Poster F6

Trastuzumab deruxtecan in pretreated patients with HER2-expressing bladder cancer: final results from the bladder cancer cohort in Part 1 of DESTINY-PanTumor02

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Objectives

- To present subgroup analyses in the bladder cancer cohort from the final analysis of Part 1 of the DESTINY-PanTumor02 study, evaluating trastuzumab deruxtecan (T-DXd) in patients with human epidermal growth factor receptor 2 (HER2)-expressing, locally advanced, metastatic, or unresectable solid tumors

Conclusions

- Consistent with the primary analysis,[1] T-DXd continued to show durable and clinically meaningful antitumor activity in patients with HER2-expressing (immunohistochemistry [IHC] 3+/2+) bladder cancer, with the greatest benefit demonstrated in patients with HER2 IHC 3+ tumors
  - Responses were observed in patients regardless of local or central HER2 IHC testing, prior therapy received, and tumoral biomarker status
  - With extended follow up, safety remained consistent with the known profile of T-DXd, with no new safety signals observed compared with the primary analysis[1]
- These results reinforce T-DXd as a treatment option for pretreated patients with advanced HER2-positive (IHC 3+) bladder cancer

Plain language summary

Why did we perform this research?

Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate, which is a chemotherapy with a linker (together called deruxtecan) joined to an antibody (trastuzumab). T-DXd binds to human epidermal growth factor receptor 2 (HER2) on the surface of cancer cells. Once inside the cell, it releases the chemotherapy to kill these cells.[1,2] Based, in part, on the primary analysis (the main planned assessment of the data) of Part 1 of the DESTINY-PanTumor02 study,[3] T-DXd is approved in multiple countries for the treatment of people with solid tumors that have the highest level of HER2 (HER2-positive, also known as immunohistochemistry [IHC] 3+) that have spread or cannot be completely removed by surgery and who have received prior systemic treatment and/or have no satisfactory alternative treatment options available.[4–6] A final analysis (the last assessment of the data) of Part 1 of the DESTINY-PanTumor02 study was planned to further evaluate the benefit of T-DXd for people with tumors that have high levels of HER2; this analysis focuses on the benefit of T-DXd in people with bladder cancer (a type of solid tumor) from this study.

How did we perform this research?

This analysis looked at people with HER2-expressing (known as IHC 3+ or IHC 2+) bladder cancer that had spread or could not be completely removed by surgery and who had received prior systemic treatment or had no satisfactory alternative treatment options. Participants had received T-DXd in Part 1 of the DESTINY-PanTumor02 study.

What were the findings of this research?

Overall, 17 of 41 participants (41.5%) with bladder cancer had a response to T-DXd (ie their tumors reduced in size); nine out of the 16 participants with HER2 IHC 3+ tumors based on central testing (HER2 testing was completed in one specialized laboratory) had a response. Responses were seen in participants across all subgroups assessed. The most common (observed in >5% of participants) severe side effects (Grade 3 or higher) associated with T-DXd were neutropenia (reduced neutrophil count leading to neutropenia; 14.6%), fewer red blood cells leading to anemia (12.2%), and fewer neutrophils (7.3%). The side effects observed were consistent with those expected in people receiving T-DXd, and no new safety concerns were reported.

What are the implications of this research?

These results further support T-DXd as a treatment for people with HER2-positive (IHC 3+) bladder cancer that has spread or cannot be completely removed by surgery and who have received prior systemic treatment and/or have no satisfactory alternative treatment options.

Where can I access more information?

For more information about DESTINY-PanTumor02, please visit https://www.clinicaltrials.gov/study/NCT04482309. You can also speak to your doctor about this and other clinical studies.

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Poster

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Introduction

- T-DXd, a HER2-directed antibody-drug conjugate, is approved for HER2-positive, HER2-low, and HER2-ultralow breast cancer, HER2-positive gastric or gastroesophageal junction adenocarcinoma, and *HER2*-mutant non-small cell lung cancer[2–5]
- In the DESTINY-PanTumor02 Part 1 (NCT04482309) primary analysis (data cutoff June 8, 2023), T-DXd showed clinically meaningful antitumor activity in patients with HER2-expressing tumors, with an investigator-assessed objective response rate (ORR) of 37.1%[1]
  - In the bladder cancer cohort, the overall ORR was 39.0%, with rates of 56.3% and 35.0% in patients with HER2 IHC 3+ and IHC 2+ tumors, respectively[1]
  - These results contributed to the approval of T-DXd in multiple countries for patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior treatment and/or have no satisfactory alternative therapies[2–4]
- Findings from the DESTINY-PanTumor02 Part 1 final analysis, including an overall ORR of 37.5%, were consistent with the primary results[6]
- Here, we report the final subgroup analyses in the DESTINY-PanTumor02 Part 1 bladder cancer cohort (urothelial carcinoma, including transitional cell carcinoma of the renal pelvis, ureter, urinary bladder, or urethra)

Methods

Patient population

- Adults with histologically confirmed, locally advanced, metastatic, or unresectable solid tumors (excluding breast, colorectal, gastric, and non-small cell lung cancer)
- Disease progression following ≥1 prior systemic treatment or without alternative treatment options; prior HER2-directed therapy was allowed
- HER2-expressing tumors with IHC 3+/2+ scored using current American Society of Clinical Oncology / College of American Pathology (ASCO/CAP) guidelines for scoring in HER2 gastric cancer[7]
- HER2 expression at enrollment was based on local testing; however, if local testing was not available, enrollment was determined by central HER2 testing (HercepTest [DAKO])
  - Retrospective central HER2 testing was performed for patients enrolled based on a local HER2 test result

Study type

Open label, multicenter, multicohort, Phase 2

Treatment

T-DXd 5.4 mg/kg Q3W IV

Trial registration

NCT04482309

Final analysis data cutoff

October 10, 2024*

Endpoints

Primary
- Confirmed ORR†

Secondary
- DOR†
- DCR†
- PFS†
- OS
- Safety and tolerability

Exploratory
- Subgroup analyses by HER2 status
- Subgroup analyses by biomarker status

Cohorts

- Endometrial
- Cervical
- Ovarian
- Bladder
- Other tumors‡
- Biliary tract
- Pancreatic

*At data cutoff, 267 patients had received T-DXd across all tumor cohorts; †investigator-assessed per RECIST 1.1; ‡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). DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan

Results

- At final data cutoff (October 10, 2024), 41 patients with bladder cancer had received T-DXd
  - Two patients (4.9%) were ongoing treatment at data cutoff; the most common reason for treatment discontinuation was objective disease progression (65.9%)
- Of the 41 patients, 16 (39.0%) had HER2 IHC 3+ tumors and 20 (48.8%) had HER2 IHC 2+ tumors by central test result (**Table 1**)
- Median (range) follow up was 12.65 (0.4–42.9) months
- Median (range) duration of T-DXd exposure was 6.2 (0.4–40.8) months, and the median number of treatment cycles was 8.0 (14.6% of patients received ≥18 cycles [~12 months of treatment])

Table 1. Baseline demographics and clinical characteristics

		N=41
Age, median (range), years		67 (43–85)
Race, n (%)	White	25 (61.0)
	Asian	16 (39.0)
ECOG performance status, n (%)	0	19 (46.3)
	1	22 (53.7)
Primary tumor location, n (%)	Bladder	30 (73.2)
	Ureter	9 (22.0)
	Urethra	1 (2.4)
	Renal pelvis	1 (2.4)
HER2 IHC status at enrollment, n (%)*	IHC 3+	27 (65.9)
	IHC 2+	14 (34.1)
HER2 IHC status by central testing, n (%)†	IHC 3+	16 (39.0)
	IHC 2+	20 (48.8)
	IHC 1+	2 (4.9)
	IHC 0	2 (4.9)
Number of prior lines of therapy, n (%)‡	≤2	22 (53.7)
	>2	19 (46.3)
	Median (range)	2.0 (0–9)
Prior treatments received, n (%)	HER2 therapy	3 (7.3)
	Anti-PD-(L)1 therapy	28 (68.3)
	Cystectomy	17 (41.5)
PD-L1 IC prevalence, n (%)	≥1%	27 (65.9)
	<1%	11 (26.8)
	Unknown§	3 (7.3)
***FGFR1/2/3* mutation, n (%)¶**	Detected	8 (19.5)
	Not detected	33 (80.5)
***BRCA1/2* mutation, n (%)¶**	Detected	6 (14.6)
	Not detected	35 (85.4)

*HER2 expression for enrollment was based on local assessment (33/41; 80.5%), when available, otherwise enrollment was based on central testing; †one patient had unknown central IHC test result; ‡one patient had received no prior regimens; §data unknown owing to insufficient or no tumor tissue available, or technical problems; ¶evaluated in a central laboratory, as detected by ctDNA
BRCA, breast cancer susceptibility gene; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; *FGFR*, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; IC, immune cell; IHC, immunohistochemistry; PD-(L)1, programmed cell death (ligand) 1

Efficacy

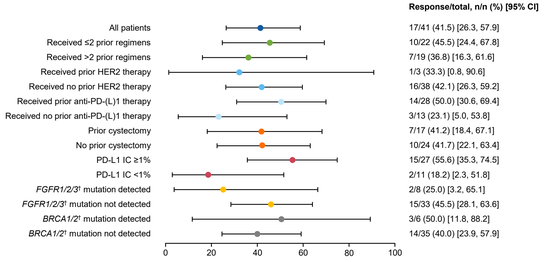
- Investigator-assessed ORR for all patients was 41.5% (**Table 2**)
  - The greatest benefit was observed in patients with HER2 IHC 3+ tumors by central testing; greater response rates were also seen in patients with HER2 IHC 3+ tumors than those with HER2 IHC 2+ tumors at enrollment
  - An additional patient had a partial response (HER2 IHC 2+ by central testing) by investigator assessment in this analysis compared with the primary analysis[5]
- Investigator-assessed objective responses were observed in patients across varied treatment backgrounds and tumoral biomarkers (**Figure 1**)

Table 2. Investigator-assessed ORR and best objective response by HER2 IHC status*

	All patients	HER2 IHC status by central testing		HER2 IHC status at enrollment†	
		IHC 3+	IHC 2+	IHC 3+	IHC 2+
n‡	41	16	20	27	14
Patients with an objective response, n (%) [95% CI]	17 (41.5) [26.3, 57.9]	9 (56.3) [29.9, 80.2]	8 (40.0) [19.1, 63.9]	12 (44.4) [25.5, 64.7]	5 (35.7) [12.8, 64.9]
Complete response, n (%)	1 (2.4)	1 (6.3)	0	1 (3.7)	0
Partial response, n (%)	16 (39.0)	8 (50.0)	8 (40.0)	11 (40.7)	5 (35.7)
Stable disease ≥5 weeks, n (%)	17 (41.5)	5 (31.3)	8 (40.0)	10 (37.0)	7 (50.0)
Progressive disease, n (%)§	7 (17.1)	2 (12.5)	4 (20.0)	5 (18.5)	2 (14.3)

*According to RECIST 1.1; †HER2 expression for enrollment was based on local assessment, when available, otherwise enrollment was based on central testing; ‡discrepancies in n numbers are owing to patients with central HER2 IHC status of 1+/0/unknown enrolled as IHC 3+/2+ by local testing; §includes RECIST-defined disease progression and death
CI, confidence interval; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumours

Figure 1. Investigator-assessed ORR in all patients and by subgroup*



*Responses by investigator assessment according to RECIST 1.1; †evaluated in a central laboratory, as detected by ctDNA. Prior therapy and biomarker subgroup analyses do not account for HER2 IHC status owing to small sample sizes. Error bars show 95% CI
BRCA, breast cancer susceptibility gene; CI, confidence interval; ctDNA, circulating tumor DNA; *FGFR*, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; IC, immune cell; IHC, immunohistochemistry; ORR, objective response rate; PD-(L)1, programmed cell death (ligand) 1; RECIST, Response Evaluation Criteria in Solid Tumours

- Overall, investigator-assessed median progression-free survival (PFS) and median overall survival were 7.0 months and 12.8 months, respectively (**Table 3**)
- Results by investigator assessment were consistent with those by independent central review (ICR):
  - Confirmed ORR (95% confidence interval [CI]) by ICR was 41.5% (26.3%, 57.9%)
  - Median PFS (95% CI) by ICR was 6.9 (5.6, 8.6) months

Table 3. Secondary efficacy endpoints by HER2 IHC status

	All patients	HER2 IHC status by central testing		HER2 IHC status at enrollment*	
		IHC 3+	IHC 2+	IHC 3+	IHC 2+
n†	41	16	20	27	14
Median DOR, months (95% CI)‡	9.5 (4.3, 11.8)	8.7 (2.8, 10.6)	10.3 (4.3, 17.8)	8.7 (4.1, 10.6)	11.8 (4.1, NE)
DCR at 12 weeks, % (95% CI)‡§	70.7 (54.5, 83.9)	75.0 (47.6, 92.7)	70.0 (45.7, 88.1)	70.4 (49.8, 86.2)	71.4 (41.9, 91.6)
Median PFS, months (95% CI)‡	7.0 (4.2, 9.7)	7.4 (3.0, 11.9)	7.8 (2.6, 11.6)	7.0 (3.9, 11.5)	7.0 (2.6, 13.0)
Median OS, months (95% CI)	12.8 (11.2, 15.1)	13.4 (6.7, 19.8)	13.1 (11.0, 19.9)	12.6 (6.7, 17.2)	13.5 (8.0, 19.9)

*HER2 expression for enrollment was based on local assessment, when available, otherwise enrollment was based on central testing; †discrepancies in n numbers are owing to patients with central HER2 IHC status of 1+/0/unknown enrolled as IHC 3+/2+ by local testing; ‡investigator-assessed per RECIST 1.1; §confirmed complete or partial response or with stable disease for ≥11 weeks after first dose
CI, confidence interval; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NE, not evaluable; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours

Safety

- Drug-related Grade ≥3 adverse events (AEs) occurred in 17 patients (41.5%) (**Table 4**)
  - The most common (>5%) Grade ≥3 drug-related AEs were neutropenia (14.6%), anemia (12.2%), and neutrophil count decreased (7.3%)
- Adjudicated drug-related interstitial lung disease / pneumonitis occurred in four patients (9.8%); all events were low grade (Grade 1: n=1; Grade 2: n=3)

Table 4. Safety summary

AE category, n (%)	N=41
Any AE	41 (100)
Any drug-related AE	38 (92.7)
Grade ≥3	17 (41.5)
Drug-related serious AEs	4 (9.8)
Drug-related AEs associated with dose interruptions	12 (29.3)
Drug-related AEs associated with dose reductions	6 (14.6)
Drug-related AEs associated with drug discontinuations	4 (9.8)
Drug-related AEs associated with deaths	1 (2.4)

Drug-related AEs refer to those possibly related to study drug as assessed by investigator; analyses included all patients who received ≥1 dose of T-DXd (n=41); median (range) total treatment duration was 6.2 (0.4–40.8) months
AE, adverse event; T-DXd, trastuzumab deruxtecanmedian (range) total treatment duration was 6.2 (0.4–40.8) months

Limitations

- It was not possible to include a comparator arm given the range of tumor types included
- The small sample sizes within each of the subgroups assessed limit interpretation
- ASCO/CAP guidelines[7] for scoring HER2 for gastric cancer were utilized, per study protocol; however, these are not specific to bladder cancer

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Disclosures

Dr Kyung Hae Jung reports a consulting/advisory role for AstraZeneca, Bixink, Celgene, Daewoong Pharmaceutical, Daiichi Sankyo, Eisai, Everest Medicine, Gilead Sciences, ImmuneOncia, Merck, MSD, Novartis, Pfizer, Roche, and Takeda.

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