SINGAPORE 2023 ESMO ASIA

DESTINY-PanTumor02

Trastuzumab deruxtecan for pretreated patients with HER2-expressing solid tumors: primary analysis from the DESTINY-PanTumor02 study

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On behalf of the DESTINY-PanTumor02 investigators

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Declaration of interests

Do-Youn Oh

- Research grants or contracts from Array BioPharma, AstraZeneca, BeiGene, Eli Lilly, Handok, MSD, Novartis, and Servier
- Participation on a Data Safety Monitoring Board or Advisory Board for ASLAN Pharmaceuticals, Arcus Biosciences, AstraZeneca, Basilea Pharmaceutica, Bayer, BeiGene, BMS/Celgene, Genentech/Roche, Halozyme, IQVIA, Merck, MSD, Novartis, Serono, Taiho Pharmaceutical, Turning Point Therapeutics, Yuhan, and Zymeworks

DESTINY-PanTumor02: a Phase 2 study of T-DXd for HER2-expressing solid tumors

An open-label, multicenter study (NCT04482309)

Key eligibility criteria

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer scoring[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1

T-DXd
5.4 mg/kg Q3W

40 per cohort[b]

- Endometrial cancer
- Cervical cancer
- Ovarian cancer
- Bladder cancer
- Other tumors[c]
- Biliary tract cancer
- Pancreatic cancer

Primary analysis data cutoff: Jun 8, 2023
Median follow up: 12.75 months

Primary endpoint

- Confirmed ORR (investigator)

Secondary endpoints

- DOR, DCR, PFS, OS
- Safety

Exploratory analysis

- Subgroup analyses by HER2 status

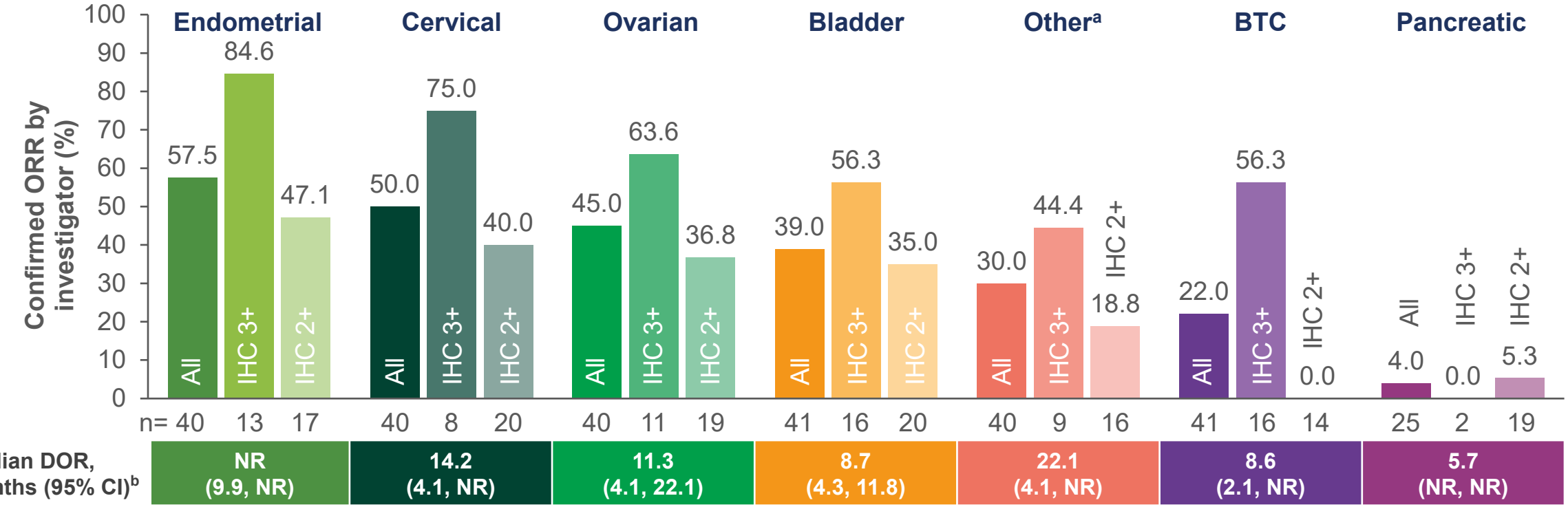
Baseline characteristics

- 267 patients received treatment; 202 (75.7%) based on local HER2 testing
  - 111 (41.6%) patients were IHC 3+ based on HER2 test (local or central) at enrollment, primary efficacy analysis (all patients)
  - **75 (28.1%) patients were IHC 3+ on central testing,** sensitivity analysis on efficacy endpoints (subgroup analyses)
- Median age was 62 years (23–85) and **109 (40.8%) patients had received ≥3 lines of therapy**

[a]Patients were eligible for either test. All patients were centrally confirmed; [b]planned recruitment, cohorts with no objective responses in the first 15 patients were to be closed; [c]patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer. 2L, second-line; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization.

1. Hofmann M, et al. *Histopathology*. 2008;52:797–805

Objective response and duration of response

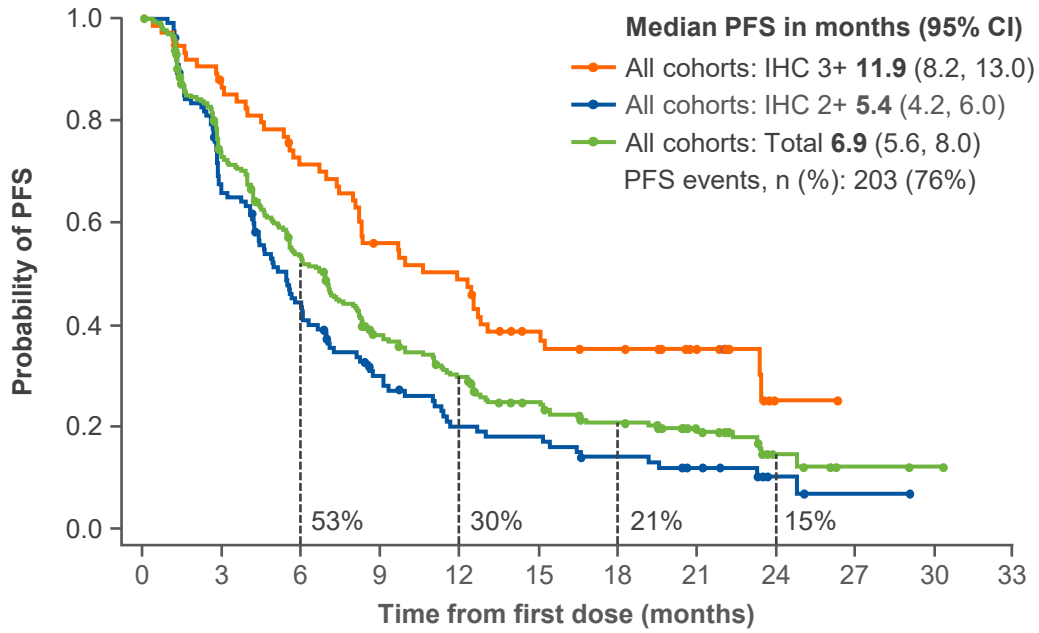


	All patients (N=267)	IHC 3+ (n=75)	IHC 2+ (n=125)
ORR, % (95% CI)	37.1 (31.3, 43.2)	61.3 (49.4, 72.4)	27.2 (19.6, 35.9)
Median DOR, months (95% CI)[b]	11.3 (9.6, 17.8)	22.1 (9.6, NR)	9.8 (4.3, 12.6)

Analysis of ORR by investigator was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. [a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer; [b]includes patients with a confirmed objective response only. BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NR, not reached; ORR, objective response rate; T-DXd, trastuzumab deruxtecan

Efficacy endpoint: PFS and OS by HER2 status

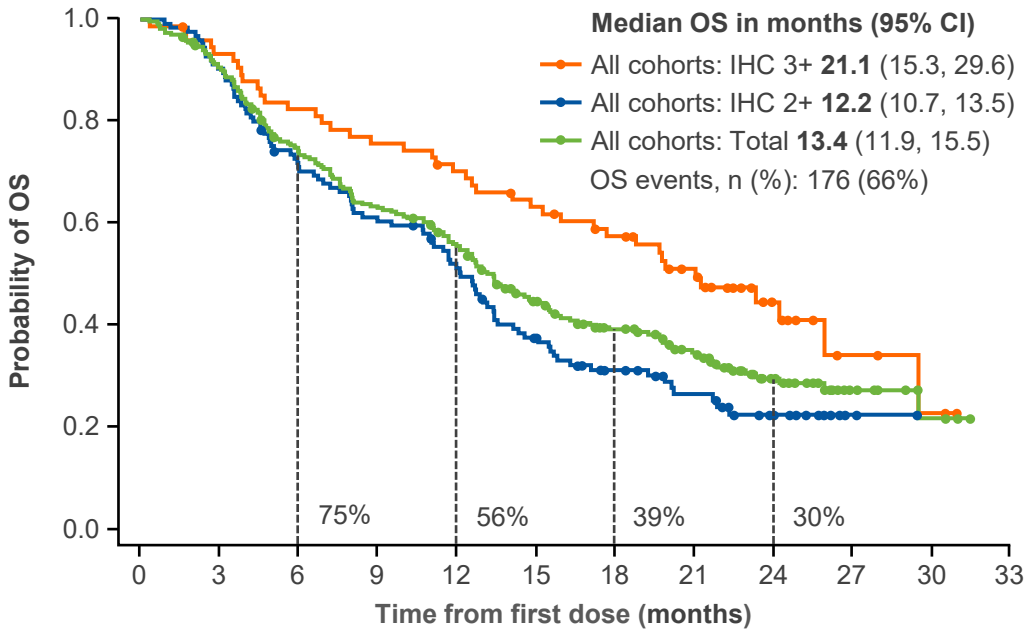
K-M estimates of PFS by investigator assessment (all cohorts)



Number at risk, month

All cohorts: IHC 3+	75	63	51	39	34	23	19	12	1	0		
All cohorts: IHC 2+	125	78	50	31	20	18	13	9	3	1	0	
All cohorts: Total	267	185	132	89	68	51	39	25	6	2	1	0

K-M estimates of OS (all cohorts)



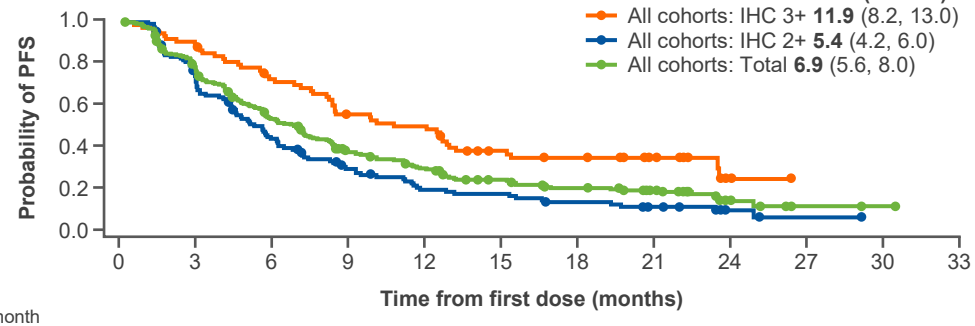
Number at risk, month

All cohorts: IHC 3+	75	69	61	56	51	45	39	29	13	4	2	0
All cohorts: IHC 2+	125	113	88	75	62	43	31	22	12	2	0	
All cohorts: Total	267	239	194	165	143	108	86	65	34	10	4	0

Circle indicates a censored observation
CI, confidence interval; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; K-M, Kaplan-Meier; OS, overall survival; PFS, progression-free survival

Efficacy endpoint: PFS by HER2 status per cohort

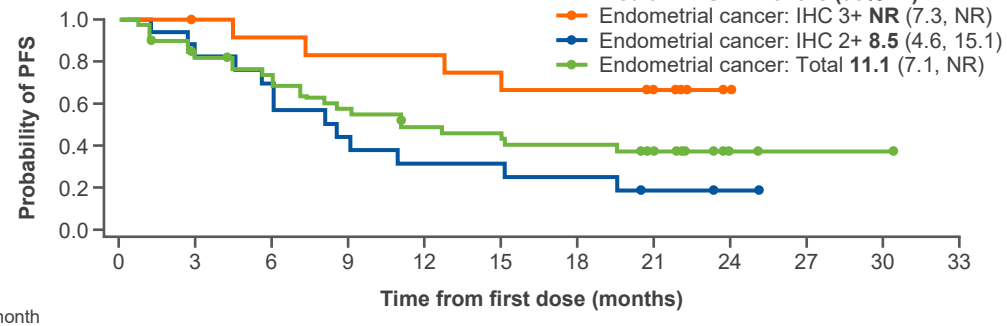
All cohorts



Number at risk, month

All cohorts: IHC 3+	75	63	51	39	34	23	19	12	1	0	
All cohorts: IHC 2+	125	78	50	31	20	18	13	9	3	1	0
All cohorts: Total	267	185	132	89	68	51	39	25	6	2	1	0

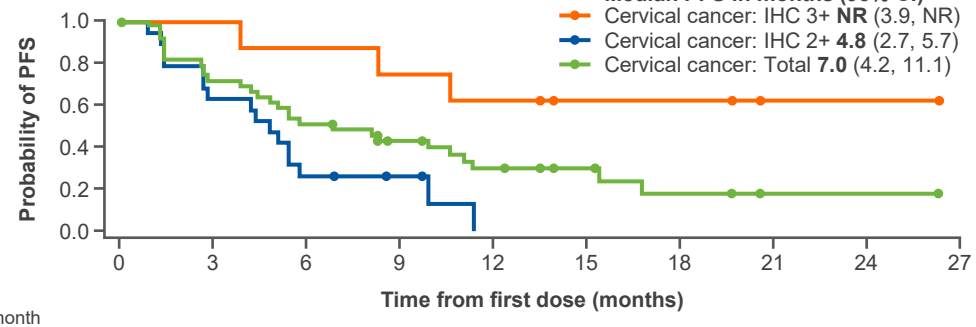
Endometrial cancer



Number at risk, month

Endometrial cancer: IHC 3+	13	12	11	10	10	9	8	5	0		
Endometrial cancer: IHC 2+	17	14	11	7	5	5	4	2	1	0	
Endometrial cancer: Total	40	31	27	21	17	16	14	8	2	1	1	0

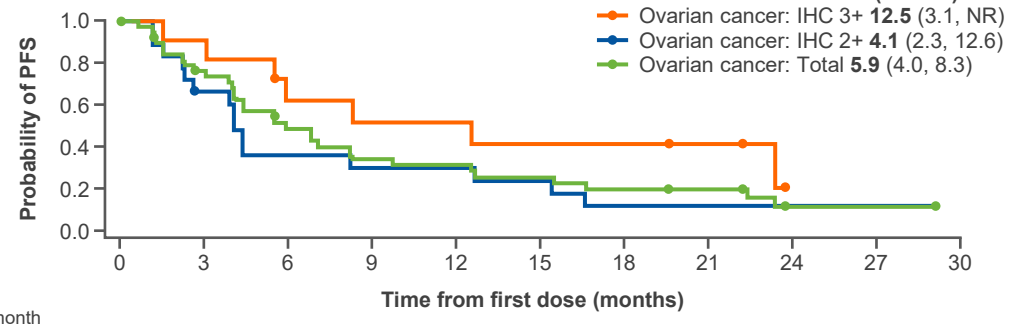
Cervical cancer



Number at risk, month

Cervical cancer: IHC 3+	8	8	7	6	5	3	3	1	1	0
Cervical cancer: IHC 2+	20	12	5	3	0					
Cervical cancer: Total	40	28	20	14	9	6	3	1	1	0

Ovarian cancer



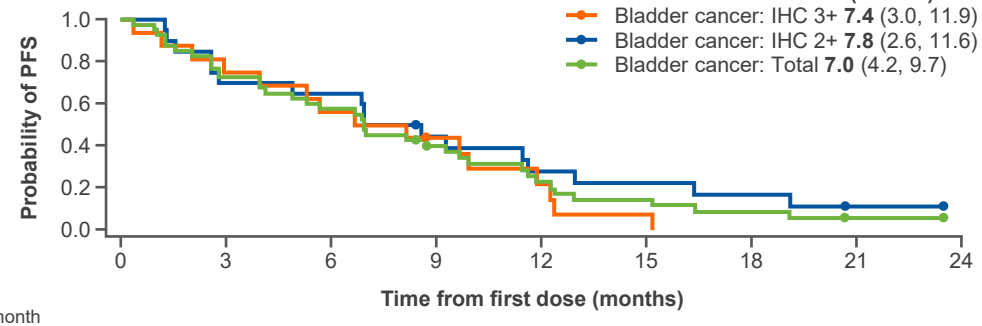
Number at risk, month

Ovarian cancer: IHC 3+	11	10	6	5	5	4	4	3	0		
Ovarian cancer: IHC 2+	19	11	6	5	5	4	2	2	1	1	0
Ovarian cancer: Total	40	28	17	12	11	9	7	6	1	1	0

Circle indicates a censored observation
CI, confidence interval; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NR, not reached; PFS, progression-free survival

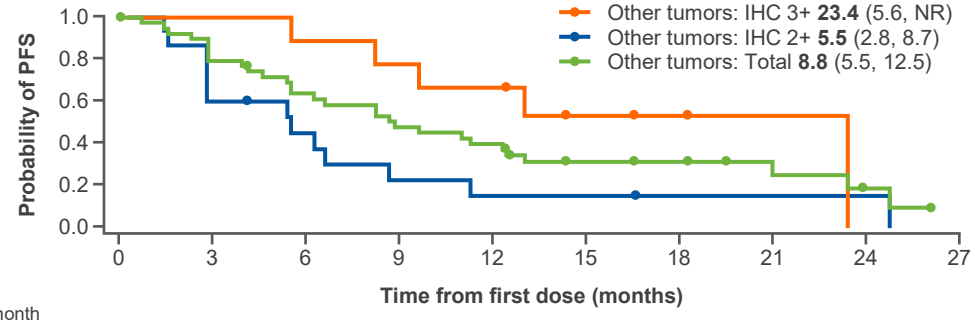
Efficacy endpoint: PFS by HER2 status per cohort

Bladder cancer



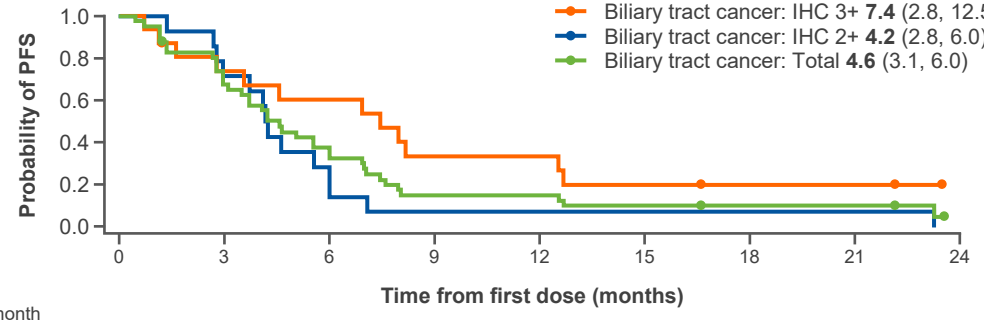
Number at risk, month									
Bladder cancer: IHC 3+	16	12	9	6	3	1	0		
Bladder cancer: IHC 2+	20	14	13	8	5	4	3	1	0
Bladder cancer: Total	41	29	23	14	8	5	3	1	0

Other tumors



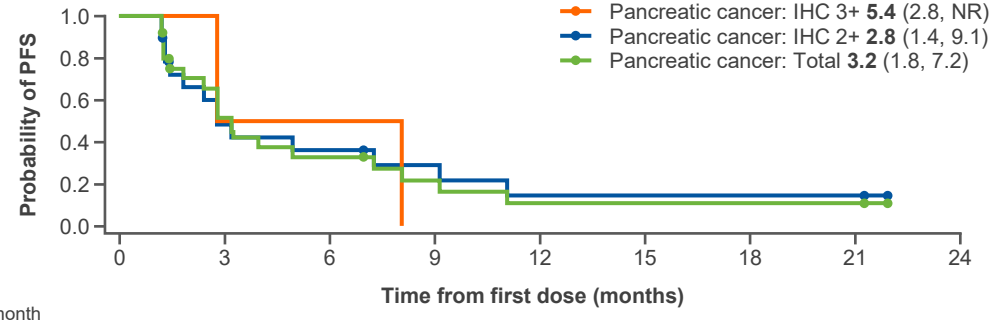
Number at risk, month										
Other tumors: IHC 3+	9	9	8	7	6	3	2	1	0	
Other tumors: IHC 2+	16	9	6	3	2	2	1	1	1	0
Other tumors: Total	40	31	24	18	15	9	7	4	2	0

Biliary tract cancer



Number at risk, month									
Biliary tract cancer: IHC 3+	16	11	9	5	5	3	2	2	0
Biliary tract cancer: IHC 2+	14	10	3	1	1	1	1	1	0
Biliary tract cancer: Total	41	27	14	6	6	4	3	3	0

Pancreatic cancer

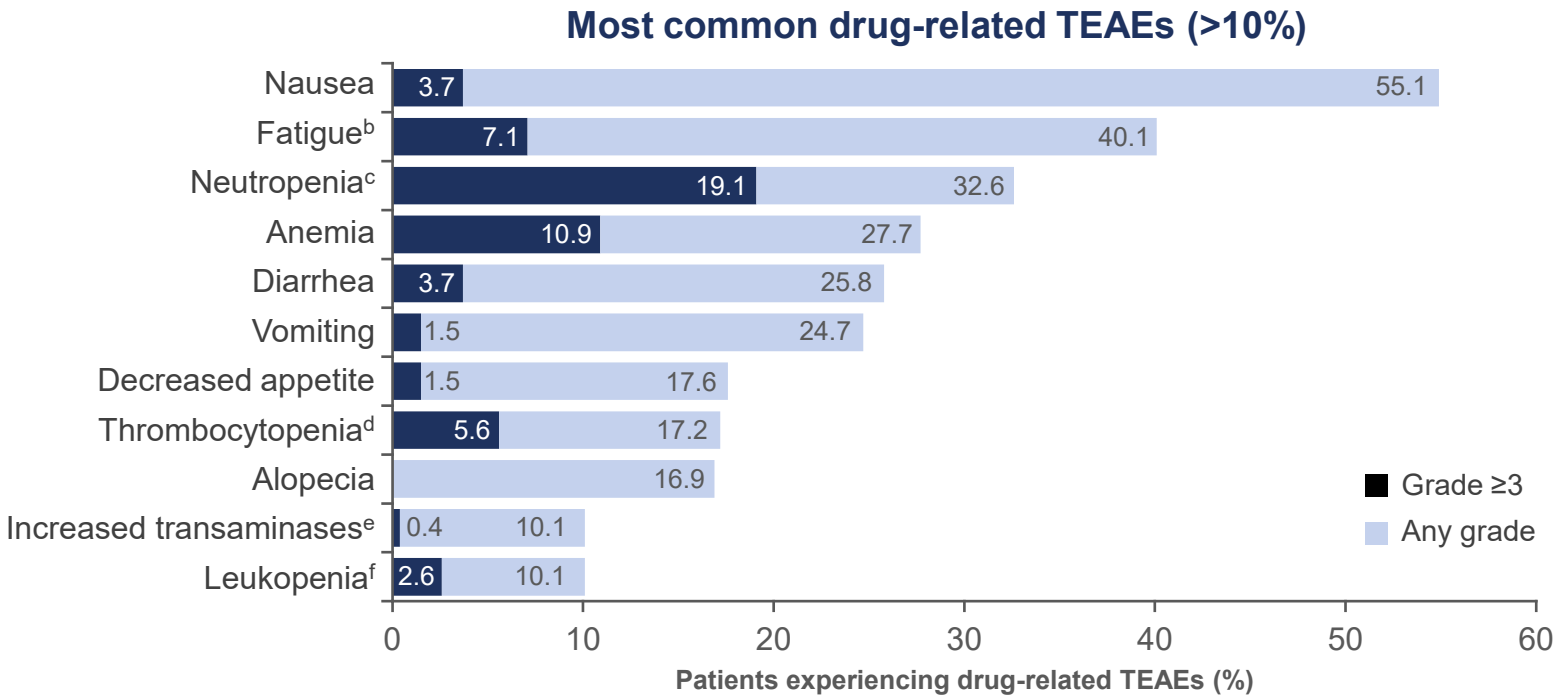


Number at risk, month									
Pancreatic cancer: IHC 3+	2	1	1	0					
Pancreatic cancer: IHC 2+	19	8	6	4	2	2	2	2	0
Pancreatic cancer: Total	25	11	7	4	2	2	2	2	0

Circle indicates a censored observation
CI, confidence interval; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NR, not reached; PFS, progression-free survival

Safety summary

n (%)	All patients (N=267)
Any drug-related TEAEs	226 (84.6)
Drug-related TEAEs Grade ≥3	109 (40.8)
Serious drug-related TEAEs	36 (13.5)
Drug-related TEAEs associated with dose discontinuations	23 (8.6)
Drug-related TEAEs associated with dose interruptions	54 (20.2)
Drug-related TEAEs associated with dose reductions	54 (20.2)
Drug-related TEAEs associated with deaths	4 (1.5)[a]



ILD/pneumonitis adjudicated as T-DXd related, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
All patients (N=267)	7 (2.6)	17 (6.4)	1 (0.4)	0	3 (1.1)	28 (10.5)

Analyses were performed in patients who received ≥1 dose of T-DXd (N=267); median total treatment duration 5.6 months (range 0.4–31.1)
[a]Included pneumonia (n=1), organizing pneumonia (n=1), pneumonitis (n=1), and neutropenic sepsis (n=1); [b]category includes the preferred terms fatigue, asthenia, and malaise; [c]category includes the preferred terms neutrophil count decreased and neutropenia; [d]category includes the preferred terms platelet count decreased and thrombocytopenia; [e]category includes the preferred terms aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, hypertransaminasemia; [f]category includes the preferred terms white blood cell count decreased and leukopenia
ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event

Conclusions

The robust response rates and survival outcomes are encouraging and were observed across tumor types in heavily pretreated patients

T-DXd demonstrated clinically meaningful activity across a broad range of HER2-expressing solid tumors:

- **ORR:** 37.1% in all patients and 61.3% in patients with IHC 3+
- **Durable responses:** median DOR 11.3 months in all patients and 22.1 months in patients with IHC 3+

Durable responses led to clinically meaningful progression-free and overall survival outcomes:

- **PFS:** 6.9 months in all patients and 11.9 months in patients with IHC 3+
- **OS:** 13.4 months in all patients and 21.1 months in patients with IHC 3+

The safety of T-DXd was consistent with the known profile

DESTINY-PanTumor02 supports the potential role of T-DXd as a tumor-agnostic therapy for patients with HER2-expressing solid tumors

DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

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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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DOI https://doi.org/10.1200/JCO.23.02005

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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View Online Article

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

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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