2024 ASCO ANNUAL MEETING

DESTINY BREAST07

DESTINY-Breast07: dose-expansion analysis of T-DXd monotherapy and T-DXd + pertuzumab in patients with previously untreated HER2+ mBC

Saturday, June 1, 2024

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On behalf of the DESTINY-Breast07 investigators

[1]Gustave Roussy, Paris-Saclay University, Villejuif, France

DESTINY-Breast07: key takeaways

This is the first dataset of T-DXd monotherapy and T-DXd + pertuzumab as first-line treatment for HER2+ mBC

- The data showed robust efficacy in terms of **ORR, median DOR, and PFS rate at 12 months**
- There are **62.7%** and **56.0%** of patients receiving **ongoing study treatment**, with a **median duration of follow up** of **23.9 months** and **25.3 months**, in the T-DXd monotherapy and T-DXd + pertuzumab modules, respectively
- Encouraging clinical activity was observed with T-DXd monotherapy and T-DXd + pertuzumab in first-line HER2+ mBC, irrespective of disease status and HR status
- The **safety profiles** of T-DXd and pertuzumab were **consistent** with their individual known profiles
  - There were **no ILD/pneumonitis-related deaths** in either module

DOR, duration of response; HER2+, human epidermal growth factor receptor 2–positive; HR, hormone receptor; ILD, interstitial lung disease; mBC, metastatic breast cancer; ORR, objective response rate; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

Study background and rationale

- HER2+ breast cancer occurs in up to approximately 20% of primary breast cancers[1,2]
- The current first-line therapy for HER2+ mBC is THP based on the CLEOPATRA study, which reported a median PFS of 18.7 months[3,4]
- T-DXd monotherapy has demonstrated impressive efficacy in HER2+ mBC and is approved for adult patients with HER2+ advanced/mBC progressing after trastuzumab and taxanes, based on the results from DESTINY-Breast03[5–8]
- DESTINY-Breast07 is a Phase 1b/2, multicenter, open-label, modular study exploring the safety, tolerability, and antitumor activity of T-DXd alone or in combination with other anticancer agents in patients with HER2+ mBC who have received no prior therapy in the metastatic setting (NCT04538742; Part 2, Modules 0–5)
- These results are from an interim analysis of the dose-expansion phase, assessing T-DXd alone and in combination with pertuzumab as first-line treatment in HER2+ mBC

HER2+, human epidermal growth factor receptor 2–positive; mBC, metastatic breast cancer; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; THP, taxane, trastuzumab, and pertuzumab

1. Wolff AC, et al. *J Clin Oncol*. 2013;31:3997–4013; 2. Morales S, et al. *Cancers (Basel)*. 2021;13:5771; 3. Giordano SH, et al. *J Clin Oncol*. 2022;40:2612–2635; 4. Swain SM, et al. *Lancet Oncol*. 2020;21:519–530; 5. Modi S, et al. *N Engl J Med*. 2020;382:610–621; 6. Cortés J, et al. *N Engl J Med*. 2022;386:1143–1154; 7. André F, et al. *Lancet*. 2023;401:1773–1785; 8. Enhertu (fam-trastuzumab deruxtecan-nxki): highlights of prescribing information. 2022. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761139s021lbl.pdf (Accessed March 18, 2024)

Study design

DESTINY-Breast07: a Phase 1b/2, multicenter, open-label, two-part, modular study (NCT04538742)

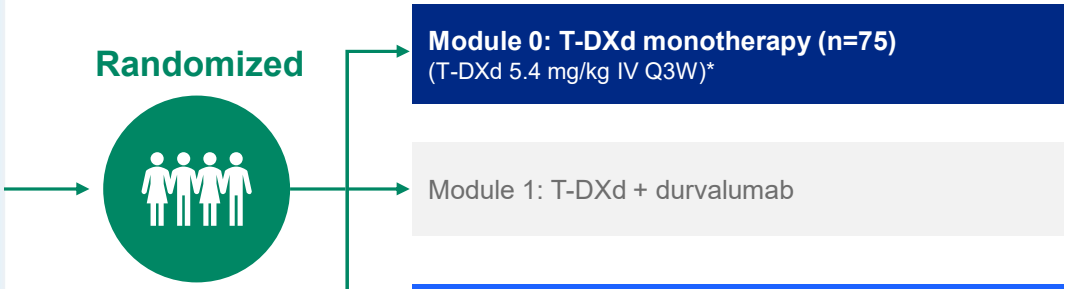
PATIENT POPULATION

- Locally assessed HER2+ (IHC 3+, IHC 2+/ISH+) advanced/mBC, with measurable disease per RECIST 1.1
- Either no brain metastases or previously treated stable brain metastases
- ECOG PS of 0 or 1

Prior lines of therapy

- No prior therapy for mBC was allowed
- A disease-free interval of ≥12 months from adjuvant HER2-directed therapy or chemotherapy was required
- Prior taxane, trastuzumab, and pertuzumab exposure was allowed in the (neo)adjuvant setting

This is the first dataset of T-DXd monotherapy and T-DXd + pertuzumab as first-line treatment for HER2+ mBC



Stratification factors

- HR status
- Disease status
- PD-L1 status

Endpoints for the Part 2 dose-expansion phase

Primary
Safety and tolerability, including AEs and SAEs

Key secondary
ORR, PFS (evaluated by investigator per RECIST 1.1), and DOR

DCO: December 22, 2023‡

Results reported here are from an interim analysis of the Part 2 dose-expansion phase for Modules 0 and 2 only; the Part 1 dose-finding phase of the study has been described previously[1]

*Patients in Module 0 received the approved T-DXd dose for HER2+ breast cancer; †patients received the RP2D from the study's dose-finding phase; ‡the corresponding abstract reported data from the August 1, 2023, DCO
AE, adverse event; DCO, data cutoff; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HER2+, human epidermal growth factor receptor 2–positive; HR, hormone receptor; IHC, immunohistochemistry; ISH+, in situ hybridization–positive; IV, intravenous; mBC, metastatic breast cancer; ORR, objective response rate; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; RP2D, recommended Phase 2 dose; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan

1. André F, et al. Poster presented at ASCO 2022 (Abstract 3025)

Baseline characteristics

	T-DXd monotherapy (n=75)	T-DXd + pertuzumab (n=50)
Median age, years (range)	57.0 (33.0–80.0)	56.5 (24.0–75.0)
Female, n (%)	74 (98.7)*	50 (100)
Race, n (%)		
White	52 (69.3)	37 (74.0)
Asian	20 (26.7)	12 (24.0)
Black or African American	2 (2.7)	0
Not reported	1 (1.3)	0
Other	0	1 (2.0)
HER2 status, n (%)		
IHC 3+†	60 (80.0)	41 (82.0)
IHC 2+/ISH+	14 (18.7)	9 (18.0)
IHC 2+	1 (1.3)	0
HR status, n (%)		
Positive‡	47 (62.7)	34 (68.0)
Negative	28 (37.3)	16 (32.0)
Disease status, n (%)		
Recurrent§	27 (36.0)	20 (40.0)
De novo¶	48 (64.0)	30 (60.0)
ECOG PS, n (%)		
0	49 (65.3)	37 (74.0)
1	26 (34.7)	13 (26.0)

DCO was December 22, 2023

*Male, n=1; †regardless of ISH status; ‡defined as ER- and/or PR-positive (ER or PR ≥1%); §defined as previously treated in the (neo)adjuvant setting with chemotherapy, HER2-directed agents, or endocrine therapy and includes previously treated HER2-negative patients who now have HER2-positive disease in the metastatic setting; ¶defined as no prior systemic therapy in the (neo)adjuvant setting with chemotherapy, HER2-directed agents, or endocrine therapy

DCO, data cutoff; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; ISH+, in situ hybridization–positive; mBC, metastatic breast cancer; PR, progesterone receptor; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Baseline characteristics

	T-DXd monotherapy (n=75)	T-DXd + pertuzumab (n=50)
Median age, years (range)	57.0 (33.0–80.0)	56.5 (24.0–75.0)
Female, n (%)	74 (98.7)*	50 (100)
Race, n (%)		
White	52 (69.3)	37 (74.0)
Asian	20 (26.7)	12 (24.0)
Black or African American	2 (2.7)	0
Not reported	1 (1.3)	0
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IHC 3+[†]	60 (80.0)	41 (82.0)
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HR status, n (%)		
Positive[‡]	47 (62.7)	34 (68.0)
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Disease status, n (%)		
Recurrent[§]	27 (36.0)	20 (40.0)
De novo[¶]	48 (64.0)	30 (60.0)
ECOG PS, n (%)		
0	49 (65.3)	37 (74.0)
1	26 (34.7)	13 (26.0)

Prior HER2-directed therapy in patients with recurrent mBC

n (%)	T-DXd monotherapy (n=27)	T-DXd + pertuzumab (n=20)
Trastuzumab	14 (51.9)	13 (65.0)
Pertuzumab	4 (14.8)	2 (10.0)
T-DM1	2 (7.4)	0

DCO was December 22, 2023

*Male, n=1; [†]regardless of ISH status; [‡]defined as ER- and/or PR-positive (ER or PR ≥1%); [§]defined as previously treated in the (neo)adjuvant setting with chemotherapy, HER2-directed agents, or endocrine therapy and includes previously treated HER2-negative patients who now have HER2-positive disease in the metastatic setting; [¶]defined as no prior systemic therapy in the (neo)adjuvant setting with chemotherapy, HER2-directed agents, or endocrine therapy

DCO, data cutoff; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; ISH+, in situ hybridization–positive; mBC, metastatic breast cancer; PR, progesterone receptor; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

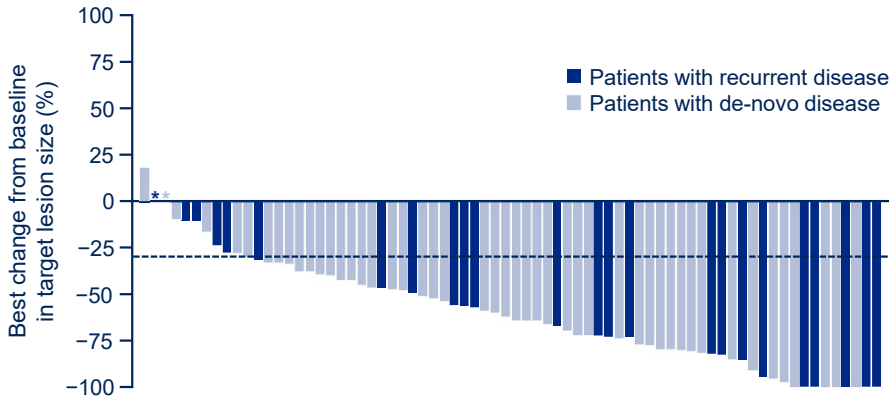
Patient disposition

	T-DXd monotherapy (n=75)	T-DXd + pertuzumab (n=50)
Median duration of follow up, months	23.9	25.3
Ongoing study treatment, n (%)	47 (62.7)	28 (56.0)
Discontinued treatment, n (%)	28 (37.3)	22 (44.0)
Objective disease progression	10 (13.3)	8 (16.0)
Adverse event	7 (9.3)	9 (18.0)
Withdrawal by patient	6 (8.0)	2 (4.0)
Other	5 (6.7)	3 (6.0)
Death*	2 (2.7)	1 (2.0)

DCO was December 22, 2023
*Includes death while on treatment with investigational product; investigators did not specifically record a reason for discontinuation of investigational product
DCO, data cutoff; T-DXd, trastuzumab deruxtecan

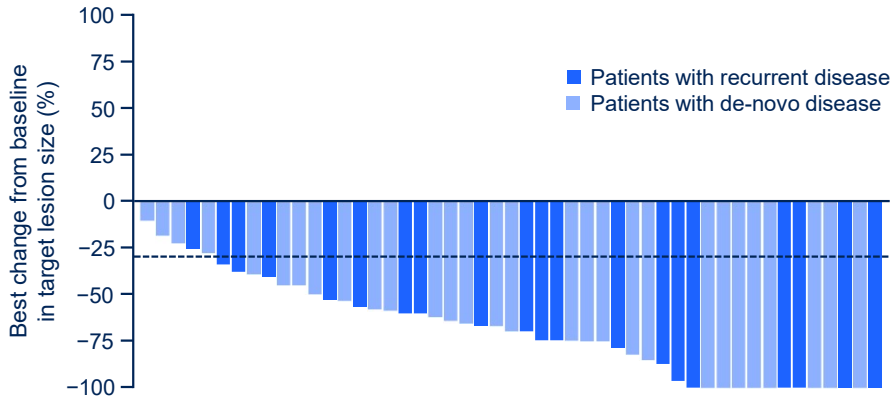
Response to treatment per RECIST 1.1 by investigator

T-DXd monotherapy (n=75)



Confirmed ORR, % (80% CI)	76.0 (68.5–82.4)
Complete response, n (%)	6 (8.0)
Partial response, n (%)	51 (68.0)
Median DOR, months (range)	NE (2.1–28.5)

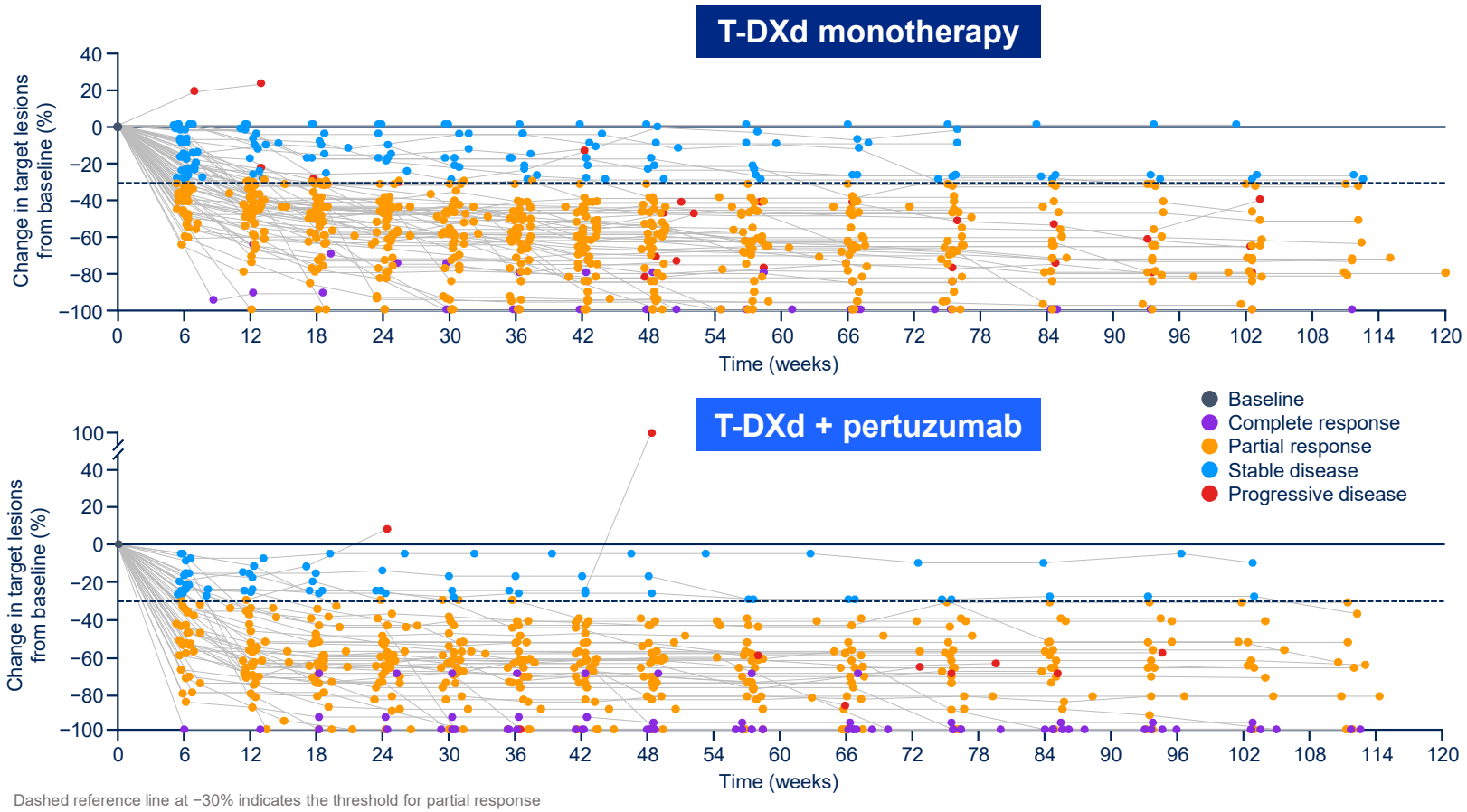
T-DXd + pertuzumab (n=50)



Confirmed ORR, % (80% CI)	84.0 (75.3–90.5)
Complete response, n (%)	10 (20.0)
Partial response, n (%)	32 (64.0)
Median DOR, months (range)	NE (4.5–28.3)

Dashed reference line at −30% indicates the threshold for partial response
Responses are captured for patients with baseline data and at least one follow-up assessment
DCO was December 22, 2023. Median duration of follow up was 23.9 months for T-DXd monotherapy and 25.3 months for T-DXd + pertuzumab
*Patients had 0% change from baseline
CI, confidence interval; DCO, data cutoff; DOR, duration of response; NE, not evaluable; ORR, objective response rate; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan

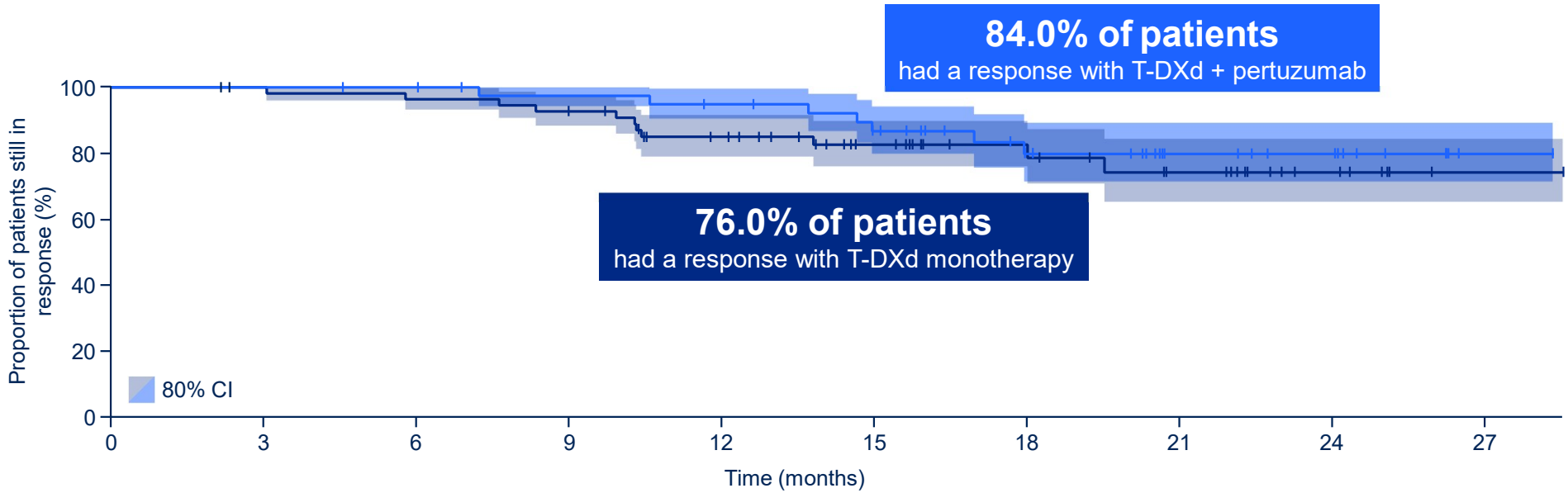
Percentage change in target lesion size from baseline



The majority of responses were observed by the 12-week scan and were durable

Dashed reference line at −30% indicates the threshold for partial response
DCO was December 22, 2023. Median duration of follow up was 23.9 months for T-DXd monotherapy and 25.3 months for T-DXd + pertuzumab. DCO, data cutoff; T-DXd, trastuzumab deruxtecan

Duration of response



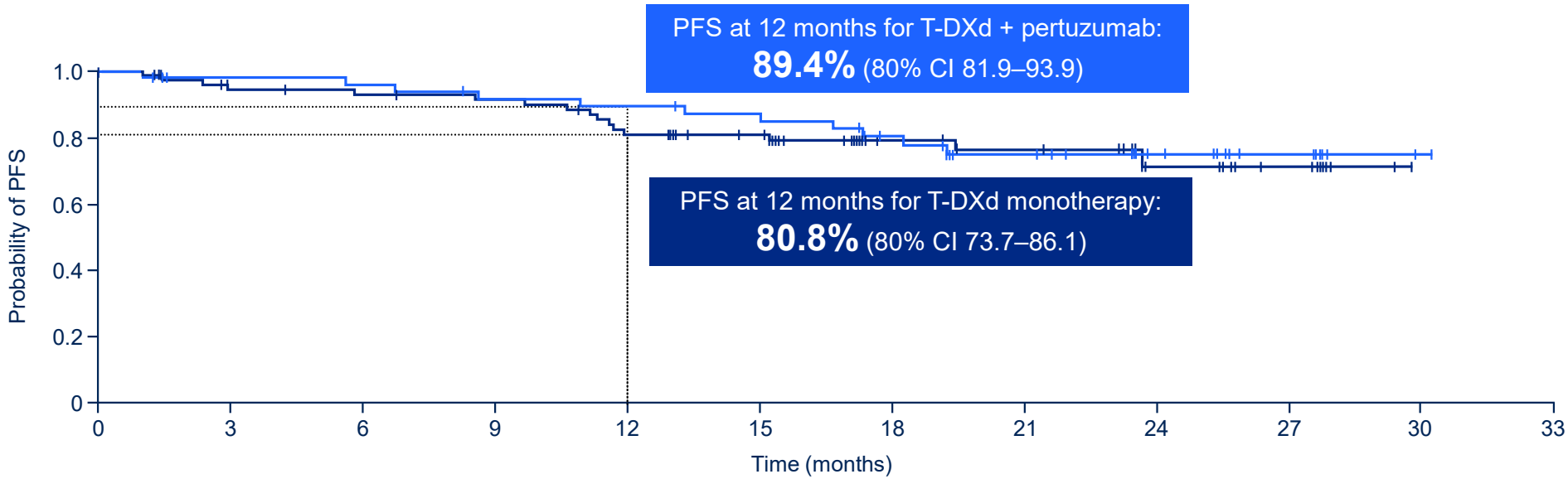
Number at risk										
T-DXd monotherapy	57	55	53	50	41	28	21	15	7	1
T-DXd + pertuzumab	42	42	41	38	36	31	21	13	10	1

Number of randomized patients / number of events

T-DXd monotherapy	**75 / 11**
T-DXd + pertuzumab	**50 / 7**

DCO was December 22, 2023. Median duration of follow up was 23.9 months for T-DXd monotherapy and 25.3 months for T-DXd + pertuzumab
CI, confidence interval; DCO, data cutoff; T-DXd, trastuzumab deruxtecan

Progression-free survival



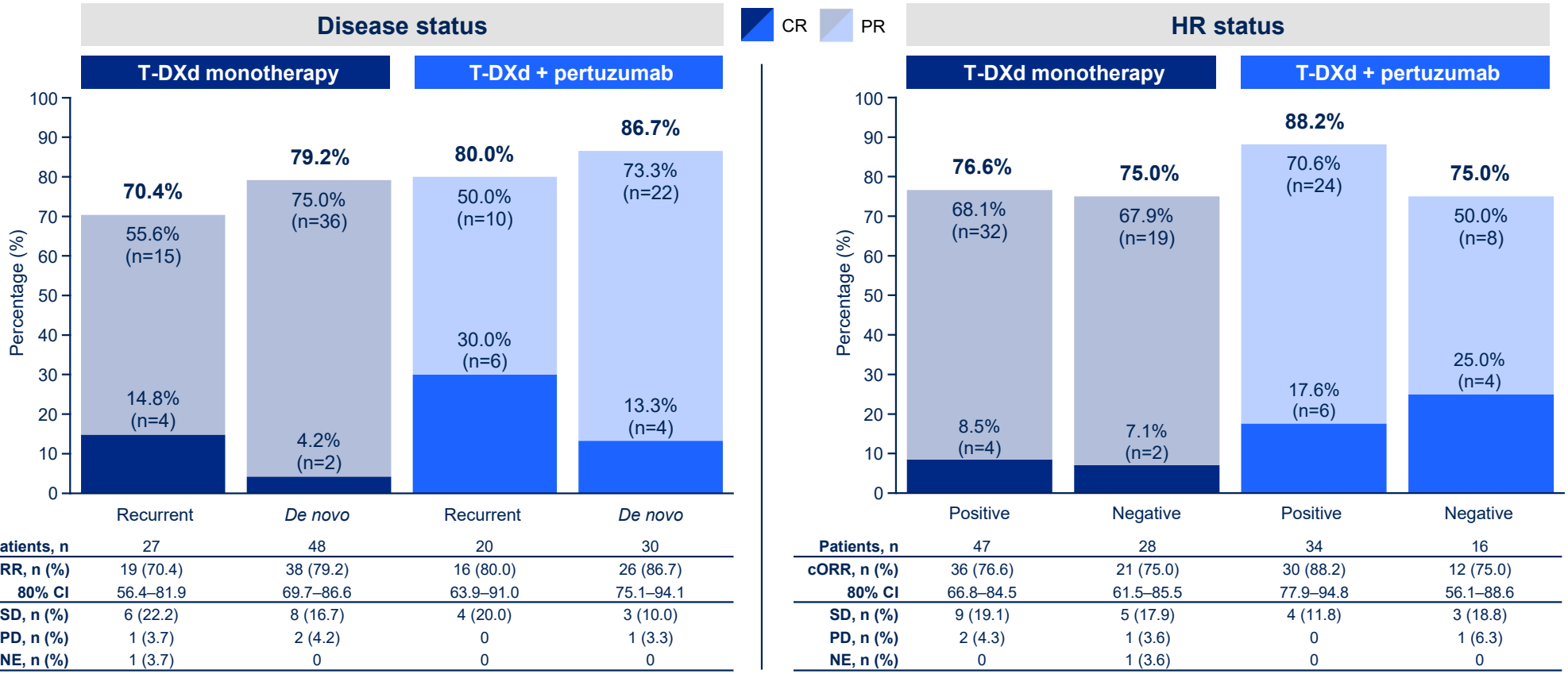
Number at risk												
T-DXd monotherapy	75	65	63	61	53	47	27	24	13	8	0	0
T-DXd + pertuzumab	50	46	45	42	41	38	31	23	13	7	1	0

Number of randomized patients / number of events

T-DXd monotherapy	**75 / 16**
T-DXd + pertuzumab	**50 / 11**

The number of PFS events is small, and most patients were censored
DCO was December 22, 2023. Median duration of follow up was 23.9 months for T-DXd monotherapy and 25.3 months for T-DXd + pertuzumab
CI, confidence interval; DCO, data cutoff; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

cORR and BOR by subgroup per RECIST 1.1 by investigator



	Disease status				HR status			
	T-DXd monotherapy		T-DXd + pertuzumab		T-DXd monotherapy		T-DXd + pertuzumab	
Patients, n	27	48	20	30	47	28	34	16
cORR, n (%)	19 (70.4)	38 (79.2)	16 (80.0)	26 (86.7)	36 (76.6)	21 (75.0)	30 (88.2)	12 (75.0)
80% CI	56.4–81.9	69.7–86.6	63.9–91.0	75.1–94.1	66.8–84.5	61.5–85.5	77.9–94.8	56.1–88.6
SD, n (%)	6 (22.2)	8 (16.7)	4 (20.0)	3 (10.0)	9 (19.1)	5 (17.9)	4 (11.8)	3 (18.8)
PD, n (%)	1 (3.7)	2 (4.2)	0	1 (3.3)	2 (4.3)	1 (3.6)	0	1 (6.3)
NE, n (%)	1 (3.7)	0	0	0	0	1 (3.6)	0	0

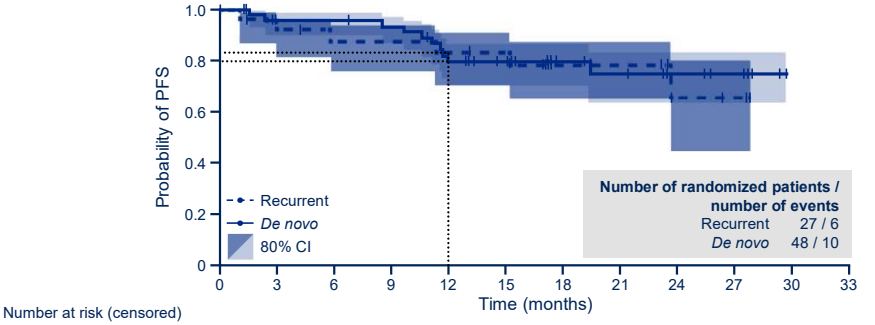
DCO was December 22, 2023

BOR, best overall response; CI, confidence interval; cORR, confirmed objective response rate; CR, complete response; DCO, data cutoff; HR, hormone receptor; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease; T-DXd, trastuzumab deruxtecan

Progression-free survival by subgroup

Disease status

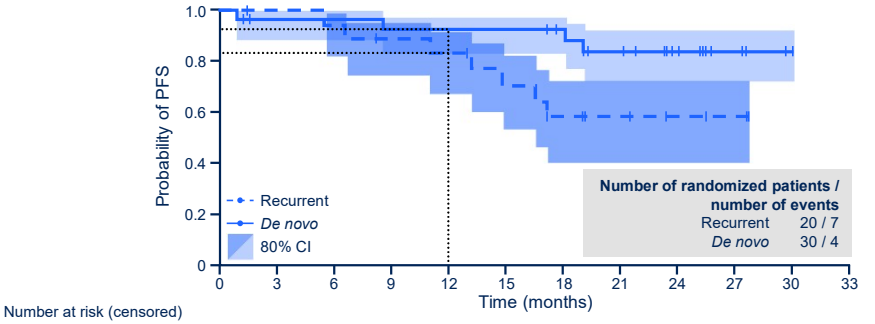
T-DXd monotherapy



Number at risk (censored)

Recurrent	27 (0)	22 (3)	20 (4)	20 (4)	19 (4)	18 (5)	10 (12)	9 (13)	3 (18)	2 (19)	0 (21)	0 (21)
De novo	48 (0)	43 (3)	43 (3)	41 (4)	34 (5)	29 (10)	17 (22)	15 (23)	10 (28)	6 (32)	0 (38)	0 (38)

T-DXd + pertuzumab

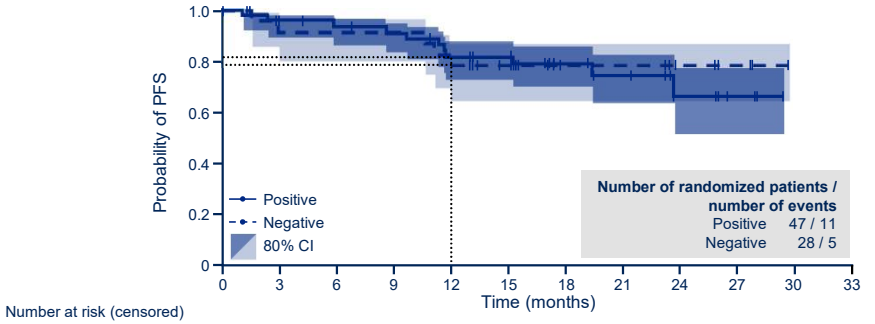


Number at risk (censored)

Recurrent	20 (0)	19 (1)	18 (1)	16 (2)	15 (2)	12 (3)	8 (5)	5 (8)	3 (10)	2 (11)	0 (13)	0 (13)
De novo	30 (0)	27 (2)	27 (2)	26 (2)	26 (2)	26 (2)	23 (5)	18 (8)	10 (16)	5 (21)	1 (25)	0 (26)

HR status

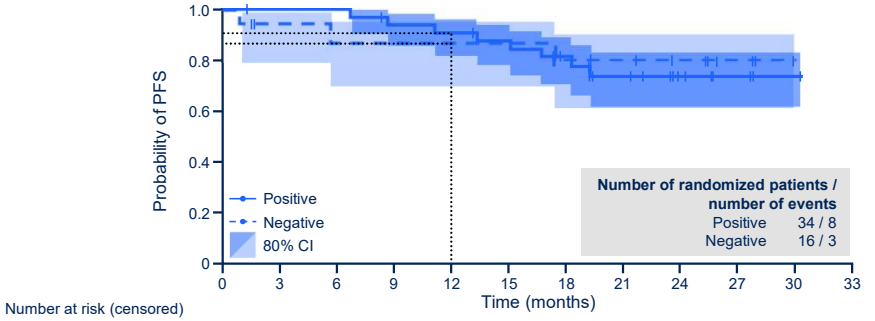
T-DXd monotherapy



Number at risk (censored)

Positive	47 (0)	44 (1)	42 (2)	40 (3)	35 (4)	33 (6)	18 (20)	15 (22)	7 (29)	4 (32)	0 (36)	0 (36)
Negative	28 (0)	21 (5)	21 (5)	21 (5)	18 (5)	14 (9)	9 (14)	9 (14)	6 (17)	4 (19)	0 (23)	0 (23)

T-DXd + pertuzumab



Number at risk (censored)

Positive	34 (0)	33 (1)	33 (1)	30 (2)	29 (2)	26 (3)	22 (6)	15 (11)	7 (19)	4 (22)	1 (25)	0 (26)
Negative	16 (0)	13 (2)	12 (2)	12 (2)	12 (2)	12 (2)	9 (4)	8 (5)	6 (7)	3 (10)	0 (13)	0 (13)

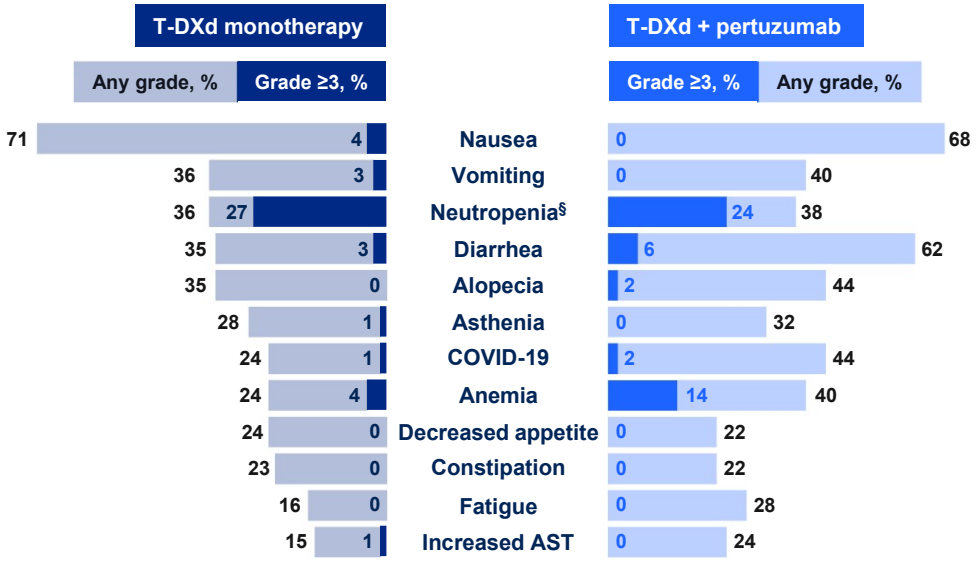
The number of PFS events is small, and most patients were censored

DCO was December 22, 2023. CI, confidence interval; DCO, data cutoff; HR, hormone receptor; PFS, progression-free survival, T-DXd, trastuzumab deruxtecan

Safety overview

	T-DXd monotherapy (n=75)	T-DXd + pertuzumab (n=50)
Median actual treatment duration, months (range)*		
T-DXd	16.3 (0.7–30.9)	17.8 (0.9–30.7)
Pertuzumab	N/A	17.6 (0.9–30.7)
Any AE, n (%)	75 (100)	50 (100)
Any AEs Grade ≥3, n (%)	39 (52.0)	31 (62.0)
AEs associated with drug interruptions of T-DXd, n (%)	44 (58.7)	32 (64.0)
AEs associated with dose reduction of T-DXd, n (%)	12 (16.0)	8 (16.0)
AEs associated with discontinuation of T-DXd, n (%)†	8 (10.7)	8 (16.0)
Any SAEs, n (%)	13 (17.3)	13 (26.0)
AEs leading to death, n (%)	1 (1.3)‡	0
AESIs, n (%)		
Pneumonitis (adjudicated as ILD related to T-DXd)	7 (9.3)	7 (14.0)
Grade 1	2 (2.7)	0
Grade 2	5 (6.7)	6 (12.0)
Grade 3	0	1 (2.0)
LV dysfunction (possibly related to T-DXd)	5 (6.7)	2 (4.0)

Any-grade AEs (>20% of patients in either module) with incidence of Grade ≥3 events



Grade 2 diarrhea events were reported in:
- **13.3%** of patients in the **T-DXd monotherapy** module
- **32.0%** of patients in the **T-DXd + pertuzumab** module

DCO was December 22, 2023

*Total treatment duration, excluding dose delays; †discontinuation of T-DXd due to toxicities resulted in the discontinuation of pertuzumab until resolved; ‡reported by investigator as non-treatment-related post-acute COVID-19 syndrome; §grouped term including neutropenia, decreased neutrophil count, and febrile neutropenia events

AE, adverse event; AESI, adverse event of special interest; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; DCO, data cutoff; ILD, interstitial lung disease; LV, left ventricular; N/A, not applicable; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan

Conclusions (1/2)

- This is the **first dataset** of **T-DXd monotherapy** and **T-DXd + pertuzumab** as **first-line treatment** for **HER2+ mBC**
- T-DXd monotherapy (n=75) and T-DXd + pertuzumab (n=50) showed robust efficacy:
  - **Confirmed ORR** was **76.0%** and **84.0%** for T-DXd monotherapy and T-DXd + pertuzumab, respectively
  - **Median DOR** was **not reached** for T-DXd monotherapy or T-DXd + pertuzumab
  - **PFS rate at 12 months** was **80.8%** and **89.4%** for T-DXd monotherapy and T-DXd + pertuzumab, respectively; the number of PFS events was small and most patients were censored
- There are **62.7%** and **56.0%** of patients receiving **ongoing study treatment**, with a **median duration of follow up** of **23.9 months** and **25.3 months**, in the T-DXd monotherapy and T-DXd + pertuzumab modules, respectively
- Encouraging clinical activity was observed with T-DXd monotherapy and T-DXd + pertuzumab in first-line HER2+ mBC, irrespective of disease status and HR status

DOR, duration of response; HER2+, human epidermal growth factor receptor 2–positive; HR, hormone receptor; mBC, metastatic breast cancer; ORR, objective response rate; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

Conclusions (2/2)

- The **safety profiles** of T-DXd and pertuzumab were **consistent** with their individual known profiles
  - The incidence of **ILD/pneumonitis events** was **9.3%** and **14.0%** in the T-DXd monotherapy and T-DXd + pertuzumab modules, respectively; there were **no ILD/pneumonitis-related deaths** in either module
- T-DXd monotherapy and T-DXd + pertuzumab are being evaluated versus THP, in patients with HER2+ mBC in the first-line setting, in the Phase 3 DESTINY-Breast09 clinical trial

HER2+, human epidermal growth factor receptor 2–positive; ILD, interstitial lung disease; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan; THP, taxane, trastuzumab, and pertuzumab

Acknowledgments

Thank you:

- **Patients and their families for their participation**
- **Study site staff for their contributions**
- **Members of the Safety Review Committee and its independent Chair, Dr. Kathy Miller, for their support**

This study was sponsored and designed by:

AstraZeneca
Daiichi Sankyo

Supplementary content is available:

- Plain language summary infographic

More highlights for T-DXd in HER2+ mBC

Poster session: June 2, 2024; 9:00 AM–12:00 PM

DB-03 OS update: abstract ID #1025

Pooled analysis by best confirmed response from DB-01, -02, -03: abstract ID #1023

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DB, DESTINY-Breast; HER2+, human epidermal growth factor receptor 2–positive; mBC, metastatic breast cancer; OS, overall survival; QR, quick response; T-DXd, trastuzumab deruxtecan