17 August 2026

Enhertu demonstrated statistically significant and clinically meaningful improvement in progression-free survival as 1st-line treatment of patients with HER2-mutant advanced non-small cell lung cancer in DESTINY-Lung04 Phase III trial

AstraZeneca and Daiichi Sankyo's Enhertu is the first and only HER2-directed medicine to improve progression-free survival over global standard of care in a Phase III trial in this setting

Positive high-level results from the DESTINY-Lung04 Phase III trial showed *Enhertu* (trastuzumab deruxtecan) demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) versus global standard of care (platinum-pemetrexed doublet chemotherapy plus pembrolizumab) as 1st-line treatment of patients with unresectable, locally advanced or metastatic *HER2*-mutant non-squamous non-small cell lung cancer (NSCLC). The trial will continue as planned to evaluate secondary endpoints including overall survival.

The global standard of care for patients with *HER2*-mutant NSCLC in the 1st-line metastatic setting is a combination of immunotherapy and platinum-based chemotherapy.[1-3] However, many patients do not respond to 1st-line treatment and experience disease progression, underscoring the need for additional treatment options.[3-7] Approximately 2-4% of patients with NSCLC have tumours with a *HER2* mutation.[8-10]

Susan Galbraith, Executive Vice President, Oncology Haematology R&D, AstraZeneca, said: "Our oncology pipeline continues to advance with DESTINY-Lung04 becoming the first Phase III trial to demonstrate a progression-free survival benefit versus the global standard of care in this first-line setting, supporting the potential for *Enhertu* to move earlier in the treatment of *HER2*-mutant non-small cell lung cancer. This aggressive lung cancer often affects younger patients and has historically had limited first-line targeted treatment options, making these positive results an important step forward in bringing additional effective therapies to patients at metastatic diagnosis when there is the greatest opportunity to improve outcomes."

John Tsai, Global Head, R&D, Daiichi Sankyo, said: "*Enhertu* is already established as the first and only antibody drug conjugate for the second-line treatment of *HER2*-mutant metastatic non-small cell lung cancer. The positive results seen in DESTINY-Lung04 show that treatment with *Enhertu* in the first-line setting delays disease progression compared to the global standard of care, highlighting its potential to improve outcomes for patients earlier in the treatment of metastatic disease."

The safety profile of *Enhertu* observed in DESTINY-Lung04 was generally consistent with its known profile, with no new safety concerns identified.

The DESTINY-Lung04 data will be presented at a forthcoming medical meeting and shared with global regulatory authorities.

Enhertu is currently approved to treat patients with previously treated metastatic NSCLC whose tumours have activating *HER2* (*ERBB2*) mutations, and to treat patients with HER2-positive solid tumours, including HER2-overexpressing metastatic NSCLC, who have received prior treatment and who have no satisfactory treatment options.

Enhertu is a specifically engineered HER2-directed DXd antibody drug conjugate (ADC) discovered by Daiichi Sankyo and being jointly developed and commercialised by AstraZeneca and Daiichi Sankyo.

Notes

HER2-mutant NSCLC

Lung cancer is the most commonly diagnosed cancer globally and remains the leading cause of cancer-related death in both men and women.[11] In 2024, approximately 2.6 million new lung cancer cases were reported worldwide, with an estimated 1.8 million deaths.[11] NSCLC is the most common

type of lung cancer, accounting for approximately 85% of cases.[12] Prognosis is particularly poor for patients with metastatic NSCLC as only approximately 10% will live beyond five years after diagnosis.[13-15]

HER2 is a tyrosine kinase receptor protein involved in cell growth and differentiation and expressed on the surface of multiple tumour types. *HER2* mutations have been identified in NSCLC as distinct molecular targets and have been reported in approximately 2-4% of patients with non-squamous NSCLC.[8-10] These *HER2* mutations are predominantly seen in younger women and people with no smoking history and have been independently associated with cancer cell growth and poor prognosis, with an increased incidence of brain metastases.[8,16-20]

The global standard of care in the 1st-line metastatic setting for patients with *HER2*-mutant NSCLC is a combination of immunotherapy and platinum-based chemotherapy.[1-3] While these treatment regimens have been shown to improve survival in NSCLC, many patients do not respond to 1st-line treatment and experience disease progression, underscoring the need for additional treatment options.[3-7]

DESTINY-Lung04
DESTINY-Lung04 is a global, randomised, open-label, Phase III trial evaluating the efficacy and safety of *Enhertu* (5.4mg/kg) compared to standard of care (platinum-pemetrexed doublet chemotherapy in combination with pembrolizumab) in patients with unresectable, locally advanced or metastatic, non-squamous NSCLC harbouring a *HER2* exon 19 or 20 mutation.

Patients were randomised 1:1 to receive either *Enhertu* or standard of care. Randomisation was stratified by smoking history and presence or history of brain metastasis. The primary endpoint of DESTINY-Lung04 is PFS as assessed by blinded independent central review (BICR). Secondary endpoints include OS, investigator-assessed PFS, overall response rate and duration of response as assessed by BICR and investigator, pharmacokinetics and safety.

DESTINY-Lung04 enrolled 454 patients across multiple sites in Asia, Europe and North America. For more information about the trial, visit ClinicalTrials.gov.

Enhertu
Enhertu is a HER2-directed ADC. Designed using the proprietary DXd ADC Technology of Daiichi Sankyo, *Enhertu* is the lead ADC in the oncology portfolio of Daiichi Sankyo and the most advanced programme in AstraZeneca's ADC scientific platform. *Enhertu* consists of a HER2 monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers.

Enhertu (5.4mg/kg) followed by THP is approved in the US, China, Singapore and India as a neoadjuvant treatment for adult patients with HER2-positive (IHC 3+ or ISH+) Stage II or III breast cancer based on the results from the DESTINY-Breast11 trial. Continued approval in China for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Enhertu (5.4mg/kg) is approved in Brazil and the US as an adjuvant treatment for adult patients with HER2-positive (IHC 3+ or ISH+) breast cancer who have residual invasive disease following trastuzumab (with or without pertuzumab) and taxane-based treatment based on the DESTINY-Breast05 trial.

Enhertu (5.4mg/kg) in combination with pertuzumab is approved in more than ten countries as a 1st-line treatment for adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer based on the results from the DESTINY-Breast09 trial.

Enhertu (5.4mg/kg) is approved in more than 75 countries worldwide for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low (IHC 1+ or IHC 2+/ ISH-) or HER2-ultralow (IHC 0 with membrane staining) breast cancer, as determined by a locally or regionally authorised test, that have progressed on one or more endocrine therapies in the metastatic setting based on the results from the DESTINY-Breast06 trial.

Enhertu (5.4mg/kg) is approved in more than 100 countries worldwide for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+ or ISH+) breast cancer who have received a prior anti-HER2-based regimen, either in the metastatic setting or in the neoadjuvant or adjuvant setting, and have developed disease recurrence during or within six months of completing therapy based on the results from the DESTINY-Breast03 trial.

Enhertu (5.4mg/kg) is approved in more than 100 countries worldwide for the treatment of adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH) breast cancer who have received a prior systemic therapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy based on the results from the DESTINY-Breast04 trial.

Enhertu (5.4mg/kg) is approved in more than 80 countries worldwide for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumours have activating *HER2* (*ERBB2*) mutations, as detected by a locally or regionally approved test, and who have received a prior systemic therapy based on the results from the DESTINY-Lung02 and/or DESTINY-Lung05 trials. Continued approval in China and the US for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Enhertu (6.4mg/kg) is approved in more than 90 countries worldwide for the treatment of adult patients with locally advanced or metastatic HER2-positive (IHC 3+ or IHC 2+/ISH+) gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen based on the results from the DESTINY-Gastric01, DESTINY-Gastric02 and/or DESTINY-Gastric04 trials.

Enhertu (5.4mg/kg) is approved in more than 45 countries/regions worldwide for the treatment of adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumours who have received prior systemic treatment and have no satisfactory alternative treatment options based on efficacy results from the DESTINY-PanTumor02, DESTINY-Lung01, DESTINY-CRC02 and/or HERALD trials. Continued approval in the US for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Enhertu clinical development programme

A comprehensive global clinical development programme is underway evaluating the efficacy and safety of *Enhertu* as a monotherapy, in combination or sequentially with other cancer medicines across multiple HER2-targetable cancers.

Daiichi Sankyo collaboration

AstraZeneca and Daiichi Sankyo entered into a global collaboration to jointly develop and commercialise *Enhertu* in March 2019 and *Datroway* (datopotamab deruxtecan) in July 2020, except in Japan where Daiichi Sankyo maintains exclusive rights for each ADC. Daiichi Sankyo is responsible for the manufacturing and supply of *Enhertu* and *Datroway*.

AstraZeneca in lung cancer

AstraZeneca is working to bring patients with lung cancer closer to cure through the detection and treatment of early-stage disease, while also pushing the boundaries of science to improve outcomes in the resistant and advanced settings. By defining new therapeutic targets and investigating innovative approaches, the Company aims to match medicines to the patients who can benefit most.

The Company's comprehensive portfolio includes leading lung cancer medicines and the next wave of innovations, including *Tagrisso* and *Iressa* (gefitinib); *Imfinzi* (durvalumab) and *Imjudo* (tremelimumab); *Enhertu* (trastuzumab deruxtecan) and *Datroway* in collaboration with Daiichi Sankyo; *Orpathys* in collaboration with HUTCHMED; as well as a pipeline of potential new medicines and combinations across diverse mechanisms of action.

AstraZeneca is a founding member of the Lung Ambition Alliance, a global coalition working to accelerate innovation and deliver meaningful improvements for people with lung cancer, including and beyond treatment.

AstraZeneca in oncology
AstraZeneca is leading a revolution in oncology with the ambition to provide cures for cancer in every form, following the science to understand cancer and all its complexities to discover, develop and deliver life-changing medicines to patients.

The Company's focus is on some of the most challenging cancers. It is through persistent innovation that AstraZeneca has built one of the most diverse portfolios and pipelines in the industry, with the potential to catalyse changes in the practice of medicine and transform the patient experience.

AstraZeneca has the vision to redefine cancer care and, one day, eliminate cancer as a cause of death.

AstraZeneca
AstraZeneca (LSE/STO/NYSE: AZN) is a global, science-led biopharmaceutical company that focuses on the discovery, development, and commercialisation of prescription medicines in Oncology, Rare Disease, and BioPharmaceuticals, including Cardiovascular, Renal & Metabolism, and Respiratory & Immunology. Based in Cambridge, UK, AstraZeneca's innovative medicines are sold in more than 125 countries and used by millions of patients worldwide. Please visit astrazeneca.com and follow the Company on Social Media @AstraZeneca.

Contacts
For details on how to contact the Investor Relations Team, please click here. For Media contacts, click here.

References

1. Hendriks LE, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34(4):339-357.
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Version 5.2026. March 13, 2026. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed August 2026.
3. Man J, et al. Response Rate and Survival at Key Timepoints With PD-1 Blockade vs Chemotherapy in PD-L1 Subgroups: Meta-Analysis of Metastatic NSCLC Trials. *JNCI Cancer Spectr*. 2021;5(3):pkab012.
4. Paz-Ares L, et al. A Randomized, Placebo-Controlled Trial of Pembrolizumab Plus Chemotherapy in Patients With Metastatic Squamous NSCLC: Protocol-Specified Final Analysis of KEYNOTE-407. *J Thorac Oncol*. 2020 Oct;15(10):1657-1669.
5. Mok TSK, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019 May 4;393(10183):1819-1830.
6. Rodríguez-Abreu D et al. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189. *Ann Onc*. 2021 Jul;32(7):881-895.
7. Brahmer J.R. et al. KEYNOTE-024 5-year OS update: First-line (1L) pembrolizumab (pembro) vs platinum-based chemotherapy (chemo) in patients (pts) with metastatic NSCLC and PD-L1 tumour proportion score (TPS) ≥50%. *ESMO 2021 Virtual Congress*; Abstract LBA51.
8. Mazieres J, et al. Lung Cancer That Harbors an *HER2* Mutation: Epidemiologic Characteristics and Therapeutic Perspectives. *J Clin Oncol*. 2013;31(16):1997-2003.
9. cBioPortal for Cancer Genomics. Available at: https://www.cbioportal.org/. Accessed August 2026.
10. Yoshizawa A, et al. HER2 Status In Lung Adenocarcinoma: A Comparison Of Immunohistochemistry, Fluorescence In Situ Hybridization (FISH), Dual-ISH, and Gene Mutations. *Lung Cancer*. 2014;85(3):373-378.
11. World Health Organization. Lung Cancer Fact Sheet. Available at: https://gco.iarc.who.int/today/en/fact-sheets-cancers/15/trachea-bronchus-and-lung. Accessed August 2026.
12. Leiter A, et al. The global burden of lung cancer: current status and future trends. *Nat Rev Clin Oncol*. 2023;20(9):624-639.
13. Tamura T, et al. Specific organ metastases and survival in metastatic non-small-cell lung cancer. *Mol Clin Oncol*. 2015;3(1):217-221.
14. Goldstraw P, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol*. 2016;11(1):39-51.

15. Siegel RL, et al. Cancer Statistics, 2021. *CA Cancer J Clin*. 2021;71(1):7-33.
16. Liu S, et al. Targeting HER2 Aberrations in Non-Small Cell Lung Cancer with Osimertinib. *Clin Cancer Res*. 2018;24(11):2594-2604.
17. Stephens P, et al. Lung cancer: intragenic ERBB2 kinase mutations in tumours. *Nature*. 2004;431:525-6.
18. Arcila ME, et al. Prevalence, Clinicopathologic Associations, and Molecular Spectrum of ERBB2 (HER2) Tyrosine Kinase Mutations in Lung Adenocarcinomas. *Clin Cancer Res*. 2012;18:4910-8.
19. Pillai RN, et al. *HER2* mutations in lung adenocarcinomas: A report from the Lung Cancer Mutation Consortium. *Cancer*. 2017;123:4099-105.
20. Offin M, et al. Frequency and outcomes of brain metastases in patients with HER2-mutant lung cancers. *Cancer*. 2019;125:4380-7.

Matthew Bowden
Company Secretary
AstraZeneca PLC