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ORIGINAL ARTICLE

Trastuzumab deruxtecan in hormone receptor-positive, HER2-low/-ultralow metastatic breast cancer (DESTINY-Breast06): outcome analyses by time to progression on prior first-line endocrine therapy with CDK4/6 inhibitor and baseline burden of disease

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Background: In DESTINY-Breast06, trastuzumab deruxtecan (T-DXd) improved progression-free survival (PFS) versus physician's choice of chemotherapy (TPC) for patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-low/-ultralow metastatic breast cancer (mBC), without new safety signals. We report additional analyses exploring outcomes for patients with characteristics that affect prognosis.

Patients and methods: Patients were randomly assigned 1 : 1 to receive T-DXd (5.4 mg/kg) once every 3 weeks or TPC. Subgroups were specified *post hoc* from the intent-to-treat population ($N = 866$). Outcomes were PFS, objective response rate (ORR), and duration of response (DOR) by blinded independent central review via RECIST 1.1. Time from randomization until second progression or death (PFS2) by investigator and safety were also assessed.

Results: Within subgroups, baseline disease characteristics and prior therapies were balanced across treatments. Median PFS (95% confidence interval) favored T-DXd versus TPC regardless of time to progression (TTP) on prior first-line endocrine therapy (ET) + cyclin-dependent kinase 4 and 6 inhibitor (CDK4/6i): <6 months: 14.0 (11.2-15.9) versus 6.5 (4.2-8.4) months for T-DXd versus TPC; 6-12 months: 13.2 (8.6-16.4) versus 6.9 (4.3-10.4) months; >12 months: 12.9 (9.8-17.1) versus 8.2 (6.9-10.9) months. A consistent PFS benefit with T-DXd over TPC was observed for patients with primary or secondary endocrine resistance, and across indicators of high or low disease burden (defined as visceral/non-visceral disease, presence/absence of liver metastases, three or more/less than three disease sites, and >median/≤median baseline tumor size). In all subgroups, confirmed ORR favored T-DXd (36.7% to 67.7%) versus TPC (16.7% to 37.5%), and median DOR (confirmed response) was longer with T-DXd. T-DXd also prolonged PFS2 versus TPC across subgroups. Safety profiles of T-DXd and TPC in subgroups were consistent with the overall safety population.

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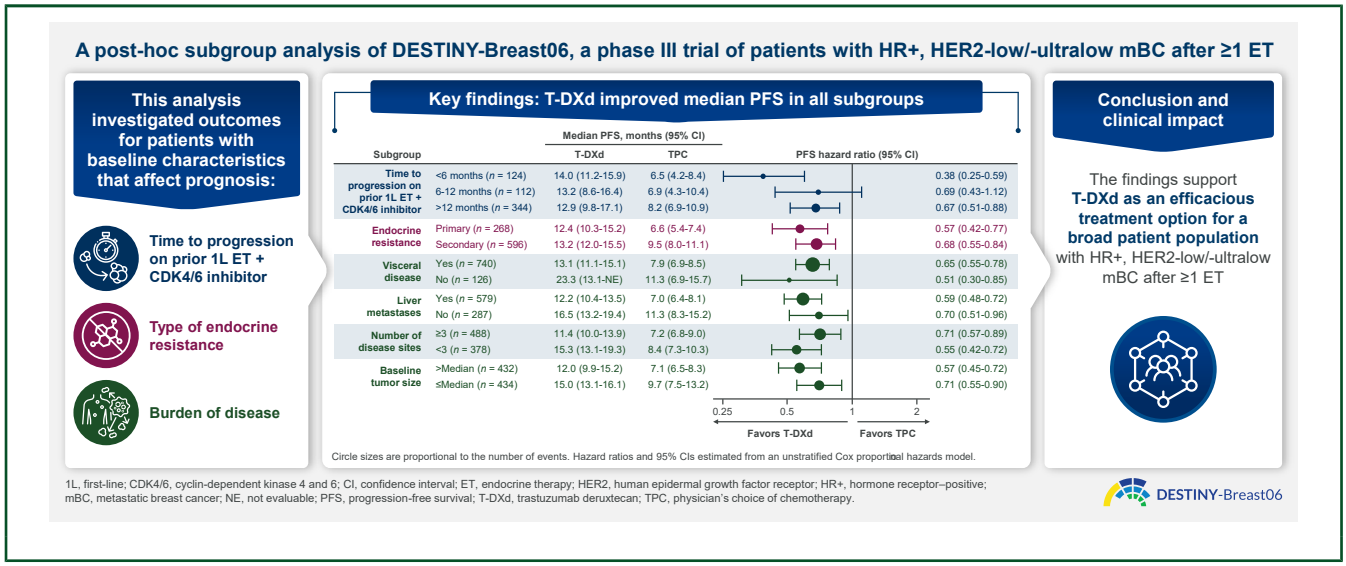
Conclusions: These data support T-DXd as a broadly efficacious treatment for patients with HR-positive, HER2-low/-ultralow mBC after one or more ETs, regardless of TTP on prior first-line ET + CDK4/6i, endocrine resistance, or disease burden.

Key words: metastatic breast cancer, trastuzumab deruxtecan, subgroup analysis, endocrine resistance, burden of disease, time to progression

GRAPHICAL ABSTRACT



INTRODUCTION

For patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (mBC), first-line (1L) treatment is endocrine therapy (ET) with a cyclin-dependent kinase 4 and 6 inhibitor (CDK4/6i), which provides a favorable median progression-free survival (PFS) of at least 2 years.[1-4] However, the benefit of ET decreases following exposure to 1L CDK4/6i, with a median PFS range of 1.9-5.5 months when using ET-based regimens in second line and later.[5,6] Better treatment options after ET are needed, given that conventional single-agent chemotherapy in later lines offers limited efficacy benefit (median PFS range of 5.7-8.0 months when used as the first systemic therapy).[7,8] Patients with characteristics that can affect prognosis represent an additional clinical challenge in this setting; among other factors, a poorer response to, and shorter duration of, prior therapy (including ET), a greater number of metastatic sites, and specific sites of metastases (such as liver) are associated with worse PFS and overall survival.[9]

Individualized treatment is becoming increasingly important in the management of HR-positive mBC, tailored by actionable tumor biomarkers, such as positive HER2 expression and presence of *PIK3CA*- *or ESR1*-activating mutations.[2,3] It is becoming evident that breast cancers traditionally classified as 'HER2-negative' can actually exhibit some level of HER2 expression, and can be now categorized as 'HER2-low' [immunohistochemistry (IHC) 1+ or IHC 2+/*in situ* hybridization-negative] or 'HER2-ultralow' (IHC 0 with membrane staining) and may be sensitive to HER2-directed treatments.[10-12]

Trastuzumab deruxtecan (T-DXd) is an antibody—drug conjugate consisting of an anti-HER2 antibody, cleavable linker, and topoisomerase I inhibitor payload.[13,14] Based on results of the phase III DESTINY-Breast04 trial, T-DXd was approved globally for patients with unresectable or metastatic HER2-low breast cancer who received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.[15,16] The phase III DESTINY-Breast06 trial evaluated T-DXd compared with physician's choice of chemotherapy (TPC) for patients with HR-positive, HER2-low or HER2-ultralow mBC who received one or more prior lines of endocrine-based therapy. In the primary analysis, T-DXd showed a statistically significant and clinically meaningful PFS benefit versus TPC in the HER2-low population, with consistent results in the intent-to-treat (ITT; HER2-low and HER2-ultralow) population {median PFS [95% confidence interval (CI)] by blinded independent central review (BICR) in ITT of 13.2 (12.0-15.2) months for T-DXd versus 8.1 (7.0-9.0) months for TPC; hazard ratio 0.64, 95% CI 0.54-0.76, $P < 0.001$}, and no new safety signals were identified.[12] T-DXd was subsequently approved in the USA and European Union, the latter for patients with HR-positive, HER2-low or HER2-ultralow unresectable breast cancer or mBC, who have received at

least one ET in the metastatic setting and are not considered to be suitable for ET as the next line of treatment.[15,16]

We conducted additional analyses of DESTINY-Breast06 to explore the potential benefit of T-DXd for patients with characteristics known to affect prognosis. In this article, we report the efficacy and safety outcomes by time to progression on prior 1L ET + CDK4/6i, type of endocrine resistance, or burden of disease.

PATIENTS AND METHODS

Trial design and patients

Complete methods have been published previously.[12] In brief, DESTINY-Breast06 (NCT04494425) is a phase III, open-label, multicenter, randomized trial of patients with HR-positive, HER2-low or HER2-ultralow mBC. Patients must have had disease progression after receiving at least two previous lines of ET for metastatic disease. Patients were also eligible after one previous line if they had disease recurrence within the first 24 months after starting adjuvant ET or within 6 months after starting 1L ET with CDK4/6i for metastatic disease. Patients must not have previously received chemotherapy for advanced or metastatic disease. Participants were randomly assigned 1 : 1 to receive either T-DXd (5.4 mg/kg intravenously) once every 3 weeks or TPC (capecitabine, nab-paclitaxel, or paclitaxel). Treatment with study medication continued until disease progression or unacceptable toxicity.

Trial oversight

The trial was sponsored and designed by AstraZeneca in collaboration with Daiichi Sankyo. It was approved by the institutional review board or ethics committee at each investigational site before initiation and conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and local regulations on the conduct of clinical research. All patients provided written informed consent.

Patient subgroups

To explore previous responses to ET, analyses were conducted according to the time to progression on prior 1L ET + CDK4/6i (<6 months, 6-12 months, or >12 months) and type of endocrine resistance (primary or secondary). Endocrine resistance was assessed by investigators per the fifth European School of Oncology—European Society for Medical Oncology Advanced Metastatic Breast Cancer criteria. Primary endocrine resistance was defined as relapse in the first 2 years of adjuvant ET, or progression of disease within the first 6 months of 1L ET for mBC. Secondary (acquired) endocrine resistance was defined as relapse after the first 2 years of adjuvant ET, or relapse within 12 months of completing adjuvant ET, or progression of disease at least 6 months after initiating ET for mBC.[17] To explore the impact of baseline burden of disease, the following subgroups were analyzed: visceral disease (yes or no), liver metastases (yes or no), number of disease sites (three or more or less than three), and tumor size (>median or ≤median). Baseline tumor size was determined by BICR according to RECIST 1.1.[18] Non-measurable, bone-only disease was permitted as per the trial entry criteria and recorded as a baseline tumor size of 0 mm.

Outcome measures

The primary data cut-off (18 March 2024) was used for subgroup analyses. Efficacy outcome measures evaluated in subgroups were PFS, objective response rate (ORR), and duration of response (DOR) (all by BICR according to RECIST 1.1[18]), and randomization to second progression or death (PFS2). PFS2 was defined by investigators according to local standard clinical practice as the earliest progression event during the first subsequent treatment after discontinuation of study treatment and may have involved any of the following: objective radiological imaging, symptomatic progression, or death. All efficacy outcomes were assessed in the ITT population. Safety outcomes were assessed in the safety analysis set, which included all patients who received at least one dose of study treatment.

Statistical analysis

Subgroups were specified *post hoc* from the overall ITT population. No adjustment to the significance level of the primary analysis was carried out because all subgroup analyses were considered to be exploratory and could only be supportive of the primary analysis of PFS in the HER2-low population.[12] No formal statistical testing was conducted. Hazard ratios and corresponding 95% CIs for PFS and PFS2 were estimated from an unstratified Cox proportional hazards model only containing a term for treatment. Median time to event was calculated using the Kaplan—Meier technique, and corresponding CIs were based on the Brookmeyer—Crowley method. CIs for confirmed ORR were calculated using the Clopper—Pearson method. CIs were not adjusted for multiplicity.

RESULTS

Baseline characteristics

The ITT population comprised 866 patients; 436 patients were randomly assigned to receive T-DXd and 430 patients to TPC (59.8% capecitabine, 24.4% nab-paclitaxel, and 15.8% paclitaxel).

Time to progression on prior 1L ET + CDK4/6i. Overall, 773 patients (89.3%) had at least one prior line of ET + CDK4/6i in the metastatic setting (in any line). The time-to-progression subgroup analysis included 570 patients (65.8% of the ITT) who received prior ET + CDK4/6i as their 1L treatment for mBC. Of these patients, 124 (21.8%) had a time to progression of <6 months, 112 (19.6%) had 6-12 months, and 334 (58.6%) had >12 months. Baseline disease characteristics and prior therapies were balanced across treatments in each subgroup (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.

2026.02.015). In the <6-month subgroup, 20.2% of patients had *de novo* disease at diagnosis, compared with 42.0% in the 6- to 12-month and 37.4% in the >12-month subgroups. As in the ITT population, the incidence of bone-only disease at baseline was low across the subgroups, with a relatively higher proportion among those in the >12-month subgroup (5.1%; $n = 17$) than in the <6-month (0.8%; $n = 1$) and 6- to 12-month (1.8%; $n = 2$) subgroups. Overall, there was a higher proportion of prior adjuvant/neoadjuvant ET and chemotherapy use among the <6-month subgroup (74.2% and 63.7%, respectively) than among the 6- to 12-month (51.8% and 46.4%, respectively) and >12-month subgroups (53.3% and 45.2%, respectively).

Endocrine resistance. The endocrine resistance analysis included 864 patients, of whom 268 (31.0%) had primary endocrine resistance and 596 (69.0%) had secondary endocrine resistance. Baseline disease characteristics and prior therapies were balanced across treatments in each subgroup (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2026.02.015). In the primary subgroup, 13.8% of patients had *de novo* disease at diagnosis, compared with 38.3% of the secondary subgroup. Although the incidence of bone-only disease was low overall, this was relatively higher in those with secondary endocrine resistance (4%; $n = 24$) than in those with primary endocrine resistance (0.7%; $n = 2$). As expected, a greater proportion of patients with primary endocrine resistance received only one prior line of ET for mBC than those with secondary endocrine resistance (49.8% versus 2.5%, respectively), who more frequently received two or at least three prior lines. Patients with primary endocrine resistance also had more frequent use of prior adjuvant/neoadjuvant ET (82.8%) and chemotherapy (69.0%) than those with secondary endocrine resistance (51.5% versus 46.3%, respectively).

Burden of disease. The burden-of-disease subgroups included the following: 740 patients (85.5%) with visceral disease and 126 patients (14.5%) without; 579 patients (66.9%) with liver metastases and 287 patients (33.1%) without; 488 patients (56.4%) with three or more disease sites at baseline and 378 patients (43.6%) with less than three disease sites; and 432 patients (49.9%) with >median tumor size and 434 patients (50.1%) with ≤median tumor size. Median baseline tumor size in the ITT population was 48.6 mm. In total, 26 randomized patients (3.0%) had bone-only disease. In each burden-of-disease category, baseline characteristics and prior therapies were balanced across treatment groups (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2026.02.015). Patients with visceral disease had a lower proportion of *de novo* disease (28.9%) than those without (40.5%). Patients with three or more disease sites had a higher proportion of *de novo* disease (36.1%) than those with less than three disease sites (23.5%). The frequency of bone-only disease was higher in patients with baseline tumor size ≤median (5.5%; $n = 24$) than in those with baseline tumor size >median (0.5%; $n = 2$). Patients with three or more disease sites had relatively lower use of prior adjuvant/neoadjuvant ET (56.1%) and chemotherapy (48.6%) compared with those with less than three disease sites (68.0% and 59.5%, respectively).

Efficacy

Time to progression on prior 1L ET + CDK4/6i. T-DXd improved PFS regardless of time to progression on prior 1L ET + CDK4/6i. Median PFS (95% CI) for T-DXd versus TPC, respectively, was 14.0 (11.2-15.9) versus 6.5 (4.2-8.4) months (hazard ratio 0.38, 95% CI 0.25-0.59) in the <6-month subgroup, 13.2 (8.6-16.4) versus 6.9 (4.3-10.4) months (hazard ratio 0.69, 95% CI 0.43-1.12) in the 6- to 12-month subgroup, and 12.9 (9.8-17.1) versus 8.2 (6.9-10.9) months (hazard ratio 0.67, 95% CI 0.51-0.88) in the >12-month subgroup (Figure 1A). Confirmed ORR (95% CI) for T-DXd versus TPC, respectively, was 67.7% (54.9% to 78.8%) versus 25.4% (15.0% to 38.4%) in the <6-month subgroup, 60.0% (46.5% to 72.4%) versus 28.8% (17.1% to 43.1%) in the 6- to 12-month subgroup, and 59.5% (51.7% to 67.0%) versus 33.1% (26.0% to 40.8%) in the >12-month subgroup (Figure 1B). For those with a confirmed response, the median DOR was longer with T-DXd than with TPC in all subgroups (Figure 1C). T-DXd improved PFS2 compared with TPC across all subgroups, with medians (95% CI) of 18.9 (14.4-24.0) versus 15.2 (10.9-17.5) months in the <6-month subgroup, 17.1 (13.9-31.8) versus 13.7 (10.4-17.2) months in the 6- to 12-month subgroup, and 20.0 (18.6-25.3) versus 14.3 (12.7-15.9) months in the >12-month subgroup (Figure 1D).

Anticancer therapies received in the immediate line after discontinuation of study treatment in the overall population are provided in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2026.02.015. Among those who received therapy in the immediate line after discontinuation (T-DXd, $n = 282$; TPC, $n = 326$), chemotherapy was documented in 46.6% of patients in the T-DXd group and 47.7% of patients in the TPC group. Use of antibody–drug conjugates, which included T-DXd, was documented in 1.8% and 9.3% of patients in the T-DXd and TPC groups, respectively.

Endocrine resistance. PFS was longer with T-DXd than with TPC regardless of the type of endocrine resistance (Figure 2A). In the primary endocrine resistance subgroup, median PFS (95% CI) was 12.4 (10.3-15.2) versus 6.6 (5.4-7.4) months, respectively (hazard ratio 0.57, 95% CI 0.42-0.77). In the secondary endocrine resistance subgroup, median PFS was 13.2 (12.0-15.5) versus 9.5 (8.0-11.1) months, respectively (hazard ratio 0.68, 95% CI 0.55-0.84). Confirmed ORR (95% CI) was 57.8% (48.8% to 66.5%) with T-DXd versus 25.7% (18.7% to 33.8%) with TPC in the primary endocrine resistance subgroup, and 57.1% (51.4% to 62.7%) with T-DXd versus 34.0% (28.6% to 39.8%) with TPC in the secondary endocrine resistance subgroup (Figure 2B). Median DOR was longer with T-DXd than with

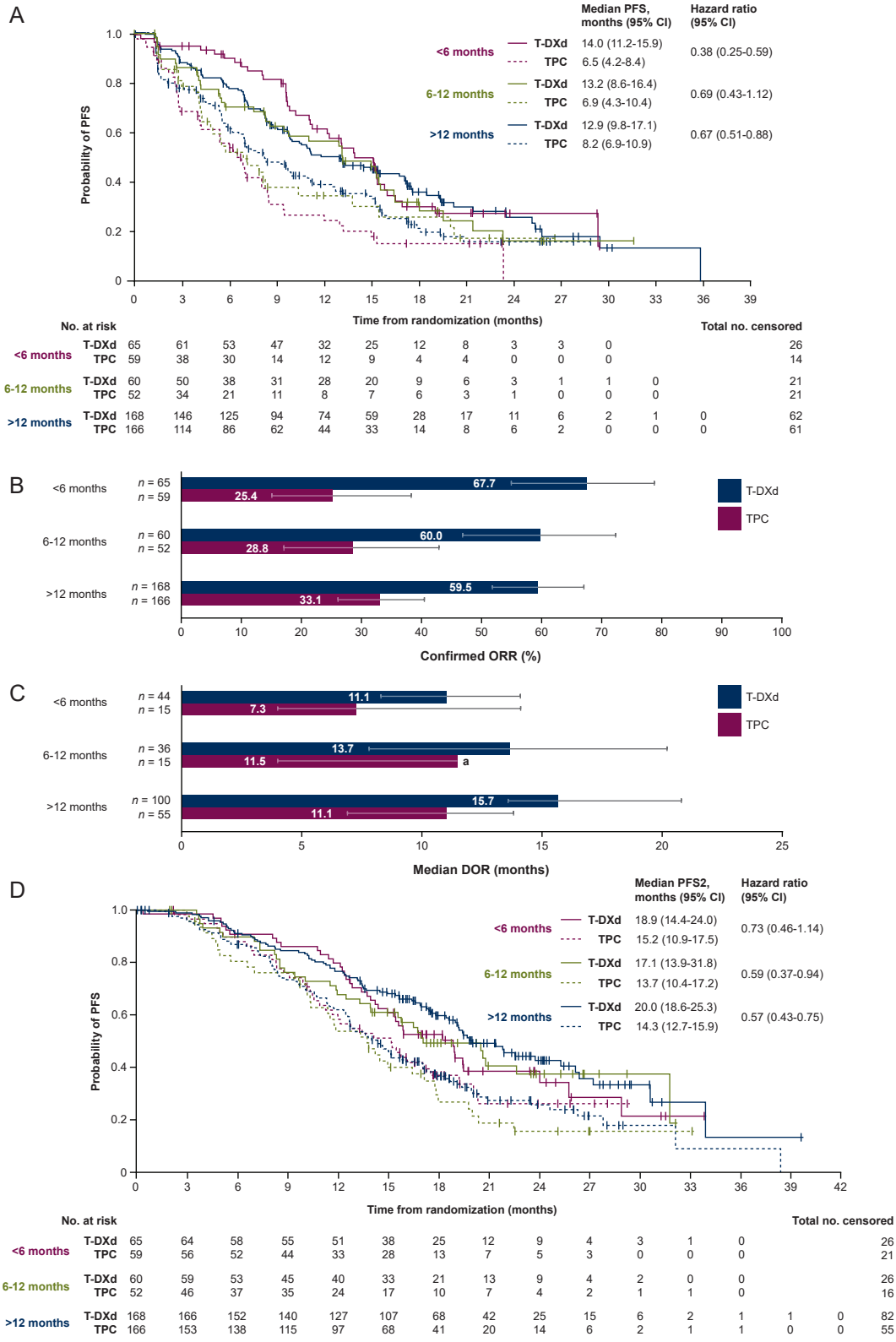


Figure 1. Efficacy outcomes by time to progression on prior 1L ET + CDK4/6i. (A) PFS by BICR according to RECIST 1.1. (B) Confirmed ORR by BICR according to RECIST 1.1. Responses required confirmation after 4 weeks. Error bars indicate 95% CIs. (C) Median DOR (confirmed response) by BICR according to RECIST 1.1. Error bars indicate 95% CIs. (D) PFS2 by investigator. PFS2 was defined by investigators according to local standard clinical practice.

1L, first-line; BICR, blinded independent central review; CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CI, confidence interval; DOR, duration of response; ET, endocrine therapy; ORR, objective response rate; PFS, progression-free survival; PFS2, time from randomization to second progression or death; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy.

[a]95% CI not evaluable.

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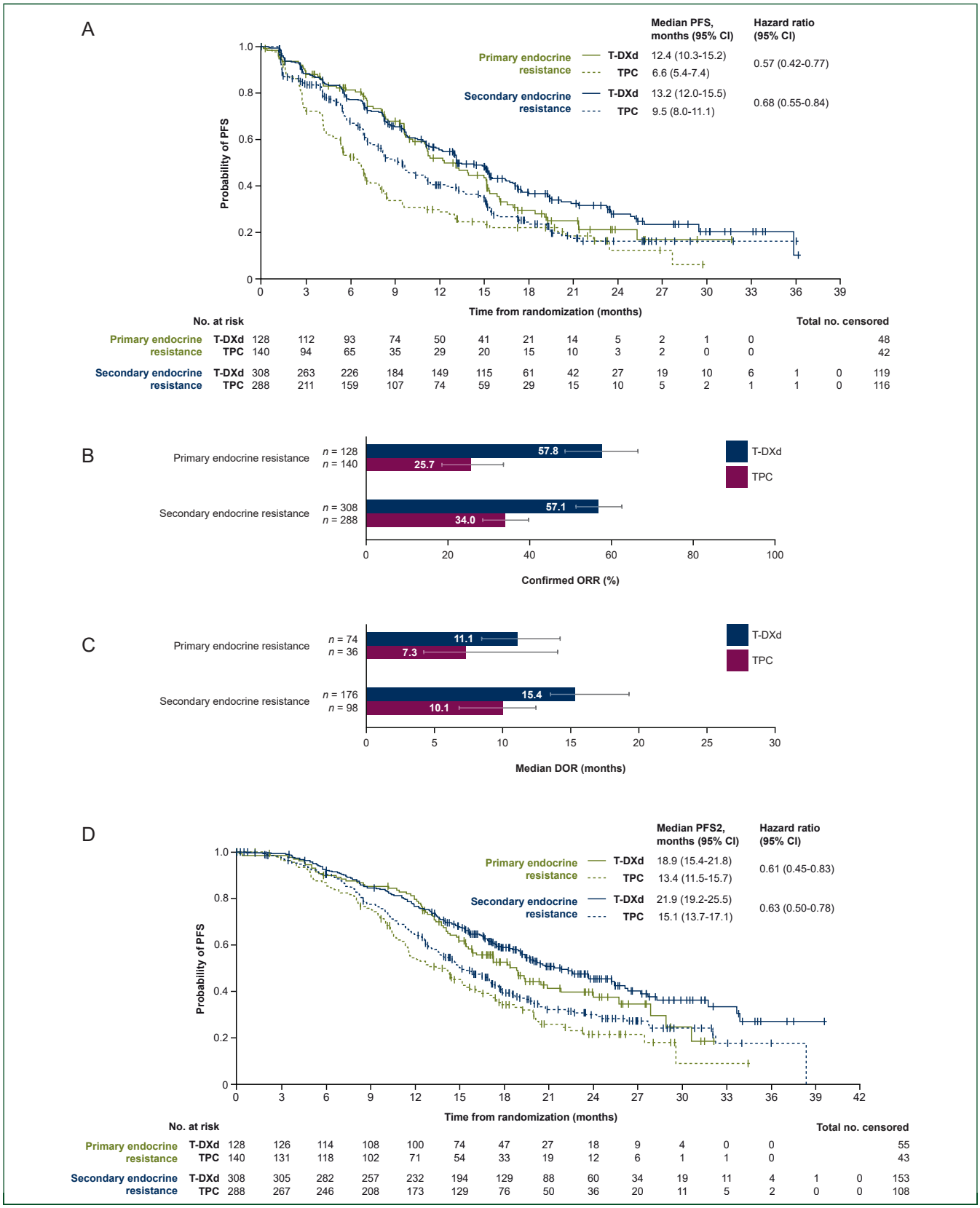

Figure 2. Efficacy outcomes by type of endocrine resistance. (A) PFS by BICR according to RECIST 1.1. (B) Confirmed ORR by BICR according to RECIST 1.1. Responses required confirmation after 4 weeks. Error bars indicate 95% CIs. (C) Median DOR (confirmed response) by BICR according to RECIST 1.1. Error bars indicate 95% CIs. (D) PFS2 by investigator. PFS2 was defined by investigators according to local standard clinical practice. Endocrine resistance was assessed by investigators as per ESO—ESMO ABC-5 criteria.

BICR, blinded independent central review; CI, confidence interval; DOR, duration of response; ESO—ESMO ABC-5, fifth European School of Oncology—European Society for Medical Oncology Advanced Metastatic Breast Cancer; ORR, objective response rate; PFS, progression-free survival; PFS2, time from randomization to second progression or death; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy.

TPC in both subgroups (Figure 2C). PFS2 favored T-DXd over TPC regardless of the type of endocrine resistance: median PFS2 (95% CI) was 18.9 (15.4-21.8) months with T-DXd versus 13.4 (11.5-15.7) months with TPC in the primary subgroup, and 21.9 (19.2-25.5) months with T-DXd versus 15.1 (13.7-17.1) months with TPC in the secondary subgroup (Figure 2D).

Burden of disease. T-DXd consistently improved PFS compared with TPC regardless of the burden of disease (Figure 3A). Across the 'high' burden-of-disease subgroups, median PFS (95% CI) with T-DXd versus TPC was 13.1 (11.1-15.1) versus 7.9 (6.9-8.5) months (visceral disease), 12.2 (10.4-13.5) versus 7.0 (6.4-8.1) months (liver metastases), 11.4 (10.0-13.9) versus 7.2 (6.8-9.0) months (three or more disease sites), and 12.0 (9.9-15.2) versus 7.1 (6.5-8.3) months (>median baseline tumor size), respectively. There was also notable T-DXd efficacy in 'low' burden-of-disease subgroups; median PFS (95% CI) for T-DXd versus TPC, respectively, was 23.3 (13.1-not evaluable) versus 11.3 (6.9-15.7) months (no visceral disease), 16.5 (13.2-19.4) versus 11.3 (8.3-15.2) months (no liver metastases), 15.3 (13.1-19.3) versus 8.4 (7.3-10.3) months (less than three disease sites), and 15.0 (13.1-16.1) versus 9.7 (7.5-13.2) months (≤median baseline tumor size). Across all burden-of-disease subgroups, confirmed ORR favored T-DXd versus TPC (Figure 3B), and median DOR was consistently longer with T-DXd than with TPC (Figure 3C). In line with PFS data, PFS2 was also prolonged with T-DXd versus TPC for all patients in 'high' and 'low' burden-of-disease subgroups (Figure 3D).

Safety

Safety outcomes for T-DXd and TPC across the subgroup categories were generally consistent with those of the overall safety population, as previously reported (Table 1; Supplementary Tables S5 and S6, available at https://doi.org/10.1016/j.annonc.2026.02.015).[12] Time to progression on prior 1L ET + CDK4/6i, type of endocrine resistance, and burden of disease did not affect safety outcomes with either treatment. Across subgroup categories, the incidences of any-grade treatment-emergent adverse events (TEAEs) were similar regardless of treatment. The frequencies of grade ≥3 TEAEs were numerically higher in subgroups treated with T-DXd than with TPC, with frequencies ranging from 45.8% to 63.3% and from 34.9% to 46.2%, respectively, except for patients with >12 months' time to progression, in whom incidences were similar between treatments (T-DXd, 45.8%; TPC, 42.9%). The most common grade ≥3 TEAEs across subgroup categories included neutrophil count decreased, neutropenia, and anemia with T-DXd, and neutropenia, neutrophil count decreased, and palmar-plantar erythrodysesthesia with TPC (Supplementary Tables S7-S9, available at https://doi.org/10.1016/j.annonc.2026.02.015). Compared with TPC, T-DXd was generally associated with higher rates of serious TEAEs [frequencies across subgroups ranging from 15.3% to 28.3% (T-DXd) and from 10.9% to 19.8% (TPC)] and TEAEs leading to discontinuation [frequencies across subgroups ranging from 9.2% to 21.7% (T-DXd) and from 6.1% to 12.6% (TPC)]. The proportion of patients with adjudicated drug-related interstitial lung disease (ILD) or pneumonitis ranged from 7.6% to 13.9% among patients treated with T-DXd and from 0% to 0.5% among those treated with TPC, and the frequency of left ventricular dysfunction ranged from 5.9% to 10.7% and from 2.3% to 6.3%, respectively.

DISCUSSION

In this exploratory *post hoc* analysis of DESTINY-Breast06, T-DXd demonstrated favorable efficacy outcomes across all patient subgroups, as defined by time to progression on prior 1L ET + CDK4/6i, type of endocrine resistance, or baseline burden of disease. Safety profiles for T-DXd and TPC across subgroups were in line with that of the overall safety population.

Efficacy of T-DXd and TPC in analyzed subgroups was generally consistent with that of the overall ITT population in DESTINY-Breast06, in which median PFS (by BICR) was 13.2 months with T-DXd and 8.1 months with TPC.[12] In nearly all subgroups, median PFS was ≥12 months with T-DXd and ≥6.5 months with TPC. Confirmed ORR and DOR data for both treatments were also in line with those of the ITT population, with response rates numerically favoring T-DXd across all subgroups. Median PFS2 with T-DXd exceeded 17 months across subgroup categories (versus 12.7 months with TPC), demonstrating that treatment with T-DXd does not compromise response to post-discontinuation therapy.

There was strong efficacy with T-DXd for patients with rapid (<6 months) disease progression on prior 1L ET + CDK4/6i, based on a favorable median PFS of 14.0 months and median PFS2 of 18.9 months. In contrast, the benefit of TPC was reduced as compared with the overall ITT population, with a median PFS of 6.5 months (versus 8.1 months in ITT). Patients with rapid disease progression represent a difficult-to-treat population in clinical practice, who could now be candidates for T-DXd as the next line of therapy. TPC also underperformed for patients with primary endocrine resistance (median PFS of 6.6 months). Given that endocrine-resistant breast cancers are typically associated with unfavorable survival outcomes,[19] T-DXd may represent an additional treatment option over conventional chemotherapy for these patients. Other emerging strategies have shown promising efficacy, such as inavolisib + ET + CDK4/6i as an upfront treatment for patients with endocrine-resistant and *PIK3CA*-mutated disease[20,21]; however, further investigation into the potential sequencing of T-DXd with such therapies will be needed to identify the optimal treatment pathway for patients with endocrine-resistant disease.

The burden-of-disease analysis demonstrated that the efficacy benefit of T-DXd for patients with a 'high' burden of disease also extended to those with a comparably 'low' disease burden. For the latter, T-DXd prolonged median PFS by 5.2-12.0 months and median DOR by 5.3-16.3 months

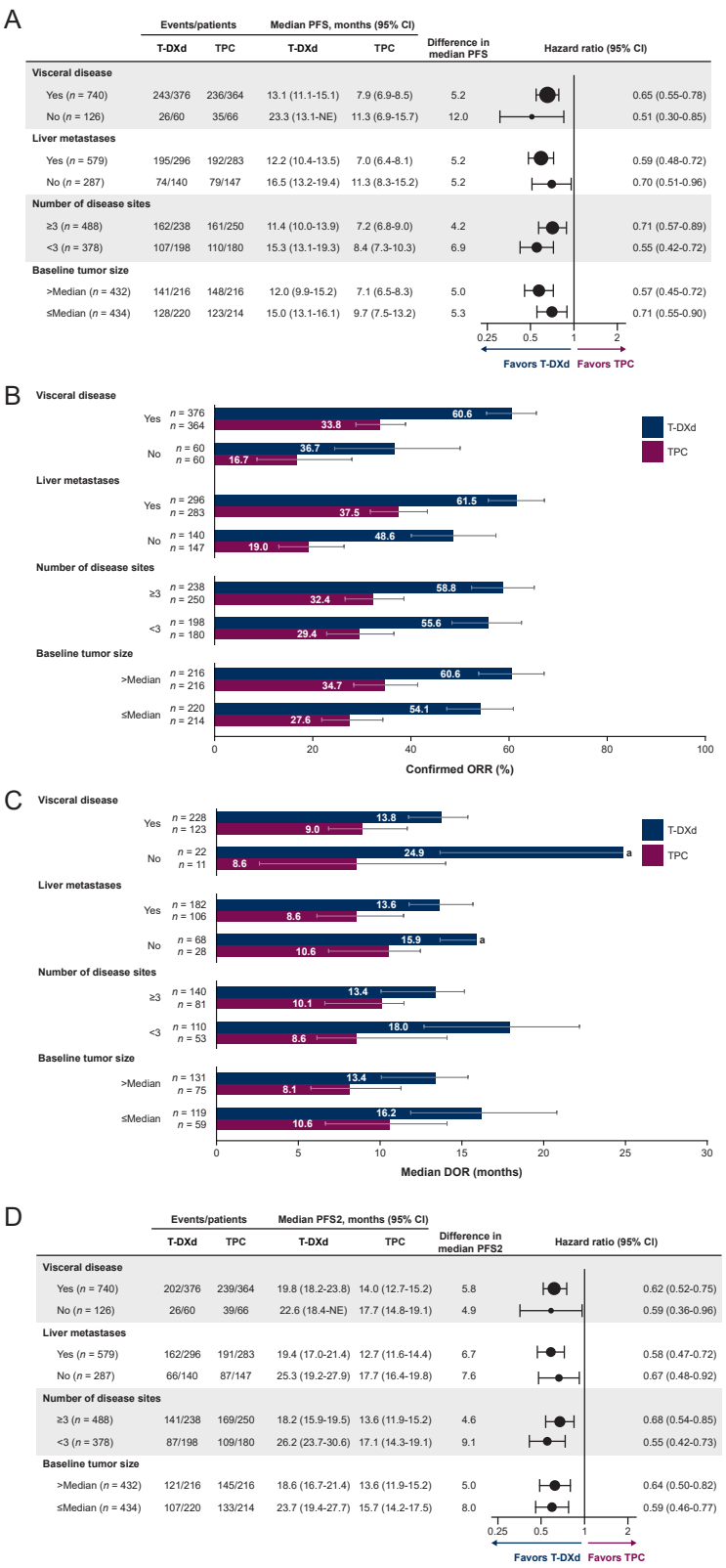

Figure 3. Efficacy outcomes by burden of disease. (A) PFS by BICR according to RECIST 1.1. Circle sizes are proportional to the number of events. (B) Confirmed ORR by BICR according to RECIST 1.1. Responses required confirmation after 4 weeks. Error bars indicate 95% CIs. (C) Median DOR (confirmed response) by BICR, according to RECIST 1.1. Error bars indicate 95% CIs. (D) PFS2 by investigator. PFS2 was defined by investigators according to local standard clinical practice. Circle sizes are proportional to the number of events. Median baseline tumor size in the ITT population (per BICR) was 48.6 mm, considering '0' to be baseline tumor size for patients without target lesion at baseline.

BICR, blinded independent central review; CI, confidence interval; DOR, duration of response; ITT, intent-to-treat; NE, not evaluable; ORR, objective response rate; PFS, progression-free survival; PFS2, time from randomization to second progression or death; T-DXd, trastuzumab deruxtecan; TPC, physician's choice of chemotherapy.

[a]95% CI not evaluable.

Table 1. Safety summary by baseline burden of disease

n (%)	Visceral disease				Liver metastases				Number of disease sites				Baseline tumor size			
	Yes		No		Yes		No		≥3		<3		>Median		≤Median	
	T-DXd ($n = 374$)	TPC ($n = 354$)	T-DXd ($n = 60$)	TPC ($n = 63$)	T-DXd ($n = 294$)	TPC ($n = 275$)	T-DXd ($n = 140$)	TPC ($n = 142$)	T-DXd ($n = 236$)	TPC ($n = 243$)	T-DXd ($n = 198$)	TPC ($n = 174$)	T-DXd ($n = 197$)	TPC ($n = 187$)	T-DXd ($n = 194$)	TPC ($n = 190$)
Any TEAEs	370 (98.9)	339 (95.8)	59 (98.3)	58 (92.1)	290 (98.6)	260 (94.5)	139 (99.3)	137 (96.5)	232 (98.3)	233 (95.9)	197 (99.5)	164 (94.3)	194 (98.5)	178 (95.2)	192 (99.0)	182 (95.8)
Grade ≥3 TEAEs	191 (51.1)	163 (46.0)	38 (63.3)	22 (34.9)	151 (51.4)	127 (46.2)	78 (55.7)	58 (40.8)	125 (53.0)	111 (45.7)	104 (52.5)	74 (42.5)	105 (53.3)	75 (40.1)	94 (48.5)	86 (45.3)
Serious TEAEs	71 (19.0)	60 (16.9)	17 (28.3)	7 (11.1)	55 (18.7)	44 (16.0)	33 (23.6)	23 (16.2)	53 (22.5)	48 (19.8)	35 (17.7)	19 (10.9)	46 (23.4)	28 (15.0)	30 (15.5)	31 (16.3)
TEAEs associated with discontinuation	49 (13.1)	33 (9.3)	13 (21.7)	6 (9.5)	40 (13.6)	26 (9.5)	22 (15.7)	13 (9.2)	33 (14.0)	17 (7.0)	29 (14.6)	22 (12.6)	23 (11.7)	13 (7.0)	26 (13.4)	22 (11.6)
Adjudicated drug-related ILD/ pneumonitis	44 (11.8)	1 (0.3)	5 (8.3)	0	32 (10.9)	1 (0.4)	17 (12.1)	0	28 (11.9)	1 (0.4)	21 (10.6)	0	15 (7.6)	1 (0.5)	27 (13.9)	0
Left ventricular dysfunction	30 (8.0)	12 (3.4)	5 (8.3)	4 (6.3)	22 (7.5)	9 (3.3)	13 (9.3)	7 (4.9)	14 (5.9)	12 (4.9)	21 (10.6)	4 (2.3)	16 (8.1)	9 (4.8)	14 (7.2)	5 (2.6)

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). Includes ILD/pneumonitis with an onset date or worsening on or after the date of first dose. Includes left ventricular dysfunctions 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. Median baseline tumor size in the ITT population (per BICR) was 48.6 mm, considering '0' to be baseline tumor size for patients without target lesion at baseline.
AE, adverse event; BICR, blinded independent central review; ILD, interstitial lung disease; ITT, intent-to-treat; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, physician's choice of chemotherapy.

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compared with TPC. These findings support consideration of T-DXd over TPC regardless of disease burden, where clinically appropriate.

Safety profiles of T-DXd and TPC in subgroups were generally in line with the overall population.[12] Rates of grade ≥3 TEAEs, serious TEAEs, and TEAEs associated with discontinuation were numerically higher with T-DXd than with TPC across most subgroup categories. In contrast to the overall safety population, grade ≥3 TEAEs for patients without visceral disease were numerically higher with T-DXd and lower with TPC, although this may be attributed to the limited patient numbers in this subgroup. Rates of adjudicated drug-related ILD/pneumonitis and left ventricular dysfunction for T-DXd and TPC were also generally consistent with those of the overall safety population. Close monitoring for ILD/pneumonitis remains an important consideration of T-DXd treatment and will be especially pertinent for patients who receive T-DXd for a prolonged duration, such as those with a 'low' burden of disease.

Since trial enrollment, updated criteria for endocrine resistance have been published, with a broader definition of secondary endocrine resistance.[17,22] In addition to 'disease progression at least 6 months after initiating 1L endocrine-based therapy' (as per previous guidelines), criteria also now include 'disease progression after any duration of second or subsequent lines of endocrine-based therapy for mBC' or 'presence of an *ESR1* mutation'[22]; however, because the definition of primary endocrine resistance is unchanged, it is unlikely that such updates would affect the composition of subgroups and findings of the current analysis.

Following the primary results of DESTINY-Breast06,[12] the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer were updated and currently recommend (as of V.1.2026) systemic chemotherapy, such as oral capecitabine, as the preferred 1L treatment of recurrent unresectable or stage IV, HR-positive, and HER2-negative mBC that is with visceral crisis or endocrine refractory, with T-DXd recommended as an 'other preferred' option, based on individuals' clinical features and preference.[23] Considering the results of the current subgroup analyses, T-DXd has now shown a broad efficacy benefit over conventional single-agent chemotherapies, including for patients with visceral disease, rapid progression following prior 1L ET + CDK4/6i, and endocrine resistance, with a manageable safety profile.

Data presented here complement other analyses from the trial. In a TPC subgroup analysis, T-DXd demonstrated superior efficacy over treatment with either capecitabine or taxane, and in a patient-reported outcome analysis, T-DXd maintained overall quality of life while reducing the risk of deterioration in pain, fatigue, and functioning (physical, role, emotional), compared with TPC.[24,25] In an exploratory biomarker analysis, T-DXd also demonstrated a greater clinical benefit versus TPC regardless of mutations of the phosphoinositide 3-kinase (PI3K) pathway, *ESR1*, and *BRCA1/2*.[26] Collectively, these analyses supplement the primary results and add further support for T-DXd as a broadly efficacious treatment option when used after one or more prior ETs, once such therapies no longer provide clinical benefit.

Similar subgroup analyses were conducted in the DESTINY-Breast04 trial, which showed consistent efficacy of T-DXd independent of disease burden, prior CDK4/6i treatment, or rapid progression status.[27] Results of those analyses are consistent with current subgroup findings of DESTINY-Breast06. Importantly, the current manuscript provides new data for clinically relevant subgroups that were not otherwise explored in the DESTINY-Breast04 analysis; for example, additional granularity regarding 'high' and 'low' burden of disease and evaluation of primary and secondary endocrine resistance.

These subgroup analyses were not powered to show statistically significant differences between treatment groups in the outcomes assessed; rather, the findings were intended to reinforce the primary analysis, providing evidence of a consistent efficacy benefit with T-DXd across a range of patient groups with relevance to real-world clinical practice. Limitations of the overall study have been discussed previously.[12]

Conclusion

In conclusion, these analyses demonstrate that the clinical benefit of T-DXd in the overall DESTINY-Breast06 population is consistent across patient subgroups, irrespective of time to progression on prior 1L ET + CDK4/6i, type of endocrine resistance, or baseline burden of disease, with safety data similar to the primary safety analysis. The findings support T-DXd as an efficacious treatment option for a wide range of patients with HR-positive, HER2-low or HER2-ultralow mBC following one or more lines of endocrine-based therapy.

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DATA SHARING

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://www.astrazenecaclinicaltrials.com/our-transparency-commitments/. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. The AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

REFERENCES

1. Burstein HJ, Somerfield MR, Barton DL, et al. Endocrine treatment and targeted therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: ASCO guideline update. *J Clin Oncol*. 2021;39(35):3959-3977.
2. Burstein HJ, DeMichele A, Fallowfield L, et al. Endocrine and targeted therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer—capivasertib-fulvestrant: ASCO rapid recommendation update. *J Clin Oncol*. 2024;42(12):1450-1453.
3. Gennari A, André F, Barrios CH, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. *Ann Oncol*. 2021;32(12):1475-1495.
4. Grinshpun A, Tolaney SM, Burstein HJ, Jeselsohn R, Mayer EL. The dilemma of selecting a first line CDK4/6 inhibitor for hormone receptor-positive/HER2-negative metastatic breast cancer. *NPJ Breast Cancer*. 2023;9(1):15.
5. Bidard F-C, Kaklamani VG, Neven P, et al. Elacestrant (oral selective estrogen receptor degrader) versus standard endocrine therapy for estrogen receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: results from the randomized Phase III EMERALD trial. *J Clin Oncol*. 2022;40(28):3246-3256.
6. Turner NC, Oliveira M, Howell SJ, et al. Capivasertib in hormone receptor-positive advanced breast cancer. *N Engl J Med*. 2023;388(22):2058-2070.
7. Tolaney SM, Punie K, Carey LA, et al. Real-world treatment patterns and outcomes in patients with HR+/HER2− metastatic breast cancer treated with chemotherapy in the United States. *ESMO Open*. 2024;9(9):103691.
8. Robert NJ, Diéras V, Glaspy J, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. *J Clin Oncol*. 2011;29(10):1252-1260.
9. Cuyún Carter G, Mohanty M, Stenger K, et al. Prognostic factors in hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) advanced breast cancer: a systematic literature review. *Cancer Manag Res*. 2021;13:6537-6566.
10. Tarantino P, Viale G, Press MF, et al. ESMO expert consensus statements (ECS) on the definition, diagnosis, and management of HER2-low breast cancer. *Ann Oncol*. 2023;34(8):645-659.
11. Wolff AC, Somerfield MR, Dowsett M, et al. Human epidermal growth factor receptor 2 testing in breast cancer: ASCO—College of American Pathologists guideline update. *J Clin Oncol*. 2023;41(22):3867-3872.
12. Bardia A, Hu X, Dent R, et al. Trastuzumab deruxtecan after endocrine therapy in metastatic breast cancer. *N Engl J Med*. 2024;391(22):2110-2122.
13. Ogitani Y, Aida T, Hagihara K, et al. DS-8201a, a novel HER2-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. *Clin Cancer Res*. 2016;22(20):5097-5108.
14. Nakada T, Sugihara K, Jikoh T, Abe Y, Agatsuma T. The latest research and development into the antibody-drug conjugate, [fam-] trastuzumab deruxtecan (DS-8201a), for HER2 cancer therapy. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185.
15. European Medicines Agency (EMA). ENHERTU: summary of product characteristics (SmPC). Available at https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf. Accessed September 19, 2025.
16. U.S. Food and Drug Administration (FDA). ENHERTU (fam-trastuzumab deruxtecan-nxki): highlights of prescribing information (PI). Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761139s032s035lbl.pdf. Accessed September 19, 2025.
17. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol*. 2020;31(12):1623-1649.
18. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.
19. Lambertini M, Blondeaux E, Bisagni G, et al. Prognostic and clinical impact of the endocrine resistance/sensitivity classification according to international consensus guidelines for advanced breast cancer: an individual patient-level analysis from the Mammella InterGruppo (MIG) and Gruppo Italiano Mammella (GIM) studies. *EClinicalMedicine*. 2023;59:101931.
20. European Medicines Agency. Itovebi: summary of product characteristics. Available at https://www.ema.europa.eu/en/documents/product-information/itovebi-epar-product-information_en.pdf. Accessed October 16, 2025.
21. Jhaveri KL, Im S-A, Saura C, et al. Overall survival with inavolisib in PIK3CA-mutated advanced breast cancer. *N Engl J Med*. 2025;393(2):151-161.
22. Cardoso F, Paluch-Shimon S, Schumacher-Wulf E, et al. 6th and 7th international consensus guidelines for the management of advanced breast cancer (ABC guidelines 6 and 7). *Breast*. 2024;76:103756.
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24. Barrios CH, Bardia A, Hu X, et al. DESTINY-Breast06 (DB-06) post-hoc analysis by physician's choice of chemotherapy (TPC): efficacy and safety of trastuzumab deruxtecan (T-DXd) vs TPC in hormone receptor—positive (HR+), HER2-low or -ultralow metastatic breast cancer (mBC). *ESMO Open*. 2025;10(suppl 4):104871 (Abstract 299MO).
25. Hu X, Curigliano G, Yonemori K, et al. Patient-reported outcomes with trastuzumab deruxtecan in hormone receptor-positive, HER2-low or HER2-ultralow metastatic breast cancer: results from the randomized DESTINY-Breast06 trial. *ESMO Open*. 2025;10(5):105082.
26. Dent RA, Curigliano G, Hu X, et al. Exploratory biomarker analysis of trastuzumab deruxtecan (T-DXd) vs physician's choice of chemotherapy (TPC) in HER2-low/ultralow, hormone receptor—positive (HR+) metastatic breast cancer (mBC) in DESTINY-Breast06 (DB-06). *J Clin Oncol*. 2025;43(suppl 16):1013 (Abstract).
27. Harbeck N, Modi S, Jacot W, et al. *Trastuzumab deruxtecan vs treatment of physician's choice in patients with HER2-low unresectable and/or metastatic breast cancer: subgroup analyses from DESTINY-Breast04 (Abstract P1-11-01)*. San Antonio, TX, USA: Poster presented at the San Antonio Breast Cancer Symposium (SABCS) Annual Meeting; December 6-10, 2022.