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Annual Congress

DESTINY-Breast06 post-hoc analysis by physician's choice of chemotherapy (TPC): efficacy and safety of trastuzumab deruxtecan (T-DXd) vs TPC in hormone receptor–positive, HER2-low or -ultralow metastatic breast cancer

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DESTINY Breast06

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

Declaration of interests

Carlos H Barrios

Commercial interests	Nature of relationship
AstraZeneca, Libbs, Lilly, MSD Oncology, Novartis, Pfizer, Roche/Genentech, United Medical	Consulting fees
Adium Pharma, AstraZeneca, Bayer, Daiichi Sankyo, Eisai, Lilly, MSD, Novartis, Pfizer, Roche/Genentech, Sanofi, Zodiac Pharma	Payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events
AstraZeneca, BMS Brazil, Lilly, MSD Oncology, Novartis, Pfizer, Roche/Genentech	Support for attending meetings and/or travel
MedSIR, Tummi	Stock or stock options

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Background and objective

PFS in ITT (HER2-low and HER2-ultralow)[1]

Hazard ratio 0.64; P<0.001
(95% CI 0.54, 0.76)

In **DESTINY-Breast06** (DB-06), T-DXd demonstrated a **statistically significant** and **clinically meaningful PFS (by BICR) benefit** versus TPC in HR+, HER2-low or HER2-ultralow mBC after ≥1 ET in the metastatic setting[1]

T-DXd also demonstrated a **clinically meaningful PFS2 (by investigator) benefit**[2]

The primary analysis led to the FDA approval of T-DXd in this population, as determined by an FDA-approved test, and EU approval for patients who are not considered suitable for subsequent ET as the next line of treatment[3,4]

This post-hoc analysis of DB-06 explores efficacy and safety outcomes for T-DXd versus TPC type (capecitabine or taxane) in the ITT (HER2-low and HER2-ultralow) population

The ITT population was defined as all randomized patients
BICR, blinded independent central review; CI, confidence interval; ET, endocrine therapy; EU, European Union; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; ITT, intent-to-treat; mBC, metastatic breast cancer; PFS, progression-free survival; PFS2, time from randomization to second progression or death; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy

1. Bardia A, et al. *N Engl J Med*. 2024;391:2110–2122; 2. Bardia A, et al. Oral presentation at SABCS 2024 (Abstract LB1-04); 3. Fam-trastuzumab deruxtecan-nxki: highlights of prescribing information. 2025. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761139s032s035lbl.pdf (Accessed May 8, 2025); 4. Trastuzumab deruxtecan: summary of product characteristics. 2025. Available from: https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf (Accessed May 8, 2025)

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DB-06 study design

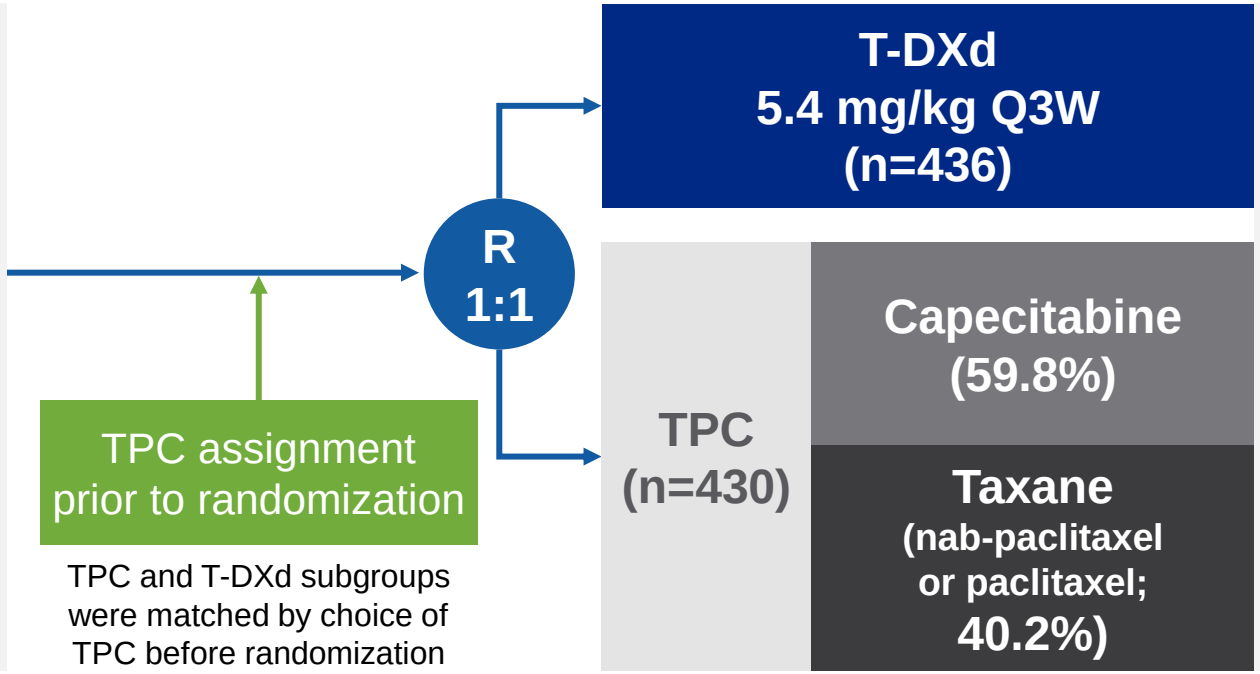
A Phase 3, randomized, multicenter, open-label study (NCT04494425)[1,2]

Patient population

- HR+, HER2-low (IHC 1+ or IHC 2+/ISH−) or HER2-ultralow (IHC 0 with membrane staining) mBC
- Chemotherapy naïve in the mBC setting

Prior therapy

- ≥2 lines of ET ± targeted therapy for mBC **OR**
- 1 line for mBC **AND**
  - Progression ≤6 months of starting first-line ET + CDK4/6i **OR**
  - Recurrence ≤24 months of starting adjuvant ET



Outcomes in this analysis (in ITT)

- PFS (BICR)
- ORR
- DOR
- PFS2
- Safety

Median duration of follow up: 18.2 months (ITT)[2]

BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; IHC, immunohistochemistry; ISH, in situ hybridization; ITT, intent-to-treat; mBC, metastatic breast cancer; ORR, objective response rate; PFS, progression-free survival; PFS2, time from randomization to second progression or death; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy

1. NCT04494425. Updated April 2, 2025. Available from: https://clinicaltrials.gov/study/NCT04494425 (Accessed May 8, 2025); 2. Bardia A, et al. *N Engl J Med*. 2024;391:2110–2122

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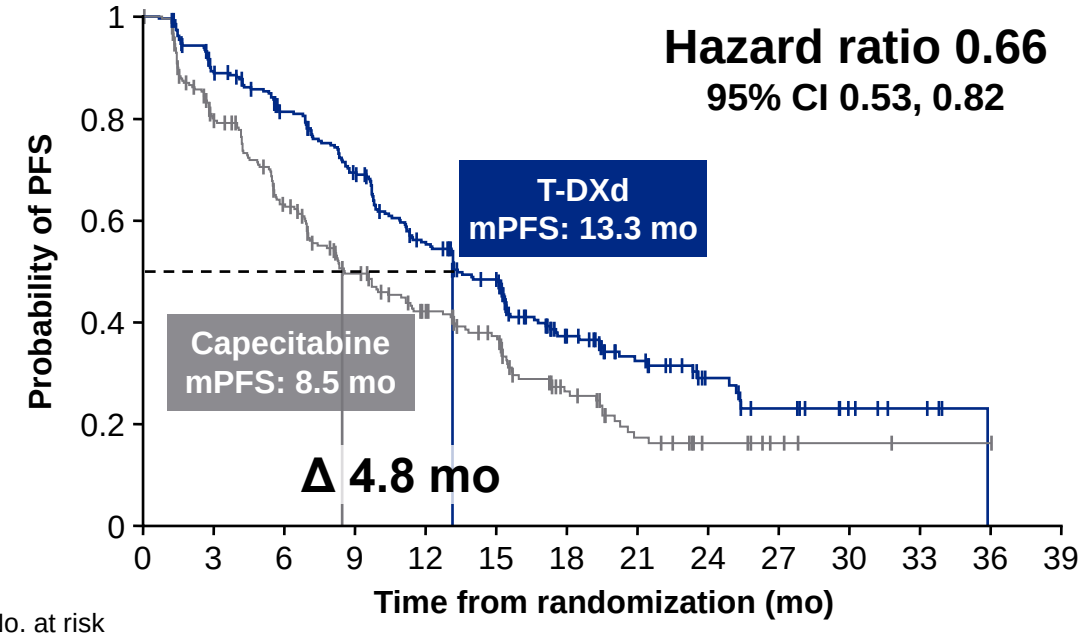
PFS (BICR)

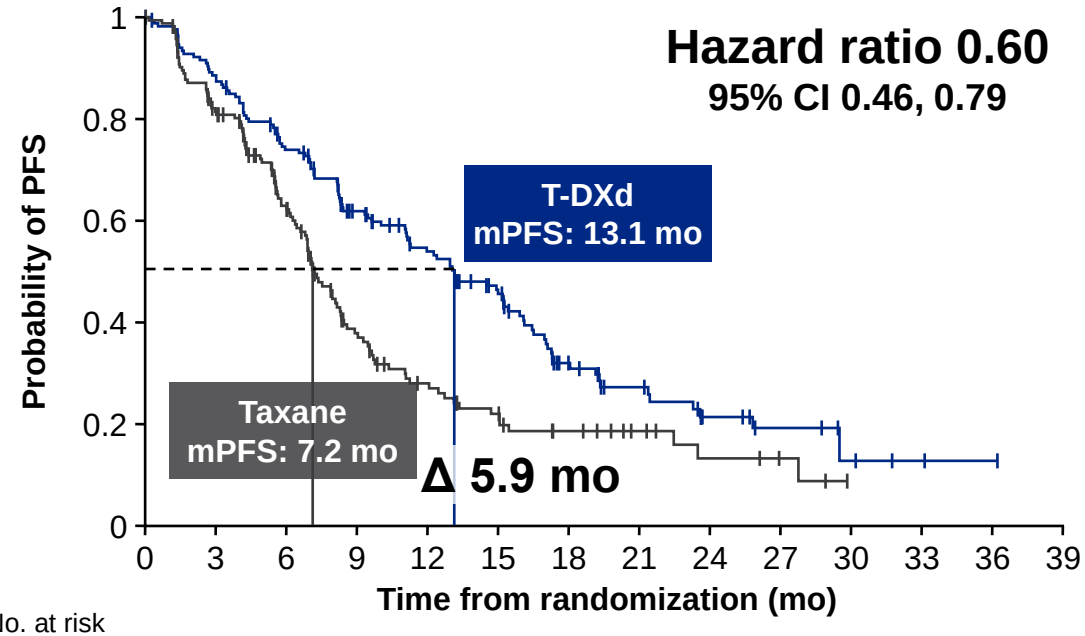
T-DXd (n=266) versus capecitabine (n=257; 59.8% of TPC group)



No. at risk

T-DXd	266	228	199	167	126	100	53	36	20	13	7	4	0	0
Capecitabine	257	178	136	98	74	58	30	16	8	4	2	1	1	0

T-DXd (n=170) versus taxane (n=173; 40.2% of TPC group)



No. at risk

T-DXd	170	147	120	91	73	56	29	20	12	8	4	2	1	0
Taxane	173	128	88	44	29	21	14	9	5	3	0	0	0	0

T-DXd demonstrated improvements in median PFS regardless of type of TPC

Progression was determined by BICR according to RECIST 1.1
BICR, blinded independent central review; CI, confidence interval; mo, months; (m)PFS, (median) progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy

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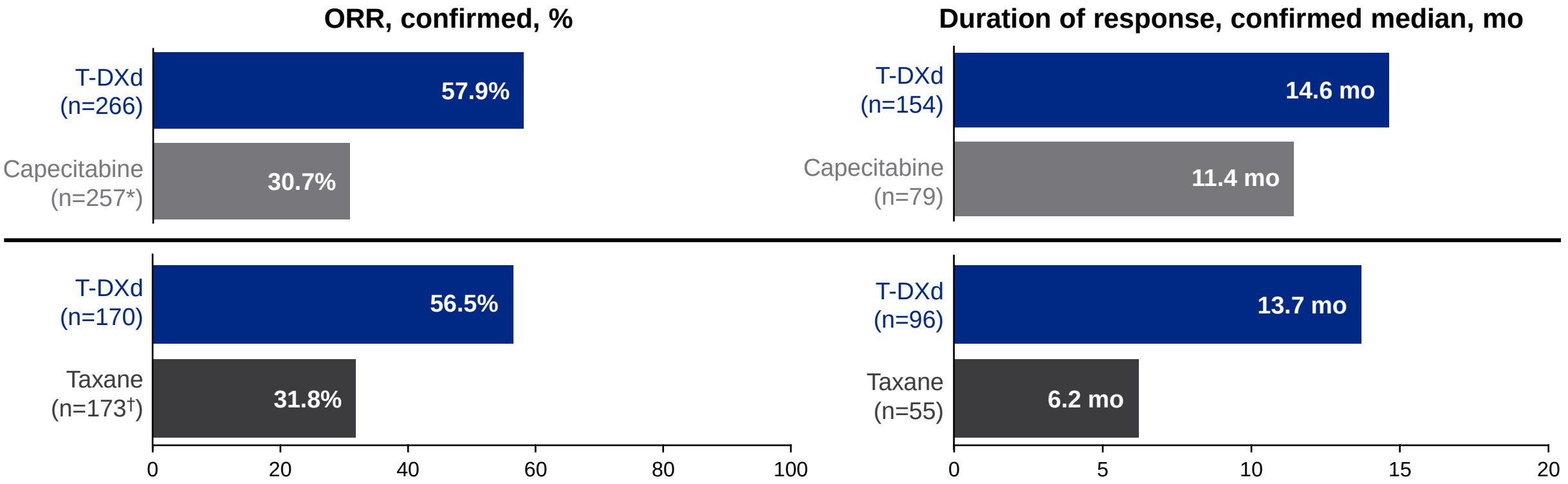
Confirmed ORR and DOR according to RECIST 1.1 by BICR



T-DXd improved confirmed ORR and DOR versus both TPC subgroups, with an approximate two-fold increase in ORR and a DOR of more than 1 year

Responses required confirmation after 4 weeks. Median DOR calculated using the Kaplan-Meier technique. *59.8% of TPC group; †40.2% of TPC group
BICR, blinded independent central review; DOR, duration of response; mo, months; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy

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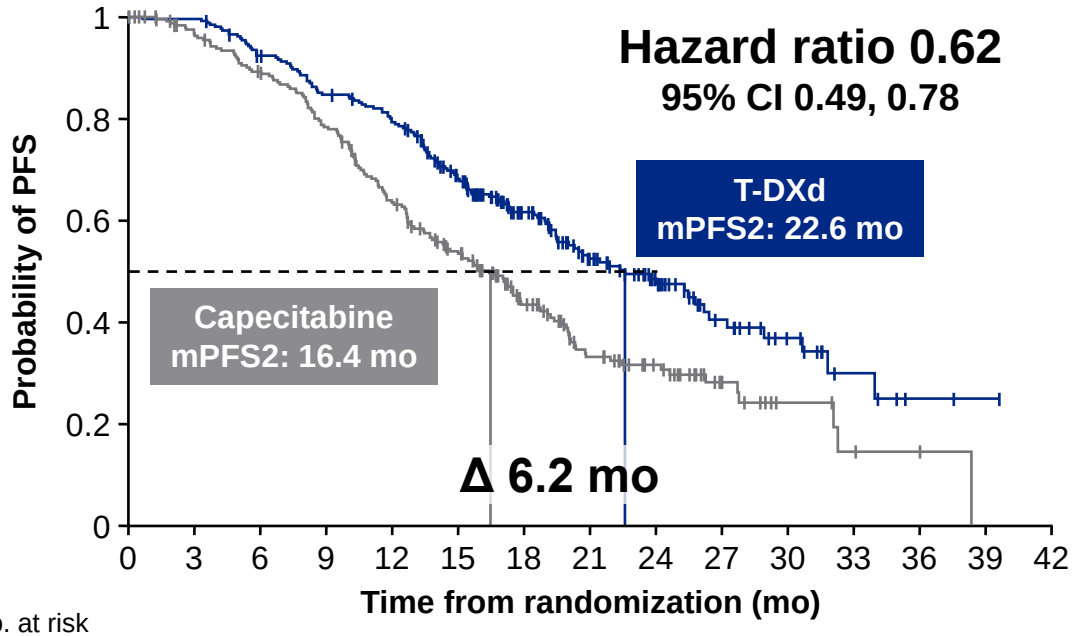
PFS2 (investigator assessed)

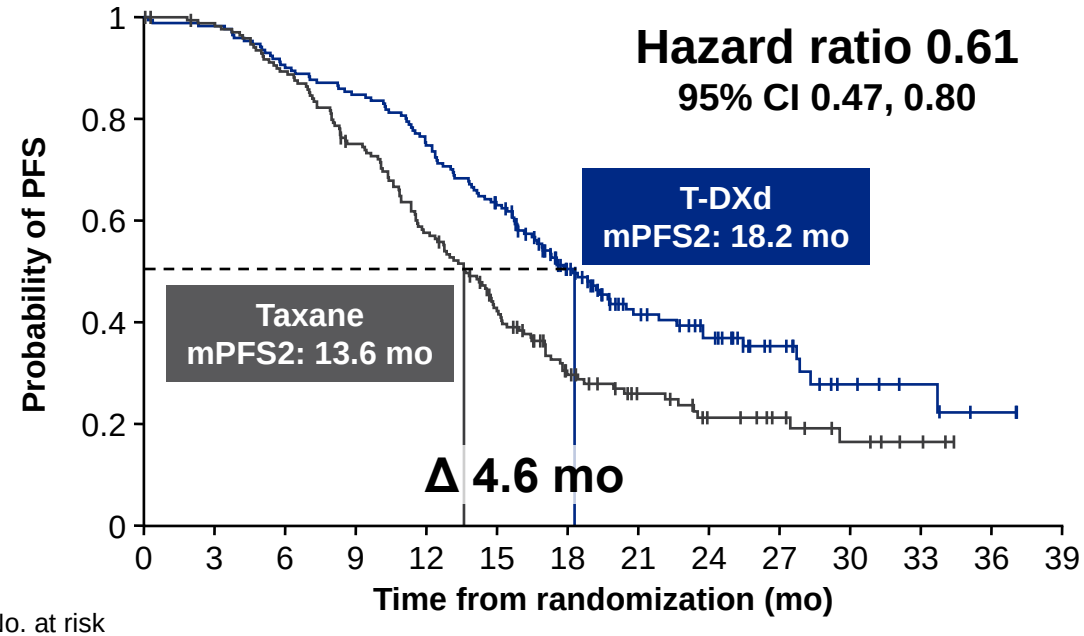
T-DXd (n=266) versus capecitabine (n=257; 59.8% of TPC group)



No. at risk

T-DXd	266	264	242	221	205	163	112	75	48	26	15	6	2	1	0
Capecitabine	257	234	215	187	149	117	72	46	33	15	6	3	2	0	0

T-DXd (n=170) versus taxane (n=173; 40.2% of TPC group)



No. at risk

T-DXd	170	167	154	144	127	105	64	40	30	17	8	5	2	0	
Taxane	173	165	150	124	95	66	37	23	15	11	6	3	0	0	

Treatment with T-DXd was associated with an improved PFS2 versus capecitabine and taxane, with a 6.2-month improvement in median PFS2 compared with capecitabine

Second progression was determined by the investigator according to local standard clinical practice
CI, confidence interval; mo, months; (m)PFS2, (median) time from randomization to second progression or death; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy

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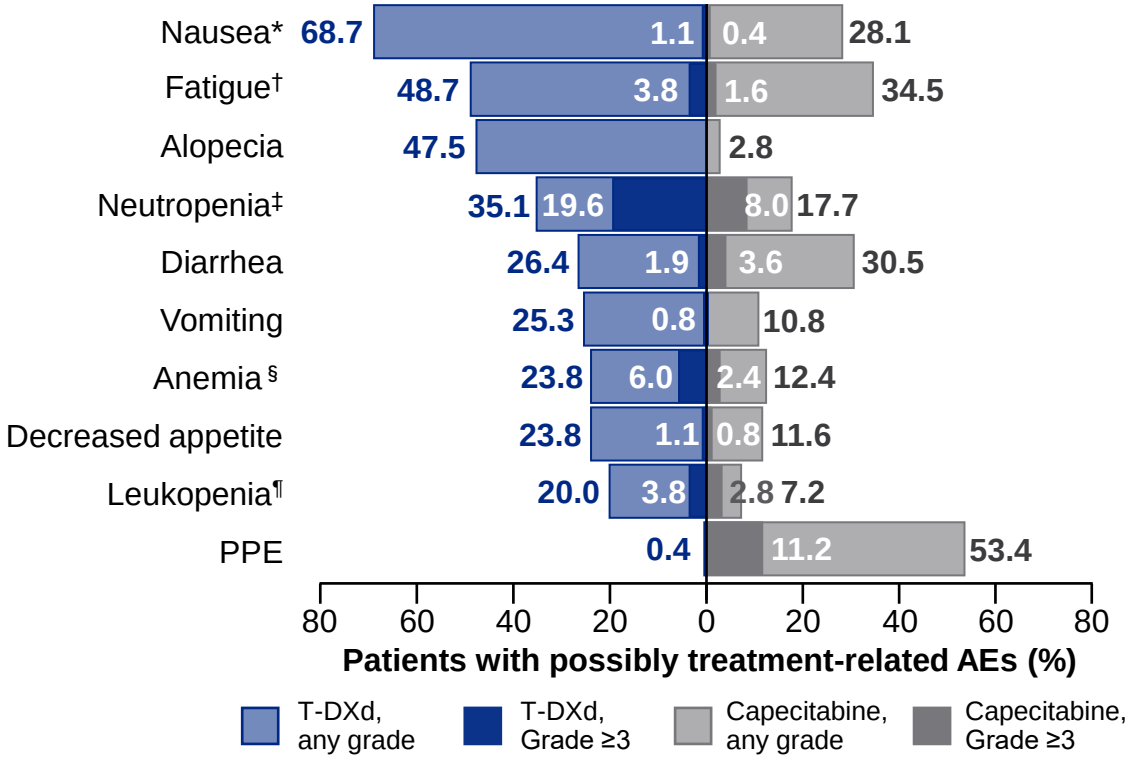
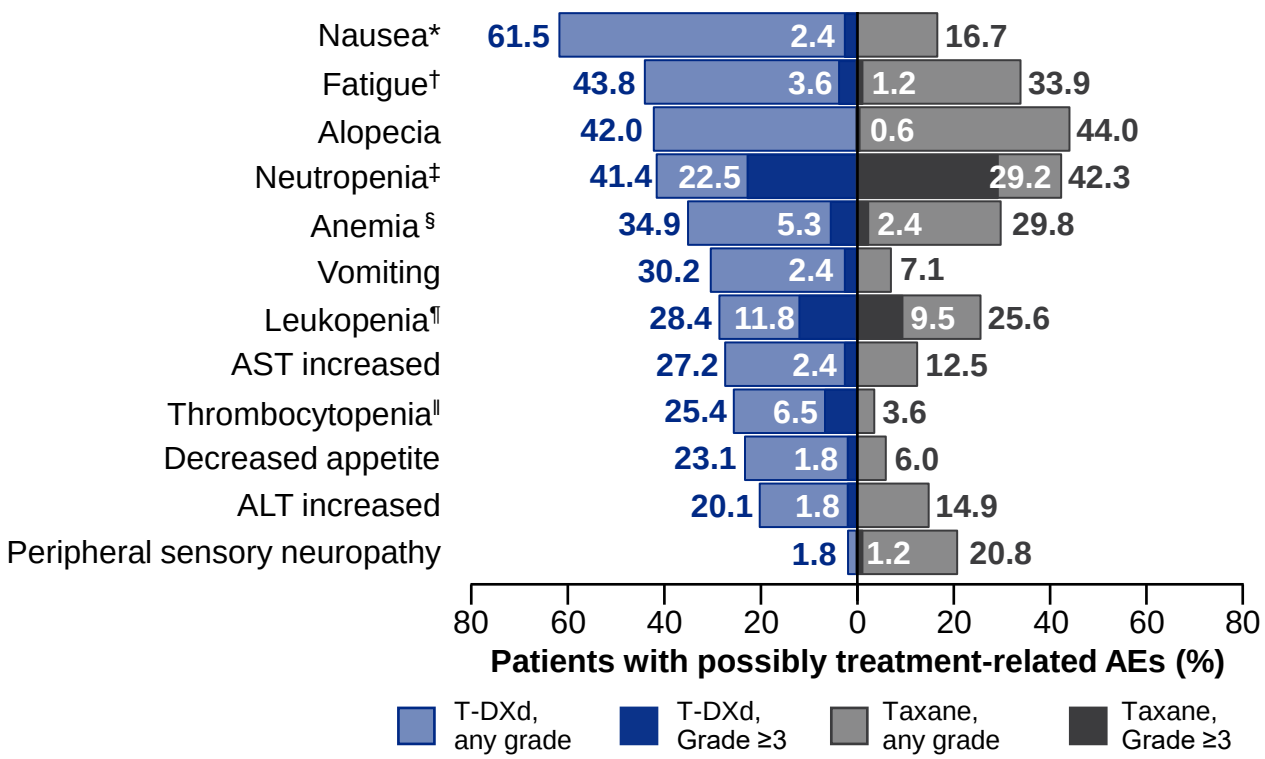
Treatment-related AEs in ≥20% of patients

T-DXd (n=265) versus capecitabine (n=249; 59.8% of TPC group)



T-DXd (n=169) versus taxane (n=168; 40.2% of TPC group)



Neutropenia was the most common Grade ≥3 treatment-related AE with T-DXd and taxane, with similar rates; in capecitabine, the most common Grade ≥3 treatment-related AE was PPE, with rates exceeding 10%

*Use of antiemetic agents was recommended, but not mandated, prior to each dose of T-DXd for prevention of chemotherapy-induced nausea and vomiting; †includes the preferred terms fatigue, asthenia, malaise, and lethargy; ‡includes the preferred terms neutropenia and neutrophil count decreased; §includes the preferred terms anemia, hemoglobin decreased, hematocrit decreased, and red blood cell count decreased; ¶includes the preferred terms leukopenia and white blood cell count decreased; ‖includes the preferred terms platelet count decreased and thrombocytopenia
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPE, palmar-plantar erythrodysesthesia; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy

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Overall and exposure-adjusted safety outcomes across subgroups

	T-DXd (n=265)	Capecitabine (n=249)	T-DXd (n=169)	Taxane (n=168)
Total exposure, patient years	271.79	171.59	166.67	91.94
TEAEs Grade ≥3, n (%)	138 (52.1)	107 (43.0)	91 (53.8)	78 (46.4)
EAIR per patient year	0.51	0.62	0.55	0.85
TEAEs associated with drug interruptions, n (%)	138 (52.1)	92 (36.9)	72 (42.6)	68 (40.5)
EAIR per patient year	0.51	0.54	0.43	0.74
TEAEs associated with dose reduction, n (%)	59 (22.3)	113 (45.4)	48 (28.4)	48 (28.6)
EAIR per patient year	0.22	0.66	0.29	0.52
TEAEs associated with treatment discontinuation, n (%)	39 (14.7)	15 (6.0)	23 (13.6)	24 (14.3)
EAIR per patient year	0.14	0.09	0.14	0.26
TEAEs leading to death, n (%)	5 (1.9)	6 (2.4)	6 (3.6)	0
EAIR per patient year	0.02	0.03	0.04	0

When adjusted for treatment duration, the overall safety profile of T-DXd was generally similar to or better than that of capecitabine or taxane

Includes AEs with an onset date or worsening on or after the date of first dose and up to and including 47 days following the date of last dose of study medication or before the initiation of the first subsequent cancer therapy (whichever occurs first). Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. EAIR was defined as the number of patients with at least one event divided by the sum of the patient years of exposure among all the patients in the treatment group

AE, adverse event; EAIR, exposure-adjusted incidence rate; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event

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Conclusions

In this analysis of DB-06, **T-DXd demonstrated a clinically meaningful efficacy benefit over both TPC subgroups**, with improved PFS, ORR, DOR, and PFS2

Safety outcomes for T-DXd were consistent with those previously reported

These findings further support T-DXd as an effective treatment option in HR+, HER2-low or HER2-ultralow mBC after ≥1 ET, with demonstrable benefits over treatment with capecitabine or a taxane (nab-paclitaxel or paclitaxel)

Thank you to the patients and their families for their participation and the study-site staff for their contributions

A separate DB-06 PRO analysis showed that the **safety profile of T-DXd did not impact QOL outcomes** when compared with either capecitabine or taxane[1]

Scan here to access a link to the PRO manuscript, as well as a copy of this presentation's abstract, slides, supplementary data, and infographic PLS

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DOR, duration of response; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; iPLS, infographic plain language summary; mBC, metastatic breast cancer; ORR, objective response rate; PFS, progression-free survival; PFS2, time from randomization to second progression or death; PRO, patient-reported outcome; QOL, quality of life; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy

1. Hu X, et al. *ESMO Open*. 2025;doi 10.1016/j.esmoop.2025.105082: May 15 [Epub ahead of print]

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