Phase 1b study of first-line trastuzumab deruxtecan plus volrustomig in patients with HER2-overexpressing non-small cell lung cancer: DESTINY-Lung03 Part 5

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Plain language summary

Why are we performing this research?

Human epidermal growth factor receptor 2 (HER2) is a protein found at a high level in some cancers, including non-small cell lung cancer (NSCLC). These cancers may be referred to as HER2-overexpressing (HER2-OE; HER2 immunohistochemistry [IHC] 3+/2+) NSCLC.[1] Currently, there are limited HER2-directed treatment options for people with HER2-OE NSCLC,[2] despite its association with poor outcomes.[3] Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate, comprising a chemotherapy with a linker (together called deruxtecan) joined to an antibody (trastuzumab).[4,5] T-DXd is approved in more than 10 countries as a treatment for people with HER2-positive (IHC 3+) solid tumors that cannot be removed with surgery (unresectable) or have spread to other parts of the body (advanced/metastatic), and who have received prior treatment and/or have no alternative treatment options; treatment of HER2 IHC 3+ NSCLC is included in the approval.[6,7]
The combination of chemotherapy with immunotherapy, including drugs targeting programmed cell death protein 1 (PD-1), has been shown to provide clinical benefit,[8,9] and is an established standard of care in NSCLC.[2] Volrustomig is a novel drug that blocks both PD-1 and cytotoxic T-lymphocyte-associated protein 4 on the surface of cells in the immune system, thereby helping the immune system kill cancer cells.[10]
Part 5 of the DESTINY-Lung03 study will assess whether combining T-DXd with volrustomig could benefit people with HER2-OE NSCLC.[11]

How are we performing this research?

DESTINY-Lung03 is an ongoing multipart study evaluating T-DXd alone and in combination with other cancer treatments. Part 5 of the study will evaluate the safety and benefit of T-DXd with volrustomig in people with HER2-OE (IHC 3+/2+) NSCLC. The primary outcome of interest is the proportion of participants who experience side effects.

Who will participate in this study?

Part 5 will include people with unresectable locally advanced or metastatic HER2-OE (IHC 3+/2+) NSCLC. People cannot participate if they have had previous treatment for their advanced or metastatic disease.

Where can I access more information?

For more information about DESTINY-Lung03, please visit https://clinicaltrials.gov/study/NCT04686305. You may also speak to your doctor about this and other studies.

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Background

- Approximately 1−23% of non-small cell lung cancers (NSCLCs) are human epidermal growth factor receptor 2 (HER2) immunohistochemistry (IHC) 2+, and 1−5% are IHC 3+,[1–5] with HER2 overexpression (IHC 3+/2+) being associated with poor prognosis[6]
  - No first-line HER2-directed therapies are approved for HER2-overexpressing (HER2-OE; IHC 3+/2+) NSCLC[7]
- Trastuzumab deruxtecan (T-DXd) is a HER2-directed antibody-drug conjugate approved in multiple countries for adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior treatment and/or have no alternative treatment options[8–10]
- DESTINY-Lung03 (NCT04686305) is a Phase 1b, open-label, multipart study evaluating T-DXd regimens in HER2-OE (IHC 3+/2+) NSCLC[11]
  - In Part 1, T-DXd monotherapy (5.4 mg/kg) demonstrated clinical benefit in pretreated HER2-OE NSCLC, with a confirmed objective response rate of 44.4%, median progression-free survival of 8.2 months, and median overall survival of 17.1 months[12]
- Chemotherapy and immunotherapy combinations remain well-established standards of care for advanced or metastatic NSCLC;[7] data from an interim analysis of the U106 study demonstrated antitumor activity with the combination of T-DXd plus pembrolizumab, a programmed cell death 1 (PD-1) inhibitor, in HER2-expressing (IHC 3+/2+/1+) NSCLC (objective response rate, 54.5%; median progression-free survival,15.1 months)[13]
  - Volrustomig is a monovalent, dual checkpoint inhibitor, bispecific, humanized, immunoglobulin G1 monoclonal antibody against PD-1 / cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)[14]
  - Volrustomig has shown increased antitumor activity compared with either anti-PD-1 or anti-CTLA-4 antibodies alone in preclinical settings,[14] and is being investigated in various solid tumors, including NSCLC, either as monotherapy or in combination with chemotherapy or other agents[15,16]

DESTINY-Lung03 Part 5 will assess first-line T-DXd with volrustomig in treatment-naïve patients with unresectable locally advanced or metastatic HER2-OE (IHC 3+/2+) NSCLC

Study design

DESTINY-Lung03 (NCT04686305) is a Phase 1b, open-label, dose-escalation (Part 1), dose-expansion (Parts 2–4),* and dose-confirmation (Parts 3 and 5) study evaluating T-DXd as monotherapy or in combination with immunotherapy and/or chemotherapy in unresectable locally advanced or metastatic HER2-OE (IHC 3+ or IHC 2+)† NSCLC[11]

Part 1 (ENROLLMENT COMPLETE)
T-DXd monotherapy or in combination with immunotherapy and chemotherapy in previously treated patients with HER2-OE NSCLC

Part 3 (ENROLLMENT COMPLETE)
T-DXd plus volrustomig, with or without chemotherapy, in treatment-naïve patients with HER2-OE NSCLC

Part 4 (CURRENTLY RECRUITING)
T-DXd plus rilvegostomig, with or without chemotherapy, in treatment-naïve patients with HER2-OE NSCLC

Part 5 (CURRENTLY RECRUITING)

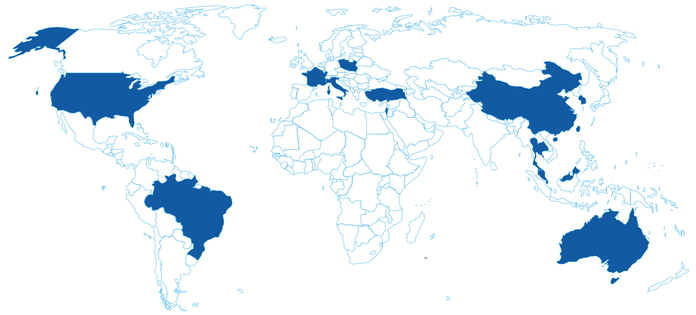
N≈30

T-DXd IV plus **volrustomig** IV in treatment-naïve patients with HER2-OE NSCLC
Volrustomig will be administered as a single priming dose, followed by a fixed maintenance dose‡

For more information about DESTINY-Lung03, please visit https://clinicaltrials.gov/study/NCT04686305

*Part 2 was planned but not initiated; †overexpression defined as ≥25% of tumor cells with IHC 3+/2+ staining; ‡second arm (T-DXd + volrustomig at a fixed dose only) to open at the discretion of the sponsor
HER2-OE, human epidermal growth factor receptor 2-overexpressing; IHC, immunohistochemistry; IV, intravenous; NSCLC, non-small cell lung cancer; T-DXd, trastuzumab deruxtecan

Part 5 enrollment start: October 30, 2025



Countries with participating study sites

Australia, Brazil, China, France, Israel, Italy, Malaysia, Poland, Republic of Korea, Taiwan, Thailand, Türkiye, United States

Key inclusion criteria for Part 5

- Aged ≥18 years
- Histologically documented, unresectable locally advanced (Stage III) or metastatic (Stage IV) nonsquamous NSCLC
- Treatment-naïve for advanced or metastatic NSCLC
  - Prior (neo)adjuvant therapies or definitive chemoradiation for advanced disease are permitted if progression occurred >6 months from the end of the last therapy
- HER2-OE status (IHC 3+/2+) as determined by central assessment of tumor tissue
- Tumors without known genomic alterations or actionable driver kinases for which targeted therapies are available
- World Health Organization / Eastern Cooperative Oncology Group performance status score of 0 or 1
- ≥1 measurable lesion as assessed by the investigator using Response Evaluation Criteria In Solid Tumours (RECIST) 1.1
- Protocol-defined adequate organ and bone marrow function within 14 days prior to treatment assignment

Key exclusion criteria for Part 5

- Known *HER2*-activating mutation
- Mixed small cell lung cancer, squamous NSCLC, and sarcomatoid histology variant NSCLC
- History of non-infectious interstitial lung disease (ILD)/pneumonitis requiring steroids, current ILD/pneumonitis, or suspected ILD/pneumonitis that cannot be ruled out by imaging at screening
- Lung-specific, intercurrent, clinically significant illnesses, including any underlying pulmonary disorder, and prior pneumonectomy
- Any autoimmune, connective tissue, or inflammatory disorders
- Spinal cord compression or clinically active central nervous system metastases
- Ascites or pericardial effusion that requires drainage, peritoneal shunt, pleuroperitoneal shunt, or cell-free and concentrated ascites reinfusion therapy
- Cardiomyopathy of any etiology; heart failure (as defined by New York Heart Association classification >II); uncontrolled hypertension; unstable angina pectoris; clinically significant coronary, carotid, or peripheral artery stenosis; prior arterial or peripheral vascular intervention within the 12 months prior to randomization; ventricular arrhythmia requiring treatment; pacemaker-untreated high degree (≥II) atrioventricular block or sinus node dysfunction; and/or congenital or family history of long QT syndrome
- Participation in a concurrent interventional study and/or previously treated with T-DXd
- Prior exposure to anti-PD-1, anti-programmed cell death-ligand 1, anti-CTLA-4, anti-T cell immunoglobulin and immunoreceptor with tyrosine-based inhibitory motif domain agents, or any other experimental immunotherapy in any setting

Key study endpoints for Part 5

1° Primary endpoints

- Frequency of adverse events (AEs; including serious AEs) and AEs of special interest
- Changes from baseline in laboratory parameters, vital signs, and electrocardiogram results

2° Secondary endpoints

- Investigator-assessed (per RECIST 1.1)
  - Confirmed objective response rate
  - Duration of response
  - Disease control rate at 6 weeks and 12 weeks
  - Progression-free survival*
- Overall survival*
- Serum concentrations of T-DXd, total anti-HER2 antibody, deruxtecan, and volrustomig
- Presence of anti-drug antibodies for T-DXd and volrustomig

*Including landmark analysis of progression-free survival at 6 months and 12 months, and overall survival at 12 months

Poster

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Disclosures

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DESTINY Lung03

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