Datopotamab Deruxtecan in Advanced or Metastatic HR+/HER2− and Triple-Negative Breast Cancer: Results From the Phase I TROPION-PanTumor01 Study

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ABSTRACT

PURPOSE Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate consisting of a humanized antitrophoblast cell-surface antigen 2 (TROP2) monoclonal antibody linked to a potent, exatecan-derived topoisomerase I inhibitor payload via a plasma-stable, selectively cleavable linker.

PATIENTS AND METHODS TROPION-PanTumor01 (ClinicalTrials.gov identifier: NCT03401385) is a phase I, dose-escalation, and dose-expansion study evaluating Dato-DXd in patients with previously treated solid tumors. The primary study objective was to assess the safety and tolerability of Dato-DXd. Secondary objectives included evaluation of antitumor activity and pharmacokinetics. Results from patients with advanced/metastatic hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2−) breast cancer (BC) or triple-negative BC (TNBC) are reported.

RESULTS At data cutoff (July 22, 2022), 85 patients (HR+/HER2− BC = 41, and TNBC = 44) had received Dato-DXd. The objective response rate by blinded independent central review was 26.8% (95% CI, 14.2 to 42.9) and 31.8% (95% CI, 18.6 to 47.6) for patients with HR+/HER2− BC and TNBC, respectively. The median duration of response was not evaluable in the HR+/HER2− BC cohort and 16.8 months in the TNBC cohort. The median progression-free survival in patients with HR+/HER2− BC and TNBC was 8.3 and 4.4 months, respectively. All-cause treatment-emergent adverse events (TEAEs; any grade, grade ≥3) were observed in 100% and 41.5% of patients with HR+/HER2− BC and 100% and 52.3% of patients with TNBC. Stomatitis was the most common TEAE (any grade, grade ≥3) in both HR+/HER2− BC (82.9%, 9.8%) and TNBC (72.7%, 11.4%) cohorts.

CONCLUSION In patients with heavily pretreated advanced HR+/HER2− BC and TNBC, Dato-DXd demonstrated promising clinical activity and a manageable safety profile. Dato-DXd is currently being evaluated in phase III studies.

ACCOMPANYING CONTENT

Data Supplement

Protocol

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INTRODUCTION

Hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2−) breast cancer (BC) and triple-negative BC (TNBC) together represent approximately 80% of BC cases in the United States.[1] Although recent advances in therapy have improved outcomes, the 5-year survival rate in patients with metastatic disease remains poor (34% and 13% for HR+/HER2− BC and TNBC, respectively).[1]

For patients with metastatic HR+/HER2− BC, the recommended standard of care is endocrine therapy (ET) plus a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor.[2-5] However, approximately 10% of patients with HR+ metastatic BC show primary resistance to CDK4/6 inhibitors, and secondary or acquired endocrine resistance is inevitable in most patients.[6-8] For patients with TNBC, chemotherapy remains the standard treatment option for advanced/metastatic disease.[5,9-11] For patients who have disease progression or are refractory to standard therapies, treatment options remain limited.[5,11-13]

CONTEXT

Key Objective

The phase I TROPION-PanTumor01 study evaluated Dato-DXd, a TROP2-directed antibody-drug conjugate (ADC), in solid tumors, including hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) breast cancer (BC) and triple-negative BC (TNBC).

Knowledge Generated

The confirmed objective response rate was 26.8% and 31.8%, and the median progression-free survival was 8.3 months and 4.4 months for patients with HR+/HER2– BC and TNBC, respectively. Stomatitis was the most common treatment-emergent adverse event, and one adjudicated drug-related interstitial lung disease case was reported.

Relevance *(K.D. Miller)*

Data-DXd is a new ADC with significant activity in previously treated BC. Additional studies are needed to evaluate the mechanisms of resistance to ADCs and to determine the optimal sequence of therapies.*

*Relevance section written by *JCO* Senior Deputy Editor Kathy D. Miller, MD.

Antibody-drug conjugates (ADCs) aim to address this unmet need by potentially reducing systemic toxicity and improving response rates through selective payload delivery to tumors.[14,15] Trophoblast cell-surface antigen 2 (TROP2) is a transmembrane protein sporadically expressed in healthy tissue but broadly expressed and associated with poor prognosis in HR+/HER2– BC and TNBC,[16-20] making TROP2 an attractive tumor-associated antigen for treatment of these BC subtypes. Datopotamab deruxtecan (Dato-DXd) is a TROP2-directed ADC comprising a humanized anti-TROP2 immunoglobulin G1 monoclonal antibody covalently linked to a highly potent topoisomerase I (topo I) inhibitor, a derivative of exatecan, via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker, resulting in reduced systemic exposure and off-target adverse effects.[21] Internalization of Dato-DXd into TROP2-expressing cells leads to death of target tumor cells and bystander killing of neighboring cells in the tumor microenvironment.[21]

Efficacy and safety results of Dato-DXd in patients with previously treated advanced/metastatic HR+/HER2– BC and TNBC are presented from the phase I TROPION-PanTumor01 trial.

PATIENTS AND METHODS

Study Design and Patients

The TROPION-PanTumor01 clinical trial (ClinicalTrials.gov identifier: NCT03401385) is an ongoing phase I, two-part, multicenter, open-label, multiple-dose study of Dato-DXd in patients with advanced solid tumors including HR+/HER2– BC and TNBC conducted at 17 sites in Japan and the United States (Data Supplement, Fig S1, online only). The study comprises a dose-escalation portion to determine the maximum tolerated dose and recommended dose for expansion (RDE) and an ongoing dose-expansion portion to assess safety and tolerability. The full study design, dose escalation, and results for the non–small cell lung cancer cohort have been reported previously.[22]

Enrolled patients were 18 years and older with HR+/HER2– BC or TNBC with tumors that had relapsed or progressed after local standard treatments or for which no standard treatment was available. Patient disposition is described in the Data Supplement.

Study Treatment

Intravenous Dato-DXd was administered on Day 1 of each 21-day cycle. Patients received Dato-DXd until unacceptable toxicity, progressive disease (PD), or withdrawal of consent. During the study, 6 mg/kg once every 3 weeks was determined to have the optimal benefit-risk ratio and was declared the RDE.[22] In the dose-expansion portion, patients received the RDE (6 mg/kg once every 3 weeks).

End Points and Assessments

The primary objective of dose escalation and expansion was to investigate the safety and tolerability of Dato-DXd. Secondary objectives for each portion were to characterize the pharmacokinetic (PK) properties of Dato-DXd, total anti-TROP2 antibody, and MAAA-1181a (DXd payload); investigate the antitumor activity of Dato-DXd; and assess the incidence of antidrug antibodies (ADAs) against Dato-DXd.

Tumor response was evaluated using RECIST version 1.1[23] and included confirmed objective response rate (ORR), disease control rate (DCR), clinical benefit rate (CBR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and time to response (TTR). Tumor response definitions are included in the Data Supplement.

Safety end points included adverse events (AEs), serious AEs (SAEs), treatment-emergent AEs (TEAEs), and AEs of special interest (AESIs). AEs were investigator-determined and graded (1 to 5) according to the National Cancer Institute Common Terminology Criteria for AEs version 5.0.[24] AESIs consisted of grouped terms of predefined Medical Dictionary for Regulatory Activities preferred terms. An independent interstitial lung disease (ILD) adjudication committee was responsible for reviewing all potential cases of ILD/pneumonitis to confirm the diagnosis and assess drug-relatedness. Toxicity management guidelines for ILD were introduced from the beginning of the study, with guidelines for other AESIs added to the protocol at later dates.

PK parameter calculations are included in the Data Supplement.

Statistical Analysis

The data cutoff date was July 22, 2022. The full analysis set (FAS) and the safety analysis set included all patients who received at least one dose of study drug. The FAS was used for all efficacy analyses, unless otherwise specified.

Patient disposition, demographic and baseline characteristics, treatment exposure, TTR, ADA incidence, and AEs were summarized descriptively. ORR, DCR, and CBR were summarized along with two-sided 95% exact CIs using the Clopper-Pearson method. DOR, PFS, and OS were summarized and displayed using the Kaplan-Meier method; median time to event for these end points with two-sided 95% CIs was summarized using the Brookmeyer-Crowley method. Statistical power and software are described in the Data Supplement.

Trial Oversight

Study conduct details are included in the Data Supplement.

RESULTS

Patients

Between June 30, 2020, and October 7, 2021, 85 patients with BC were enrolled in the TROPION-PanTumor01 study, of whom 41 and 44 had advanced/unresectable or metastatic HR+/HER2− BC and TNBC, respectively (Data Supplement, Fig S2). All 85 patients received Dato-DXd (6 mg/kg once every 3 weeks, n = 83; 8 mg/kg once every 3 weeks, n = 2 [both TNBC]). Patients who received Dato-DXd 8.0 mg/kg once every 3 weeks were enrolled before 6 mg/kg once every 3 weeks being declared the RDE on the basis of emerging data from the non–small cell lung cancer cohort.[22] At data cutoff, 36 and 41 patients with HR+/HER2− BC and TNBC, respectively, had discontinued treatment, and five and three patients were ongoing. The primary reason for treatment discontinuation was PD (including radiographic PD or clinical progression), reported in 58.5% and 77.3% of patients with HR+/HER2− BC and TNBC, respectively, per RECIST version 1.1. The median (range) study duration for patients with HR+/HER2− BC and TNBC was 13.7 (9-16) and 19.3 (15-25) months; the median (range) treatment duration was 4.8 (0.7-14.9) and 4.3 (0.7-21.8) months. All patients with HR+/HER2− BC were naïve to topo I inhibitor–based ADC therapy (topo I naïve). Among patients with TNBC, 30 were topo I naïve and 14 had received previous topo I therapy (topo I exposed; 11 received sacituzumab govitecan, two received trastuzumab deruxtecan, and one received patritumab deruxtecan). Patient demographics and baseline characteristics are summarized in Table 1 and the Data Supplement (Table S1). Patients with HR+/HER2− BC and TNBC were heavily pretreated, with a median (range) of five (3-10) and three (1-10) previous regimens for advanced/metastatic disease, respectively (Table 1). Most patients with HR+/HER2− BC (39 [95.1%]) received previous CDK4/6 inhibitors in the advanced or metastatic setting. Most patients with TNBC (41 [93.2%]) received previous taxane therapy.

Efficacy

Confirmed responses (complete response [CR] or partial response [PR]) were observed in 11 of 41 patients with HR+/HER2− BC (all PR) and 14 of 44 patients with TNBC (one CR and 13 PR), with confirmed ORRs of 26.8% (95% CI, 14.2 to 42.9) and 31.8% (95% CI, 18.6 to 47.6), respectively (Table 2). In the topo I–naïve TNBC subgroup, confirmed responses were observed in 12 of 30 patients (one CR and 11 PR) and the confirmed ORR was 40.0% (95% CI, 22.7 to 59.4; Table 2). Best percentage change from baseline in target lesion size for all patients and percentage change from baseline over time, assessed by blinded independent central review (BICR) per RECIST version 1.1, are shown in Figures 1A-1D. Representative scans from a patient with HR+/HER2− BC who achieved a PR and the patient with TNBC who achieved a CR are shown in Figures 1E and 1F.

The median DOR was not evaluable (NE; 95% CI, 4.4 to NE) in the HR+/HER2− BC cohort and 16.8 months (95% CI, 5.6 to NE months) in the TNBC cohort. The DCR and CBR were 85.4% (95% CI, 70.8 to 94.4) and 43.9% (95% CI, 28.5 to 60.3), respectively, in the HR+/HER2− BC cohort and 79.5% (95% CI, 64.7 to 90.2) and 38.6% (95% CI, 24.4 to 54.5), respectively, in the TNBC cohort (Table 2). In the topo I–naïve TNBC subgroup, the DCR and CBR were 83.3% (95% CI, 65.3 to 94.4) and 50.0% (95% CI, 31.3 to 68.7), respectively (Table 2).

The median PFS by BICR was 8.3 months (95% CI, 5.5 to 11.1 months) and 4.4 months (95% CI, 3.0 to 7.3 months) in the HR+/HER2− BC and TNBC cohorts, respectively (Fig 2; Table 2). In the topo I–naïve TNBC subgroup, the median PFS was 7.3 months (95% CI, 3.0 to 18.0 months; Fig 2; Table 2). The median OS was not reached for the HR+/HER2− BC cohort and was 13.5 months (95% CI, 10.1 to 16.3 months) in the TNBC cohort. The median OS was 14.3 months (95% CI, 10.5 to NE months) in the topo I–naïve TNBC subgroup (Data Supplement, Fig S3; Table 2).

TABLE 1. Patient Demographics and Baseline Clinical Characteristics

Characteristic	HR+/HER2− BC (N = 41)	TNBC (N = 44)
Age, years, median (range)	57 (33-75)	52.5 (32-82)
Sex, female, No. (%)	40 (97.6)	44 (100)
Race, No. (%)		
White	29 (70.7)	22 (50.0)
Black or African American	1 (2.4)	3 (6.8)
Asian	8 (19.5)	14 (31.8)
Other	3 (7.3)	5 (11.4)
Country, No. (%)		
United States	35 (85.4)	31 (70.5)
Japan	6 (14.6)	13 (29.5)
ECOG PS, No. (%)		
0	20 (48.8)	18 (40.9)
1	21 (51.2)	26 (59.1)
Time from initial diagnosis to enrollment, months, median (range)	86.7 (19.0-351.0)	39.7 (5.1-185.2)
Time from initial treatment for metastatic disease to first dose, months, median (range)	42.7 (10.2-131.1)	15.3 (2.1-117.3)
De novo metastatic disease, No. (%)		
Yes	21 (51.2)	14 (31.8)
No	20 (48.8)	30 (68.2)
Most common sites of metastasis, No. (%)		
Liver	26 (63.4)	15 (34.1)
Chest wall	4 (9.8)	14 (31.8)
Lung	8 (19.5)	11 (25.0)
History of brain metastases, No. (%)	6 (14.6)	5 (11.4)
Previous therapies, median (range)	6 (4-11)	4 (1-12)
Previous therapies in locally advanced/metastatic setting, median (range)	5 (3-10)	3 (1-10)
Previous lines of therapy in locally advanced/metastatic setting, No. (%)		
<3	0	17 (38.6)
≥3	41 (100)	23 (52.3)
Missing	0	4 (9.1)
Chemotherapy, No. (%)		
Capecitabine	34 (82.9)	27 (61.4)
Anthracyclines	22 (53.7)	33 (75.0)
Platinum-based chemotherapy	2 (4.9)	23 (52.3)
(Neo)adjuvant chemotherapy	15 (36.6)	29(65.9)
Previous chemotherapy regimens in locally advanced/metastatic setting, median (range)	2 (1-6)	3 (1-7)
CDK4/6 inhibitors, No. (%)	39 (95.1)	6 (13.6)
≤12 months	19 (46.3)	4 (9.1)
>12 months	20 (48.8)	2 (4.5)
Previous systemic treatment, No. (%)		
Taxanes	24 (58.5)	41 (93.2)
mTOR inhibitors	11 (26.8)	2 (4.5)
PI3K inhibitors	8 (19.5)[a]	0
PARP inhibitor	6 (14.6)	8 (18.2)
TKI therapy	4 (9.8)	3 (6.8)
Immunotherapy	3 (7.3)	20 (45.5)
Topo I inhibitor–based ADC[b]	—	14 (31.8)
Endocrine therapy, No. (%)	41 (100)	11 (25.0)
Previous endocrine therapy in locally advanced/metastatic setting <6 months	7 (17.1)	2 (4.5)
Previous endocrine therapy in locally advanced/metastatic setting ≥6 months	33 (80.5)	3 (6.8)

(continued on following page)

TABLE 1. Patient Demographics and Baseline Clinical Characteristics (continued)

Characteristic	HR+/HER2− BC (N = 41)	TNBC (N = 44)
BRCA1 mutation, No. (%)		
Positive	0	1 (2.3)
Negative	27 (65.9)	28 (63.6)
Unknown	14 (34.1)	15 (34.1)
BRCA2 mutation, No. (%)		
Positive	3 (7.3)	3 (6.8)
Negative	23 (56.1)	25 (56.8)
Unknown	15 (36.6)	16 (36.4)
HER2 expression (IHC), No. (%)		
0	23 (56.1)	19 (43.2)
1+	9 (22.0)	12 (27.3)
2+	7 (17.1)	4 (9.1)
Unknown	2 (4.9)	9 (20.5)
HER2 gene amplification (ISH), No. (%)		
Negative	26 (63.4)	34 (77.3)
Unknown	15 (36.6)	10 (22.7)

Abbreviations: ADC, antibody-drug conjugate; BC, breast cancer; BRCA, breast cancer gene; CDK, cyclin-dependent kinase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mTOR, mammalian or mechanistic target of rapamycin; PARP, poly(ADP-ribose) polymerase; PI3K, phosphatidylinositol-3 kinase; TKI, tyrosine kinase inhibitor; TNBC, triple-negative BC; topo I, topoisomerase I.

[a]One patient (in the HR+/HER2− BC cohort) received a dual mTOR/PI3K inhibitor.

[b]Previous topo I inhibitor–based ADC use was an exclusion criterion for the HR+/HER2− BC cohort. Eleven patients in the TNBC cohort received sacituzumab govitecan, two received trastuzumab deruxtecan, and one received patritumab deruxtecan. Of the patients who received trastuzumab deruxtecan, one was eligible because of the study definition of HER2− including HER2-low BC, and the other was HER2− when enrolled in this study but previously had enrolled in a study including those with HER2+ or HER2-low BC. The patient who received patritumab deruxtecan was enrolled in a previous trial as HER3+ and HER2−.

Safety

All-cause TEAEs (any grade, grade ≥3) were reported in 100% and 41.5% of patients with HR+/HER2− BC and 100% and 52.3% of patients with TNBC (Table 3). Drug-related TEAEs (any grade, grade ≥3) were reported in 100% and 22.0% of patients with HR+/HER2− BC and 97.7% and 25.0% of patients with TNBC. TEAEs leading to dose reductions, treatment interruptions, and discontinuations were seen in five (12.2%), 15 (36.6%), and five (12.2%) patients, respectively, in the HR+/HER2− BC cohort and seven (15.9%), 12 (27.3%), and one (2.3%) patients, respectively, in the TNBC cohort.

Two on-treatment deaths occurred in the HR+/HER2− BC cohort during the study. One patient died because of disease progression, which occurred 253 days after the first dose and 8 days after the last dose of Dato-DXd. Another patient died because of grade 5 dyspnea that developed 39 days after the first dose and 15 days after the last dose of Dato-DXd. This death was determined to be unrelated to study treatment by the investigator and associated with disease progression.

The most common TEAEs (any grade, grade ≥3) reported in the HR+/HER2− BC cohort were stomatitis (82.9%, 9.8%), nausea (56.1%, 0%), and fatigue (46.3%, 2.4%). In the TNBC cohort, the most common TEAEs were stomatitis (72.7%, 11.4%), nausea (65.9%, 2.3%), and vomiting (38.6%, 4.5%; Table 4). Diarrhea (any grade) was reported in seven (17.1%) and seven (15.9%) patients in the HR+/HER2− BC and TNBC cohorts, respectively, with no grade ≥3 events reported. Anemia (any grade) was reported in seven (17.1%) patients with HR+/HER2− BC and seven (15.9%) with TNBC, with grade ≥3 events reported in three (7.3%) and one (2.3%) patients, respectively. Neutropenia (any grade) was reported in three (7.3%) and nine (20.5%) patients with HR+/HER2− BC and TNBC, respectively, with zero and one (2.3%) reporting a grade ≥3 event. In the HR+/HER2− BC cohort, one drug-related grade 4 TEAE of platelet count decreased was reported. No instances of drug-related grade 4 TEAEs were identified in the TNBC cohort; however, one case of lymphopenia (grade 4) and one pericardial effusion/cardiac tamponade event (grade 4) were observed; both were assessed by the investigator as not related to the study drug.

Adjudicated drug-related ILD/pneumonitis, infusion-related reactions (IRRs), ocular surface toxicity (OST), oral mucositis/stomatitis, and mucosal inflammation other than oral mucositis/stomatitis were AESIs in this study. No AESI-associated deaths were reported (Table 3). AESIs were reported in 92.7% and 93.2% of the HR+/HER2− BC and TNBC

TABLE 2. Antitumor Activity Assessed by BICR per RECIST Version 1.1

		TNBC (N = 44)	
Treatment Response[a]	HR+/HER2− BC (N = 41)	All (N = 44)	Topo I–Naïve (n = 30)
Confirmed ORR	11 (26.8) [14.2 to 42.9]	14 (31.8) [18.6 to 47.6]	12 (40.0) [22.7 to 59.4]
Confirmed CR, No. (%)	0	1 (2.3)	1 (3.3)
Confirmed PR, No. (%)	11 (26.8)	13 (29.5)	11 (36.7)
Non-CR/non-PD, No. (%)	1 (2.4)[b]	3 (6.8)[b]	3 (10.0)[b]
SD, No. (%)	23 (56.1)	18 (40.9)	10 (33.3)
PD, No. (%)	5 (12.2)	8 (18.2)	4 (13.3)
NE for BOR, No. (%)	1 (2.4)	1 (2.3)	1 (3.3)
DCR	35 (85.4) [70.8 to 94.4]	35 (79.5) [64.7 to 90.2]	25 (83.3) [65.3 to 94.4]
CBR[c]	18 (43.9) [28.5 to 60.3]	17 (38.6) [24.4 to 54.5]	15 (50.0) [31.3 to 68.7]
DOR, months, median [95% CI]	NE [4.4 to NE]	16.8 [5.6 to NE]	16.8 [5.6 to NE]
TTR, months, median (range)	2.8 (1.2-5.6)	1.36 (1.2-2.8)	1.38 (1.2-2.8)
PFS, months, median [95% CI]	8.3 [5.5 to 11.1]	4.4 [3.0 to 7.3]	7.3 [3.0 to 18.0]
OS, months, median [95% CI]	NE [10.1 to NE]	13.5 [10.1 to 16.3]	14.3 [10.5 to NE]

NOTE. Data are No. (%) [95% CI] unless indicated otherwise.
Abbreviations: BC, breast cancer; BICR, blinded independent central review; BOR, best overall response; CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TNBC, triple-negative BC; topo I, topoisomerase I; TTR, time to response.
[a]Postbaseline tumor response assessments were not available for two patients at data cutoff: one in the HR+/HER2− BC cohort and one in the TNBC cohort).
[b]One patient with HR+/HER2− BC and three patients with TNBC were not confirmed to have a target lesion per BICR and had a best overall response of non-CR/non-PD.
[c]CR + PR + SD for ≥6 months.

cohorts, with 14.6% and 11.4%, respectively, experiencing a grade ≥3 event. Most patients with HR+/HER2− BC (35 of 38 [92.1%]) and TNBC (38 of 41 [92.7%]) had drug-related AESIs (investigator-reported).

One patient with HR+/HER2− BC experienced grade 3 adjudicated drug-related ILD/pneumonitis and subsequently discontinued treatment; no cases were reported in the TNBC cohort (Table 3). Eight patients with HR+/HER2− BC (19.5%) and TNBC (18.2%) experienced IRRs, six (14.6%) and seven (15.9%) of which were drug-related; no grade ≥3 IRRs were reported. IRR was the most commonly occurring preferred term within that grouped category, reported in four (9.8%) patients with HR+/HER2− BC and six (13.6%) patients with TNBC (Data Supplement, Table S2). In total, 17 (41.5%) patients with HR+/HER2− BC and 16 (36.4%) patients with TNBC experienced OSTs, 15 (36.6%) and 14 (31.8%) of which, respectively, were drug-related. Dry eye was the most commonly occurring OST AESI, experienced by 10 (24.4%) and seven (15.9%) patients with HR+/HER2− BC and TNBC, respectively; all events were grade 1 to 2 (two [4.9% and 4.5%] patients in each cohort experienced a grade 2 event). Keratitis was reported in four (9.8%) patients with HR+/HER2− BC and one (2.3%) patient with TNBC. Two (4.9%) patients with HR+/HER2− BC discontinued treatment because of OSTs (one because of a grade 3 event of keratitis and one because of a grade 2 event of keratopathy; Data Supplement, Table S2). Although not a defined OST, cataracts were reported in six (14.6%) and four (9.1%) patients in the HR+/HER2− BC and TNBC cohorts, respectively; all cases were grade 1 to 2, and only one considered to be drug-related. This patient had AEs of drug-related vision blurred followed by cataracts 31 days after treatment discontinuation for disease progression. An additional patient in the TNBC cohort had cataract surgery for grade 2 cataracts that were reported as not related to Dato-DXd; cataracts were noted at screening. This patient also had drug-related grade 2 keratitis.

A total of 37 (90.2%) and 35 (79.5%) patients with HR+/HER2− BC and TNBC, respectively, experienced events of oral mucositis/stomatitis, 34 (82.9%) and 34 (77.3%) of which were drug-related. Four (9.8%) and five (11.4%) patients with HR+/HER2− BC and TNBC, respectively, reported grade ≥3 events; one (2.4%) patient with HR+/HER2− BC discontinued treatment because of grade 3 stomatitis. No AESIs of mucosal inflammation other than oral mucositis/stomatitis were reported. AESI incidence is given in the Data Supplement (Table S2).

PKs and Immunogenicity

PK profiles of Dato-DXd and anti-TROP2 antibody were similar, and exposure of the DXd payload was low (Data

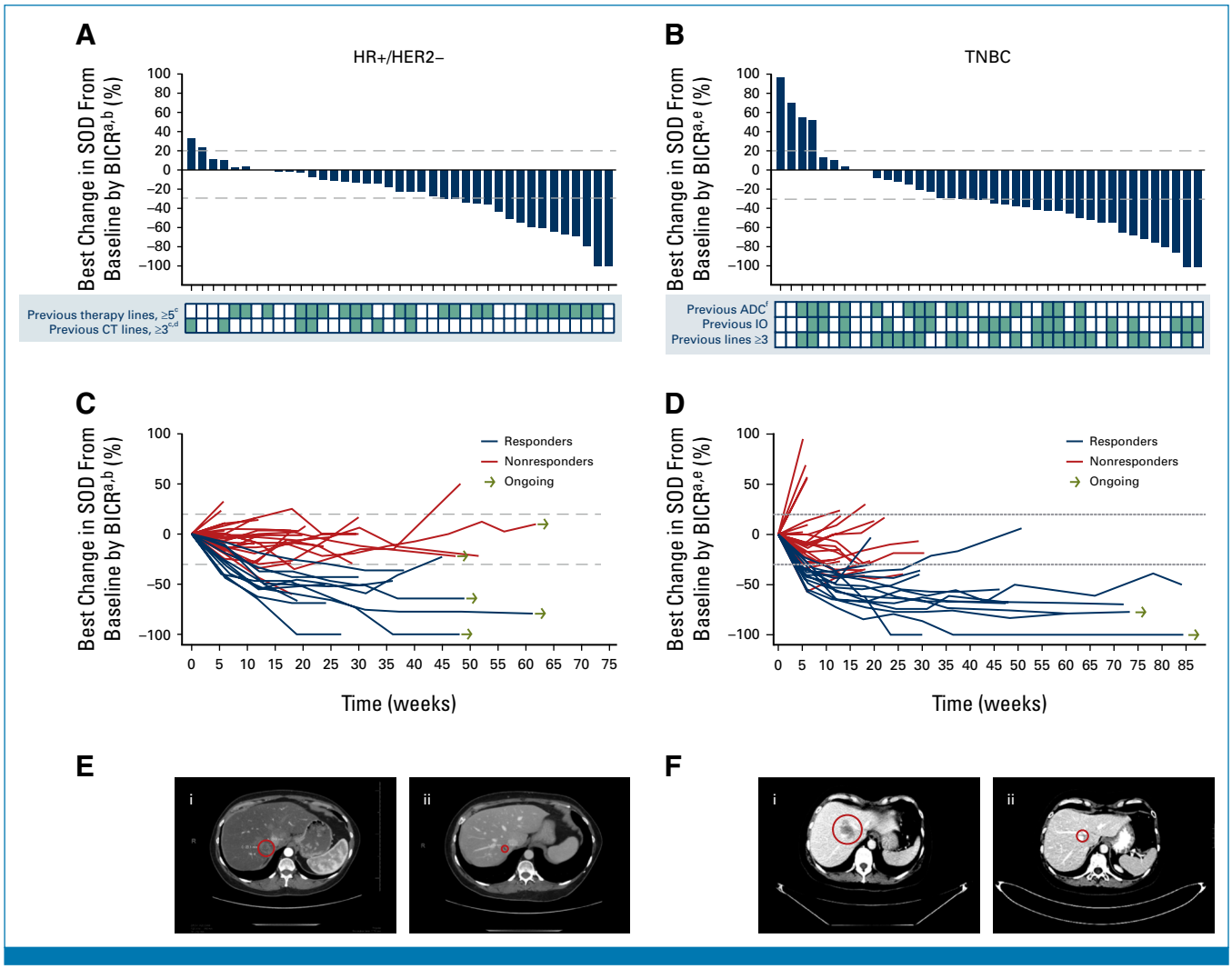

FIG 1. Antitumor activity of datopotamab deruxtecan (Dato-DXd). Waterfall plot of best percent change in SOD in target lesions in patients with (A) HR+/HER2− BC and (B) TNBC as assessed by BICR per RECIST version 1.1 (full analysis set). Dashed lines represent partial response (≥30% decrease) and progressive disease (≥20% increase) per RECIST version 1.1. Kinetics of tumor burden over time in patients with (C) HR+/HER2− BC and (D) TNBC. Spider plot shows percentage change in SOD in target lesions as assessed by BICR per RECIST 1.1. (E) Computed tomography scan depicting a right liver lesion (red circles) in a 53-year-old woman with HR+/HER2− BC at (i) study baseline and (ii) partial response after 16 cycles of treatment with Dato-DXd 6 mg/kg once every 3 weeks over 48 weeks, resulting in a 66% reduction in tumor lesion diameter per RECIST version 1.1. (F) Computed tomography scan of a liver lesion in a 53-year-old woman diagnosed with TNBC at (i) study baseline and (ii) showing a significant decrease in hepatic lesion (from 4.1 × 3.0 cm to 0.9 × 0.5 cm), after 42 cycles of treatment with Dato-DXd over 30 months, resulting in overall 90% reduction in tumor lesion diameter per RECIST version 1.1. [a]Postbaseline tumor assessments were not available for one patient in each cohort at data cutoff. [b]n = 39. [c]In locally advanced or metastatic setting. [d]CDK4/6 inhibitors were not counted as CT in this study. [e]n = 40. [f]Eleven patients received sacituzumab govitecan, two received trastuzumab deruxtecan, and one received patritumab deruxtecan. ADC, antibody-drug conjugate; BC, breast cancer; BICR, blinded independent central review; CT, chemotherapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IO, immuno-oncology therapy; SD, stable disease; SOD, sum of the diameters; TNBC, triple-negative BC.

Supplement, Fig S4). In patients with HR+/HER2− BC, mean ± standard deviation (SD) half-lives of Dato-DXd, anti-TROP2 antibody, and DXd were 4.9 ± 1.4, 5.3 ± 1.6, and 5.8 ± 1.2 days, respectively, for Cycle 1. In patients with TNBC (6-mg/kg dose once every 3 weeks [n = 40]; Data Supplement, Fig S4), mean ± SD half-lives were 5.0 ± 0.8, 5.6 ± 1.1, and 6.0 ± 1.1 days, respectively.

ADA incidence, defined as frequency of treatment-emergent ADA, was reported in three (7.3%) and three (6.8%) patients with HR+/HER2− BC and TNBC, respectively. In the HR+/HER2− BC cohort, two (4.9%) patients were positive for neutralizing antibodies. No patients with a positive treatment-emergent ADA experienced a serious TEAE. Impact on PK parameters, efficacy, or safety was not fully evaluated because of the limited number of ADA-positive patients.

DISCUSSION

In this first-in-human phase I study of Dato-DXd, encouraging antitumor activity and manageable safety profile

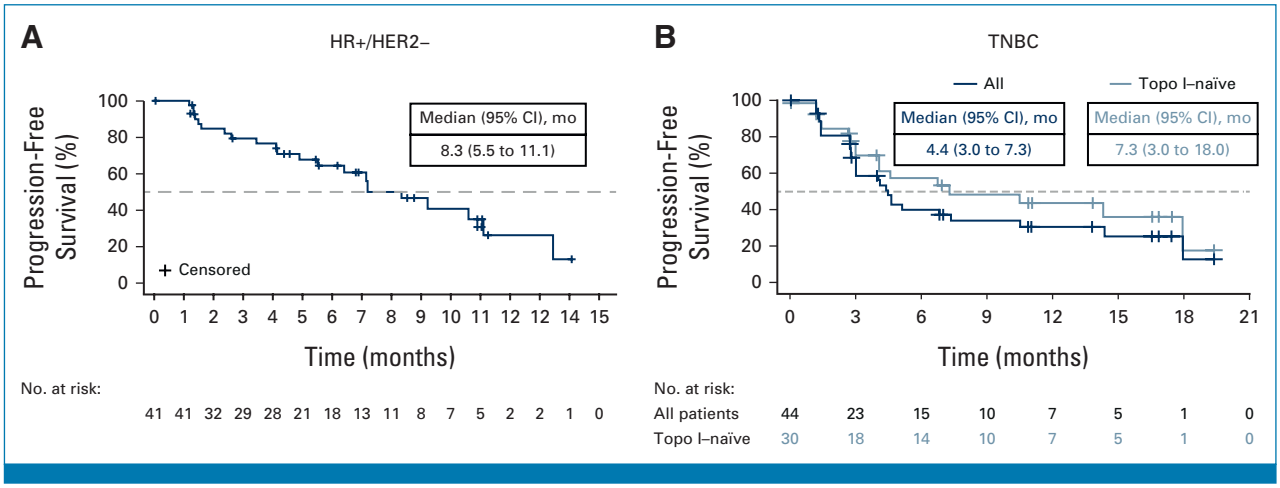

FIG 2. Progression-free survival. Kaplan-Meier plots of progression-free survival by blinded independent central review per RECIST v1.1 in (A) the HR+/HER2− BC and (B) TNBC cohorts. BC, breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; Topo I, topoisomerase I; TNBC, triple-negative BC.

were observed in patients with heavily pretreated advanced HR+/HER2− BC and TNBC.

Dato-DXd demonstrated clinical activity (confirmed ORR 26.8% [HR+/HER2− BC] and 31.8% [TNBC]), and responses were durable (DOR NE [HR+/HER2− BC] and 16.8 months [TNBC]). Although patient numbers were small, the higher ORR and longer median OS and PFS observed in the topo I–naïve TNBC subgroup compared with those in the overall TNBC population also suggest that tumors may start to develop resistance to topo I inhibition through previous exposure. Alternatively, with 11 of 14 ADC-pretreated patients having received sacituzumab govitecan, outcomes may be related to previous targeting of TROP2 in these patients. Overall, the topo I–naïve subgroup was moderately less pretreated, which could also contribute to the improved efficacy profile observed. Although no patients in the HR+/HER2− BC cohort received previous topo I inhibitor–based ADC therapy, patients with a ≥30% decrease in measurable tumor sum of the diameters had only 1-2 previous lines of chemotherapy, suggesting that increasing resistance to topo I inhibition may be partly due to the cumulative effect of previous treatment with DNA-damaging agents.[25] Together, these results provide rationale for further evaluation of Dato-DXd in earlier lines of treatment for patients with HR+/HER2− BC and TNBC.

The safety profile of Dato-DXd in both BC cohorts was manageable, with low incidences of grade ≥3 TEAEs, few dose modifications, and no drug-related deaths. While nausea was common, it was generally manageable with antiemetic prophylaxis (Data Supplement). Modest incidences of hematologic toxicities were observed, and few grade ≥3 events were reported.

Cataracts were observed in patients across both cohorts, with treatment-emergent grade 1 to 2 events reported in six (14.6%) and four (9.1%) patients in the HR+/HER2− BC and TNBC cohorts, respectively. While these incidences are notable, most events were not considered drug-related by the investigator, and known risk factors for cataract development were enriched in the study population on the basis of age, sex, and treatment history.[26-28] Development of cataracts and other ocular events continues to be monitored in ongoing trials of Dato-DXd.

The most common GI toxicity, stomatitis, is a known AESI for Dato-DXd. Events of the AESIs, IRR and OST, were grade 1 to 2 except for one grade 3 event of OST in the HR+/HER2− BC cohort. One case of adjudicated ILD (grade 3) was observed in the HR+/HER2− BC cohort.

Preventative measures and toxicity management guidelines for oral mucositis/stomatitis, OST, and IRR were implemented and updated during trial conduct. Stomatitis prophylaxis (Data Supplement) was not implemented before the start of enrollment of the BC cohorts. ILD is another recognized AESI seen with DXd-containing ADCs[29-31]; toxicity management guidelines for ILD/pneumonitis were implemented at the start of the conduct of the trial (Data Supplement).

The safety and efficacy profiles of Dato-DXd appear to be favorable compared with those of the current standards of care for metastatic HR+/HER2− BC and TNBC. For patients with HR+/HER2− BC who develop resistance to both ET and CDK4/6 inhibitors,[6,7] subsequent therapy is typically targeted on the basis of underlying mutations, and therefore, patients without specific somatic or germline mutations have limited treatment options. Chemotherapy has limited efficacy as treatment for TNBC and is associated with significant toxicity. Responses are further reduced in second and later lines.[10] Grade ≥3 toxicities such as myelosuppression and neuropathy are common, and up to 20% of patients discontinue treatment because of TEAEs.[10]

TABLE 3. Summary of TEAEs and AESIs in the Safety Analysis Set

	HR+/HER2− BC (N = 41), No. (%)		TNBC (N = 44), No. (%)	
Patients With Events	Any Grade	Grade ≥3	Any Grade	Grade ≥3
TEAEs[a]	41 (100)	17 (41.5)	44 (100)	23 (52.3)
Drug-related TEAE[b]	41 (100)	9 (22.0)	43 (97.7)	11 (25.0)
Dose adjustments because of TEAEs				
Dose reduction[c]	5 (12.2)	2 (4.9)	7 (15.9)	4 (9.1)
Treatment interruption[d]	15 (36.6)	3 (7.3)	12 (27.3)	6 (13.6)
Treatment discontinuation[e]	5 (12.2)	3 (7.3)	1 (2.3)	0
Serious TEAE[f]	6 (14.6)	6 (14.6)	9 (20.5)	9 (20.5)
Drug-related	1 (2.4)	1 (2.4)	2 (4.5)	2 (4.5)
Drug-related death	0	0	0	0
AESIs	38 (92.7)	6 (14.6)	41 (93.2)	5 (11.4)
Adjudicated ILD/pneumonitis	1 (2.4)	1 (2.4)	0	0
Infusion-related reactions	8 (19.5)	0	8 (18.2)	0
Ocular surface toxicity	17 (41.5)	1 (2.4)	16 (36.4)	0
Oral mucositis/stomatitis	37 (90.2)	4 (9.8)	35 (79.5)	5 (11.4)
Drug-related AESI	35 (85.4)	6 (14.6)	38 (86.4)	5 (11.4)
Dose adjustments because of AESIs				
Dose reduction	5 (12.2)	2 (4.9)	3 (6.8)	2 (4.5)
Treatment interruption	7 (17.1)	1 (2.4)	8 (18.2)	3 (6.8)
Treatment discontinuation[g]	5 (12.2)	3 (7.3)	1 (2.3)	0
Serious AESI	1 (2.4)	1 (2.4)	0	0
Drug-related	1 (2.4)	1 (2.4)	0	0
Drug-related death	0	0	0	0

Abbreviations: AE, adverse event; AESI, adverse event of special interest; BC, breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ILD, interstitial lung disease; TEAE, treatment-emergent AE; TNBC, triple-negative BC; topo I, topoisomerase I.

[a]Of the grade ≥3 TEAEs, four (9.8%) and one (2.4%) grade 4 and 5 events in the HR+/HER2− BC cohort and two (4.5%) and zero grade 4 and 5 events in the TNBC cohort were reported.

[b]One (2.4) and zero grade 4 and 5 events, respectively, were reported in the HR+/HER2− BC cohort; zero grade 4 or 5 events were reported in the TNBC cohort.

[c]Dose reductions occurred in five patients in the HR+/HER2− BC cohort because of stomatitis (n = 4), decreased appetite (n = 1), fatigue (n = 1), and keratitis (n = 1) and in seven patients in the TNBC cohort because of stomatitis (n = 2), fatigue (n = 2), dry eye (n = 1), retinal exudates (n = 1), and dysgeusia (n = 1). Some patients had >1 AE.

[d]Fifteen patients in the HR+/HER2− BC cohort had treatment delayed because of stomatitis (n = 7), fatigue (n = 2), cellulitis (n = 1), COVID-19 (n = 1), decreased lymphocyte count (n = 1), dysphagia (n = 1), fall (n = 1), malaise (n = 1), nasal congestion (n = 1), nausea (n = 1), otitis media (n = 1), retinopathy (n = 1), and urinary tract infection (n = 1). Twelve patients in the TNBC cohort had treatment delayed because of stomatitis (n = 7), dry eye (n = 1), blurred vision (n = 1), bronchitis (n = 1), skin infection (n = 1), musculoskeletal chest pain (n = 1), dysgeusia (n = 1), chronic obstructive pulmonary disease (n = 1), dermatitis acneiform (n = 1), and dyspnea (n = 1). Some patients had more than one AE.

[e]Five patients in the HR+/HER2− BC cohort discontinued treatment because of pneumonitis (n = 2), keratitis (n = 1), keratopathy (n = 1), and stomatitis (n = 1). One patient in the TNBC cohort discontinued treatment because of grade 1 pneumonitis (which was centrally adjudicated as not ILD).

[f]In the HR+/HER2− BC cohort, the only drug-related serious TEAE was one event of pneumonitis. Drug-related serious TEAEs in the TNBC cohort included nausea, upper GI hemorrhage, and vomiting. Some patients had more than one AE.

[g]One patient in the TNBC cohort discontinued treatment because of grade 1 ILD/pneumonitis, adjudicated as not drug-related.

Sacituzumab govitecan was recently approved by the US Food and Drug Administration for the treatment of HR+/HER2− BC and TNBC after the phase III TROPiCS-02 and ASCENT trials.[32-34] In the TROPiCS-02 trial, the ORR for patients with HR+/HER2− BC receiving sacituzumab govitecan was 21%. The median PFS and OS were 5.5 and 13.9 months, respectively.[33] More than half of sacituzumab govitecan–treated patients in the study experienced diarrhea and nausea. High incidences of hematologic toxicities, including neutropenia, were reported.[33] In patients with TNBC (all topo I naïve) who received sacituzumab govitecan in the ASCENT trial, the ORR was 31% and the median DOR was 6.3 months, with the OS and PFS of 11.8 and 4.8 months, respectively. Hematologic and GI toxicities were commonly observed (>50% of patients).[34]

TABLE 4. Incidence of TEAEs Observed in ≥10% of Patients in Either BC Cohort

	HR+/HER2− BC (N = 41)				TNBC (N = 44)			
	Any Grade		Grade ≥3		Any Grade		Grade ≥3	
Patients With TEAEs, No. (%)	Any TEAE	Drug-Related TEAE	Any TEAE	Drug-Related TEAE	Any TEAE	Drug-Related TEAE	Any TEAE	Drug-Related TEAE
Overall TEAE incidence	41 (100)	41 (100)	17 (41.5)	9 (22.0)	44 (100)	43 (97.7)	23 (52.3)	11 (25.0)
GI disorders								
Stomatitis[a]	34 (82.9)	33 (80.5)	4 (9.8)	4 (9.8)	32 (72.7)	32 (72.7)	5 (11.4)	5 (11.4)
Nausea[a]	23 (56.1)	21 (51.2)	0	0	29 (65.9)	29 (65.9)	1 (2.3)	1 (2.3)
Constipation	11 (26.8)	4 (9.8)	0	0	10 (22.7)	7 (15.9)	0	0
Vomiting	10 (24.4)	9 (22.0)	0	0	17 (38.6)	13 (29.5)	2 (4.5)	2 (4.5)
Diarrhea	7 (17.1)	7 (17.1)	0	0	7 (15.9)	4 (9.1)	0	0
Dry mouth	5 (12.2)	4 (9.8)	0	0	4 (9.1)	3 (6.8)	0	0
Dyspepsia	1 (2.4)	1 (2.4)	0	0	5 (11.4)	5 (11.4)	0	0
Hematologic disorders								
Anemia[b]	7 (17.1)	3 (7.3)	3 (7.3)	2 (4.9)	7 (15.9)	5 (11.4)	1 (2.3)	1 (2.3)
Lymphopenia[c]	6 (14.6)	1 (2.4)	6 (14.6)	1 (2.4)	9 (20.5)	4 (9.1)	4 (9.1)	0
Leukopenia[d]	4 (9.8)	2 (4.9)	0	0	7 (15.9)	7 (15.9)	0	0
Neutropenia[e]	3 (7.3)	2 (4.9)	0	0	9 (20.5)	8 (18.2)	1 (2.3)	1 (2.3)
Other								
Fatigue	19 (46.3)	18 (43.9)	1 (2.4)	0	15 (34.1)	15 (34.1)	3 (6.8)	3 (6.8)
Alopecia	15 (36.6)	15 (36.6)	0	0	16 (36.4)	16 (36.4)	0	0
Headache	12 (29.3)	5 (12.2)	0	0	11 (25.0)	7 (15.9)	0	0
Dry eye	10 (24.4)	9 (22.0)	0	0	7 (15.9)	5 (11.4)	0	0
Decreased appetite	7 (17.1)	5 (12.2)	0	0	7 (15.9)	7 (15.9)	0	0
Rash	7 (17.1)	6 (14.6)	0	0	7 (15.9)	6 (13.6)	0	0
Dyspnea	7 (17.1)	1 (2.4)	1 (2.4)[f]	0	4 (9.1)	0	1 (2.3)	0
Cough	6 (14.6)	1 (2.4)	0	0	8 (18.2)	2 (4.5)	0	0
Hypokalemia	6 (14.6)	0	0	0	7 (15.9)	1 (2.3)	0	0
Cataracts[g]	6 (14.6)	0	0	0	4 (9.1)	1 (2.3)	0	0
Pyrexia	5 (12.2)	2 (4.9)	0	0	8 (18.2)	4 (9.1)	0	0
Oropharyngeal pain	5 (12.2)	2 (4.9)	0	0	4 (9.1)	3 (6.8)	0	0
Skin hyperpigmentation	5 (12.2)	5 (12.2)	0	0	2 (4.5)	2 (4.5)	0	0
Aspartate aminotransferase increased	4 (9.8)	0	0	0	6 (13.6)	2 (4.5)	2 (4.5)	0
Dizziness	4 (9.8)	1 (2.4)	0	0	6 (13.6)	4 (9.1)	0	0
Infusion-related reaction	4 (9.8)	4 (9.8)	0	0	6 (13.6)	6 (13.6)	0	0
Alanine aminotransferase increased	3 (7.3)	0	0	0	5 (11.4)	0	2 (4.5)	0
Hypoalbuminemia	2 (4.9)	0	1 (2.4)	0	5 (11.4)	1 (2.3)	0	0

(continued on following page)

TABLE 4. Incidence of TEAEs Observed in ≥10% of Patients in Either BC Cohort (continued)

	HR+/HER2− BC (N = 41)				TNBC (N = 44)			
	Any Grade		Grade ≥3		Any Grade		Grade ≥3	
Patients With TEAEs, No. (%)	Any TEAE	Drug-Related TEAE	Any TEAE	Drug-Related TEAE	Any TEAE	Drug-Related TEAE	Any TEAE	Drug-Related TEAE
Rash maculopapular	2 (4.9)	2 (4.9)	0	0	5 (11.4)	4 (9.1)	0	0
Dysgeusia	1 (2.4)	1 (2.4)	0	0	6 (13.6)	6 (13.6)	0	0
Pruritus	1 (2.4)	1 (2.4)	0	0	6 (13.6)	6 (13.6)	0	0
Anxiety	1 (2.4)	0	0	0	5 (11.4)	1 (2.3)	1 (2.3)	0
Weight decreased	1 (2.4)	0	0	0	5 (11.4)	3 (6.8)	1 (2.3)	1 (2.3)

NOTE. If a patient reported more than one event per grouped PT, the patient was counted once within each grade.

Abbreviations: BC, breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PT, preferred term; TEAE, treatment-emergent adverse event; TNBC, triple-negative BC.

[a]TEAEs experienced by >50% of patients.

[b]Grouped PTs of anemia, hemoglobin decreased, and RBC count decreased. All events reported were under the individual PT of anemia.

[c]Grouped PTs of lymphopenia and lymphocyte count decreased. In the HR+/HER2− BC cohort, four grade 3 and two grade 4 events of PT lymphocyte count decreased and two grade 4 events of PT lymphopenia were reported. In the TNBC cohort, three grade 3 events of PT lymphocyte count decreased and one grade 4 event of PT lymphopenia were reported.

[d]Grouped PTs of leukopenia and WBC count decreased. In the TNBC cohort, one grade 2 event of PT leukopenia was reported; the remaining events in each cohort were reported under the individual PT of WBC count decreased.

[e]Grouped PTs of neutropenia and neutrophil count decreased. All events were reported under the individual PT of neutrophil count decreased.

[f]Grade 5.

[g]Grade 1 = asymptomatic; grade 2 = symptomatic with moderate decrease in visual acuity.[24]

Although their payloads have similar mechanisms of action, sacituzumab govitecan and Dato-DXd have demonstrated distinct AE profiles in similar but not identical patient populations. The mode of action of Dato-DXd may contribute to its safety profile compared with other TROP2-directed ADCs. The selective payload delivery of Dato-DXd, which is enabled by the selectively cleavable plasma-stable linker that releases DXd after proteolytic processing by tumor cell–enriched lysosomal enzymes, reduces systemic exposure while achieving a sustained response, resulting in an improved benefit-risk profile.[21] This may account for the comparatively low incidences of neutropenia and diarrhea in this study compared with sacituzumab govitecan.[35]

Study limitations include the relatively small number of patients in each cohort and the single-arm open-label study design without a comparator. However, the findings from this study provide rationale for further investigation of Dato-DXd as a treatment option for advanced/metastatic HR+/HER2– BC and TNBC, which is ongoing in several phase III trials. In patients with advanced/metastatic HR+/HER2– BC, Dato-DXd is being compared with single-agent chemotherapy as second- or third-line therapy in the randomized, phase III TROPION-Breast01 trial (ClinicalTrials.gov identifier: NCT05104866), which recently met its primary PFS end point (median PFS 6.9 months and confirmed ORR 36.4%).[36] In patients with advanced/metastatic TNBC, Dato-DXd is being investigated as first-line therapy compared with chemotherapy in the randomized, phase III TROPION-Breast02 trial (ClinicalTrials.gov identifier: NCT05374512).[37] Additional studies investigating Dato-DXd in combination with the immune checkpoint inhibitor durvalumab in patients with TNBC are also underway, including the phase III TROPION-Breast03 (ClinicalTrials.gov identifier: NCT05629585), TROPION-Breast04 (ClinicalTrials.gov identifier: NCT06112379), TROPION-Breast05 (ClinicalTrials.gov identifier: NCT06103864), and the BEGONIA phase Ib/II trials (ClinicalTrials.gov identifier: NCT03742102).[37-40]

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DISCLAIMER

The study was designed by the funder in collaboration with the study investigators.

EQUAL CONTRIBUTION

A.B. and I.E.K. contributed equally to this work.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.23.01909.

DATA SHARING STATEMENT

Deidentified individual participant data and applicable supporting clinical trial documents may be available on request at Vivli—Center for Global Clinical Research Data. In cases where trial data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo will continue to protect the privacy of our clinical trial patients. Details on data sharing criteria and the procedure for requesting access can be found online at https://vivli.org/ourmember/daiichi-sankyo/.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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