Poster CT248

Trastuzumab deruxtecan in Chinese patients with previously treated HER2 mutant non-small cell lung cancer: primary analysis from the Phase 2 DESTINY-Lung05 trial

Ying Cheng,[1] Lin Wu,[2] Yong Fang,[3] Yun Fan,[4] Xingya Li,[5] Mingjun Zhang,[6] Yan Yu,[7] Yu Yao,[8] Ruilian Xu,[9] Jun Guo,[10] Huaping Yang,[11] Jian Fang,[12] Feng Luo,[13,14] Xuhong Min,[15] Ke-jing Tang,[16] Jie Hu,[17] Yunru Chen,[18] Victor Zhang,[19] Jingyi Li,[20] Dairong Li[21]

[1]Medical Oncology, Jilin Cancer Hospital, Changchun, China; [2]2nd Department of Thoracic Medicine, Hunan Cancer Hospital, Changsha, China; [3]Medical Oncology, Sir Run Run Shaw Hospital School of Medicine, Hangzhou, Zhejiang University, China; [4]Department of Medical Thoracic Tumors, Zhejiang Cancer Hospital, Hangzhou, China; [5]Oncology Department 2nd Ward, The First Affiliated Hospital of Zhengzhou University, China; [6]Oncology Department, The Second Hospital of Anhui Medical University, Hefei, China; [7]3rd Respiratory Medicine, Harbin Medical University Cancer Hospital, China; [8]Medical Oncology, The First Affiliated Hospital of Xi'an Jiaotong University, China; [9]Medical Oncology, Shenzhen People's Hospital, China; [10]1st Respiratory Medicine, Shandong Cancer Hospital , Jinan, China; [11]Department of Pulmonary and Critical Care Medicine, Xiangya Hospital Central South University, Changsha, China; [12]2nd Department of Thoracic Medicine, Beijing Cancer Hospital, China; [13]Department of Medical Oncology, Lung Cancer Center, West China Hospital Affiliated to Sichuan University, Chengdu, China; [14]Lung Cancer Center, West China Hospital, Sichuan University, Chengdu, China; [15]Neoplasm Radiotherapy Department, Anhui Chest Hospital, Hefei, China; [16]Department of Pulmonary and Critical Care Medicine, The First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China; [17]Department of Pulmonary and Critical Care Medicine, Shanghai Geriatric Center, Zhongshan Hospital, Fudan University, China; [18]AstraZeneca, Shanghai, China; [19]Biometrics Department, AstraZeneca, Shanghai, China; [20]AstraZeneca, Gaithersburg, MD, US; [21]Department of Medical Oncology, Chongqing University Cancer Hospital & Chongqing Cancer Institute & Chonqing Cancer Hospital, China

Objective

- The objective of the Phase 2, single-arm DESTINY-Lung05 (DL-05) trial was to evaluate the efficacy and safety of trastuzumab deruxtecan (T-DXd) 5.4 mg/kg in Chinese patients with human epidermal growth factor receptor 2 (*ERBB2*) mutant (HER2m) metastatic non-small cell lung cancer (NSCLC) with disease progression on or after ≥1 prior anticancer therapy
- The primary endpoint was to determine the confirmed objective response rate (ORR) by independent central review (ICR)
- Secondary endpoints included investigator-assessed (INV) confirmed ORR; duration of response (DOR), disease control rate (DCR), progression-free survival (PFS) by ICR and INV; and safety

Conclusions

- T-DXd 5.4 mg/kg demonstrated clinically meaningful and strong, durable responses, with an acceptable and generally manageable safety profile in Chinese patients with pretreated HER2m metastatic NSCLC
- The response rates observed in DL-05, albeit in a small patient population, were similar to those observed in DESTINY-Lung02,[1] and the safety profile was consistent with the established profile of T-DXd

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 (DXd) to kill these cells.[1,2] T-DXd is approved in the US, EU, and Japan for people with non-small cell lung cancer (NSCLC) who have received prior anticancer treatment, and whose tumor cells have a mutation in the gene that codes for the HER2 protein (known as HER2 mutant [m]) and have spread to nearby tissues or elsewhere in the body (advanced or metastatic cancer).[3–5] In China, there are no treatments specifically approved for people with HER2m NSCLC.

How did we perform this research?

In DESTINY-Lung05, we evaluated how well T-DXd works in Chinese people with HER2m metastatic cancer who had received one or more prior anticancer treatment and the cancer continued to grow, spread, or get worse. We also evaluated the safety of T-DXd in study participants.

What were the findings of this research?

This clinical study demonstrated that 58.3% of participants who had received previous treatment for HER2m metastatic NSCLC had a response to T-DXd, and ~92% of participants' tumors shrank or remained stable. The study also demonstrated that the side effects were generally manageable in these participants.

What are the implications of this research?

These results support further evaluation of T-DXd in Chinese people with HER2m metastatic NSCLC.

Where can I access more information?

For more information about DESTINY-Lung05, please visit https://clinicaltrials.gov/study/NCT05246514 or reach out to Ying Cheng at jl.cheng@163.com.

This clinical study was sponsored by AstraZeneca in collaboration with Daiichi Sankyo. Poster presented at AACR 2024 by Jingyi Li.

1. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67:173–185; 2. Ogitani Y, et al. *Clin Cancer Res.* 2016;22:5097–5108; 3. Enhertu (fam-trastuzumab deruxtecan-nxki) highlights of prescribing information. 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s026lbl.pdf (Accessed March 18, 2024); 4. Enhertu (trastuzumab deruxtecan) summary of product characteristics. 2024. Available from: https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf (Accessed March 18, 2024); 5. Pharmaceuticals and Medical Devices Agency (PMDA). List of approved products (April 2023 to August 2023). 2023. Available from: https://www.pmda.go.jp/files/000265535.pdf (Accessed March 18, 2024)

Poster presented at AACR 2024, April 5–10, San Diego, CA, US

Corresponding author email address: jl.cheng@163.com

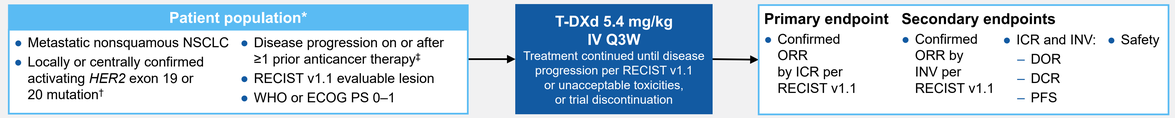
Introduction

- *HER2* mutations have been identified in ~2–4% of tumors in patients with NSCLC globally, including in patients from China[2–6]
- In China, there are no treatments specifically approved for patients with HER2m NSCLC
- T-DXd is approved in the US, EU, and Japan for the treatment of adult patients with unresectable or advanced/metastatic HER2m NSCLC who have received prior systemic therapy[7–9]
  - Approvals were based on data from the DESTINY-Lung02 trial, in which T-DXd 5.4 mg/kg demonstrated durable responses and clinically meaningful survival outcomes in 102 patients with previously treated HER2m NSCLC[1]
- Here, we present the primary analysis from the DL-05 trial (NCT05246514)

Methods

- DL-05 is an open-label, single-arm, Phase 2 trial evaluating the efficacy and safety of T-DXd 5.4 mg/kg in patients with HER2m metastatic NSCLC with disease progression on or after ≥1 prior anticancer therapy (**Figure 1**)
- Locally or centrally confirmed *HER2* mutation was acceptable for trial eligibility and retrospective central confirmation was performed on all patients enrolled based on local testing

Figure 1. DL-05 trial design



*Approximately 80 patients were planned for enrollment, with 72 patients enrolled at data cutoff. †Based on a pre-existing tissue test result from a local laboratory or prospective central confirmation of the *HER2* tissue mutation test result.
‡Treatment with prior HER2-directed therapy, except for pan-HER2 class tyrosine kinase inhibitors, and prior treatment with an ADC that consists of an exatecan derivative that is a topoisomerase I inhibitor were not allowed
ADC, antibody-drug conjugate; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; ICR, independent central review; INV, investigator assessed; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; PS, performance status; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization

Results and interpretation

Patient characteristics

- At data cutoff (September 23, 2023), 72 patients with centrally confirmed HER2m metastatic NSCLC were enrolled (full analysis set) and had received ≥1 dose of T-DXd
- Patient demographics and clinical characteristics are presented in **Table 1**
- The median (range) duration of follow up was 9.8 (1.0–14.0) months

Table 1. Patient demographics and clinical characteristics

Full analysis set*	N=72
Median age, years (min, max)	57.0 (34, 76)
Female, n (%)	41 (56.9)
Former smoker, n (%)	22 (30.6)
ECOG PS, n (%)	
0	24 (33.3)
1	48 (66.7)
Prior lines of therapy, n (%)	
1	30 (41.7)
≥2	42 (58.3)
Median (range)	2.0 (1–7)
Most common prior treatment modalities, n (%)	
Cytotoxic chemotherapy	67 (93.1)
Platinum chemotherapy	65 (90.3)
Immunotherapy	49 (68.1)
Antiangiogenic therapy	49 (68.1)

*Patients with HER2m NSCLC assessed by central testing; including patients with *HER2* exon 19 (n=2), exon 20 (n=69), and exon 19 and 20 (n=1) mutations
ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HER2m, human epidermal growth factor receptor 2 mutant; NSCLC, non-small cell lung cancer; PS, performance status

Efficacy

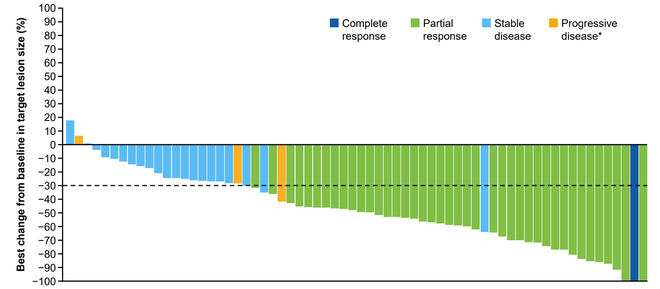
- The confirmed ORR by both ICR and INV was 58.3% (95% confidence interval [CI] 46.1, 69.8); one patient achieved a complete response and 41 patients achieved partial responses as assessed by ICR (**Table 2**)
- Best change from baseline in target lesion size by ICR is shown in **Figure 2**
- The median (range) time to onset of response from enrollment by ICR and INV was 1.6 (1.0–7.0) and 2.4 (1.0–8.0) months, respectively
- The median DOR by ICR and INV was not estimable (NE; 95% CI 6.1, NE) and 9.0 (7.2, NE) months, respectively
  - The DOR by ICR for each patient is presented in **Figure 3**
- DCR by ICR was 91.7% (95% CI 82.7, 96.9) and 93.1% (95% CI 84.5, 97.7) by INV
- PFS by ICR is shown in **Figure 4**; median PFS by ICR and INV was NE (95% CI 7.2, NE) months and 10.8 (95% CI 7.2, NE) months, respectively

Table 2. Best confirmed objective response by ICR

Best confirmed objective response, n (%)	N=72
Complete response	1 (1.4)
Partial response	41 (56.9)
Stable disease	24 (33.3)
Progression*	5 (6.9)
Not evaluable	1 (1.4)

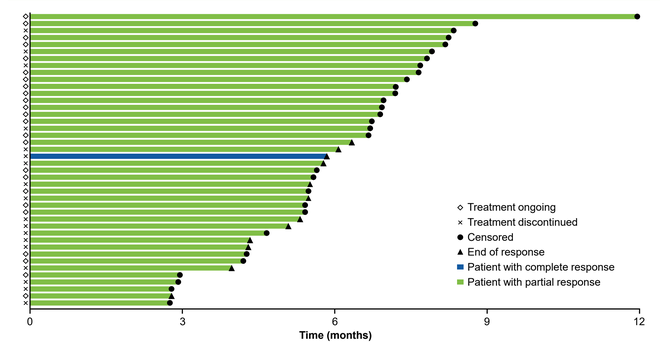
Analyses were performed by ICR in patients with HER2m NSCLC by central testing. *Included RECIST v1.1-defined disease progression and death ≤13 weeks without RECIST v1.1-defined disease progression
HER2m, human epidermal growth factor receptor 2 mutant; ICR, independent central review; NSCLC, non-small cell lung cancer; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1

Figure 2. Best change from baseline in target lesion size by ICR



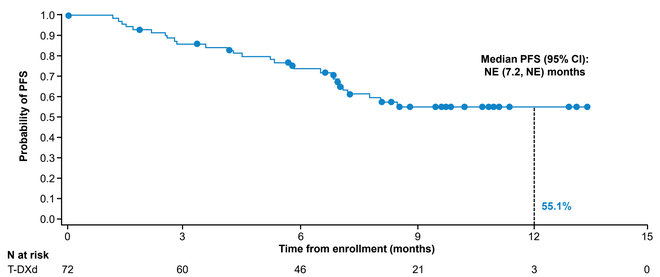
Best percentage change is the maximum reduction or minimum increase from baseline in the target lesion size determined by ICR. Analyses were performed in patients with HER2m NSCLC by central testing with at least one post-baseline target lesion assessment (n=66). The dashed line at −30% change in target lesion size indicates the threshold for partial response. The color of each bar indicates the confirmed best objective response per RECIST v1.1 determined by ICR.
*Included RECIST v1.1-defined disease progression and death ≤13 weeks without RECIST v1.1-defined disease progression
HER2m, human epidermal growth factor receptor 2 mutant; ICR, independent central review; NSCLC, non-small cell lung cancer; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1

Figure 3. Duration of response by ICR



Analyses were performed via ICR in patients with HER2m NSCLC by central testing. DOR was defined as the time from the first documented complete or partial response (n=42) until the date of progression or death or the last evaluable RECIST v1.1 assessment
DOR, duration of response; HER2m, human epidermal growth factor receptor 2 mutant; ICR, independent central review; NSCLC, non-small cell lung cancer; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1

Figure 4. Kaplan-Meier estimates of PFS by ICR



Analyses were performed by ICR in patients with HER2m NSCLC by central testing. Symbols indicate a censored observation; progression events that did not occur within two missed visits of the last evaluable assessment or enrollment are censored
CI, confidence interval; HER2m, human epidermal growth factor receptor 2 mutant; ICR, independent central review; NE, not estimable; NSCLC, non-small cell lung cancer; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

Safety

- Median (range) T-DXd exposure was 7.9 (0.7–13.5) months
- The safety profile of T-DXd is shown in **Tables 3** and **4**
- The most common (≥5%) drug-related Grade ≥3 adverse events by grouped term were neutropenia (26.4%), thrombocytopenia (18.1%), leukopenia (11.1%), and lymphopenia (6.9%)
- Most cases of adjudicated drug-related interstitial lung disease/pneumonitis (6/7) were of low grade (Grade 2)

Table 3. Safety profile of T-DXd

n (%)	N=72*†
Any drug-related AEs	71 (98.6)
Grade ≥3 drug-related AEs	37 (51.4)
Grade 5 drug-related AEs	0
Serious drug-related AEs	17 (23.6)
Drug-related AEs associated with dose interruption	26 (36.1)
Drug-related AEs associated with dose reduction	14 (19.4)
Drug-related AEs associated with discontinuation	2 (2.8)

*Analyses were performed in all patients who received ≥1 dose of T-DXd. †Investigator assessed
AE, adverse event; T-DXd, trastuzumab deruxtecan

Table 4. Adjudicated drug-related interstitial lung disease/pneumonitis*

n (%)	N=72
Any grade	7 (9.7)
Grade 2	6 (8.3)
Grade 5	1 (1.4)†

*Assessed by the independent ILD adjudication committee. Analyses were performed in all patients who received ≥1 dose of T-DXd. †Re-adjudicated as drug-related ILD/pneumonitis of maximum Grade 3 following updated information provided by the investigator after data cutoff; the adjudication committee initially concluded that there was not enough information to assess whether the death was caused by ILD/pneumonitis
ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan

Disclosures

Ying Cheng reports no conflicts of interest.

Acknowledgments

We thank the patients who participated in this trial, as well as their families and caregivers. Additionally, we would like to thank Rui Mao (AstraZeneca) for their significant contributions to the trial design and data interpretation. This trial was 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). Under the guidance of the authors and in accordance with Good Publication Practice, medical writing and editorial support was provided by Abbie Dodd, BSc, of Helios Medical Communications, and was funded by AstraZeneca.

References

1. Goto K, et al. *J Clin Oncol.* 2023;41:4852–4863
2. Mazières J, et al. *J Clin Oncol.* 2013;31:1997–2003
3. Shigematsu H, et al. *Cancer Res.* 2005;65:1642–1646
4. Stephens P, et al. *Nature.* 2004;431:525–526
5. Yoshizawa A, et al. *Lung Cancer.* 2014;85:373–378
6. Song Z, et al. *Oncotarget.* 2016;7:78152–78158
7. Enhertu (fam-trastuzumab deruxtecan-nxki) highlights of prescribing information. 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s026lbl.pdf (Accessed March 18, 2024)
8. Enhertu (trastuzumab deruxtecan) summary of product characteristics. 2024. Available from: https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf (Accessed March 18, 2024)
9. Pharmaceuticals and Medical Devices Agency (PMDA). List of approved products (April 2023 to August 2023). 2023. Available from: https://www.pmda.go.jp/files/000265535.pdf (Accessed March 18, 2024)