Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial

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ABSTRACT

PURPOSE Trastuzumab deruxtecan (T-DXd) is a human epidermal growth factor 2 (HER2)–directed antibody-drug conjugate approved in HER2-expressing breast and gastric cancers and HER2-mutant non–small-cell lung cancer. Treatments are limited for other HER2-expressing solid tumors.

METHODS This open-label phase II study evaluated T-DXd (5.4 mg/kg once every 3 weeks) for HER2-expressing (immunohistochemistry [IHC] 3+/2+ by local or central testing) locally advanced or metastatic disease after ≥1 systemic treatment or without alternative treatments. The primary end point was investigator-assessed confirmed objective response rate (ORR). Secondary end points included safety, duration of response, progression-free survival (PFS), and overall survival (OS).

RESULTS At primary analysis, 267 patients received treatment across seven tumor cohorts: endometrial, cervical, ovarian, bladder, biliary tract, pancreatic, and other. The median follow-up was 12.75 months. In all patients, the ORR was 37.1% (n = 99; [95% CI, 31.3 to 43.2]), with responses in all cohorts; the median DOR was 11.3 months (95% CI, 9.6 to 17.8); the median PFS was 6.9 months (95% CI, 5.6 to 8.0); and the median OS was 13.4 months (95% CI, 11.9 to 15.5). In patients with central HER2 IHC 3+ expression (n = 75), the ORR was 61.3% (95% CI, 49.4 to 72.4), the median DOR was 22.1 months (95% CI, 9.6 to not reached), the median PFS was 11.9 months (95% CI, 8.2 to 13.0), and the median OS was 21.1 months (95% CI, 15.3 to 29.6). Grade ≥3 drug-related adverse events were observed in 40.8% of patients; 10.5% experienced adjudicated drug-related interstitial lung disease (ILD), with three deaths.

CONCLUSION Our study demonstrates durable clinical benefit, meaningful survival outcomes, and safety consistent with the known profile (including ILD) in pretreated patients with HER2-expressing tumors receiving T-DXd. Greatest benefit was observed for the IHC 3+ population. These data support the potential role of T-DXd as a tumor-agnostic therapy for patients with HER2-expressing solid tumors.

ACCOMPANYING CONTENT

Appendix

Protocol

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INTRODUCTION

Human epidermal growth factor receptor 2 (HER2) is a transmembrane tyrosine kinase receptor involved in the stimulation of cell proliferation, differentiation, and survival.[1] HER2 overexpression can occur in a range of solid tumors, including breast, gastric, biliary tract, bladder, pancreatic, and gynecological tumors.[2] HER2 overexpression is associated with a biologically aggressive tumor phenotype, poor prognosis, increased risk of disease recurrence, and limited benefit from chemotherapy.[1,3-5] HER2-directed therapy is standard of care for HER2-expressing unresectable or metastatic breast cancer, HER2-positive locally advanced or metastatic gastric cancers, colorectal and gastroesophageal junction adenocarcinomas, and HER2-mutant non–small-cell lung cancer.[6-9] However, many patients with other HER2-expressing solid tumors will progress on standard therapy, with poor prognosis

CONTEXT

Key Objective

What is the efficacy and safety of trastuzumab deruxtecan (T-DXd; 5.4 mg/kg once every 3 weeks) in previously treated patients with locally advanced or metastatic human epidermal growth factor 2 (HER2)–expressing (immunohistochemistry [IHC] 3+/2+) solid tumors?

Knowledge Generated

DESTINY-PanTumor02 demonstrated that treatment with T-DXd resulted in durable responses across multiple tumor types, alongside clinically meaningful rates of progression-free survival and overall survival, with the greatest benefit observed in the HER2 IHC 3+ population. The safety profile was consistent with the known profile for T-DXd, including the incidence of interstitial lung disease (ILD).

Relevance *(G.F. Fleming)*

T-DXd provides meaningful benefit for patients with multiple types of solid tumors that express HER2, particularly for those whose tumors express HER2 at the 3+ level on central review.*

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

and limited alternatives.[5,10-13] This represents an opportunity to improve outcomes for such patients with novel HER2-targeted therapeutics.

Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody-drug conjugate composed of a humanized immunoglobulin G1 anti-HER2 monoclonal antibody, a tetrapeptide-based cleavable linker, and a potent topoisomerase I inhibitor payload.[14] T-DXd is currently approved in the United States and European Union for treatment of HER2-expressing breast cancer and HER2-positive gastric or gastroesophageal junction adenocarcinoma and in the United States and Japan for HER2-mutant non–small cell lung cancer.[15-17] In early-phase studies, T-DXd demonstrated antitumor activity in a range of HER2-expressing malignancies, including colorectal, salivary gland, biliary tract, and endometrial cancer.[18] In August 2023, T-DXd was granted breakthrough therapy designations in the United States for adult patients with unresectable or metastatic HER2-positive (immunohistochemistry [IHC] 3+) solid tumors that have progressed after prior treatment and have no satisfactory alternatives and for patients with HER2-positive (IHC 3+) metastatic colorectal cancer who have received ≥2 prior treatment regimens.[19] The aim of this study (ClinicalTrials.gov identifier: NCT04482309) was to assess the efficacy and safety of T-DXd in patients with selected, locally advanced, metastatic, or unresectable HER2-expressing solid tumors.

METHODS

Study Design and Participants

This open-label, multicenter, phase II study (ClinicalTrials.gov identifier: NCT04482309) evaluated the efficacy and safety of T-DXd 5.4 mg/kg once every 3 weeks in patients with previously treated HER2-expressing solid tumors in seven cohorts.

Eligible patients were age 18 years or older; had histologically confirmed locally advanced, unresectable, or metastatic biliary tract, bladder, cervical, endometrial, ovarian, pancreatic, or other solid cancers (excluding breast, colorectal, gastric, and non–small-cell lung cancers); who progressed after ≥1 systemic treatment or had no satisfactory alternative treatment options; Eastern Cooperative Oncology Group performance status of 0-1[20]; HER2-overexpressing tumors with IHC 3+/2+ (local or central testing) scored using current ASCO/College of American Pathology guidelines for scoring HER2 in gastric cancer[21]; and had ≥1 investigator-assessed measurable lesion on the basis of RECIST 1.1.[22] Patients with noninfectious interstitial lung disease (ILD)/pneumonitis requiring steroids, or if suspected ILD/pneumonitis could not be ruled out by imaging at screening, were excluded. HER2 expression for eligibility was based on local assessment, where available. Otherwise, eligibility was determined by central testing. HER2 IHC status was assessed centrally using HER2 HercepTest (DAKO) and scored according to gastric-specific criteria. Prior HER2-targeted therapy was permitted. Eligibility criteria are provided in Appendix 2, online only.

The study Protocol (online only) was approved by the institutional review board at each site and was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice, the Declaration of Helsinki, and local regulations on the conduct of clinical research. All patients provided written informed consent before study participation.

Procedures

T-DXd was administered intravenously once every 3 weeks at 5.4 mg/kg of body weight. RECIST scans were performed at

screening and every 6 weeks until documented disease progression (RECIST 1.1) or withdrawal of consent. Treatment continued until documented disease progression (RECIST 1.1), withdrawal of consent, or when discontinuation criteria were met. Dose interruptions and/or reduction and supportive therapy were permitted for clinically significant and/or unacceptable toxicity. For suspected ILD/pneumonitis, treatment was interrupted pending evaluation, and all events were followed until resolution (including after discontinuation) regardless of severity (Appendix 2).

End Points

The primary end point was investigator-assessed confirmed objective response rate (ORR), defined as the proportion of patients with a confirmed complete or partial response by RECIST 1.1 (Appendix 2). Secondary efficacy end points included duration of response (DOR; time from date of first documented response [complete or partial] until the date of documented progression or death in the absence of disease progression); disease control rate (percentage of patients with a best objective response of confirmed complete response or partial response, or with stable disease for at least 5 weeks after first dose); progression-free survival (PFS; time from first dose until date of objective disease progression or death regardless of withdrawal or receipt of another cancer therapy); and overall survival (OS; time from date of first dose until death due to any cause). An independent central review per RECIST 1.1 was performed and reported alongside the investigator-assessed results for secondary outcomes. Exploratory endpoints included subgroup analysis by HER2 status.

Secondary safety end points included the occurrence of adverse events (including drug-related adverse events, serious adverse events, and adverse events of special interest [ILD/pneumonitis and left ventricular dysfunction]) and changes in vital sign measurements and standard clinical laboratory parameters. Adverse events were coded and graded according to the Medical Dictionary for Regulatory Activities (version 26.0) and National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). Potential cases of ILD/pneumonitis were evaluated by an independent adjudication committee.

Statistical Analysis

A sample size of 40 patients per cohort was determined to provide sufficient precision for the estimation of objective response in each cohort (eg, for ORR 35%, exact CI would be 20.6 to 51.7). Efficacy and safety results are presented by cohort and overall on the basis of the full analysis set (patients who received at least one dose of study medication). Outcomes are reported in all patients enrolled by local and central testing; subgroup analyses by HER2 status are reported as confirmed by central testing alone. Descriptive statistics were used to summarize each end point. Kaplan-Meier estimations were used to describe DOR, PFS, and OS. Exact 95% CIs for binomial proportions were calculated using the Clopper-Pearson method.

RESULTS

Between October 7, 2020, and July 7, 2022, a total of 268 patients with HER2-expressing solid tumors were enrolled from >120 sites across 15 countries. Of them, 267 (99.6%) patients received at least one dose of study treatment and were included in the full analysis set; one patient withdrew before receiving treatment (Appendix Fig A1).

The median age was 62 (range, 23-85) years. Patients had received a median of two lines of prior therapy (range, 0-12; Table 1). Across all cohorts, 40.8% had received ≥three prior lines, and 14.2% had received prior HER2 therapy (trastuzumab [12.4%], pertuzumab [1.9%], zanidatamab [1.5%], trastuzumab emtansine [1.1%], trastuzumab duocarmazine [0.4%], and/or tucatinib [0.4%]). The other tumors cohort included patients with salivary gland cancer (n = 19), malignant neoplasm of unknown primary site (n = 5), extramammary Paget disease (n = 3), cutaneous melanoma (n = 2), oropharyngeal neoplasm (n = 2), adenoid cystic carcinoma, head and neck cancer, lip and/or oral cavity cancer, esophageal adenocarcinoma, intestinal adenocarcinoma, appendiceal adenocarcinoma, esophageal squamous cell carcinoma, testicular cancer, and vulvar carcinoma (all n = 1).

In total, 202 patients were enrolled on the basis of local HER2 testing, and 65 patients were enrolled on the basis of central HER2 testing. According to HER2 testing for eligibility, 111 patients were enrolled with IHC 3+ expression, 151 with IHC 2+ expression, and five with IHC 1+ expression (Table 1). On the basis of central testing, there were 75 patients with IHC 3+ expression, 125 with IHC 2+ expression, 25 with IHC 1+ expression, 30 with IHC 0 expression, and 12 patients were unknown, owing to unavailable/unevaluable samples for central testing (Appendix Table A1).

At data cutoff (June 8, 2023), the median follow-up duration across all cohorts was 12.75 months (range, 0.4-31.6); 235 patients had discontinued treatment (progressive disease [n = 167, 62.5%], any adverse event [n = 32, 12.0%], death during study [n = 18, 6.7%], patient decision [n = 11, 4.1%], investigator decision [n = 4, 1.5%], unknown [n = 2, 0.7%], lost to follow-up [n = 1, 0.4%]), and 32 (12.0%) patients remained on treatment. The median number of 21-day treatment cycles for all patients was eight.

Among the 267 patients, 99 patients (37.1%; [95% CI, 31.3 to 43.2]) had a confirmed objective response by investigator assessment. Investigator-assessed ORRs in all patients by cohort (Fig 1 and Appendix Table A2) were 57.5% for endometrial (95% CI, 40.9 to 73.0), 50.0% for cervical (95% CI, 33.8 to 66.2), 45.0% for ovarian (95% CI, 29.3 to 61.5), 39.0% for bladder (95% CI, 24.2 to 55.5), 30.0% for other tumors (95% CI, 16.6 to 46.5), 22.0% for biliary tract (95% CI, 10.6 to 37.6), and 4.0% for pancreatic

TABLE 1. Demographics and Baseline Clinical Characteristics

Baseline Characteristic	Endometrial Cancer (n = 40)	Cervical Cancer (n = 40)	Ovarian Cancer (n = 40)	Bladder Cancer (n = 41)	Other Tumors (n = 40)	Biliary Tract Cancer (n = 41)	Pancreatic Cancer (n = 25)
Age, years, median (range)	67 (37-79)	49 (28-78)	56 (34-72)	67 (43-85)	61 (38-81)	64 (31-80)	62 (23-80)
Female, No. (%)	40 (100.0)	40 (100.0)	40 (100.0)	14 (34.1)	13 (32.5)	21 (51.2)	10 (40.0)
Race, No. (%)							
White	23 (57.5)	29 (72.5)	22 (55.0)	25 (61.0)	27 (67.5)	20 (48.8)	17 (68.0)
Black or African American	4 (10.0)	0	1 (2.5)	0	0	0	1 (4.0)
Asian	10 (25.0)	7 (17.5)	17 (42.5)	16 (39.0)	10 (25.0)	21 (51.2)	6 (24.0)
Other	0	3 (7.5)	0	0	2 (5.0)	0	1 (4.0)
Not reported	3 (7.5)	1 (2.5)	0	0	1 (2.5)	0	0
ECOG performance status,[a] No. (%)							
0	23 (57.5)	22 (55.0)	26 (65.0)	19 (46.3)	15 (37.5)	13 (31.7)	8 (32.0)
1	17 (42.5)	18 (45.0)	13 (32.5)	22 (53.7)	25 (62.5)	28 (68.3)	17 (68.0)
2	0	0	1 (2.5)	0	0	0	0
HER2 testing for eligibility,[b] No. (%)							
Local	31 (77.5)	23 (57.5)	37 (92.5)	33 (80.5)	29 (72.5)	34 (82.9)	15 (60.0)
Central	9 (22.5)	17 (42.5)	3 (7.5)	8 (19.5)	11 (27.5)	7 (17.1)	10 (40.0)
HER2 IHC status (eligibility),[c] No. (%)							
IHC 3+	16 (40.0)	10 (25.0)	15 (37.5)	27 (65.9)	16 (40.0)	22 (53.7)	5 (20.0)
IHC 2+	24 (60.0)	25 (62.5)	25 (62.5)	14 (34.1)	24 (60.0)	19 (46.3)	20 (80.0)
IHC 1+[c]	0	5 (12.5)	0	0	0	0	0
Centrally confirmed HER2 IHC status, No. (%)							
IHC 3+	13 (32.5)	8 (20.0)	11 (27.5)	16 (39.0)	9 (22.5)	16 (39.0)	2 (8.0)
IHC 2+	17 (42.5)	20 (50.0)	19 (47.5)	20 (48.8)	16 (40.0)	14 (34.1)	19 (76.0)
IHC 1+	4 (10.0)	8 (20.0)	5 (12.5)	2 (4.9)	2 (5.0)	3 (7.3)	1 (4.0)
IHC 0	5 (12.5)	4 (10.0)	5 (12.5)	2 (4.9)	4 (10.0)	7 (17.1)	3 (12.0)
Unknown[d]	1 (2.5)	0	0	1 (2.4)	9 (22.5)	1 (2.4)	0
Prior therapy lines							
Median (range)	2 (0-7)	2 (1-6)	3 (1-12)	2 (0-9)	2 (0-8)	2 (1-5)	2 (1-4)
0, No. (%)	1 (2.5)	0	0	1 (2.4)	1 (2.5)	0	0
1, No. (%)	8 (20.0)	6 (15.0)	8 (20.0)	13 (31.7)	15 (37.5)	14 (34.1)	7 (28.0)
2, No. (%)	18 (45.0)	15 (37.5)	8 (20.0)	8 (19.5)	9 (22.5)	15 (36.6)	11 (44.0)
3, No. (%)	6 (15.0)	9 (22.5)	5 (12.5)	10 (24.4)	10 (25.0)	9 (22.0)	6 (24.0)
4, No. (%)	3 (7.5)	6 (15.0)	5 (12.5)	4 (9.8)	0	2 (4.9)	1 (4.0)
≥5, No. (%)	4 (10.0)	4 (10.0)	14 (35.0)	5 (12.2)	5 (12.5)	1 (2.4)	0
Prior HER2 therapy, No. (%)	9 (22.5)	1 (2.5)	2 (5.0)	3 (7.3)	14 (35.0)	7 (17.1)	2 (8.0)
Trastuzumab	5 (12.5)	1 (2.5)	2 (5.0)	3 (7.3)	14 (35.0)	6 (14.6)	2 (8.0)
Pertuzumab	0	1 (2.5)	0	1 (2.4)	2 (5.0)	1 (2.4)	0
Zanidatamab	2 (5.0)	0	0	0	1 (2.5)	1 (2.4)	0
Trastuzumab emtansine	1 (2.5)	1 (2.5)	0	1 (2.4)	0	0	0
Trastuzumab duocarmazine	1 (2.5)	0	0	0	0	0	0
Tucatinib	0	0	0	0	0	0	1 (4.0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.
[a]ECOG performance status scores range from 0 to 5, with higher scores indicating greater disability.
[b]HER2 expression for eligibility was based on local assessment where available or local testing.
[c]In the cervical cohort, five patients with IHC 1+ status were included after the protocol-specified interim analysis (Appendix 2).
[d]Includes patients whose samples were not evaluable and may have included patients who did not provide a sample for central testing.

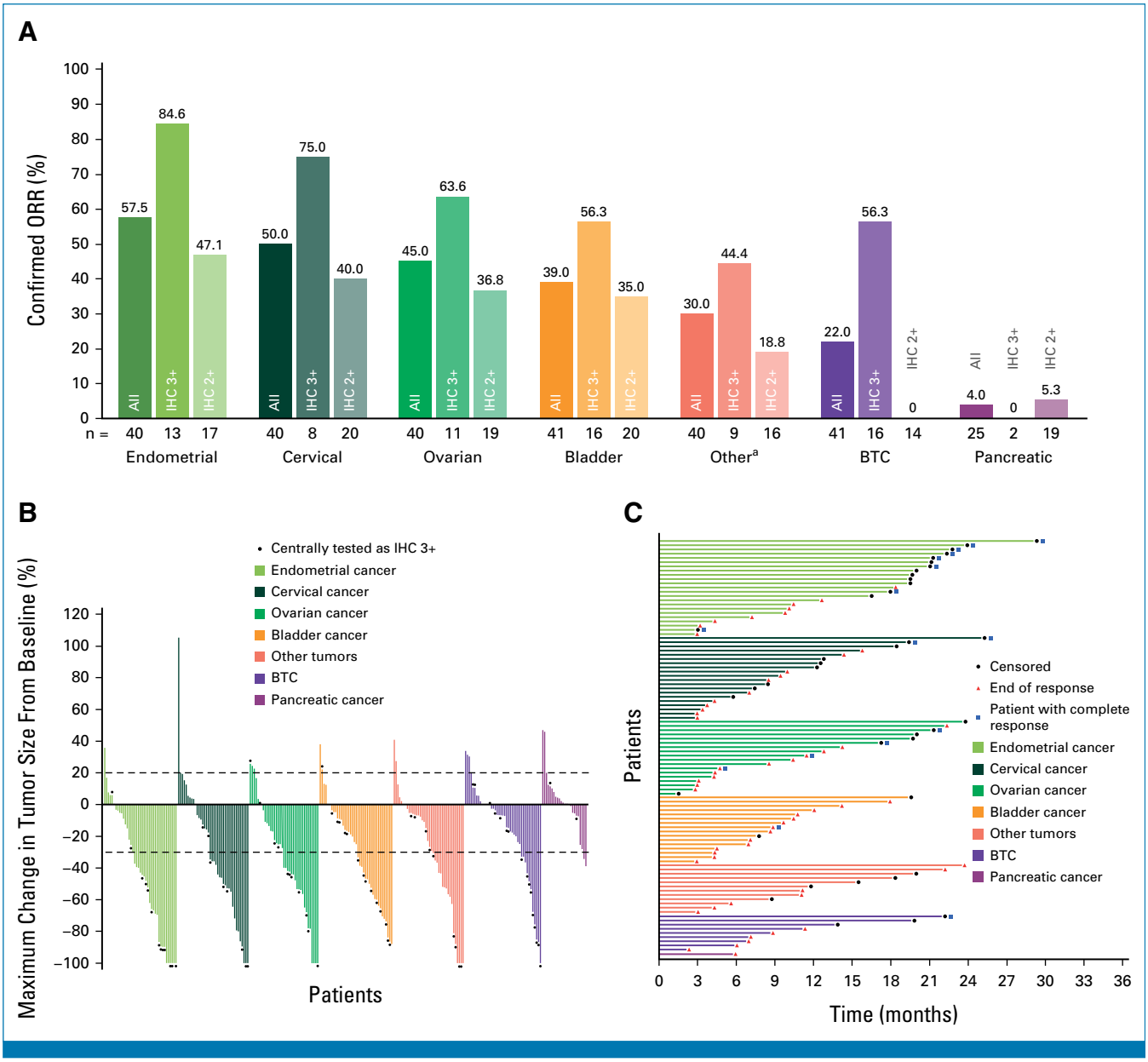

FIG 1. Investigator-assessed responses as per RECIST 1.1. (A) ORR across tumor cohorts, according to HER2 status by central testing. [a]Responses in the other tumors cohort include responses in extramammary Paget disease, oropharyngeal neoplasm, head and neck cancer, and salivary gland cancer. (B) The maximum change in tumor size, according to tumor type. Patients with IHC 3+ status (central testing) are marked with a dot. The other tumors cohort includes responses in extramammary Paget disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer. (C) DOR in patients with an objective response, according to tumor type. DOR was defined as the time from the date of first documented response (complete response or partial response) until the date of documented progression, or death in the absence of disease progression. Response was determined by investigator assessment according to RECIST 1.1 and required confirmation after the first observed response at least 4 weeks later. Censored patients are marked with a rounded dot, patients who stopped responding are marked with a triangular dot, and patients with a complete response are marked with a square dot. BTC, biliary tract cancer; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate.

(95% CI, 0.1 to 20.4). In patients with centrally confirmed HER2 IHC 3+ expression (n = 75), investigator-assessed ORRs by cohort (Fig 1) were 84.6% for endometrial (n = 13 [95% CI, 54.6 to 98.1]), 75.0% for cervical (n = 8 [95% CI, 34.9 to 96.8]), 63.6% for ovarian (n = 11 [95% CI, 30.8 to 89.1]), 56.3% for bladder (n = 16 [95% CI, 29.9 to 80.2]), 44.4% for other tumors (n = 9 [95% CI, 13.7 to 78.8]), 56.3% for biliary tract (n = 16 [95% CI, 29.9 to 80.2]), and 0% for pancreatic cancer (n = 2). In the pancreatic cohort, no objective response was observed in the first 15 patients, and the cohort was closed for further recruitment according to prespecified futility criterion, by which time 25 patients had been enrolled. Investigator-assessed ORRs by central IHC 3+/2+ status are provided in Figure 1A.

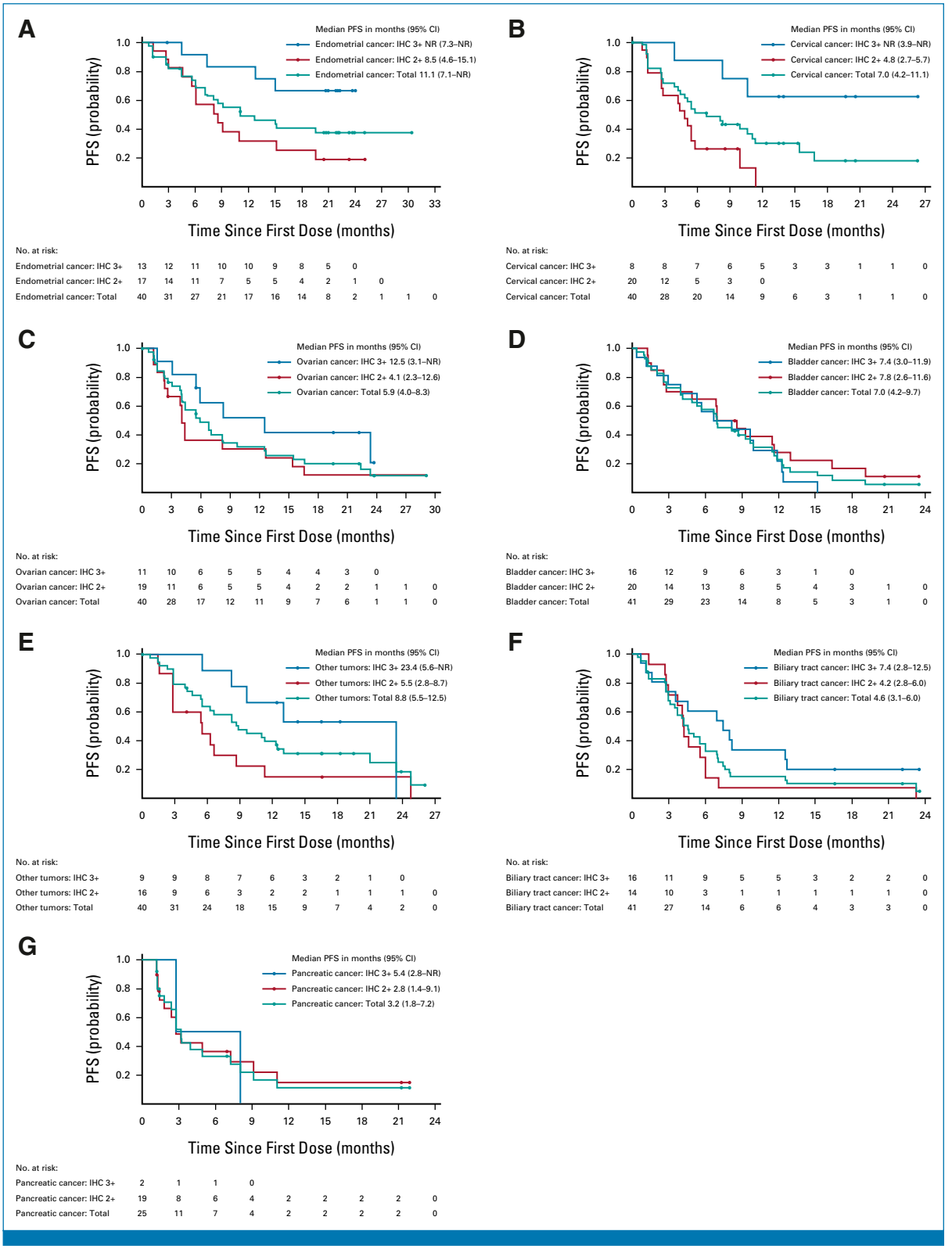

FIG 2. Kaplan-Meier estimates of PFS, according to tumor type. (A) Endometrial cancer, (B) cervical cancer, (C) ovarian cancer, (D) bladder cancer, (E) other tumors, (F) biliary tract cancer, and (G) pancreatic cancer. IHC, immunohistochemistry; NR, not reached; PFS, progression-free survival.

Responses were observed in patients who received (n = 38; 36.8% [95% CI, 21.8 to 54.0]) or did not receive (n = 227; 37.4% [95% CI, 31.1 to 44.1]) prior HER2 therapy. Across all tumor types, 100 patients (37.5% [95% CI, 31.6 to 43.6]) had a confirmed ORR by independent central review. By cohort, ORRs by independent central review in all patients were 57.5% for endometrial (95% CI, 40.9 to 73.0), 37.5% for cervical (95% CI, 22.7 to 54.2), 42.5% for ovarian (95% CI, 27.0 to 59.1), 41.5% for bladder (95% CI, 26.3 to 57.9), 35.0% for other tumors (95% CI, 20.6 to 51.7), 26.8% for biliary tract (95% CI, 14.2 to 42.9), and 12.0% for pancreatic (95% CI, 2.5 to 31.2).

The investigator-assessed median DOR (Fig 1C and Appendix Table A2) across all cohorts was 11.3 months (95% CI, 9.6 to 17.8), ranging from 5.7 months in the pancreatic cohort to 22.1 months in the other tumors cohort; median DOR was not reached in the endometrial cohort. In all HER2 subgroups, the longest median DOR was in patients with IHC 3+ (22.1 months [95% CI, 9.6 to not reached]).

The investigator-assessed median PFS (Fig 2 and Appendix Table A2) was 6.9 months (95% CI, 5.6 to 8.0), ranging from 3.2 months in the pancreatic cohort to 11.1 months in the endometrial cohort. In all HER2 subgroups, the longest median PFS was in patients with IHC 3+ (11.9 months [95% CI, 8.2 to 13.0]). PFS by tumor cohort and HER2 status is provided in Figure 2 and Appendix Table A2.

Across all cohorts, the median OS (Fig 3 and Appendix Table A2) was 13.4 months (95% CI, 11.9 to 15.5; 66% maturity), ranging from 5.0 months in the pancreatic cohort to 26.0 months in the endometrial cohort. In all HER2 subgroups, the longest median OS was in patients with IHC 3+ (21.1 months [95% CI, 15.3 to 29.6]). OS by tumor cohort and HER2 status is provided in Figure 3 and Appendix Table A2.

Percentage change of target lesion size from baseline and a full breakdown of efficacy in the other tumors cohort are shown in Appendix Fig A2 and Appendix Table A3, respectively.

Among 267 treated patients (median follow-up of 12.75 months), ≥1 investigator-assessed drug-related adverse event was experienced by 226 (84.6%) patients (Table 2), with the most common being nausea (55.1%), anemia (27.7%), diarrhea (25.8%), vomiting (24.7%), and fatigue (24.7%). Grade 3 or higher drug-related adverse events occurred in 109 (40.8%) patients, with the most common being neutropenia (10.9%) and anemia (10.9%). Serious drug-related adverse events occurred in 36 (13.5%) patients. Drug-related adverse events led to discontinuation in 23 (8.6%) patients and dose reduction in 54 (20.2%) patients. Drug-related adverse events and non–drug-related adverse events resulting in death occurred in four (1.5%) and 19 (7.1%) patients, respectively. Adjudicated drug-related events of ILD/pneumonitis occurred in 28 (10.5%) patients, with the majority as low grade (grade 1, n = 7 [2.6%]; grade 2, n = 17 [6.4%]). There was one (0.4%) grade 3 event and three (1.1%) fatal adjudicated drug-related cases of ILD/pneumonitis, one each in the biliary tract, endometrial, and other tumors cohorts. Non-drug–related adverse events are provided in Appendix Table A4.

DISCUSSION

In this phase II study, T-DXd demonstrated durable responses across multiple tumor types, alongside clinically meaningful PFS and OS in pretreated patients. The highest response rates and longest DOR, PFS, and OS were observed in tumors with IHC 3+ expression. Responses were also observed irrespective of prior HER2 therapy.

HER2 protein expression, gene amplification, and gene mutation have been identified as therapeutic targets in multiple tumor types.[23] However, HER2-targeted therapy is not currently approved beyond breast, gastric, colorectal, and lung cancer.[5,15,24] The tumor types investigated here were predefined on the basis of epidemiological frequency, prevalence of HER2 expression, and unmet medical need.[2,5] Investigations are supported by phase I clinical data of T-DXd and encouraging results from the HERALD phase II basket trial which assessed T-DXd in advanced solid tumors with HER2 amplification.[18,25]

Of note are the magnitudes of benefit observed in the endometrial, cervical, and ovarian cohorts; the highest ORRs were observed in these cohorts across all studied tumor types (57.5% for endometrial, 50.0% for cervical, 45.0% for ovarian). To the best of our knowledge, this is the first report of a HER2-directed antibody-drug conjugate in these gynecological tumors. In the endometrial cohort, 77.5% of patients had ≥two prior lines of therapy. The ORR in patients with HER2 IHC 3+ expression was 84.6%. In all patients with endometrial cancer, median PFS and OS were 11.1 months and 26.0 months, respectively. The clinically significant response and survival rates observed in this study are encouraging for HER2-expressing endometrial cancers, which are typically associated with high risk for progression and poor survival rates.[10] In the cervical cohort, 85.0% of patients had ≥two prior lines of therapy, and the ORR in patients with HER2 IHC 3+ expression was 75.0%. The median OS in this cohort was 13.6 months in all patients, not reached in IHC 3+ patients, and 11.5 months in IHC 2+ patients. These data are promising in a cohort with few treatment options and a typically low response rate to treatment.[11] The median number of prior treatments in the ovarian cohort was three, and 35.0% of patients had five or more prior lines of therapy; the median OS was 13.2 months in all patients and 20.0 months in patients with HER2 IHC 3+ expression. The results from this study further support use of a HER2 antibody-drug conjugate for treating ovarian cancer, and the outcomes are promising for a disease subgroup with a high mortality rate.[12,26]

Although there was only one investigator-assessed responder in the pancreatic cohort (4.0%; closed to recruitment with 25 patients enrolled), when assessed by independent central

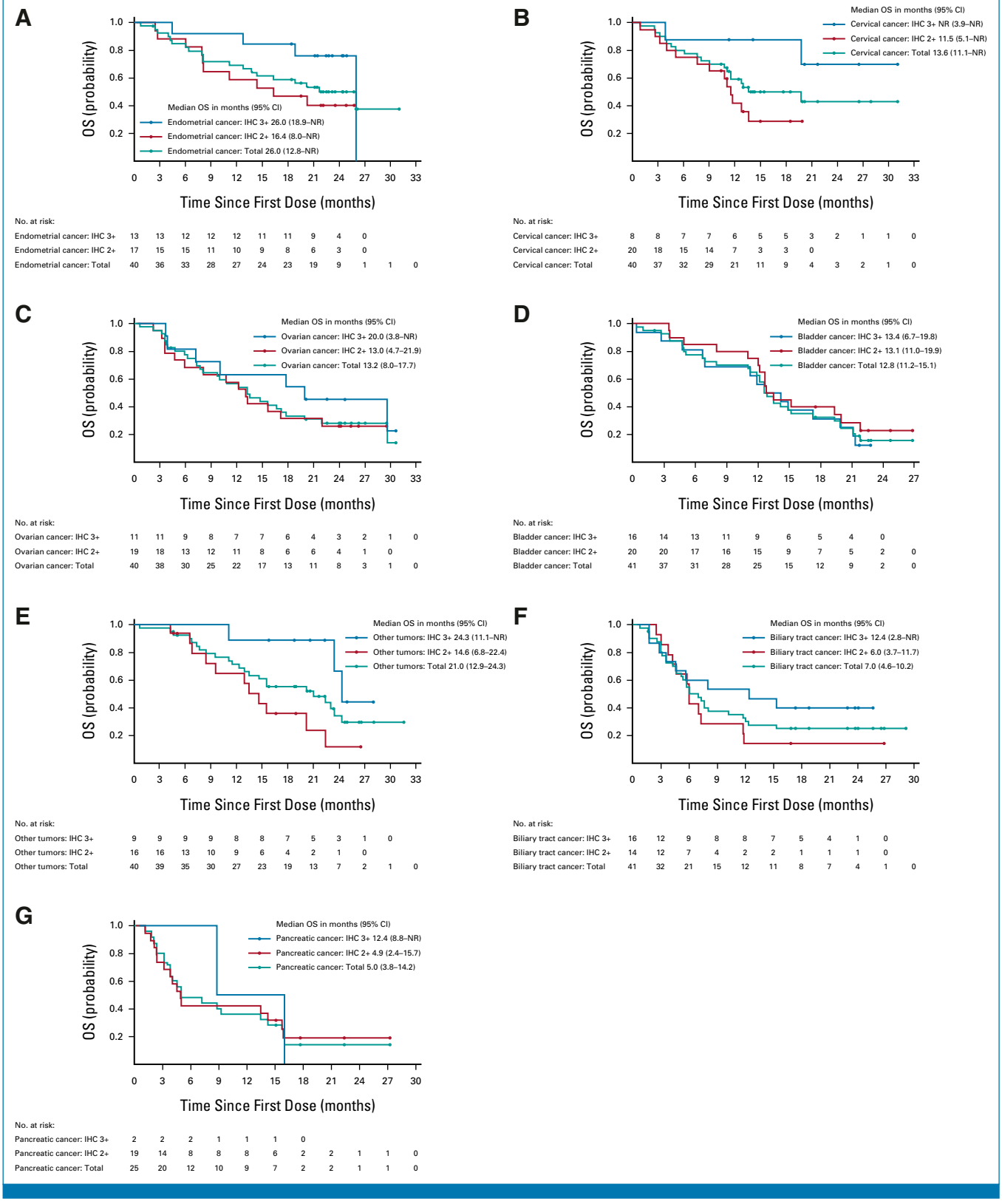

FIG 3. Kaplan-Meier estimates of OS, according to tumor type. (A) Endometrial cancer, (B) cervical cancer, (C) ovarian cancer, (D) bladder cancer, (E) other tumors, (F) biliary tract cancer, and (G) pancreatic cancer. IHC, immunohistochemistry; NR, not reached; OS, overall survival.

TABLE 2. Incidence of Drug-Related Adverse Events

Adverse Event	Endometrial Cancer (n = 40)	Cervical Cancer (n = 40)	Ovarian Cancer (n = 40)	Bladder Cancer (n = 41)	Other Tumors (n = 40)	Biliary Tract Cancer (n = 41)	Pancreatic Cancer (n = 25)
Drug-related adverse events, No. (%)	36 (90.0)	36 (90.0)	34 (85.0)	38 (92.7)	34 (85.0)	33 (80.5)	15 (60.0)
Grade ≥3	14 (35.0)	19 (47.5)	21 (52.5)	17 (41.5)	15 (37.5)	16 (39.0)	7 (28.0)
Serious adverse events	4 (10.0)	3 (7.5)	11 (27.5)	4 (9.8)	6 (15.0)	5 (12.2)	3 (12.0)
Leading to discontinuation	3 (7.5)	3 (7.5)	1 (2.5)	4 (9.8)	6 (15.0)	5 (12.2)	1 (4.0)
Leading to dose modification[a]	13 (32.5)	13 (32.5)	18 (45.0)	15 (36.6)	13 (32.5)	13 (31.7)	0
Associated with death	2 (5.0)	0	0	1 (2.4)	1 (2.5)	0	0
Most common drug-related adverse events (>10% of total patients), No. (%)							
Nausea	29 (72.5)	26 (65.0)	22 (55.0)	21 (51.2)	23 (57.5)	19 (46.3)	7 (28.0)
Anemia	7 (17.5)	15 (37.5)	15 (37.5)	12 (29.3)	11 (27.5)	10 (24.4)	4 (16.0)
Diarrhea	16 (40.0)	15 (37.5)	8 (20.0)	13 (31.7)	6 (15.0)	8 (19.5)	3 (12.0)
Fatigue	10 (25.0)	9 (22.5)	11 (27.5)	11 (26.8)	12 (30.0)	9 (22.0)	4 (16.0)
Vomiting	16 (40.0)	10 (25.0)	7 (17.5)	6 (14.6)	15 (37.5)	9 (22.0)	3 (12.0)
Neutropenia	4 (10.0)	8 (20.0)	5 (12.5)	11 (26.8)	9 (22.5)	9 (22.0)	4 (16.0)
Decreased appetite	8 (20.0)	7 (17.5)	8 (20.0)	8 (19.5)	7 (17.5)	7 (17.1)	2 (8.0)
Asthenia	11 (27.5)	9 (22.5)	6 (15.0)	3 (7.3)	8 (20.0)	6 (14.6)	3 (12.0)
Alopecia	9 (22.5)	8 (20.0)	5 (12.5)	5 (12.2)	7 (17.5)	9 (22.0)	2 (8.0)
Thrombocytopenia	2 (5.0)	2 (5.0)	5 (12.5)	6 (14.6)	7 (17.5)	5 (12.2)	3 (12.0)

[a]Dose modification includes adverse events with action taken of dose reduced or drug interrupted. Adverse events associated with death included pneumonia (n = 1), organizing pneumonia (n = 1), pneumonitis (n = 1), and neutropenic sepsis (n = 1).

review, three responses were observed (12.0%). PFS and OS results showed potential in the late-line pancreatic cancer setting; however, it is challenging to draw conclusions from this cohort owing to the low patient numbers, particularly in the IHC 3+ group.

Biliary tract cancer (BTC) is uncommon[12] but has a high mortality rate[13] and limited clinical benefit from second-line chemotherapy.[27] The phase II trial of T-DXd in patients with unresectable or recurrent HER2-expressing BTCs showed promising activity in patients with HER2-positive (IHC 3+ and IHC 2+/in-situ hybridization+) BTC.[28] The data in the DESTINY-PanTumor02 trial further support HER2 as a therapeutic target in BTC where an ORR of 56.3% and OS of 12.4 months were observed in patients with IHC 3+ tumors.

Safety findings for T-DXd in this trial were consistent with the established safety profile.[15] A risk of pulmonary adverse events, primarily ILD/pneumonitis, has been observed in patients receiving T-DXd and is an important consideration for these patients.[29,30] Although most cases of adjudicated drug-related ILD in this trial were low-grade and manageable and overall incidence was consistent with that in previous studies,[31] three adjudicated drug-related ILD/pneumonitis-related deaths occurred. Multidisciplinary guidelines for diagnosing and managing T-DXd–related ILD/pneumonitis have been published.[29] T-DXd–related ILD/pneumonitis can be safely managed with a multidisciplinary team, who should manage the ILD/pneumonitis jointly with the medical oncologist and may include a primary care physician, nurse practitioner, pulmonologist, pathologist, pharmacist, infectious disease specialist, and radiologist. Patients should be proactively monitored for ILD/pneumonitis, and suspected cases should be actively managed by a multidisciplinary team; T-DXd treatment should be interrupted in the event of grade 1 ILD/pneumonitis, and the event must resolve before treatment may resume.[29]

This tumor-agnostic biomarker-driven approach represents an innovative application of the principles of precision medicine.[5] Despite the prospects of the tumor-agnostic strategy, only six drugs have received US Food and Drug Administration approval on the following basis: pembrolizumab for microsatellite instability high, mismatch repair deficient, or tumor mutational burden high tumors; dostarlimab for mismatch repair deficient tumors; larotrectinib or entrectinib for tumors with *NTRK* gene fusions; dabrafenib plus trametinib for tumors with *BRAF* V600E mutations; and selpercatinib for tumors with *RET* gene fusions.[32] As with those studies, this trial has a clear rationale on the basis of preclinical/clinical data and demonstrates meaningful antitumor activity across endometrial, cervical, ovarian, bladder, biliary tract, and other tumor cohorts.

A tumor-agnostic investigative approach has some limitations, most notably the single-arm nature of the studies. It was not possible to include a single comparator, given the range of tumor types that were included. Another potential limitation is the few patients included with HER2 IHC 1+ tumors. The protocol allowed for recruitment of patients with HER2 IHC 1+ tumors once 3 of 15 responders within a cohort had been observed in centrally confirmed HER2 IHC 3+ or IHC 2+ tumors. However, only the cervical cohort prospectively opened enrollment to patients with IHC 1+ tumors as recruitment in other cohorts was complete by the time response rate data were available on the first 15 patients. There is limited evidence available from this study in HER2-low patients, a population of growing clinical interest after the approval of T-DXd in HER2-low breast cancer.[15] The few responses in patients who were determined to be IHC 1+/0 on retrospective central testing suggest that further exploration in patients with IHC 1+ tumors is warranted beyond breast cancer.

In this global, multicenter phase II study, treatment with T-DXd demonstrated robust clinical activity providing durable clinical benefit for pretreated patients with selected HER2-expressing solid tumors. The observed safety profile, including ILD, was consistent with that in previously reported studies of T-DXd. These data provide clinical evidence for antitumor activity of T-DXd across multiple tumor types, suggesting potential tumor-agnostic activity in patients with HER2-expressing solid tumors.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial

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Consulting or Advisory Role: Roche (less than $10,000 USD in a single calendar year), Pfizer (less than $10,000 USD in a single calendar year), Bristol Myers Squibb (less than $10,000 USD in a single calendar year), Astellas Pharma (less than $10,000 USD in a single calendar year), Novartis (less than $10,000 USD in a single calendar year), MSD (less than $10,000 USD in a single calendar year), Merck Serono (less than $10,000 USD in a single calendar year), AstraZeneca (less than $10,000 USD in a single calendar year), Eisai (less than $10,000 USD in a single calendar year), Lilly (less than $10,000 USD in a single calendar year)
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No other potential conflicts of interest were reported.

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APPENDIX 2. METHODS

Patients

Male and female patients were at least 18 years of age at the time of giving signed informed consent. Patients with locally advanced, unresectable, or metastatic solid tumors with histology specific to respective cohorts, who have progressed after at least one prior systemic treatment for metastatic or advanced disease, or who have no satisfactory alternative treatment option, were recruited; patients with prior human epidermal growth factor receptor 2 (HER2)–targeted therapy were permitted. The following are the respective cohorts for patient inclusion:

- Cohort 1 (biliary tract cancer): metastatic or advanced biliary tract cancers, including intrahepatic or extrahepatic cholangiocarcinoma and tumors arising in the ampulla of Vater or gallbladder
- Cohort 2 (bladder cancer): metastatic or advanced urothelial carcinoma, including transitional cell or predominantly transitional cell carcinoma of the renal pelvis, ureter, urinary bladder, or urethra
- Cohort 3 (cervical cancer): metastatic or advanced cervical carcinoma
- Cohort 4 (endometrial cancer): metastatic or advanced endometrial carcinoma
- Cohort 5 (ovarian cancer): metastatic or advanced epithelial ovarian carcinoma
- Cohort 6 (pancreatic cancer): metastatic or advanced pancreatic cancer
- Cohort 7 (other tumors): metastatic or advanced rare tumors with HER2 overexpression (immunohistochemistry [IHC] 3+ and 2+), excluding the tumors mentioned above, and breast, non–small-cell lung, gastric, and colorectal cancers

Patients must have had HER2 overexpression (IHC 3+ or IHC 2+) as determined by local or central assessment scored using current ASCO/College of American Pathologists guidelines for scoring HER2 in gastric cancer. Central assessment may have been offered on the basis of site need. For each cohort, 1-6, up to 10 IHC 1+ patients may have been included if ≥3 objective responses were observed in the first 15 patients with confirmed HER2 overexpression (IHC 3+ or IHC 2+) by central testing. For the other tumors cohort (cohort 7), only patients with HER2 overexpression (IHC 3+ or IHC 2+) were enrolled. Patients must have provided an existing formalin-fixed paraffin-embedded (FFPE) tumor sample for tissue-based IHC staining to centrally determine HER2 expression and other correlatives. The mandatory FFPE tumor sample needed to have been obtained at the time of diagnosis of metastatic or locally advanced, unresectable, solid tumors (most recent pre-enrollment tumor sample must have been provided). Specimens with limited tumor content and fine needle aspirates were inadequate for defining tumor HER2 status. Patients were also required to have measurable target disease assessed by the investigator on the basis of RECIST 1.1, an Eastern Cooperative Oncology Group performance status of 0-1, left ventricular ejection fraction ≥50% by either echocardiography or multiple-gated acquisition scan within 28 days before treatment assignment, adequate organ function within 14 days before trastuzumab deruxtecan (T-DXd) administration, and adequate treatment washout period before study drug treatment.

Patients were excluded from the study if they had a known somatic DNA mutation of *HER2* (*ERBB2*) without tumoral HER2 expression, primary diagnosis of adenocarcinoma of the breast, adenocarcinoma of the colon or rectum, adenocarcinoma of the gastric body or gastroesophageal junction, or non–small-cell lung cancer. Substance abuse or any other medical conditions (eg, clinically significant cardiac or psychological conditions) that may, in the opinion of the investigator, have interfered with the patient's participation in the clinical study or evaluation of the clinical study results also warranted exclusion from the study.

Central HER2 Testing

Tumor tissue samples collected from patients will be analyzed for HER2 status by a central laboratory designated by the sponsor using a validated assay. Tumor lesions used to acquire samples for HER2 testing were not target lesions, unless there were no other lesions suitable for biopsy. Samples with limited tumor content and fine needle aspirate specimens were considered not acceptable.

Treatment and Responses

Patients received a dose of 5.4 mg/kg once every 3 weeks, and the number of treatment cycles with T-DXd until RECIST 1.1 disease progression and withdrawal of consent parameters were not fixed. On commencing study treatment, patients continued receiving T-DXd until RECIST 1.1 disease progression, withdrawal of consent, or any of the discontinuation criteria were met.

T-DXd was administered using an intravenous bag containing 5% (w/v) dextrose injection infusion solution and delivered through an intravenous administration set with a 0.2 or 0.22 μm filter. The standard infusion time for T-DXd was approximately 90 minutes for the first infusion. If the first infusion was well tolerated and the participant did not experience an infusion-related reaction, the minimum infusion time for subsequent cycles was at least 30 minutes. If there were interruptions during the infusion, the total infusion time was not allowed to exceed 3 hours at room temperature. The participant's weight at screening (baseline) was used to calculate the initial dose. If, during treatment, the participant's weight changed by ≥10%, the participant's dose was recalculated on the basis of the participant's updated weight.

All dose modifications (interruption, reduction, and/or discontinuation) should be based on the worst preceding toxicity. Dosing was interrupted (or discontinued in the case of a dose-limiting toxicity), and supporting therapy was administered as required. On improvement of an adverse event leading to dose interruption, T-DXd therapy could be resumed at the same dose. If a further episode of the same adverse event, or a different adverse event, required dose interruption, therapy could be restarted at a reduced dose on improvement (dose level 1: 4.4 mg/kg of body weight once every 3 weeks; dose level 2: 3.2 mg/kg of body weight once every 3 weeks). Treatment-emergent adverse events were assessed by the study investigator as related to use of T-DXd.

Interstitial Lung Disease/Pneumonitis

Interstitial lung disease (ILD) is considered an important identified risk based on a comprehensive cumulative review of potential ILD/pneumonitis cases reviewed by the independent ILD Adjudication Committee, the available safety data from the clinical development program, available data from recent epidemiology/literature, biological plausibility, and safety information from drugs of similar class. High-resolution computed tomography and pulmonary function were measured at baseline and at the time of suspected ILD/pneumonitis events. Pulmonologist consultation, pulse oximetry (SpO_2), arterial blood gases if clinically indicated, and one blood sample were collected for pharmacokinetics as soon as ILD/pneumonitis was suspected, if feasible.

Multidisciplinary guidelines for diagnosing and managing T-DXd-related ILD/pneumonitis have been published and are available at Swain et al.[29]

Visit Responses

For all patients, the RECIST tumor response data were used to determine each patient's visit response according to RECIST 1.1. They were also used to determine if a patient had progressed in accordance with RECIST and their best objective response to study treatment.

Baseline radiological tumor assessments were performed no more than 28 days before the start of study treatment and were performed as close as possible to the start of study treatment. Postbaseline tumor assessments by the investigator were performed at the following time points:

- Every 6 weeks (±1 week) relative to the date of first dose of T-DXd, until RECIST 1.1-defined radiological disease progression
- Tumor assessment scans continued if patients discontinued T-DXd owing to toxicity without progression until progressive disease was detected

If an unscheduled assessment was performed and the patient had not progressed, every attempt should have been made to complete the subsequent assessments at their scheduled visits. This schedule was followed to minimize any unintentional bias caused by some patients being assessed at a different frequency from other patients.

At each visit, patients were assigned a RECIST 1.1 visit response of complete response, partial response, stable disease, or progressive disease, using the information from target lesions, nontarget lesions, and new lesions and depending on the status of their disease compared with baseline and previous assessments. If a patient had a tumor assessment that could not be evaluated, the patient was assigned a visit response of not evaluable unless there was evidence of progression, in which case the response was assigned as progressive disease.

Interim Analyses

Interim efficacy analyses were performed using the centrally determined analysis set after 15 centrally determined HER2-eligible patients within a cohort had the opportunity to complete two scheduled postbaseline scans according to RECIST 1.1. Safety data were reviewed alongside efficacy to support any decision to expand the inclusion criteria or size of a cohort. No adjustment for multiple testing was planned for this study.

Once 15 patients within a cohort were centrally determined as having HER2 IHC 3+ or IHC 2+ and had the opportunity to complete at least two scheduled postbaseline scans according to RECIST 1.1, the following applied:

- For each tumor-specific cohort (cohorts 1-6), the inclusion criteria were expanded to include up to 10 IHC 1+ patients, if three or more responses were observed in the first 15 patients. If one or two responses were observed in the first 15 patients, the cohort continued recruiting without change. If zero responses were observed in the first 15 patients, the cohort was closed to further recruitment
- For the other tumors cohort (cohort 7), if one or more responses were observed in the first 15 patients, the cohort continued recruiting without change. If zero responses were observed in the first 15 patients, the cohort was closed to further recruitment
- During the study, both the bladder and cervical cohorts met the protocol-specified criteria to open recruitment of IHC 1+ patients, and only the cervical cohort prospectively recruited patients who were 1+ after this point and so available data for 1+ patients are very limited. The cohorts for biliary tract cancer, endometrial cancer, and ovarian cancer had almost fully enrolled to 40 patients at the time the first 15 centrally confirmed patients were evaluable for response. Recruitment to the pancreatic cohort was closed (March 24, 2022) as zero responses in the first 15 patients had been observed (Appendix Table A5)

Statistical Analyses

All RECIST 1.1 assessments, whether scheduled or unscheduled, were included in the calculation of efficacy variables, regardless of whether a patient discontinued study treatment or received another anticancer therapy. At the time of final analysis, all efficacy end points were summarized by cohort for the full analysis set. Selected efficacy end points were also summarized by cohort for the centrally determined efficacy analysis set (Appendix Table A6).

TABLE A1. HER2 Status at Baseline, Local versus Central Test Results

		Patients, No. (%)					
		Central HER2 IHC Results					
Group	Local Results	IHC 3+	IHC 2+	IHC 1+	IHC 0	Unknown	Total
Endometrial cancer	IHC 3+	9 (22.5)	3 (7.5)	1 (2.5)	1 (2.5)	0	14 (35.0)
	IHC 2+	2 (5.0)	7 (17.5)	3 (7.5)	4 (10.0)	1 (2.5)	17 (42.5)
	IHC 1+	0	0	0	0	0	0
	No local result	2 (5.0)	7 (17.5)	0	0	0	9 (22.5)
	Total	13 (32.5)	17 (42.5)	4 (10.0)	5 (12.5)	1 (2.5)	40 (100)
Cervical cancer	IHC 3+	6 (15.0)	1 (2.5)	1 (2.5)	0	0	8 (20.0)
	IHC 2+	0	7 (17.5)	3 (7.5)	3 (7.5)	0	13 (32.5)
	IHC 1+	0	1 (2.5)	0	1 (2.5)	0	2 (5.0)
	No local result	2 (5.0)	11 (27.5)	4 (10.0)	0	0	17 (42.5)
	Total	8 (20.0)	20 (50.0)	8 (20.0)	4 (10.0)	0	40 (100)
Ovarian cancer	IHC 3+	7 (17.5)	6 (15.0)	0	0	0	13 (32.5)
	IHC 2+	2 (5.0)	12 (30.0)	5 (12.5)	5 (12.5)	0	24 (60.0)
	IHC 1+	0	0	0	0	0	0
	No local result	2 (5.0)	1 (2.5)	0	0	0	3 (7.5)
	Total	11 (27.5)	19 (47.5)	5 (12.5)	5 (12.5)	0	40 (100)
Bladder cancer	IHC 3+	12 (29.3)	8 (19.5)	1 (2.4)	2 (4.9)	1 (2.4)	24 (58.5)
	IHC 2+	1 (2.4)	7 (17.1)	1 (2.4)	0	0	9 (22.0)
	IHC 1+	0	0	0	0	0	0
	No local result	3 (7.3)	5 (12.2)	0	0	0	8 (19.5)
	Total	16 (39.0)	20 (48.8)	2 (4.9)	2 (4.9)	1 (2.4)	41 (100)
Other tumors	IHC 3+	4 (10.0)	2 (5.0)	0	1 (2.5)	5 (12.5)	12 (30.0)
	IHC 2+	1 (2.5)	7 (17.5)	2 (5.0)	3 (7.5)	4 (10.0)	17 (42.5)
	IHC 1+	0	0	0	0	0	0
	No local result	4 (10.0)	7 (17.5)	0	0	0	11 (27.5)
	Total	9 (22.5)	16 (40.0)	2 (5.0)	4 (10.0)	9 (22.5)	40 (100)
Biliary tract cancer	IHC 3+	12 (29.3)	4 (9.8)	1 (2.4)	1 (2.4)	0	18 (43.9)
	IHC 2+	0	7 (17.1)	2 (4.9)	6 (14.6)	1 (2.4)	16 (39.0)
	IHC 1+	0	0	0	0	0	0
	No local result	4 (9.8)	3 (7.3)	0	0	0	7 (17.1)
	Total	16 (39.0)	14 (34.1)	3 (7.3)	7 (17.1)	1 (2.4)	41 (100)
Pancreatic cancer	IHC 3+	1 (4.0)	2 (8.0)	0	1 (4.0)	0	4 (16.0)
	IHC 2+	0	8 (32.0)	1 (4.0)	2 (8.0)	0	11 (44.0)
	IHC 1+	0	0	0	0	0	0
	No local result	1 (4.0)	9 (36.0)	0	0	0	10 (40.0)
	Total	2 (8.0)	19 (76.0)	1 (4.0)	3 (12.0)	0	25 (100)

NOTE. Unknown central HER2 test results include patients whose samples were unevaluable (for various technical reasons) and may include patients who did not provide a sample for central testing.
Abbreviations: HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

TABLE A2. Efficacy by Tumor Cohort

Outcome	Endometrial Cancer	Cervical Cancer	Ovarian Cancer	Bladder Cancer	Other Tumors	Biliary Tract Cancer	Pancreatic Cancer
All patients	40	40	40	41	40	41	25
Confirmed ORR (investigator)	23 (57.5)	20 (50.0)	18 (45.0)	16 (39.0)	12 (30.0)	9 (22.0)	1 (4.0)
95% CI	40.9 to 73.0	33.8 to 66.2	29.3 to 61.5	24.2 to 55.5	16.6 to 46.5	10.6 to 37.6	0.1 to 20.4
Best overall response							
CR, No. (%)	8 (20.0)	2 (5.0)	4 (10.0)	1 (2.4)	0	1 (2.4)	0
PR, No. (%)	15 (37.5)	18 (45.0)	14 (35.0)	15 (36.6)	12 (30.0)	8 (19.5)	1 (4.0)
SD, No. (%)	12 (30.0)	11 (27.5)	14 (35.0)	16 (39.0)	20 (50.0)	23 (56.1)	16 (64.0)
PD, No. (%)	4 (10.0)	7 (17.5)	7 (17.5)	7 (17.1)	3 (7.5)	7 (17.1)	7 (28.0)
NE, No. (%)	0	1 (2.5)	1 (2.5)	0	1 (2.5)	0	0
Median DOR,[a] No.	23	20	18	16	12	9	1
Median, months	NR	14.2	11.3	8.7	22.1	8.6	5.7
95% CI	9.9 to NR	4.1 to NR	4.1 to 22.1	4.3 to 11.8	4.1 to NR	2.1 to NR	NR to NR
DCR at 12 weeks, No. (%)	32 (80.0)	27 (67.5)	28 (70.0)	29 (70.7)	30 (75.0)	27 (65.9)	9 (36.0)
95% CI	64.4 to 90.9	50.9 to 81.4	53.5 to 83.4	54.5 to 83.9	58.8 to 87.3	49.4 to 79.9	18.0 to 57.5
Kaplan-Meier estimate of patients with extended DOR							
≥12 months	68.3%	50.6%	47.1%	20.8%	56.3%	33.3%	0
Median PFS, months	11.1	7.0	5.9	7.0	8.8	4.6	3.2
95% CI	7.1 to NR	4.2 to 11.1	4.0 to 8.3	4.2 to 9.7	5.5 to 12.5	3.1 to 6.0	1.8 to 7.2
PFS, 6 months	74.0	51.3	48.9	57.6	63.7	35.1	32.8
95% CI	57.0 to 85.1	34.8 to 65.5	32.1 to 63.7	41.0 to 71.1	46.5 to 76.6	20.9 to 49.7	14.8 to 52.3
PFS, 12 months	49.2	29.9	31.6	22.8	39.8	15.1	10.9
95% CI	32.4 to 64.0	15.8 to 45.4	17.4 to 46.9	11.0 to 37.2	24.4 to 54.7	6.1 to 27.7	1.9 to 28.9
Median OS, months	26.0	13.6	13.2	12.8	21.0	7.0	5.0
95% CI	12.8 to NR	11.1 to NR	8.0 to 17.7	11.2 to 15.1	12.9 to 24.3	4.6 to 10.2	3.8 to 14.2
OS, 6 months	84.7	80.0	77.3	77.6	92.4	52.6	48.0
95% CI	69.0 to 92.8	64.0 to 89.5	61.0 to 87.5	61.4 to 87.7	78.3 to 97.5	36.2 to 66.6	27.8 to 65.6
OS, 12 months	69.3	59.1	56.7	62.6	71.3	30.0	36.0
95% CI	52.3 to 81.2	42.0 to 72.7	39.9 to 70.5	45.8 to 75.5	54.2 to 83.0	16.8 to 44.4	18.2 to 54.2

Abbreviations: CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; NR, not reached; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
[a]DOR includes only patients with an objective response.

TABLE A3. Efficacy by Tumor Type in the Other Tumors Cohort

Tumor Type	Group Term	All Patients	Confirmed ORR (investigator) 95% CI	Median DOR, n Median, Months 95% CI	Median PFS, Months 95% CI
Adenocarcinoid tumor of the appendix	Appendix	1	0	—	NR NR to NR
Adenoid cystic carcinoma	Salivary gland	1	0	—	8.3 NR to NR
Salivary gland cancer	Salivary gland	19	8 (42.1%) 20.3 to 66.5	6 20.1 5.6 to NR	12.5 8.8 to NR
Extramammary Paget disease	Extramammary Paget disease	3	2 (66.7%) 9.4 to 99.2	2 12.4 5.4 to NR	15.7 6.6 to NR
Head and neck	Head and neck (other)	1	1 (100.0%) 2.5 to 100	1 NR NR to NR	NR NR to NR
Lip and/or oral cavity cancer	Head and neck (other)	1	0	—	4.7 4.2 to NR
Oropharyngeal neoplasm	Head and neck (other)	2	1 (50.0%) 1.3 to 98.7	1 NR NR to NR	NR 4.2 to NR
Intestinal adenocarcinoma	Small intestine	1	0	1 5.6 NR to NR	8.3 NR to NR
Malignant neoplasm of unknown primary site	Cancer of unknown primary site	5	0	1 NR NR to NR	2.8 2.4 to NR
Cutaneous melanoma	Cutaneous melanoma	2	0	—	1.5 1.4 to NR
Esophageal adenocarcinoma	Esophageal	1	0	1 2.8 NR to NR	6.3 NR to NR
Esophageal squamous cell carcinoma	Esophageal	1	0	—	0.7 NR to NR
Testis cancer	Testis	1	0	—	NR NR to NR
Vulva cancer	Vulva	1	0	1 2.6 NR to NR	5.6 NR to NR
Total other tumors	—	40	12 (30.0%) 16.6 to 46.5	14 19.4 5.4 to NR	8.8 5.5 to 12.5

Abbreviations: DOR, duration of response; NR, not reached; ORR, objective response rate; PFS, progression-free survival.

TABLE A4. Safety (non–drug-related AEs)

Adverse Event	Endometrial Cancer	Cervical Cancer	Ovarian Cancer	Bladder Cancer	Other Tumors	Biliary Tract Cancer	Pancreatic Cancer
No. of patients	40	40	40	41	40	41	25
Any AE, No. (%)	39 (97.5)	40 (100.0)	38 (95.0)	41 (100.0)	38 (95.0)	41 (100.0)	24 (96.0)
Any AE of CTCAE grade 3 or higher	26 (65.0)	26 (65.0)	25 (62.5)	26 (63.4)	22 (55.0)	30 (73.2)	14 (56.0)
Any with outcome of death	3 (7.5)	1 (2.5)	1 (2.5)	3 (7.3)	3 (7.5)	6 (14.6)	2 (8.0)
Any serious AE (including events with outcome of death)	15 (37.5)	15 (37.5)	16 (40.0)	17 (41.5)	19 (47.5)	23 (56.1)	9 (36.0)
Any AE leading to discontinuation of T-DXd	3 (7.5)	4 (10.0)	3 (7.5)	4 (9.8)	7 (17.5)	8 (19.5)	3 (12.0)
Any AE leading to dose modification of T-DXd	20 (50.0)	22 (55.0)	23 (57.5)	26 (63.4)	22 (55.0)	17 (41.5)	3 (12.0)
Any AE leading to dose reduction of T-DXd	12 (30.0)	9 (22.5)	17 (42.5)	7 (17.1)	6 (15.0)	10 (24.4)	0
Any AE leading to dose interruption of T-DXd	14 (35.0)	17 (42.5)	19 (47.5)	24 (58.5)	21 (52.5)	13 (31.7)	3 (12.0)
Any AE leading to hospitalization	15 (37.5)	15 (37.5)	14 (35.0)	17 (41.5)	17 (42.5)	21 (51.2)	8 (32.0)
Most common adverse events (>10% of total patients), No. (%)							
Nausea	32 (80.0)	30 (75.0)	25 (62.5)	23 (56.1)	28 (70.0)	23 (56.1)	12 (48.0)
Anemia	14 (35.0)	21 (52.5)	25 (62.5)	19 (46.3)	17 (42.5)	16 (39.0)	8 (32.0)
Diarrhea	19 (47.5)	16 (40.0)	13 (32.5)	18 (43.9)	10 (25.0)	10 (24.4)	4 (16.0)
Vomiting	19 (47.5)	13 (32.5)	9 (22.5)	7 (17.1)	16 (40.0)	12 (29.3)	7 (28.0)
Fatigue	12 (30.0)	10 (25.0)	14 (35.0)	12 (29.3)	17 (42.5)	10 (24.4)	6 (24.0)
Decreased appetite	12 (30.0)	8 (20.0)	13 (32.5)	15 (36.6)	9 (22.5)	11 (26.8)	5 (20.0)
Asthenia	14 (35.0)	11 (27.5)	10 (25.0)	5 (12.2)	8 (20.0)	11 (26.8)	5 (20.0)
Constipation	12 (30.0)	14 (35.0)	4 (10.0)	9 (22.0)	10 (25.0)	5 (12.2)	3 (12.0)
Neutropenia	5 (12.5)	8 (20.0)	6 (15.0)	11 (26.8)	9 (22.5)	9 (22.0)	6 (24.0)
Alopecia	12 (30.0)	9 (22.5)	5 (12.5)	5 (12.2)	7 (17.5)	11 (26.8)	2 (8.0)
Neutrophil count decreased	5 (12.5)	4 (10.0)	10 (25.0)	10 (24.4)	7 (17.5)	4 (9.8)	1 (4.0)
Abdominal pain	6 (15.0)	6 (15.0)	10 (25.0)	6 (14.6)	5 (12.5)	6 (14.6)	1 (4.0)
Hypokalemia	8 (20.0)	9 (22.5)	8 (20.0)	5 (12.2)	2 (5.0)	6 (14.6)	1 (4.0)
Aspartate aminotransferase increased	7 (17.5)	4 (10.0)	9 (22.5)	3 (7.3)	5 (12.5)	4 (9.8)	4 (16.0)
COVID-19	5 (12.5)	6 (15.0)	7 (17.5)	7 (17.1)	7 (17.5)	2 (4.9)	1 (4.0)
Thrombocytopenia	3 (7.5)	3 (7.5)	5 (12.5)	7 (17.1)	8 (20.0)	6 (14.6)	3 (12.0)
Alanine aminotransferase increased	5 (12.5)	3 (7.5)	7 (17.5)	4 (9.8)	5 (12.5)	4 (9.8)	4 (16.0)
Urinary tract infection	6 (15.0)	7 (17.5)	8 (20.0)	6 (14.6)	2 (5.0)	2 (4.9)	0
Pyrexia	4 (10.0)	3 (7.5)	11 (27.5)	4 (9.8)	5 (12.5)	1 (2.4)	0
Hypoalbuminemia	1 (2.5)	4 (10.0)	7 (17.5)	5 (12.2)	4 (10.0)	1 (2.4)	5 (20.0)
Platelet count decreased	2 (5.0)	2 (5.0)	9 (22.5)	6 (14.6)	5 (12.5)	3 (7.3)	0
Weight decreased	4 (10.0)	2 (5.0)	5 (12.5)	6 (14.6)	4 (10.0)	4 (9.8)	2 (8.0)

NOTE. Adverse events associated with death included COVID-19 (n = 1), COVID-19 pneumonia (n = 1), neutropenic sepsis (n = 1), pneumonia (n = 3), sepsis (n = 1), cerebrovascular accident (n = 1), cardiac arrest (n = 2), hypotension (n = 1), organizing pneumonia (n = 1), pneumonitis (n = 1), pulmonary embolism (n = 1), and general disorders and administration site conditions (n = 5).
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; T-DXd, trastuzumab deruxtecan.

Table A5. Visit Response Summary

Target Lesion Visit Responses	Description
Complete response	Disappearance of all target lesions. Any pathological lymph nodes selected as target lesions must have had a reduction in short axis to <10 mm
Partial response	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters as long as criteria for progressive disease were not met
Stable disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease
Progressive disease	A ≥20% increase in the sum of diameters of target lesions and an absolute increase of ≥5 mm, taking as reference the smallest sum of diameters since treatment started, including the baseline sum of diameters
Not evaluable	Only relevant in certain situations (ie, if any of the target lesions were not assessed or not evaluable or had a lesion intervention at this visit and scaling up could not be performed for lesions with interventions). Note: if the sum of diameters met the progressive disease criteria, progressive disease was overridden (ie, the lesions were not evaluable as a target lesion response)
Not applicable	No target lesions recorded at baseline

Nontarget Lesion Visit Responses	Description
Complete response	Disappearance of all nontarget lesions present at baseline with all lymph nodes nonpathological in size (<10 mm short axis)
Noncomplete response/ nonprogressive disease	Persistence of one or more nontarget lesions with no evidence of progression
Progressive disease	Unequivocal progression of existing nontarget lesions. Unequivocal progression may have been due to an important progression in one lesion only or in several lesions. In all cases, the progression must have been clinically significant for the physician to consider changing (or stopping) therapy
Not evaluable	Only relevant when one or some of the nontarget lesions were not assessed, and in the investigator's opinion, they are not able to provide an evaluable overall nontarget lesion assessment at this visit. Note: For patients without target lesions at baseline, this was relevant if any of the nontarget lesions were not assessed at this visit and the progression criteria were not met
Not applicable	Only relevant if there were no nontarget lesions at baseline

Overall Visit Response

Target	Nontarget	New Lesions	Overall
Complete response	Complete response or not applicable	No (or not evaluable)	Complete response
Complete response	Noncomplete response, nonprogressive disease, or not evaluable	No (or not evaluable)	Partial response
Partial response	Nonprogressive disease, not evaluable, or not applicable	No (or not evaluable)	Partial response
Stable disease	Nonprogressive disease, not evaluable, or not applicable	No (or not evaluable)	Stable disease
Progressive disease	Any	Any	Progressive disease
Any	Progressive disease	Any	Progressive disease
Any	Any	Yes	Progressive disease
Not evaluable	Nonprogressive disease, not evaluable, or not applicable	No (or not evaluable)	Not evaluable
Not applicable	Complete response	No (or not evaluable)	Complete response
Not applicable	Noncomplete response or nonprogressive disease	No (or not evaluable)	Stable disease
Not applicable	Not evaluable	No (or not evaluable)	Not evaluable

Table A6. Efficacy Analyses Summary

End Points Analyzed	Notes
Confirmed ORR	No. and percentage of patients achieving confirmed objective response as determined by the investigator according to RECIST 1.1 (with the associated two-sided 95% exact CI)
DOR	A Kaplan-Meier plot of DOR will be presented. The Kaplan-Meier estimate of median response and the corresponding two-sided 95% CIs will be reported
Disease control rate	No. and percentage of patients achieving disease control (with the associated two-sided 95% exact CI)
PFS	A Kaplan-Meier plot of PFS will be presented. The Kaplan-Meier estimate of median PFS and the corresponding two-sided 95% CIs will be reported. The proportion of patients alive and progression free at 6 and 12 months (Kaplan-Meier estimates) will be presented
OS	A Kaplan-Meier plot of OS will be presented. The Kaplan-Meier estimate of median OS and the corresponding two-sided 95% CIs will be reported. The proportion of patients alive at 6 and 12 months (Kaplan-Meier estimates) will be presented
Safety	Summary statistics for adverse events, serious adverse events, laboratory findings, vital signs, and echocardiography, electrocardiography, or multiple-gated acquisition results, Eastern Cooperative Oncology Group/WHO performance status, and deaths

Abbreviations: DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

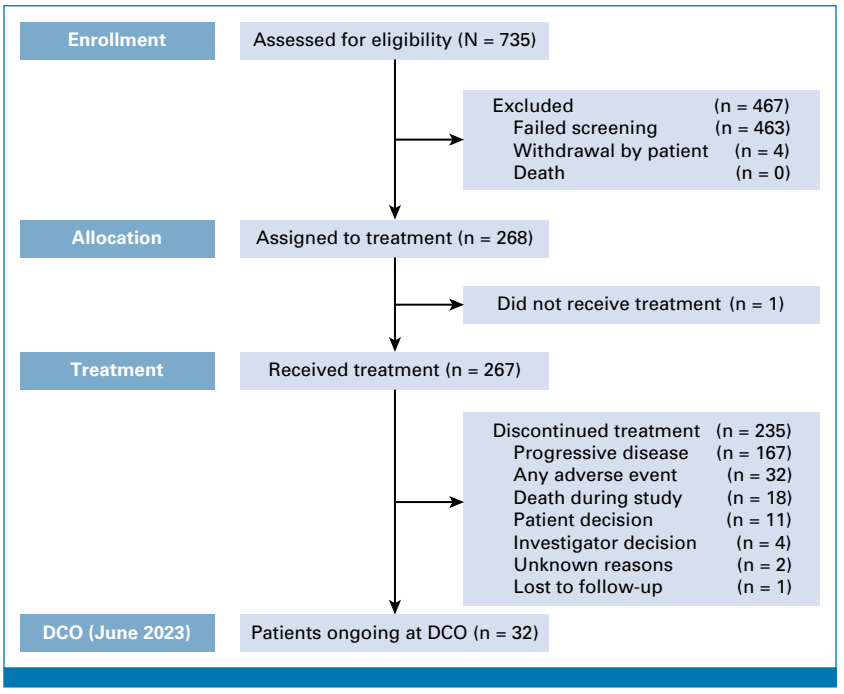

FIG A1. Patient disposition. DCO, data cutoff.

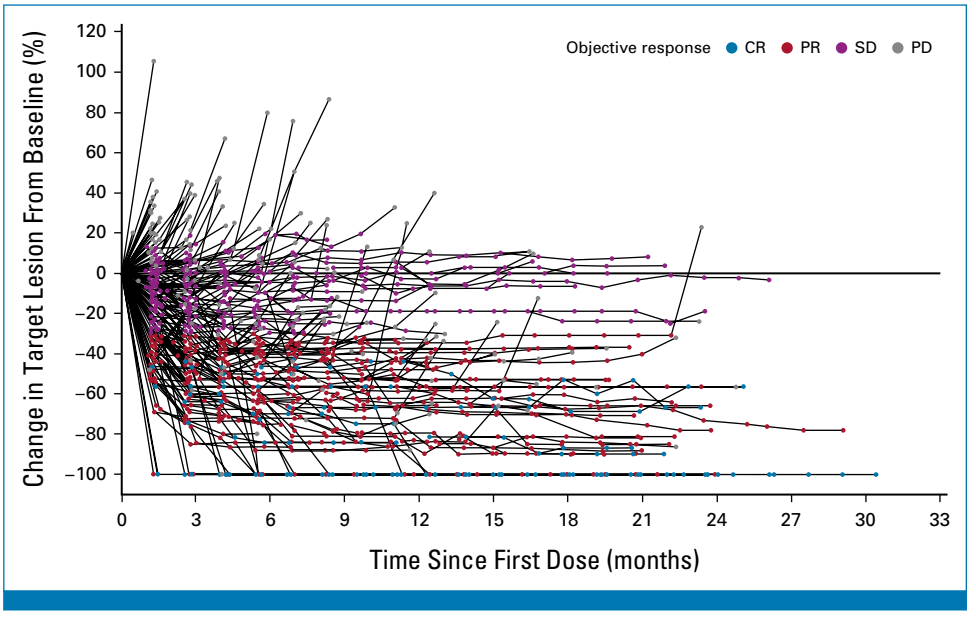

FIG A2. Target lesions size, percentage change from baseline over time (full analysis set). CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.