Trastuzumab deruxtecan (Enhertu®) as monotherapy for the treatment of patients with advanced non-small cell lung cancer (NSCLC) whose tumours have an activating HER2 (ERBB2) mutation

General information

Drug description (1)

Trastuzumab deruxtecan (Enhertu®, DS-8201a) is a HER2-directed antibody and topoisomerase inhibitor conjugate.

Indication (2)

Enhertu® as monotherapy is indicated for the treatment of adult patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy.

Incidence

- In Austria, in 2020, the age-standardised incidence rate[1] of cancer of the lung, trachea and bronchus was 67.4 per 100,000 men and 41.1 per 100,000 women (3).
- In 2017 - 2019, NSCLC accounted for approximately 79% of all lung cancer cases reported to cancer registries via hospitals, practices, or pathologies (based on cancer registry data from the individual German states). 15% were small cell lung cancer, and in approximately 5% of cases, no assignment was possible due to nonspecific histology information. Adenocarcinomas formed the largest group within NSCLC at 54%, followed by squamous cell carcinomas (28%) (4).

Current treatment (4)

- HER2 is mutated in 1-4% of NSCLC and overexpressed in 30%. Underlying genetic aberrations include mutations and amplifications, or overexpression of the protein. Retrospective data suggest the efficacy of chemo-immunotherapy in this patient population.
- Strategies for targeted therapy include monotherapy with trastuzumab, combination chemotherapy with trastuzumab, double antibody blockade with trastuzumab/pertuzumab, and use of the antibody conjugates trastuzumab emtansine and trastuzumab deruxtecan.
- When refractory to standard therapy, therapy with trastuzumab deruxtecan resulted in a remission rate of 55%, a median PFS of 8.2 months, and a median OS of 17.8 months in a phase II study of 91 patients. A particular side effect is interstitial lung disease; it occurred in 26% of patients.

Regulatory status

EMA (2)

Approval status for this indication: On 14 September 2023, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Enhertu®.

The CHMP adopted a new indication as follows:

- Enhertu® as monotherapy is indicated for the treatment of adult patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy.

Other indications: Enhertu® is indicated:

- as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens.
- as monotherapy for the treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

FDA (1, 5)

Approval status for this indication: On 11 August 2022, the FDA granted accelerated approval to fam-trastuzumab deruxtecan-nxki (Enhertu®) for adult patients with unresectable or metastatic NSCLC whose tumours have activating human epidermal growth factor receptor 2 HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy. This is the first drug approved for HER2-mutant NSCLC.

FDA also approved the Life Technologies Corporation's Oncomine™ Dx Target Test (tissue) and the Guardant Health, Inc.'s Guardant360® CDx (plasma) as companion diagnostics for Enhertu®. If no mutation is detected in a plasma specimen, the tumour tissue should be tested.

- ✓ Priority review
- ✓ Breakthrough designation

Other indications: Enhertu® is indicated for the treatment of:

- adult patients with unresectable or metastatic HER2-positive 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.

[1] European Standard Population 2013.

❖ as monotherapy for the treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen. ✓ **Medicine under additional monitoring** ✓ **Medicine received a conditional marketing authorisation**[2]	❖ adult patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer, as determined by an FDA-approved test, who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. This indication is approved under accelerated approval based on objective response rate and duration of response. ❖ adult patients with locally advanced or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma who have received a prior trastuzumab-based regimen.

Manufacturer

Enhertu® is manufactured by Daiichi Sankyo.

Costs

Enhertu® powder for concentrate for solution for infusion 100 mg = € 1,600.00 (ex-factory price) (6)

Posology (7)

- In order to prevent medicinal product errors, it is important to check the vial labels to ensure that the medicinal product being prepared and administered is Enhertu® (trastuzumab deruxtecan) and not trastuzumab or trastuzumab emtansine.
- Enhertu® should not be substituted with trastuzumab or trastuzumab emtansine.
- **Patient selection: NSCLC**
  - Patients treated with trastuzumab deruxtecan for advanced NSCLC should have an activating HER2 (ERBB2) mutation detected by a CE-marked in vitro diagnostic (IVD) medical device. If a CE-marked IVD is not available, the HER2 mutation status should be assessed by an alternate validated test.
- **Premedication**
  - Enhertu® is emetogenic, which includes delayed nausea and/or vomiting. Prior to each dose of Enhertu®, patients should be premedicated with a combination regimen of two or three
  - medicinal products (e.g., dexamethasone with either a 5-HT3 receptor antagonist and/or an NK1 receptor antagonist, as well as other medicinal products as indicated) for prevention of chemotherapy-induced nausea and vomiting.

Warnings and precautions (1, 7)

- **Interstitial lung disease (ILD) and pneumonitis**
  - ILD and pneumonitis including fatal cases, have been reported with Enhertu®.
  - Monitor for and promptly investigate signs and symptoms including cough, dyspnoea, fever, and other new or worsening respiratory symptoms.
  - Permanently discontinue Enhertu® in all patients with Grade 2 or higher ILD/pneumonitis.
  - Advise patients of the risk and to immediately report symptoms.
- Exposure to Enhertu® during pregnancy can cause **embryo-foetal harm**.
  - Advise patients of these risks and the need for effective contraception.
- **Neutropenia**
  - Monitor complete blood counts prior to initiation of Enhertu® and prior to each dose, and as clinically indicated.
  - Manage through treatment interruption or dose reduction.
- **Left ventricular dysfunction (LVEF)**
  - Assess LVEF prior to initiation of Enhertu® and at regular intervals during treatment as clinically indicated.
  - Manage through treatment interruption or discontinuation.
  - Permanently discontinue Enhertu® in patients with symptomatic congestive heart failure.
- **Traceability**

[2] The approval of a medicine that address unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data must indicate that the medicine's benefits outweigh its risks and the applicant should be in a position to provide the comprehensive clinical data in the future.

- In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

❖ **Patients with moderate or severe hepatic impairment**

- There are limited data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment. As metabolism and biliary excretion are the primary routes of elimination of the topoisomerase I inhibitor, DXd, Enhertu® should be administered with caution in patients with moderate and severe hepatic impairment.

Study characteristics (1, 8, 9, 10, 11)

Trial name	*n*	Intervention (I)	Intervention 2 (I2)	PE	Median follow-up	Characteristics	Biomarker	Funding	Publication(s)
DESTINY-Lung02 NCT04644237	52 2:1[3]	Trastuzumab deruxtecan 5.4 mg/kg every 3 weeks	Trastuzumab deruxtecan 6.4 mg/kg every 3 weeks	Confirmed ORR by BICR	Median follow-up duration was 5.6/5.4 months and 3.8/3.9 months	**ongoing**[4], multicentre, multi-cohort, randomized, blinded, dose- optimisation, phase 2 trial	HER2	Daiichi Sankyo, Inc., and AstraZeneca.	DESTINY-Lung02 (9)

Inclusion criteria

- ❖ ≥18 years with pathologically documented metastatic NSCLC with a known activating HER2 mutation.
- ❖ Previous treatment including platinum therapy in the metastatic/locally advanced setting and not amenable to curative surgery or radiation. Participant must have progressed during or after the last treatment regimen or discontinued because of unacceptable toxicity.
- ❖ Presence of at least 1 measurable lesion confirmed by the BICR based on RECIST version 1.1.
- ❖ Willing and able to provide an archival tumour tissue sample. A fresh biopsy is required if an archival tumour tissue sample cannot be supplied. Resection and core needle biopsy are acceptable. Fine needle aspirates or cell block are not acceptable.
- ❖ ECOG PS 0 to 1.
- ❖ LVEF ≥ 50% within 28 days before randomization. Resection and core needle biopsy are acceptable. Adequate organ function as specified in protocol within 14 days before randomization.
- ❖ Adequate treatment washout period before randomization.
- ❖ Participants of reproductive/childbearing potential agree to use a highly effective form of contraception (or avoid intercourse) during

Exclusion criteria

- ❖ Known driver mutation in the EGFR, BRAF, or MET exon 14 gene or a known ALK, ROS1, RET, or NTRK fusion.
- ❖ Medical history of myocardial infarction within 6 months before randomization, symptomatic CHF (NYHA Class II to IV). Participants with troponin levels above ULN at screening (as defined by the manufacturer) and without any MI-related symptoms should have a cardiologic consultation before randomization to rule out MI.
- ❖ Corrected QT interval (QTcF) prolongation > 470 msec (females) or >450 msec (males) based on average of the triplicate12-lead electrocardiogram at screening.
- ❖ History of non-infectious ILD/pneumonitis that required steroids, current ILD/pneumonitis, or where suspected ILD/pneumonitis cannot be ruled out by imaging at screening.
- ❖ Spinal cord compression or clinically active CNS metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms.
- ❖ Multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumours curatively treated.
- ❖ History of severe hypersensitivity reactions to either the drug substances or inactive ingredients in the drug product.
- ❖ History of severe hypersensitivity reactions to other monoclonal antibodies.
- ❖ Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.
- ❖ Substance abuse or any other medical conditions such as clinically significant cardiac or psychological conditions, that may, in the opinion of the investigator, interfere with the participant's

Patient characteristics at baseline (I vs. I2, n=102 vs. n=50)

- ❖ Median age (range): 59.4 (31-84) vs. 61.3 (28-86) years
- ❖ Male sex: 36.3% vs. 32.0%
- ❖ Race:
  - Asian: 63.7% vs. 62.0%
  - White: 22.5% vs. 10.0%
  - Others: 13.7% vs. 24.0%
- ❖ Region:
  - Asia: 61.8% vs. 60.0%
  - North America: 3.9% vs. 4.0%
  - Europe: 32.4% vs. 34.0%
  - Australia: 2.0% vs. 2.0%
- ❖ ECOG PS:
  - 0: 28.4% vs. 38.0%
  - 1: 71.6% vs. 62.0%
- ❖ Histology:
  - Adenocarcinoma: 98.0% vs. 100.0%
  - Squamous: 1.0% vs. 0
  - Others: 1.0% vs. 0
- ❖ HER2 mutations:
  - Kinase domain: 97.1% vs. 100.0%
  - Extracellular domain: 2.9% vs. 0
- ❖ CNS metastasis at baseline: 34.3% vs. 44.0%
- ❖ History of prior lung resection: 21.6% vs. 24.0%
- ❖ Renal function at baseline:
  - Normal renal function: 37.3% vs. 32.0%
  - Mild renal impairment: 40.2% vs. 58.0%
  - Moderate renal impairment: 22.5% vs. 10.0%
- ❖ Hepatic function at baseline:
  - Normal hepatic function: 74.5% vs. 78.0%

[3] The study was not powered to statistically compare the doses.

[4] DESTINY-Lung02 is currently ongoing; the estimated study completion date is 03/2024.

study period and up to 7 months (females) and 4 months (males) after last study dose. ❖ Males should not freeze or donate sperm throughout the study period up to at least 4 months after last study dose; females should not donate or retrieve ova for their own use throughout the study period and up to at least 7 months after last study dose. ❖ Life expectancy of ≥3 months.	participation in the clinical study or evaluation of the clinical study results. ❖ Known HIV infection ❖ Known active, clinically relevant liver disease such as those with serologic evidence of viral infection within 28 days of Cycle 1, Day 1. ❖ Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤ 1 or baseline. ❖ Pregnant, breastfeeding, or planning to become pregnant. ❖ Otherwise considered inappropriate for the study by the Investigator. ❖ Lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder. ❖ Any autoimmune, connective tissue or inflammatory disorders where there is documented, or a suspicion of pulmonary involvement at the time of screening. ❖ Prior complete pneumonectomy. ❖ Prior treatment with any agent, including an antibody drug conjugate, containing a chemotherapeutic agent targeting topoisomerase I.	• Mild hepatic impairment: 25.5% vs. 22.0% ❖ Smoking history: • Former: 46.1% vs. 42.0% • Never: 53.9% vs. 58.0% ❖ Any prior systemic anticancer therapy: • Yes: 100.0% vs. 100.0% ❖ No. of prior therapy regimens: • ≤2: 63.7% vs. 62.0% • >2: 36.3% vs. 38.0% • Median (range): 2 (1-12) vs. 2 (1-7) ❖ Previous systemic anticancer: • Platinum-based therapy: 100.0% vs. 100.0% • Anti–PD-(L)1: 73.5% vs. 78.0% • Platinum and anti–PD-(L)1 (in combination): 50.0% vs. 58.0% • Platinum and anti–PD-(L)1 (not in combination) 23.5% vs. 20.0% • Docetaxel: 29.% vs. 34.0% ❖ Prior radiation therapy: 56.9% vs. 50.0% ❖ Prior cancer surgery: 24.5% vs. 26.0%

Efficacy (I vs. I2)	Safety (SAS[5], I vs. I2, n=101 vs. n=50)
Data cut-off: 22 June 2022, n=52 **Confirmed ORR:** 57.7% (95% CI; 43.2-71.3) **CR:** 1.9% **PR:** 55.8% **Median DoR:** 8.7 months (95% CI, 7.1-NE) **Efficacy I (n=52) vs. C (n=28)** **cORR:** 53.8 (95% CI; 39.5-67.8) vs. 42.9% (95% CI, 24.5-62.8) **CR:** 1.9% vs. 3.6% **PR**: 51.9% vs. 39.3% **Stable disease:** 36.5% vs. 50.0% **Progressive disease**: 3.8% vs. 3.6% **Nonevaluable:** 5.8% vs. 3.6% **Disease control rate**: 90.4% (95% CI, 79.0-96.8) vs. 92.9% (95% CI, 76.5-99.1) **Median DoR**: NE (95% CI, 4.2-NE) vs. 5.9 months (95% CI, 2.8-NE) **Primary results; data cutoff 23 December 2022; median duration of follow-up 11.5 vs. 11.8 months; n=102 vs. n=50:** **Confirmed ORR by BICR**: 49.0% (95% CI, 39.0-59.1) vs. 56.0% (95% CI, 41.3-70.0)	**Drug-related TEAEs all grades:** 92.1% vs. 100% **Drug-related TEAEs grade ≥3:** 31.7% vs. 58.0% **Drug-related TEAEs assoc. with drug discontinuation:** 7.9% vs. 16.0% **Primary results; data cutoff 23 December 2022:** **Drug-related any-grade TEAEs**: 96.0% vs. 100% **Drug-related grade ≥3 TEAEs**: 38.6% (95% CI, 29.1-48.8) vs. 58.0% (95% CI, 43.2-71.8) **Drug-related TEAEs leading to drug discontinuation[6]:** 13.9% vs. 20.0% **Adjudicated drug-related ILD**: 12.9% vs. 28.0% **Left ventricular dysfunction**: 1% vs. 0 **Myocarditis**: 2% vs. 0 **Hypertension**: 1.0% vs. 4.0%

[5] The safety analysis set (SAS) was all randomized patients who received ≥1 dose of trastuzumab deruxtecan.
[6] Drug-related TEAEs most commonly associated with drug discontinuation, as reported by the investigator, were ILD (5.9% vs. 8.0%) and pneumonitis (5.0% vs. 4.0%) in the. Drug-relatedTEAEs were associated with death in one patient in each arm; the cause of both deaths was adjudicated drug-related ILD.

Median DoR: 16.8 months (95% CI, 6.4-NE)] vs. NE (95% CI, 8.3-NE),
Median time to initial response: 1.8 months (range, 1.2-7.0) vs.1.6 months (range, 1.2-11.2)
Estimated proportion of responders maintaining a response at 12 months: 54.4% (95% CI, 37.6 to 68.5) vs. 64.1% (95% CI, 38.2-81.4).
Median PFS by BICR: 9.9 months (95% CI, 7.4-NE) vs. 15.4 months (95% CI, 8.3-NE)
Estimated PFS rate at 12 months as determined by BICR: 45% (95% CI, 33-56) vs. 53% (95% CI, 36-67)
Median OS: 19.5 months (95% CI, 13.6-NE) vs. NE (95% CI, 12.1-NE)
Estimated 12-month OS rate: 67% (95% CI, 56-76) vs. 73% (95% CI, 57-84)

Biomarker Analysis

- Overall, most (93%) HER2 mutations were exon 20 insertions in the kinase domain.
- Exon 19 and 21 substitutions in the kinase domain and exon 8 substitutions in the extracellular domain were also observed.
- At both trastuzumab deruxtecan doses, tumour reduction was observed regardless of HER2 mutation type and HER2 amplification status in the trastuzumab deruxtecan 5.4 mg/kg once every 3 weeks arm.

Patient-reported outcomes

Currently, patient-reported outcomes are not available.

ESMO-MCBS version 1.1 (12)

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	3	-	-	-	ORR (PR+CR) ≥40-<60%	2	-	NA	-	2

Due to the low level of evidence (single-arm study design) the adapted scale was not applied.

Risk of bias - study level (case series) (13)

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	no[7]	yes	yes	yes	yes
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	yes	yes	yes	no[8]	yes	yes	yes	yes

Overall risk of bias: moderate

Ongoing trials (14)

NCT number/trial name	Description	Estimated study completion date
NCT04644237/ DESTINY-Lung02	Please see above.	03/2024
NCT03505710/ DESTINY-Lung01	A phase 2, multicentre, open-label, 2-cohort study of trastuzumab deruxtecan (DS-8201a), an anti-HER2 antibody drug conjugate, for HER2-over-expressing or -mutated, unresectable and/or metastatic NSCLC.	03/2024

[7] Baseline characteristics are heterogenous.
[8] No information available regarding loss to follow-up.

NCT05246514/ DESTINY-Lung05	An open-label, single-arm, phase 2 study to evaluate the efficacy and safety of trastuzumab deruxtecan for patients with HER2-mutant metastatic NSCLC who have disease progression on or after at least one-line of treatment.	06/2024
NCT03334617/ HUDSON	An open-label, multi-drug, biomarker-directed, multi-centre phase II umbrella study in patients with NSCLC, who progressed on an anti-PD-1/PD-L1 containing therapy.	09/2024
NCT05048797/ DESTINY-Lung04	An open-label, randomized, multicentre, phase 3 study to assess the efficacy and safety of trastuzumab deruxtecan as first-line treatment of unresectable, locally advanced, or metastatic NSCLC harbouring HER2 Exon 19 or 20 mutations.	03/2027

Available assessments

- In January 2021, NIHR published a Health Technology Briefing "Trastuzumab deruxtecan for HER2 mutant unresectable and/or metastatic non-squamous non-small cell lung cancer – second line" (15).
- No assessments were identified via NICE, CADTH, ICER and G-BA.

Other aspects and conclusions

- In September 2023, the **CHMP adopted** a **new indication for Enhertu®** as monotherapy for the treatment of adult patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy. In August 2022, the **FDA granted accelerated approval** to Enhertu® for adult patients with unresectable or metastatic NSCLC whose tumours have activating human epidermal growth factor receptor 2 HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.
- **DESTINY-Lung02** (NCT04644237), is an **ongoing,** multicentre, multi-cohort, randomized, blinded, dose-optimization, **phase 2** trial. Eligible patients were required to have unresectable or metastatic HER2-mutant non-squamous NSCLC with disease progression after 1 prior systemic therapy. Patients with a history of steroid dependent ILD/pneumonitis, clinically significant cardiac disease, clinically active brain metastases, and ECOG performance status >1 were excluded.
- The **primary endpoint** of DESTINY-Lung02 is **confirmed ORR** by BICR is 49.0% (95% CI, 39.0-59.1) and 56.0% (95% CI, 41.3-70.0) in patients who received trastuzumab at a dose of 5.4 mg/kg and 6.4 mg/kg, respectively.
- Patient-reported outcome results are **not available** yet.
- The **original ESMO-MCBS** was applied, resulting in a final adjusted magnitude of clinical benefit of **2**. Due to the low level of evidence (single-arm study design) the adapted scale was not applied.
- The risk of bias was considered moderate; it is increase by the heterogeneity of baseline characteristics and the fact that no information on loss to follow-up could be found.
- Beside the DESTINY-Lung02 trial, one further ongoing phase 3 trial and three ongoing phase 2 trials, assessing the efficacy and safety of trastuzumab deruxtecan in NSCLC, were identified.
- Considering the small number of patients participating in DESTINY-Lung02, further robust phase 3 data, including QoL data, is required to assess the role of trastuzumab deruxtecan in pretreated patients with advanced NSCLC and activating HER2 (ERBB2) mutation.

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Abbreviations: AE=adverse event, AJ=adjustment, ALK=anaplastic lymphoma kinase, BICR=blinded independent central review, C=comparator, CADTH=Canada´s Drug and Health Technology Agency, CHF=congestive heart failure, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CNS=central nervous system, cORR=confirmed objective response rate, CR=complete response, DoR=duration of response, EGFR=epidermal growth factor receptor, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, G-BA=Gemeinsamer Bundesausschuss, HER2=human epidermal growth factor receptor 2, HIV=human immunodeficiency virus, HR=hazard ratio, I=intervention, ICER=Institute for Clinical and Economic Review, IHC= immunohistochemistry, ILD=interstitial lung disease, Int.=intention, ISH=In Situ Hybridization, IVD=in-vitro-diagnostic, LVEF=left ventricular ejection fraction, MG=median gain, MI=myocardial infarction, n=number of patients, NE=not evaluable, NICE=National Institute for Health Care Excellence, NIHR=National Institute for Health and Research, NSCLC=non-small cell lung cancer, NYHA=New York Heart Association, ORR=objective response rate, OS=overall survival, PD-1= Programmed Cell Death Protein 1, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, QoL=Quality of Life, RECIST=response evaluation criteria in solid tumours, SAE=serious adverse event, SAS=safety analysis set, ST=standard treatment, TEAE=treatment-emergent adverse event, ULN=upper limit of normal

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