Poster 4565

Trastuzumab deruxtecan in patients with HER2-expressing bladder cancer: outcomes from DESTINY-PanTumor02

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Objectives

- Evaluate subgroup analyses in the bladder cancer cohort (urothelial carcinoma including transitional cell carcinoma of the renal pelvis, ureter, urinary bladder, or urethra) from the DESTINY-PanTumor02 study
- Characterize patients who achieved an objective response (OR) in the bladder cancer cohort from the DESTINY-PanTumor02 study

Conclusions

- Trastuzumab deruxtecan (T-DXd) demonstrated clinically meaningful benefit in pretreated patients with human epidermal growth factor receptor 2 (HER2)-expressing bladder tumors in DESTINY-PanTumor02
  - 16/41 (39.0%) patients had a confirmed OR by investigator
  - The greatest response was seen in patients with immunohistochemistry (IHC) 3+ tumors (central testing)
  - Durable responses were observed, with a median duration of response (DOR) of 8.7 months in all patients
- The safety findings were consistent with the established profile for T-DXd
  - The most common Grade ≥3 drug-related treatment-emergent adverse events (TEAEs) (>5%) were neutropenia, anemia, and decreased neutrophil count
  - Interstitial lung disease (ILD) / pneumonitis remains an important identified risk; proactive monitoring, early detection, and active management are critical in preventing high-grade ILD / pneumonitis
- These data support T-DXd as a recommended treatment option for pretreated patients with HER2 IHC 3+ expressing bladder cancer, and as a potential treatment option in patients with HER2 IHC 2+ expression

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 (deruxtecan) joined to an antibody (trastuzumab). Trastuzumab binds to a protein found on cancer cells called human epidermal growth factor receptor 2 (HER2), where it releases the chemotherapy to kill these cells.[1,2] Based partly on results from the DESTINY-PanTumor02 study, T-DXd is a recommended treatment in the USA for people with solid tumors that have higher-than-normal levels of HER2 (HER2-positive, also known as immunohistochemistry [IHC] 3+) and have spread or cannot be completely removed with surgery and who have received prior systemic treatment and have no satisfactory alternative treatment options available.[3] Further evaluation of people with bladder cancer (a type of solid tumor) who received T-DXd as part of the DESTINY-PanTumor02 study is needed.

How did we perform this research?
This analysis looked at people with HER2-expressing (IHC 3+ and IHC 2+) bladder cancer who had received prior systemic treatment or had no satisfactory alternative treatment options available and who received T-DXd as part of the DESTINY-PanTumor02 study.

What were the findings of this research?
Overall, 16 out of 41 participants with bladder cancer had a response to T-DXd (ie their tumor reduced in size); 9 out of 16 participants with IHC 3+ tumors had a response. Side effects were as expected for T-DXd. Severe side effects associated with T-DXd treatment that were observed in >5% of participants included a decrease in a type of blood cell called neutrophils leading to neutropenia (14.6%), fewer red blood cells leading to anemia (12.2%), and fewer neutrophils (7.3%).

What are the implications of this research?
These results support use of T-DXd as a treatment for people with HER2-positive (IHC 3+) bladder cancers that have spread or cannot be completely removed with surgery and who have received prior systemic treatment or have no satisfactory alternative treatment options available.

Where can I access more information?
For information about DESTINY-PanTumor02, please visit https://clinicaltrials.gov/study/NCT04482309, or see primary data published in the *Journal of Clinical Oncology* here. Please also reach out to Dr. Wysocki at piotr.wysocki@uj.edu.pl

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Introduction

- HER2 expression is seen in a wide range of solid tumors and is associated with a biologically aggressive phenotype[1–5]
- HER2-directed therapy is standard of care in HER2-expressing and HER2-low unresectable or metastatic breast cancer, HER2-positive unresectable or metastatic gastric and colorectal cancers, and gastroesophageal junction adenocarcinomas, and HER2-mutant non-small cell lung cancer (NSCLC)[6–10]
  - Other HER2-expressing solid tumors are associated with a poor prognosis, with limited treatment options available and many patients experiencing disease progression on standard therapies[11–14]
- In DESTINY-PanTumor02, T-DXd demonstrated clinically meaningful objective response rates (ORRs), progression-free survival (PFS), and overall survival (OS) in HER2-expressing solid tumors[15]
  - The greatest benefit was observed in patients with HER2 IHC 3+[15]
- In April 2024,T-DXd was granted accelerated approval in the USA for adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors that have progressed after prior treatment and have no alternative therapies[16]
- This poster reports further subgroup analyses from the DESTINY-PanTumor02 bladder cancer cohort, and characterizes patients with an OR

Bladder cancer: HER2 prevalence[3,17–20]

Methods

Patient population

- Aged ≥18 years
- Histologically confirmed locally advanced, unresectable, solid cancers (excluding breast, colorectal, gastric, and NSCLC)
- Progression after ≥1 prior systemic treatment or without alternative treatment options
- Prior HER2-directed therapy allowed
- HER2-expressing tumors with IHC 3+/2+ scored using current ASCO / College of American Pathology guidelines for scoring HER2 in gastric cancer (in situ hybridization testing not required)[21]
  - Patients were enrolled based on local HER2 IHC assessment, where available; otherwise, enrollment was based on central testing
  - HER2 IHC status was assessed centrally using HER2 HercepTest (DAKO) and scored according to gastric-specific criteria[21]
- Eastern Cooperative Oncology Group performance status: 0–1

Study type

Open label, multicenter, multicohort, Phase 2

Treatment

T-DXd 5.4 mg/kg IV Q3W (n≈40 per cohort*)

Trial registration

NCT04482309

Data cutoff

June 8, 2023

Endpoints

Primary:
- Confirmed ORR†

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

Exploratory:
- Subgroup analyses by HER2 status
- Subgroup analyses by biomarkers

Endometrial | Cervical | Ovarian | **Bladder** | Other tumors‡ | Biliary tract | Pancreatic

*Planned recruitment; cohorts with no objective responses in the first 15 patients were to be closed; †Confirmed ORR per RECIST 1.1, as assessed by investigator; ‡patients with tumors that express HER2 (IHC 3+ or 2+), excluding tumors in the tumor-specific cohorts, and breast cancer, NSCLC, gastric cancer, and colorectal cancer. DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IV, intravenous; NSCLC, non-small cell lung cancer; 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 and interpretation

- All 41 patients who were assigned to treatment received T-DXd (Table 1)
  - The most common reason for treatment discontinuation was objective disease progression (61.0%)
- Median (range) follow up was 12.65 (0.4–26.8) months

Table 1. Patient disposition

	Bladder cancer
Assigned to treatment, n	41
Treated, n	41
T-DXd treatment ongoing at data cutoff,* n (%)	4 (9.8)
Discontinued treatment at data cutoff,* n (%)	37 (90.2)
Objective disease progression	25 (61.0)
Adverse event	4 (9.8)
Patient decision	2 (4.9)
Investigator decision	1 (2.4)
Subjective disease progression	2 (4.9)
Other†	3 (7.3)
Median treatment cycles received,‡ (range)	8.0 (1–34)

*Data cutoff was June 8, 2023; †in case of death while on treatment, investigators did not specifically record a reason for discontinuation of T-DXd; ‡a treatment cycle was 21 days
T-DXd, trastuzumab deruxtecan

- Patients with a central HER2 IHC status of 1+/0/unknown were enrolled as HER2 IHC 3+/2+ by local testing, as per the eligibility criteria
- The patient population was heavily pretreated, with 27 (65.9%) patients having received ≥2 prior regimens (Table 2)
  - 28 (68.3%) patients had received prior immuno-oncology (IO) therapy
- 27 (65.9%) patients had a programmed cell death ligand 1 (PD-L1) immune cell (IC) status of ≥1% at baseline (Table 2)

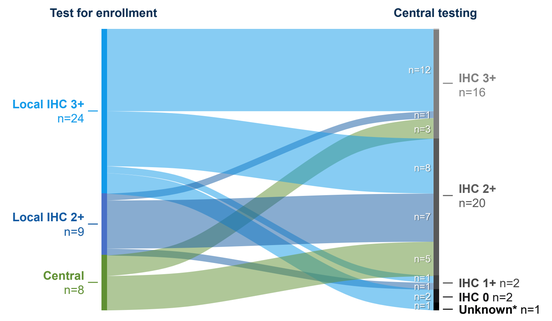
Table 2. Baseline demographics and clinical characteristics

Characteristic			Bladder cancer (n=41)
Age, median (range), years			67.0 (43–85)
Race, n (%)		White	25 (61.0)
		Asian	16 (39.0)
ECOG performance status, n (%)		0	19 (46.3)
		1	22 (53.7)
HER2 status by enrollment test, n (%)		IHC 3+	27 (65.9)
		IHC 2+	14 (34.1)
HER2 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)
		IHC unknown	1 (2.4)
Prior regimens*	Median (range)		2 (0–9)
	n (%)	≤1	14 (34.1)
		≥2	27 (65.9)
Prior IO therapy, n (%)			28 (68.3)
PD-L1 IC prevalence, n (%)		≥1%	27 (65.9)
		<1%	11 (26.8)
		Unknown†	3 (7.3)
FGFR1/2/3,‡§ n (%)		Mutation detected	8 (19.5)
		Mutation not detected	33 (80.5)
BRCA1/2,‡ n (%)		Mutation detected	6 (14.6)
		Mutation not detected	35 (85.4)

*One patient had received no prior regimens; †data unknown due to insufficient or no tumor tissue available, or technical problems; ‡evaluated in a central laboratory; as detected by ctDNA; §no FGFR4 mutations were detected
BRCA1/2, breast cancer susceptibility gene 1/2; 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; IO, immuno-oncology; PD-L1, programmed cell death ligand 1

- 33 (80.5%) and 8 (19.5%) patients were enrolled by local and central testing, respectively (Figure 1)
  - The local test for enrollment and central test had a positive percentage agreement of 52.2% for IHC 3+ and 77.8% for IHC 2+

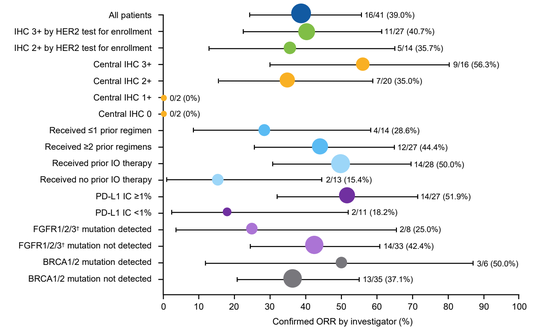
Figure 1. Agreement between local enrollment HER2 test and central HER2 test



Patients with a central HER2 IHC status of 1+/0/unknown were enrolled as HER2 IHC 3+/2+ by local testing, as per the eligibility criteria. Positive percentage agreement was defined as the percentage of samples classified with the same IHC score by both local and central testing; agreement was calculated excluding central IHC unknown samples. *Includes patients whose samples were not evaluable and may have included patients who did not provide a sample for central testing
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry

- The ORR for all patients was 39.0% and the response rate was greatest in the central HER2 IHC 3+ subgroup (Figure 2)
  - By HER2 test used for enrollment, ORR was 40.7% and 35.7% in the HER2 IHC 3+ and IHC 2+ subgroups, respectively
  - By central testing, ORR was 56.3% and 35.0% in the HER2 IHC 3+ and IHC 2+ subgroups, respectively
- 16 patients achieved an OR (Figure 2); of these:
  - 12 had received ≥2 prior regimens
  - 14 had received prior IO therapy
  - 14 had a PD-L1 IC prevalence of ≥1%
- Median PFS and OS for all patients were 7.0 and 12.8 months, respectively (Table 3)

Figure 2. ORR in all patients and by subgroup*



*Responses by investigator assessment according to RECIST 1.1; †no FGFR4 mutations were detected. Patients with central HER2 IHC status 0/unknown were enrolled as IHC 3+/2+ by local testing; one patient had a central IHC status unknown. Circle sizes are proportional to the number of patients in each subgroup. Prior therapy and biomarker subgroup analyses do not account for HER2 IHC status. Error bars show 95% CI
BRCA1/2, breast cancer susceptibility gene 1/2; CI, confidence interval; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; IC, immune cell; IHC, immunohistochemistry; IO, immuno-oncology; ORR, objective response rate; PD-L1, programmed cell death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumours

Table 3. Secondary efficacy endpoints (central HER2 IHC testing)

Characteristic	All patients	HER2 IHC 3+	HER2 IHC 2+	HER2 IHC 1+	HER2 IHC 0
n	41	16	20	2	2
Confirmed ORR, n (%) 95% CI	16 (39.0) 24.2, 55.5	9 (56.3) 29.9, 80.2	7 (35.0) 15.4, 59.2	0	0
Median DOR, months 95% CI	8.7 4.3, 11.8	8.7 2.8, 10.6	10.3 4.3, 17.8	–	–
Median PFS, months 95% CI	7.0 4.2, 9.7	7.4 3.0, 11.9	7.8 2.6, 11.6	5.5 4.0, NE	2.6 1.0, NE
Median OS, months 95% CI	12.8 11.2, 15.1	13.4 6.7, 19.8	13.1 11.0, 19.9	9.1 4.8, NE	3.0 1.0, 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	100 15.8, 100	50.0 1.3, 98.7

Confirmed ORR determined by investigator assessment according to RECIST 1.1; DOR defined as time from date of first documented response (complete or partial), until the date of documented progression or death in the absence of disease progression; PFS defined as time from first dose until date of objective disease progression or death due to any cause, regardless of discontinuation of treatment or receipt of another cancer therapy. OS defined as time from date of first dose until death due to any cause; DCR defined as percentage of patients with a best OR of confirmed complete response or partial response, or with stable disease for at least 11 weeks after first dose. Patients with a central HER2 IHC status of 0/unknown were enrolled as HER2 IHC 3+/2+ by local testing. CIs omitted where 0%
CI, confidence interval; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NE, not evaluable; OR, objective response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours

- Grade ≥3 drug-related TEAEs were experienced by 17 (41.5%) patients (Table 4)
  - The most common Grade ≥3 drug-related TEAEs (>5%) were neutropenia (14.6%), anemia (12.2%), and neutrophil count decreased (7.3%)
    - Neutropenia and neutrophil count decrease are listed separately owing to how events were coded based on reported terms (adverse event or laboratory abnormality)
- Adjudicated drug-related ILD/pneumonitis occurred in 4/41 (9.8%) patients (Grade 1: n=1; Grade 2: n=3)

Table 4. Safety summary

n (%)	All patients (n=41)
Any drug-related TEAEs	38 (92.7)
Drug-related TEAEs Grade ≥3	17 (41.5)
Serious drug-related TEAEs	4 (9.8)
Drug-related TEAEs associated with dose discontinuations	4 (9.8)
Drug-related TEAEs associated with dose interruptions	12 (29.3)
Drug-related TEAEs associated with dose reductions	6 (14.6)
Drug-related TEAEs associated with deaths	1 (2.4)

Analyses (by investigator) included patients who received ≥1 dose of T-DXd (n=41); median total treatment duration was 6.21 (range 0.4–24.7) months
TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan

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