Trastuzumab Deruxtecan after Endocrine Therapy in HER2-Low/-Ultralow Metastatic Breast Cancer

Aditya Bardia, M.D.[1], Xichun Hu, M.D., Ph.D.[2,3], Rebecca Dent, M.D.[4], Kan Yonemori, M.D.[5], Carlos H. Barrios, M.D.[6], Joyce A. O'Shaughnessy, M.D.[7], Hans Wildiers, M.D., Ph.D.[8], Jean-Yves Pierga, M.D., Ph.D.[9], Qingyuan Zhang, M.D., Ph.D.[10], Cristina Saura, M.D., Ph.D.[11], Laura Biganzoli, M.D.[12], Joohyuk Sohn, M.D., Ph.D.[13], Seock-Ah Im, M.D., Ph.D.[14], Christelle Lévy, M.D.[15], William Jacot, M.D., Ph.D.[16], Natasha Begbie, M.B.B.S., M.Res.[17], Jun Ke, Ph.D.[18], Gargi Patel, M.B. B.Chir., Ph.D.[17], Giuseppe Curigliano, M.D., Ph.D.[19,20] for the DESTINY-Breast06 investigators

1. University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA, US
2. Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China
3. Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China
4. Division of Medical Oncology, National Cancer Centre Singapore, Singapore
5. National Cancer Center Hospital, Tokyo, Japan
6. Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil
7. Baylor University Medical Center, Texas Oncology and US Oncology, Dallas, TX, US
8. Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium
9. Department of Medical Oncology, Institut Curie and Université Paris Cité, Paris, France
10. Harbin Medical University Cancer Hospital, Harbin, China

11. Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona, Spain

12. Department of Oncology, Santo Stefano Hospital, Azienda USL Toscana Centro, Prato, Italy

13. Division of Medical Oncology, Yonsei Cancer Center, Seoul, Republic of Korea

14. Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea

15. Centre François Baclesse, Caen, France

16. Department of Medical Oncology, Institut du Cancer de Montpellier, Université de Montpellier, INSERM U1194, Montpellier, France

17. Clinical Development, Late-Stage Development, Oncology R&D, AstraZeneca, Cambridge, UK

18. Biometrics Oncology, Late-Stage Development, Oncology R&D, AstraZeneca, Waltham, MA, US

19. European Institute of Oncology, IRCCS, Milan, Italy

20. Department of Oncology and Hematology-Oncology, University of Milan, Milan, Italy

Co-corresponding authors:

Professor Bardia can be contacted at abardia@mednet.ucla.edu or at University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA, US, 90404

Professor Curigliano can be contacted at giuseppe.curigliano@ieo.it or at the European Institute of Oncology, IRCCS, 20141; Department of Oncology and Hematology-Oncology, University of Milan, 20122, both Milan, Italy

A list of investigators in the DESTINY-Breast06 trial is provided in the Supplementary Appendix, available at NEJM.org.

ABSTRACT

Background

Outcomes for patients with hormone receptor–positive (HR+), metastatic breast cancer (mBC) decline after ≥1 endocrine-based therapies. Trastuzumab deruxtecan (T-DXd) has demonstrated efficacy in HER2-low (immunohistochemistry [IHC] 1+ or 2+/in situ hybridization [ISH]-negative) mBC after prior chemotherapy.

Methods

We conducted an open-label, multicenter, randomized phase 3 trial involving patients with HR+, HER2-low or HER2-ultralow (IHC 0 with membrane staining) mBC who received ≥1 line of endocrine-based therapy and no prior chemotherapy for mBC. Patients were randomized 1:1 to receive T-DXd 5.4 mg/kg or physician's choice of chemotherapy (capecitabine, nab-paclitaxel, or paclitaxel). The primary endpoint was progression-free survival per blinded independent central review in the HER2-low population. Secondary endpoints included progression-free survival in the intent-to-treat (HER2-low and -ultralow) population, overall survival, and safety.

Results

In total, 866 patients (HER2-low, n=713; HER2-ultralow, n=153) were randomized. At primary analysis, T-DXd significantly improved progression-free survival versus chemotherapy in HER2-low mBC (hazard ratio, 0.62; 95% confidence interval [CI], 0.51 to 0.74; P<0.0001; median, 13.2 [95% CI, 11.4 to 15.2] vs. 8.1 months [95% CI, 7.0 to 9.0]). Results were consistent in the intent-to-treat population (hazard ratio, 0.63; 95% CI, 0.53 to 0.75; P<0.0001; median, 13.2 [95% CI, 12.0 to 15.2] vs. 8.1 months [95% CI, 7.0 to 9.0]). Results were also consistent in the exploratory HER2-ultralow population. Overall survival was immature. Grade ≥3 adverse events occurred in 52.8% and 44.4% of patients receiving T-DXd and chemotherapy. Adjudicated interstitial lung disease/pneumonitis occurred in 49

(11.3%; n=3 Grade 5) patients receiving T-DXd and 1 (0.2%, Grade 2) patient receiving chemotherapy.

Conclusions

T-DXd improved progression-free survival versus chemotherapy in patients with HR+, HER2-low or -ultralow mBC treated with ≥1 lines of endocrine-based therapy. No new safety signals were identified.

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INTRODUCTION

Hormone receptor–positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative breast cancer is the most common breast cancer subset, comprising nearly 70% of all cases.[1] Within breast cancers categorized as “HER2-negative”, defined as immunohistochemistry (IHC) 0, IHC 1+, or IHC 2+/in situ hybridization (ISH)-negative(−),[2] a spectrum of HER2 expression exists. Those with IHC 1+ or IHC 2+/ISH− are currently defined as “HER2-low”, while subdivision of the IHC 0 category into membrane staining that is faint and in ≤10% of tumor cells (“HER2-ultralow”) or no observable staining is proposed.[2,3]

Currently, standard treatment for patients with HR+, HER2-negative metastatic breast cancer (mBC) is an endocrine therapy (ET)-based regimen, usually with a cyclin-dependent kinase 4 and 6 inhibitor (CDK4/6i) in first line, and with/without targeted therapies in second line.[4–6] Despite good outcomes with first-line ET plus CDK4/6i,[7–9] optimal sequencing of post-progression therapies remains unclear. The benefit of ET-based regimens declines post CDK4/6i exposure.[10,11] After progression on multiple lines of ET-based therapy, or rapid progression on prior adjuvant or first-line ET, conventional single-agent chemotherapy shows limited efficacy in later lines (median progression-free survival 6–7 months after ≤1 prior chemotherapy regimen).[12–14]

Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate composed of a humanized immunoglobulin G1 monoclonal antibody specifically targeting HER2, a tetrapeptide-based cleavable linker, and a potent topoisomerase I inhibitor payload.[15,16] In DESTINY-Breast04, patients (HR+ and HR− together) with HER2-low mBC had a statistically significant and clinically meaningful benefit with T-DXd compared with standard chemotherapy.[17] This led to approval of T-DXd for patients with unresectable or metastatic HER2-low tumors who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.[18,19]

Given that additional patients may benefit from HER2-directed treatment in earlier lines,[20] DESTINY-Breast06 sought to evaluate the efficacy and safety of T-DXd compared with physician's choice of chemotherapy (single agent capecitabine, nab-paclitaxel, or paclitaxel) in patients with HR+, HER2-low or -ultralow mBC who had received one or more endocrine-based therapies but no prior chemotherapy in the metastatic disease setting.

METHODS

Trial design and treatment

We conducted an open-label, multicenter, randomized phase 3 trial involving patients with HR+, HER2-low and HER2-ultralow mBC. The primary efficacy population comprised patients with HER2-low (IHC 1+ or IHC 2+/ISH−) expression per interactive response technology. The secondary efficacy population (referred to as the intent-to-treat population) comprised all randomized patients: the HER2-low population as well as the prespecified exploratory HER2-ultralow (IHC 0 with membrane staining, defined here as IHC >0<1+) population. HER2 expression was centrally confirmed using a sample taken in the metastatic setting. Further information can be found in the **Supplementary Methods** and **Table S1** in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Patients were eligible if they had disease progression on at least two lines of prior endocrine-based therapy in the metastatic setting. Patients with one prior line of ET for metastatic disease were also eligible if they demonstrated disease recurrence within 24 months of starting adjuvant ET or disease progression within 6 months of starting first-line ET plus CDK4/6i in the metastatic setting. Patients were chemotherapy-naïve for advanced or metastatic disease. For further details on eligibility criteria, see **Supplementary Methods**.

Patients were randomly assigned in a 1:1 ratio to T-DXd (5.4 mg/kg intravenously) once every 3 weeks or physician's choice of single-agent chemotherapy (capecitabine, nab-paclitaxel, or paclitaxel) until disease progression (per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1)[21] or unacceptable toxicity. Chemotherapy regimens were as follows: capecitabine (1250 or 1000 mg/m^2) orally twice daily for 2 weeks, followed by a 1-week rest period in 3-week cycles; nab-paclitaxel (100 mg/m^2) administered intravenously every week for 3 weeks, followed by a 1-week rest period in 4-week cycles; paclitaxel (80 mg/m^2) administered intravenously every week in 3-week cycles. Patients were stratified according

to prior CDK4/6i use (yes vs. no), HER2 expression (IHC 1+ vs. IHC 2+/ISH− vs. IHC 0 with membrane staining), and prior taxane use (yes vs. no) in the non-metastatic setting.

Trial oversight

This trial (NCT04494425) was sponsored by AstraZeneca and Daiichi Sankyo. The trial was designed by AstraZeneca in collaboration with Daiichi Sankyo and the study steering committee co-chairs and approved by the institutional review board or ethics committee at each investigational site before initiation. The trial was performed 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. An independent data monitoring committee monitored efficacy and patient safety. Patients provided written informed consent. The authors had full access to the data in the trial and vouch for the completeness and accuracy of the data and adherence of the trial to the protocol (available at NEJM.org). The authors, steering committee members, and sponsors guided the manuscript development with editorial assistance from professional medical writers funded by AstraZeneca. The first draft of the manuscript was prepared by a professional writer in collaboration with representatives of the sponsor and the authors. All drafts of the manuscript were reviewed and approved by the authors.

Endpoints

The primary endpoint was progression-free survival in the HER2-low population by blinded independent central review per RECIST v1.1.[23] Key secondary endpoints were progression-free survival in the intent-to-treat population by blinded independent central review and overall survival in the HER2-low and intent-to-treat populations. Other secondary endpoints included progression-free survival in the HER2-low population by investigator assessment, objective response rate and duration of response in the HER2-low and intent-to-treat populations, and safety.

Safety

Treatment-emergent adverse events were coded using Medical Dictionary for Regulatory Activities v6.0 preferred terms and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. Potential cases of interstitial lung disease (ILD) / pneumonitis were evaluated by an independent adjudication committee. Pulmonary toxicity management guidelines were as described previously.[17] For further details, see **Supplementary Methods**.

Statistical analysis

A stratified log-rank test was used to compare progression-free survival between treatment groups. It was determined that approximately 456 patients experiencing disease progression or death would provide at least 95% power to detect a hazard ratio of 0.55 at a two-sided alpha level of 5% in the HER2-low population. To control the Type 1 family-wise error rate at 5% in terms of the primary and key secondary endpoints, a multiple testing procedure with a gatekeeping strategy was employed. Efficacy analyses included all randomized patients. Hazard ratios and corresponding 95% confidence intervals (CIs) for progression-free survival and overall survival were estimated with the use of a stratified Cox regression analysis. Analyses in patients with HER2-ultralow expression were exploratory; as such, no formal statistical testing of significance was performed in this population, and the corresponding CI for the hazard ratio was not adjusted for multiplicity. Safety analyses included all patients who received ≥1 dose of study treatment. Further details are in the **Supplementary Methods**.

RESULTS

Patients

From July 2020 to March 2024, 866 patients were randomized across 324 sites; 436 were assigned to T-DXd and 430 to chemotherapy (59.8% capecitabine, 24.4% nab-paclitaxel, and 15.8% paclitaxel) **(Fig. S1)**; 713 patients were stratified into the HER2-low population and 153 into the HER2-ultralow population. Baseline characteristics were balanced between the trial groups **(Table 1** and **Table S2)**. Patients received a median of 2 previous lines (range, 1 to 5) of endocrine-based therapy in the metastatic setting. Most patients in the intent-to-treat population (783; 90%) had prior CDK4/6i for metastatic disease; 584 (67%) and 217 (25%) had received ET plus CDK4/6i as first-line and second-line metastatic treatment, respectively, and 636 patients (73%) had received fulvestrant as single or combination therapy for metastatic disease. The median duration of follow-up in the intent-to-treat population was 18.2 months (range, 0.0 to 42.9); 89 patients (20.5%) in the T-DXd group and 30 (7.2%) in the chemotherapy group remained on treatment at data cutoff.

Efficacy

Progression-free survival

At data cutoff (March 18, 2024), progression-free survival by blinded independent central review in the HER2-low population was significantly longer in the T-DXd group than in the chemotherapy group (hazard ratio for disease progression or death, 0.62; 95% CI, 0.51 to 0.74; P<0.0001) **(Fig. 1A)**. Median progression-free survival was 13.2 months (95% CI, 11.4 to 15.2) with T-DXd and 8.1 months (95% CI, 7.0 to 9.0) with chemotherapy. In the intent-to-treat population, T-DXd significantly improved progression-free survival compared with chemotherapy. Median progression-free survival was 13.2 months (95% CI, 12.0 to 15.2) with T-DXd and 8.1 months (95% CI, 7.0 to 9.0) with chemotherapy (hazard ratio for disease progression or death, 0.63; 95% CI, 0.53 to 0.75; P<0.0001) **(Fig. 1B)**. Consistent efficacy

was observed in the prespecified exploratory HER2-ultralow population. Median progression-free survival was 13.2 months (95% CI, 9.8 to 17.3) with T-DXd and 8.3 months (95% CI, 5.8 to 15.2) with chemotherapy (hazard ratio for disease progression or death, T-DXd vs. chemotherapy, 0.78; 95% CI, 0.50 to 1.21) **(Fig. 1C)**. Results were similar per investigator assessment **(Fig. S2** and **Table S3)**. Progression-free survival also consistently favored T-DXd versus chemotherapy in patients with HER2 IHC 1+ and IHC 2+/ISH−, and regardless of prior CDK4/6i use, prior taxane use in the non-metastatic setting, and chemotherapy choice **(Fig. 2)**.

Overall survival

Overall survival data were 37.9% mature for the T-DXd group (136 deaths out of 359 patients) and 41.2% mature (146 out of 354 patients) for the chemotherapy group in the HER2-low population. At data cutoff, the difference in overall survival between treatment groups in the HER2-low population was not statistically significant (hazard ratio, 0.83; 95% CI, 0.66 to 1.05); estimated 12-month overall survival rates were 87.6% and 81.7% with T-DXd and chemotherapy, respectively **(Fig. S3A)**. Results were consistent in the intent-to-treat **(Fig. S3B)** and HER2-ultralow **(Fig. S3C)** populations. Overall, 20.1% of patients in the HER2-low population (17.9% in intent-to-treat) assigned to chemotherapy received T-DXd after study treatment discontinuation.

Response to treatment

The confirmed objective response in the HER2-low population was 56.5% (95% CI, 51.2 to 61.7) with T-DXd and 32.2% (95% CI, 27.4 to 37.3) with chemotherapy **(Table 2** and **Fig. S4)**; complete (confirmed) responses were observed in 9 (2.5%) patients in the T-DXd group versus none in the chemotherapy group. In the intent-to-treat population, the confirmed objective response was 57.3% (95% CI, 52.5 to 62.0) with T-DXd and 31.2% (95% CI, 26.8 to 35.8) with chemotherapy. Consistent results were observed in the HER2-ultralow population; confirmed objective response was 61.8% (95% CI, 50.0 to 72.8) with T-DXd and 26.3% (95% CI, 16.9 to 37.7) with chemotherapy. The median duration of response in the HER2-low population was 14.1 months in the T-DXd group and 8.6 months in the chemotherapy group **(Table 2)**. In the intent-to-treat population, the median duration of response was 14.3 months with T-DXd and 8.6 months with chemotherapy. Results were similar by investigator assessment **(Table S3)**.

Safety

In total, 851 patients were included in the safety analysis: 434 in the T-DXd group and 417 in the chemotherapy group. The median duration of treatment was 11.0 (range, 0.4 to 39.6) and 5.6 months (0.1 to 35.9) in the T-DXd and chemotherapy groups, respectively.

The incidence of treatment-emergent adverse events was similar with T-DXd and chemotherapy (98.8% and 95.2%, respectively) **(Table S4** and **Table S5)**. The three most common drug-related adverse events were nausea, fatigue, and alopecia in the T-DXd group, and fatigue, palmar-plantar erythrodysesthesia syndrome, and neutropenia in the chemotherapy group **(Table 3)**. Grade ≥3 adverse events occurred in 52.8% and 44.4% of patients in the T-DXd and chemotherapy groups, respectively; the three most common Grade ≥3 adverse events across both treatment groups were neutropenia, leukopenia, and anemia. Adverse events associated with dose reductions occurred in 24.7% of patients in the T-DXd group and 38.6% in the chemotherapy group **(Table S4)**. The rates of adverse

events leading to discontinuation were 14.3% with T-DXd and 9.4% with chemotherapy. The incidence of serious adverse events was 20.3% (T-DXd) and 16.1% (chemotherapy). Fatal adverse events occurred in 2.5% in the T-DXd group and 1.4% in the chemotherapy group; fatal drug-related adverse events occurred in 5 patients (1.2%) receiving T-DXd and none receiving chemotherapy.

Adjudicated drug-related ILD/pneumonitis occurred in 49 patients (11.3%) who received T-DXd, including 7 (1.6%) with a Grade 1 event, 36 (8.3%) with a Grade 2 event, 3 (0.7%) with a Grade 3 event, and 3 (0.7%) with a Grade 5 event **(Table S6** and **Table S7)**. Of these patients, 20 were reported as having recovered, 2 were reported as recovered with sequelae, and 3 were reported as recovering at data cutoff. In the chemotherapy group, ILD occurred in 1 patient (0.2%); this was a Grade 2 event that resolved after treatment discontinuation. The median time to onset of adjudicated ILD in the T-DXd group was 141 days (range, 37 to 835).

Left ventricular dysfunction (LVD) was reported in 35 patients (8.1%) in the T-DXd group and 16 patients (3.8%) in the chemotherapy group. In the T-DXd group, the frequency of LVD events was primarily driven by decreased ejection fraction, which was Grade 1 in 1 patient, Grade 2 in 31 patients, and Grade 3 in 3 patients. No events of cardiac failure were reported in the T-DXd group versus 3 patients (0.7%) in the chemotherapy group (1 event each of Grades 2, 3, and 4, respectively) **(Table S6)**.

DISCUSSION

In this phase 3, randomized clinical trial, T-DXd showed a statistically significant progression-free survival benefit and no new safety signals compared with chemotherapy in patients with HR+, HER2-low mBC, as well as in patients with tumors expressing either HER2-low or -ultralow staining (intent-to-treat), after one or more lines of ET-based regimens. Previously noted ILD and LVD effects of T-DXd were reported in a small number of patients.

DESTINY-Breast04 established HER2-low tumors as a targetable clinical entity, with patients deriving a clinical benefit with T-DXd after receiving chemotherapy.[17] In this trial, T-DXd showed efficacy in earlier lines of treatment, following post-metastatic endocrine-based therapies. T-DXd therefore represents an additional treatment option between ET and standard chemotherapy for patients who have received one or more lines of ET-based therapy in the metastatic setting. T-DXd induced a median progression-free survival of 13.2 months, an improvement of ~5 months over chemotherapy, in the HER2-low, intent-to-treat, and HER2-ultralow populations. Furthermore, progression-free survival benefit with T-DXd was observed regardless of HER2 expression status, previous CDK4/6i treatment, and prior taxane use in the non-metastatic setting. Superior efficacy with T-DXd was demonstrated regardless of chemotherapy type in the control group, and despite a longer median progression-free survival with capecitabine and nab-paclitaxel compared with previous data.[13,14] In practice, if T-DXd is approved for use before chemotherapy in this setting, clinicians will need to use these data to make the appropriate benefit-risk decisions for each individual patient.

DESTINY-Breast06 studied a HER2-directed therapy in patients with HER2-ultralow tumors (IHC 0 with membrane staining). Taken alongside DESTINY-Breast04,[17] and trials in HER2-positive disease,[22,23] T-DXd has shown clinical benefit in HER2-expressing mBC across the continuum of expression, from IHC 0 with membrane staining to IHC 3+. Uptake of T-DXd is

thought to be facilitated by very low levels of HER2 and subsequent death of neighboring tumor cells via the bystander effect.[15,16] Our findings are aligned with the phase 2 DAISY study, which showed that a subset of IHC 0 tumors were sensitive to T-DXd.[20] The most recent American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidance concluded that the current system of HER2 IHC categorization was sufficient to identify patients likely to benefit from targeted therapy, based on the data available at that time;[2] however, DESTINY-Breast06 results indicate that a subset of patients currently categorized as IHC 0 (with membrane staining) can also benefit from T-DXd. Indeed, the current data suggest no need to discriminate between HER2-low and HER2-ultralow disease because of the consistent benefit in both populations, albeit with limited patient numbers in the HER2-ultralow population. To enable access for all patients who may benefit from T-DXd, pathologists will have to separate the current HER2 IHC 0 category (per ASCO/CAP guidelines[2]) into two: IHC 0 with membrane staining (HER2-ultralow) and IHC 0 without membrane staining. Although both are captured as part of the HER2 IHC 0 category in the current ASCO/CAP guidelines,[2] differentiating between the two is not yet part of standard clinical practice. Appropriate training and education to ensure optimal identification of HER2-low and HER2-ultralow tumor samples are warranted, as supported by a study showing improvements in HER2-low scoring after training.[24]

The difference in overall survival was not significant at this first interim analysis (data maturity in the HER2-low population, 39.6%). As post-progression survival is long in this patient population, subsequent anticancer therapies are expected to have a substantial impact on overall survival, and indeed, approximately one-fifth of all patients in the chemotherapy group went on to receive T-DXd. Among others, sacituzumab govitecan is now also an effective option for these patients.[25]

Overall, T-DXd demonstrated a safety profile consistent with that observed in patients with HER2-positive[22,23] and HER2-low[17] mBC, with a longer median duration of treatment versus chemotherapy (11.0 vs. 5.6 months, respectively). While most cases of ILD in the trial were

mild or moderate, in keeping with previous studies,[17] the adjudication committee concluded that drug-related ILD could not be ruled out as a cause of death in 3 patients in the T-DXd group. Guidelines for surveillance and toxicity management of ILD/pneumonitis were provided in the study protocol, including management with dose interruptions, reductions, or discontinuations, and prescription of glucocorticoids; however, the administered steroid dose was lower than recommended in the Grade 5 cases, and 1 out of 3 patients with Grade 5 adjudicated drug-related ILD received a T-DXd dose the day after their scan revealed Grade 1 ILD.

Regarding study limitations, while the patients in DESTINY-Breast06 were largely representative of the overall population with HER2-low and HER2-ultralow metastatic breast cancer in the regions involved in the trial, we acknowledge the underrepresentation of Black/African-American participants (**Table S8**). Another potential limitation is that anthracycline was not available as an option in the control group; however, it was not considered an appropriate first-line treatment in this setting, and anthracycline-related cardiotoxicity could have limited the treatment duration. Additionally, prior use of PI3K inhibitors and other targeted agents may have been less common than expected and could have been limited by local testing and variable access to such agents in this global study. The trial was not powered to show statistical significance in the HER2-ultralow population, and it should also be acknowledged that patients with HR-negative disease were not included, so it remains unclear whether T-DXd could replace first-line chemotherapy in this population.

In conclusion, the efficacy benefit of T-DXd over chemotherapy observed in DESTINY-Breast06 suggests T-DXd as a treatment option in patients with HR+, HER2-low and -ultralow mBC who have received one or more lines of endocrine-based therapy but no chemotherapy in the metastatic setting, with no new safety signals identified. ILD remains an important safety risk of T-DXd.

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FIGURE LEGENDS

Figure 1. Progression-free Survival by Blinded Independent Central Review, All Populations: (A) HER2-low, (B) Intent-to-treat, and (C) HER2-ultralow Populations.

Circles indicate censored data. For (A), a P-value of <0.05 is statistically significant; for (B), a P-value of <0.015 is significant; for (C), statistical significance was not tested. CI denotes confidence interval; mo, months; TPC, chemotherapy treatment of physician's choice.

Figure 2. Subgroup Analysis of Progression-free Survival by Blinded Independent Central Review, HER2-low Population.

Size of circle is proportional to the number of events.
* Based on central laboratory data (i.e., the HER2 result from the most recent evaluable sample before randomization).
† Primary endocrine resistance is defined as relapse while on the first 2 years of adjuvant ET, or progressive disease within first 6 months of first-line ET for metastatic breast cancer, while on ET; secondary (acquired) endocrine resistance is defined as relapse while on adjuvant ET but after the first 2 years, or relapse within 12 months of completing adjuvant ET, or progressive disease >6 months after initiating ET for metastatic breast cancer, while on ET.
‡ Capecitabine, nab-paclitaxel, and paclitaxel were specified by the investigator before randomization. Grouping of taxanes was performed as a post-hoc analysis.
CDK4/6i denotes cyclin-dependent kinase 4 and 6 inhibitor; CI, confidence interval; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mo, months; NE, not evaluable; TPC, chemotherapy treatment of physician's choice.

Table 1. Demographics and Baseline Clinical Characteristics, All Populations.

	HER2-low*		Intent-to-treat*		HER2-ultralow*	
	T-DXd (N=359)	TPC (N=354)	T-DXd (N=436)	TPC (N=430)	T-DXd (N=76)	TPC (N=76)
Median age (range) — yr	58.0 (28–87)	57.0 (32–83)	58.0 (28–87)	57.0 (32–83)	58.0 (33–85)	57.5 (34–82)
Female sex — no. (%)	359 (100)	353 (99.7)	436 (100)	429 (99.8)	76 (100)	76 (100)
Race — no. (%)						
White	194 (54.0)	186 (52.5)	231 (53.0)	230 (53.5)	36 (47.4)	44 (57.9)
Black or African American	1 (0.3)	3 (0.8)	4 (0.9)	3 (0.7)	3 (3.9)	0
Asian	122 (34.0)	127 (35.9)	154 (35.3)	151 (35.1)	32 (42.1)	24 (31.6)
Other	6 (1.7)	10 (2.8)	7 (1.6)	12 (2.8)	1 (1.3)	2 (2.6)
Not reported	35 (9.7)	28 (7.9)	39 (8.9)	34 (7.9)	4 (5.3)	6 (7.9)
ECOG performance status at baseline — no. (%)†						
0	207 (57.7)	218 (61.6)	252 (57.8)	257 (59.8)	44 (57.9)	39 (51.3)
1	148 (41.2)	128 (36.2)	178 (40.8)	163 (37.9)	30 (39.5)	35 (46.1)
2	1 (0.3)	0	1 (0.2)	1 (0.2)	0	1 (1.3)
HER2 status — no. (%)						
IHC 0	1 (0.3)	1 (0.3)	1 (0.2)	1 (0.2)	–	–
IHC 0 with membrane staining (HER2-ultralow)	–	–	76 (17.4)	76 (17.7)	76 (100)	76 (100)
IHC 1+ (HER2-low)	238 (66.3)	234 (66.1)	239 (54.8)	234 (54.4)	–	–
IHC 2+/ISH− (HER2-low)	117 (32.6)	118 (33.3)	117 (26.8)	118 (27.4)	–	–
IHC 2+	3 (0.8)	1 (0.3)	3 (0.7)	1 (0.2)	–	–
Primary endocrine resistance — no. (%)‡	105 (29.2)	116 (32.8)	128 (29.4)	140 (32.6)	23 (30.3)	24 (31.6)
De-novo disease — no. (%)	111 (30.9)	104 (29.4)	133 (30.5)	132 (30.7)	22 (28.9)	28 (36.8)
Bone-only disease at baseline — no. (%)	11 (3.1)	10 (2.8)	13 (3.0)	13 (3.0)	2 (2.6)	3 (3.9)
Visceral disease at baseline — no. (%)	309 (86.1)	299 (84.5)	376 (86.2)	364 (84.7)	66 (86.8)	65 (85.5)
Liver mets. at baseline — no. (%)	243 (67.7)	232 (65.5)	296 (67.9)	283 (65.8)	52 (68.4)	51 (67.1)
Brain/CNS mets. at baseline — no. (%)§	33 (9.2)	25 (7.1)	37 (8.5)	33 (7.7)	4 (5.3)	8 (10.5)
Median no. of disease sites (range)	3 (1–10)	3 (1–11)	3 (1–10)	3 (1–11)	3 (1–6)	3 (1–8)
Lines of ET for met. disease						
Median no. of lines (range)	2 (1–4)	2 (1–5)	2 (1–4)	2 (1–5)	2 (1–4)	2 (1–5)
No. of lines — no. of patients (%)						
1	54 (15.1)	67 (19.0)	65 (14.9)	82 (19.2)	11 (14.5)	15 (19.7)
≤6 mo on first-line ET with CDK4/6i	33 (9.2)	33 (9.4)	37 (8.5)	40 (9.3)	4 (5.3)	7 (9.2)
2	242 (67.6)	236 (67.0)	295 (67.8)	288 (67.3)	52 (68.4)	52 (68.4)
≥3	62 (17.3)	49 (13.9)	75 (17.2)	58 (13.6)	13 (17.1)	9 (11.8)
Prior therapies for met. disease — no. (%)						
ET monotherapy	189 (52.6)	183 (51.7)	230 (52.8)	223 (51.9)	41 (53.9)	40 (52.6)
Any ET-based¶	358 (99.7)	352 (99.4)	435 (99.8)	428 (99.5)	76 (100.0)	76 (100.0)
ET with CDK4/6i	318 (88.6)	316 (89.3)	388 (89.0)	385 (89.5)	69 (90.8)	69 (90.8)
ET with targeted therapy other than CDK4/6i‖	120 (33.4)	105 (29.7)	143 (32.8)	127 (29.5)	22 (28.9)	22 (28.9)

Owing to rounding, some percentages may not add up to 100% (see also footnotes below).
* HER2-low status determined per IRT data, and HER2-ultralow status determined per central laboratory data; with mis-stratification, the combined sample size of these two populations did not match the intent-to-treat total. Two patients were randomly assigned in error to the intent-to-treat population (one per treatment group) and were subsequently found to have HER2 IHC 0 without membrane staining per central laboratory testing. One patient who was initially listed as having HER2-ultralow expression per IRT was reclassified as HER2-low based on an updated biopsy (the screening sample was from the pre-metastatic setting). Therefore, this patient was not included in the HER2-ultralow subgroup analysis or the HER2-low primary population but was included in the intent-to-treat population.
† 14 patients in the intent-to-treat had missing ECOG performance status at baseline (n=5, T-DXd; n=9, TPC) but had ECOG 0 or 1 recorded within 6 days of randomization.
‡ Defined as relapse while on the first 2 years of adjuvant endocrine therapy, or progressive disease within the first 6 months of first-line endocrine therapy for metastatic breast cancer.
§ Patients with clinically active CNS mets. (untreated, or symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms) were excluded.
¶ Includes both monotherapy and combination therapy.
‖ Other targeted therapies in the T-DXd and TPC intent-to-treat groups included mTOR inhibitors (23.9% and 23.7%), PI3K inhibitors (5.5% and 2.8%), or PARP inhibitors (0.7% and 1.2%).
CDK4/6i denotes cyclin-dependent kinase 4 and 6 inhibitor; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IRT, interactive response technology; ISH, in situ hybridization; met., metastatic; mets., metastases; mo, months; PARP, poly (adenosine diphosphate ribose) polymerase; PI3K, phosphoinositide 3-kinase; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician’s choice.

Table 2. Antitumor Activity by Blinded Independent Central Review, All Populations.

	HER2-low		Intent-to-treat		HER2-ultralow	
	T-DXd (N=359)	**TPC (N=354)**	**T-DXd (N=436)**	**TPC (N=430)**	**T-DXd (N=76)**	**TPC (N=76)**
Confirmed objective response (95% CI) — %	56.5 (51.2–61.7)	32.2 (27.4–37.3)	57.3 (52.5–62.0)	31.2 (26.8–35.8)	61.8 (50.0–72.8)	26.3 (16.9–37.7)
Best confirmed response — no. (%)						
Complete response	9 (2.5)	0	13 (3.0)	0	4 (5.3)	0
Partial response	194 (54.0)	114 (32.2)	237 (54.4)	134 (31.2)	43 (56.6)	20 (26.3)
Stable disease	125 (34.8)	170 (48.0)	148 (33.9)	212 (49.3)	22 (28.9)	42 (55.3)
Progressive disease	22 (6.1)	43 (12.1)	28 (6.4)	50 (11.6)	6 (7.9)	7 (9.2)
Not evaluable	5 (1.4)	25 (7.1)	6 (1.4)	31 (7.2)	1 (1.3)	6 (7.9)
Median duration of response — mo	14.1	8.6	14.3	8.6	14.3	14.1
Median time to first response — mo	2.6	2.7	2.7	2.7	1.9	2.8
Clinical benefit rate — no. (%)*	275 (76.6)	190 (53.7)	334 (76.6)	223 (51.9)	58 (76.3)	33 (43.4)
Disease control rate — no. (%)†	328 (91.4)	284 (80.2)	398 (91.3)	346 (80.5)	69 (90.8)	62 (81.6)

Owing to rounding and because patients with no evidence of disease are not included in this table, percentages may not add up to 100%.

* Defined as complete response rate + partial response rate + stable disease rate at Week 24 by blinded independent central review.

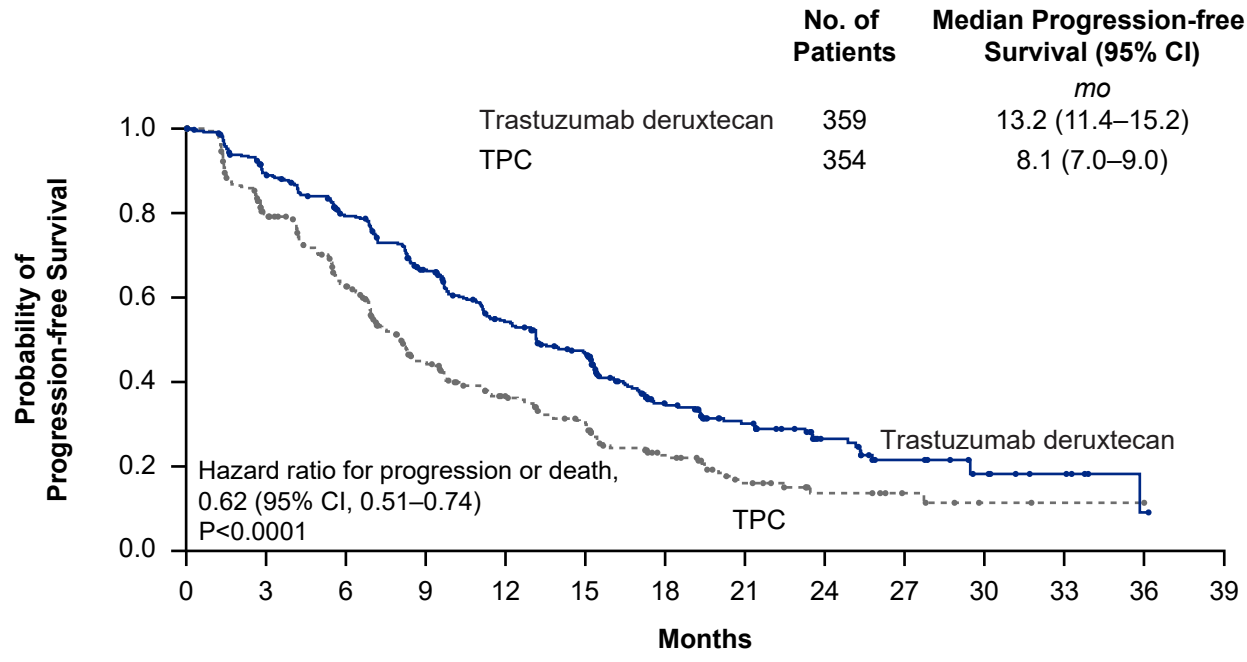
† Defined as complete response rate + partial response rate + stable disease rate by blinded independent central review.

CI denotes confidence interval; HER2, human epidermal growth factor receptor 2; mo, months; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice.

Table 3. Most Common Drug-related Adverse Events (in ≥20% of Patients in Either Treatment Group), Safety Analysis Set.

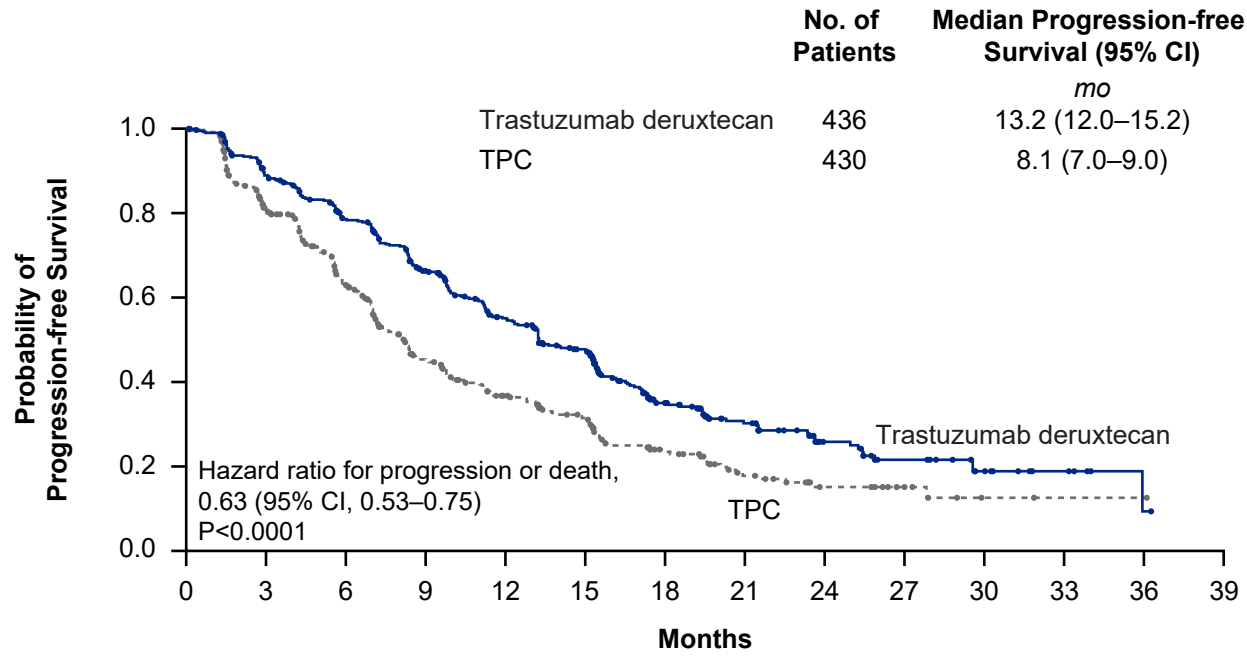
	T-DXd (N=434)		TPC (N=417)	
	All grades	Grade ≥3	All grades	Grade ≥3
Any adverse event — no. (%)				
Nausea	286 (65.9)	7 (1.6)	98 (23.5)	1 (0.2)
Fatigue*	203 (46.8)	16 (3.7)	143 (34.3)	6 (1.4)
Alopecia†	197 (45.4)	0	81 (19.4)	1 (0.2)
Neutropenia‡	163 (37.6)	90 (20.7)	115 (27.6)	69 (16.5)
Transaminases increased§	128 (29.5)	10 (2.3)	49 (11.8)	0
Anemia¶	122 (28.1)	25 (5.8)	81 (19.4)	10 (2.4)
Vomiting	118 (27.2)	6 (1.4)	39 (9.4)	0
Diarrhea	103 (23.7)	8 (1.8)	94 (22.5)	10 (2.4)
Decreased appetite	102 (23.5)	6 (1.4)	39 (9.4)	2 (0.5)
Leukopenia‖	101 (23.3)	30 (6.9)	61 (14.6)	23 (5.5)
PPE syndrome	2 (0.5)	0	135 (32.4)	28 (6.7)

No. (%) of patients with adverse events, sorted in decreasing frequency for preferred term in the T-DXd group. Includes adverse events 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 occurred first).
* Includes the preferred terms fatigue, asthenia, malaise, and lethargy.
† Given that alopecia severity can be classified no higher than Grade 2, it is assumed that the 1 patient with a Grade ≥3 event represents a misclassification.
‡ Includes the preferred terms neutrophil count decreased and neutropenia.
§ Includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal, and liver function test increased.
¶ Includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased.
‖ Includes the preferred terms white blood cell count decreased and leukopenia.
PPE denotes palmar-plantar erythrodysesthesia; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician’s choice.



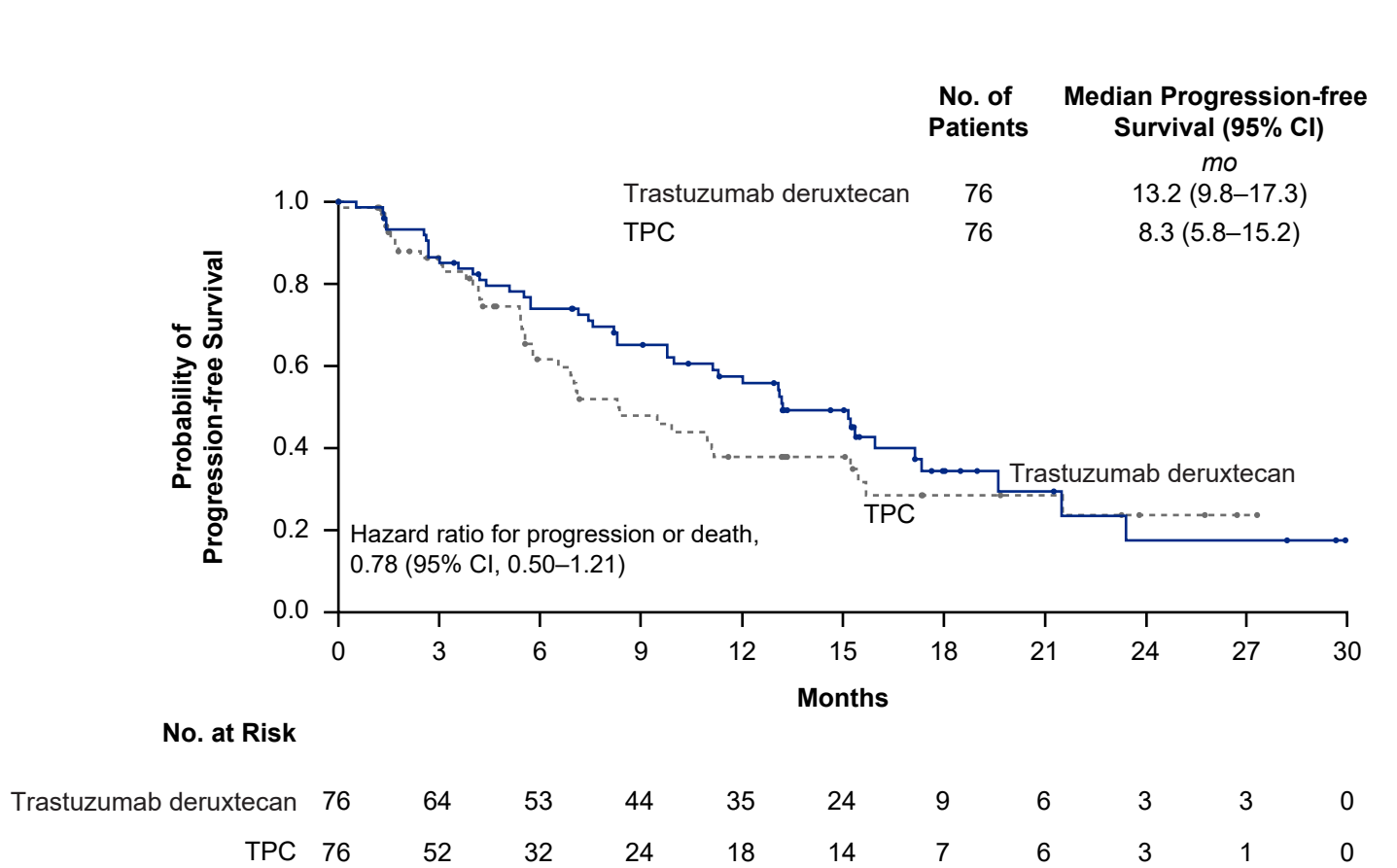
No. at Risk

Trastuzumab deruxtecan	359	310	265	213	163	131	72	49	28	17	10	6	1	0
TPC	354	254	192	118	85	65	37	19	10	6	2	1	1	0



No. at Risk

Trastuzumab deruxtecan	436	375	319	258	199	156	82	56	32	21	11	6	1	0
TPC	430	306	224	142	103	79	44	25	13	7	2	1	1	0


No. of Patients
Median Progression-free Survival (95% CI)
mo
Trastuzumab deruxtecan 76 13.2 (9.8–17.3)
TPC 76 8.3 (5.8–15.2)
Probability of Progression-free Survival
1.0
0.8
0.6
0.4
0.2
0.0
Trastuzumab deruxtecan
TPC
Hazard ratio for progression or death, 0.78 (95% CI, 0.50–1.21)
0 3 6 9 12 15 18 21 24 27 30
Months
No. at Risk
Trastuzumab deruxtecan 76 64 53 44 35 24 9 6 3 3 0
TPC 76 52 32 24 18 14 7 6 3 1 0

	Events/Total no. of patients		Median Progression-free Survival, *mo* (95% CI)		Hazard Ratio for Disease Progression or Death (95% CI)
	Trastuzumab deruxtecan	TPC	Trastuzumab deruxtecan	TPC	
Age					
<65 years	158/252	157/244	13.2 (11.2–15.2)	7.8 (6.9–8.6)	0.59 (0.47–0.74)
≥65 years	67/107	75/110	13.2 (9.7–17.0)	8.5 (6.9–11.5)	0.68 (0.49–0.95)
HER2 status*					
IHC 1+	157/238	150/234	12.9 (11.0–15.2)	8.2 (7.1–9.8)	0.74 (0.59–0.93)
IHC 2+/ISH−	65/117	80/118	15.2 (12.2–21.4)	7.0 (6.2–8.4)	0.43 (0.31–0.60)
Prior CDK4/6i					
Yes	206/324	212/320	13.1 (11.2–15.2)	7.9 (6.9–8.6)	0.61 (0.51–0.74)
No	19/35	20/34	16.1 (9.7–NE)	11.1 (6.9–20.6)	0.64 (0.34–1.21)
Prior taxane use (adjuvant/neoadjuvant setting)					
Yes	94/151	101/151	12.9 (9.7–14.0)	7.4 (6.3–9.3)	0.64 (0.48–0.85)
No	131/208	131/203	15.0 (11.3–16.5)	8.3 (7.0–9.7)	0.59 (0.46–0.76)
Number of prior lines of ET (metastatic setting)					
1	27/54	45/67	15.2 (9.7–19.1)	8.0 (5.7–8.5)	0.45 (0.27–0.72)
2	158/242	153/236	13.1 (11.2–15.2)	8.3 (6.9–10.0)	0.69 (0.55–0.86)
≥3	39/62	33/49	12.3 (8.3–18.5)	8.1 (5.4–9.7)	0.53 (0.33–0.86)
Endocrine resistance†					
Primary	66/105	83/116	13.1 (10.0–15.2)	6.8 (5.3–8.1)	0.56 (0.40–0.78)
Secondary	159/254	148/236	13.2 (11.3–15.5)	9.0 (7.5–11.1)	0.65 (0.52–0.82)
Choice of chemotherapy‡					
Capecitabine	131/220	134/208	13.5 (11.4–15.4)	8.5 (7.0–11.4)	0.62 (0.49–0.79)
Taxanes (nab-paclitaxel **or** paclitaxel)	94/139	98/146	12.9 (9.6–15.4)	7.3 (6.4–8.3)	0.62 (0.46–0.82)
Paclitaxel	38/59	43/56	14.5 (9.6–19.1)	6.3 (5.0–6.9)	0.37 (0.23–0.58)
Nab-paclitaxel	56/80	55/90	12.4 (8.3–15.2)	8.3 (7.1–11.2)	0.82 (0.56–1.20)
Liver metastases					
Yes	163/243	166/232	11.4 (9.8–13.2)	7.0 (6.4–8.1)	0.58 (0.46–0.72)
No	62/116	66/122	17.0 (15.0–19.4)	11.3 (8.2–14.8)	0.66 (0.46–0.93)