Poster 6037

Trastuzumab deruxtecan in patients with HER2-expressing head and neck tumors: outcomes from DESTINY-PanTumor02

Funda Meric-Bernstam,[1] Seung Tae Kim,[2] Napa Parinyanitikul,[3] Alberto Moreno,[4] Chia-Chi Lin,[5] Dmitry Gornastolev,[6] Jarin Chindaprasirt,[7] Iwona Ługowska,[8] Daniil Stroyakovskiy,[9] Jacek Jassem,[10] Michelle Harrison,[11] Vikas Ostwal,[12] Flavia Michelini,[13] Lindsey Jung,[14] Nataliya Kuptsova-Clarkson,[14] Soham Puvvada,[14] Hui K Gan[15]

[1]University of Texas MD Anderson Cancer Center, Houston, TX, US; [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [3]King Chulalongkorn Memorial Hospital and Chulalongkorn University, Bangkok, Thailand; [4]Hospital Universitario Reina Sofía and IMIBIC, Córdoba, Spain; [5]National Taiwan University Hospital, Taipei, Taiwan; [6]Hadassah Medical Moscow, Oncology Department, Moscow, Russia; [7]Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand; [8]Early Phase Clinical Trials Unit, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [9]Moscow City Oncology Hospital No. 62, Moscow, Russia; [10]Medical University of Gdańsk, Gdańsk, Poland; [11]Chris O'Brien Lifehouse, Camperdown, Australia; [12]Tata Memorial Hospital, Mumbai, India; [13]AstraZeneca, Waltham, MA, US; [14]AstraZeneca, Gaithersburg, MD, US; [15]Austin Health, Heidelberg, Australia

Objectives

- Evaluate subgroup analyses in a subset of patients with head and neck cancers (most of which were salivary gland tumors previously included in the 'other tumor' cohort) from the DESTINY-PanTumor02 study
- Characterize patients with head and neck cancer who achieved an objective response (OR) in 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 head and neck tumors in DESTINY-PanTumor02
  - 10/24 (41.7%; salivary gland: n=8; squamous cell carcinoma: n=1; lacrimal gland: n=1) patients had a confirmed OR by investigator
  - Durable responses were observed, with a median duration of response (DOR) of 22.1 months in all patients
  - Durable responses led to clinically meaningful progression-free and overall survival outcomes
- The safety findings were consistent with the established profile for T-DXd
  - The most common drug-related Grade ≥3 treatment-emergent adverse events (TEAEs) were fatigue, lymphocyte count decreased, anemia, neutropenia, neutrophil count decreased, and vomiting
  - 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 head and neck cancer, and may warrant further exploration in tumors with other HER2 expression levels

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 head and neck 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+) head and neck 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, 10 out of 24 participants with head and neck cancer had a response to T-DXd (ie reduction in tumor size); 4 out of 7 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 fatigue (12.5%), a decrease in certain types of blood cells called lymphocytes (12.5%), a decrease in another type of blood cell called neutrophils leading to neutropenia (8.3%), fewer red blood cells leading to anemia (8.3%), and vomiting (8.3%).

What are the implications of this research?
These results support use of T-DXd as a treatment for people with HER2-positive (IHC 3+) head and neck cancers that have spread or cannot be completely removed with surgery and who have received prior systemic treatment and 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. Meric-Bernstam at fmeric@mdanderson.org.

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Poster | Narrated poster video

This study was supported by and sponsored by AstraZeneca in collaboration with Daiichi Sankyo. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201)
Presented at ASCO 2024, May 31–June 4, Chicago, IL, US by Dr. Funda Meric-Bernstam. Corresponding author email address: fmeric@mdanderson.org

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 for patients with head and neck cancer who were retrospectively identified from the 'other tumor' cohort of the DESTINY-PanTumor02 study

Head and neck cancer: HER2 prevalence[3,17,18]

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)[19]
  - 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[19]
- 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 ORs in the first 15 centrally confirmed 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; 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

- 24 patients with head and neck cancer were assigned to treatment and received T-DXd (Table 1)
  - The most common reason for treatment discontinuation was objective disease progression (41.7%)
- Median (range) follow up was 20.80 (4.7–31.6) months

Table 1. Patient disposition

		Head and neck cancer
Assigned to treatment, n		24
Treated, n		24
T-DXd treatment ongoing at data cutoff,* n (%)		4 (16.7)
Discontinued treatment at data cutoff,* n (%)	Objective disease progression	10 (41.7)
	Adverse event	5 (20.8)
	Subjective disease progression	2 (8.3)
	Other†	2 (8.3)
	Patient decision	1 (4.2)
Median treatment cycles received,‡ (range)		14.5 (2–33)

*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 and these are included under 'other' (one death); ‡a treatment cycle was 21 days
T-DXd, trastuzumab deruxtecan

- For the 24 patients who received treatment, primary tumor sites were salivary gland (n=19), squamous cell carcinoma (n=3), adenoid cystic carcinoma (n=1), and lacrimal gland (n=1)
- Four patients were enrolled with HER2 IHC 3+/2+ by local testing per the eligibility criteria and had a central HER2 IHC status of 0, and 7 patients had an unknown central HER2 IHC status
- The patient population was heavily pretreated, with 15 (62.5%) patients having received ≥2 prior regimens (Table 2)
  - 20 (83.3%) patients had received prior radiation therapy
- 11 (45.8%) patients had a programmed cell death ligand 1 (PD-L1) immune cell (IC) status of ≥1% at baseline (Table 2)

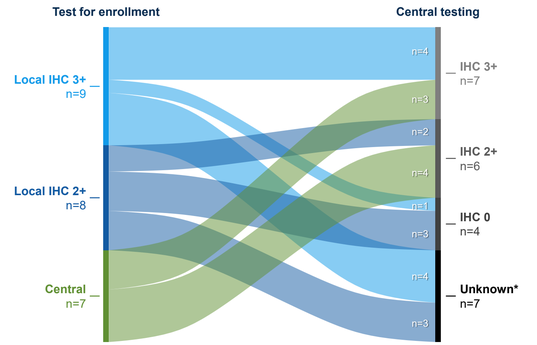
Table 2. Baseline demographics and clinical characteristics

Characteristic			Head and neck cancer (n=24)
Age, median (range), years			56.5 (38–81)
Race, n (%)		White	16 (66.7)
		Asian	5 (20.8)
		Other	2 (8.3)
		Not reported	1 (4.2)
ECOG performance status, n (%)		0	10 (41.7)
		1	14 (58.3)
HER2 status by enrollment test, n (%)		IHC 3+	12 (50.0)
		IHC 2+	12 (50.0)
HER2 status by central testing, n (%)		IHC 3+	7 (29.2)
		IHC 2+	6 (25.0)
		IHC 1+	0
		IHC 0	4 (16.7)
		IHC unknown	7 (29.2)
Prior regimens*	Median (range)		2 (0–8)
	n (%)	≤1	9 (37.5)
		≥2	15 (62.5)
Prior HER2 therapy, n (%)			9 (37.5)
Prior radiation therapy, n (%)			20 (83.3)
PD-L1 IC prevalence, n (%)		≥1%	11 (45.8)
		<1%	6 (25.0)
		Unknown†	7 (29.2)

*One patient had received no prior regimens; †data unknown due to insufficient or no tumor tissue available, or technical problems
ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IC, immune cell; IHC, immunohistochemistry; PD-L1, programmed cell death ligand 1

- 17 (70.8%) and 7 (29.2%) 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 80.0% for IHC 3+ and 40.0% for IHC 2+

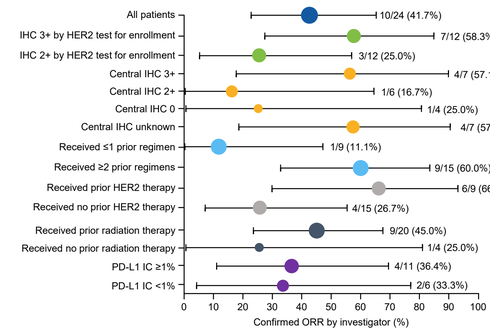
Figure 1. Agreement between local enrollment HER2 test and central HER2 test



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 41.7% (Figure 2; tumor types: salivary gland [n=8], squamous cell carcinoma [n=1], and lacrimal gland [n=1])
  - By the HER2 test used for enrollment, ORR was 58.3% and 25.0% in the HER2 IHC 3+ and IHC 2+ subgroups, respectively
  - By central testing, ORR was 57.1% and 16.7% in the HER2 IHC 3+ and IHC 2+ subgroups, respectively
- Median DOR for all patients was 22.1 months (Table 3)
- Median PFS and OS for all patients were 12.4 months and 23.0 months, respectively (Table 3)

Figure 2. ORR in all patients and by subgroup*



*Response determined by investigator assessment according to RECIST 1.1. Patients with a central HER2 IHC status of 0/unknown were enrolled as HER2 IHC 3+/2+ by local testing. 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
HER2, human epidermal growth factor receptor 2; IC, immune cell; IHC, immunohistochemistry; ORR, objective response rate; PD-L1, programmed cell death ligand 1

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

Characteristic	All patients	HER2 IHC 3+	HER2 IHC 2+	HER2 IHC 0	HER2 unknown
n	24	7	6	4	7
Confirmed ORR, n (%) 95% CI	10 (41.7) 22.1, 63.1	4 (57.1) 18.4, 90.1	1 (16.7) 0.4, 64.1	1 (25.0) 0.6, 80.6	4 (57.1) 18.4, 90.1
Median DOR, months 95% CI	22.1 2.8, NE	22.1 4.1, NE	2.8	NR	NR 10.9, NE
Median PFS, months 95% CI	12.4 8.7, 23.4	23.4 9.7, NE	7.1 2.9, NE	6.5 4.2, NE	12.5 8.8, NE
Median OS, months 95% CI	23.0 20.2, NE	NR 23.4, NE	20.2 9.6, NE	17.7 4.7, NE	NR 11.5, NE
DCR at 12 weeks, % 95% CI	87.5 67.6, 97.3	100 59.0, 100	66.7 22.3, 95.7	75.0 19.4, 99.4	100 59.0, 100

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 n<1
CI, confidence interval; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NE, not evaluable; NR, not reached; 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 10 (41.7%) patients (Table 4)
  - The most common Grade ≥3 drug-related TEAEs (>5%) were fatigue (12.5%), lymphocyte count decreased (12.5%), anemia (8.3%), neutropenia (8.3%), neutrophil count decreased (8.3%), and vomiting (8.3%)
    - Neutropenia and neutrophil count decrease are listed separately owing to how these events were coded based on reported terms (adverse event or laboratory abnormality)
- Adjudicated drug-related ILD / pneumonitis occurred in 3/24 (12.5%) patients (Grade 1: n=1; Grade 2: n=1; Grade 5: n=1)

Table 4. Safety summary

n (%)	All patients (n=24)
Any drug-related TEAEs	22 (91.7)
Drug-related TEAEs Grade ≥3	10 (41.7)
Serious drug-related TEAEs	4 (16.7)
Drug-related TEAEs associated with dose discontinuations	5 (20.8)
Drug-related TEAEs associated with dose interruptions	8 (33.3)
Drug-related TEAEs associated with dose reductions	4 (16.7)
Drug-related TEAEs associated with deaths	1 (4.2)

Analyses (by investigator) included patients who received ≥1 dose of T-DXd (n=24); median total treatment duration was 10.3 months (range 1.4–23.4)
TEAE, treatment-emergent adverse event

Acknowledgments

- Thank you to the patients and their caregivers for their participation, and the study site staff for their contributions
- The authors would also like to thank members of the interstitial lung disease adjudication committee
- This study was supported by and sponsored by AstraZeneca in collaboration with Daiichi Sankyo
- Under the guidance of the authors and in accordance with Good Publication Practice, medical writing and editorial support was provided by Neil Patel, MSc, of Helios Medical Communications, part of Helios Global Group, and was funded by AstraZeneca

Disclosures – Dr. Funda Meric-Bernstam

Consulting for AbbVie Inc., Aduro BioTech Inc., Alkermes, AstraZeneca, Black Diamond Therapeutics, Calibr (a division of Scripps Research), Daiichi Sankyo Co., Debiopharm International, EcoR1 Capital, eFFECTOR Therapeutics, F. Hoffmann-La Roche, GT Apeiron Therapeutics, Genentech Inc., Harbinger Health, IBM Watson, Infinity Pharmaceuticals Inc., Jackson Laboratory, Kolon Life Science Inc., LegoChem Bio, Lengo Therapeutics Inc., Loxo Oncology Inc., Menarini Group, OnCusp Therapeutics, OrigiMed, PACT Pharma Inc, Parexel International, Pfizer Inc., Protai Bio, Samsung Bioepis Co., Seagen Inc., Tallac Therapeutics Inc., Tyra Biosciences Inc., Xencor Inc., Zymeworks Inc. Data **Safety Monitoring Boards or Advisory Boards** for Black Diamond Therapeutics, Biovica International AB, Eisai Co., FogPharma, Immunomedics, Inflection Biosciences, Karyopharm Therapeutics, Loxo Oncology Inc., Mersana Therapeutics Inc., OnCusp Therapeutics, Puma Biotechnology Inc., Protai Bio, Sanofi, Seagen Inc., Silverback Therapeutics, Spectrum Pharmaceuticals Inc., Theratechnologies Inc., Zentalis Pharmaceuticals. **Investigator** for Aileron Therapeutics, AstraZeneca, Bayer Healthcare, Calithera Biosciences Inc., Curis Inc., CytomX Therapeutics Inc., Daiichi Sankyo Co., Debiopharm International, eFFECTOR Therapeutics, Genentech, Guardant Health, Klus Pharma, Novartis,Taiho Pharmaceutical Co. **Research grants** for Aileron Therapeutics, AstraZeneca, Bayer Healthcare, Calithera Biosciences Inc., Curis Inc., CytomX Therapeutics Inc., Daiichi Sankyo Co., Debiopharm International, eFFECTOR Therapeutics, Genentech Inc., Guardant Health Inc., KLUS Pharma Inc., Puma Biotechnology Inc., Takeda Pharmaceutical Co., Taiho Pharmaceutical Co., Repare Therapeutics. **Travel support** from European Organisation for Research and Treatment of Cancer, European Society for Medical Oncology, Cholangiocarcinoma Foundation

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