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Trastuzumab Deruxtecan in Patients With HER2-Overexpressing Metastatic Non–Small Cell Lung Cancer: Results From the DESTINY-Lung01 Trial

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Background

- 85% of all lung cancers are non–small cell lung cancer (NSCLC)[1]
- Human epidermal growth factor receptor 2 (HER2) alterations, including overexpression, amplification, and mutations, are a molecular target in advanced NSCLC[1,2]
  - There is a lack of standardized criteria for defining HER2 overexpression in NSCLC. HER2 overexpression has been reported in approximately 10% to 15% of NSCLC, with an incidence as high as 30% in adenocarcinoma[3-7]
- Currently, there are no approved or recommended HER2-targeted therapies for patients with HER2-overexpressing (HER2-OE) NSCLC. Moreover, current treatment options, including HER2-directed therapy, are associated with poor outcomes[8,9]
- Trastuzumab deruxtecan (T-DXd), a HER2-targeting antibody-drug conjugate, has shown initial positive results in patients with HER2-OE NSCLC[10]
- In August 2022, T-DXd was approved by the US Food and Drug Administration as the first ever HER2-directed treatment for adult patients with unresectable or metastatic *HER2*-mutant NSCLC who have received prior systemic therapy[11]
- Encouraging early efficacy of T-DXd was demonstrated in patients with HER2-OE in an interim analysis of DESTINY-Lung01[12]
- Here, we present the updated results of DESTINY-Lung01 (NCT03505710), an ongoing, multicenter, phase 2 study assessing 2 dose levels of T-DXd (6.4 mg/kg and 5.4 mg/kg) in patients with HER2-OE NSCLC

Conclusions

- Both T-DXd doses (6.4 mg/kg and 5.4 mg/kg) had encouraging and consistent antitumor activity in heavily pretreated patients with HER2-OE NSCLC
  - Efficacy was observed across patients with HER2 immunohistochemistry (IHC) 3+ and HER2 IHC 2+
- The overall safety profile was generally acceptable and consistent with previous trials[2,10]; the most common treatment-emergent adverse events (TEAEs) were mostly gastrointestinal in nature
  - T-DXd 5.4 mg/kg was associated with a better safety profile versus the 6.4 mg/kg dose
- Interstitial lung disease (ILD)/pneumonitis remains an important risk; all-grade and grade 5 ILD rates were lower with the 5.4 mg/kg dose than with the 6.4 mg/kg dose
- Overall efficacy and safety data from DESTINY-Lung01 support continued exploration and development of T-DXd for the treatment of HER2-OE NSCLC

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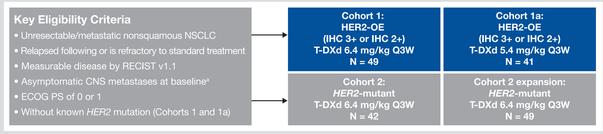
Methods

- DESTINY-Lung01 is an open-label, 2-cohort study evaluating the efficacy and safety of T-DXd in patients with HER2-OE (Cohorts 1 and 1a) or *HER2*-mutant (Cohort 2) unresectable and/or metastatic NSCLC (**Figure 1**)[13]
  - In Cohorts 1 and 1a, patients with HER2 IHC 3+ or 2+ (without known *HER2* mutation) received T-DXd 6.4 mg/kg (Cohort 1) or 5.4 mg/kg (Cohort 1a) every 3 weeks (Q3W)
  - HER2 IHC status was centrally determined by testing archived tumor specimens using an IHC assay modified to assess HER2 expression in NSCLC; there is currently no standard HER2 IHC assay available for NSCLC[14]
  - Samples were scored according to the American Society of Clinical Oncology/College of American Pathologists guidelines for HER2 IHC scoring for gastric and gastroesophageal junction cancer[15]
- The primary endpoint was confirmed objective response rate (ORR) by independent central review (ICR)
- Additional endpoints were disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety

Figure 1. Study Design



[a]Patients with asymptomatic brain metastases not requiring ongoing steroid or anticonvulsant therapy were allowed to enroll.

Results

Patients

- As of December 3, 2021, a total of 49 and 41 patients were enrolled, and 2 patients (4.1%) and 5 patients (12.2%) were ongoing treatment in Cohorts 1 and 1a, respectively; after enrollment in Cohort 1 was complete, Cohort 1a was initiated
  - The median treatment duration was 4.1 months (range, 0.7-27.8 months) and 5.5 months (range, 0.7-16.5 months) in Cohorts 1 and 1a, respectively
  - The median duration of follow-up was 12.0 months (range, 0.4-36.0 months) and 10.6 months (range, 0.6-16.9 months) in Cohorts 1 and 1a, respectively
- Patient demographics and baseline clinical characteristics are shown in **Table 1**

Table 1. Baseline Characteristics and Prior Therapies

Demographic and Baseline Characteristic	Cohort 1 (6.4 mg/kg) N = 49	Cohort 1a (5.4 mg/kg) N = 41
Age, median (range), years	63.0 (37-85)	62.0 (31-76)
Female, %	38.8	46.3
Region, %		
Asia	24.5	7.3
North America	38.8	31.7
Europe	36.7	61.0
HER2 status, %		
IHC 3+	20.4	41.5
IHC 2+	79.6	58.5
Other gene abnormality status, %		
EGFR/ALK/ROS1/BRAF	18.4	14.6
No *EGFR/ALK/ROS1/BRAF*	53.1	75.6
Not reported	28.6	9.8
ECOG PS 0 | 1, %	28.6 | 71.4	12.2 | 87.8
Presence of CNS metastases, %	34.7	29.3
Smoking status, %		
Never	32.7	22.0
Former	57.1	73.2
Current	10.2	4.9
History of prior lung resection, %		
Yes	24.5	17.1
No	75.5	82.9
Renal function at baseline,[a] %		
Normal renal function	40.8	31.7
Mild renal impairment	38.8	41.5
Moderate renal impairment	18.4	26.8
Severe renal impairment	2.0	0
Prior therapies, %	100	100
Platinum-based	91.8	97.6
Anti–PD-1/PD-L1	73.5	80.5
Docetaxel	24.5	22.0
Number of prior lines of therapies, median (range)	3 (1-8)	3 (1-5)

[a]Renal function was determined by baseline creatinine clearance (calculated using the Cockcroft-Gault equation): ≥90 mL/min (normal), ≥60 and <90 mL/min (mild), ≥30 and <60 mL/min (moderate), and ≥15 and <30 mL/min (severe).

Efficacy

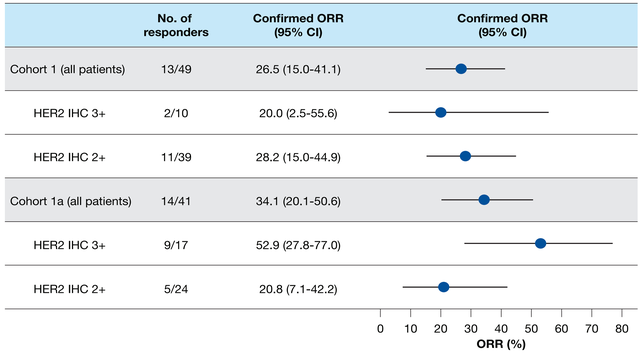
- Efficacy results for Cohorts 1 and 1a are summarized in **Table 2**
  - ORR by ICR was 26.5% (95% CI, 15.0-41.1) and 34.1% (95% CI, 20.1-50.6) in Cohorts 1 and 1a, respectively
  - Median DoR was 5.8 months (95% CI, 4.3-NE) and 6.2 months (95% CI, 4.2-9.8) in Cohorts 1 and 1a, respectively
  - DCR was 69.4% (95% CI, 54.6-81.8) and 78.0% (95% CI, 62.4-89.4) in Cohorts 1 and 1a, respectively

Table 2. Efficacy of T-DXd in Patients With HER2-OE NSCLC

	Cohort 1 (6.4 mg/kg) N = 49	Cohort 1a (5.4 mg/kg) N = 41
ORR by ICR, % (95% CI)	26.5 (15.0-41.1)	34.1 (20.1-50.6)
CR	0	4.9
PR	26.5	29.3
SD	42.9	43.9
PD	22.4	9.8
NE	8.2	12.2
DCR, % (95% CI)	69.4 (54.6-81.8)	78.0 (62.4-89.4)
DoR, median (95% CI), months	5.8 (4.3-NE)	6.2 (4.2-9.8)

- The ORR by HER2 IHC status for Cohorts 1 and 1a is shown in **Figure 2**
  - In Cohort 1, the confirmed ORR was 20.0% (95% CI, 2.5-55.6) in patients with HER2 IHC 3+
  - In Cohort 1a, the confirmed ORR was 52.9% (95% CI, 27.8-77.0) in patients with HER2 IHC 3+

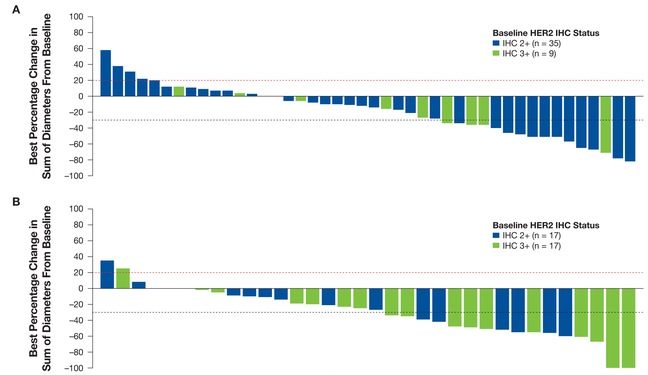
Figure 2. Response to T-DXd by HER2 IHC Status



- The best percentage change from baseline in target lesions in Cohorts 1 and 1a is shown in **Figure 3**
- Median PFS was 5.7 months (95% CI, 2.8-7.2) and 6.7 months (95% CI, 4.2-8.4), and median OS was 12.4 months (95% CI, 7.8-17.2) and 11.2 months (95% CI, 8.4-NE) in Cohorts 1 and 1a, respectively

Figure 3. Best Percentage Change From Baseline in Target Lesions in (A) Cohort 1 and (B) Cohort 1a

Results (continued)



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 PD, and black line at −30% indicates PR (when considering only target lesions). Full analysis set data are shown.

Safety

- TEAEs are summarized in **Table 3**; all patients had at least 1 TEAE
- Grade ≥3 TEAEs occurred in 81.6% and 51.2% of patients in Cohorts 1 and 1a, respectively
  - Drug-related grade ≥3 TEAEs occurred in 53.1% and 22.0% of patients in Cohorts 1 and 1a, respectively

Table 3. Overall Safety Summary of T-DXd in Patients With HER2-OE NSCLC

Event, %	Cohort 1 (6.4 mg/kg) N = 49	Cohort 1a (5.4 mg/kg) N = 41
Any-grade TEAEs	100	100
Drug-related	89.8	92.7
Grade ≥3 TEAEs	81.6	51.2
Drug-related	53.1	22.0
TEAEs associated with drug discontinuation	26.5	17.1
Drug-related	16.3	7.3
TEAEs associated with dose reduction	36.7	17.1
Drug-related	34.7	17.1
TEAEs associated with drug interruption	49.0	24.4
Drug-related	34.4	9.8
TEAEs associated with death	20.4	17.1
Drug-related	2.0[a]	0[b]

[a]In Cohort 1, 1 patient had grade 5 (ie, fatal) pneumonitis that was assessed as drug-related by the investigator. The reported event was subsequently adjudicated as drug-related grade 5 ILD by the ILD adjudication committee. Two patients had grade 4 respiratory failure that was assessed as not drug-related by the investigator; both died and the reported respiratory failure was subsequently adjudicated as drug-related grade 5 ILD.
[b]In Cohort 1a, 1 patient had grade 3 respiratory failure that was assessed as not drug-related by the investigator and died; the reported respiratory failure was subsequently adjudicated as drug-related grade 5 ILD. All adjudicated events of drug-related ILD are reported in **Table 4**.

- The most common TEAEs occurring in ≥20% of patients in either cohort were mostly gastrointestinal and included nausea (59.2% and 73.2%), fatigue (59.2% and 70.7%), decreased appetite (44.9% and 46.3%), vomiting (30.6% and 31.7%), constipation (30.6% and 24.4%), and diarrhea (28.6% and 36.6%), among others, in Cohorts 1 and 1a, respectively
- Independently adjudicated drug-related ILD of any grade occurred in 20.4% and 4.9% of patients in Cohorts 1 and 1a, respectively (**Table 4**)
  - No potential ILD cases were pending adjudication by data cutoff

Table 4. Adjudicated Drug-Related ILD[a]

Event, %	Cohort 1 (6.4 mg/kg) N = 49	Cohort 1a (5.4 mg/kg) N = 41
Grade 1	4.1	0
Grade 2	10.2	2.4
Grade 3	0	0
Grade 4	0	0
Grade 5	6.1	2.4
Overall	20.4	4.9

[a]The events in this table are based on adjudicated ILD events including all adjudicated ILD and are considered study drug–related events by the ILD Adjudication Committee.

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-OE, human epidermal growth factor receptor 2–overexpressing; ICR, independent central review; IHC, immunohistochemistry; ILD, interstitial lung disease; NE, non-evaluable; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; PR, partial response; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SD, stable disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

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Disclosures

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