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# Phase 2 Trial of Trastuzumab Deruxtecan in Patients With *HER2*-Mutant Metastatic Non–Small Cell Lung Cancer: Updated Analyses From DESTINY-Lung01


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## Background

- Human epidermal growth factor 2 (*HER2*) mutations drive 2%-4% of non–small cell lung cancers (NSCLC) and are associated with slightly younger age, female sex, a history of never smoking, a poor prognosis, and an increased incidence of brain metastasis[1-5]
- In August 2022, trastuzumab deruxtecan (T-DXd) 5.4 mg/kg was approved by the U.S. Food and Drug Administration (FDA) as the first-ever HER2-directed treatment for adult patients with unresectable or metastatic NSCLC whose tumors have activating *HER2* mutations, as indicated by an FDA-approved test, and who have received a prior systemic therapy[6]
  - Interstitial lung disease (ILD) and pneumonitis, including fatal cases, have been reported with T-DXd. Exposure to T-DXd during pregnancy can cause embryo-fetal harm
- In the primary analysis of DESTINY-Lung01 (NCT03505710; data cutoff [DCO] May 3, 2021), T-DXd 6.4 mg/kg in patients with previously treated *HER2*-mutant (*HER2*m) NSCLC had a confirmed objective response rate (ORR) of 55% (95% CI, 44%-65%) and a safety profile generally consistent with previous reports[7]
- Here we present additional post hoc subgroup analyses and longer follow-up (data cutoff December 3, 2021) of all patients with *HER2*m NSCLC treated in DESTINY-Lung01

## Conclusions

- With 7 months of additional follow up, T-DXd continued to demonstrate strong and durable anticancer activity in patients with previously treated *HER2*m NSCLC
  - ORR was similar in patients with and without asymptomatic central nervous system (CNS) metastases at baseline, as well as those with ≤2 and >2 prior lines of therapy at baseline
  - In this follow up, patients with ≤2 prior lines of treatment at baseline had numerically longer duration of response (DoR) versus those in the overall population (14.1 months vs 10.6 months, respectively)
  - Patients with asymptomatic CNS metastases at baseline also had clinically meaningful responses, though differences in DoR were observed compared to those without CNS metastases. A higher percentage of patients with asymptomatic CNS metastases at baseline had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 1 and received >2 prior lines of therapy, which was an independent parameter related to a lower duration of response, compared with the overall population
- Overall, the safety profile was consistent with previously reported studies, with no new safety signals identified after a longer follow up period and treatment duration
  - Most adjudicated drug-related ILD cases were of low grade
  - ILD/pneumonitis remains an important identified risk. Effective early detection and management are critical in preventing high-grade ILD/pneumonitis
- In August 2022, T-DXd 5.4 mg/kg was approved by the FDA as the first-ever HER2-directed treatment for adult patients with unresectable or metastatic *HER2*m NSCLC who have received a prior systemic therapy. This accelerated approval was based on the totality of the positive results from DESTINY-Lung02 and DESTINY-Lung01 phase 2 trials, which demonstrated robust and durable tumor responses in previously treated *HER2*m metastatic NSCLC[7,8]
- Updated results from DESTINY-Lung01 provide further evidence of antitumor activity with T-DXd in the second-line or later setting and support its establishment as a new treatment standard in patients with previously treated *HER2*m NSCLC

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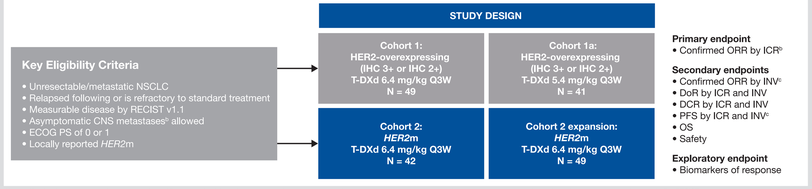
## Methods

- DESTINY-Lung01 is an open-label, multicenter, 2-cohort, phase 2 study evaluating the efficacy and safety of T-DXd in patients with HER2-overexpressing (cohort 1 and 1a) or *HER2*m (cohort 2) unresectable and/or metastatic NSCLC (**Figure 1**)[10]

**Figure 1. Study Design[a]**




[a]No stratification factors were used to assign patients. [b]Patients with clinically inactive, treated brain metastases that were asymptomatic and not requiring ongoing steroid or anticonvulsant therapy were allowed to enroll. [c]Per RECIST v1.1.

## Results

### Patients

- As of December 3, 2021, 91 patients with *HER2*m NSCLC were enrolled in cohort 2, and 11 (12.1%) patients were ongoing treatment
  - The median treatment duration was 6.9 months (range, 0.7-33.8 months)
  - The median duration of follow-up was 16.7 months (range, 0.7-36.9 months)
- 80 patients (87.9%) had discontinued, primarily for progressive disease (40.7%) and adverse events (30.8%)
- Patient demographics and baseline clinical characteristics for the overall population are shown in **Table 1**
- Among patients with (n = 33) and without (n = 58) asymptomatic CNS metastases at baseline:
  - 57.6% and 70.7% were female
  - 18.2%/81.8% and 29.3%/70.7% had ECOG PS of 0/1
  - 60.6%/39.4% and 70.7%/29.3% had ≤2/>2 prior lines of treatment

**Table 1. Demographics and Baseline Characteristics in the Overall *HER2*m NSCLC Population[7]**

| | Overall Population[a] (N = 91) |
|---|---|
| **Age, median (range), years** | 60.0 (29.0-88.0) |
| **Female, %** | 65.9 |
| **Race,[b] %** | |
| Asian | 34.1 |
| White | 44.0 |
| Black | 1.1 |
| Other | 20.9 |
| **Region, %** | |
| Asia | 25.3 |
| Europe | 36.3 |
| North America | 38.5 |
| **ECOG PS,[c] %** | |
| 0 | 25.3 |
| 1 | 74.7 |
| ***HER2* mutation, %** | |
| Kinase domain | 93.4 |
| Extracellular domain | 6.6 |
| **Asymptomatic CNS metastases at baseline, %** | 36.3 |
| **Smoking status, %** | |
| Never | 57.1 |
| Former | 40.7 |
| Current | 2.2 |
| **History of prior lung resection, %** | 22.0 |
| **Prior lines of treatment in the advanced/metastatic setting, %** | |
| ≤2 lines | 67.0 |
| >2 lines | 33.0 |
| **Prior treatment with anti–PD-(L)1 therapy, %** | 65.9 |


[a]Percentages may not total 100 because of rounding. [b]Race was reported by the patients. [c]ECOG PS scores range from 0 to 5, with higher scores reflecting greater disability.

### Efficacy Results

- Efficacy results for the overall population and subgroups are summarized in **Table 2**
  - In the follow-up analysis, confirmed ORR by independent central review (ICR) in the overall population was 54.9% (95% CI, 44.2%-65.4%)
    - Confirmed ORR by ICR was similar across subgroups (54.5% [95% CI, 36.4%-71.9%] and 55.2% [95% CI, 41.5%-68.3%] in patients with and without CNS metastases, respectively; 55.7% [95% CI, 42.5%-68.5%] in patients with ≤2 prior lines of therapy and 53.3% [95% CI, 34.3%-71.1%] in those with >2 prior lines)

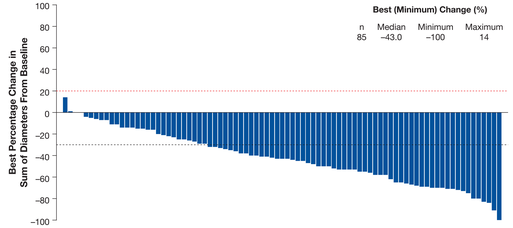
**Table 2. Efficacy of T-DXd in the Overall *HER2*m NSCLC Population and Key Subgroups (Data Cutoff: December 3, 2021)**

| Response Assessment by ICR | CNS Metastases: Yes (n = 33) | CNS Metastases: No (n = 58) | Prior Therapy: ≤2 lines (n = 61) | Prior Therapy: >2 lines (n = 30) | Overall Population (N = 91) |
|---|---|---|---|---|---|
| **Confirmed ORR,[a,b] n (%)** [95% CI] | 18 (54.5) [36.4-71.9] | 32 (55.2) [41.5-68.3] | 34 (55.7) [42.5-68.5] | 16 (53.3) [34.3-71.7] | 50 (54.9) [44.2-65.4] |
| **Best overall response, n (%)** | | | | | |
| CR | 0 | 1 (1.7) | 1 (1.6) | 0 | 1 (1.1) |
| PR | 18 (54.5) | 31 (53.4) | 33 (54.1) | 16 (53.3) | 49 (53.8) |
| SD | 14 (42.4) | 20 (34.5) | 22 (36.1) | 12 (40.0) | 34 (37.4) |
| PD | 0 | 3 (5.2) | 3 (4.9) | 0 | 3 (3.3) |
| NE | 1 (3.0) | 3 (5.2) | 2 (3.3) | 2 (6.7) | 4 (4.4) |
| **DCR,[c] n (%)** [95% CI] | 32 (97.0) [84.2-99.9] | 52 (89.7) [78.8-96.1] | 56 (91.8) [81.9-97.3] | 28 (93.3) [77.9-99.2] | 84 (92.3) [84.8-96.9] |
| **Median DoR, months** [95% CI] | 7.2 [5.3-11.1] | 14.7 [5.7-NE] | 14.1 [5.9-NE] | 5.8 [4.2-12.0] | 10.6 [5.6-18.3] |
| **Median time to initial response, months** [range] | 1.4 [1.2-6.3] | 2.1 [1.2-9.3] | 1.5 [1.2-9.3] | 1.5 [1.2-9.3] | 1.5 [1.2-9.3] |

[a]Primary endpoint. [b]Proportion of patients with confirmed CR or PR assessed by ICR per RECIST v1.1. [c]Proportion of patients with confirmed CR, PR, or SD assessed by ICR.

- At the December 3, 2021, DCO, median DoR in the overall population (10.6 months) was consistent with the primary analysis (9.3 months; DCO: May 3, 2021)[10]
- DoR by subgroups was assessed in the follow-up analysis (**Supplementary Figure 1**)
  - Patients with and without CNS metastases at baseline had a median DoR of 7.2 months (95% CI, 5.3-11.1 months) and 14.7 months (95% CI, 5.7 months-NE), respectively
  - Median DoR was 14.1 months (95% CI, 5.9-NE months) in patients with ≤2 prior lines of therapy and 5.8 months (95% CI, 4.2-12.0 months) in those with >2 prior lines
- The best percentage change from baseline in target lesions in the overall population is shown in **Figure 2**
  - The best percentage change from baseline in target lesions in patients with or without asymptomatic CNS metastases at baseline and in those with ≤2 or >2 prior therapy lines are shown in **Figure 3**
  - The percentage change from baseline in target lesions over time by patient are shown in **Supplementary Figure 2**

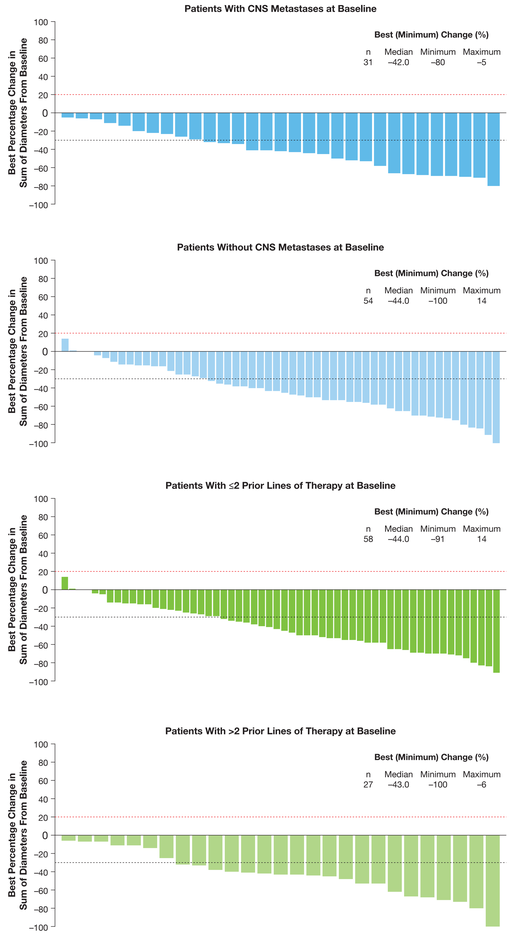
**Figure 2. Best Percentage Change From Baseline in Target Lesions by ICR for the Overall NSCLC *HER2*m Population (Data Cutoff: December 3, 2021)**




Best (minimum) percentage change from baseline in the sum of diameters for all target lesions, based on ICR. Baseline was last measurement taken before enrollment. Red line at 20% indicates progressive disease, and black line at −30% indicates partial response (when considering only target lesions). Full analysis set data are shown.

## Results (continued)

**Figure 3. Best Percentage Change in Target Lesion by ICR for Key *HER2*m NSCLC Subgroups (Data Cutoff: December 3, 2021)**




The line at 20% indicates progressive disease, and the line at −30% indicates a partial response.

- Median progression free survival (PFS) (**Supplementary Figures 3 and 4**) and overall survival (OS) (**Supplementary Figures 5 and 6**) for the overall population and key subgroups were assessed in the follow-up analysis
  - Median PFS was 8.2 months (95% CI, 6.0-11.9 months) and median OS was 18.6 months (95% CI, 13.8-25.8 months) in the overall population
    - Patients with and without asymptomatic CNS metastases at baseline had a median PFS of 7.1 months (95% CI, 5.5-9.8 months) and 9.7 months (95% CI, 4.5-16.9 months), respectively; median OS was 14.0 months (95% CI, 9.8-19.5 months) and 27.0 months (95% CI, 15.3 months-NE), respectively
    - Patients with ≤2 or >2 prior therapy lines at baseline had a median PFS of 8.3 months (95% CI, 5.8-15.2 months) and 6.8 months (95% CI, 4.4-9.8 months), respectively; median OS was 22.1 months (95% CI, 14.0-31.3 months) and 13.8 months (95% CI, 7.1-18.6 months), respectively

### Safety

- Median treatment duration was 6.9 months (range, 0.7-33.8 months)
- Drug-related treatment-emergent adverse events (TEAEs) for the overall population are summarized in **Table 3**; all patients had at least 1 TEAE
  - The most common drug-related TEAEs associated with treatment discontinuation were investigator-reported pneumonitis (13.2%) and ILD (5.5%)
  - The most common drug-related TEAEs associated with dose reduction were nausea (11.0%) and fatigue (8.8%)
  - Serious drug-related TEAEs occurred in 19.8% of patients in the overall population

**Table 3. Safety Summary of T-DXd in the Overall *HER2*m NSCLC Population (Data Cutoff: December 3, 2021)**

| n (%) | Overall Population (N = 91) |
|---|---|
| **Any grade TEAEs** | 91 (100) |
| **Drug-related TEAEs** | 88 (96.7) |
| **Drug-related grade ≥3 TEAEs** | 42 (46.2) |
| **Serious drug-related TEAEs** | 18 (19.8) |
| **Drug-related TEAEs associated with:** | |
| Drug discontinuation[a] | 24 (26.4) |
| Dose reduction | 33 (36.3) |
| Drug interruption | 31 (34.1) |
| Drug-related TEAEs associated with an outcome of death | 2 (2.2)[b] |

Relationship to study drug was determined by the treating investigator.
[a]Pneumonitis (n = 12) and interstitial lung disease (n = 5) were among the drug-related TEAEs associated with discontinuation. [b]1 patient who experienced grade 3 ILD as reported by investigator died due to disease progression. The reported grade 3 ILD was subsequently adjudicated as grade 5 (fatal) by the ILD adjudication committee.

- The most common (occurring in ≥20% of patients) drug-related TEAEs reported by investigator were gastrointestinal and hematologic events and most were grade 1 or 2 (**Supplementary Table 1**)
  - Neutropenia (22.2%), anemia (9.9%), and nausea (8.8%) were the most common grade ≥3 TEAEs
  - Nausea, decreased appetite, and vomiting were reported early (<10 days since starting the study drug); fatigue, constipation, and anemia were reported as lasting for >120 days (**Supplementary Table 2**)
- In the follow-up analysis, independently adjudicated drug-related ILD of any grade occurred in 27.5% of patients in the overall population (**Table 4**)
  - Most (76%) adjudicated drug-related ILD cases were low grade (grade 1/2)
- 23 of 25 patients with adjudicated drug-related ILD received ≥1 dose of glucocorticoids
  - However, not all glucocorticoid treatment was administered per the ILD management guidelines
- At the time of data cutoff, 52% (13/25) of investigator-reported cases had fully resolved

**Table 4. Adjudicated Drug-Related ILD in the Overall *HER2*m NSCLC Population (Data Cutoff: December 3, 2021)[a]**

| | Overall Population (N = 91) |
|---|---|
| **Any grade, n (%)** | 25 (27.5) |
| Grade 1 | 3 (3.3) |
| Grade 2 | 16 (17.6) |
| Grade 3 | 4 (4.4) |
| Grade 4 | 0 |
| Grade 5 | 2 (2.2) |
| **Median time to first onset, days (range)** | 125 (14-461) |
| **Median duration, days (95% CI)** | 43 (29-94) |
| **Outcome of event as reported by investigator, n (%)** | |
| Fatal | 1 (4.0) |
| Not recovered/not resolved | 8 (32.0)[b] |
| Recovering/resolving | 1 (4.0) |
| Recovered/resolved with sequelae | 2 (8.0) |
| Recovered/resolved | 13 (52.0) |

[a]Drug-related ILD was determined by the Independent Adjudication Committee based on the current MedDRA version for the narrow ILD standard MedDRA query (SMQ), selected terms from the broad ILD SMQ, and respiratory failure and acute respiratory failure. [b]1 patient with grade 3 ILD with an outcome of not recovered/not resolved, as reported by investigator, was adjudicated as a drug-related grade 5 (fatal) ILD event.

### Abbreviations

CNS, central nervous system; CR, complete response; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; *HER2*m, mutant human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ILD, interstitial lung disease; INV, investigator assessed; MedDRA, Medical Dictionary for Regulatory Activities; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-(L)1, programmed death ligand 1; PFS, progression-free survival; PR, partial response; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; SMQ, standard MedRA query; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

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