Trastuzumab Deruxtecan + Pembrolizumab as First-Line Treatment in HER2-Overexpressing, PD-L1 TPS <50% NSCLC (DESTINY-Lung06)

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Plain language summary

Why are we performing this research?

- There are currently no approved first-line (1L) human epidermal growth factor receptor 2 (HER2)-directed therapies for patients with HER2-overexpressing non–small cell lung cancer (NSCLC).[1,2] These patients often respond poorly to existing 1L treatments, particularly those with low programmed death-ligand 1 (PD-L1) expression (tumor proportion score [TPS] <50%), underscoring a need for new therapies[3-7]
- Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody bound to a cytotoxic chemotherapy agent that is designed to target and kill tumor cells expressing HER2[8]
- T-DXd monotherapy has been approved as the first HER2-directed therapy for unresectable/metastatic HER2-positive (IHC 3+) solid tumors after prior systemic treatment and no satisfactory alternative treatment options[9]
- T-DXd has also been shown to be effective in patients with HER2-overexpressing NSCLC who have received prior therapies[10,11]
- Preliminary data from a phase 1b trial (DS8201-A-U106) showed promising results with T-DXd + pembrolizumab in patients with HER2-expressing (IHC 1+, 2+, or 3+) NSCLC who had not received previous treatment.[12] These results support a larger phase 3 study to further examine this treatment combination
- The DESTINY-Lung06 trial aims to establish T-DXd, in combination with pembrolizumab, as a replacement for 1L standard chemotherapy in patients with HER2-overexpressing, PD-L1 TPS <50% NSCLC, offering a more targeted approach to improve outcomes in this population

How are we performing this research?

- Patients will be randomly assigned to 2 treatment groups
  - The first group will receive T-DXd + pembrolizumab every 3 weeks
  - The second group will receive pemetrexed + platinum-based chemotherapy + pembrolizumab every 3 weeks
- The primary endpoint is progression-free survival by blinded independent central review, a measure of the time interval from the date of randomization to the date of radiographic disease progression or death due to any cause
- The key secondary endpoint is overall survival, a measure of the time interval from the date of randomization to the date of the death due to any cause

Who will participate in this study?

- Adults with locally advanced, unresectable/metastatic non-squamous NSCLC with HER2 overexpression and PD-L1 TPS <50% who have had no prior systemic treatment for advanced/metastatic NSCLC and have no known actionable genomic alterations with locally available therapies targeting them in the 1L setting

Where can I access more information?

- To learn more about the trial in this study, you can visit: https://clinicaltrials.gov/study/NCT06899126

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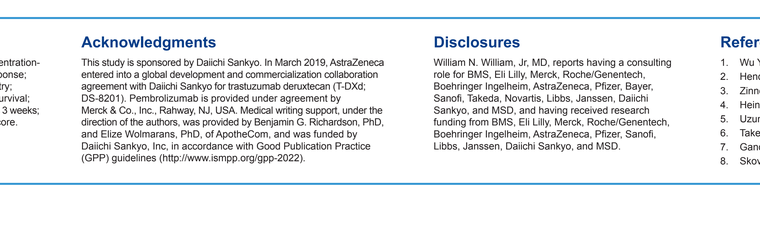
Trial design

- DESTINY-Lung06 (NCT06899126) is a global, open-label, randomized, phase 3 trial designed to evaluate the safety and efficacy of T-DXd + pembrolizumab versus platinum-based chemotherapy + pembrolizumab as a 1L therapy in patients with HER2-overexpressing, PD-L1 TPS <50%, unresectable/metastatic, non-squamous NSCLC
- Approximately 686 patients will be randomly assigned 1:1 to receive T-DXd 5.4 mg/kg + pembrolizumab 200 mg every 3 weeks (Q3W) or pemetrexed 500 mg/m^2 + platinum-based chemotherapy (cisplatin 75 mg/m^2, or carboplatin area under the concentration-time curve [AUC] 5 mg/mL*min) + pembrolizumab 200 mg Q3W
- Randomization will be stratified by:
  - Prior neoadjuvant/adjuvant therapy: yes versus no
  - Smoking history: ever smoked versus never smoked
  - PD-L1 expression: TPS <1% versus 1%-49%
  - HER2 IHC expression: IHC 3+ versus non-IHC 3+

DESTINY-Lung06 study design



[a]For example, *ALK, ROS1, EGFR, NTRK, BRAF, RET, or MET* (by local testing).
[b]If approved or validated local test is available.
[c]T-DXd 5.4 mg/kg + pembrolizumab 200 mg IV Q3W.
[d]Pembrolizumab 200 mg + pemetrexed 500 mg/m^2 + platinum-based chemotherapy [cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL*min] IV Q3W.

Study start: September, 2025 | Recruiting

DESTINY-Lung06 is planned to be conducted at approximately 250 trial sites located in Asia, Europe, North America, and South America

Key inclusion criteria

- Adults ≥18 years old
- Histologically documented non-squamous, locally advanced, unresectable/metastatic NSCLC
- No known AGAs that have locally available therapies targeting their AGAs in the 1L advanced/metastatic setting
- No known *HER2* mutation based on existing test results
- Centrally confirmed HER2 overexpression and PD-L1 TPS <50%
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Left ventricular ejection fraction of ≥50% within 28 days before randomization
- No previous treatment with systemic anticancer therapy for advanced/metastatic non-squamous NSCLC
  - Patients who received adjuvant/neoadjuvant therapy, including immune checkpoint inhibitors or a platinum-based regimen are eligible if the last dose was given at least 6 months before the date of first trial dose and should not have progressed on or within 6 months of the last dose date of adjuvant/neoadjuvant therapy
  - Patients who received any agent containing a chemotherapeutic agent targeting topoisomerase I or a HER2-targeted antibody-based anticancer therapy are not eligible
- Patients with asymptomatic central nervous system metastases who do not require steroid or anticonvulsant treatment for at least 14 days before trial intervention may participate
  - Patients with previously treated brain metastases may also participate provided they are clinically and radiologically stable for at least 4 weeks after the end of radiotherapy as confirmed by repeat imaging performed during screening

Key exclusion criteria

- History of myocardial infarction within 6 months before randomization/enrollment or symptomatic congestive heart failure
- Corrected QT interval prolongation to >480 ms based on the average of the screening triplicate 12-lead electrocardiogram
- History of (noninfectious) ILD/pneumonitis that required steroids, currently has ILD/pneumonitis, or is suspected of having ILD/pneumonitis which cannot be ruled out by imaging at screening
- Lung-specific, intercurrent, clinically significant illnesses including, but not limited to, any underlying pulmonary disorder such as pulmonary emboli (within 3 months of trial randomization), severe asthma, severe chronic obstructive pulmonary disease, restrictive lung disease, or pleural effusion
- Prior complete pneumonectomy
- Spinal cord compression, symptomatic central nervous system metastases, and/or carcinomatous meningitis

Background

- Currently, no human epidermal growth factor receptor 2 (HER2)-targeted therapies are available in the first-line (1L) setting for HER2-overexpressing non–small cell lung cancer (NSCLC)[1,2]
- HER2-overexpression (immunohistochemistry [IHC] 3+ or IHC 2+) occurs in ~13%-20% of patients with NSCLC and is associated with poor prognosis[3-6]
- Approximately 60%-70% of patients with NSCLC have tumors with programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) <50%, which is also associated with worse outcomes[7-10]
- The recommended 1L treatment for non-squamous HER2-overexpressing NSCLC is pembrolizumab + platinum-based chemotherapy.[1,2] However, efficacy outcomes with pembrolizumab + platinum-based chemotherapy are lower in patients with a PD-L1 TPS <50%[7,10]
  - In the KEYNOTE-189 trial, patients with a PD-L1 TPS of 1%-49% had progression-free survival (PFS) of 9.4 months and overall survival (OS) of 21.8 months, compared with patients with a PD-L1 TPS ≥50% (PFS, 11.1 months; OS, 27.7 months)[10]
- Together this highlights an unmet need in patients with HER2-overexpressing NSCLC with PD-L1 TPS <50%
- Findings from DESTINY-Lung01, DESTINY-PanTumor02, and DESTINY-CRC02 led to the approval of trastuzumab deruxtecan (T-DXd) monotherapy as the first tumor-agnostic HER2-directed therapy for unresectable/metastatic HER2-positive (IHC 3+) solid tumors after prior systemic treatment and no satisfactory alternative treatment options[11]
- Preclinical data in an immunocompetent mouse model demonstrated better efficacy with the combination of T-DXd and an anti–PD-1 antibody compared with either as monotherapy[12]
- Furthermore, preliminary data from the phase 1b DS8201-A-U106 trial showed encouraging efficacy with T-DXd + pembrolizumab in patients with HER2-expressing (IHC 1+, 2+, or 3+) NSCLC[13]
  - In patients with immuno-oncology–naive HER2-expressing NSCLC (n = 22), the confirmed objective response rate by independent central review was 54.5%, median duration of response (DOR) was 20.2 months, and median PFS was 15.1 months
  - In the treatment-naive NSCLC subgroup (n = 8), the confirmed objective response rate by independent central review was 62.5%, median DOR was 20.2 months, and median PFS was 23.5 months
  - The safety profile of the combination was consistent with the known profiles of the individual drugs; adjudicated drug-related interstitial lung disease (ILD)/pneumonitis occurred in 2 patients (9.1%; 1 grade 2 and 1 grade 3) in the HER2-expressing NSCLC cohort (n = 22)
- Therefore, a combined approach using immuno-oncology and a targeted therapy, T-DXd, in DESTINY-Lung06 could help overcome the limited progress made by available treatments in NSCLC with HER2 overexpression and PD-L1 TPS <50%
- T-DXd is expanding into earlier treatment lines and DESTINY-Lung06 aims to enhance 1L standard-of-care immuno-oncology by replacing standard chemotherapy with T-DXd + pembrolizumab for patients with HER2-overexpressing, PD-L1 TPS <50% NSCLC. This trial is one of the few to seek antibody-drug conjugate development in the 1L setting in a personalized, biomarker-driven approach

Endpoints

1° Primary

- PFS by blinded independent central review (BICR)[a]

2° Key secondary

- OS

Other secondary

- PFS by investigator assessment[a]
- Overall response rate by BICR and investigator assessment[a]
- DOR by BICR and investigator assessment[a]
- Safety and tolerability
- Patient-reported outcomes

[a]By Response Evaluation Criteria in Solid Tumours, version 1.1

Poster

This study was sponsored by 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).

Abbreviations

1L, first-line; AGA, actionable genomic alteration; AUC, area under the concentration-time curve; BICR, blinded independent central review; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ILD, interstitial lung disease; NSCLC, non–small cell lung cancer; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPS, tumor proportion score.

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Disclosures

William N. William, Jr, MD, reports having a consulting role for BMS, Eli Lilly, Merck, Roche/Genentech, Boehringer Ingelheim, AstraZeneca, Pfizer, Bayer, Sanofi, Takeda, Novartis, Libbs, Janssen, Daiichi Sankyo, and MSD, and having received research funding from BMS, Eli Lilly, Merck, Roche/Genentech, Boehringer Ingelheim, AstraZeneca, Pfizer, Sanofi, Libbs, Janssen, Daiichi Sankyo, and MSD.

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DESTINY Lung06

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