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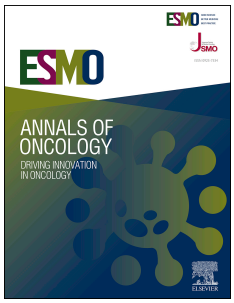

Datopotamab deruxtecan in patients with untreated, advanced triple-negative breast cancer (TROPION-Breast02): a randomised, open-label, international, phase III trial

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Short title: Dato-DXd in untreated, advanced triple-negative breast cancer (TROPION-Breast02)

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*A complete list of investigators who enrolled patients in TROPION-Breast02 is provided as Supplementary Material

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Figures/Tables: 5; 6 total figures and tables limit

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Abstract

Background

Prognosis is poor and treatment options are limited for patients with previously untreated, advanced triple-negative breast cancer (TNBC), especially for those who are not candidates for immunotherapy.

Patients and methods

In the randomised, open-label, phase III TROPION-Breast02 trial, patients with previously untreated, locally recurrent inoperable or metastatic TNBC for whom immunotherapy was not an option were randomised 1:1 to datopotamab deruxtecan (Dato-DXd; 6 mg/kg intravenously every 3 weeks) or investigator's choice of chemotherapy. Randomisation was stratified by geographic location, disease-free interval and programmed cell death ligand-1 status. Dual primary endpoints were progression-free survival (PFS; blinded independent central review per Response Evaluation Criteria in Solid Tumors, version 1.1) and overall survival (OS). Efficacy analyses were performed in the intention-to-treat population. Safety analyses included all patients who received ≥1 dose of study treatment.

Results

Between 16 May 2022 and 11 June 2024, 644 patients were randomised to Dato-DXd (*n* = 323) or chemotherapy (*n* = 321). Median PFS was 10.8 months (95% confidence interval [CI] 8.6–13.0) with Dato-DXd and 5.6 months (95% CI 5.0–7.0) with chemotherapy (hazard ratio 0.57 [99% CI 0.44–0.73]; *P* < 0.0001). Median OS was 23·7 months (95% CI 19.8–25.6) and 18.7 months (95% CI 16.0–21.8) with Dato-DXd and chemotherapy, respectively (hazard ratio 0.79 [95.01% CI 0.64–0.98]; *P* = 0.029). Treatment-related adverse events (TRAEs) of grade ≥3 were reported in 105 (33%) and 89 (29%) patients who received Dato-DXd and chemotherapy, respectively, and TRAEs led to treatment

discontinuation in 14 (4%) and 23 (7%) patients. There were no treatment-related deaths in either arm.

Conclusions

Dato-DXd demonstrated significantly improved PFS and OS versus chemotherapy in patients with previously untreated, locally recurrent inoperable or metastatic TNBC for whom immunotherapy was not an option. Safety was consistent with the known profile for Dato-DXd.

ClinicalTrials.gov: NCT05374512.

Keywords: Datopotamab deruxtecan; Dato-DXd; antibody-drug conjugate; first-line; triple-negative breast cancer; TROPION-Breast02.

Highlights

- In TROPION-Breast02, Dato-DXd demonstrated statistically significantly improved PFS by BICR and OS versus chemotherapy.
- Confirmed ORR was higher, and median DoR was longer, with Dato-DXd compared with chemotherapy.
- The safety profile of Dato-DXd was consistent with previous studies.
- Rates of serious and grade ≥3 TRAEs were similar and discontinuation due to TRAEs was lower with Dato-DXd versus chemotherapy.

Introduction

Approximately 10–20% of patients diagnosed with breast cancer each year have triple-negative breast cancer (TNBC), an aggressive subtype defined by the absence of oestrogen receptors, progesterone receptors and human epidermal growth factor receptor 2 (HER2) overexpression/amplification,[1-4] and associated with early recurrence, high metastasis rates including brain and visceral metastases, and short median survival with metastatic disease.[1-4] First-line treatment options for metastatic TNBC have expanded in recent years for patients with programmed cell death ligand-1 (PD-L1)-positive tumours or germline *BRCA* mutations.[5,6] However, for most patients, including the approximately 70% who are not candidates for immunotherapy,[7] chemotherapy remains the mainstay of first-line therapy and is associated with modest response rates and limited durability of responses.[2,7-9] While real-world data have inherent limitations, studies have shown that approximately half of patients with metastatic TNBC do not receive treatment beyond first line therapy.[7,10] Novel strategies are therefore needed to provide improved clinical outcomes with first-line treatment.

Datopotamab deruxtecan (Dato-DXd) is a trophoblast cell-surface antigen 2 (TROP2)-directed antibody-drug conjugate (ADC) consisting of a humanised anti-TROP2 immunoglobulin G1 monoclonal antibody attached to a highly potent topoisomerase I inhibitor payload via a plasma-stable, tumour-selective cleavable linker.[11] Dato-DXd is approved for the treatment of adult patients with unresectable or metastatic, hormone receptor-positive, HER2-negative breast cancer who have received prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease, based on results from the phase III TROPION-Breast01 trial (NCT05104866).[12-15] Dato-DXd also demonstrated encouraging activity and a manageable safety profile in patients with previously treated metastatic TNBC in the phase I TROPION-PanTumor01 trial (NCT03401385).[16]

We conducted the international, open-label phase III TROPION-Breast02 trial (NCT05374512) to assess Dato-DXd monotherapy versus investigator's choice of chemotherapy in patients with

previously untreated, locally recurrent inoperable or metastatic TNBC for whom immunotherapy was not an option.

Methods

Study Design and Patients

Full details of the TROPION-Breast02 trial design have been published previously.[17] Patients were aged ≥18 years and had an Eastern Cooperative Oncology Group performance status of 0 or 1, histologically or cytologically documented locally recurrent inoperable or metastatic TNBC (as defined by American Society of Clinical Oncology/College of American Pathologists guidelines), with no prior therapy in this setting and at least one measurable lesion per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Patients must have had PD-L1-low tumours (combined positive score <10) or PD-L1-high tumours (combined positive score ≥10) with: disease relapse after prior PD-(L)1 inhibitor therapy for early-stage breast cancer; comorbidities precluding PD-(L)1 inhibitor therapy; or no regulatory access to PD-(L)1 inhibitor therapy. Details of the PD-(L)1 testing methods are provided in the Supplementary Methods. The percentage of patients with PD-L1-high tumours who would otherwise have been eligible for pembrolizumab but did not have regulatory access was capped at approximately 10% of randomised patients. Patients with known germline *BRCA* pathogenic variants (based on testing performed as part of routine clinical practice) presenting with locally recurrent inoperable or metastatic TNBC were eligible for the study, if another therapy (such as a poly adenosine diphosphate-ribose polymerase inhibitor) was not considered the best treatment option for the patient in the opinion of the treating physician. There was no required minimum disease-free interval (DFI; time from completion of treatment with curative intent to the first documented local or distant disease recurrence). The percentage of patients with a DFI of 0–12 months was capped at approximately 20% of randomised patients. Complete eligibility criteria are provided in the protocol (Supplementary Material).

The institutional review board or ethics committee at each investigational site approved the trial before initiation, and the trial was performed in accordance with the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice guidelines and all applicable laws and regulations. All patients provided written informed consent.

Procedures

Patients were randomly assigned 1:1 to receive either intravenous Dato-DXd 6 mg/kg once every 3 weeks or investigator's choice of chemotherapy. The chemotherapy regimen was selected based on DFI and prior taxane exposure. For patients with no prior taxane, or prior taxane in the neoadjuvant or adjuvant setting and a DFI >12 months, investigator's choice of chemotherapy could be paclitaxel or nab-paclitaxel, per treatment guidelines.[18,19] For patients with prior taxane exposure and a disease-free interval ≤12 months, investigator's choice of chemotherapy could be carboplatin, eribulin mesylate/eribulin, or capecitabine. Further details are provided in the Supplementary Methods. Randomisation was stratified according to geographic location (United States, Canada, and Europe versus other geographic regions), DFI (*de novo* disease versus prior DFI 0–12 months versus prior DFI >12 months), and PD-L1 status as assessed by a central laboratory (PD-L1-high versus PD-L1-low). Randomisation was performed using central interactive response technology. Treatment continued until investigator-defined disease progression according to RECIST version 1.1, unacceptable toxicity, withdrawal of consent or another discontinuation criterion was met. No crossover between study arms was allowed; however, following progression or discontinuation of study treatment, patients could receive subsequent therapies in either arm, including approved ADCs, at the investigator's discretion.

Outcomes

The dual primary endpoints were progression-free survival (PFS; time from randomisation until progression per RECIST version 1.1 or death due to any cause) by blinded independent central review (BICR) and overall survival (OS; time from randomisation until death due to any cause).

Secondary endpoints reported in this article are objective response rate (ORR), duration of response (DoR), disease control rate at 12 weeks, all by BICR, PFS by investigator assessment, patient-reported outcomes (time to deterioration in pain, physical functioning, global health status/quality of life and breast and arm symptoms using the European Organisation for Research and Treatment of Cancer [EORTC] item libraries [IL] 146 and 116) and safety. Other secondary endpoints are detailed in the Supplementary Methods.

Tumour assessments per RECIST version 1.1 were conducted at baseline, within 28 days of treatment initiation, every 6 weeks from randomisation for 48 weeks and then every 9 weeks until radiologic disease progression per investigator assessment, followed by an additional assessment after progression. In the assessment of patient-reported outcomes endpoints, time to deterioration was assessed in the intention-to-treat (ITT) population and was defined in two ways as prespecified in the protocol: time to first deterioration, defined as the time from the date of randomisation to the date of the first deterioration based on derived meaningful change thresholds, and time to confirmed deterioration, which required deterioration to be confirmed at a subsequent timepoint. Analysis of time to deterioration used the same methodology as PFS analyses. Further details of the assessment of patient-reported outcome secondary endpoints are provided in the Supplementary Methods. Safety and tolerability were assessed continuously throughout the study period from 28 days before treatment until the last study follow-up. AEs were coded using the Medical Dictionary for Regulatory Activities and graded according to the National Cancer Institute Common Terminology Criteria for AEs version 5.0. Methods for a post-hoc analysis of exposure-adjusted incidence of AEs, and details of the prevention and management of AEs, are provided in the Supplementary Methods.

Statistical analysis

Approximately 1100 participants were planned to be screened/enrolled to randomise 600 patients to study intervention. A prospectively specified multiple testing procedure with an alpha-exhaustive

recycling strategy was implemented for the dual primary endpoints to control the two-sided type 1 error rate at 5%. The overall alpha of 5% was split with 1% to evaluate PFS and 4% to evaluate OS. Statistical methods, powering, and planned interim analyses are described in the Supplementary Methods. If PFS met its significance boundary, the 1% alpha could be reallocated and OS tested at the 5% level. If at least 323 OS events (representing 95% of the 340 planned events required for the final analysis) had occurred at the time of the primary PFS analysis, a single OS analysis was to be performed at that time. To control for type I error more conservatively in this scenario, 0.01% alpha was to be deducted from the overall two-sided type I error, and OS was to be tested at a significance level of 3.99% (two-sided) if PFS was not statistically significant or 4.99% (two-sided) if PFS was statistically significant.

All efficacy analyses were conducted in the ITT population, comprising all randomised patients. The safety analysis set comprised all patients who had received at least one dose of study treatment. A log rank test stratified by DFI and PD-L1 status was used to compare PFS by BICR between the treatment groups. The hazard ratio (HR) and 99% confidence intervals (CIs) were estimated from a stratified Cox proportional hazards model. OS was analysed using a similar methodology as PFS, stratified by DFI; a HR with 95.01% CIs was estimated. Pre-defined subgroup analyses of PFS and OS were performed, including by stratification factors and baseline characteristics, with HRs and 95% CIs calculated using unstratified Cox proportional hazards models. The widths of the 95% CIs for analyses beyond the primary comparison were not adjusted for multiplicity and should not be used in place of hypothesis testing.

To better understand the impact of subsequent anti-cancer therapies on OS, an OS sensitivity analysis methodology was prespecified using inverse probability censoring weighting (IPCW), with adjustment for pre-defined baseline prognostic covariates in both the weighting and outcome models. Details of this methodology are provided in the Supplementary Methods. Sensitivity

analyses for subgroups were not prespecified; however, in a post-hoc analysis, the prespecified IPCW methodology was applied to the United States/Canada/Europe subgroup.

Results

Between 16 May 2022 and 11 June 2024, 1277 patients were screened across 229 centres in 23 countries; a full list of locations is provided in the Supplementary Appendix. Of 323 patients who were randomly assigned to the Dato-DXd arm and 321 patients assigned to the chemotherapy arm (174 [54%] to nab-paclitaxel, 89 [28%] paclitaxel, 36 [11%] eribulin/eribulin mesylate, 15 [5%] carboplatin and 7 [2%] capecitabine), 319 (99%) and 309 (96%) received treatment, respectively (Supplementary Figure S1). Details of important protocol deviations are provided in Supplementary Table S1.

Patient demographics and baseline characteristics were similar between treatment arms (Table 1). In the Dato-DXd and chemotherapy arms, respectively, 47 (15%) and 51 (16%) patients had a DFI of 0–6 months. At data cutoff (25 August 2025), the median duration of study follow-up was 27.5 (range 13.3–38.7) months; 45/319 (14%) patients in the Dato-DXd arm and 8/309 (3%) patients in the chemotherapy arm remained on treatment.

PFS by BICR was significantly longer with Dato-DXd compared with chemotherapy (HR for progression or death, 0.57 [99% CI 0.44–0.73]; $P < 0.0001$; Figure 1A). Median PFS was 10.8 months (95% CI 8.6–13.0) in the Dato-DXd arm and 5.6 months (95% CI 5.0–7.0) in the chemotherapy arm. A consistent benefit was observed across all prespecified patient subgroups (Figure 1B). PFS by investigator assessment was consistent with PFS by BICR (HR for progression or death, 0.56 [95% CI 0.47–0.67]; Supplementary Figure S2).

OS was significantly longer with Dato-DXd compared with chemotherapy (HR for death, 0.79 [95.01% CI 0.64–0.98]; $P = 0.029$; Figure 2A). Median OS was 23.7 months (95% CI 19.8–25.6) in the Dato-DXd arm and 18.7 months (95% CI 16.0–21.8) in the chemotherapy arm. The improvement in OS was

consistent across most prespecified patient subgroups, except for the geographic region comprising the United States, Canada and Europe (HR 1.22 [95% CI 0.86–1.73]), patients with a DFI of 0–12 months (HR 1.02 [95% CI 0.68–1.53]) and patients with eribulin mesylate/eribulin (HR 1.11 [95% CI 0.64–1.96]) or carboplatin (HR 1.23 [95% CI 0.51–2.89]) as pre-selected choice of chemotherapy (Figure 2B).

At data cutoff, 210 (65%) patients in the Dato-DXd arm and 232 (72%) in the chemotherapy arm had received any post-progression/discontinuation anticancer therapy, of whom 44/210 (21%) and 95/232 (41%) had received subsequent ADC therapy, respectively (Supplementary Table S2a). In a comparison of the pre-defined baseline covariates incorporated into the IPCW in the United States/Canada/Europe subgroup, some imbalances between treatment arms were observed, such as a higher number of patients with three metastatic sites (23% versus 15%), more than three metastatic sites (13% versus 8%), liver metastases (31% versus 29%) and brain metastases (10% versus 6%) in the Dato-DXd arm compared with the chemotherapy arm. Additionally, use of subsequent ADCs was higher in the United States/Canada/Europe subgroup compared with the overall study population (51% versus 31% of those who received any subsequent therapy), and within the United States/Canada/Europe subgroup, their use was more frequent in the chemotherapy arm compared with the Dato-DXd arm (70% versus 31%; Supplementary Table S2a). When the prespecified IPCW methodology was applied to the United States/Canada/Europe subgroup, the analysis adjusting for pre-defined baseline covariates and subsequent ADC use yielded an adjusted OS HR of 0.90 (95% CI 0.54–1.51).

The ORR was 63% (202 patients) with Dato-DXd and 29% (94 patients) with chemotherapy, and 9% (29 patients) and 2% (8 patients), respectively, had a complete response (Table 2). The improvement in ORR with Dato-DXd versus chemotherapy was consistent across all subgroups (Supplementary Figure S3a). The median DOR was 12.3 months (95% CI 9.1–15.9) in the Dato-DXd arm and 7.1 months (95% CI 5.6–8.9) in the chemotherapy arm (Table 2; Supplementary Figure S2b).

At data cutoff, the median duration of treatment was 8.5 months (range 0.7–38.0) in the Dato-DXd arm and 4.1 months (range 0.1–32.0) in the chemotherapy arm. In the Dato-DXd arm, 35% (112 patients) of patients had total treatment exposure of >12 months, compared with 9% (29 patients) in the chemotherapy arm. Treatment-related adverse events (TRAEs) occurred in 296 (93%) and 257 (83%) patients who received Dato-DXd and chemotherapy, respectively; TRAEs of grade ≥3 were reported in 105 (33%) and 89 (29%) patients, respectively (Table 3). With Dato-DXd and chemotherapy, respectively, TRAEs led to discontinuation of treatment in 14 (4%) and 23 (7%) of patients. There were no fatal TRAEs in either arm. In a post-hoc exploratory analysis of exposure-adjusted incidence of AEs, rates of any-grade TRAEs, grade ≥3 TRAEs, serious TRAEs, and TRAEs associated with discontinuation were lower with Dato-DXd compared with chemotherapy (Supplementary Figure S4). Treatment-emergent AEs are summarised in Supplementary Table S3.

The most common TRAEs of any grade were stomatitis (182 [57%]), nausea (142 [45%]) and alopecia (130 [41%]) in the Dato-DXd arm, and alopecia (96 [31%]), neutropenia (90 [29%]; grouped term comprising neutropenia and neutrophil count decreased) and fatigue (86 [28%]; grouped term comprising fatigue, asthenia and malaise) in the chemotherapy arm (Table 3).

TRAEs of special interest for Dato-DXd are shown in Supplementary Table S4. Treatment-related oral mucositis/stomatitis events were mostly grade 1 or 2 (maximum grade 1/grade 2/grade 3: 78 [24%]/ 87 [27%]/ 27 [8%] patients) and led to dose interruption or reduction in 11 (3%) and 36 (11%) patients, respectively; no patients discontinued treatment due to treatment-related oral mucositis/stomatitis. Median time to onset of events was 26.0 days, and median time to resolution of grade ≥2 events to grade ≤1 was 40.5 days (Supplementary Table S5). Treatment-related ocular surface events with Dato-DXd were also mostly grade 1 or 2 (maximum grade 1/grade 2/grade ≥3: 76 [24%]/ 50 [16%]/ 23 [7%] patients; Supplementary Table S4) and led to dose interruption, reduction and discontinuation in 18 (6%), 14 (4%) and 3 (1%) patients, respectively. Median time to onset of events was 77.5 days, and median time to resolution of grade ≥2 events to grade ≤1 was

64.0 days (Supplementary Table S5). The most frequent ocular surface event was grade 1 dry eye (51 [16%] patients). Nine (3%) patients in the Dato-DXd arm had adjudicated drug-related interstitial lung disease/pneumonitis events; all but one of these patients had grade 1 or 2 events, and one patient had a grade 5 event (Supplementary Table S4). The grade 5 event was characterised by the investigator as grade 3 pneumonitis, with death assessed as related to breast cancer. The patient received 20 cycles of Dato-DXd, and the death occurred 56 days after discontinuation of Dato-DXd. Median time to onset of interstitial lung disease/pneumonitis events was 259.0 days, and median time to full resolution of events was 112.5 days (Supplementary Table S5).

Regarding patient-reported outcomes, baseline compliance with EORTC IL146 was 71% and 67% with Dato-DXd and chemotherapy, respectively, and 64% and 58% overall, and baseline compliance with EORTC IL116 was 72% and 68% with Dato-DXd and chemotherapy, respectively, and 65% and 58% overall. Time to first and confirmed deterioration in pain, physical functioning, global health status/quality of life, and breast and arm symptoms were numerically in favour (HR <1) of the Dato-DXd arm compared with the chemotherapy arm (Supplementary Table S6).

Discussion

In this phase III, randomised trial, first-line Dato-DXd demonstrated a significant improvement in both dual primary endpoints of PFS and OS in patients with advanced TNBC for whom immunotherapy was not an option, with median PFS and OS both approximately 5 months longer than with chemotherapy. Furthermore, with Dato-DXd versus chemotherapy, confirmed ORR was higher, and median DoR was longer. Patients were on treatment for substantially longer in the Dato-DXd arm, but rates of serious and grade ≥3 TRAEs were similar, and the rate of discontinuation due to TRAEs was lower, versus chemotherapy. After adjusting for the differences in treatment exposure between arms, rates of TRAEs (any-grade, grade ≥3, serious and associated with discontinuation) were lower with Dato-DXd compared with chemotherapy.

TROPION-Breast02 addresses a need to improve clinical outcomes with first-line treatment for patients with metastatic TNBC for whom immunotherapy is not an option, a group that represents approximately 70% of patients with metastatic TNBC.[7] Chemotherapy options for these patients are associated with modest response rates and limited DoR.[8,9] Participants in TROPION-Breast02 were largely representative of the real-world population with metastatic TNBC at the time of study enrolment, and included patients with a DFI of 0–12 months and/or brain metastases. Furthermore, patients with early progression or relapse on or following curative intent therapy, with a DFI of 0–6 months, comprised 15% of the TROPION-Breast02 population; these patients are typically excluded from clinical trials and have particularly poor clinical outcomes.[20]

In subgroup analyses, the improvements in PFS and ORR with Dato-DXd versus chemotherapy were consistent across all patient subgroups, including by geographic region, PD-L1 status and DFI. The improvement in OS with Dato-DXd versus chemotherapy was also seen across most subgroups; the observation of HRs >1 in a small number of subgroups should be interpreted with caution due to wide 95% CIs that crossed 1, the fact that subgroup analyses were descriptive and not adjusted for multiplicity, and small patient numbers in some subgroups. The OS HR observed in the United States/Canada/Europe region subgroup was 1.22 (95% CI 0.86–1.73); the study was not powered to assess treatment effects within individual regions, so these results are exploratory in nature. It is likely that there were multiple factors contributing to the OS result in this subgroup. We observed imbalances in some baseline characteristics, with a higher proportion of patients with poor prognostic features in the Dato-DXd arm than in the chemotherapy arm (such as ≥3 metastatic sites, liver metastases and brain metastases). Furthermore, there was greater use of subsequent ADCs in the United States/Canada/Europe subgroup compared with the overall study population, and in the chemotherapy arm compared with the Dato-DXd arm within the United States/Canada/Europe subgroup. To better understand the observed result in this region, we applied the prespecified IPCW sensitivity analysis method to the subgroup, which yielded an adjusted OS HR of 0.90 (95% CI 0.54–1.51). This indicates that the OS HR in the United States/Canada/Europe region subgroup may be

confounded by the observed imbalances in subsequent ADC use and baseline prognostic characteristics between the two arms.

The phase III ASCENT-03 trial assessed another TROP2-directed ADC, sacituzumab govitecan, as first-line treatment for advanced TNBC; sacituzumab govitecan demonstrated improved PFS versus chemotherapy, and the reported OS HR, in a descriptive analysis at the time of the primary PFS analysis, was 0.98 (95% CI 0.75–1.30). ORRs were similar between arms, but median DoR was longer with sacituzumab govitecan than with chemotherapy.[22] Data from both TROPION-Breast02 and ASCENT-03 demonstrate that TROP2-directed ADCs improve efficacy outcomes compared with chemotherapy as first-line treatment for patients with metastatic TNBC. There were key differences in design between ASCENT-03 and TROPION-Breast02; ASCENT-03 permitted patients with DFI >6 months while TROPION-Breast02 included patients regardless of DFI, and chemotherapy options were different between the two studies, although ≥50% of patients in the control arm of both studies received taxane monotherapy. In both ASCENT-03 and TROPION-Breast02, patients could receive subsequent ADC therapy. In ASCENT-03, patients randomised to chemotherapy were eligible for protocol-specified crossover to sacituzumab govitecan upon disease progression. In the sacituzumab govitecan arm compared with the chemotherapy arm, 45% versus 64% of patients, respectively, received any subsequent therapy, and 82% of the patients who received subsequent therapy in the chemotherapy arm received sacituzumab govitecan.[22] In TROPION-Breast02, following progression or discontinuation of study treatment, patients could receive any appropriate subsequent therapy at the discretion of the investigator, and so treatment options reflected regulatory approvals, available standard of care and real-world practice. Overall, 65% and 72% of patients in Dato-DXd and chemotherapy arms, respectively, received subsequent therapy. Among those who received subsequent therapy, 21% in the Dato-DXd arm and 41% in the chemotherapy arm received a subsequent ADC, with sacituzumab govitecan being the most commonly used option, followed by trastuzumab deruxtecan. Both TROPION-Breast02 and ASCENT-03 shared a primary endpoint of PFS by BICR. In TROPION-Breast02, there were 408 PFS events by BICR, and

499 PFS events by investigator assessment. In the study, treatment discontinuation was based on investigator-assessed disease progression; as such, the main reason for censoring for PFS events by BICR was discontinuation of tumour imaging scans by the investigator after investigator-assessed disease progression. The rate of discordance between investigator-assessed and BICR PFS on the study is consistent with available data from other clinical trials for metastatic breast cancer.[23,24] Importantly, the result for the secondary endpoint of PFS by investigator assessment (HR 0.56) was consistent with the result for the dual primary endpoint of PFS by BICR (HR 0.57).

The safety profile of Dato-DXd in TROPION-Breast02 was consistent with previous studies.[12,16] Common TRAEs with Dato-DXd included stomatitis, nausea and other gastrointestinal events, and dry eye, reflecting the expression of TROP2 not only on the surface of tumour cells but also on many normal tissue cells, including in the oral mucosa, oesophagus, stomach and corneal epithelium.[25] Notably, the majority of oral mucositis/stomatitis and ocular surface events related to Dato-DXd were grade 1 or 2, and most grade ≥2 events had resolved to grade ≤1 at data cutoff; no patients discontinued Dato-DXd treatment due to oral mucositis/stomatitis, and three patients (1%) discontinued due to ocular surface events. The safety profiles of other TROP2-directed ADCs (sacituzumab govitecan and sacituzumab tirumotecan) in breast cancer studies differ from that of Dato-DXd, likely due to differences in payload, linker stability and cleavage mechanisms, rates of internalisation and drug-to-antibody ratio.[11,26,27] Haematologic toxicity is a recognised common feature of the safety profiles of sacituzumab govitecan and sacituzumab tirumotecan.[22,28-31]

Patient-reported outcomes provide meaningful insights on patients' experiences of symptoms, functioning and quality of life, supplementing physician-reported safety data and supporting the evaluation of treatment tolerability in oncology trials. In TROPION-Breast02, Dato-DXd had a favourable impact compared with chemotherapy on the secondary endpoints of time to deterioration in pain, physical functioning, global health status/quality of life, and breast and arm symptoms.

Limitations of the TROPION-Breast02 trial include the open-label design. Additionally, the treatment landscape for TNBC is rapidly evolving, and the TROPION-Breast02 patient population reflects the landscape at the time of trial recruitment. While (neo)adjuvant chemotherapy plus pembrolizumab is now the recommended treatment for high-risk early-stage disease, it was first approved in the United States in July 2021,[32] less than a year before the start of enrolment in TROPION-Breast02; the timing of subsequent approvals in other regions, and the interval between (neo)adjuvant treatment and disease recurrence prior to study entry, is likely to have limited the number of patients in TROPION-Breast02 who had received prior PD-(L)1 inhibitor therapy (approximately 5% of patients in each arm). Another limitation of this study is that, while trial diversity goals were met globally and multiple initiatives were employed to recruit a diverse patient population in TROPION-Breast02 (including the selection of study sites based on diversity enrolment goals, diversity awareness trainings and patient-friendly materials, and collaboration with health literacy and patient advocacy groups), the percentage of Black patients enrolled was small (approximately 4%). Considering the higher rate of TNBC in Black women compared with other racial and ethnic groups,[33] continued efforts are needed to ensure Black patients are represented in clinical studies in this setting.

In TROPION-Breast02, first-line Dato-DXd demonstrated clinically meaningful and significant improvements in PFS and OS and a higher ORR compared with chemotherapy, as well as a manageable safety profile, with PROs complementing the efficacy and safety results observed. These data support Dato-DXd as a first-line treatment option for patients with locally recurrent inoperable or metastatic TNBC for whom immunotherapy is not an option.

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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/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

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Figure 1. PFS by BICR and subgroup analysis in the ITT population

Figure 1 file uploaded separately

a Numbers are rounded; median PFS was 10.84 (95% CI 8.57–12.98) months with Dato-DXd and 5.55 (95% CI 4.96–6.97) months with chemotherapy, with a delta of 5.29 months.

b The HR (95% CI) for the treatment comparison is not shown in instances in which fewer than 20 events were reported across both treatment groups in a subgroup.

BICR, blinded independent central review; CI, confidence interval; CPS, combined positive score; Dato-DXd, datopotamab deruxtecan; DFI, disease-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescent in situ hybridisation; HR, hazard ratio; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridisation; ITT, intention-to-treat; PD-L1, programmed cell death ligand-1; PFS, progression-free survival.

Figure 2. OS and subgroup analysis in the ITT population

Figure 2 file uploaded separately

a The HR (95% CI) for the treatment comparison is not shown in instances in which fewer than 20 events were reported across both treatment groups in a subgroup.

CI, confidence interval; CPS, combined positive score; Dato-DXd, datopotamab deruxtecan; DFI, disease-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescent in situ hybridisation; HR, hazard ratio; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridisation; ITT, intention-to-treat; OS, overall survival; PD-1, programmed cell death ligand; PD-L1, programmed cell death ligand.

Table 1. Demographic and clinical characteristics of all randomised patients at baseline

Characteristic	Dato-DXd (*N* = 323)	Chemotherapy (*N* = 321)
Median age, years (range)	56 (27–85)	57 (23–83)
Age ≥65 years	78 (24)	82 (26)
Female sex	323 (100)	319 (99)
Race		
Asian	151 (47)	131 (41)
White	131 (41)	153 (48)
Black or African American	13 (4)	14 (4)
Other/mixed race	7 (2)	6 (2)
Not reported	21 (7)	17 (5)
Ethnicity		
Hispanic or Latino	45 (14)	52 (16)
Not Hispanic or Latino	271 (84)	265 (83)
Missing	7 (2)	4 (1)
Region		
United States, Canada, and Europe	120 (37)	120 (37)
Other geographic regions	203 (63)	201 (63)
ECOG PS		
0	195 (60)	182 (57)
1	128 (40)	139 (43)
Disease characteristics		
Overall disease classification		
Locally recurrent inoperable	9 (3)	9 (3)

Characteristic	Dato-DXd (*N* = 323)	Chemotherapy (*N* = 321)
Recurrent metastatic	205 (63)	202 (63)
De novo metastatic	109 (34)	110 (34)
HER2 expression		
Negative	323 (100)	320 (>99)
IHC negative	21 (7)	12 (4)
IHC 0	188 (58)	192 (60)
IHC 1+ and IHC 2+/FISH/ISH-ve	112 (35)	115 (36)
IHC missing and FISH/ISH-ve	2 (<1)	1 (<1)
Missing	0	1 (<1)
Sites of metastasis		
Brain	36 (11)	28 (9)
Liver	93 (29)	98 (31)
Visceral	253 (78)	233 (73)
Number of metastatic sites		
<3	207 (64)	215 (67)
≥3	116 (36)	106 (33)
DFI history		
De novo	109 (34)	110 (34)
0–12 months	67 (21)	66 (21)
0–6 months	47 (15)	51 (16)
>12 months	147 (46)	145 (45)
PD-L1 status		
Low (CPS <10)	287 (89)	291 (91)

Characteristic	Dato-DXd (*N* = 323)	Chemotherapy (*N* = 321)
High (CPS ≥10)	34 (11)	29 (9)
Missing/not applicable	2 (<1)	1 (<1)
PD-L1 high – reason for inclusion		
Prior (neo)adjuvant PD-(L)1 inhibitor therapy	4 (1)	5 (2)
Comorbidities that preclude PD-1/PD-L1 inhibitor therapy	3 (<1)	4 (1)
No regulatory access to PD-1/PD-L1 inhibitor therapy	27 (8)	20 (6)
BRCA mutation status		
BRCA testing reported	96 (30)	89 (28)
Deleterious mutation, known or suspected	8 (3)	11 (3)
No deleterious mutation, known or suspected	88 (27)	76 (24)
Missing data	0	2 (<1)
BRCA testing not reported	227 (70)	232 (72)
Prior therapies and choice of chemotherapy		
Previous neoadjuvant/adjuvant therapy		
Neoadjuvant therapy	125 (39)	125 (39)
Adjuvant therapy	170 (53)	153 (48)
Previous cancer therapy		
Any	215 (67)	207 (64)

Characteristic	Dato-DXd (*N* = 323)	Chemotherapy (*N* = 321)
Taxanes	186 (58)	179 (56)
Nitrogen mustard analogues	185 (57)	183 (57)
Anthracyclines[a]	182 (56)	178 (55)
Pyrimidine analogues	87 (27)	84 (26)
Platinum compounds	51 (16)	52 (16)
PD-1/PD-L1 inhibitors	15 (5)	18 (6)
Pre-selected choice of chemotherapy[b]		
Nab-paclitaxel	180 (56)	172 (54)
Paclitaxel	82 (25)	92 (29)
Eribulin mesylate/eribulin	43 (13)	35 (12)
Carboplatin	11 (3)	14 (4)
Capecitabine	7 (2)	8 (2)

Data are *n* (%) unless otherwise stated.

a Includes anthracycline-related substances.

b As reported by the investigator at screening. The chemotherapy received by patients after randomisation could differ from this.

CPS, combined positive score; Dato-DXd, datopotamab deruxtecan; DFI, disease-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescent in situ hybridisation; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridisation; PD-(L)1, programmed cell death (ligand)-1.

Table 2. Overview of response by BICR in the ITT population

Variable	Dato-DXd (*N* = 323)	Chemotherapy (*N* = 321)
Confirmed objective response, *n* (%)	202 (63)	94 (29)
Odds ratio (95% CI)	4.24 (3.03–5.95)	
Best objective response, *n* (%)		
Complete response	29 (9)	8 (2)
Partial response	173 (54)	86 (27)
Stable disease	87 (27)	151 (47)
Stable disease ≥5 weeks[a]	72 (22)	125 (39)
Unconfirmed partial response[b]	15 (5)	25 (8)
Unconfirmed complete response[b]	0	1 (<1)
Progressive disease	27 (8)	52 (16)
RECIST progression	26 (8)	43 (13)
Death	1 (<1)	9 (3)
Not evaluable[c]	7 (2)	24 (7)
Incomplete post-baseline assessment	5 (2)	16 (5)
Stable disease <5 weeks	0	1 (<1)
No evidence of disease	1 (<1)	3 (1)
Disease control rate at 12 weeks	84%	60%
Odds ratio (95% CI)	3.71 (2.53–5.46)	
Median time to response — months (IQR)	1.4 (1.3–2.8)	1.6 (1.5–2.9)
Median DoR — months (95% CI)	12.3 (9.1–15.9)	7.1 (5.6–8.9)

Percentages are rounded to whole numbers; values reported for individual rows may therefore not sum to total values reported for combined categories.

a Tumour imaging was performed every 6 weeks ±7 days from random assignment, and so stable disease was recorded at least 5 weeks/35 days after random assignment (to allow for an early assessment within the assessment window).

b Responses were achieved but no confirmation assessment was performed, or a confirmation assessment was performed but the response was not confirmed.

c For *n* = 1 patient in the Dato-DXd arm and *n* = 4 patients in the chemotherapy arm, reason for not being evaluable was reported as 'not applicable'.

BICR, blinded independent central review; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; IQR, interquartile range; ITT, intention-to-treat; RECIST, Response Evaluation Criteria in Solid Tumours.

Table 3. TRAEs (safety population)

TRAEs, *n* (%)	Dato-DXd (*N* = 319)		Chemotherapy (*N* = 309)	
Any event	296 (93)		257 (83)	
Grade ≥3	105 (33)		89 (29)	
Serious	29 (9)		26 (8)	
Associated with dose interruption	76 (24)		60 (19)	
Associated with dose reduction	85 (27)		56 (18)	
Associated with treatment discontinuation	14 (4)		23 (7)	
Associated with death	0		0	
Occurring in ≥10% of patients,[a] *n* (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Stomatitis	182 (57)	27 (8)	27 (9)	0
Nausea	142 (45)	2 (<1)	53 (17)	2 (<1)
Alopecia	130 (41)	NA[g]	96 (31)	NA[g]
Fatigue[b]	101 (32)	8 (3)	86 (28)	9 (3)
Dry eye	76 (24)	4 (1)	9 (3)	0
Constipation	72 (23)	1 (<1)	31 (10)	0
Vomiting	65 (20)	4 (1)	23 (7)	1 (<1)
Decreased appetite	49 (15)	1 (<1)	20 (6)	1 (<1)
Anaemia[c]	48 (15)	6 (2)	64 (21)	10 (3)
Keratitis	42 (13)	7 (2)	1 (<1)	0

TRAEs, *n* (%)	Dato-DXd (*N* = 319)		Chemotherapy (*N* = 309)	
Neutropenia[d]	39 (12)	10 (3)	90 (29)	40 (13)
Amylase increased	33 (10)	20 (6)	4 (1)	0
Rash	32 (10)	2 (<1)	20 (6)	0
AST increased	30 (9)	1 (<1)	23 (7)	2 (<1)
Leukopenia[e]	27 (8)	3 (1)	55 (18)	13 (4)
Diarrhoea	18 (6)	0	41 (13)	3 (1)
Peripheral neuropathy[f]	14 (4)	0	75 (24)	5 (2)
Pneumonia	10 (3)	4 (1)	5 (2)	3 (1)
Febrile neutropenia	0	0	4 (1)	4 (1)

a Also includes TRAEs that occurred at grade ≥3 in ≥1% of patients in either arm. Relatedness to treatment was as assessed by the investigators.

b Grouped term comprising preferred terms of fatigue, asthenia, and malaise.

c Grouped term comprising preferred terms of haemoglobin decreased, red blood cell count decreased, anaemia and haematocrit decreased.

d Grouped term comprising preferred terms of neutrophil count decreased and neutropenia.

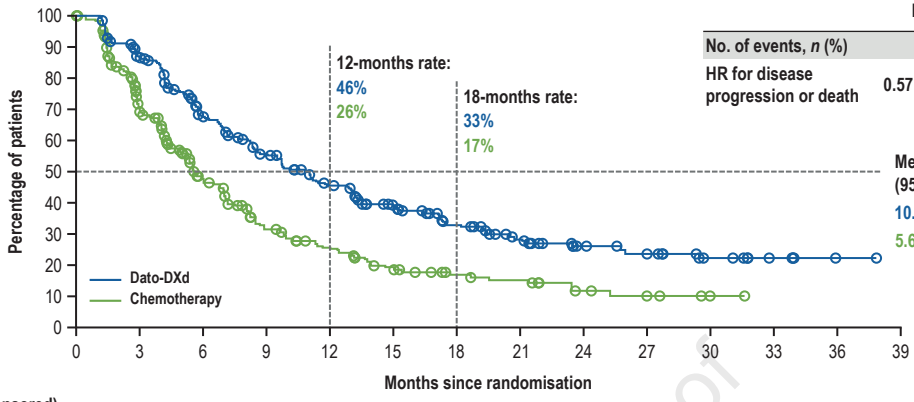
e Grouped term comprising preferred terms of white blood cell count decreased and leukopenia.

f Grouped term comprising preferred terms of neuropathy peripheral, peripheral motor neuropathy, polyneuropathy, paraesthesia and peripheral sensory neuropathy.

g Per Common Terminology Criteria for Adverse Events version 5.0, the maximum grade for alopecia is grade 2.

AST, aspartate aminotransferase; Dato-DXd, datopotamab deruxtecan; NA, not applicable; TRAE, treatment-related adverse event.

A PFS



	Dato-DXd	Chemotherapy
No. of events, *n* (%)	199 (62)	209 (65)
HR for disease progression or death	0.57 (99% CI 0.44–0.73) *P* < 0.0001	

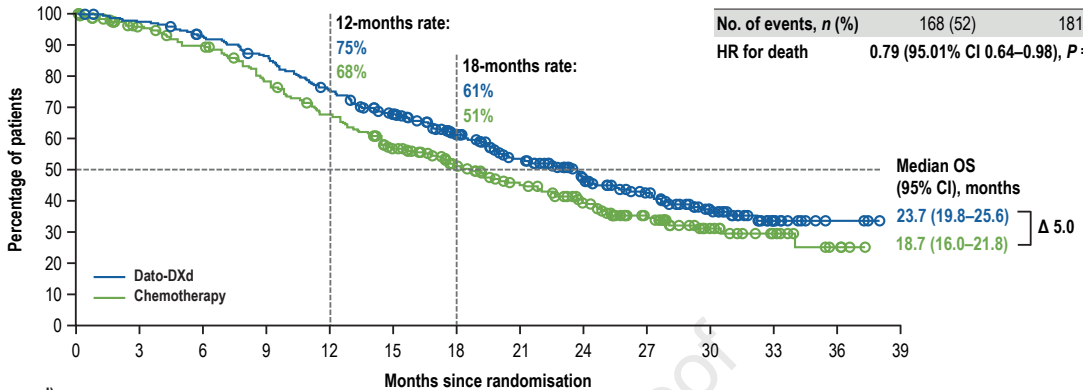
No. at risk (censored)

Dato-DXd	323 (0)	265 (15)	191 (33)	150 (41)	116 (49)	84 (65)	56 (81)	41 (89)	24 (103)	20 (105)	10 (114)	5 (119)	1 (123)	0 (124)
Chemotherapy	321 (0)	191 (40)	107 (70)	64 (81)	46 (86)	29 (92)	19 (99)	16 (100)	8 (105)	6 (106)	1 (111)	0 (112)	0 (112)	0 (112)

B Subgroup analysis of PFS

		No. of events/ No. of patients		*Median PFS, months (95% CI)*		HR for disease progression or death (95% CI)
		Dato-DXd	Chemotherapy	Dato-DXd	Chemotherapy	
All patients		199/323	209/321	10.8 (8.6–13.0)	5.6 (5.0–7.0)	**0.57** (0.47–0.69)
Age at randomisation	<65 years	153/245	153/239	9.8 (8.3–12.9)	5.5 (4.2–7.0)	**0.58** (0.46–0.73)
	≥65 years	46/78	56/82	11.8 (8.5–19.4)	5.9 (5.0–8.1)	**0.50** (0.34–0.74)
Race	Asian	91/151	90/131	13.0 (9.7–13.5)	5.5 (4.3–7.0)	**0.47** (0.35–0.64)
	Non-Asian	94/151	114/173	9.1 (6.8–11.3)	5.6 (4.2–7.0)	**0.60** (0.45–0.79)
Geographic region	US/Canada/Europe	79/120	70/120	8.5 (6.7–11.9)	6.9 (5.2–8.5)	**0.69** (0.50–0.95)
	Other geographic regions	120/203	139/201	11.4 (9.7–13.3)	5.5 (4.2–6.8)	**0.50** (0.39–0.64)
ECOG PS	0	107/195	115/182	13.3 (10.1–17.2)	6.5 (5.5–7.5)	**0.51** (0.39–0.67)
	1	92/128	94/139	8.5 (6.3–9.8)	4.6 (4.0–6.8)	**0.63** (0.47–0.84)
HER2 expression	IHC 0	117/188	128/192	9.7 (7.7–11.1)	5.5 (4.2–7.0)	**0.55** (0.43–0.71)
	IHC 1+ and IHC2+/FISH/ISH-ve	67/112	74/115	13.2 (9.1–17.2)	6.8 (4.4–8.2)	**0.52** (0.37–0.73)
Brain metastases	Yes	26/36	19/28	6.8 (5.5–9.7)	3.5 (1.6–6.0)	**0.39** (0.21–0.74)
	No	173/287	190/293	11.1 (9.5–13.2)	5.6 (5.3–7.0)	**0.56** (0.46–0.70)
Liver metastases	Yes	70/93	72/98	5.8 (5.4–8.3)	4.1 (2.9–5.5)	**0.57** (0.40–0.80)
	No	129/230	137/223	13.1 (10.8–17.2)	7.0 (5.5–8.1)	**0.55** (0.43–0.70)
Number of metastatic sites	<3	119/207	135/215	13.0 (10.4–17.2)	6.1 (5.3–8.1)	**0.54** (0.42–0.69)
	≥3	80/116	74/106	7.7 (5.7–9.7)	4.2 (3.0–6.5)	**0.57** (0.41–0.79)
DFI history	*De novo*	63/109	77/110	9.8 (7.7–17.2)	5.4 (4.4–6.5)	**0.46** (0.32–0.64)
	Prior DFI 0–12 months	44/67	49/66	5.7 (4.0–8.4)	2.9 (2.7–4.1)	**0.62** (0.41–0.94)
	Prior DFI >12 months	92/147	83/145	12.8 (10.1–15.2)	7.1 (6.8–9.9)	**0.65** (0.48–0.87)
PD-L1 status	Low (CPS <10)	176/287	191/291	8.6 (4.1–11.8)	4.3 (2.7–14.0)	**0.53** (0.43–0.65)
	High (CPS ≥10)	22/34	18/29	11.1 (9.5–13.2)	5.6 (5.0–7.0)	**0.77** (0.41–1.45)
Prior PD-1/PD-L1 inhibitor therapy	Yes	11/15	13/18	5.7 (2.8–13.2)	4.0 (2.0–7.1)	**0.61** (0.26–1.37)
	No	188/308	196/303	11.0 (9.1–13.1)	5.6 (5.3–7.0)	**0.56** (0.46–0.68)
Pre-selected choice of chemotherapy	Nab-paclitaxel	111/180	105/172	11.3 (9.7–13.4)	5.9 (5.4–8.0)	**0.61** (0.46–0.80)
	Paclitaxel	47/82	61/92	11.9 (8.5–19.3)	6.9 (4.4–8.1)	**0.45** (0.30–0.66)
	Eribulin mesylate/eribulin	26/43	27/35	5.8 (2.7–9.5)	2.9 (2.0–5.3)	**0.57** (0.33–0.99)
	Carboplatin	10/11	9/14	5.4 (1.4–8.2)	3.6 (1.3–12.1)	[b]
	Capecitabine	5/7	7/8	5.9 (1.2–NC)	3.4 (1.2–NC)	[b]

A OS



	Dato-DXd	Chemotherapy
No. of events, *n* (%)	168 (52)	181 (56)
HR for death	0.79 (95.01% CI 0.64–0.98), *P* = 0.029	

No. at risk (censored)

Dato-DXd	323	311	291	272	235	201	157	122	86	64	37	14	3	0
	(0)	(5)	(8)	(9)	(10)	(22)	(47)	(64)	(86)	(101)	(120)	(141)	(152)	(155)
Chemotherapy	321	290	268	231	199	158	122	93	70	48	27	12	4	0
	(0)	(18)	(21)	(24)	(26)	(35)	(57)	(72)	(84)	(99)	(115)	(129)	(136)	(140)

B Subgroup analysis of OS

		No. of events/ No. of patients		*Median OS, months (95% CI)*		HR for death (95% CI)
		Dato-DXd	Chemotherapy	Dato-DXd	Chemotherapy	
All patients		168/323	181/321	23.7 (19.8–25.6)	18.7 (16.0–21.8)	**0.79** (0.64–0.98)
Age at randomisation	<65 years	128/245	132/239	23.4 (19.5–25.6)	18.1 (15.6–21.8)	**0.80** (0.63–1.02)
	≥65 years	40/78	49/82	25.4 (19.0–29.5)	20.3 (13.6–24.4)	**0.71** (0.46–1.08)
Race	Asian	76/151	78/131	26.8 (21.5–30.9)	18.4 (14.4–23.7)	**0.66** (0.48–0.90)
	Non-Asian	82/151	98/173	19.8 (16.4–24.2)	18.1 (13.9–21.8)	**0.87** (0.65–1.17)
Geographic region	US/Canada/Europe	72/120	59/120	19.5 (15.7–22.5)	22.1 (16.8–27.0)	**1.22** (0.86–1.73)
	Other geographic regions	96/203	122/201	27.2 (23.7–32.1)	17.5 (14.3–20.3)	**0.60** (0.46–0.79)
ECOG PS	0	93/195	92/182	24.0 (20.4–29.0)	21.1 (18.2–24.9)	**0.80** (0.60–1.07)
	1	75/128	89/139	19.5 (15.6–24.0)	14.5 (12.4–17.8)	**0.78** (0.57–1.05)
HER2 expression	IHC 0	102/188	112/192	23.4 (17.5–25.6)	17.4 (14.3–20.3)	**0.78** (0.60–1.02)
	IHC 1+ and IHC2+/FISH/ISH-ve	54/112	61/115	23.7 (19.8–32.1)	22.6 (17.4–24.6)	**0.74** (0.51–1.07)
Brain metastases	Yes	21/36	19/28	12.8 (10.2–NC)	10.7 (8.5–16.0)	**0.61** (0.33–1.15)
	No	147/287	162/293	23.7 (20.3–26.8)	19.3 (17.4–22.5)	**0.79** (0.63–0.99)
Liver metastases	Yes	64/93	66/98	17.7 (13.0–19.8)	13.2 (11.1–16.5)	**0.85** (0.60–1.20)
	No	104/230	115/223	26.0 (23.7–32.1)	21.1 (18.2–24.4)	**0.74** (0.57–0.97)
Number of metastatic sites	<3	92/207	108/215	27.3 (23.9–32.1)	22.5 (17.8–27.0)	**0.73** (0.55–0.96)
	≥3	76/116	73/106	15.6 (12.8–19.7)	14.3 (11.0–17.6)	**0.81** (0.59–1.12)
DFI history	*De novo*	51/109	63/110	25.6 (19.5–32.1)	17.4 (14.3–22.5)	**0.67** (0.46–0.97)
	Prior DFI 0–12 months	51/67	45/66	13.5 (10.5–20.6)	13.1 (9.5–20.8)	**1.02** (0.68–1.53)
	Prior DFI >12 months	66/147	73/145	26.8 (20.4–NC)	21.1 (17.8–25.3)	**0.75** (0.54–1.05)
PD-L1 status	Low (CPS <10)	149/287	163/291	19.5 (11.4–NC)	17.4 (10.9–NC)	**0.77** (0.61–0.96)
	High (CPS ≥10)	17/34	18/29	23.7 (19.8–25.6)	18.7 (15.6–22.0)	**0.77** (0.39–1.50)
Prior PD-1/PD-L1 inhibitor therapy	Yes	10/15	11/18	23.7 (9.1–29.0)	14.3 (8.2–27.0)	**0.87** (0.36–2.07)
	No	158/308	170/303	23.7 (19.8–26.0)	19.1 (16.7–22.0)	**0.77** (0.62–0.96)
Pre-selected choice of chemotherapy	Nab-paclitaxel	84/180	93/172	25.6 (20.4–NC)	19.3 (16.8–24.9)	**0.75** (0.56–1.01)
	Paclitaxel	37/82	48/92	24.2 (18.2–NC)	19.1 (12.9–24.4)	**0.63** (0.41–0.97)
	Eribulin mesylate/eribulin	31/43	21/35	14.4 (9.1–21.4)	13.2 (8.6–20.8)	**1.11** (0.64–1.96)
	Carboplatin	10/11	12/14	20.6 (4.8–24.0)	22.0 (4.5–27.0)	**1.23** (0.51–2.89)
	Capecitabine	6/7	7/8	13.1 (9.3–27.3)	13.2 (4.5–27.3)	[a]