Datopotamab Deruxtecan Versus Chemotherapy in Previously Treated Inoperable/Metastatic Hormone Receptor–Positive Human Epidermal Growth Factor Receptor 2–Negative Breast Cancer: Primary Results From TROPION-Breast01

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ABSTRACT

PURPOSE The global, phase 3, open-label, randomized TROPION-Breast01 study assessed the trophoblast cell surface antigen 2–directed antibody-drug conjugate datopotamab deruxtecan (Dato-DXd) versus investigator's choice of chemotherapy (ICC) in hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) breast cancer.

METHODS Adult patients with inoperable/metastatic HR+/HER2– breast cancer, who had disease progression on endocrine therapy, for whom endocrine therapy was unsuitable, and had received one to two previous lines of chemotherapy in the inoperable/metastatic setting, were randomly assigned 1:1 to Dato-DXd (6 mg/kg once every 3 weeks) or ICC (eribulin/vinorelbine/capecitabine/gemcitabine). Dual primary end points were progression-free survival (PFS) by blinded independent central review (BICR) and overall survival (OS).

RESULTS Patients were randomly assigned to Dato-DXd (n = 365) or ICC (n = 367). Dato-DXd significantly reduced the risk of progression or death versus ICC (PFS by BICR hazard ratio [HR], 0.63 [95% CI, 0.52 to 0.76]; $P < .0001$). Consistent PFS benefit was observed across subgroups. Although OS data were not mature, a trend favoring Dato-DXd was observed (HR, 0.84 [95% CI, 0.62 to 1.14]). The rate of grade ≥3 treatment-related adverse events (TRAEs) with Dato-DXd was lower than ICC (20.8% *v* 44.7%). The most common TRAEs (any grade; grade ≥3) were nausea (51.1%; 1.4%) and stomatitis (50%; 6.4%) with Dato-DXd and neutropenia (grouped term, 42.5%; 30.8%) with ICC.

CONCLUSION Patients receiving Dato-DXd had statistically significant and clinically meaningful improvement in PFS and a favorable and manageable safety profile, compared with ICC. Results support Dato-DXd as a novel treatment option for patients with inoperable/metastatic HR+/HER2– breast cancer who have received one to two previous lines of chemotherapy in this setting.

ACCOMPANYING CONTENT

Appendix

Protocol

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View Online Article

INTRODUCTION

Patients with metastatic hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) breast cancer are initially treated with endocrine therapy with/without other targeted therapies such as cyclin-dependent kinase 4/6 (CDK4/6) inhibitors.[1-4] Until recently, for patients with endocrine-resistant disease or patients

CONTEXT

Key Objective

Does the trophoblast cell surface antigen 2–directed antibody-drug conjugate datopotamab deruxtecan (Dato-DXd) improve survival outcomes compared with investigator's choice of chemotherapy (ICC) in patients with previously treated inoperable or metastatic hormone receptor–positive/human epidermal growth factor receptor 2–negative breast cancer?

Knowledge Generated

In TROPION-Breast01, patients receiving Dato-DXd had statistically significant and clinically meaningful improvement in progression-free survival (assessed by blinded independent central review) compared with ICC. Dato-DXd also demonstrated a favorable and manageable safety profile, with nausea and stomatitis being the most common treatment-related adverse events.

Relevance *(G.F. Fleming)*

Dato-DXd is on track to be the third active antibody-drug conjugate for use in breast cancer. Optimal sequencing of these agents in therapy remains to be determined.*

*Relevance section written by *JCO* Associate Editor Gini F. Fleming, MD, FASCO.

ineligible for endocrine therapy, single-agent chemotherapy was the standard of care.[1,2] However, chemotherapy is associated with limited clinical benefit[5,6] and substantial toxicities that negatively affect the quality of life of patients.[7,8] With the advent of novel antibody-drug conjugate (ADC) therapies, a new treatment paradigm is emerging for the postendocrine therapy setting after chemotherapy with HER2-targeted ADC trastuzumab deruxtecan for HER2-low disease[9-13] and trophoblast cell surface antigen 2 (TROP2)–directed ADC sacituzumab govitecan for HER2-negative disease.[14-17] However, there remains an unmet need for novel treatment options to further improve efficacy and safety outcomes in this patient population.

TROP2 is a transmembrane glycoprotein broadly expressed in multiple solid tumors,[18] including breast cancer.[19,20] Datopotamab deruxtecan (Dato-DXd) is a TROP2-directed ADC consisting of a humanized anti-TROP2 immunoglobulin G1 monoclonal antibody attached to a highly potent topoisomerase I inhibitor payload via a plasma-stable, tumor-selective, cleavable linker.[21] In the phase 1 TROPION-PanTumor01 study, Dato-DXd showed encouraging antitumor activity and a manageable safety profile in patients with heavily pretreated HR+/HER2− breast cancer, with an objective response rate (ORR) of 27% and a disease control rate (DCR) of 85%.[22] Dato-DXd has also shown promising antitumor activity in patients with triple-negative breast cancer (TNBC) in TROPION-PanTumor01,[22] and several phase 3 studies in TNBC are ongoing.[23-27]

Here, we report the primary results from the phase 3 TROPION-Breast01 study, which evaluated Dato-DXd versus investigator's choice of chemotherapy (ICC) in patients with inoperable or metastatic HR+/HER2− breast cancer who had received one or two previous lines of chemotherapy in this setting.

METHODS

Study Design and Patient Eligibility Criteria

TROPION-Breast01 (ClinicalTrials.gov identifier: NCT05104866) was a global, phase 3, open-label, randomized study. Full details of its design have been published previously,[28] and additional details are provided in the Protocol (online only). Key eligibility criteria were as follows: age ≥18 years, an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, inoperable or metastatic HR+/HER2− breast cancer (per ASCO–College of American Pathologists guidelines[29,30]; HER2− defined as IHC 0, 1+ or 2+/ISH−), and received one or two previous lines of chemotherapy in the inoperable/metastatic setting. Patients who had experienced progression on endocrine therapy and for whom further endocrine therapy was unsuitable (per investigator assessment) were eligible for enrollment in the final amended protocol although the original protocol allowed endocrine therapy–naïve patients to enroll if endocrine therapy was unsuitable. Previous treatment with CDK4/6 inhibitor(s) was not required because of geographic variations in availability, but there was a cap applied to patients who had NOT received previous CDK4/6 inhibitor therapy. Previous treatment involving a chemotherapeutic agent targeting topoisomerase I (including ADCs) and previous TROP2-targeted therapy were not permitted. Patients with clinically stable brain metastases were eligible.

Patients were randomly assigned 1:1 to intravenous Dato-DXd 6 mg/kg once every 3 weeks or single-agent ICC (eribulin, 1.4 mg/m^2 intravenously on days 1 and 8, once every 3 weeks; capecitabine, 1,000 or 1,250 mg/m^2 orally twice daily

on days 1-14, once every 3 weeks; vinorelbine, 25 mg/m² intravenously on days 1 and 8, once every 3 weeks; or gemcitabine, 1,000 mg/m² intravenously on days 1 and 8, once every 3 weeks). Random assignment was centrally performed using an Interactive Response Technology system and stratified by the number of previous lines of chemotherapy (1 *v* 2), geographic region (United States/Canada/Europe *v* other geographic regions of the world), and previous use of a CDK4/6 inhibitor (yes *v* no).

Treatment continued until investigator-assessed radiologic progression (per RECIST v1.1), unacceptable toxicity, withdrawal of consent, or until any other predefined protocol discontinuation criterion was met.

Study Oversight

A global steering committee provided oversight for the study in conjunction with the sponsor. The study protocol was approved by institutional review boards at each site. The study was performed in accordance with the ethical principles set out in the Declaration of Helsinki and consistent with the International Conference on Harmonisation Good Clinical Practice guidelines and other applicable regulatory requirements. All patients provided written informed consent before study participation.

End Points

Dual primary end points were progression-free survival (PFS; defined as time from random assignment to progression, assessed by blinded independent central review [BICR] per RECIST v1.1, or death due to any cause) and overall survival (OS) (defined as time from random assignment to death due to any cause). Secondary end points were PFS by investigator assessment and response outcomes (per RECIST v1.1 as assessed by BICR/per investigator assessment), including ORR, DCR at 12 weeks (defined as the percentage of patients with confirmed complete response [CR], partial response [PR] or stable disease), duration of response, time to first subsequent therapy or death (TFST), time to second subsequent therapy or death (TSST), and time to second progression or death (PFS2). Safety and tolerability were also assessed.

Study Assessments

Tumor imaging assessments were conducted per RECIST v1.1 every 6 weeks (±7 days) for 48 weeks and every 9 weeks (±7 days) thereafter until investigator-assessed progressive disease (PD). After PD, one further follow-up scan could be performed per the assessment schedule.

Safety was assessed from screening until 35 days after the last dose of study drug; protocol prespecified adverse events of special interests (AESIs) were to be followed until resolution. Adverse events (AEs) were graded by Common Terminology Criteria for Adverse Events version 5.0 and were treated according to Dato-DXd toxicity management guidelines for patients in the experimental arm (Appendix Table A1, online only). Study drug doses could be delayed for up to 3 consecutive cycles from the planned date of administration, and treatment was discontinued if further delays were required. Up to two dose reductions were permitted for Dato-DXd (4.0 mg/kg intravenously once every 3 weeks and 3.0 mg/kg intravenously once every 3 weeks), but doses could not be re-escalated per protocol; if toxicity requiring further dose reduction occurred, treatment was discontinued. In the ICC arm, toxicity and dosing modifications were managed per drug label and standard institutional practice by the investigator. An independent interstitial lung disease (ILD) adjudication committee reviewed all cases of potential ILD/pneumonitis to assess whether the event was ILD/pneumonitis and, if so, whether it was related to the study drug. As part of an oral care plan starting before study drug initiation and continuing throughout treatment in both arms, prophylactic mouthwash use (four times daily) was advised with steroid-containing mouthwash highly recommended but not mandated. Prophylactic cryotherapy (ice chips or ice water held in the mouth throughout the infusion) was also suggested. To comply with regulatory requirements for Dato-DXd, ophthalmologic assessments were mandated for both study arms at screening, every three cycles, as clinically indicated during the study and at the end of treatment; daily use of artificial tears and avoidance of contact lenses were recommended. Prophylactic antiemetic agents were highly recommended before infusion of Dato-DXd and on subsequent days as needed. Premedication was required before any dose of Dato-DXd including antihistamines and acetaminophen, with or without glucocorticoids.

Statistical Analysis

Primary efficacy analysis for the dual primary end points was performed in the intention-to-treat population, comprising all randomly assigned patients. PFS and OS were analyzed using a log-rank test stratified by the number of previous lines of chemotherapy in the inoperable/metastatic setting, previous use of CDK4/6 inhibitors, and geographic region. The hazard ratios (HRs) and CIs were estimated using a stratified Cox proportional hazards model. Subgroup analyses of PFS were performed. In the analysis of PFS, data for patients whose disease had not progressed or who had died were censored at the time of their last evaluable RECIST v1.1 assessment. In the analysis of OS, data for patients who were not known to have died were censored at the last recorded date the patient was known to be alive.

The planned sample size was 700 randomly assigned patients; assuming a 30% screen failure rate, the planned enrollment was 1,000 patients. Assuming a true HR for PFS of 0.55, 419 PFS events would provide >99% power to demonstrate PFS significance at the two-sided alpha level of 1%. Hypotheses were tested using a multiple testing procedure including the dual primary end points. To control for type I error at a two-sided alpha level of 5%, an alpha level of 1%

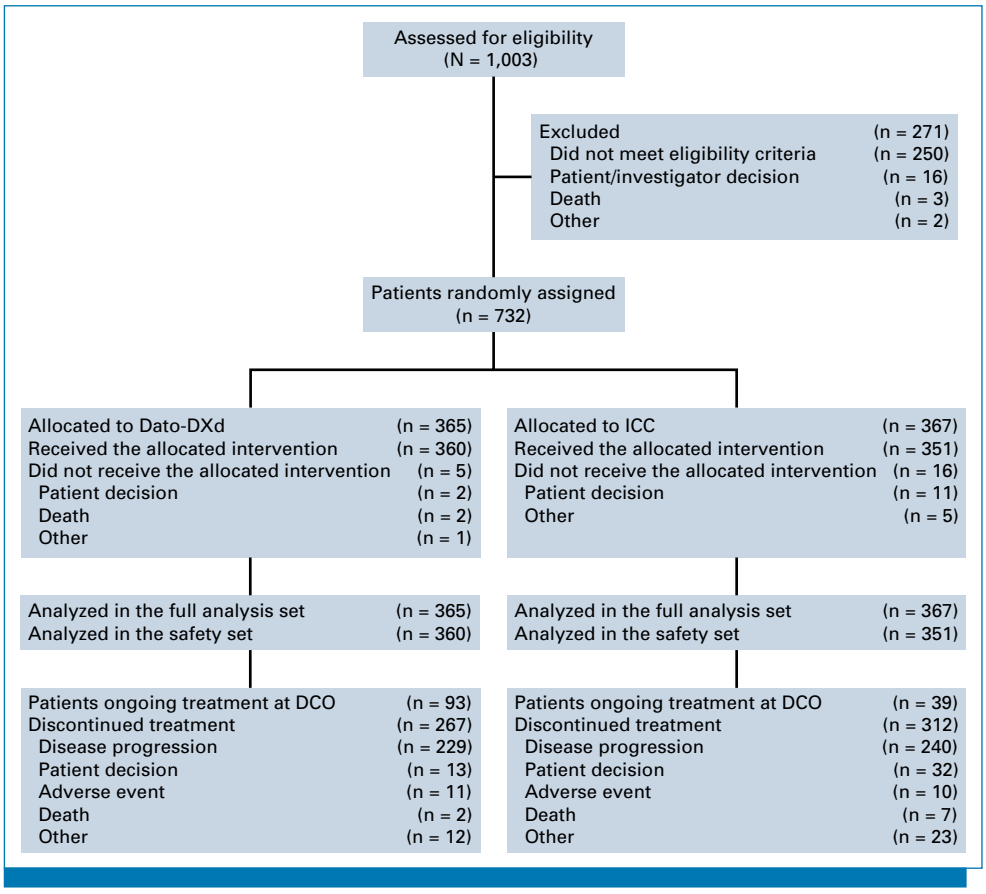

FIG 1. CONSORT diagram. Dato-DXd, datopotamab deruxtecan; DCO, data cutoff; ICC, investigator's choice of chemotherapy.

was allocated to the PFS dual primary analysis and the remaining 4% alpha level was allocated to the OS analysis. As the PFS crossed the efficacy threshold, the 1% type I error allocated to the PFS end point was reallocated to the OS end point for a total two-sided type I error of 5%. Final analysis of OS will be performed when approximately 444 OS events have occurred. Details of statistical methods are provided in the Protocol.

RESULTS

Patient Characteristics

Between October 18, 2021, and December 26, 2022, a total of 1,003 patients were enrolled across 166 centers in 20 countries (Fig 1). Overall, 732 patients were randomly assigned to treatment: 365 to the Dato-DXd arm and 367 to the ICC arm. Five (1.4%) and 16 (4.4%) patients, respectively, were randomly assigned but did not receive their allocated intervention, so 360 patients received Dato-DXd and 351 received ICC (207 [59%] eribulin, 75 [21.4%] capecitabine, 38 [10.8%] vinorelbine, and 31 [8.8%] gemcitabine).

Patient demographics and baseline characteristics in the two treatment groups were generally well balanced (Table 1). Previous CDK4/6 inhibitor therapy had been received by a majority (82.5%) of patients. At data cutoff (DCO, July 17, 2023), almost 2.5 times the number of patients remained on treatment with Dato-DXd compared with ICC (93 of 360 patients [25.8%] in the Dato-DXd arm and 39 of 351 patients [11.1%] in the ICC arm).

Efficacy

The median duration of study follow-up in TROPION-Breast01 was 10.8 months. In total, 212 of 365 patients (58.1%) who were randomly assigned to Dato-DXd and 235 of 367 (64%) patients who were randomly assigned to ICC had a PFS event as assessed by BICR. Dato-DXd demonstrated a 37% reduction in risk of progression or death compared with ICC (HR, 0.63 [95% CI, 0.52 to 0.76]; $P < .0001$; Fig 2A). The median PFS by BICR was 6.9 months (95% CI, 5.7 to 7.4) with Dato-DXd versus 4.9 months (95% CI, 4.2 to 5.5) with ICC. At 9 months, 37.5% of patients in the Dato-DXd arm versus 18.7% in the ICC arm were progression-free, as were 25.5% versus 14.6%, respectively, at 12 months (Fig 2A). The improvement in PFS by BICR was consistent across prespecified patient subgroups, including by previous lines of therapy, geographic region, and previous use of CDK4/6 inhibitor therapy (Fig 3). PFS by investigator

TABLE 1. Demographic and Clinical Characteristics of All Randomly Assigned Patients at Baseline (intention-to-treat population)

Characteristic	Dato-DXd (n = 365)	ICC (n = 367)
Median age, years (range)	56 (29-86)	54 (28-86)
Age ≥65 years, No. (%)	91 (24.9)	72 (19.6)
Female, No. (%)	360 (98.6)	363 (98.9)
Region, No. (%)		
United States/Europe/Canada	186 (51)	182 (49.6)
Other geographic regions	179 (49)	185 (50.4)
Race, No. (%)		
Asian	146 (40)	152 (41.4)
White	180 (49.3)	170 (46.3)
Black or African American	4 (1.1)	7 (1.9)
Other	3 (0.8)	6 (1.6)
Not reported	32 (8.8)	32 (8.7)
ECOG PS, No. (%)		
0	197 (54)	220 (59.9)
1	165 (45.2)	145 (39.5)
2	3 (0.8)	1 (0.3)
Missing	0	1 (0.3)
Estrogen receptor–positive, No. (%)	360 (98.6)	364 (99.2)
Progesterone receptor–positive, No. (%)	237 (64.9)	252 (68.7)
HER2-negative,[a] No. (%)	360 (98.6)	366 (99.7)
Missing	5 (1.4)	1 (0.3)
Locally advanced/inoperable disease, No. (%)	9 (2.5)	2 (0.5)
Metastatic disease, No. (%)	356 (97.5)	365 (99.5)
Bone	260 (71.2)	251 (68.4)
Brain	35 (9.6)	23 (6.3)
Liver	275 (75.3)	251 (68.4)
Lung	92 (25.2)	87 (23.7)
Previous lines of anticancer therapy, median (range)	3 (1-7)	3 (1-8)
Previous CDK4/6 inhibitor, No. (%)	304 (83.3)	300 (81.7)
<12 months[b]	151 (49.7)	136 (45.3)
≥12 months[b]	153 (50.3)	164 (54.7)
Previous taxanes and anthracyclines, No. (%)		
Taxanes	295 (80.8)	296 (80.7)
Anthracyclines	228 (62.5)	239 (65.1)
Previous cancer therapy in the metastatic/inoperable setting, No. (%)		
Cytotoxic chemotherapy	365 (100)	366 (99.7)
Hormonal therapy[c]	322 (88.2)	326 (88.8)
Targeted therapy	312 (85.5)	309 (84.2)
Immunotherapy	16 (4.4)	13 (3.5)
PARP inhibitor	8 (2.2)	16 (4.4)
Antibody-drug conjugate	1 (0.3)	4 (1.1)
Other	24 (6.6)	24 (6.5)
No. of previous lines of chemotherapy for inoperable/metastatic disease,[d] No. (%)		
1	229 (62.7)	225 (61.3)
2	135 (37)	141 (38.4)

Abbreviations: CDK4/6, cyclin-dependent kinase 4/6; Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH/ISH, fluorescence in situ hybridization/in situ hybridization; HER2, human epidermal growth factor receptor 2; ICC, investigator's choice of chemotherapy; IHC, immunohistochemistry; PARP, poly (ADP-ribose) polymerase.

[a]HER2-negative defined as IHC 0; IHC 1+; IHC 2+ FISH/ISH-negative.

[b]Percentages on the basis of the number of patients with previous use of CDK4/6 inhibitor.

[c]95.3% of patients in the Dato-DXd arm and 96.2% in the ICC arm had received any previous hormonal therapy, including the adjuvant setting.

[d]One patient in the Dato-DXd arm had received three previous lines of chemotherapy and one patient in the ICC arm had received four previous lines of chemotherapy.

assessment was consistent with PFS by BICR (HR, 0.64 [95% CI, 0.53 to 0.76]; Appendix Fig A1).

A trend in interim OS data favoring the Dato-DXd arm was observed (HR, 0.84 [95% CI, 0.62 to 1.14]) although OS data were immature at this analysis (maturity, 23.4%; information fraction, 38.5%). The study is continuing to the next planned analysis for OS.

ORR by BICR was improved with Dato-DXd versus ICC (36.4% *v* 22.9%; odds ratio, 1.95 [95% CI, 1.41 to 2.71]; Table 2). In the Dato-DXd arm, there were two CRs and 131 PRs; in the ICC arm, there were no CRs and 84 PRs. The median duration of response (95% CI) was 6.7 months (5.6 to 9.8) in the Dato-DXd arm compared with 5.7 months (4.9 to 6.8) in the ICC arm. The DCR at 12 weeks was 75.3% (n = 275) in the Dato-DXd arm versus 63.8% (n = 234) in the ICC arm.

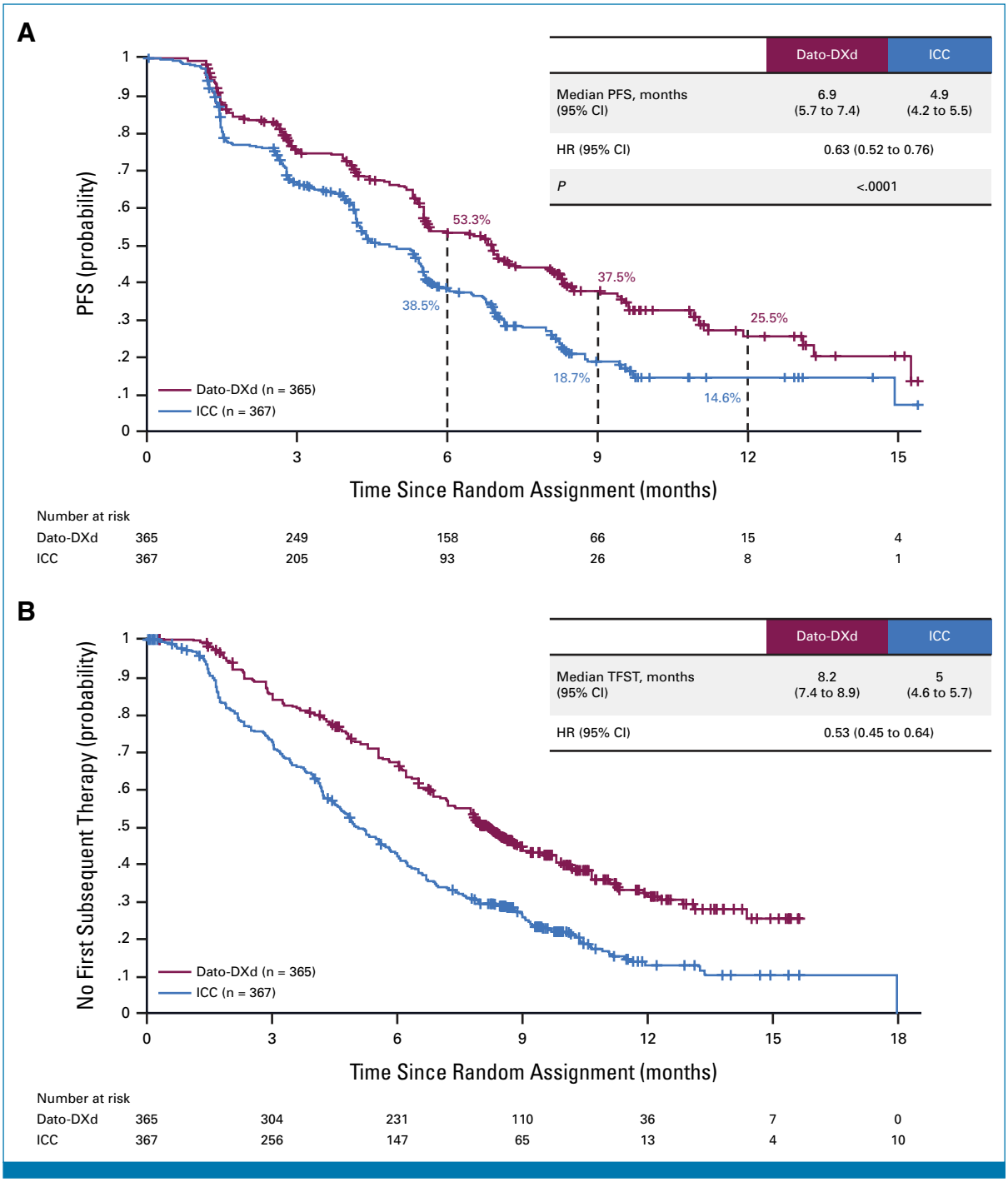

FIG 2. (A) PFS by blinded independent central review and (B) TFST (intention-to-treat population). Dato-DXd, datopotamab deruxtecan; HR, hazard ratio; ICC, investigator's choice of chemotherapy; PFS, progression-free survival; TFST, time to first subsequent therapy.

Time to first and second subsequent therapies and PFS2 were all prolonged with Dato-DXd versus ICC (Fig 2B, Appendix Table A2). A lower proportion of patients in the Dato-DXd arm than in the ICC arm had received a subsequent anticancer therapy in any treatment line at DCO (192 [52.6%] *v* 247 [67.3%]; Appendix Table A3). Fifteen patients (4.1%) in the Dato-DXd arm and 52 patients (14.2%) in the ICC arm had received a subsequent ADC in any treatment line (trastuzumab deruxtecan: 3% in the Dato-DXd arm, 12% in the ICC arm; sacituzumab govitecan: 1.1% in the Dato-DXd arm, 4.1% in the ICC arm).

Safety

At DCO, the median duration of treatment was longer in the Dato-DXd arm compared with the ICC arm (6.7 months [range, 0.7-15.6] *v* 4.1 months [range, 0.2-17.4]). Treatment-related AEs (TRAEs) occurred in 93.6% and 86.3% of patients in the Dato-DXd (n = 360) and ICC (n = 351) safety populations, respectively. However, the rate of grade ≥3 TRAEs with Dato-DXd was less than half that with ICC (20.8% *v* 44.7%). Serious TRAEs occurred in 5.8% of patients in the Dato-DXd arm and 9.1% in the ICC arm. TRAEs led to dose reductions in 20.8% of patients in the Dato-DXd arm versus 30.2% in the ICC arm and dose interruptions in 11.9% versus 24.5% of patients, respectively (if multiple dose adjustments were made for a TRAE, only the worst action taken was captured). Treatment discontinuations because of TRAEs were reported in 2.5% of patients in the Dato-DXd arm and 2.6% in the ICC arm. No fatal TRAEs were reported in the Dato-DXd arm by the investigator, whereas one patient in the ICC arm died because of a TRAE (febrile neutropenia).

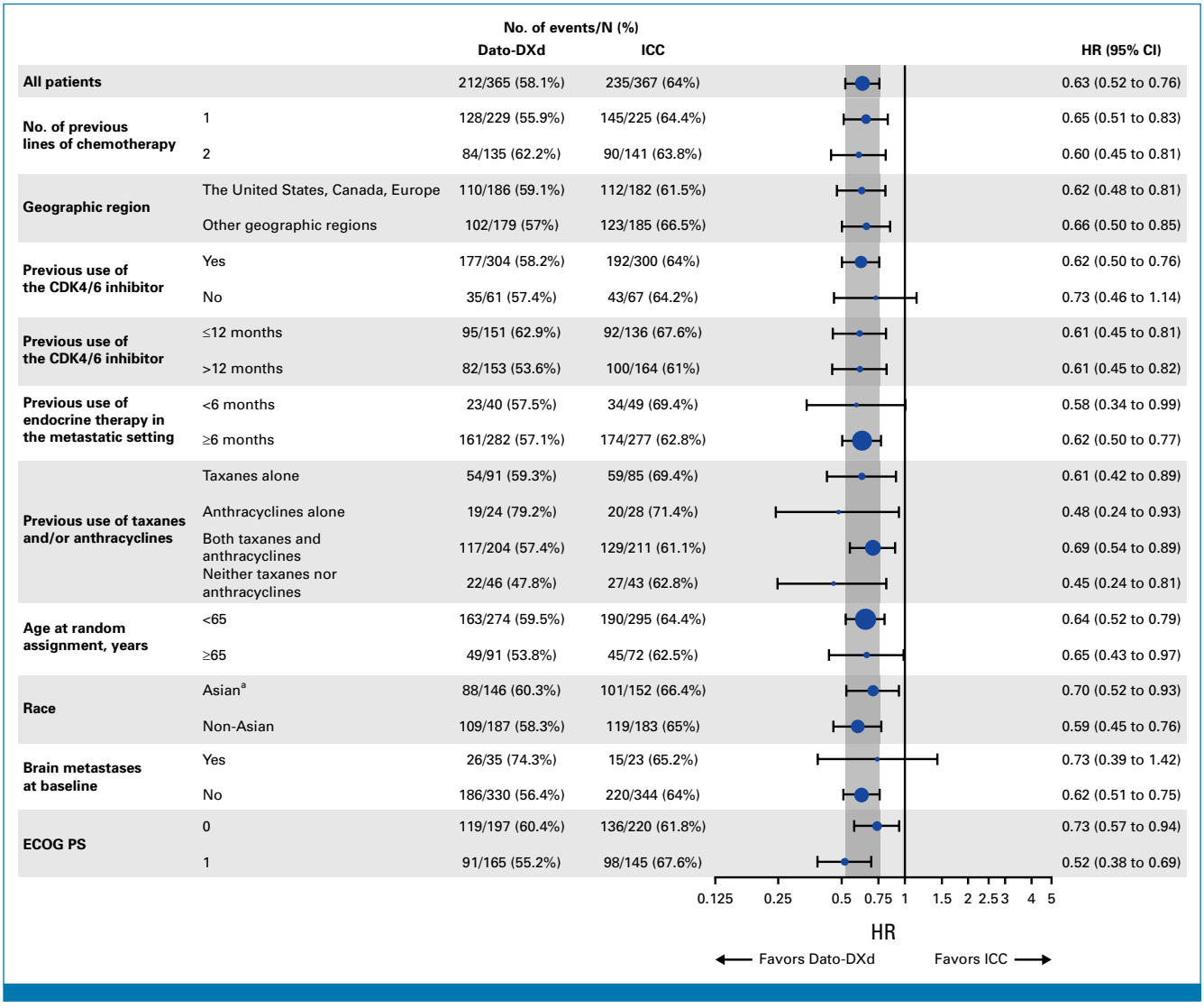

FIG 3. Subgroup analysis of PFS by blinded independent central review (intention-to-treat population). Size of circle is proportional to the number of events across both treatment groups. [a]Asian = Patients from China, Japan, South Korea, Taiwan. CDK4/6, cyclin-dependent kinase 4/6; Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ICC, investigator's choice of chemotherapy; PFS, progression-free survival.

TABLE 2. Overview of Response by BICR (intention-to-treat population)

Variable	Dato-DXd (n = 365)	ICC (n = 367)
Confirmed overall response, No. (%)	133 (36.4)	84 (22.9)
Odds ratio (95% CI)	1.95 (1.41 to 2.71)	
Best overall response, No. (%)		
Complete response	2 (0.5)	0
Partial response	131 (35.9)	84 (22.9)
Stable disease ≥5 weeks[a]	168 (46)	176 (48)
No evidence of disease ≥5 weeks	1 (0.3)	0
Progressive disease	58 (15.9)	76 (20.7)
Not evaluable	5 (1.4)	31 (8.4)
Incomplete postbaseline assessments	5 (1.4)	28 (7.9)
Stable disease <5 weeks	0	2 (0.5)
Death	0	1 (0.3)[c]
Disease control rate at 12 weeks, %[b]	275 (75.3)	234 (63.8)
Median duration of response, months (95% CI)	6.7 (5.6 to 9.8)	5.7 (4.9 to 6.8)
Median time to response, months (IQR)	2.7 (1.4-3.9)	2.6 (1.4-2.9)

Abbreviations: BICR, blinded independent central review; Dato-DXd, datopotamab deruxtecan; ICC, investigator's choice of chemotherapy.
[a]Tumor imaging was performed every 6 weeks ± 7 days from random assignment, 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]Disease control rate at 12 weeks was defined as the percentage of patients who have a confirmed complete response or partial response or who have stable disease, per RECIST 1.1, as assessed by BICR.
[c]Patient with no evaluable RECIST assessments who died >7 weeks after random assignment.

Details of the most frequently reported TRAEs by preferred term are shown in Table 3. In the Dato-DXd versus ICC arms, the most common TRAEs of any grade (>25% of patients) were nausea (51.1% *v* 23.6%), stomatitis (50% *v* 13.1%), alopecia (36.4% *v* 20.5%), and neutropenia (grouped term comprising neutropenia and neutrophil count decreased; 10.8% *v* 42.5%).

Treatment-related AESIs are shown in Appendix Table A4; most were manageable per toxicity management guidelines. Oral mucositis/stomatitis events in the Dato-DXd arm were mostly low grade (any grade/grade 1/grade 2: 55.6%/25.3%/23.3%) and led to discontinuation in one patient. Ocular surface events were mostly grade 1 (any grade/grade 1/grade 2: 40%/31.9%/7.2%) and led to discontinuation in one patient (with dry eye). Patients in the ICC arm also underwent the ophthalmologic assessments every three cycles during the study and had a 11.7% ocular surface event rate. In both arms (Dato-DXd *v* ICC), the most frequent ocular surface events were dry eye (21.7% *v* 7.7%). Three patients had grade 3 ocular surface events in the Dato-DXd arm (one patient with dry eye, one patient with punctate keratitis, and one patient with dry eye and ulcerative keratitis; no grade 4/5 events); there were no grade ≥3 ocular surface events with ICC. Twelve patients (3.3%) in the Dato-DXd arm had adjudicated drug-related ILD/pneumonitis (Appendix Table A4); most events were grade 1/2, but two patients had adjudicated grade 3 drug-related events, and one patient had an adjudicated grade 5 drug-related event (this grade 5 event was characterized by the investigator as grade 3 pneumonitis, with death attributed to disease progression).

Hematologic toxicity was the most notable feature of the safety profile in the ICC arm, including TRAEs of neutropenia (grouped term: any grade, 42.5%; grade ≥3, 30.8%), anemia (any grade, 19.7%; grade ≥3, 2%), and leukopenia (any grade, 17.1%; grade ≥3, 6.8%). Febrile neutropenia occurred in 2.3% of patients (any grade ≥3). Granulocyte-colony stimulating factor was used during treatment in 22.1% of patients in the ICC arms compared with 2.7% of patients in the Dato-DXd arm.

DISCUSSION

In this primary analysis, TROPION-Breast01 met its dual primary PFS end point; Dato-DXd reduced the risk of disease progression or death by 37% versus ICC in patients with inoperable or metastatic HR+/HER2− breast cancer who had received one or two previous lines of chemotherapy in this setting (HR, 0.63; $P < .0001$ per BICR). Consistent PFS benefit was observed across prespecified subgroups, including previous therapies (taxanes/anthracyclines, CDK4/6 inhibitors, and endocrine therapy), geographic region, age, race, and ECOG performance status. PFS benefit was maintained over time, with 9-month PFS rates approximately double with Dato-DXd compared with ICC (37.5% vs 18.7%), and 12-month PFS rates of 25.5% vs 14.6%. For the dual primary end point of OS, a trend in improvement was observed with Dato-DXd versus ICC; however, OS data were immature at

TABLE 3. TRAEs (all grades) Occurring in ≥10% of Patients and Grade ≥3 TRAEs in ≥1% of Patients in Either Arm (safety population)

	Dato-DXd (n = 360)		ICC (n = 351)	
TRAE, No. (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TRAE	337 (93.6)	75 (20.8)	303 (86.3)	157 (44.7)
Nausea	184 (51.1)	5 (1.4)	83 (23.6)	2 (0.6)
Stomatitis	180 (50)	23 (6.4)	46 (13.1)	9 (2.6)
Alopecia	131 (36.4)	0	72 (20.5)	0
Fatigue	85 (23.6)	6 (1.7)	64 (18.2)	7 (2)
Dry eye	78 (21.7)	2 (0.6)	27 (7.7)	0
Vomiting	71 (19.7)	4 (1.1)	27 (7.7)	2 (0.6)
Constipation	65 (18.1)	0	32 (9.1)	0
Keratitis[a]	52 (14.4)	2 (0.6)	17 (4.8)	0
Decreased appetite	50 (13.9)	3 (0.8)	41 (11.7)	2 (0.6)
Asthenia	45 (12.5)	3 (0.8)	46 (13.1)	4 (1.1)
Anemia	40 (11.1)	4 (1.1)	69 (19.7)	7 (2)
Neutropenia[b]	39 (10.8)	4 (1.1)	149 (42.5)	108 (30.8)
AST increased	31 (8.6)	2 (0.6)	39 (11.1)	2 (0.6)
Diarrhea	27 (7.5)	0	43 (12.3)	4 (1.1)
Leukopenia[c]	26 (7.2)	2 (0.6)	60 (17.1)	24 (6.8)
Palmar-plantar erythrodysesthesia syndrome	7 (1.9)	0	42 (12)	7 (2)
Platelet count decreased	7 (1.9)	0	18 (5.1)	4 (1.1)
Febrile neutropenia	0	0	8 (2.3)	8 (2.3)

NOTE. Includes adverse events assessed by the investigator as possibly related to study treatment.
Abbreviations: AST, aspartate aminotransferase; Dato-DXd, datopotamab deruxtecan; ICC, investigator's choice of chemotherapy; TRAE, treatment-related adverse event.
[a]Grouped term comprising keratitis, punctate keratitis, and ulcerative keratitis.
[b]Grouped term comprising neutropenia and neutrophil count decreased.
[c]Grouped term comprising leukopenia and white blood cell count decreased.

this DCO, and the study is continuing to the next planned analysis for OS. Of note, at DCO, almost 2.5 times the number of patients remained on treatment with Dato-DXd compared with ICC. ORR was superior with Dato-DXd (36.4%; two CRs) compared with ICC (22.9%; no CRs); duration of response and DCR at 12 weeks were also numerically improved with Dato-DXd versus ICC. Moreover, TFST, PFS2, and TSST were all delayed in the Dato-DXd arm, indicating that the benefits of Dato-DXd versus ICC extended beyond the first progression.

Dato-DXd demonstrated a favorable and manageable safety profile in TROPION-Breast01, consistent with that observed in previous studies of Dato-DXd.[22,31] Notably, the rate of grade ≥3 TRAEs in the Dato-DXd arm was less than half that in the ICC arm, and TRAEs led to fewer dose reductions and interruptions in the Dato-DXd arm versus the ICC arm. The use of prophylactic mouthwash (steroid-containing, if available) was recommended but not mandated to prevent oral mucositis/stomatitis; these events were mostly grade 1-2. Most ocular surface events with Dato-DXd were grade 1-2, and over half were dry eye; patients were advised to use artificial tears and avoid contact lenses. Importantly, the frequent ophthalmologic assessments that were mandated throughout the study (every three cycles), per regulatory requirement, likely contributed to the rate of reported ocular surface events, as demonstrated by the observed rates of ocular surface events in the ICC arm (11.7%) where the incidence is higher than that generally associated with chemotherapy.[32] The rate of adjudicated drug-related ILD was low (3.3%) and consistent with rates reported previously with Dato-DXd in breast cancer.[22]

Until recently, the standard treatment for patients with endocrine-refractory (or ineligible) metastatic breast cancer was single-agent chemotherapy.[1,2] The median PFS of 4.9 months in the ICC arm of TROPION-Breast01 was generally consistent with previous reports for single-agent chemotherapy.[5,6] The approvals of the ADCs, trastuzumab deruxtecan[9,10] and sacituzumab govitecan,[14,15] were based on studies involving patient populations with differences in HER2 expression levels and number of previous lines of chemotherapy compared with TROPION-Breast01,[13,17] limiting efficacy comparisons.

Differences in ADC antibody targets, payload used, linker, and drug-to-antibody ratio may lead to variations in the overall safety profiles of each agent.[33,34] For example,

sacituzumab govitecan has a linker with a lower serum stability,[35,36] whereas Dato-DXd has a linker that exhibits high serum stability and only releases a low level of payload in plasma, which may decrease systemic toxicity.[21] While hematologic toxicity was uncommon with Dato-DXd in TROPION-Breast01, sacituzumab govitecan treatment-related neutropenia occurred in 70% of patients (grade ≥3 in 51%) in TROPiCS-02.[17] Hematologic toxicities were also frequently observed with the TROP2-directed ADC, sacituzumab tirumotecan (SKB264/MK-2870), in an early phase trial, where the most common grade ≥3 TRAEs were decreased neutrophil count (37%), decreased white blood cell count (22%), and anemia (15%).[37] Diarrhea is also a common TRAE with sacituzumab govitecan (grade ≥3 in 9%),[17] whereas no grade ≥3 diarrhea events were reported with Dato-DXd in TROPION-Breast01. There is also variation in stomatitis rates between different TROP2-directed ADCs: 50% with Dato-DXd in TROPION-Breast01, 46.3% with sacituzumab tirumotecan,[37] and <10% with sacituzumab govitecan in TROPiCS-02.[17]

Notable differences in dosing schedule between ADCs may affect physician and patient preferences for specific ADCs; Dato-DXd requires less frequent administration (once every 3 weeks) than sacituzumab govitecan (day 1 and day 8 every 3 weeks). Further studies are required to understand the potential impact of specific properties of ADCs on safety and efficacy and to evaluate ADC sequencing. Real-world retrospective studies show that the preferred sequence of ADCs remains unclear, and prospective studies are underway evaluating optimal ADC sequencing.

The TROPION-Breast01 study had several potential limitations. First, there was a change in treatment landscape for endocrine-refractory HR+ metastatic breast cancer during the conduct of the study. Second, slightly more patients randomly assigned to the ICC arm than the Dato-DXd arm did not receive their allocated treatment, which is likely due to patient preference not to receive standard chemotherapy in an open-label study. Third, the use of prophylactic steroid-containing mouthwash was recommended but not mandated (because it is not globally available), and it was challenging to accurately assess the impact of mouthwash use on the prevention of stomatitis since the study was not designed to address this question.

Overall, Dato-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS and a favorable and manageable safety profile compared with ICC for a patient population with previously unmet need for more efficacious and less toxic therapies. Further phase 3 studies are now in progress evaluating Dato-DXd in other breast cancer settings, including early and metastatic TNBC, either as monotherapy or in combination with immunotherapy.[23-27] The results of TROPION-Breast01 support Dato-DXd as a potential new therapeutic option for patients with previously treated, inoperable or metastatic, HR+/HER2− breast cancer.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Datopotamab Deruxtecan Versus Chemotherapy in Previously Treated Inoperable/Metastatic Hormone Receptor–Positive Human Epidermal Growth Factor Receptor 2–Negative Breast Cancer: Primary Results From TROPION-Breast01

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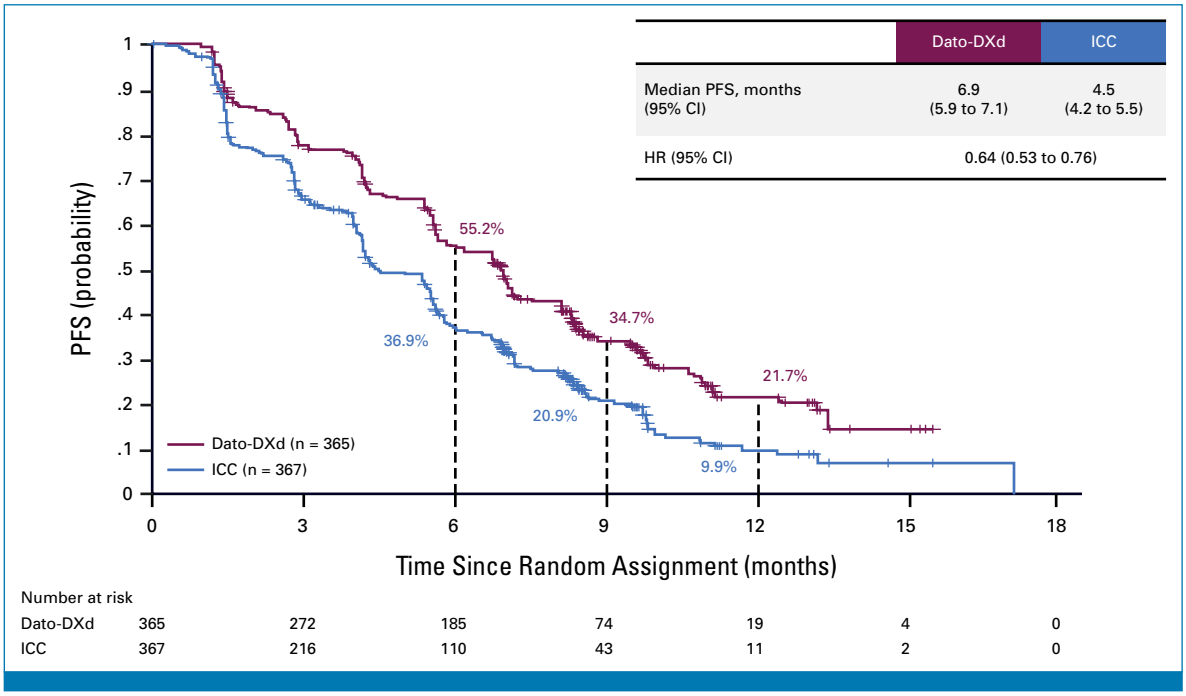

FIG A1. PFS by investigator assessment (intention-to-treat population). Dato-DXd, datopotamab deruxtecan; HR, hazard ratio; ICC, investigator's choice of chemotherapy; PFS, progression-free survival.

TABLE A1. Dato-DXd Toxicity Management Guidelines

Worst Grade Toxicity (CTCAE v5.0)	Management Guidelines
No toxicity	Maintain dose and schedule
IRR	
Grade 1	If IRR (such as fever and chills, with and without nausea/vomiting, pain, headache, dizziness, dyspnea, grade 1 or 2 hypotension) is observed during administration, the infusion rate should be reduced to 50% of the initial infusion rate and the patient should be closely monitored. If no other reactions appear on resumption of Dato-DXd at the above reduced infusion rate, then the infusion rate for subsequent treatment cycles may be resumed at the initial infusion rate
Grade 2	Administration of Dato-DXd should be interrupted briefly. Symptomatic treatment should be started. If the event resolves or improves to grade 1, infusion can be restarted at a 50% reduced infusion rate (ie, 180 minutes for a 90-minute infusion and 60 minutes for a 30-minute infusion). The next administration should be given at the reduced rate, and, if no IRR occurs, then Dato-DXd can be administered at the initial planned infusion rate for subsequent treatment cycles (unless a new IRR event occurs in the future)
Grade 3	Administration of Dato-DXd should be interrupted immediately, and the remainder of the dose should be withheld for that cycle. Symptomatic treatment should be started. If the IRR resolves within the same day of Dato-DXd infusion with symptomatic treatment and/or interruption of infusion, no recurrence of symptoms occurs after initial improvement and no hospitalization is necessary for clinical sequelae, then for the subsequent cycle, Dato-DXd can be readministered at a 50% reduced infusion rate (ie, 60 minutes for a 30-minute infusion); if no IRR occurs, then Dato-DXd can be administered at the initial planned infusion rate (30 minutes) for subsequent treatment cycles (unless a new IRR event occurs in the future)
Grade 4	Administration of Dato-DXd must be discontinued immediately and permanently. Urgent intervention is indicated. Epinephrine, antihistamines, steroids, bronchodilators, vasopressors, IV fluid therapy, supplemental oxygen, etc should be considered as clinically indicated
Hematologic toxicity	
Neutrophil count decreased and/or WBC count decreased	
Grade 3	Delay dose until resolution to grade ≤2, then maintain dose
Grade 4	Delay dose until resolution to grade ≤2. If resolved in ≤14 days from the day of onset, maintain dose. If resolved in >14 days from the day of onset, reduce dose by one level
Febrile neutropenia	
Grade 3	Delay dose until resolution, then reduce dose by one level
Grade 4	Discontinue study treatment
Lymphocyte count decreased	
Grade 4	Delay dose until resolution to grade ≤2. If resolved in ≤14 days from the day of onset, maintain dose. If resolved in >14 days from the day of onset, reduce dose by one level
Anemia	
Grade 3	Delay dose until resolution to grade ≤2, then maintain dose
Grade 4	Delay dose until resolution to grade ≤2, then reduce dose by one level
Platelet count decreased	
Grade 3	Delay dose until resolution to grade ≤1. If resolved in ≤7 days from the day of onset, maintain dose. If resolved in >7 days from the day of onset, reduce dose by one level
Grade 4	Delay dose until resolution to grade ≤1, then reduce dose by one level
Nonhematologic toxicities	
Pulmonary toxicity	
	If a patient develops radiographic changes potentially consistent with interstitial lung disease (ILD)/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough, or fever, rule out ILD/pneumonitis. If the AE is confirmed to have an etiology other than treatment-related ILD/pneumonitis, follow the management guidance outlined in the Other nonlaboratory adverse events dose modification section below. If the AE is suspected to be ILD/pneumonitis, Dato-DXd treatment should be delayed pending further evaluations, including high-resolution CT, pulmonologist consultation (Infectious Diseases consultation as clinically indicated), bronchoscopy and BAL if clinically indicated and feasible, pulmonary function tests (including FVC and CO diffusing capacity) and pulse oximetry (SpO_2), and clinical laboratory tests (arterial blood gases if clinically indicated, blood culture, blood cell count, differential, WBC count, C-reactive protein, COVID-19 test). If the AE is confirmed to be ILD/pneumonitis as per the above evaluations, follow the ILD/pneumonitis management guidance as outlined below. All events of ILD/pneumonitis regardless of severity or seriousness must be followed until resolution, including after Dato-DXd discontinuation

(continued on following page)

TABLE A1. Dato-DXd Toxicity Management Guidelines (continued)

Worst Grade Toxicity (CTCAE v5.0)	Management Guidelines
Grade 1	Administration of Dato-DXd must be delayed for any ILD/pneumonitis events regardless of grade. Monitor and closely follow up in 2-7 days for the onset of clinical symptoms and pulse oximetry. Consider follow-up imaging in 1-2 weeks (or as clinically indicated). Consider starting systemic steroids (eg, at least 0.5 mg/kg once per day prednisone or equivalent) until improvement, followed by gradual taper over at least 4 weeks. If the event worsens despite initiation of corticosteroids, then follow grade 2 guidelines. If the patient is asymptomatic but is given steroid treatment, then the patient should be considered as grade 1. For grade 1 events, Dato-DXd can be restarted only if the event is resolved to grade 0 (full resolution of ILD/pneumonitis, including the disappearance of radiologic findings associated with active ILD/pneumonitis; residual scarring or fibrosis after recovery of ILD/pneumonitis is not considered to be active disease). If resolved in ≤28 days from the day of onset, maintain dose. If resolved in >28 days from the day of onset, reduce dose by one level. However, if the grade 1 ILD/pneumonitis event does not resolve within 84 days from the last infusion, Dato-DXd should be permanently discontinued
Grade 2	Permanently discontinue study treatment. Promptly start and treat with systemic steroids for at least 14 days or until complete resolution of clinical and chest CT findings, followed by gradual taper over at least 4 weeks. Monitor symptoms closely. Reimage as clinically indicated. If worsening or no improvement in clinical or diagnostic observations in 5 days, consider increasing dose of steroids and switching to IV administration, reconsider additional workup for alternative etiologies as described above, and escalate care as clinically indicated
Grade 3 and 4	Permanently discontinue study treatment. Hospitalization required. Promptly initiate empiric high-dose methylprednisolone IV treatment, followed by at least 1 mg/kg once per day of prednisone (or equivalent) for at least 14 days or until complete resolution of clinical and chest CT findings, followed by gradual taper over at least 4 weeks. Reimage as clinically indicated. If still no improvement within 3-5 days, reconsider additional workup for alternative etiologies as described above and consider other immunosuppressants and/or treat per local practice
Ocular surface events	
General considerations	Consider obtaining an ophthalmologic assessment to ensure accurate diagnosis, event grading, appropriate treatment, and event resolution, as appropriate. Advise patients to avoid the use of contact lenses and to use artificial tears four times per day as a preventative measure and up to eight times per day as clinically needed. Use of eye medications (eg, topical corticosteroids) other than artificial tears should be at the discretion of an ophthalmologist or if unavailable, another licensed eye care provider. The following grading scale replaces the CTCAE 5.0 grades for triggering the toxicity management guidelines for cornea-related adverse events Corneal Toxicity Severity Grading Scale Normal = Clear cornea, no epithelial defects Grade 1 = Nonconfluent superficial keratitis Grade 2 = Confluent superficial keratitis, a cornea defect, or three-line or more loss in best corrected distance visual acuity Grade 3 = Corneal ulcer or stromal opacity or best corrected distance visual acuity 20/200 or worse Grade 4 = Corneal perforation
Grade 1	Consider obtaining an ophthalmologic assessment
Grade 2	Obtain an ophthalmologic assessment. Delay dose until resolution to grade ≤1, then maintain dose
Grade 3	Obtain an ophthalmologic assessment. Delay dose until resolution to grade ≤1, then reduce dose by one level
Grade 4	Obtain an urgent ophthalmologic assessment. Discontinue study treatment
GI	
Nausea/vomiting	
Grade 3	If prophylaxis and supportive medications have *not yet* been optimized: Delay dose until resolution to grade ≤1 or baseline, optimize medications, and then maintain dose. If prophylaxis and supportive medications have *already* been optimized: Delay dose until resolution to grade ≤1 or baseline, and then reduce dose by one level
Grade 4	Discontinue study treatment
Oral mucositis/stomatitis	
General considerations	Increase the frequency of bland mouth rinses up to every hour, if necessary and applicable. Provide adequate pain management. As soon as oral pain, inflammation, and/or ulceration develops, strongly consider steroid-containing mouth rinses. May consider oral nystatin suspension or other topical antifungal agents at least 15 minutes after the steroid-containing mouthwash according to clinician preference on the basis of institutional/local guidelines. Consider cryotherapy (ice chips or ice water held in the mouth) throughout the infusion. For severe and/or persistent events, consider referral to a dentist or oral surgeon

(continued on following page)

TABLE A1. Dato-DXd Toxicity Management Guidelines (continued)

Worst Grade Toxicity (CTCAE v5.0)	Management Guidelines
Grade 1	Maintain dose. Optimize prophylactic and supportive medications as above
Grade 2	Optimize prophylactic and supportive medications as above. Consider a dose delay or reduction if clinically indicated
Grade 3	If prophylaxis and supportive medications have *not yet* been optimized: Delay dose until resolution to grade ≤1 or baseline, optimize medications, and then maintain dose. If prophylaxis and supportive medications have *already* been optimized: Delay dose until resolution to grade ≤1 or baseline, then reduce dose by one level
Grade 4	Discontinue study treatment
Diarrhea	
Grade 3	If prophylaxis and supportive medications have not yet been optimized: Delay dose until resolution to grade ≤1 or baseline, optimize medications, and then maintain dose. If prophylaxis and supportive medications have already been optimized: Delay dose until resolution to grade ≤1 or baseline, then reduce dose by one level
Grade 4	Discontinue study treatment
Other laboratory adverse events	
Grade 3	Delay dose until resolution to grade ≤1 or baseline level, and then reduce by one dose level if determined by the investigator to be clinically significant
Grade 4	Discontinue study treatment
Other nonlaboratory adverse events	
Grade 3	Delay dose until resolution to grade ≤1 or baseline level, and then reduce by one dose level if determined by the investigator to be clinically significant
Grade 4	Discontinue study treatment

Abbreviations: AE, adverse event; BAL, bronchoalveolar lavage; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; Dato-DXd, datopotamab deruxtecan; FVC, forced vital capacity; ILD, interstitial lung disease; IRR, infusion-related reaction; IV, intravenous; WBC, white blood cell.

TABLE A2. TFST, TSST, and PFS2 (intention-to-treat population)

Variable	Dato-DXd (n = 365)		ICC (n = 367)
TFST			
Events, No. (%)	219 (60)		283 (77.1)
TFST, months, median (95% CI)	8.2 (7.4 to 8.9)		5 (4.6 to 5.7)
HR (95% CI)[a]		0.53 (0.45 to 0.64)	
TSST			
Events, No. (%)	126 (34.5)		144 (39.2)
TSST, months, median (95% CI)	13.3 (11.4 to NC)		11.5 (10.3 to 13.1)
HR (95% CI)[a]		0.75 (0.59 to 0.96)	
PFS2			
Events, No. (%)	117 (32.1)		121 (33)
PFS2, months, median (95% CI)	12.7 (11.1 to NC)		10.4 (9.5 to 12.6)
HR (95% CI)[a]		0.71 (0.55 to 0.92)	

Abbreviations: CDK4/6, cyclin-dependent kinase 4/6; Dato-DXd, datopotamab deruxtecan; HR, hazard ratio; ICC, investigator's choice of chemotherapy; NC, not calculable; PFS2, time to second progression or death; TFST, time to first subsequent therapy or death; TSST, time to second subsequent therapy or death.

[a]The analysis was performed using a stratified Cox proportional hazards model with stratification variables: number of previous lines of chemotherapy, geographic region, and previous use of a CDK4/6 inhibitor. A HR <1 favored Dato-DXd.

TABLE A3. Summary of Subsequent Anticancer Therapy (in any treatment line) by Therapy Class (intention-to-treat population)

Subsequent Therapy	Dato-DXd (n = 365)	ICC (n = 367)
Any subsequent therapy	192 (52.6)	247 (67.3)
Antibody-drug conjugate	15 (4.1)	52 (14.2)
Trastuzumab deruxtecan	11 (3)	44 (12)
Sacituzumab govitecan	4 (1.1)	15 (4.1)
Disitamab vedotin	0	1 (0.3)
Chemotherapy	165 (45.2)	186 (50.7)
Endocrine therapy	39 (10.7)	46 (12.5)
Other drug classes	55 (15.1)	48 (13.1)

Abbreviations: Dato-DXd, datopotamab deruxtecan; ICC, investigator's choice of chemotherapy.

TABLE A4. Summary of TRAEs of Special Interest for Dato-DXd; by AESI Categories and Individual Preferred Terms Reported in ≥5 Patients in Either Arm (safety population)

TRAEs of Special Interest,[a] No. (%), Preferred Term	Dato-DXd (n = 360)						ICC (n = 351)					
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Oral mucositis/stomatitis[b]	200 (55.6)	91 (25.3)	84 (23.3)	25 (6.9)	0	0	52 (14.8)	31 (8.8)	12 (3.4)	9 (2.6)	0	0
Stomatitis	180 (50)	78 (21.7)	79 (21.9)	23 (6.4)	0	0	46 (13.1)	26 (7.4)	11 (3.1)	9 (2.6)	0	0
Oropharyngeal pain	13 (3.6)	12 (3.3)	1 (0.3)	0	0	0	3 (0.9)	2 (0.6)	1 (0.3)	0	0	0
Mouth ulceration	12 (3.3)	8 (2.2)	3 (0.8)	1 (0.3)	0	0	5 (1.4)	4 (1.1)	1 (0.3)	0	0	0
Oral pain	5 (1.4)	3 (0.8)	2 (0.6)	0	0	0	1 (0.3)	1 (0.3)	0	0	0	0
Mucosal inflammation other than oral mucositis/stomatitis	5 (1.4)	1 (0.3)	4 (1.1)	0	0	0	1 (0.3)	1 (0.3)	0	0	0	0
Ocular surface events[c]	144 (40)	115 (31.9)	26 (7.2)	3 (0.8)	0	0	41 (11.7)	34 (9.7)	7 (2)	0	0	0
Dry eye	78 (21.7)	69 (19.2)	7 (1.9)	2 (0.6)	0	0	27 (7.7)	24 (6.8)	3 (0.9)	0	0	0
Keratitis[d]	52 (14.4)	41 (11.4)	9 (2.5)	2 (0.6)	0	0	17 (4.8)	14 (4)	3 (0.9)	0	0	0
Increased lacrimation	23 (6.4)	22 (6.1)	1 (0.3)	0	0	0	2 (0.6)	1 (0.3)	1 (0.3)	0	0	0
Meibomian gland dysfunction	21 (5.8)	19 (5.3)	2 (0.6)	0	0	0	1 (0.3)	1 (0.3)	0	0	0	0
Blepharitis	17 (4.7)	14 (3.9)	3 (0.8)	0	0	0	3 (0.9)	3 (0.9)	0	0	0	0
Blurred vision	11 (3.1)	10 (2.8)	1 (0.3)	0	0	0	2 (0.6)	2 (0.6)	0	0	0	0
Conjunctivitis	10 (2.8)	7 (1.9)	3 (0.8)	0	0	0	1 (0.3)	1 (0.3)	0	0	0	0
Xerophthalmia	5 (1.4)	3 (0.8)	2 (0.6)	0	0	0	1 (0.3)	1 (0.3)	0	0	0	0
Adjudicated drug-related ILD[e]	12 (3.3)	5 (1.4)	4 (1.1)	2 (0.6)	0	1 (0.3)[g]	0	0	0	0	0	0
Pneumonitis	7 (1.9)	3 (0.8)	1 (0.3)	2 (0.6)	0	1 (0.3)[g]	0	0	0	0	0	0
ILD	5 (1.4)	2 (0.6)	3 (0.8)	0	0	0	0	0	0	0	0	0
Infusion-related reactions[f]	26 (7.2)	17 (4.7)	8 (2.2)	1 (0.3)	0	0	9 (2.6)	8 (2.3)	1 (0.3)	0	0	0
Infusion-related reaction	10 (2.8)	5 (1.4)	5 (1.4)	0	0	0	0	0	0	0	0	0
Pruritus	8 (2.2)	6 (1.7)	2 (0.6)	0	0	0	0	0	0	0	0	0

Abbreviations: AE, adverse event; AESI, AE of special interest; Dato-DXd, datopotamab deruxtecan; ICC, investigator's choice of chemotherapy; ILD, interstitial lung disease; TRAE, treatment-related adverse event.

[a]For the Dato-DXd clinical program, AESIs were identified on the basis of the available preclinical data, review of the cumulative literature, reported toxicities for drugs with a similar monoclonal antibody and payload of Dato-DXd, and biologic plausibility.

[b]Comprising the preferred terms of aphthous ulcer, dysphagia, glossitis, mouth ulceration, odynophagia, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, and stomatitis.

[c]Comprising the preferred terms of blepharitis, conjunctivitis, corneal disorder, corneal erosion, corneal lesion, dry eye, foreign body sensation in eyes, keratitis, keratopathy, lacrimation increased, limbal stem cell deficiency, meibomian gland dysfunction, ocular toxicity, photophobia, punctate keratitis, superior limbic keratoconjunctivitis, ulcerative keratitis, vision blurred, visual impairment, and xerophthalmia.

[d]Grouped term comprising keratitis, punctate keratitis, and ulcerative keratitis.

[e]Comprising the preferred terms of ILD and pneumonitis.

[f]Comprising the preferred terms of bronchospasm, hypotension, infusion-related reaction, pruritus, pyrexia, rash, and urticaria, occurring on the day of infusion.

[g]Characterized by the investigator as grade 3 pneumonitis, with death attributed to disease progression.