Trastuzumab Deruxtecan (T-DXd) in Patients With *HER2*-Mutated (*HER2*m) Metastatic Non–Small Cell Lung Cancer (NSCLC): A Phase 2 Study (DESTINY-Lung02)

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Background

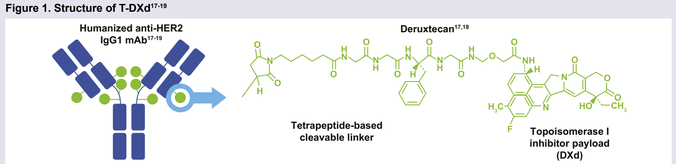
HER2 Mutations in NSCLC

- Human epidermal growth factor receptor 2 (HER2) mutations are oncogenic drivers in NSCLC and are found in approximately 3% of patients with NSCLC[1-3]
  - HER2 is considered a distinct molecular target as *HER2* mutations tend to be mutually exclusive from aberrations in other driver mutations[4]
  - Median overall survival (OS) is shorter and the incidence of brain metastasis is greater in patients with *HER2*m advanced NSCLC compared with patients with tumors harboring other driver mutations[1,2,5]
- There are no approved HER2-targeted therapies for patients with NSCLC[6]
  - Several studies with HER2-targeted tyrosine kinase inhibitors in this population have been conducted or are ongoing; however, clinical responses with these HER2-targeted agents in *HER2*m NSCLC produced limited activity and inconsistent results, with objective response rates (ORRs) ranging from 0 to 30%[7-11]
  - Trastuzumab emtansine, a HER2 antibody–drug conjugate (ADC), has shown more encouraging activity, with an ORR of 44%; receptor–ADC internalization is thought to be a mechanism of action[12-13]
- For patients with *HER2*m NSCLC, chemotherapy and/or immune checkpoint inhibitors remain the standard of care but have limited activity in second or later line settings
  - With combination therapy, ORR ranges from 12 to 23% and median duration of response (DOR) is ≈5 months[14,15]
  - Moreover, immune checkpoint inhibitor monotherapy may not be effective in patients with *HER2*m NSCLC (ORR, 7%)[16]

T-DXd Is Designed to Deliver an Optimal Antitumor Effect

- T-DXd is an ADC with 3 components (**Figure 1**)[17,18]:
  - Humanized anti-HER2 immunoglobulin G1 monoclonal antibody that has the same amino acid sequence as trastuzumab
  - Topoisomerase I inhibitor payload, an exatecan derivative
  - Tetrapeptide-based cleavable linker

Figure 1. Structure of T-DXd[17-19]



HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; mAb, monoclonal antibody; T-DXd, trastuzumab deruxtecan.

- T-DXd has been approved to treat adult patients with
  - HER2-positive unresectable/metastatic breast cancer who received prior chemotherapy or ≥2 prior anti-HER2–based regimens, at the 5.4 mg/kg every 3 weeks (Q3W) dose[20-23]
  - HER2-positive advanced/metastatic gastric cancer who received a prior trastuzumab-based regimen (United States and Israel) or whose disease progressed after chemotherapy (Japan), at the 6.4mg/kg Q3W dose[20,21,23]
- T-DXd is approved in the United States and Japan with boxed warnings for interstitial lung disease (both countries) and embryo-fetal toxicity (United States only)[20,21]
- In the DS8201-A-J101 dose escalation and expansion phase 1 trial (NCT02564900), 2 recommended phase 2 doses of T-DXd were established: 5.4 mg/kg and 6.4 mg/kg Q3W[24]
- T-DXd 6.4 mg/kg Q3W was investigated in a phase 2 trial (DESTINY-Lung01; NCT03505710) in patients with metastatic *HER2*m NSCLC (**Table 1**),[25] with the primary analysis presented at ESMO 2021 (Abstract #LBA45)[26]
  - Although T-DXd 5.4 mg/kg and T-DXd 6.4 mg/kg have shown clinical efficacy in multiple cancer indications,[27-29] T-DXd 5.4 mg/kg has not been tested in patients with *HER2*m NSCLC
  - T-DXd 5.4 mg/kg and T-DXd 6.4 mg/kg are being evaluated in patients with HER2-overexpressing NSCLC (DESTINY-Lung01; NCT03505710)
  - T-DXd in combination with durvalumab is being evaluated in patients with HER2-expressing NSCLC (DESTINY-Lung03; NCT04686305)
- T-DXd is also being evaluated in studies of other solid tumor types, including a *HER2*m tumor-agnostic trial (DESTINY-PanTumor01; NCT04639219)

Table 1. Interim Analysis Efficacy Results in Patients With *HER2*m NSCLC (DESTINY-Lung01)[24]

Response Assessment by ICR	Cohort 2 Patients (N = 42)
Confirmed ORR, % n (95% CI)	**61.9** 26 (45.6-76.4)
DCR, % n (95% CI)	**90.5** 38 (77.4-97.3)
Median DOR, months (95% CI)	NE (5.3-NE)
Median PFS, months (95% CI)	14 (6.4-14.0)
Median OS, months (95% CI)	NE (11.8-NE)

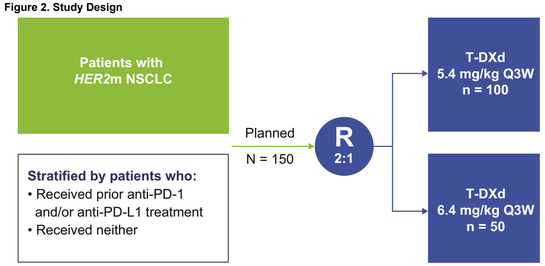
Data cutoff: November 25, 2019.
DCR, disease control rate; DOR, duration of response; *HER2*m, human epidermal growth factor receptor 2-mutated; ICR, independent central review; NE, not estimable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Methods

Study Design and Population

- DESTINY-Lung02 is a global, multicenter, 2-arm, randomized phase 2 study (**Figure 2**)

Figure 2. Study Design



*HER2*m, human epidermal growth factor receptor 2–mutated; NSCLC, non–small cell lung cancer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan.

Key Inclusion Criteria

- Adults (according to local regulation) and able to provide informed consent
- Metastatic NSCLC with a known activating *HER2* mutation (by local detection)
- One or more lines of previous treatment, including platinum therapy
- Presence of ≥1 measurable lesion confirmed by BICR, based on RECIST v1.1
- ECOG PS of 0 or 1
- LVEF ≥50% within 28 days before randomization
- Willing and able to provide an adequate tumor tissue sample

Key Exclusion Criteria

- Known driver mutation in the *EGFR* or *BRAF* gene or a known *ALK* or *ROS1* fusion
- History of ILD/pneumonitis that required steroids, current ILD/pneumonitis, or suspected ILD/pneumonitis that cannot be ruled out by imaging at screening
- MI ≤6 months before randomization or symptomatic CHF
- Spinal cord compression or clinically active CNS metastases
- Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder

ALK, anaplastic lymphoma kinase; *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; BICR, blinded independent central review; CHF, congestive heart failure; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSCLC, non–small cell lung cancer; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; *ROS1*, ROS proto-oncogene 1, receptor tyrosine kinase.

Study Endpoints

Primary	• **Confirmed ORR by BICR-assessed RECIST v1.1[a]**		
Secondary	Efficacy • ORR by investigator-assessed RECIST v1.1 • DOR • DCR • PFS • OS	Safety • AEs, including TEAEs, SAEs, and AEs of special interest graded according to NCI-CTCAE v5.0 • ECOG PS, vital sign measurements, ophthalmologic findings, standard clinical laboratory parameters, ECG parameters, ECHO/MUGA findings, and radiologic findings	Pharmacokinetics • Serum concentrations of T-DXd, total anti-HER2 antibody, and MAAA 1181 Immunogenicity • Incidence of antidrug antibodies Health Economics and Outcomes Research • PROs of change from baseline in EORTC core QLQ-C30 and EORTC QLQ-LC13 scale scores and time to deterioration in EORTC QLQ-C30 scores

AE, adverse event; BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; ECG, electrocardiogram; ECHO, echocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC, European Organization for Research and Treatment of Cancer; HER2, human epidermal growth factor receptor 2; MUGA, multi-gated acquisition; NCI-CTCAE v5.0, National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; QLQ-C30, quality-of-life questionnaire core 30; QLQ-LC13, quality-of-life questionnaire for lung cancer trials; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]Confirmed ORR defined as the proportion of patients with a best overall response of confirmed complete response or partial response as assessed by blinded data review and based on RECIST v1.1.

Statistical Analyses

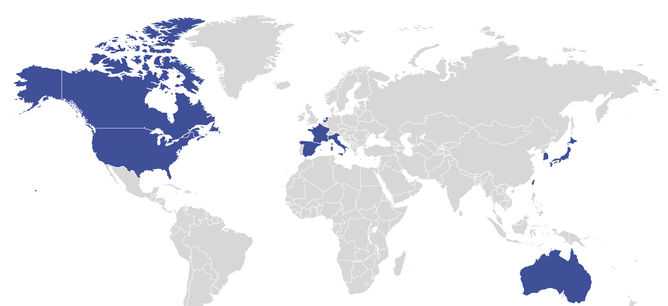
- Efficacy analyses will be completed on the full analysis set, which will include all patients who are randomly assigned to a study treatment
  - ORR will be estimated along with the 2-sided 95% CIs
  - Median DOR, PFS, and OS will be summarized using the Kaplan–Meier method
- Safety analyses will be performed on the safety analysis set, which will include all patients who receive ≥1 dose of T-DXd
- Pharmacokinetic (PK) analyses will be performed using the PK analysis set, which will include all patients who receive ≥1 dose of T-DXd and have measurable serum concentrations of T-DXd
  - Serum concentrations of T-DXd, total anti-HER2 antibody, and MAAA 1181a will be listed and summarized using descriptive statistics at each time point by dose level
- Immunogenicity will be assessed by characterizing the incidence and titer of antidrug antibodies
- Descriptive statistics will be calculated to summarize the change from baseline in symptoms, physical functioning, and general health-related quality-of-life scales at each scheduled assessment time point by dose level

Objective

- This randomized phase 2 study will characterize the benefit-risk profile of T-DXd in patients with metastatic *HER2*m NSCLC who have experienced disease recurrence or progression during or after ≥1 regimen of prior anticancer therapy, including platinum therapy
  - The efficacy and safety of the 5.4 mg/kg dose in patients with *HER2*m NSCLC will be evaluated for the first time, and the efficacy and safety of the 6.4 mg/kg dose will be further assessed in this population
  - The primary endpoint is confirmed ORR by blinded independent central review

Enrollment

- This trial is actively enrolling, with approximately 150 patients to be enrolled from 45 sites in Australia, Canada, France, Italy, Japan, Netherlands, South Korea, Spain, Taiwan, and the United States
- For more information or to refer a patient, please visit ClinicalTrials.gov (NCT04644237)



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Disclosures

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