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ORIGINAL RESEARCH

Efficacy of Trastuzumab Deruxtecan in HER2-Expressing Solid Tumors by Enrollment HER2 IHC Status: Post Hoc Analysis of DESTINY-PanTumor02

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ABSTRACT

Introduction: DESTINY-PanTumor02 (NCT04482309) evaluated the efficacy and safety of trastuzumab deruxtecan (T-DXd) in pretreated patients with human epidermal growth factor receptor 2 (HER2)-expressing [immunohistochemistry (IHC) 3+/2+] solid tumors across seven cohorts: endometrial, cervical, ovarian, bladder, biliary tract, pancreatic, and other. Subgroup analyses by HER2 status were previously reported by central HER2 IHC testing, determined at enrollment or confirmed retrospectively. Reflecting the testing methods available in clinical practice, most patients (n = 202; 75.7%) were enrolled based on local HER2 IHC testing. Here, we report outcomes by HER2 IHC

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status as determined by the local or central test results used for study enrollment.

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

***Results*:** In total, 111 (41.6%) and 151 (56.6%) patients were enrolled with IHC 3+ and IHC 2+ tumors, respectively. In patients with IHC 3+ tumors, investigator-assessed confirmed ORR was 51.4% [95% confidence interval (CI) 41.7, 61.0], and median DOR was 14.2 months (95% CI 10.3, 23.6). In patients with IHC 2+ tumors, investigator-assessed ORR was 26.5% (95% CI 19.6, 34.3), and median DOR was 9.8 months (95% CI 4.5, 12.6). Safety was consistent with the known profile of T-DXd.

***Conclusion*:** In line with previously reported results, T-DXd demonstrated clinically meaningful benefit in patients with HER2-expressing tumors, with the greatest benefit in patients with IHC 3+ tumors. These data support the antitumor activity of T-DXd in HER2-expressing solid tumors, irrespective of whether patients are identified by local or central HER2 IHC testing.

Keywords: Advanced/metastatic solid tumors; HER2-expressing; HER2 testing; Trastuzumab deruxtecan

Key Summary Points

In DESTINY-PanTumor02, trastuzumab deruxtecan (T-DXd) demonstrated durable responses across multiple solid tumor types, with the greatest benefit in those with human epidermal growth factor receptor 2 (HER2) immunohistochemistry (IHC) 3+ tumors (HER2 test result by central testing).

Reflecting the testing methods available in clinical practice, most patients (75.7%) were enrolled into DESTINY-PanTumor02 based on local HER2 IHC testing.

This post hoc analysis reports outcomes by HER2 IHC status used for study enrollment, as determined by the local or central test results.

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T-DXd demonstrated clinically meaningful benefit in patients with HER2-expressing tumors when HER2 expression was determined by the local or central test results used for study enrollment; greatest benefit was observed in those with IHC 3+ tumors.

Patients with HER2-expressing (IHC 3+) solid tumors can be identified for potential T-DXd treatment using local HER2 IHC test results, which reflects HER2 testing practices.

INTRODUCTION

Trastuzumab deruxtecan (T-DXd) is an antibody–drug conjugate comprising a humanized immunoglobulin G1 monoclonal antibody specifically targeting human epidermal growth factor receptor 2 (HER2), a tetrapeptide-based cleavable linker, and a potent topoisomerase I inhibitor payload [1]. T-DXd is approved in multiple countries worldwide for various indications, including HER2-positive and HER2-low breast cancer, HER2-positive gastric or gastroesophageal junction adenocarcinoma, and HER2-mutant non-small cell lung cancer (NSCLC) [2–4]. In April 2024, based in part on primary results from the DESTINY-PanTumor02 trial, T-DXd was granted accelerated approval in the USA for adult patients with unresectable or metastatic HER2-positive [immunohistochemistry (IHC) 3+] solid tumors that have progressed after prior treatment and have no satisfactory alternative therapy [2, 5].

In the open-label phase 2 DESTINY-PanTumor02 trial, T-DXd demonstrated clinically meaningful antitumor activity in pretreated patients with HER2-expressing solid tumors [6]. Subgroup analyses by HER2 status were previously reported by central HER2 IHC testing, with the greatest benefit reported in patients whose tumors had HER2 IHC 3+ expression [6]. HER2 expression for study enrollment was based on local or central IHC test result [6] and, reflective of HER2 testing methods used in clinical practice [7, 8], the majority of patients were enrolled based on results from local HER2 IHC testing (n = 202; 75.7%) [6].

Here, we report a post hoc efficacy analysis of T-DXd in DESTINY-PanTumor02 according to the local or central HER2 IHC test result used for enrollment.

METHODS

Study Design and Participants

DESTINY-PanTumor02 (NCT04482309) was an open-label, phase 2 study evaluating T-DXd (5.4 mg/kg once every 3 weeks) for HER2-expressing locally advanced or metastatic disease after ≥ 1 systemic treatment or without alternative treatments. Study design details and outcome measures have been previously published [6]. Briefly, eligible patients were aged ≥ 18 years with histologically confirmed locally advanced, unresectable, or metastatic biliary tract, bladder, cervical, endometrial, ovarian, pancreatic, or other solid cancers (excluding NSCLC, breast, gastric, and colorectal cancers) that had progressed following prior treatment or with no satisfactory alternative treatment options.

HER2 expression for enrollment was based on a local IHC test result, where available; otherwise, enrollment was determined via a central IHC test result using the HER2 HercepTest™ (Dako). HER2 IHC scoring was based on current American Society of Clinical Oncology/College of American Pathologists guidelines for scoring HER2 for gastric cancer (in situ hybridization testing not required) [9]. Patients who were enrolled based on a local test result also had HER2 expression determined by retrospective central testing using the HER2 HercepTest™ (Dako) and scored according to gastric-specific criteria [9].

Procedures

T-DXd was administered intravenously once every 3 weeks at 5.4 mg/kg until documented disease progression [Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1)],

withdrawal of consent, or if any other discontinuation criteria were met.

Endpoints

The primary endpoint was confirmed objective response rate (ORR) by investigator assessment; secondary endpoints included safety, duration of response (DOR), progression-free survival (PFS), and overall survival (OS). An independent central review (ICR) per RECIST 1.1 was also conducted to support the investigator-assessed results for secondary outcomes. Exploratory endpoints included subgroup analysis by HER2 status. Secondary safety endpoints included occurrence of adverse events (AEs), including AEs of special interest [interstitial lung disease (ILD)/pneumonitis and left ventricular dysfunction].

Ethics

All patients provided written informed consent. The study was approved by independent institutional review boards of each participating site and was conducted in accordance with the ethics principles of the Declaration of Helsinki and with Good Clinical Practice guidelines defined by the International Conference on Harmonisation. A list of these individual review boards has been provided as a supplementary appendix.

RESULTS

As reported previously, 268 patients with HER2-expressing solid tumors were enrolled between October 7, 2020, and July 7, 2022 [6]; 267 patients (99.6%) received ≥ 1 dose of T-DXd and were included in the full analysis set.

In total, 202 (75.7%) and 65 (24.3%) patients were enrolled based on local and central HER2 IHC test results, respectively. Per the local or central HER2 IHC test result used for study enrollment, 111 (41.6%) and 151 (56.6%) patients with IHC 3+ and IHC 2+ tumors were enrolled, respectively; 5 patients with IHC 1+ tumors were included following a protocol-specified interim analysis.

Baseline demographics and clinical characteristics in the full study population, and in patients with IHC 3+ and IHC 2+ tumors according to the local or central HER2 IHC test result used for study enrollment, are summarized in Table 1.

The median (range) duration of follow-up was 16.0 months (0.4–31.6) and 11.7 months (0.7 to 31.1) in patients with IHC 3+ and IHC 2+ tumors, respectively.

Efficacy

Investigator-assessed ORR and DOR by HER2 IHC status used to determine study enrollment and by tumor cohort are reported in Fig. 1. In patients with IHC 3+ tumors, investigator-assessed confirmed ORR was 51.4% [95% confidence interval (CI) 41.7, 61.0], and median DOR was 14.2 months (95% CI 10.3, 23.6). In patients with IHC 2+ tumors, investigator-assessed ORR was 26.5% (95% CI 19.6, 34.3), and median DOR was 9.8 months (95% CI 4.5, 12.6). ORR and DOR results by ICR are also presented in Fig. 1. Investigator-assessed disease control rate at 12 weeks was 78.4% (95% CI 69.6, 85.6) in patients with IHC 3+ tumors and 60.3% (95% CI 52.0, 68.1) in those with IHC 2+ tumors. PFS (by investigator assessment and ICR) and OS by tumor cohort and HER2 IHC status used to determine enrollment are reported in Table 2 and Supplementary Material Fig. S1.

All 5 patients enrolled with HER2 IHC 1+ tumors were in the cervical cancer cohort; 2 were enrolled based on local test results, and 3 were enrolled based on central test results. Two patients (40.0%; 95% CI 5.3, 85.3) had a confirmed partial response (by both investigator assessment and ICR).

Safety

Detailed safety outcomes have been reported previously [6]. Among the 267 treated patients (median follow-up of 12.75 months), 226 patients (84.6%) had ≥ 1 investigator-assessed drug-related AE; the most common drug-related AEs were nausea (55.1%), anemia (27.7%), diarrhea (25.8%), vomiting (24.7%), and fatigue (24.7%). Adjudicated drug-related events of ILD/pneumonitis occurred in 28

Table 1 Baseline demographics and clinical characteristics

	All (*n* = 267)	**HER2 IHC 3+ by the local or central test result used for study enrollment (*n* = 111)**	**HER2 IHC 2+ by the local or central test result used for study enrollment (*n* = 151)**
Median age, years (range)	62 (23–85)	64 (23–85)	61 (30–81)
Sex			
Male	89 (33.3)	45 (40.5)	44 (29.1)
Female	178 (66.7)	66 (59.5)	107 (70.9)
Race			
White	163 (61.0)	64 (57.7)	94 (62.3)
Asian	87 (32.6)	38 (34.2)	49 (32.5)
Black or African American	6 (2.2)	4 (3.6)	2 (1.3)
Other	6 (2.2)	3 (2.7)	3 (2.0)
Not reported	5 (1.9)	2 (1.8)	3 (2.0)
ECOG performance status[a]			
0	126 (47.2)	54 (48.6)	68 (45.0)
1	140 (52.4)	57 (51.4)	82 (54.3)
HER2 IHC test used for study enrollment			
Local	202 (75.7)	93 (83.8)	107 (70.9)
Central	65 (24.3)	18 (16.2)	44 (29.1)
HER2 IHC status at enrollment (by local or central test result)			
IHC 3+	111 (41.6)	111 (100)	–
IHC 2+	151 (56.6)	–	151 (100)
IHC 1+	5 (1.9)	–	–
Centrally confirmed HER2 IHC status			
IHC 3+	75 (28.1)	69 (62.2)	6 (4.0)
IHC 2+	125 (46.8)	26 (23.4)	98 (64.9)
IHC 1+	25 (9.4)	4 (3.6)	18 (11.9)
IHC 0	30 (11.2)	6 (5.4)	23 (15.2)
Unknown	12 (4.5)	6 (5.4)	6 (4.0)
Prior therapy lines			
Median (range)	2.0 (0–12)	2.0 (0–9)	2.0 (0–12)
0	3 (1.1)	2 (1.8)	1 (0.7)
1	71 (26.6)	35 (31.5)	36 (23.8)

Table 1 continued

	All (n = 267)	HER2 IHC 3+ by the local or central test result used for study enrollment (n = 111)	HER2 IHC 2+ by the local or central test result used for study enrollment (n = 151)
2	84 (31.5)	30 (27.0)	52 (34.4)
3	55 (20.6)	21 (18.9)	32 (21.2)
4	21 (7.9)	12 (10.8)	8 (5.3)
≥ 5	33 (12.4)	11 (9.9)	22 (14.6)
Tumor type			
Biliary tract	41 (15.4)	22 (19.8)	19 (12.6)
Bladder	41 (15.4)	27 (24.3)	14 (9.3)
Cervical	40 (15.0)	10 (9.0)	25 (16.6)
Endometrial	40 (15.0)	16 (14.4)	24 (15.9)
Ovarian	40 (15.0)	15 (13.5)	25 (16.6)
Pancreatic	25 (9.4)	5 (4.5)	20 (13.2)
Other	40 (15.0)	16 (14.4)	24 (15.9)
Prior HER2 therapy			
Trastuzumab	33 (12.4)	22 (19.8)	11 (7.3)
Pertuzumab	5 (1.9)	3 (2.7)	2 (1.3)
Zanidatamab	4 (1.5)	2 (1.8)	2 (1.3)
Trastuzumab emtansine	3 (1.1)	3 (2.7)	0
Trastuzumab duocarmazine	1 (0.4)	0	1 (0.7)
Tucatinib	1 (0.4)	1 (0.9)	0

All values are n (%) unless stated otherwise. In the cervical cohort, 5 patients with IHC 1+ status were included after a protocol-specified interim analysis; for each cohort (except the "other" tumors cohort), up to 10 patients with IHC 1+ could have been included if ≥ 3 objective responses were observed in the first 15 patients with confirmed HER2 IHC 3+/2+ by central testing; for the "other" tumors cohort, only patients with HER2 IHC 3+/2+ were eligible for enrollment

ECOG Eastern Cooperative Oncology Group, *HER2* human epidermal growth factor receptor 2, *IHC* immunohistochemistry

[a]One patient with HER2 IHC 2+ by the test result used for study enrollment had an ECOG performance status of 2

patients [10.5%; grade 1, n = 7 (2.6%); grade 2, n = 17 (6.4%); grade 3, n = 1 (0.4%)]; there were 3 (1.1%) fatal adjudicated drug-related cases of ILD/pneumonitis that occurred in the biliary tract, endometrial, and other tumor cohorts. Overall, no new safety signals were reported for T-DXd.

DISCUSSION

DESTINY-PanTumor02 enrolled patients with HER2-expressing (IHC 3+/2+) solid tumors, as determined by local or central HER2 IHC test results, with 75.7% enrolled based on local HER2 IHC results. In real-world clinical practice, HER2

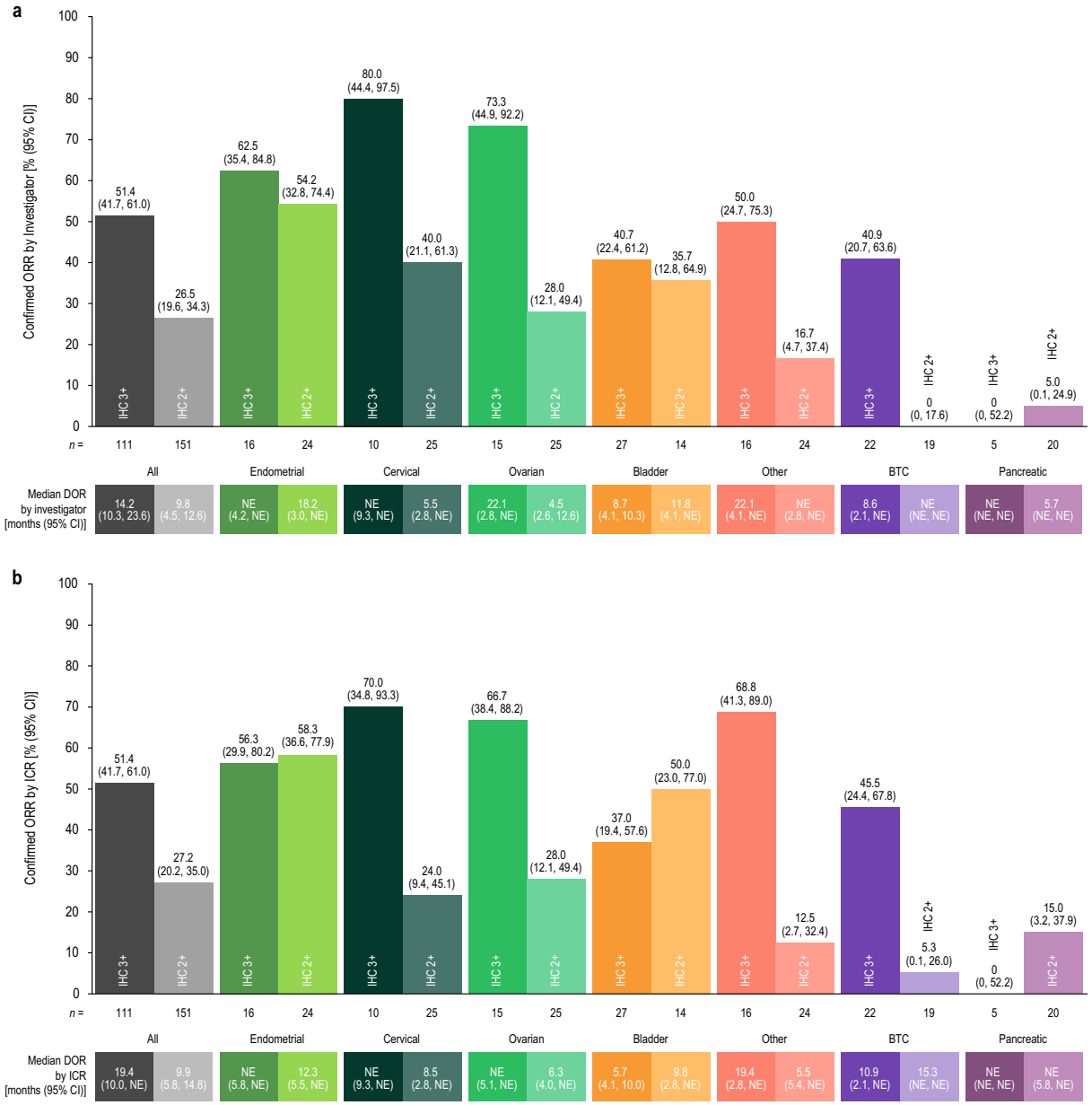

Fig. 1 ORR and DOR according to tumor type and HER2 IHC status by the local or central test result used for study enrollment by **a** investigator assessment and **b** ICR in patients with IHC 3+ and IHC 2+ tumors. *BTC* biliary tract cancer, *CI* confidence interval, *DOR* duration of response, *HER2* human epidermal growth factor receptor 2, *ICR* independent central review, *IHC* immunohistochemistry, *NE* not estimable, *ORR* objective response rate

IHC testing for breast cancer, colorectal cancer, and endometrial cancers is frequently conducted via local laboratories [7, 8]. As such, demonstrating that T-DXd antitumor activity is observed, irrespective of whether HER2 expression is identified by local or central IHC testing, is important to clinicians who are considering T-DXd as a therapeutic option for their patients following HER2 testing.

Table 2 Survival outcomes according to tumor type and HER2 IHC status by the local or central test result used for study enrollment

	HER2 status by test for study enrollment	PFS								OS			
		Investigator assessment				ICR							
		Median, months (95% CI)	6 months, % (95% CI)	12 months, % (95% CI)	18 months, % (95% CI)	Median, months (95% CI)	6 months, % (95% CI)	12 months, % (95% CI)	18 months, % (95% CI)	Median, months (95% CI)	6 months, % (95% CI)	12 months, % (95% CI)	18 months, % (95% CI)
All patients	IHC 3+ (n = 111)	9.7 (7.0, 12.5)	65.6 (55.8, 73.8)	44.0 (34.4, 53.3)	31.2 (22.4, 40.4)	10.1 (7.0, 14.2)	66.4 (56.6, 74.5)	47.3 (37.2, 56.7)	36.9 (26.9, 46.8)	17.7 (12.8, 21.8)	77.1 (68.1, 83.9)	63.3 (53.5, 71.6)	49.9 (40.1, 58.9)
	IHC 2+ (n = 151)	5.1 (4.1, 6.0)	43.2 (35.0, 51.2)	19.2 (13.1, 26.3)	13.0 (7.9, 19.6)	5.6 (4.2, 7.0)	47.4 (38.6, 55.7)	23.7 (16.1, 32.1)	18.4 (11.4, 26.7)	12.0 (9.6, 13.5)	71.9 (63.9, 78.4)	50.6 (42.2, 58.3)	31.0 (23.6, 38.7)
Endometrial cancer	IHC 3+ (n = 16)	NE (4.5, NE)	74.5 (45.4, 89.6)	60.9 (32.7, 80.3)	54.2 (27.1, 75.0)	NE (3.9, NE)	74.5 (45.4, 89.6)	67.0 (37.7, 84.9)	59.6 (30.8, 79.6)	26.0 (4.5, NE)	75.0 (46.3, 89.8)	75.0 (46.3, 89.8)	68.8 (40.5, 85.6)
	IHC 2+ (n = 24)	11.0 (6.0, 19.5)	73.9 (50.7, 87.4)	41.0 (20.7, 60.4)	30.8 (13.0, 50.6)	11.8 (6.0, 20.3)	73.9 (50.7, 87.4)	45.5 (22.5, 66.0)	32.5 (12.6, 54.3)	20.3 (8.1, NE)	91.3 (69.5, 97.8)	65.2 (42.3, 80.8)	52.2 (30.5, 70.0)
Cervical cancer	IHC 3+ (n = 10)	NE (3.9, NE)	90.0 (47.3, 98.5)	68.6 (30.5, 88.7)	51.4 (14.3, 79.6)	NE (2.9, NE)	90.0 (47.3, 98.5)	77.1 (34.5, 93.9)	57.9 (15.3, 85.2)	NE (3.9, NE)	90.0 (47.3, 98.5)	90.0 (47.3, 98.5)	90.0 (47.3, 98.5)
	IHC 2+ (n = 25)	4.6 (1.4, 8.1)	33.3 (15.9, 51.9)	14.3 (2.9, 34.4)	0.0 (NE, NE)	4.6 (2.7, 8.3)	36.1 (16.7, 56.0)	9.6 (0.7, 33.1)	NE (NE, NE)	11.7 (8.0, NE)	72.0 (50.1, 85.5)	46.9 (26.6, 64.9)	31.3 (13.4, 51.0)
Ovarian cancer	IHC 3+ (n = 15)	12.6 (4.1, NE)	59.3 (30.7, 79.3)	59.3 (30.7, 79.3)	44.4 (18.9, 67.4)	13.9 (4.4, NE)	79.4 (48.8, 92.9)	61.8 (30.4, 82.3)	44.1 (16.7, 68.8)	20.0 (7.2, NE)	86.7 (56.4, 96.5)	73.3 (43.6, 89.1)	53.3 (26.3, 74.4)
	IHC 2+ (n = 25)	4.4 (2.3, 7.1)	42.1 (21.8, 61.2)	14.0 (3.5, 31.6)	4.7 (0.3, 19.4)	5.6 (1.5, 8.2)	48.9 (26.5, 68.0)	18.3 (4.7, 39.0)	12.2 (2.1, 31.9)	10.7 (5.9, 14.8)	71.6 (49.4, 85.3)	46.3 (26.0, 64.4)	21.1 (7.7, 38.8)
Bladder cancer	IHC 3+ (n = 27)	7.0 (3.9, 11.5)	58.0 (37.0, 74.1)	18.9 (6.2, 36.9)	4.7 (0.3, 19.4)	6.8 (2.6, 9.9)	57.5 (36.4, 73.8)	21.6 (7.4, 40.4)	10.8 (1.9, 28.4)	12.6 (6.7, 17.2)	73.3 (52.0, 86.3)	54.0 (33.4, 70.7)	30.9 (14.7, 48.7)
	IHC 2+ (n = 14)	7.0 (2.6, 13.0)	57.1 (28.4, 78.0)	28.6 (8.8, 52.4)	14.3 (2.3, 36.6)	7.0 (2.8, 11.1)	57.9 (25.6, 80.2)	19.3 (3.1, 46.0)	19.3 (3.1, 46.0)	13.5 (8.0, NE)	85.7 (53.9, 96.2)	78.6 (47.2, 92.5)	35.7 (13.0, 59.4)

Table 2 continued

	HER2 status by test for study enrollment	PFS								OS			
		Investigator assessment				ICR							
		Median, months (95% CI)	6 months, % (95% CI)	12 months, % (95% CI)	18 months, % (95% CI)	Median, months (95% CI)	6 months, % (95% CI)	12 months, % (95% CI)	18 months, % (95% CI)	Median, months (95% CI)	6 months, % (95% CI)	12 months, % (95% CI)	18 months, % (95% CI)
Other tumors	IHC 3+ (n = 16)	13.0 (6.3, NE)	81.3 (52.5, 93.5)	68.8 (40.5, 85.6)	48.6 (22.9, 70.3)	21.0 (5.6, 22.9)	68.8 (40.5, 85.6)	62.5 (34.9, 81.1)	56.3 (29.5, 76.2)	24.3 (11.1, NE)	87.5 (58.6, 96.7)	75.0 (46.3, 89.8)	75.0 (46.3, 89.8)
	IHC 2+ (n = 24)	6.6 (2.9, 8.8)	51.2 (29.4, 69.4)	18.6 (5.9, 37.0)	18.6 (5.9, 37.0)	8.4 (2.9, NE)	75.1 (49.9, 88.9)	35.0 (11.9, 59.6)	23.4 (4.6, 50.3)	15.5 (9.6, 22.4)	95.8 (73.9, 99.4)	68.5 (44.9, 83.6)	41.1 (21.0, 60.2)
Biliary tract cancer	IHC 3+ (n = 22)	6.9 (3.0, 8.0)	52.6 (29.9, 71.1)	23.9 (8.7, 43.2)	14.4 (3.6, 32.2)	6.8 (2.8, 15.0)	52.4 (29.7, 70.9)	30.0 (11.4, 51.3)	20.0 (4.4, 43.7)	7.6 (4.6, NE)	61.9 (38.1, 78.8)	42.9 (21.9, 62.3)	33.3 (14.9, 53.1)
	IHC 2+ (n = 19)	3.7 (2.8, 5.1)	15.8 (3.9, 34.9)	5.3 (0.4, 21.4)	5.3 (0.4, 21.4)	3.0 (1.7, 4.2)	10.5 (1.8, 28.4)	5.3 (0.4, 21.4)	5.3 (0.4, 21.4)	5.3 (3.1, 10.2)	42.1 (20.4, 62.5)	15.8 (3.9, 34.9)	15.8 (3.9, 34.9)
Pancreatic cancer	IHC 3+ (n = 5)	8.0 (1.2, NE)	53.3 (6.8, 86.3)	0.0 (NE, NE)	0.0 (NE, NE)	7.0 (1.4, NE)	53.3 (6.8, 86.3)	NE (NE, NE)	NE (NE, NE)	8.8 (2.4, NE)	80.0 (20.4, 96.9)	40.0 (5.2, 75.3)	0.0 (NE, NE)
	IHC 2+ (n = 20)	3.2 (1.4, 4.9)	28.4 (10.4, 49.6)	11.3 (1.9, 30.2)	11.3 (1.9, 30.2)	3.2 (1.2, 7.2)	30.1 (11.4, 51.5)	24.1 (7.7, 45.3)	24.1 (7.7, 45.3)	4.7 (3.2, 14.2)	40.0 (19.3, 60.0)	35.0 (15.7, 55.2)	18.8 (5.2, 38.6)

CI confidence interval, *HER2* human epidermal growth factor receptor 2, *ICR* independent central review, *IHC* immunohistochemistry, *NE* not estimable, *OS* overall survival, *PFS* progression-free survival

In this post hoc analysis, T-DXd showed durable and clinically meaningful benefit in patients with HER2 IHC 3+ and IHC 2+ solid tumors per local or central HER2 IHC test results for study enrollment; efficacy results according to ICR were generally consistent with investigator-assessed outcomes. The highest response rate and longest DOR were seen in patients with IHC 3+ tumors. Overall, these IHC 3+ and IHC 2+ subgroup data by study enrollment HER2 IHC test results are comparable with the ORR and median DOR subgroup analyses previously reported according to HER2 IHC central test results using the HercepTest™ (Dako; investigator-assessed ORR of 61.3% and 27.2% and median DOR of 22.1 months and 9.8 months in patients with IHC 3+ and IHC 2+ tumors, respectively) [6, 10]. Favorable antitumor activity was also observed across a broad range of tumor types with IHC 3+ and IHC 2+ expression, similar to that previously shown by HER2 IHC central test results [6]. As the majority of patients were enrolled based on local HER2 IHC testing, this analysis supports use of local IHC test results to identify patients whose tumors have HER2 IHC 3+ expression and are likely to respond to T-DXd; the magnitude of T-DXd clinical benefit is irrespective of central IHC confirmation [6]. Considering the recent accelerated approval of T-DXd in the USA [2, 5], it is important that appropriately validated HER2 tests are used at local laboratories and that pathologists are appropriately trained to evaluate and score solid tumor samples.

Across studies of solid tumors, varying prevalence of HER2 IHC 3+/IHC 2+ expression has been observed, ranging from 16 to 33% of biliary tract cancers, 9–56% of urothelial carcinomas, 21–29% of cervical cancers, 18–56% of endometrial cancers, 4–28% of ovarian cancers, and 7–16% of pancreatic cancers [11–28]. Patients with HER2-expressing solid tumors typically have an inferior prognosis [29], and there remains a high unmet clinical need for efficacious treatment options. When considering outcomes associated with current standard of care for tumor types included in this study [30–33], the magnitude of clinical benefit observed in DESTINY-PanTumor02 supports T-DXd as a new therapeutic option for pretreated patients with a range of HER2 IHC 3+ solid tumors.

As previously reported, the safety findings in this trial are consistent with the known profile of T-DXd [6]. ILD/pneumonitis remains an important identified risk, and proactive monitoring, early detection, and active management are critical to prevent high-grade ILD/pneumonitis.

Limitations of the study include the single-arm design not enabling the inclusion of comparators owing to the range of tumor cohorts investigated and the small numbers of patients, reflecting the low prevalence of IHC 3+ and IHC 2+ expression in some tumor types.

CONCLUSION

This post hoc analysis affirms the tumor-agnostic activity of T-DXd in patients with HER2 IHC 3+ and IHC 2+ solid tumors when HER2 expression is determined primarily by locally available IHC assessment, which is reflective of HER2 testing practices in clinical practice; overall benefit is consistent whether HER2 testing is conducted by local or central testing.

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Declarations

Conflict of Interest. Ana Oaknin has received consulting fees from Agenus, AstraZeneca, Clovis Oncology, Corcept Therapeutics, Daiichi Sankyo, Debiopharm, Deciphera Pharmaceuticals, Eisai, Exelisis, Genmab, GSK, ImmunoGen, Itheos, MSD, Mersana Therapeutics, Myriad Genetics, Novocure, OncXerna Therapeutics, Pfizer, PharmaMar, Regeneron Pharmaceuticals, Roche, Shattuck Labs, Sutro Biopharma, and Zentalis Pharmaceuticals; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Asociación Colombiana de Ginecológos Oncólogos, AstraZeneca, European School of Oncology, GSK, Medscape, NSGO, PeerView, and PeerVoice; support for attending meetings and/or travel from AstraZeneca, PharmaMar, and Roche; participated on a Data Safety Monitoring Board or Advisory Board for Agenus, AstraZeneca, Clovis Oncology, Corcept Therapeutics, Daiichi Sankyo, Debiopharm, Deciphera Pharmaceuticals, Eisai, Exelisis, Genmab, GSK, ImmunoGen, Itheos, MSD, Mersana Therapeutics, Myriad Genetics, Novocure, OncXerna Therapeutics, Pfizer, PharmaMar, Regeneron Pharmaceuticals, Roche, Shattuck Labs, Sutro Biopharma, and Zentalis Pharmaceuticals; and held a leadership or fiduciary role in other board, society, committee, or advocacy group, paid or unpaid, for the European Society for Medical Oncology, as European Society for Medical Oncology Guidelines Gynecology Subject Editor, as European Society for Medical Oncology Gynecology Meeting Chair, as European Society for Medical Oncology Gynecology Faculty Member, for the Gynecologic Cancer Intergroup, and as Gynecologic Cancer Intergroup Cervical Cancer Committee Chair. Jung-Yun Lee has participated on a Data Safety Monitoring

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