting or have developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. If patients had HR+ mBC, prior endocrine therapy was required.[1]

1. Modi S et al. *N Engl J Med*. 2022;387(1):9-20. 2. ClinicalTrials.gov. NCT03734029. https://clinicaltrials.gov/ct2/show/NCT03734029. Accessed March 22, 2022.

Patients treated by region



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

Demographics and baseline characteristics[1,a,b]

Characteristic	Hormone receptor–positive		All patients (HR+ and HR−)	
	T-DXd (n = 331)	**TPC** (n = 163)	**T-DXd** (n = 373)	**TPC** (n = 184)
Age, median (range), years	56.8 (31.5-80.2)	55.7 (28.4-80.0)	57.5 (31.5-80.2)	55.9 (28.4-80.5)
Female, n (%)	329 (99.4)	163 (100)	371 (99.5)	184 (100.0)
Region, n (%)				
Europe or Israel	149 (45.0)	73 (44.8)	166 (44.5)	85 (46.2)
Asia	128 (38.7)	60 (36.8)	147 (39.4)	66 (35.9)
North America	54 (16.3)	30 (18.4)	60 (16.1)	33 (17.9)
HER2 status (IHC), n (%)[c]				
1+	193 (58.3)	95 (58.3)	215 (57.6)	106 (57.6)
2+ (ISH−)	138 (41.7)	68 (41.7)	158 (42.4)	78 (42.4)
ECOG PS, n (%)[d]				
0	187 (56.5)	95 (58.3)	200 (53.6)	105 (57.1)
1	144 (43.5)	68 (41.7)	173 (46.4)	79 (42.9)
Hormone receptor, n (%)[e]				
Positive	328 (99.1)	162 (99.4)	333 (89.3)	166 (90.2)
Negative[2]	3 (0.9)	1 (0.6)	40 (10.7)	18 (9.8)
Brain metastases at baseline, n (%)	18 (5.4)	7 (4.3)	24 (6.4)	8 (4.3)
Liver metastases at baseline, n (%)	247 (74.6)	116 (71.2)	266 (71.3)	123 (66.8)
Lung metastases at baseline, n (%)	98 (29.6)	58 (35.6)	120 (32.2)	63 (34.2)
Visceral metastases at baseline, n (%)[3]	298 (90.0)	146 (89.6)	–	–

[a]Data from the primary analysis DCO (January 11, 2022). [b]Percentages may not total 100 because of rounding. [c]Low expression of HER2 was defined as a score of 1+ on IHC analysis or as an IHC score of 2+ and negative results on ISH. [d]Performance-status scores on the ECOG scale range from 0 (no disability) to 5 (death). [e]For the intent-to-treat analyses with the hormone receptor–positive cohort, hormone receptor status is based on data collected using the interactive web/voice response system at the time of randomization, which includes patients who were mis-stratified.

1. Modi S et al. *N Engl J Med*. 2022;387(1):9-20. 2. Modi S et al. Presented at American Society of Clinical Oncology (ASCO) 2022, June 2022, LBA3. 3. Ueno N et al. Presented at: European Society for Medical Oncology 2022; September 9-13, 2022; Paris, France. Presentation 217O.

Prior therapies[1,a]

Characteristic	Hormone receptor–positive		All patients (HR+ and HR−)	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Lines of systemic therapy[2,b] (metastatic setting)				
Median number of lines (range)	3 (1-9)	3 (1-8)	3 (1-9)	3 (1-8)
Number of lines, n (%)				
1	23 (7)	14 (9)	39 (10)	19 (10)
2	85 (26)	41 (25)	100 (27)	53 (29)
≥3	223 (67)	108 (66)	234 (63)	112 (61)
Lines of chemotherapy (metastatic setting)				
Median number of lines (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
Number of lines, n (%)				
0	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)
1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
≥3	3 (0.9)	0	6 (1.6)	0

Based on derived data, which includes protocol deviations.
[a]Data from the primary analysis DCO (January 11, 2022). [b]Systemic therapy refers to any type of treatment that targets the entire body.
1. Modi S et al. Presented at American Society of Clinical Oncology (ASCO) 2022, June 2022, LBA3. 2. Dictionary of Cancer Terms, National Cancer Institute. Accessed September 7, 2022. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/systemic-therapy.

Prior therapies[a] (cont.)

Characteristic	Hormone receptor–positive		All patients (HR+ and HR−)	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Lines of endocrine therapy (metastatic setting)				
Median number of lines (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
Number of lines, n (%)				
0	28 (8)	17 (10)	60 (16)	34 (18)
1	105 (32)	49 (30)	108 (29)	51 (28)
2	110 (33)	53 (33)	115 (31)	54 (29)
≥3	88 (27)	44 (27)	90 (24)	45 (24)
Prior targeted cancer therapy, n (%)				
Targeted therapy	259 (78)	132 (81)	279 (75)	140 (76)
CDK4/6i	233 (70)	115 (71)	239 (64)	119 (65)

Based on derived data, which includes protocol deviations.
[a]Data from the primary analysis DCO (January 11, 2022).
Modi S et al. Presented at American Society of Clinical Oncology (ASCO) 2022, June 2022, LBA3.

DESTINY-Breast04: Updated Survival Results

Data cutoff: March 1, 2023

Patient disposition

Screened (N = 713)

Randomized 2:1 (N = 557)

T-DXd (n = 373)
Treated (n = 371; 99.5%)[a]

- Ongoing study treatment (4.6%)
- Discontinued study treatment (95.4%)
  - Death (1.3%)
  - Adverse event (16.7%)
  - Progressive disease (69.0%)
  - Withdrawal by subject (3.8%)
  - Other[b] (4.6%)

TPC (n = 184)
Treated (n = 172; 93.5%)[a]

- Ongoing study treatment (0%)
- Discontinued study treatment (100%)
  - Death (1.2%)
  - Adverse event (8.1%)
  - Progressive disease (76.7%)
  - Withdrawal by subject (6.4%)
  - Other[b] (7.6%)

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

Updated OS analysis

- Data cutoff: March 1, 2023
- Median follow-up was 32.0 months (95% CI, 31.0-32.8 months)

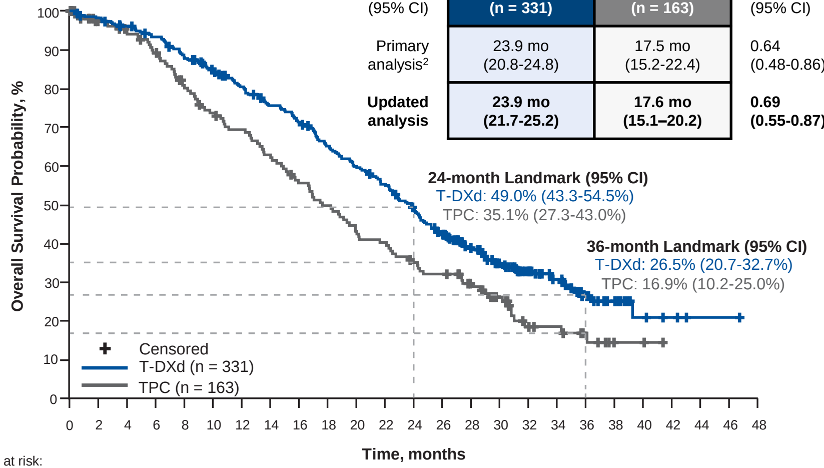
[a]Percentages are based on the number of treated patients in each arm. [b]Other includes clinical progression, physician decision, lost to follow-up, and other unknown reasons.
Modi S et al. Presented at: European Society for Medical Oncology 2023; October 20-24, 2023; Madrid, Spain. Presentation 376O.

DESTINY-Breast04: March 1, 2023, DCO

OS in HR+ and all patients[1]

HR+ cohort

Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis[2]	23.9 mo (20.8-24.8)	17.5 mo (15.2-22.4)	0.64 (0.48-0.86)
Updated analysis	**23.9 mo (21.7-25.2)**	**17.6 mo (15.1–20.2)**	**0.69 (0.55-0.87)**



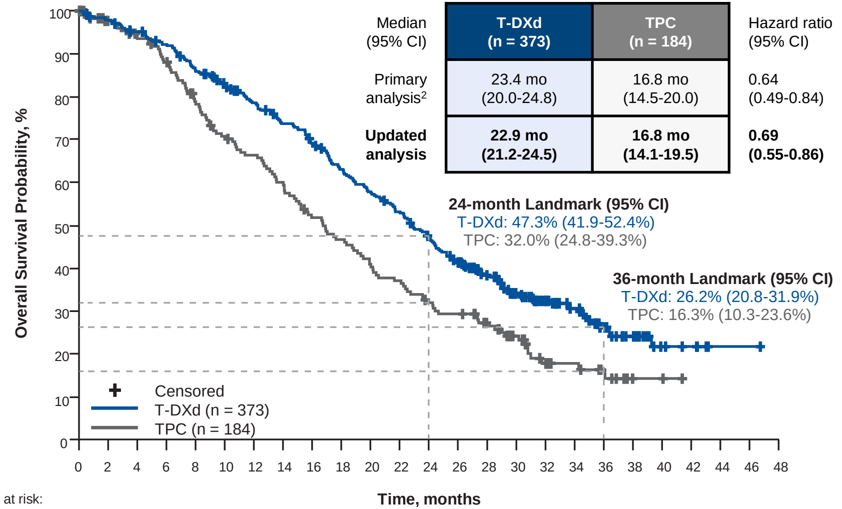
Patients still at risk:

T-DXd (n = 331) 331 325 323 317 313 307 302 292 284 279 267 258 250 243 233 230 220 212 199 189 183 176 168 155 147 135 124 109 94 81 72 66 54 46 42 34 23 17 14 7 5 4 3 2 1 1 1 0

TPC (n = 163) 163 150 144 142 138 134 129 123 114 108 103 97 96 92 87 82 76 71 68 64 59 56 55 50 47 43 43 42 35 31 25 16 13 11 11 9 7 5 2 2 2 1 0

All patients

Median (95% CI)	T-DXd (n = 373)	TPC (n = 184)	Hazard ratio (95% CI)
Primary analysis[2]	23.4 mo (20.0-24.8)	16.8 mo (14.5-20.0)	0.64 (0.49-0.84)
Updated analysis	**22.9 mo (21.2-24.5)**	**16.8 mo (14.1-19.5)**	**0.69 (0.55-0.86)**



Patients still at risk:

T-DXd (n = 373) 373 366 363 355 350 342 337 325 314 308 295 285 276 269 257 254 240 231 217 205 199 191 182 168 160 148 137 122 107 94 81 75 62 52 48 39 28 21 18 11 7 6 5 3 1 1 1 0

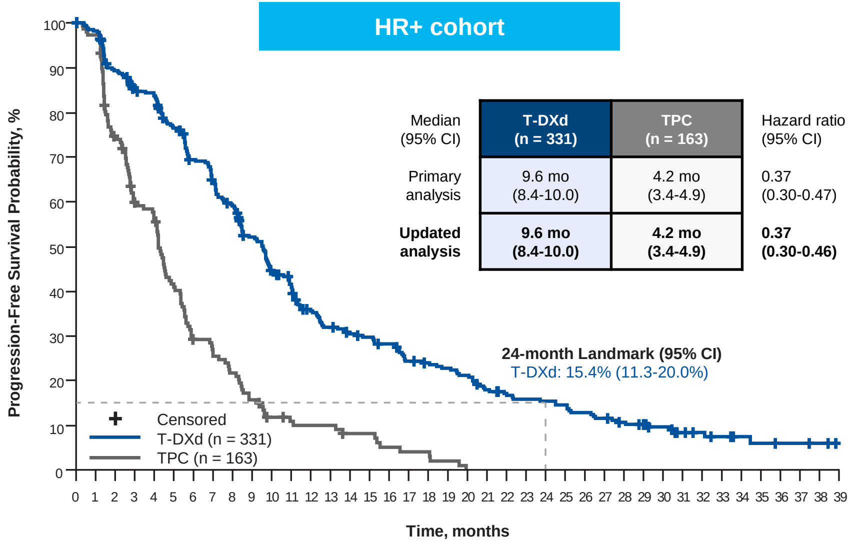
TPC (n = 184) 184 170 165 160 156 152 145 137 127 119 113 107 105 100 95 88 81 76 73 69 64 59 58 53 49 45 45 44 37 33 27 18 15 12 12 10 8 5 2 2 2 1 0

- In the HR+ cohort and all-patient cohort, median OS was consistent with results from the primary analysis,[2] showing a 31% reduction in risk of death for patients receiving T-DXd compared with those receiving TPC

1. Modi S et al. Presented at: European Society for Medical Oncology 2023; October 20-24, 2023; Madrid, Spain. Presentation 376O. 2. Modi S et al. *N Engl J Med*. 2022;387(1):9-20.

PFS (by investigator[a]) in HR+ and all patients[1]

HR+ cohort

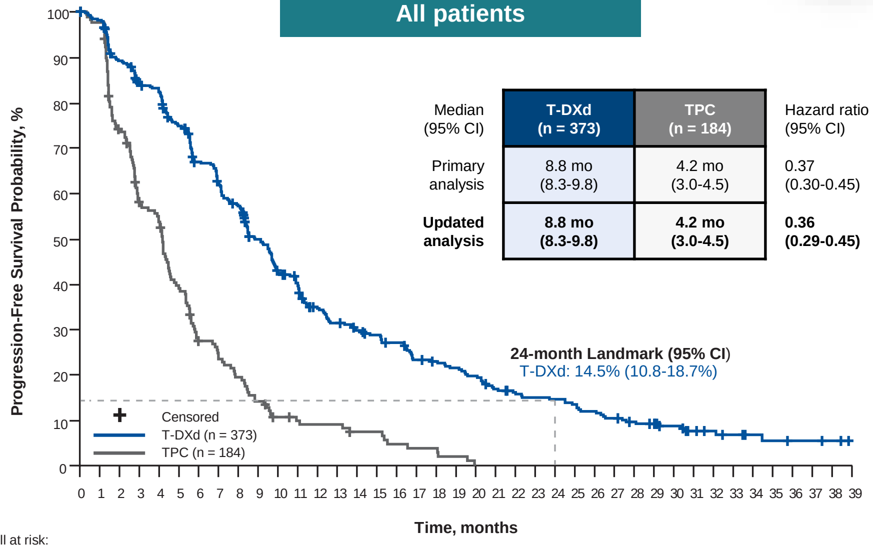


Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis	9.6 mo (8.4-10.0)	4.2 mo (3.4-4.9)	0.37 (0.30-0.47)
Updated analysis	**9.6 mo (8.4-10.0)**	**4.2 mo (3.4-4.9)**	**0.37 (0.30-0.46)**

Patients still at risk:

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
T-DXd (n = 331)	331	323	290	272	267	241	215	198	181	154	129	119	98	88	82	79	74	63	60	57	53	44	40	37	36	34	30	27	23	21	16	11	9	7	5	4	3	3	2	0
TPC (n = 163)	163	143	107	83	78	56	39	34	29	21	14	12	11	11	8	8	5	4	4	2	0																			

All patients



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

Patients still at risk:

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
T-DXd (n = 373)	373	364	327	304	297	267	234	216	198	166	140	130	107	97	90	85	79	67	64	60	55	46	42	39	38	35	31	27	23	21	16	11	9	7	5	4	3	3	2	0
TPC (n = 184)	184	163	121	92	85	61	41	35	29	21	14	12	11	11	8	8	5	4	4	2	0																			

- Median PFS was consistent with results from the primary analysis,[2] showing a reduction in risk of disease progression or death of 63% and 64% in the HR+ cohort and all patients, respectively for the T-DXd arm compared with the TPC arm

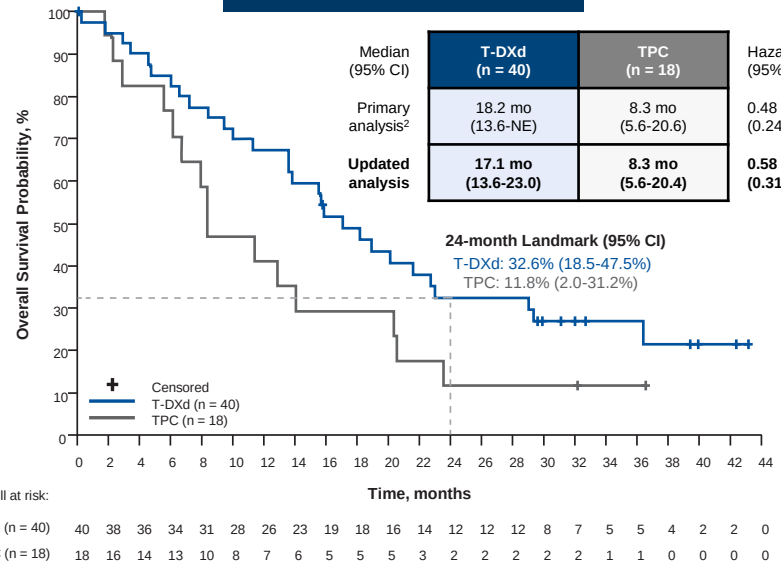
[a]PFS by BICR was stopped after the primary analysis as final PFS by BICR was achieved. At primary analysis, PFS by BICR for HR+ cohort was 10.1 mo and 5.4 mo for T-DXd and TPC, respectively (hazard ratio, 0.51). For all patients, the PFS by BICR was 9.9 mo and 5.1 mo for T-DXd and TPC, respectively (hazard ratio, 0.50). The updated analysis is based on PFS by investigator.

1. Modi S et al. Presented at: European Society for Medical Oncology 2023; October 20-24, 2023; Madrid, Spain. Presentation 376O. 2. Modi S et al. *N Engl J Med*. 2022;387(1):9-20.

Efficacy in HR− cohort (exploratory analyses)[1]

OS

Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis[2]	18.2 mo (13.6-NE)	8.3 mo (5.6-20.6)	0.48 (0.24-0.95)
Updated analysis	**17.1 mo (13.6-23.0)**	**8.3 mo (5.6-20.4)**	**0.58 (0.31-1.08)**



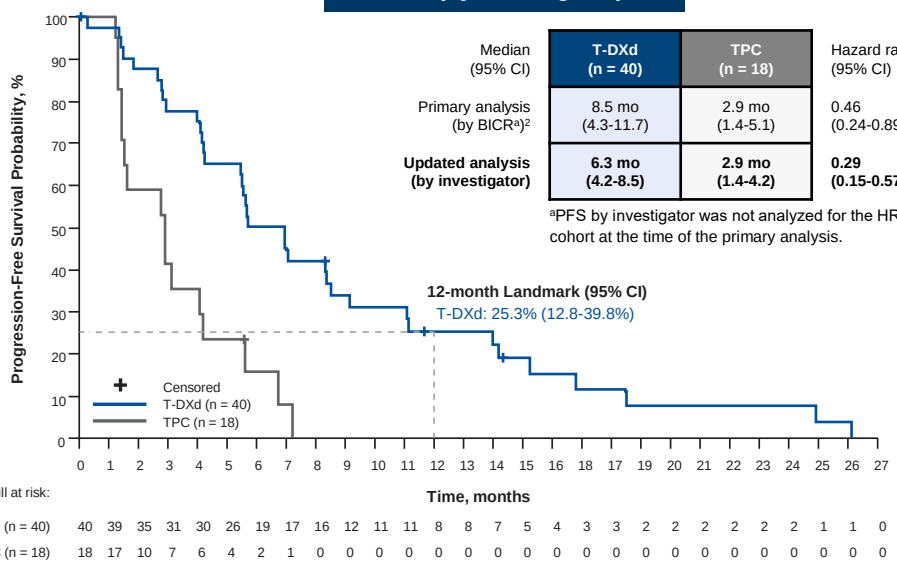
Patients still at risk:

T-DXd (n = 40)	40	38	36	34	31	28	26	23	19	18	16	14	12	12	8	7	5	5	4	2	2	0
TPC (n = 18)	18	16	14	13	10	8	7	6	5	5	5	3	2	2	2	2	1	1	0	0	0	0

PFS (by investigator)

Median (95% CI)	T-DXd (n = 40)	TPC (n = 18)	Hazard ratio (95% CI)
Primary analysis (by BICR[a])[2]	8.5 mo (4.3-11.7)	2.9 mo (1.4-5.1)	0.46 (0.24-0.89)
Updated analysis (by investigator)	**6.3 mo (4.2-8.5)**	**2.9 mo (1.4-4.2)**	**0.29 (0.15-0.57)**

[a]PFS by investigator was not analyzed for the HR− cohort at the time of the primary analysis.



Patients still at risk:

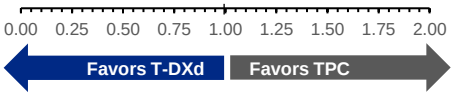
T-DXd (n = 40)	40	39	35	31	30	26	19	17	16	12	11	11	8	8	7	5	4	3	3	2	2	2	2	2	1	1	0
TPC (n = 18)	18	17	10	7	6	4	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

- There was a 42% reduction in risk of death and 71% reduction in risk of disease progression or death for HR− patients receiving T-DXd compared with TPC

1. Modi S et al. Presented at: European Society for Medical Oncology 2023; October 20-24, 2023; Madrid, Spain. Presentation 376O. 2. Modi S et al. *N Engl J Med*. 2022;387(1):9-20.

Subgroup analysis: OS in HR+ patients

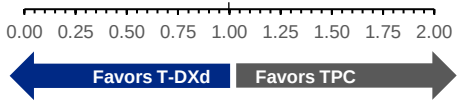
	No. of Events/No. of Patients		OS, median (95% CI), mo		Hazard Ratio for Death (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6 inhibitors					
Yes	156/233	78/115	22.3 (19.8-24.3)	16.8 (13.6-19.5)	0.71 (0.54-0.94)
No	53/96	31/47	30.3 (23.0-35.1)	22.4 (15.6-27.2)	0.63 (0.41-0.99)
IHC status					
IHC 1+	121/192	67/96	22.9 (20.8-25.2)	16.9 (13.5-22.4)	0.67 (0.50-0.91)
IHC 2+/ISH−	90/139	43/67	24.2 (20.8-26.5)	19.1 (15.1-22.3)	0.73 (0.51-1.05)
Prior lines of chemotherapy					
1	118/203	63/93	25.5 (23.9-28.8)	19.4 (16.7-23.9)	0.66 (0.48-0.89)
≥2	93/127	47/69	19.0 (16.7-22.7)	14.0 (10.8-20.0)	0.76 (0.53-1.08)
Age					
<65 years	164/260	81/120	23.0 (20.8-24.8)	17.6 (14.8-20.0)	0.67 (0.52-0.88)
≥65 years	47/71	29/43	25.5 (21.0-28.8)	19.5 (9.2-30.6)	0.72 (0.45-1.15)
Race					
White	104/156	51/78	23.9 (19.8-24.8)	15.1 (12.3-19.9)	0.65 (0.47-0.91)
Asian	80/131	46/66	23.9 (21.7-28.7)	19.9 (16.7-27.2)	0.75 (0.52-1.07)
Other	25/37	12/16	21.5 (15.0-30.4)	15.2 (6.2-23.9)	0.56 (0.28-1.12)
Region					
Asia	80/128	42/60	23.4 (21.0-27.4)	19.9 (16.7-27.2)	0.76 (0.53-1.11)
Europe and Israel	102/149	49/73	23.9 (20.8-25.7)	17.6 (12.3-20.2)	0.66 (0.47-0.93)
North America	29/54	19/30	24.5 (15.8-28.9)	16.0 (8.8-22.3)	0.59 (0.33-1.06)
ECOG performance status					
0	109/187	59/95	26.0 (23.0-29.6)	20.2 (16.7-24.4)	0.68 (0.49-0.93)
1	102/44	51/68	21.4 (17.9-23.9)	14.9 (12.6-18.4)	0.70 (0.50-0.99)
Visceral disease at baseline					
Yes	201/298	99/146	22.9 (21.4-24.5)	17.5 (14.8-20.2)	0.73 (0.57-0.93)
No	10/33	11/17	NE (20.4-NE)	18.4 (13.5-NE)	0.34 (0.14-0.81)



Modi S et al. Presented at: European Society for Medical Oncology 2023; October 20-24, 2023; Madrid, Spain. Presentation 376O.

Subgroup analysis: OS in all patients

	No. of Events/No. of Patients		OS, median (95% CI), mo		Hazard Ratio for Death (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6 inhibitors					
Yes	158/235	81/118	22.3 (19.7-24.2)	16.7 (14.0-19.4)	0.71 (0.54-0.92)
No	55/98	32/48	29.6 (22.9-35.1)	22.4 (15.6-27.2)	0.64 (0.41-0.99)
IHC status					
IHC 1+	137/214	77/107	22.7 (20.3-24.7)	15.7 (13.5-19.9)	0.65 (0.49-0.86)
IHC 2+/ISH−	105/159	51/77	23.6 (20.0-26.0)	17.1 (13.1-21.7)	0.72 (0.51-1.01)
Prior lines of chemotherapy					
1	129/221	69/100	25.5 (23.4-28.9)	18.2 (15.6-22.5)	0.62 (0.46-0.83)
≥2	113/151	59/83	18.1 (16.1-21.5)	14.0 (10.8-19.1)	0.78 (0.57-1.07)
Age					
<65 years	185/290	95/136	22.7 (20.3-24.4)	16.7 (14.0-19.1)	0.64 (0.50-0.82)
≥65 years	57/83	33/48	24.4 (18.4-28.0)	19.5 (11.1-30.2)	0.77 (0.50-1.19)
Race					
White	123/176	62/91	22.0 (18.2-24.2)	14.5 (10.7-19.4)	0.68 (0.50-0.93)
Asian	90/151	51/72	25.2 (21.7-29.6)	19.1 (15.7-24.3)	0.68 (0.48-0.96)
Other	26/38	13/17	21.2 (17.0-28.9)	15.2 (6.2-23.9)	0.55 (0.28-1.07)
Region					
Asia	90/147	47/66	24.0 (21.7-29.3)	19.1 (15.7-24.3)	0.69 (0.49-0.98)
Europe and Israel	118/166	59/85	22.3 (19.0-24.2)	14.8 (10.7-19.9)	0.67 (0.49-0.91)
North America	34/60	22/33	20.6 (13.6-25.9)	14.9 (10.5-19.5)	0.66 (0.38-1.13)
ECOG performance status					
0	117/200	68/105	25.9 (23.0-29.3)	19.4 (15.1-22.8)	0.62 (0.46-0.83)
1	125/173	60/79	20.6 (17.2-22.7)	14.5 (12.3-18.4)	0.74 (0.54-1.01)
Visceral disease at baseline					
Yes	227/332	109/157	22.4 (20.0-24.0)	16.9 (14.0-20.0)	0.71 (0.57-0.90)
No	15/41	19/27	NE (28.0-NE)	15.7 (12.9-20.6)	0.35 (0.18-0.70)



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DESTINY-Breast04: March 1, 2023, DCO

PFS2[a] and post-study anti-cancer therapies[b]

	HR+ cohort		All Patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Median PFS2 by investigator, months (95% CI)	15.5 (13.8-17.2)	10.5 (8.3-11.4)	15.4 (13.6-16.5)	9.7 (8.3-10.8)
Hazard ratio (95% CI)	0.51 (0.40-0.64)		0.51 (0.41-0.64)	
Post-study anti-cancer therapies				
Systemic treatment, n (%)	247 (74.6)	126 (77.3)	282 (75.6)	144 (78.3)
Targeted therapy[c]	119 (36.0)	70 (42.9)	134 (35.9)	75 (40.8)
CDK4/6 inhibitors	47 (14.2)	27 (16.6)	48 (12.9)	27 (14.7)
ADC	**16 (4.8)**	**15 (9.2)**	**18 (4.8)**	**15 (8.2)**
T-DXd	2 (0.6)	4 (2.5)	2 (0.5)	4 (2.2)
Sacituzumab govitecan	9 (2.7)	5 (3.1)	11 (2.9)	5 (2.7)
Endocrine therapy	102 (30.8)	56 (34.4)	103 (27.6)	57 (31.0)
Chemotherapy	222 (67.1)	109 (66.9)	257 (68.9)	126 (68.5)
Radiation, n (%)	32 (9.7)	25 (15.3)	37 (9.9)	29 (15.8)
Surgery, n (%)	3 (0.9)	1 (0.6)	5 (1.3)	1 (0.5)

[a]Defined as the time from date of randomization to the first documented progression per investigator assessment on next-line of systemic therapy or death due to any cause, whichever occurs first. [b]Participants may have been treated with more than 1 type of post-study anti-cancer therapy. [c]Class includes CDK4/6 inhibitor, immunotherapy, antibody drug conjugates, or no subclass specified.

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DESTINY-Breast04: March 1, 2023, DCO

Overall safety summary[1]

- Median treatment duration was 8.2 months (range, 0.2-39.1 months) for T-DXd and 3.5 months (range, 0.3-19.7 months) for TPC
  - 16.4% of patients underwent treatment for ≥18 months in the T-DXd arm compared with 1.2% of patients in the TPC arm
- The most common TEAEs associated with treatment discontinuation for patients receiving T-DXd and TPC were investigator-assessed ILD/pneumonitis (10.2%) and peripheral sensory neuropathy (2.3%), respectively
- The most common TEAEs associated with dose reduction were nausea (4.6%) and decreased platelet count (3.0%) among patients receiving T-DXd vs decreased neutrophil count (10.5%) and palmar-plantar erythrodysesthesia syndrome (5.2%) among patients receiving TPC
- Exposure-adjusted incidence rates for any-grade TEAEs were 1.2 and 2.6 per patient-year for the T-DXd and TPC arms, respectively
  - This supports that longer T-DXd exposure does not increase toxicity
- Overall, the safety profile is consistent with results from the primary analysis[2]

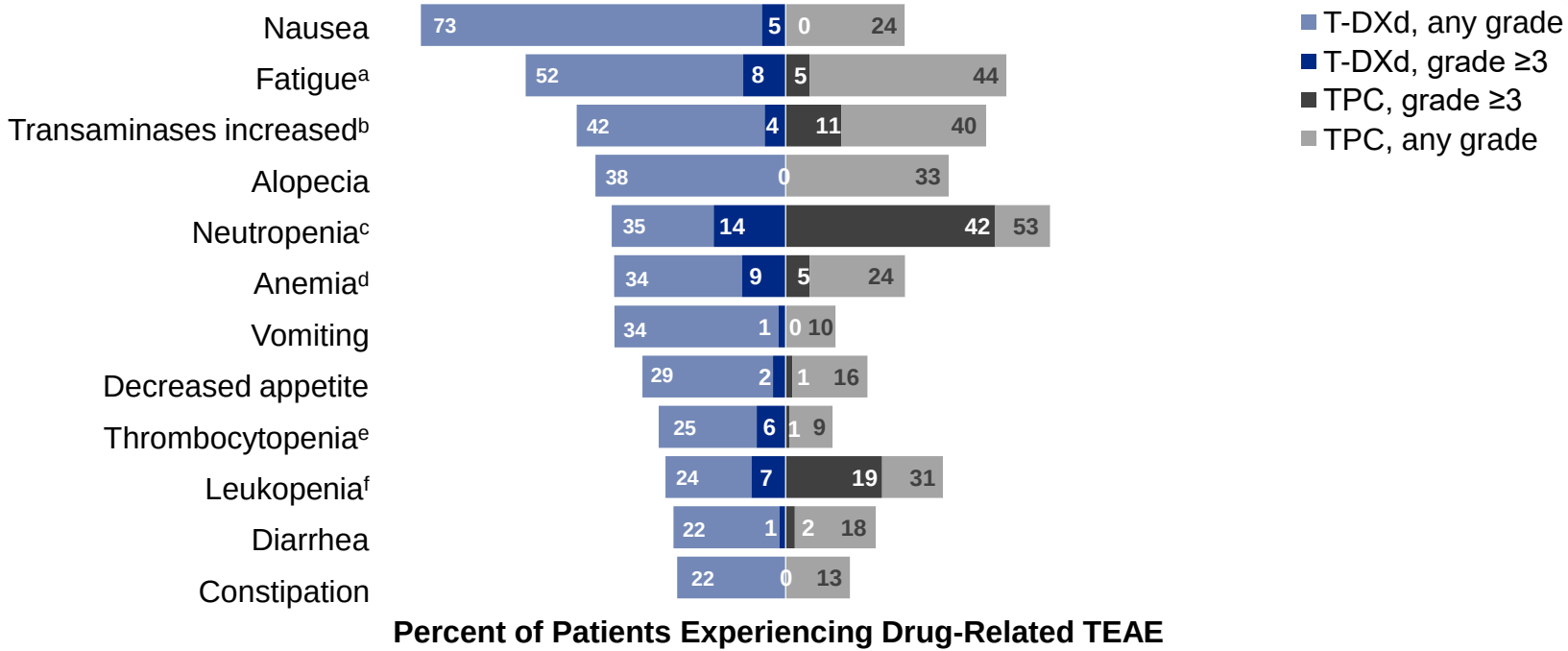
Safety analysis set[a]

n, (%)	T-DXd (n = 371)	TPC (n = 172)
TEAEs	369 (99.5)	169 (98.3)
Grade ≥3	202 (54.4)	116 (67.4)
Serious TEAEs	108 (29.1)	44 (25.6)
TEAEs associated with dose discontinuation	62 (16.7)	14 (8.1)
TEAEs associated with dose interruptions	155 (41.8)	73 (42.4)
TEAEs associated with dose reductions	89 (24.0)	65 (37.8)
TEAEs associated with deaths	15 (4.0)	5 (2.9)
Total on-treatment deaths[b]	14 (3.8)	8 (4.7)

[a]Safety analyses were performed in patients who received ≥1 dose of a study regimen. [b]On-treatment death is defined as death occurred any time from date of first dose through 47 days after the last dose of the study treatment.

1. Modi S et al. Presented at: European Society for Medical Oncology 2023; October 20-24, 2023; Madrid, Spain. Presentation 376O. 2. Modi S et al. *N Engl J Med*. 2022;387(1):9-20.

Drug-related TEAEs in ≥20% of patients



[a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, and hepatic function abnormal. [c]This category includes the preferred terms neutrophil count decreased and neutropenia. [d]This category includes the preferred terms hemoglobin decreased, red-cell count decreased, anemia, and hematocrit decreased. [e]This category includes the preferred terms platelet count decreased and thrombocytopenia. [f]This category includes the preferred terms white-cell count decreased and leukopenia.

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DESTINY-Breast04: March 1, 2023, DCO

Adverse events of special interest[1]

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
ILD/pneumonitis (adjudicated, drug-related), n (%)						
T-DXd (n = 371)	13 (3.5)	24 (6.5)	4 (1.1)[a]	0	4 (1.1)[a]	**45 (12.1)**
TPC (n = 172)	1 (0.6)	0	0	0	0	**1 (0.6)**
Left ventricular dysfunction						
Ejection fraction decreased, n (%)						
T-DXd (n = 371)	2 (0.5)	15 (4.0)	1 (0.3)	0	0	**18 (4.9)**
TPC (n = 172)	0	0	0	0	0	**0**
Cardiac failure, n (%)						
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**

- There were no new cases of ILD/pneumonitis since the primary analysis[2]

[a]At the primary analysis (DCO: January 11, 2022), grade 3 adjudicated drug-related ILD was reported in 5 patients (1.3%). At the updated analysis DCO (March 1, 2023), grade 3 adjudicated drug-related ILD is reported in 4 patients (1.1%) as 1 grade 3 ILD case worsened to grade 5 ILD. Consequently, there is an increase in the rate of grade 5 ILD (from 0.8% to 1.1%) without impact on the overall rate of adjudicated drug-related ILD. No ILD cases were pending adjudication at the updated analysis DCO.

1. Modi S et al. Presented at: European Society for Medical Oncology 2023; October 20-24, 2023; Madrid, Spain. Presentation 376O. 2. Modi S et al. *N Engl J Med*. 2022;387(1):9-20.

Overall summary of DESTINY-Breast04 updated analysis

- Results from the 32-month median follow-up for DESTINY-Breast04 confirm the sustained clinically meaningful improvement for T-DXd vs TPC previously demonstrated in HER2-low (IHC 1+, IHC 2+/ISH−) mBC,[1] regardless of HR status[2]
- With longer treatment duration, the overall safety profile of T-DXd was acceptable and generally manageable, and was consistent with the primary analysis[1]
    - Rates of ILD/pneumonitis remained unchanged with longer follow-up, and rates of left ventricular dysfunction were consistent with previously observed rates[2]

Outcomes from the longer follow-up of DESTINY-Breast04 continue to support the use of T-DXd as the new standard of care after 1L+ chemotherapy in patients with HER2-low mBC[2]

1. Modi S et al. *N Engl J Med*. 2022;387(1):9-20. 2. Modi S et al. Presented at: European Society for Medical Oncology 2023; October 20-24, 2023; Madrid, Spain. Presentation 376O.

DESTINY-Breast04: Subgroup Analysis of Centrally Assessed Brain Metastases at Baseline

Data cutoff: January 11, 2022

Centrally assessed brain metastases at baseline: Background

- Brain metastases (BM), which are a sign of poor prognosis, may develop in roughly 15% of patients with HER2-low mBC[1]
- This analysis explores the intracranial efficacy of T-DXd in patients with HER2-low mBC and baseline asymptomatic[a,b] BM, as assessed by BICR[2]
  - Exploratory analysis of intracranial activity was based on central review of brain magnetic resonance imaging (MRI) or computed tomography (CT) (DCO: January 11, 2022)
  - Endpoints included intracranial confirmed objective response rate (cORR), best overall intracranial response, intracranial clinical benefit rate (CBR), intracranial disease control rate (DCR), central nervous system (CNS)-PFS by BICR, and OS

[a]Earlier versions of the protocol allowed patients with untreated asymptomatic BM to enroll in the trial. [b]Patients with treated brain metastases were allowed to enroll in the DESTINY-Breast04 trial only if they were asymptomatic and if they did not require treatment with corticosteroids or anticonvulsants or had recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of whole brain radiotherapy and study enrollment.

1. Jin J et al. *J Transl Med*. 2023; 21:360-376; 2. Tsurutani J et al. Presented at the European Society for Medical Oncology (ESMO) Annual Meeting; Madrid, Spain, October 20-24, 2023. Poster 388P.

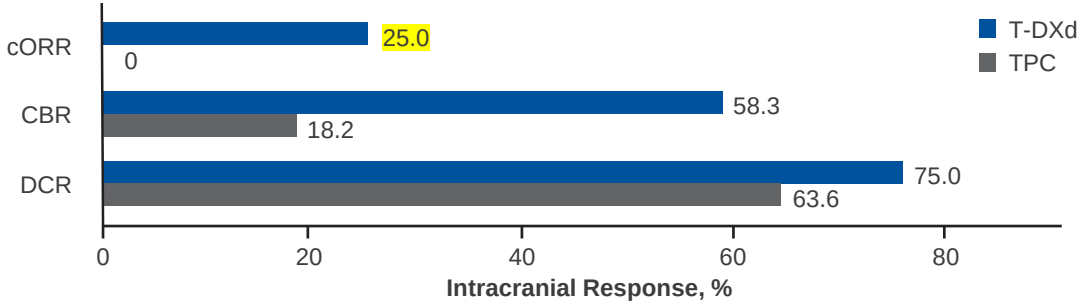
Baseline characteristics for patients with asymptomatic BM

- Of the 35 patients who had BICR-assessed, asymptomatic BM at baseline, 24 were randomly assigned to the T-DXd arm and 11 were randomly assigned to the TPC arm
  - 8/24 patients in the T-DXd arm and 7/11 patients in the TPC arm had previously untreated BM

	T-DXd (n = 24)	TPC (n = 11)
Median age, years (range)	56.9 (32.6-71.4)	48.8 (32.6-69.7)
<65 years, n (%) | ≥65 years, n (%)	21 (87.5) | 3 (12.5)	9 (81.8) | 2 (18.2)
Race, n (%)		
White | Black/African American | Asian | Other	11 (45.8) | 0 | 12 (50.0) | 1 (4.2)	5 (45.5) | 0 | 4 (36.4) | 2 (18.2)
Previous CDK4/6i, n (%)		
Yes | No | Not applicable[a]	12 (50.0) | 6 (25.0) | 6 (25.0)	7 (63.6) | 1 (9.1) | 3 (27.3)
Prior lines of chemotherapy, n (%)		
1 | 2	10 (41.7) | 14 (58.3)	6 (54.5) | 5 (45.5)
HER2 IHC/ISH status, n (%)		
HER2 IHC 1+ | HER2 IHC2+/ISH−	11 (45.8) | 13 (54.2)	6 (54.5) | 5 (45.5)
HR status,[b] n (%)		
Positive | Negative	18 (75.0) | 6 (25.0)	8 (72.7) | 3 (27.3)
Baseline visceral disease, n (%)	23 (95.8)	10 (90.9)
Baseline liver metastases, n (%)	16 (66.7)	6 (54.5)
Prior treatment for BM,[c] n (%)		
Prior radiotherapy only | Prior surgery only	13 (54.2) | 0	4 (36.4) | 0
Prior radiotherapy and surgery	3 (12.5)	0
Neither prior radiotherapy nor surgery	8 (33.3)	7 (63.6)

[a]Not applicable prior CDK4/6i data are due to patients with HER2-low, HR− mBC.
[b]HR+ is defined as being positive for either progesterone or estrogen receptors, or both. HR− is defined as being negative for both progesterone and estrogen receptors.
[c]Radiotherapy was not further subdivided because of small numbers.
Tsurutani J et al. Presented at the European Society for Medical Oncology (ESMO) Annual Meeting; Madrid, Spain, October 20-24, 2023. Poster 388P.

Intracranial efficacy in patients with asymptomatic BM at baseline



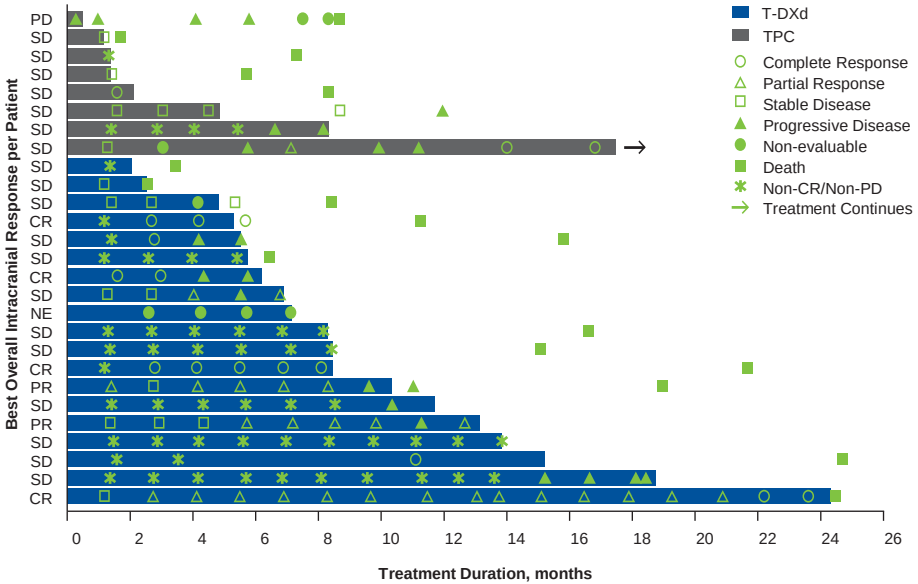
	Best Overall Intracranial Response	
n (%)	T-DXd (n = 24)	TPC (n = 11)
CR	4 (16.7)	0
PR	2 (8.3)	0
SD	12 (50.0)	7 (63.6)
PD	0	1 (9.1)
Not evaluable (NE)	1 (4.2)	0
Missing	5 (20.8)	3 (27.3)

[a]Confirmation was required for CR and PR. [b]Data were not available for analysis.
Tsurutani J et al. Presented at the European Society for Medical Oncology (ESMO) Annual Meeting; Madrid, Spain, October 20-24, 2023. Poster 388P.

- Patients in the T-DXd arm had a cORR of 25.0% (95% CI, 9.8%-46.7%) compared with 0% (95% CI, 0.0-28.5%) for patients in the TPC arm
  - 4 patients (16.7%) in the T-DXd arm achieved a complete response
- CBR was reported in 14/24 patients (58.3%) randomly assigned to the T-DXd arm (95% CI, 36.6%-77.9%) and in 2/11 patients (18.2%) randomly assigned to the TPC arm (95% CI, 2.3%-51.8%)
- DCR was reported in 18/24 patients (75.0%) randomly assigned to the T-DXd arm (95% CI, 53.3-90.2%) and in 7/11 patients (63.6%) randomly assigned to the TPC arm (95% CI, 30.8%-89.1%)

Duration of therapy and achieved responses

Swimmer plot by patients with best overall intracranial response[a,b]

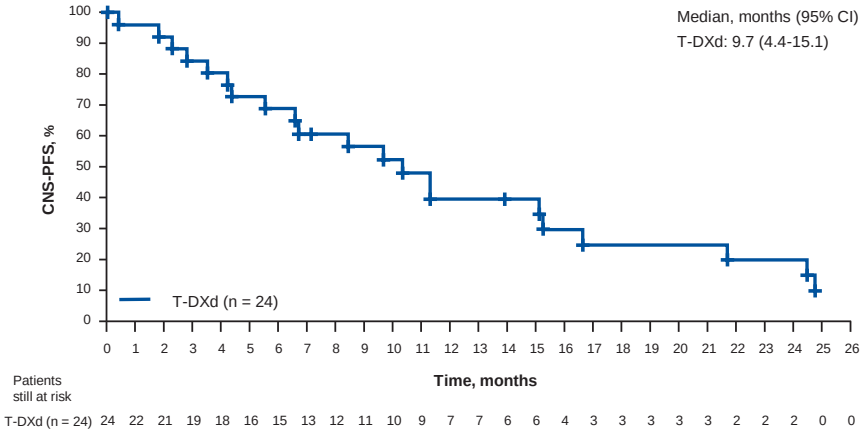


- Duration of therapy and achieved responses stratified by treatment arm suggest benefit of T-DXd vs TPC in patients with BM

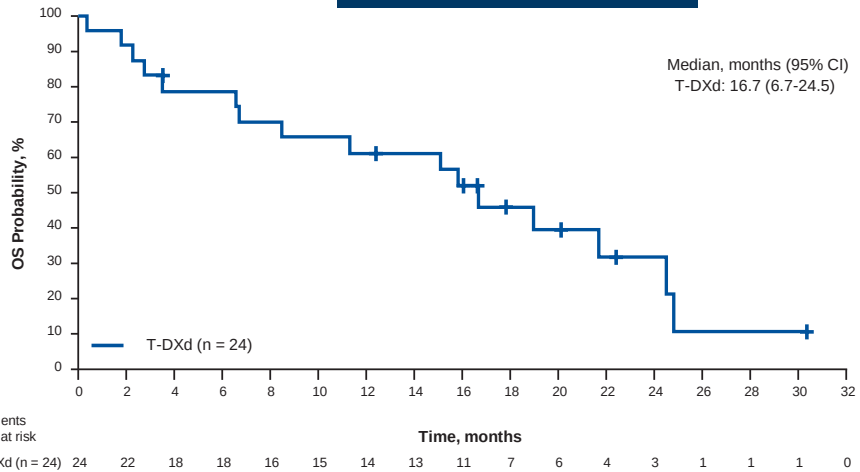
[a]Response information was not available for 8 patients. [b]Patients were only deemed to have a CR if the response was confirmed and without prior PD.
Tsurutani J et al. Presented at the European Society for Medical Oncology (ESMO) Annual Meeting; Madrid, Spain, October 20-24, 2023. Poster 388P.

Median CNS-PFS and median OS of patients with asymptomatic BM[a]

CNS-PFS



OS



- Median CNS-PFS by BICR for patients in the T-DXd arm was 9.7 months (95% CI, 4.4-15.1 months)
- Median OS for patients in the T-DXd arm was 16.7 months (95% CI, 6.7-24.5 months)

[a]The Kaplan-Meier curves only show T-DXd data because of the small event count for TPC.

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Sites of first progression in patients with asymptomatic BM

n (%)	T-DXd (n = 24)	TPC (n = 11)
Patients with progression	17 (70.8)	7 (63.6)
Sites of first progression		
Intracranial only	2 (8.3)	3 (27.3)
Extracranial only	15 (62.5)	4 (36.3)

- Of all the patients who were enrolled in the DESTINY-Breast04 trial, 60.3% and 67.4% experienced systemic disease progression as the first progressive site in the T-DXd and TPC arms, respectively
- Of patients with BM who were enrolled in the DESTINY-Breast04 trial, 70.8% and 63.6% experienced systemic disease progression as the first progressive site in the T-DXd and TPC arms, respectively

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Summary: Centrally assessed BM at baseline

- This exploratory study examined serial brain scans of all patients from the DESTINY-Breast04 trial with BICR-assessed asymptomatic BM at baseline (35 patients [24 T-DXd; 11 TPC])[1]

- Intracranial responses favored T-DXd over TPC
  - Intracranial cORR, CBR, and DCR were greater in the T-DXd arm than in the TPC arm
  - Median CNS-PFS for patients treated with T-DXd was 9.7 months
  - Median OS for patients treated with T-DXd was 16.7 months

- Although only a small number of patients were included in this exploratory study, intracranial efficacy data suggest a benefit of T-DXd over TPC; this is consistent with the overall observed efficacy of T-DXd in patients with HER2-low mBC[2,3] and the observed efficacy of T-DXd in patients with HER2+ mBC with BM[4,5]

1. Tsurutani J et al. Presented at the European Society for Medical Oncology (ESMO) Annual Meeting; Madrid, Spain, October 20-24, 2023. Poster 388P. 2. Modi S et al. *N Engl J Med*. 2022;387:9-20; 3. Harbeck N et al. Presented at: San Antonio Breast Cancer Symposium 2022; December 5-9, 2022; San Antonio, TX. Poster P1-11-0; 4. Jerusulem G et al. *Cancer Discov*. 2022;12:2754-2762; 5. Hurvitz SA. *Lancet*. 2022;401(10371):105-117.