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Trastuzumab Deruxtecan in Patients From China With Pretreated *HER2*-Mutant NSCLC: Final Results From the DESTINY-Lung05 Study

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Objective

- To report the DESTINY-Lung05 final analysis, which evaluated the antitumor activity and safety of trastuzumab deruxtecan (T-DXd) in patients from China with metastatic human epidermal growth factor receptor 2 (*HER2*)-mutant (HER2m) non-small cell lung cancer (NSCLC), who had disease progression on or after ≥1 line of treatment

Conclusions

- With a median follow-up time of more than 20 months, results of the DESTINY-Lung05 final analysis build on primary data from the study[1] and affirm that T-DXd (5.4 mg/kg) induces durable responses and clinically meaningful survival benefit in patients from China with pretreated metastatic HER2m NSCLC
- Antitumor activity was observed across *HER2* mutation subgroups
- No new safety signals were identified, and the safety profile was consistent with the known profile of T-DXd[1,2]
- These data further support the use of T-DXd (5.4 mg/kg) as a treatment option in China for patients with previously treated metastatic HER2m NSCLC[1]

Plain language summary

Why did we perform this research?

Some people with non-small cell lung cancer (NSCLC) have a mutation in a gene called human epidermal growth factor receptor 2 (*HER2*; also known as *ERBB2*). Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody-drug conjugate that kills HER2-altered cancer cells.[1,2] When the DESTINY-Lung05 study was initiated, there were no treatments specifically approved in China for people with *HER2*-mutant NSCLC that has spread to nearby tissues or other parts of the body (known as advanced or metastatic). Initial results from both the DESTINY-Lung05 study and the DESTINY-Lung02 study led to the conditional approval of T-DXd for people in China with advanced or metastatic *HER2*-mutant NSCLC who have received a previous treatment.[3–5] Here, we present final results from the DESTINY-Lung05 study.

How did we perform this research?

In DESTINY-Lung05, we evaluated how well T-DXd works in people from China with metastatic *HER2*-mutant NSCLC who had received one or more prior anticancer treatments. We also evaluated the safety of T-DXd in study participants.

What were the findings of this research?

In this clinical study, 41 out of 72 (57%) participants had a decrease in the size or number of selected tumors after treatment with T-DXd (known as an objective response; this was confirmed by independent radiologists). The length of time at which half of the participants were still alive without their cancer having grown, spread, or worsened (known as median progression-free survival) was 10 months. After starting treatment with T-DXd, 50% of the participants were still alive (known as median overall survival) after 21 months. The side effects of T-DXd were similar to those observed in other studies.[5]

What are the implications of this research?

These results further support the use of T-DXd in people from China with metastatic *HER2*-mutant NSCLC who have received one or more prior anticancer treatments.

Where can I access more information?

For more information about DESTINY-Lung05, visit https://clinicaltrials.gov/study/NCT05246514 or reach out to Professor Buhai Wang at wbhself@sina.com.

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. Cheng Y, et al. *Cancer Res*. 2024;84(Suppl. 7):CT248 (Abstract); 4. AstraZeneca. Press release. October 23, 2023. Available from: https://www.astrazeneca.com/media-centre/press-releases/2023/enhertu-approved-in-the-eu-as-the-first-her2-directed-therapy-for-patients-with-her2-mutant-advanced-non-small-cell-lung-cancer.html (Accessed August 6, 2025); 5. Goto K, et al. *J Clin Oncol*. 2023;41:4852–4863

Poster

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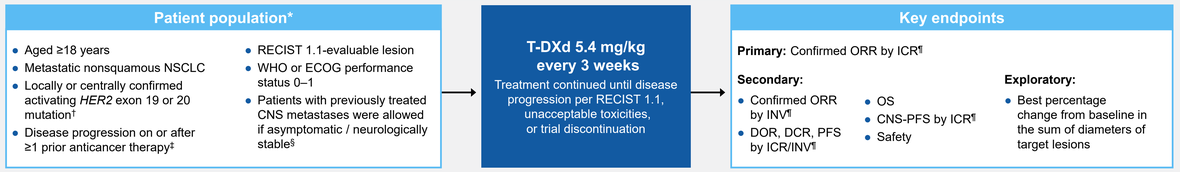
Introduction

- *HER2* (*ERBB2*) gene mutations have been identified in ~2–4% of lung adenocarcinomas globally, including in China,[3–8] and are associated with poor prognosis[8]
- T-DXd (5.4 mg/kg) is approved in multiple countries for the treatment of adult patients with unresectable or metastatic NSCLC whose tumors have activating *HER2* mutations and who have received a prior systemic therapy[9–11]
- In October 2024, T-DXd became the first HER2-directed therapy to be granted conditional approval in China for patients with previously treated unresectable or metastatic HER2m NSCLC[12]
  - This approval was supported by primary results from both DESTINY-Lung02 and DESTINY-Lung05, in which T-DXd (5.4 mg/kg) demonstrated durable responses and clinically meaningful survival outcomes in patients with HER2m NSCLC[1,2]
- Here, we report results from the final analysis of DESTINY-Lung05 (NCT05246514), which evaluated the antitumor activity and safety of T-DXd for patients from China with metastatic HER2m NSCLC who had disease progression on or after ≥1 line of treatment[1]

Methods

- DESTINY-Lung05 was an open-label, single-arm, Phase 2 trial evaluating the efficacy and safety of T-DXd (5.4 mg/kg) in patients with metastatic HER2m NSCLC with disease progression on or after ≥1 prior anticancer therapy (**Figure 1**)

Figure 1. DESTINY-Lung05 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 (retrospective central confirmation was performed for those enrolled based on existing local *HER2* mutation results); ‡treatment with prior HER2-directed therapy, except for pan-HER class tyrosine kinase inhibitors, and prior treatment with an antibody-drug conjugate that consists of an exatecan derivative that is a topoisomerase I inhibitor were not allowed; §patients with asymptomatic CNS disease at baseline were eligible if they did not need ongoing corticosteroid or anticonvulsant treatments, had recovered from acute radiotherapy toxicity, and ≥2 weeks had passed since whole-brain radiotherapy; ¶per RECIST 1.1
CNS, central nervous system; 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; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization

Results

Patient characteristics

- At data cutoff (November 4, 2024), 72 patients with metastatic, centrally confirmed HER2m NSCLC were enrolled; all patients received ≥1 dose of T-DXd and were included in both the full analysis set (FAS) and the safety analysis set
- Patient demographics and clinical characteristics are presented in **Table 1**

Table 1. Patient demographics and clinical characteristics

	N=72*
Median age, years (range)	57.0 (34–76)
Sex, n (%)	
Female	41 (56.9)
Male	31 (43.1)
Smoking status, n (%)	
Current	0
Former	22 (30.6)
Never	50 (69.4)
ECOG performance status, n (%)	
0	24 (33.3)
1	48 (66.7)
CNS metastases present at baseline, n (%)	30 (41.7)
HER2 mutation variant, n (%)†	
A775_G776insYVMA‡	55 (76.4)
P780_Y781insGSP‡	10 (13.9)
Other	8 (11.1)
G776delinsVC‡	5 (6.9)
L755P§	2 (2.8)
I767M§	1 (1.4)
Prior lines of therapy, n (%)	
1	30 (41.7)
2	18 (25.0)
≥3	24 (33.3)
Median (range)	2.0 (1–7)
Prior treatment modalities, n (%)†	
Cytotoxic chemotherapy	67 (93.1)
Platinum chemotherapy	65 (90.3)
Immunotherapy	49 (68.1)
Antiangiogenic therapy	49 (68.1)
Taxane chemotherapy	33 (45.8)
Targeted therapy	28 (38.9)
Other	4 (5.6)

*Patients with HER2m NSCLC assessed by central testing; †categories are not mutually exclusive; ‡exon 20 mutation; §exon 19 mutation
CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; HER2m, *HER2* mutant; NSCLC, non-small cell lung cancer

Efficacy

- The median (range) duration of follow up was 20.2 (2–27) months
- Response outcomes in the overall population are shown in **Table 2**; the confirmed objective response rate (ORR) by independent central review (ICR) was 56.9% (95% confidence interval [CI] 44.7, 68.6)
- A subgroup analysis of *HER2* tyrosine kinase domain mutations showed confirmed ORRs by ICR (n/n; 95% CI) as follows:
  - A775_G776insYVMA: 56.4% (31/55; 42.3, 69.7)
  - P780_Y781insGSP: 50.0% (5/10; 18.7, 81.3)
  - Other (G776delinsVC, L755P, I767M): 71.4% (5/7; 29.0, 96.3)
- 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 investigator assessment (INV) was 1.5 months (1–7) and 2.6 (1.0–13) months, respectively

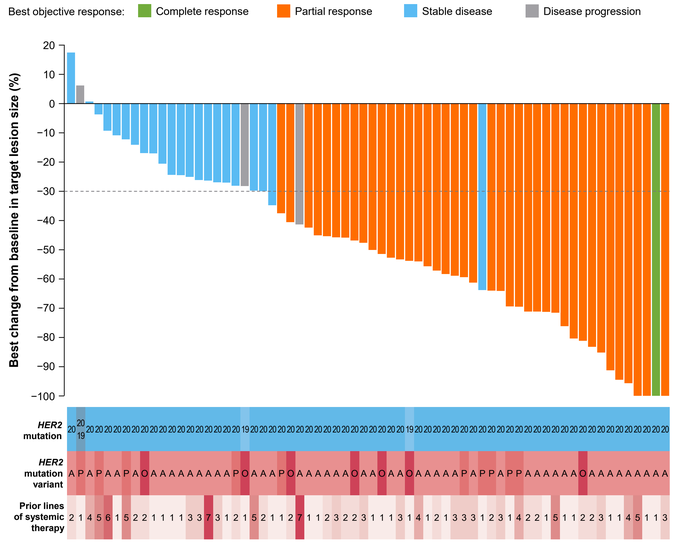
Table 2. Response outcomes

	ICR N=72	INV N=72
Confirmed ORR, % (n)	**56.9 (41)**	**59.7 (43)**
95% CI	**44.7, 68.6**	**47.5, 71.1**
Best objective response, n (%)		
Complete response	1 (1.4)	0
Partial response	40 (55.6)	43 (59.7)
Stable disease*	25 (34.7)	24 (33.3)
Disease progression†	5 (6.9)	4 (5.6)
Not evaluable	1 (1.4)	1 (1.4)
DCR, % (95% CI)	91.7 (82.7, 96.9)	93.1 (84.5, 97.7)
Median DOR, months (95% CI)	11.6 (5.8, NE)	9.4 (7.2, 13.5)

Confirmed ORR required confirmation after at least 4 weeks
*Included two patients who had PR/CR, but either no confirmation assessment was performed, or a confirmation assessment was performed but response was not confirmed; †included RECIST 1.1-defined disease progression, and death ≤13 weeks without RECIST 1.1-defined disease progression
CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; ICR, independent central review; INV, investigator assessment; NE, not evaluable; ORR, objective response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours

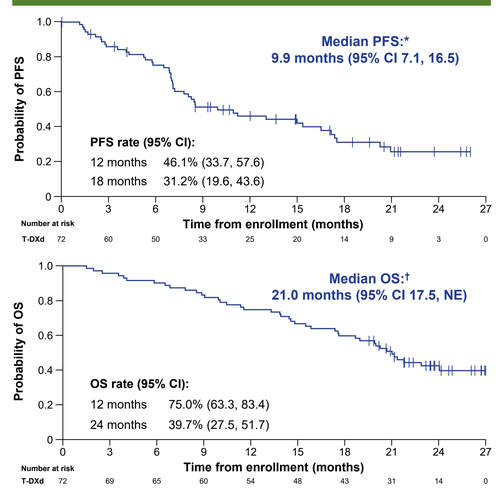
- Progression-free survival (PFS) by ICR and overall survival are shown in **Figure 3**
  - Median PFS by INV was 9.7 months (95% CI 8.1, 13.4)
- In the FAS, the median central nervous system-progression-free survival (CNS-PFS) by ICR was 15.5 months (95% CI 9.9, not evaluable)
  - This analysis included patients with CNS metastases at baseline (n=30) and those without CNS metastases at baseline (n=42); patients without CNS disease at baseline did not have brain scans as regularly as those who had CNS metastases at baseline, limiting interpretation of these data

Figure 2. Best percentage change from baseline in target lesion size



Best percentage change in target lesion size was assessed by ICR per RECIST 1.1 and was defined as the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction. The dashed reference line at −30% indicates the threshold for a partial response. Analyses were performed in patients with HER2m NSCLC by central testing with at least one post-baseline target lesion assessment (n=66). Only visits prior to subsequent anticancer therapy are included. The color of each bar indicates the confirmed best objective response per RECIST 1.1 determined by ICR. Numbers in the *HER2* mutation row indicate the exon in which the mutation occurred. Letters in the *HER2* mutation variant row correspond to the specific mutation: A, A775_G776insYVMA; P, P780_Y781insGSP; O, other (G776delinsVC, L755P, I767M)
HER2, human epidermal growth factor receptor 2; HER2m, *HER2* mutant; ICR, independent central review; NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumours

Figure 3. Kaplan-Meier estimates of PFS by ICR and OS



Symbols indicate a censored observation. PFS was assessed by ICR per RECIST 1.1
*Progression events that did not occur within two missed visits of the last evaluable assessment or enrollment date were censored; †patients not known to have died at the time of analysis were censored at the last recorded date on which they were known to be alive
CI, confidence interval; ICR, independent central review; NE, not evaluable; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan

Safety

- The median (range) duration of treatment was 8.6 months (0.7–26.9)
- A summary of safety data is presented in **Table 3**; the most common (>50%) any-grade drug-related adverse events (AEs) were thrombocytopenia (68.1%), leukopenia (66.7%), neutropenia (65.3%), transaminases increased (63.9%), nausea (56.9%), and anemia (54.2%)
- Adjudicated drug-related interstitial lung disease / pneumonitis events were mostly low grade (8 of 9 cases were Grade 1 or 2)
- There were no drug-related AEs with an outcome of death

Table 3. Summary of drug-related AEs

Safety analysis set, n (%)*	N=72
AEs	71 (98.6)
Grade ≥3 AEs	40 (55.6)
Serious AEs	23 (31.9)
AEs leading to discontinuations	4 (5.6)
AEs leading to dose reductions	16 (22.2)
AEs leading to dose interruptions	32 (44.4)
Adjudicated ILD/pneumonitis†	
Any grade	9 (12.5)
Grade 1	1 (1.4)
Grade 2	7 (9.7)
Grade 3	1 (1.4)
Left ventricular dysfunction	
Any grade	4 (5.6)‡
Grade 2	4 (5.6)‡

*Analyses include all patients who received ≥1 dose of T-DXd; †assessed by the ILD adjudication committee; ‡ejection fraction decreased
AE, adverse event; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan

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Disclosures

Professor Buhai Wang reports no conflicts of interest.

References

1. Cheng Y, et al. *Cancer Res*. 2024;84(Suppl. 7):CT248 (Abstract)
2. Goto K, et al. *J Clin Oncol*. 2023;41:4852–4863
3. Mazieres J, et al. *J Clin Oncol*. 2013;31:1997–2003
4. cBioPortal for Cancer Genomics. Available from: cBioPortal.org (Accessed June 19, 2025)
5. Yoshizawa A, et al. *Lung Cancer*. 2014;85:373–378
6. Li BT, et al. *J Thorac Oncol*. 2016;11:414–419
7. Song Z, et al. *Oncotarget*. 2016;7:78152–78158
8. Yu X, et al. *Front Oncol*. 2022;12:860313
9. Enhertu (fam-trastuzumab deruxtecan-nxki): highlights of prescribing information. 2025. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761139s032s035lbl.pdf (Accessed August 6, 2025)
10. Enhertu (trastuzumab deruxtecan): summary of product characteristics. 2025. Available from: https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf (Accessed August 6, 2025)
11. AstraZeneca. Press release. April 4, 2025. Available from: https://www.astrazeneca.com/media-centre/press-releases/2025/enhertu-approved-in-eu-in-post-et-breast-cancer.html (Accessed August 6, 2025)
12. AstraZeneca. Press release. October 14, 2024. Available from: https://www.astrazeneca.com/media-centre/press-releases/2024/enhertu-approved-in-china-as-first-her2-directe-therapy-for-patients-with-her2-mutant-metastatic-non-small-cell-lung-cancer.html (Accessed August 6, 2025)

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