Trastuzumab deruxtecan in patients with metastatic non-small-cell lung cancer (DESTINY-Lung01) primary results of the HER2-overexpressing cohorts from a single-arm, phase 2 trial

Smit, E.F.; Felip, E.; Uprety, D.; Nagasaka, M.; Nakagawa, K.; Rodríguez, L.P.A.; ... ; Jänne, P.A.

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Egbert F Smit, Enriqueta Felip, Dipesh Uprety, Misako Nagasaka, Kazuhiko Nakagawa, Luis Paz-Ares Rodríguez, Jose M Pacheco, Bob T Li, David Planchard, Christina Baik, Yasushi Goto, Haruyasu Murakami, Andreas Saltos, Kaline Pereira, Ayumi Taguchi, Yingkai Cheng, Qi Yan, Wenqin Feng, Zenta Tsuchihashi, Pasi A Jänne

Summary

Background DESTINY-Lung01 is a multicentre, open-label, phase 2 study evaluating the antitumour activity and safety of trastuzumab deruxtecan, a HER2-directed antibody-drug conjugate, in patients with HER2-overexpressing or *HER2* (*ERBB2*)-mutant unresectable or metastatic non-small-cell lung cancer (NSCLC). The results of the *HER2*-mutant cohort (cohort 2) have been reported elsewhere. Herein, we report the primary analysis of cohorts 1 and 1A, which aimed to evaluate the activity and safety of trastuzumab deruxtecan 5·4 mg/kg and 6·4 mg/kg in patients with HER2-overexpressing NSCLC.

Methods Patients aged 18 years or older with unresectable or metastatic (or both unresectable and metastatic) non-squamous NSCLC who had relapsed following or were refractory to standard treatment or for whom no standard treatment was available, with an HER2 immunohistochemistry score of 3+ or 2+ (without known *HER2* mutations) and an Eastern Cooperative Oncology Group performance status score of 0 or 1, were enrolled at 20 specialist hospitals in France, Japan, the Netherlands, Spain, and the USA. Patients were assigned to cohorts sequentially, first to cohort 1, to receive trastuzumab deruxtecan 6·4 mg/kg (cohort 1), then to cohort 1A, to receive trastuzumab deruxtecan 5·4 mg/kg, both administered intravenously once every 3 weeks. The primary endpoint was confirmed objective response rate by independent central review and was assessed in the full analysis set, which included all patients who signed an informed consent form and were enrolled in the study. Safety was assessed in all enrolled patients who received at least one dose of trastuzumab deruxtecan. This trial is registered with ClinicalTrials.gov, NCT03505710, and is ongoing (closed to recruitment).

Findings Between Aug 27, 2018, and Jan 28, 2020, 49 patients were enrolled in cohort 1 (median age 63·0 years [IQR 58·0–68·0], 30 [61%] male, 19 [39%] female, and 31 [63%] White), and from June 16 to Dec 9, 2020, 41 patients were enrolled in cohort 1A (median age 62·0 years [IQR 56·0–66·0], 22 [54%] male, 19 [46%] female, and 31 [76%] White). As of data cutoff (Dec 3, 2021), the median treatment duration was 4·1 months (IQR 1·4–7·1) in cohort 1 and 5·5 months (1·4–8·7) in cohort 1A, and median follow-up was 12·0 months (5·4–22·4) in cohort 1 and 10·6 months (4·5–13·5) in cohort 1A. Confirmed objective response rate by independent central review was 26·5% (95% CI 15·0–41·1; 13 of 49, all partial responses) in cohort 1 and 34·1% (20·1–50·6; 14 of 41; two complete responses and 12 partial responses) in cohort 1A. The most common treatment-emergent adverse events of grade 3 or worse were neutropenia (12 [24%] of 49 in cohort 1, none in cohort 1A), pneumonia (six [12%] and two [5%], respectively), fatigue (six [12%] and three [7%], respectively), and disease progression (six [12%] and four [10%], respectively). Drug-related treatment-emergent adverse events of grade 3 or worse occurred in 26 (53%) of 41 patients in cohort 1 and nine (22%) of 49 patients in cohort 1A. Drug-related serious adverse events were reported in ten (20%) patients and three (7%) patients, respectively. Deaths due to treatment-emergent adverse events occurred in ten (20%) patients in cohort 1 (disease progression in six (12%) patients and bronchospasm, hydrocephalus, respiratory failure, and pneumonitis in one [2%] patient each), and in seven (17%) patients in cohort 1A (due to disease progression in four (10%) patients and dyspnoea, malignant neoplasm, and sepsis in one (2%) patient each). One death due to a treatment-emergent adverse event was determined to be due to study treatment by the investigator, which was in cohort 1 (pneumonitis). Independent adjudication of interstitial lung disease or pneumonitis found that drug-related interstitial lung disease or pneumonitis occurred in ten (20%) patients in cohort 1 (two [4%] grade 1, five [10%] grade 2, and three [6%] grade 5) and two (5%) patients in cohort 1A (one [2%] grade 2 and one [2%] grade 5). An additional patient in cohort 1A had grade 4 pneumonitis after the data cutoff, which was subsequently adjudicated as drug-related grade 5 interstitial lung disease or pneumonitis.

Interpretation Given the low antitumour activity of existing treatment options in this patient population, trastuzumab deruxtecan might have the potential to fill a large unmet need in HER2-overexpressing NSCLC. Our findings support further investigation of trastuzumab deruxtecan in patients with HER2-overexpressing NSCLC.

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Netherlands Cancer Institute, Amsterdam, Netherlands (Prof E F Smit MD); **Department of Pulmonary Diseases, Leiden University Medical Center, Leiden, Netherlands** (Prof E F Smit); **Department of Oncology, Vall d'Hebron University and Vall d'Hebron Institute of Oncology, Barcelona, Spain** (Prof E Felip MD); **Barbara Ann Karmanos Cancer Institute, Detroit, MI, USA** (D Uprety MD); **University of California Irvine, School of Medicine, Orange, CA, USA** (M Nagasaka MD); **Department of Medical Oncology, Kindai University, Osaka-Sayama, Japan** (Prof K Nakagawa MD); **Department of Medical Oncology, Hospital Universitario 12 de Octubre, Madrid, Spain** (Prof L Paz-Ares Rodríguez MD); **Department of Medical Oncology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA** (J M Pacheco MD); **Memorial Sloan Kettering Cancer Center, New York, NY, USA** (B T Li MD); **Department of Medical Oncology, Thoracic Cancer Group, Gustave Roussy, Villejuif, France** (Prof D Planchard MD); **Department of Medical Oncology, University of Washington, Seattle, WA, USA** (C Baik MD); **National Cancer Center Hospital, Tokyo, Japan** (Y Goto MD); **Shizuoka Cancer Center, Shizuoka, Japan** (H Murakami MD); **Moffitt Cancer Center, Tampa, FL, USA** (A Saltos MD); **Daiichi Sankyo, Basking Ridge, NJ, USA** (K Pereira MD, Y Cheng MD, Q Yan PhD, W Feng PhD, Z Tsuchihashi PhD); **Daiichi Sankyo, Tokyo, Japan**

(A Taguchi PharmD); **Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA, USA**
(Prof P A Jänne MD)

Correspondence to:
Prof Egbert F Smit, Department of Pulmonary Diseases, Leiden University Medical Center, 2333 ZA Leiden, Netherlands
e.f.smit@LUMC.nl

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Introduction

Approximately 8–23% of patients with non-small-cell lung cancer (NSCLC) have HER2 overexpression; however, the levels of protein overexpression reported vary in the literature.[1] HER2 overexpression is associated with poor treatment response and worse clinical outcomes,[1,2] and HER2 overexpression or *HER2* (also known as *ERBB2*) gene amplification might contribute to EGFR tyrosine-kinase inhibitor resistance in patients with NSCLC.[3] Immunohistochemistry is the most commonly used method to detect HER2 expression in solid tumours; however, a standard for defining HER2 overexpression in NSCLC is absent.[1] Furthermore, no approved or recommended HER2-directed therapies are available for patients with HER2-overexpressing NSCLC.[4,5]

Trastuzumab deruxtecan, a HER2-directed antibody–drug conjugate, has shown durable anticancer activity in previously treated patients with *HER2*-mutant NSCLC in the DESTINY-Lung01 and DESTINY-Lung02 trials. In these trials, confirmed objective response rates were 55% (95% CI 44–65; 50 of 91 patients; DESTINY-Lung01) and 56·0% (95% CI 41·3–70·0; 28 of 50 patients; DESTINY-Lung02) with trastuzumab deruxtecan 6·4 mg/kg, and 49·0% (95% CI 39·0–59·1; 50 of 102 patients) with trastuzumab deruxtecan 5·4 mg/kg (DESTINY-Lung02).[6,7] In several countries, trastuzumab deruxtecan at 5·4 mg/kg is approved for this patient population and in patients with unresectable or metastatic HER2-positive and HER2-low breast cancer, and at 6·4 mg/kg in patients with advanced or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma.[8,9]

In a phase 1 study (DS8201-A-J101), trastuzumab deruxtecan 6·4 mg/kg showed preliminary evidence of activity, with an objective response rate of 55·6% (95% CI 30·8–78·5; 10 of 18 patients) and median duration of response of 10·7 months (95% CI 6·9–11·5) by independent central review in patients with HER2-expressing or *HER2*-mutant NSCLC.[10] On the basis of those results, DESTINY-Lung01 evaluated patients with HER2-overexpressing NSCLC, in addition to patients with *HER2*-mutant NSCLC, to assess the antitumour activity and safety of trastuzumab deruxtecan (5·4 mg/kg and 6·4 mg/kg). In this Article, we report the primary results of the HER2-overexpressing cohorts (data cutoff Dec 3, 2021); the *HER2*-mutant cohort (cohort 2) has been reported elsewhere.[6]

Methods

Study design and participants

DESTINY-Lung01 is a multicentre, open-label, two-cohort, phase 2 trial evaluating the antitumour activity

Research in context

Evidence before this study

No approved or recommended HER2-directed treatments are available for patients with HER2-overexpressing non-small-cell lung cancer (NSCLC). We searched PubMed for clinical trials evaluating HER2-directed treatments for patients with HER2-overexpressing NSCLC published between June 23, 2018, and June 23, 2023. The searched terms were,"HER2-targeted", "HER2-directed", "HER2-overexpressing", "HER2-positive", "non-small-cell lung cancer", and "NSCLC", with the search restricted to English-language publications. In the past 5 years, few trials have investigated HER2-directed agents in patients with HER2-overexpressing NSCLC, and low antitumour activity was shown. A multicentre, single-arm trial evaluated the efficacy and safety of trastuzumab emtansine in patients with HER2-positive (immunohistochemistry [IHC] 3+ or 2+ status) advanced NSCLC treated with at least one previous platinum-based chemotherapy regimen; activity was observed only in patients with HER2 IHC 3+ expression. Previous trials have also assessed the addition of trastuzumab to chemotherapy and did not observe a clinical benefit. In a randomised, open-label, phase 2 trial of gemcitabine–cisplatin with or without trastuzumab in patients with HER2-positive (IHC 3+ or 2+ or gene amplification) NSCLC, investigator-assessed responses were similar in both treatment groups.

Added value of this study

The primary results of DESTINY-Lung01 reported herein show that trastuzumab deruxtecan at both the 5·4 mg/kg and 6·4 mg/kg doses had encouraging and consistent antitumour activity in heavily pretreated patients with HER2-overexpressing NSCLC. In our study, responses were observed in patients with HER2 IHC 3+ or 2+ status tumours, regardless of the presence of stable CNS metastases at baseline, and in patients with previous anti-PD-1 and anti-PD-L1 therapy. Antitumour activity was also observed in patients with and without *HER2* amplification. Furthermore, the safety profile of trastuzumab deruxtecan was generally manageable, consistent with the known safety profile of trastuzumab deruxtecan, and favoured the 5·4 mg/kg dose.

Implications of all the available evidence

This study provides evidence that trastuzumab deruxtecan has activity in patients with HER2-overexpressing, advanced, unresectable or metastatic NSCLC. As few trials have reported on the activity of HER2-directed regimens for patients with HER2-overexpressing NSCLC to date, trastuzumab deruxtecan has the potential to fill a large unmet need in these patients. The findings of our study support further exploration and continued research on trastuzumab deruxtecan in this patient population.

and safety of trastuzumab deruxtecan in patients with HER2-overexpressing (cohorts 1 and 1A) or *HER2*-mutant (cohort 2) NSCLC at 20 specialist hospitals in France, Japan, the Netherlands, Spain, and the USA (appendix p 3). Eligible patients were aged 18 years or older (≥20 years in Japan) with pathologically documented unresectable or metastatic non-squamous NSCLC who had relapsed from or were refractory to standard treatment or for whom no standard treatment was available, had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1, and had one or more measurable lesions assessed by the investigator according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Before study enrolment, patients were required to have an adequate washout period for previous treatments, including for major surgery (≥4 weeks), radiotherapy including palliative stereotactic radiotherapy to the chest (≥4 weeks; or for palliative stereotactic radiotherapy to other areas, ≥2 weeks), anticancer chemotherapy or retinoid therapy (≥3 weeks), antibody-based anticancer therapy (≥4 weeks), and chloroquine or hydroxychloroquine (>2 weeks).

HER2 overexpression in cohorts 1 and 1A was assessed and confirmed centrally in a College of American Pathologists (CAP) Clinical Laboratory Improvement Amendments-certified laboratory (Tucson, AZ, USA) before enrolment with use of fresh or archived formalin-fixed paraffin-embedded tumour tissue. There was no maximum time limit for archived tissue. Freshly cut sections were stained with an investigational-use only version of the PATHWAY HER2/neu (4B5) antibody (catalogue number 790-2991) and the ultraView Universal DAB Detection Kit on the BenchMark ULTRA staining platform (all from Ventana Medical Systems; Tucson, Arizona, USA). HER2 overexpression was defined as an immunohistochemistry status score of 3+ or 2+, with the immunohistochemistry scoring adapted from the HER2 gastric algorithm of the CAP, American Society of Clinical Oncology (ASCO), and American Society for Clinical Pathology (ASCP).[11] An immunohistochemistry score of 3+ was defined as strong complete, basolateral, or lateral membranous reactivity in at least 10% of tumour cells from a surgical specimen, and a tumour cell cluster with strong complete, basolateral, or lateral membranous activity irrespective of percentage of tumour cells stained from a biopsy specimen. An immunohistochemistry score of 2+ was defined as weak-to-moderate complete, basolateral, or lateral membranous reactivity in at least 10% of tumour cells from a surgical sample, and a tumour cell cluster with weak-to-moderate complete, basolateral, or lateral membranous activity irrespective of percentage of tumour cells stained from a biopsy sample.[11]

Patients were excluded from the DESTINY-Lung01 trial if they had spinal cord compression or clinically active brain metastases (defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants). Per protocol, patients with clinically inactive or stable baseline brain metastases (asymptomatic; not requiring treatment with corticosteroids or anticonvulsants) could be enrolled. Patients were also excluded if they had previously received HER2-directed therapies (except for pan-HER class tyrosine-kinase inhibitors); uncontrolled or clinically significant cardiovascular disease; uncontrolled infection requiring intravenous antibiotics, antivirals, or antifungals; known HIV infection or active hepatitis B or C infection; had a history of non-infectious interstitial lung disease or pneumonitis that required steroid treatment, current interstitial lung disease or pneumonitis, or suspected interstitial lung disease or pneumonitis; or had clinically severe pulmonary compromise resulting from intercurrent pulmonary illnesses. Patients were excluded from cohorts 1 and 1A if they had a known *HER2*-activating mutation. Full eligibility criteria are in the appendix (pp 5–6).

See Online for appendix

The study was approved by the institutional review board at each site and conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and local regulations regarding the conduct of clinical research. All patients provided written, informed consent before participation in the trial. The protocol has been published previously.[6] The protocol was amended on Feb 21, 2020, to include cohort 1A to evaluate a lower dose of trastuzumab deruxtecan than previously administered in cohort 1 (version 6.0), with the aim of obtaining a preliminary assessment of safety and efficacy of the lower dose.

Procedures

Patients with HER2-overexpressing (immunohistochemistry status 3+ or 2+) unresectable or metastatic NSCLC were assigned to cohorts sequentially, first to cohort 1 until the desired sample size was reached, and then to cohort 1A. Patients enrolled in cohort 1 were treated with trastuzumab deruxtecan 6·4 mg/kg (Baxter Oncology, Halle [Westfalen], Germany), whereas patients in cohort 1A were treated with trastuzumab deruxtecan 5·4 mg/kg (Baxter Oncology), both administered intravenously as a single dose once every 3 weeks. The initial intravenous infusion was 90 min (±10) and if no infusion-related reaction occurred after the initial dose, subsequent doses were infused over 30 min (±5). Each treatment cycle of trastuzumab deruxtecan occurred every 21 days, with the number of treatment cycles unfixed. The anticipated duration of the study was approximately 43 months.

Up to two dose reductions of trastuzumab deruxtecan were permitted (for cohort 1, from 6·4 mg/kg to 5·4 mg/kg [level 1] and then to 4·4 mg/kg [level 2]; for cohort 1A, from 5·4 mg/kg to 4·4 mg/kg [level 1] and then to 3·2 mg/kg [level 2]). The dose of trastuzumab deruxtecan could be interrupted for up to 28 days from

the planned date of administration. If a patient required a longer dose delay than 28 days, the patient was permanently discontinued from the study drug. Trastuzumab deruxtecan could be discontinued for any of the following reasons: progressive disease per RECIST version 1.1 as assessed by the investigator; clinical progression; adverse event; death; pregnancy; protocol deviation; withdrawal of consent by patient; loss to follow-up; physician decision; or study termination by the sponsor. Patient follow-up was done for all patients withdrawn from study treatment to monitor any subsequent treatment and survival status. Following the end of treatment with trastuzumab deruxtecan, no subsequent anticancer treatments were specified or prohibited. Trastuzumab deruxtecan administration was interrupted for any suspected interstitial lung disease or pneumonitis case, and for those with grade 1 interstitial lung disease or pneumonitis, systemic steroids could be considered according to the protocol. For patients with grade 2 or worse interstitial lung disease or pneumonitis, steroids were to be started promptly. To manage left ventricular dysfunction, trastuzumab deruxtecan was interrupted if left ventricular ejection fraction (LVEF) was 40–45% and the decrease was 10–20% (absolute value) from baseline, and discontinued if LVEF was not recovered to within 10% (absolute value) from baseline in a repeat assessment within 3 weeks; if LVEF recovered to within 10% from baseline, treatment was resumed. Trastuzumab deruxtecan was also interrupted if LVEF was lower than 40% or had decreased by 20% (absolute value) from baseline; treatment was discontinued if LVEF values (<40%, or >20% decrease from baseline) were confirmed in a repeat assessment within 3 weeks. Trastuzumab deruxtecan was also interrupted if grade 2 infusion reactions occurred or if COVID-19 was suspected.

Tumour assessments were done at screening and every 6 weeks while the patient remained on treatment. A CT or MRI, or both, of the chest, abdomen, and pelvis was used for tumour assessment unless another method of disease assessment was necessary. The same assessment method was used throughout the study for all assessments. A CT or MRI of the brain was required every 6 weeks (±7 days) for all patients with baseline stable brain metastases. Patients without baseline brain metastases did not need additional brain scans for tumour assessments, unless clinically indicated. Treatment continued until clinical progression, progressive disease per RECIST 1.1, occurrence of unacceptable adverse events, physician decision, or withdrawal of consent. Clinical progression was defined as definitive clinical signs of disease progression but without a recent radiographic assessment meeting the criteria for progressive disease according to RECIST version 1.1. Progressive disease was defined per RECIST version 1.1. Radiographic response was assessed centrally and locally by investigators. Patients were considered not evaluable at a given timepoint when no imaging or measurement was done or if only a subset of lesion measurements were made at an assessment, unless the contribution of the individual missing lesion or lesions would not change the assigned timepoint response.

Laboratory analyses included haematology and blood chemistry tests (collected during screening; day 1, 8, and 15 of the first treatment cycle; day 1 of subsequent cycles; at the end of treatment; and during a follow-up visit at either 40 days [±7 days] after the last study drug administration, or before starting new anticancer treatment, whichever was first), troponin T (collected during screening and at the end of treatment), and urinalysis (collected during screening). Blood samples used in exploratory biomarker analyses were taken before treatment on day 1 of every cycle and at the end of treatment. Biomarker analyses were done retrospectively by analysing circulating tumour (ct)DNA from plasma with the 500-gene GuardantOMNI assay (Guardant Health, [Redwood City, CA, USA]), which was performed centrally. The GuardantOMNI assay includes a panel of genes, and the focus of our analyses was on actionable mutations in *HER2*, *EGFR*, *KRAS*, *NRAS*, and *BRAF*. Fusions in *ALK* and *ROS1* were also assessed in the panel. All possible germline mutations and clonal haematopoiesis of indeterminate potential reported with the OMNI assay were excluded from the analysis. *HER2* amplification results were obtained by fluorescence in situ hybridisation (FISH) with the Agilent HER2 IQ-FISH pharmDx assay at Mosaic Laboratories (Lake Forest, CA, USA) following the manufacturer's instructions. *HER2* amplification positivity was defined as a HER2 to chromosome 17 centromere (CEN17) ratio of 2·0 or higher according to the ASCO, CAP, and ASCP guidelines.[11]

All adverse events were recorded as reported by the patient or observed by the investigator at screening, at every study visit, at the end of treatment, and at the 40-day follow-up visit following the end of treatment; additional follow-up was done for ongoing adverse events. Adverse events were categorised with use of the Medical Dictionary for Regulatory Activities (version 23.0), and graded according to the Common Terminology Criteria for Adverse Events (CTCAE; version 5.0). Treatment-emergent adverse events were defined as an adverse event that was absent before the first dose of study drug or worsened after initiating the study drug until 47 days after the last dose of study drug. Serious adverse events were defined as an untoward medical occurrence that resulted in death, were life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or clinically significant disability or incapacity, caused a congenital abnormality or birth defect, or was an important medical event. The investigator was responsible for determining whether an adverse event was related to the study drug on the basis of their clinical

judgement; an adverse event was considered to be drug-related if it occurred within a reasonable time following administration of the study drug and could not be explained by the patient's clinical state or other factors, was a known reaction to the drug under study or its chemical group, or was predicted by known pharmacology. An adverse event would be reported as disease progression if the patient died from progressive disease with no other immediate causes. Adverse events of special interest were left ventricle dysfunction and interstitial lung disease or pneumonitis. Potential cases of interstitial lung disease or pneumonitis were evaluated by a dedicated independent adjudication committee, and the grading done according to the CTCAE (version 5.0).

Sex and race or ethnicity were captured from medical records through the electronic data capture system.

Outcomes

The primary endpoint was confirmed objective response rate by independent central review according to RECIST (version 1.1) for each cohort. Objective response rate was defined as the proportion of patients who had a best overall response of confirmed complete response or partial response. Confirmation of a response was completed no earlier than 4 weeks from the time a complete response or partial response was first suspected. If the response was not confirmed, or if there was no post-baseline tumour assessment, the best overall response was assigned as not evaluable. Secondary endpoints were disease control rate, duration of response, and progression-free survival by investigator assessment and independent central review; overall survival; and objective response rate by investigator assessment. Disease control rate was defined as the proportion of patients who had a best overall response of complete response, partial response, or stable disease. Duration of response was defined as the time from the date of the first documentation of objective response (complete response or partial response) to the date of the first objective documentation of disease progression or death due to any cause. Progression-free survival was defined as the time from the date of enrolment to the first objective documentation of radiographic disease progression or death due to any cause. Overall survival was defined as the time from the date of enrolment to the date of death due to any cause. Prespecified safety endpoints included treatment-emergent adverse events, serious adverse events, and adverse events of special interest. Prespecified exploratory endpoints included best percentage change from baseline in the sum of the diameters for all target lesions, and biomarker analyses of the mutation status of *HER2*, *EGFR*, *KRAS*, *NRAS*, and *BRAF*. The best percentage change from baseline in the sum of the diameters for all target lesions was calculated on the basis of RECIST (version 1.1) criteria, with the tumour measurement at screening used as the baseline.

Statistical analysis

Enrolment was intended to be at least 40 patients each in cohorts 1 and 1A and 90 patients in cohort 2. In cohort 1, at least ten patients with HER2 immunohistochemistry 3+ status and ten patients with HER2 immunohistochemistry 2+ status were to be enrolled. For cohorts 1 and 1A, the sample size was determined such that the distance from the limits of the respective 95% CIs to the observed objective response rate was approximately 14%, assuming the expected objective response rate was 30%. If an objective response rate of 30% was achieved, then the lower limit of the one-sided 95% CI would be at least 18%. For docetaxel in the CheckMate 057 trial, the upper 95% CI of the objective response rate was less than 20%,[12] and so for our study the 30% threshold was established by benchmarking against the estimate of an upper limit of 20% and allowing a further increment of 10% to account for the sparseness of the available data. No hypothesis testing was done and no quantitative success criteria were defined for cohorts 1 and 1A in this study.

Antitumour activity and exploratory analyses were done for the full analysis set, which included patients who signed an informed consent form and were enrolled in the study. Safety analyses were done for the safety analysis set, which included patients who received at least one dose of study drug. Generally, no missing or dropout data were imputed for data analysis; however, partial dates such as incomplete date of diagnosis to compute time since diagnosis, incomplete date of the last dose of study treatment, incomplete date of previous and concomitant medications, and incomplete adverse event start date could be imputed according to the statistical analysis plan. All patients were counted in the denominator of objective response rate; individuals with a non-evaluable response were included as non-responders. Objective response rate (independent and investigator assessment) and disease control rate (independent and investigator assessment), and their respective 95% CIs were calculated on the basis of the Clopper–Pearson method for each cohort. For duration of response, progression-free survival, and overall survival, Kaplan–Meier estimates of medians and their respective 95% CIs were calculated with use of the Brookmeyer and Crowley method for each cohort.

Prespecified exploratory subgroup analyses were done for objective response rate, duration of response, progression-free survival (all based on independent central review), and overall survival. We analysed subgroups according to number of lines of previous systemic therapy (≤2 *vs* >2), age (<65 years *vs* ≥65 years; <75 years *vs* ≥75 years), sex (female *vs* male), ECOG performance status (0 *vs* 1), smoking status (current *vs* previous *vs* never), HER2 immunohistochemistry status (3+ *vs* 2+), other gene abnormality status (presence of *EGFR*, *ALK*, *ROS1*, or *BRAF* gene abnormality *vs* no *EGFR*, *ALK*, *ROS1*, or *BRAF* gene abnormality),

histological subtype (adenocarcinoma *vs* others or unknown), renal function at baseline (normal *vs* mild impairment *vs* moderate impairment), hepatic function at baseline (normal *vs* mild dysfunction *vs* moderate dysfunction), race (White *vs* Asian *vs* Other), CNS metastasis at baseline (yes *vs* no), geographical region (Asia *vs* USA *vs* Europe), previous pneumonectomy (yes *vs* no), and pleural effusion (yes *vs* no). Additionally, prespecified exploratory subgroup analyses according to previous platinum therapy and anti-PD-1 or anti-PD-L1 treatment regimens were as follows: previous treatment with platinum therapy (yes *vs* no); previous treatment with anti-PD-1 or anti-PD-L1 therapy (yes *vs* no); previous treatment with platinum and anti-PD-1 or anti-PD-L1 therapy (yes *vs* no); previous treatment with platinum therapy and anti-PD-1 or anti-PD-L1 therapy but not in combination (yes *vs* no); and previous treatment with platinum therapy in combination with anti-PD-1 or anti-PD-L1 therapy (yes *vs* no). The results of the subgroup analyses were considered exploratory because of small sample sizes in the subgroups, which could not be prespecified. The results for a specific subgroup were not reported if the sample size was too small (n<10).

Exploratory analysis of best percentage change from baseline in the sum of diameters of target lesions was analysed with use of summary statistics, and in the post-hoc analyses, we analysed best percentage change in diameter of lesions by *EGFR*, *KRAS*, *NRAS*, and *BRAF* mutation status, *HER2* amplification, and previous therapy (HER2-related and EGFR tyrosine-kinase inhibitors). We created waterfall plots of the best percentage change in the sum of diameters for each patient by cohort, and spider plots of the percentage change in the sum of diameters for each patient by cohort.

For the **East software** see https://www.cytel.com/software/east/

For duration of response, patients who had not had progression at the data cutoff (Dec 3, 2021) were censored at the date of the last evaluable tumour assessment; patients who discontinued from the study without disease progression or death were censored at the date of the last evaluable tumour evaluation; patients who started other anticancer therapy before disease progression were censored at the date of the last evaluable tumour assessment before starting the other therapy; patients who progressed or died after missing two or more consecutive scheduled tumour assessments were censored at the date of the last evaluable tumour evaluation before progression or death; and the progression-free survival censoring rule, as follows, was applied. For progression-free survival, patients who were alive and progression-free at the data cutoff were censored at the date of the last evaluable tumour assessment; patients who discontinued from the study before the first evaluable post-baseline tumour assessment were censored at the date of enrolment; patients who discontinued the study without disease progression or death were censored at the date of the last evaluable tumour evaluation; patients who started other anticancer therapy before disease progression or death were censored at the date of the last tumour evaluable assessment before starting the other therapy; patients who had progressive disease after missing two or more consecutive scheduled tumour assessments were censored at the date of the last evaluable tumour assessment before progression; and patients without baseline evaluable tumour assessment who were alive and assessed as progression-free after the first two scheduled tumour assessments were censored at the date of enrolment. For overall survival, if no death was reported for a patient before the data cutoff (Dec 3, 2021) for overall survival analysis, overall survival was censored at the last contact date at which the patient was known to be alive.

Safety was assessed with use of descriptive statistics. As a post-hoc analysis, the association between immune checkpoint inhibitor therapy within 6 months of enrolment and occurrence of adjudicated drug-related interstitial lung disease or pneumonitis was assessed. Analysis of the time to first onset of adjudicated drug-related interstitial lung disease or pneumonitis events was prespecified, and calculated as the date of onset of first adjudicated drug-related interstitial lung disease or pneumonitis minus the first dose date plus one.

Sample size was calculated with use of East software (version 6.4) and R (version 3.5.0), and statistical analyses were done with SAS (versions 9.3 and 9.4).

The DESTINY-Lung01 trial is registered with ClinicalTrials.gov, NCT03505710, and is ongoing (closed to recruitment).

Role of the funding source

The study was designed and led by Daiichi Sankyo, who participated in data analysis. AstraZeneca entered into a collaboration agreement with Daiichi Sankyo for further clinical development of trastuzumab deruxtecan in March, 2019. Daiichi Sankyo and AstraZeneca were involved in study oversight, data collection, data interpretation, writing of the report, reviewing the manuscript, and the decision to submit the manuscript for publication.

Results

Between Aug 27, 2018, and Jan 28, 2020, 49 patients were enrolled in cohort 1 (trastuzumab deruxtecan 6·4 mg/kg) and from June 16 to Dec 9, 2020, 41 patients were enrolled in cohort 1A (trastuzumab deruxtecan 5·4 mg/kg). At the data cutoff (Dec 3, 2021), two (4%) patients in cohort 1 and five (12%) in cohort 1A were still on treatment (figure 1); the most common reason for discontinuing treatment was disease progression (22 [45%] and 13 [32%], respectively). Subsequent anticancer therapies are listed in the appendix (p 7). As of data cutoff, the median treatment duration with trastuzumab deruxtecan was 4·1 months (IQR 1·4–7·1) in cohort 1 and 5·5 months (1·4–8·7) in cohort 1A. Median

follow-up was 12·0 months (IQR 5·4–22·4) in cohort 1 and 10·6 months (4·5–13·5) in cohort 1A.

Baseline characteristics and previous therapies are summarised in table 1. Median age was 63·0 years (IQR 58·0–68·0) in cohort 1 and 62·0 years (56·0–66·0) in cohort 1A. Cohorts 1 and 1A had similar proportions of male and female patients (30 [61%] male and 19 [39%] female; and 22 [54%] male and 19 [46%] female, respectively), and the majority of patients were White (31 [63%] and 31 [76%], respectively).

In the retrospective ctDNA analysis, results were available for 86 patients (47 in cohort 1 and 39 in cohort 1A); four patients had no baseline ctDNA samples (appendix p 8). Of the genes assessed, patients most frequently had *EGFR* mutations (ten [21%] in cohort 1 and six [15%] in cohort 1A) or *KRAS* mutations (seven [15%] in cohort 1 and 13 [33%] in cohort 1A); no activating mutations in *HER2* were detected. One (2%) patient in cohort 1 and one (3%) patient in cohort 1A had both *EGFR* and *KRAS* mutations, and one (2%) patient in cohort 1 had both *KRAS* and *BRAF* mutations.

Confirmed objective response rate by independent central review was 26·5% (95% CI 15·0–41·1; 13 of 49) in cohort 1 and 34·1% (20·1–50·6; 14 of 41) in cohort 1A (table 2). In cohort 1, all responses were partial responses (13 [27%] patients). In cohort 1A, two (5%) patients had complete responses and 12 (29%) had partial responses. In the post-hoc analyses, antitumour activity was observed regardless of *EGFR* or *KRAS* mutations or *HER2* amplification, and in patients with or without previous treatment with EGFR tyrosine-kinase inhibitors, in cohorts 1 and 1A (figure 2). Disease control rate was

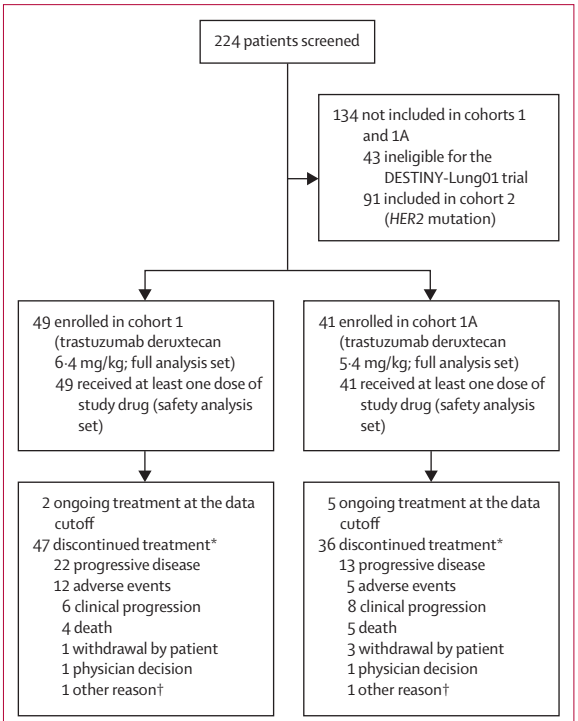


Figure 1: **Study profile**
*Primary reason for drug discontinuation. †Other reasons for discontinuation were sponsor decision in cohort 1 and a decrease in performance status due to complications of cancer in cohort 1A.

	Cohort 1 (6·4 mg/kg; N=49)	Cohort 1A (5·4 mg/kg; N=41)
Age, years	63·0 (58·0–68·0)	62·0 (56·0–66·0)
Sex		
Female	19 (39%)	19 (46%)
Male	30 (61%)	22 (54%)
Race		
American Indian or Alaska Native	0	1 (2%)
Asian	13 (27%)	4 (10%)
Black or African American	4 (8%)	2 (5%)
White	31 (63%)	31 (76%)
Other	1 (2%)	3 (7%)
Ethnicity		
Hispanic or Latino	2 (4%)	1 (2%)
Not Hispanic or Latino	46 (94%)	36 (88%)
Not reported	1 (2%)	4 (10%)
Geographical region		
Asia	12 (24%)	3 (7%)
North America	19 (39%)	13 (32%)
Europe	18 (37%)	25 (61%)
HER2 status		
IHC 3+	10 (20%)	17 (41%)
IHC 2+	39 (80%)	24 (59%)
Eastern Cooperative Oncology Group performance status		
0	14 (29%)	5 (12%)
1	35 (71%)	36 (88%)
Presence of CNS metastases		
Yes	17 (35%)	12 (29%)
No	32 (65%)	29 (71%)
Smoking status		
Never	16 (33%)	9 (22%)
Former	28 (57%)	30 (73%)
Current	5 (10%)	2 (5%)
Previous lung resection*		
Yes	12 (24%)	7 (17%)
No	37 (76%)	34 (83%)
Renal function at baseline†		
Normal renal function	20 (41%)	13 (32%)
Mild renal impairment	19 (39%)	17 (41%)
Moderate renal impairment	9 (18%)	11 (27%)
Severe renal impairment	1 (2%)	0
Previous therapies		
Yes	49 (100%)	41 (100%)
No	0	0
Types of previous therapy		
Platinum-based	45 (92%)	40 (98%)
Anti-PD-1 or anti-PD-L1	36 (73%)	33 (80%)
Docetaxel	12 (24%)	9 (22%)
HER2 or EGFR tyrosine kinase inhibitor	14 (29%)	7 (17%)

(Table 1 continues on next page)

	Cohort 1 (6·4 mg/kg; N=49)	Cohort 1A (5·4 mg/kg; N=41)
(Continued from previous page)		
Number of previous lines of therapy	3 (2–4)	3 (2–4)
HER2 amplification, by FISH	13/38 (34%)	9/37 (24%)
HER2 IHC 2+	10/13 (77%)	0/9
HER2 IHC 3+	3/13 (23%)	9/9 (100%)

Data are median (IQR), n (%), or n/N (%). FISH=fluorescence in situ hybridisation. IHC=immunohistochemistry. *Prior pneumonectomy includes both partial and complete lung resections, and patients who underwent lung surgery for localised disease. †Renal function was defined according to baseline creatinine clearance (calculated with the Cockcroft–Gault equation[13]) ≥90 mL/min (normal), ≥60 and <90 mL/min (mild impairment), ≥30 and <60 mL/min (moderate impairment), and ≥15 and <30 mL/min (severe impairment).[14,15]

Table 1: **Baseline characteristics**

	Cohort 1 (6·4 mg/kg; N=49)	Cohort 1A (5·4 mg/kg; N=41)
Confirmed objective response rate, n (%; 95% CI)	13 (26·5%; 15·0–41·1)	14 (34·1%; 20·1–50·6)
Response outcomes, n (%)		
Complete response	0	2 (5%)
Partial response	13 (27%)	12 (29%)
Stable disease	21 (43%)	18 (44%)
Progressive disease	11 (22%)	4 (10%)
Not evaluable	4 (8%)	5 (12%)
Disease control rate, n (%; 95% CI)	34 (69·4%; 54·6–81·8)	32 (78·0%; 62·4–89·4)
Duration of response, months, median (95% CI)	5·8 (4·3–not evaluable)	6·2 (4·2–9·8)

Table 2: **Summary of efficacy by independent central review**

69·4% (95% CI 54·6–81·8; 34 of 49) in cohort 1 and 78·0% (95% CI 62·4–89·4; 32 of 41) in cohort 1A. The median duration of response was 5·8 months (95% CI 4·3–not evaluable) in cohort 1 and 6·2 months (4·2–9·8) in cohort 1A (table 2). Responses with trastuzumab deruxtecan were generally durable over time in cohorts 1 and 1A (appendix p 27). At both doses of trastuzumab deruxtecan, consistent confirmed objective response rates (per independent central review) were observed across the subgroups assessed (appendix pp 24–26).

Median progression-free survival per independent central review was 5·7 months (95% CI 2·8–7·2) in cohort 1 and 6·7 months (4·2–8·4) in cohort 1A (figure 3A, B). In cohort 1, 31 (63%) patients had progression-free survival events (24 [49%] progressive disease, seven [14%] deaths), and in cohort 1A, 29 (71%) patients had progression-free survival events (17 [41%] progressive disease, 12 [29%] deaths). Median overall survival was 12·4 months (95% CI 7·8–17·2) in cohort 1 and 11·2 months (8·4–not evaluable) in cohort 1A (figure 3C, D). In cohort 1, 39 (80%) patients died and in cohort 1A, 23 (56%) patients died. Subgroup analyses for progression-free survival, duration of response (both by independent central review), and overall survival are presented in the appendix (pp 16–23). Investigator-assessed objective response rate, disease control rate, duration of response, and progression-free survival were similar to the independent central review assessment (appendix p 9).

44 (90%) of 49 patients in cohort 1 and 38 (93%) of 41 in cohort 1A had one or more drug-related treatment-emergent adverse events, and 26 (53%) patients in cohort 1 and nine (22%) patients in cohort 1A had a drug-related treatment-emergent adverse event of grade 3 or worse (appendix p 10). The most common drug-related treatment emergent adverse events of grade 3 or worse were neutropenia (12 [24%] of 49 patients in cohort 1 and none in cohort 1A) and fatigue (five [10%] patients and three [7%] patients, respectively; appendix pp 11–12). Drug-related serious adverse events were reported in ten (20%) patients in cohort 1 and three (7%) patients in cohort 1A. The most common drug-related serious adverse events in cohorts 1 and 1A were pneumonitis (four [8%] patients and one [2%] patient, respectively) and nausea (two [4%] patients and no patients, respectively; appendix p 10). Drug-related treatment-emergent adverse events associated with drug discontinuation, dose reduction, and drug interruption were reported in eight (16%), 17 (35%), and 17 (35%) patients, respectively, in cohort 1, and three (7%), seven (17%), and four (10%) patients, respectively, in cohort 1A (appendix p 10). The most common treatment-emergent adverse events that led to discontinuation in both cohorts 1 and 1A were pneumonitis (seven [14%] patients and two [5%] patients, respectively), and disease progression (two [4%] and three [7%]; appendix p 13).

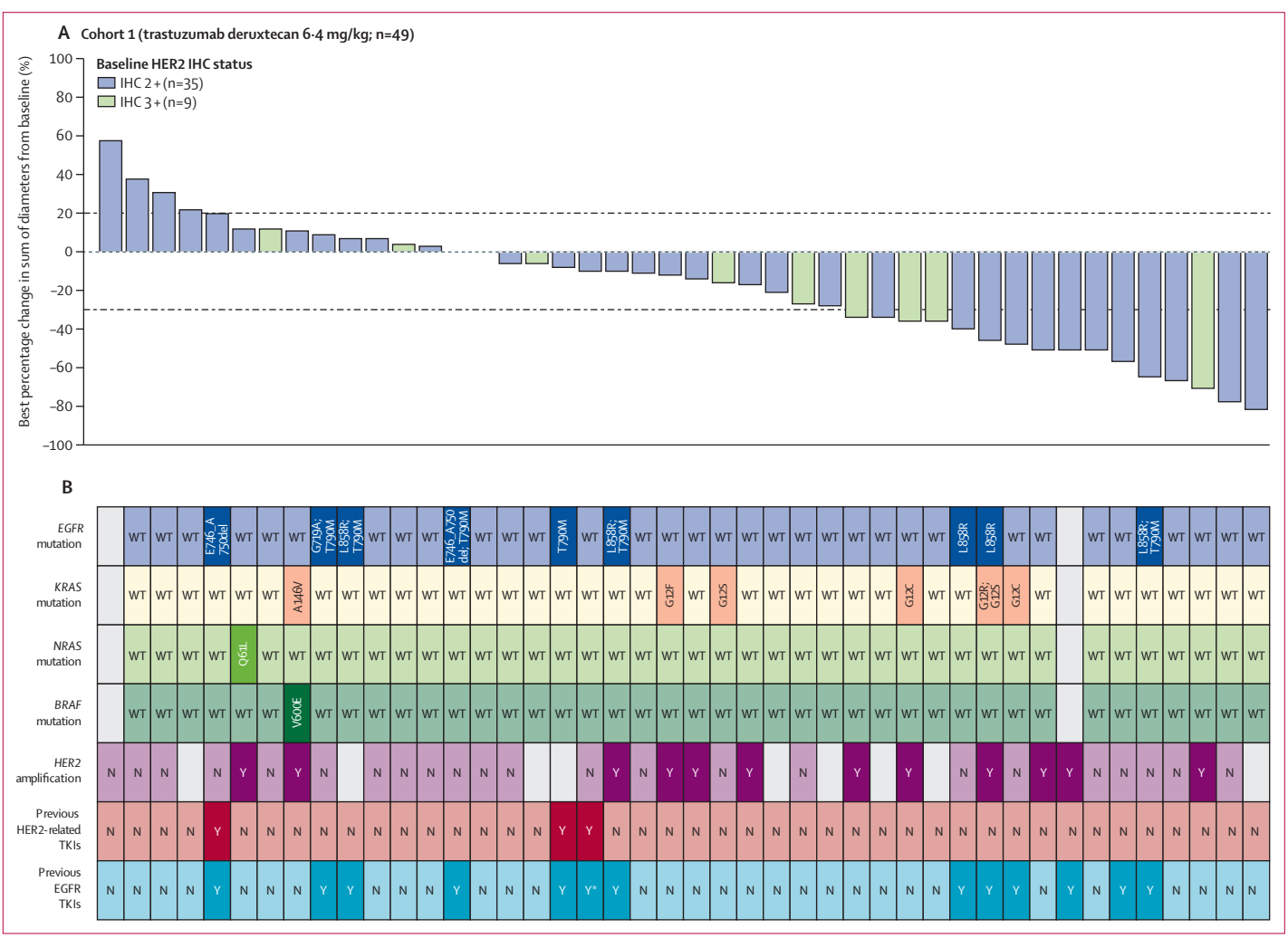
A summary of treatment-emergent adverse events in cohorts 1 and 1A is shown in table 3. The most common treatment-emergent adverse events of any grade were nausea (29 [59%] of 49 patients in cohort 1 and 30 [73%] of 41 patients in cohort 1A), fatigue (29 [59%] and 29 [71%], respectively; preferred terms fatigue, asthenia, and malaise), and decreased appetite (22 [45%] and 19 [46%], respectively; appendix p 14). The most common treatment-emergent adverse events of grade 3 or worse were neutropenia (12 [24%] of 49 in cohort 1, none in cohort 1A), pneumonia (six [12%] and two [5%], respectively), fatigue (six [12%] and three [7%], respectively), disease progression (six [12%] and four [10%], respectively), and dyspnoea (five [10%] and two [4%], respectively).

In cohort 1, deaths due to treatment-emergent adverse events as assessed by the investigator occurred in ten (20%) patients, of which the cause of death was disease progression in six (12%) patients and bronchospasm, hydrocephalus, respiratory failure, and pneumonitis in one (2%) patient each. The pneumonitis treatment-emergent adverse event was assessed to be drug-related grade 5 (ie, fatal) pneumonitis by the investigator and was subsequently adjudicated as drug-related grade 5 interstitial lung disease or pneumonitis by the independent adjudication committee. In cohort 1A, seven (17%) patients had deaths due to treatment-emergent adverse events, of which the cause of death

was disease progression in four (10%) patients and dyspnoea, malignant neoplasm, and sepsis in one (2%) patient each, of which none were assessed to be drug-related by the investigator.

Overall, ten (20%) patients in cohort 1 had independently adjudicated drug-related interstitial lung disease or pneumonitis by the data cutoff (Dec 3, 2021), which included two (4%) grade 1, five (10%) grade 2, and three (6%) grade 5 events (appendix p 15). In cohort 1A, two (5%) patients had adjudicated drug-related interstitial lung disease or pneumonitis, which included one (2%) grade 2 and one (2%) grade 5 event. In cohort 1A, one additional patient had grade 4 pneumonitis after the data cutoff and subsequently died; the reported pneumonitis was subsequently adjudicated (on Oct 27, 2022) as drug-related grade 5 interstitial lung disease or pneumonitis. The median time to onset of adjudicated drug-related interstitial lung disease or pneumonitis was 103·0 days (IQR 40·0–126·0) and 40·5 days (40·0–41·0) in cohorts 1 and 1A, respectively.

None of the patients with grade 1 interstitial lung disease or pneumonitis (two patients in cohort 1) received steroid treatment. All patients with grade 2 or worse interstitial lung disease or pneumonitis received steroid treatment (eight [100%] patients in cohort 1 and two [100%] patients in cohort 1A), with six of the ten patients promptly initiated on steroids within 1–3 days after the investigator reported the event. The longest time to onset of steroids was 15 days (event was resolved). Among the six patients who initiated steroid treatment within 1–3 days, the outcome of adjudicated drug-related interstitial lung disease or pneumonitis was resolved in three patients, not resolved in one patient, fatal in one patient (the patient with grade 5 interstitial lung disease in cohort 1), and unknown in one patient. The outcomes as of Dec 3, 2021, in all patients with adjudicated drug-related interstitial lung disease or pneumonitis events are shown in the appendix (p 15). In cohorts 1 and 1A, three (30%) of ten patients and one (50%) of two patients, respectively, with adjudicated drug-related interstitial lung disease or pneumonitis had



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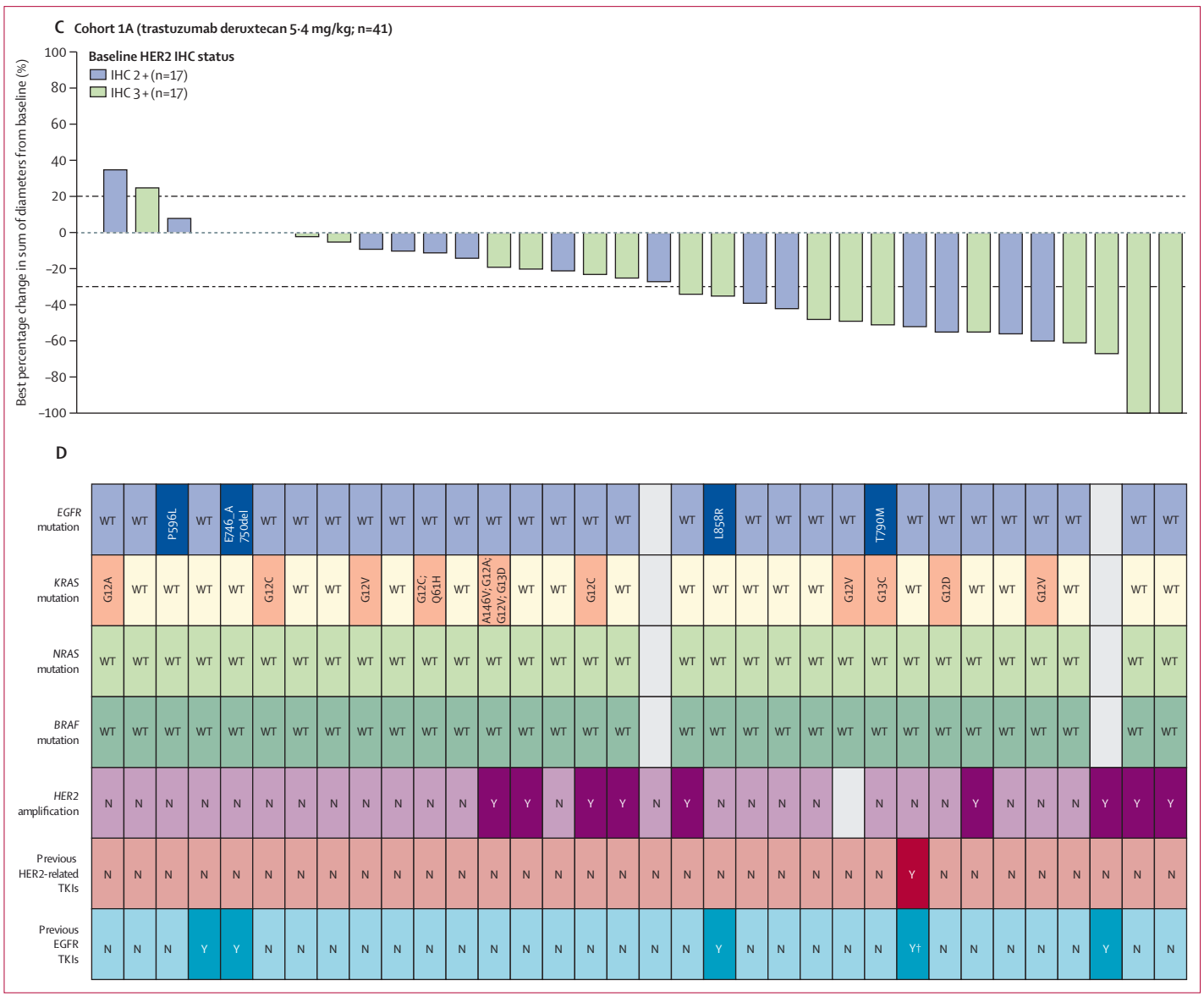

Figure 2: **Waterfall plots of best percentage change from baseline in the sum of the diameters for all target lesions (A, C) and corresponding mutation and previous treatment status (post hoc; B, D)**

Each bar in the waterfall plot aligns with a column of the table to represent a single patient (part A aligns with part B; part C aligns with part D). Two patients in cohort 1 and three patients in cohort 1A had a best percentage change of 0. Blank squares in parts B and D represent missing data. The dashed line at 20% denotes progressive disease and the dashed line at −30% denotes partial response, per Response Evaluation Criteria in Solid Tumours version 1.1. A=Ala. C=Cys. D=Asp. del=deletion. E=Glu. F=Phe. G=Gly. H=His. L=Leu. M=Met. N=no. P=Pro. Q=Gln. R=Arg. S=Ser. T=Thr. V=Val. WT=wild type. Y=yes. *The previous EGFR TKI was a pan-HER therapy (afatinib). †The previous EGFR TKI was a pan-HER therapy (tarloxotinib).

received immune checkpoint inhibitor therapy within 6 months of study enrolment (post-hoc analysis).

Discussion

In this primary analysis of the DESTINY-Lung01 trial, trastuzumab deruxtecan showed preliminary antitumour activity at both doses (5·4 mg/kg and 6·4 mg/kg) in heavily pretreated patients with HER2-overexpressing NSCLC. Responses were observed across the subgroups analysed, including in patients with HER2 immunohistochemistry 3+ or 2+ status, in patients with and without stable CNS metastases at baseline, and in patients with previous anti-PD-1 or anti-PD-L1 therapy in cohorts 1 and 1A. In addition, antitumour activity was observed in patients with and without *HER2* amplification in both cohorts. The safety profile of trastuzumab deruxtecan was generally manageable and consistent with the known safety profile of trastuzumab deruxtecan in other studies.[6,10]

There is an unmet need to investigate HER2-directed agents in patients with HER2-overexpressing NSCLC, despite HER2 overexpression being observed in 8–23%

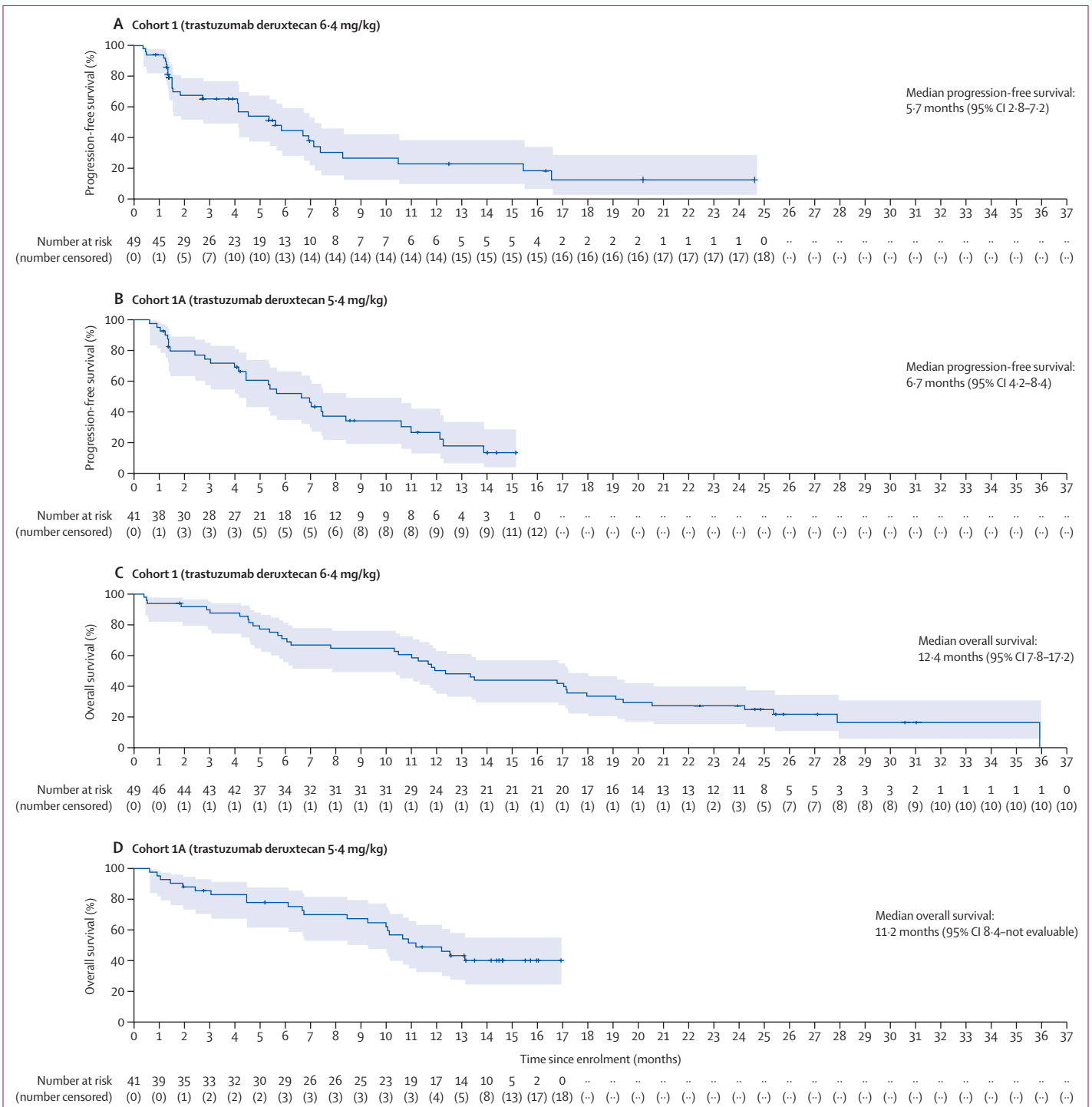

***Figure 3*: Progression-free survival in cohort 1 (A) and cohort 1a (B) and overall survival in cohort 1 (C) and cohort 1A (D)**
Progressive disease was assessed by independent central review per Response Evaluation Criteria in Solid Tumours version 1.1. Kaplan–Meier estimates of survival (blue lines) and respective 95% CIs (blue shading) were calculated with use of the Brookmeyer–Crowley method; crosses denote censored patients.

of these patients.[1] At present, no approved or recommended HER2-directed therapies are available for patients with HER2-overexpressing NSCLC, and thus far, few trials have reported efficacy results for HER2-directed regimens in this patient population.[16,17] Adding trastuzumab to gemcitabine–cisplatin in the first-line setting did not result in a notable benefit when compared with gemcitabine–cisplatin alone (objective response rate

	Cohort 1 (6·4 mg/kg); N=49				Cohort 1A (5·4 mg/kg); N=41			
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Nausea	26 (53%)	3 (6%)	0	0	28 (68%)	2 (5%)	0	0
Fatigue	23 (47%)	6 (12%)	0	0	26 (63%)	3 (7%)	0	0
Decreased appetite	20 (41%)	2 (4%)	0	0	19 (46%)	0	0	0
Constipation	15 (31%)	0	0	0	10 (24%)	0	0	0
Vomiting	13 (27%)	2 (4%)	0	0	12 (29%)	1 (2%)	0	0
Diarrhoea	12 (24%)	2 (4%)	0	0	13 (32%)	2 (5%)	0	0
Weight decreased	12 (24%)	0	0	0	7 (17%)	1 (2%)	0	0
Anaemia	10 (20%)	3 (6%)	1 (2%)	0	8 (20%)	3 (7%)	0	0
Alopecia	10 (20%)	0	0	0	5 (12%)	0	0	0
Dyspnoea	8 (16%)	5 (10%)	0	0	10 (24%)	1 (2%)	0	1 (2%)
Dizziness	8 (16%)	2 (4%)	0	0	3 (7%)	0	0	0
Thrombocytopenia	7 (14%)	1 (2%)	1 (2%)	0	3 (7%)	0	0	0
Hypokalaemia	6 (12%)	2 (4%)	0	0	1 (2%)	2 (5%)	0	0
Stomatitis	6 (12%)	0	0	0	2 (5%)	0	0	0
Cough	6 (12%)	0	0	0	12 (29%)	0	0	0
Pneumonitis	5 (10%)	1 (2%)	1 (2%)	1 (2%)†	2 (5%)	0	0	0
Blood creatinine increased	5 (10%)	0	0	0	3 (7%)	0	0	0
Upper respiratory tract infection	5 (10%)	0	0	0	1 (2%)	0	0	0
Aspartate aminotransferase increased	4 (8%)	2 (4%)	0	0	3 (7%)	0	0	0
Leukopenia	4 (8%)	3 (6%)	0	0	2 (5%)	0	0	0
Abdominal pain	4 (8%)	1 (2%)	0	0	5 (12%)	0	0	0
Alanine aminotransferase increased	3 (6%)	2 (4%)	0	0	4 (10%)	0	0	0
Lymphopenia	3 (6%)	2 (4%)	0	0	0	1 (2%)	0	0
Hypotension	3 (6%)	1 (2%)	1 (2%)	0	0	1 (2%)	0	0
Epistaxis	3 (6%)	1 (2%)	0	0	4 (10%)	0	0	0
Hiccups	3 (6%)	1 (2%)	0	0	2 (5%)	0	0	0
Non-cardiac chest pain	3 (6%)	0	0	0	6 (15%)	0	0	0
Pneumonia	2 (4%)	6 (12%)	0	0	0	2 (5%)	0	0
Urinary tract infection	2 (4%)	1 (2%)	0	0	2 (5%)	0	0	0
Back pain	2 (4%)	0	0	0	5 (12%)	0	0	0
Neutropenia	2 (4%)	7 (14%)	5 (10%)	0	4 (10%)	0	0	0
Pyrexia	1 (2%)	0	0	0	3 (7%)	1 (2%)	0	0
Pleural effusion	1 (2%)	0	0	0	2 (5%)	1 (2%)	0	0
Hypophosphataemia	1 (2%)	0	0	0	1 (2%)	1 (2%)	0	0
Blood sodium decreased	1 (2%)	0	0	0	0	1 (2%)	0	0
Hypocalcaemia	1 (2%)	0	0	0	0	0	1 (2%)	0
Acute kidney injury	0	3 (6%)	0	0	0	0	0	0
Respiratory tract infection	0	2 (4%)	0	0	2 (5%)	1 (2%)	0	0
Pulmonary sepsis	0	2 (4%)	0	0	0	0	0	0
Hypoxia	0	1 (2%)	1 (2%)	0	0	2 (5%)	0	0
Ejection fraction decreased	0	1 (2%)	0	0	1 (2%)	1 (2%)	0	0
Febrile neutropenia	0	1 (2%)	0	0	0	1 (2%)	0	0
Anaemia of malignant disease	0	1 (2%)	0	0	0	0	0	0
Acute myocardial infarction	0	1 (2%)	0	0	0	0	0	0
Atrial fibrillation	0	1 (2%)	0	0	0	0	0	0
Cardiomyopathy	0	1 (2%)	0	0	0	0	0	0
Haemorrhoids	0	1 (2%)	0	0	0	0	0	0
Proctalgia	0	1 (2%)	0	0	0	0	0	0
Enterocolitis infectious	0	1 (2%)	0	0	0	0	0	0
Oesophageal infection	0	1 (2%)	0	0	0	0	0	0

(Table 3 continues on next page)

	Cohort 1 (6·4 mg/kg); N=49				Cohort 1A (5·4 mg/kg); N=41			
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Pneumonia staphylococcal	0	1 (2%)	0	0	0	0	0	0
Radiation necrosis	0	1 (2%)	0	0	0	0	0	0
Transfusion reaction	0	1 (2%)	0	0	0	0	0	0
Platelet count increased	0	1 (2%)	0	0	0	0	0	0
Malignant pleural effusion	0	1 (2%)	0	0	0	0	0	0
Seizure	0	1 (2%)	0	0	0	0	0	0
Syncope	0	1 (2%)	0	0	0	0	0	0
Epilepsy	0	1 (2%)	0	0	0	0	0	0
Partial seizures	0	1 (2%)	0	0	0	0	0	0
Mental status changes	0	1 (2%)	0	0	0	0	0	0
Pneumonia aspiration	0	1 (2%)	0	0	0	0	0	0
Respiratory distress	0	1 (2%)	0	0	0	0	0	0
Deep vein thrombosis	0	1 (2%)	0	0	0	0	0	0
Orthostatic hypotension	0	1 (2%)	0	0	0	0	0	0
Respiratory failure	0	0	2 (4%)	1 (2%)	0	1 (2%)	0	0
Disease progression‡	0	0	0	6 (12%)	1 (2%)	0	0	4 (10%)
Hydrocephalus	0	0	0	1 (2%)	0	0	0	0
Bronchospasm	0	0	0	1 (2%)	0	0	0	0
Bone pain	0	0	0	0	2 (5%)	1 (2%)	0	0
Pericardial effusion	0	0	0	0	1 (2%)	1 (2%)	0	0
Sepsis	0	0	0	0	0	1 (2%)	0	1 (2%)
Cholangitis	0	0	0	0	0	1 (2%)	0	0
COVID-19 pneumonia	0	0	0	0	0	1 (2%)	0	0
Empyema	0	0	0	0	0	1 (2%)	0	0
Vocal cord paralysis	0	0	0	0	0	1 (2%)	0	0
Pneumothorax	0	0	0	0	0	1 (2%)	0	0
Hypercalcaemia	0	0	0	0	0	0	1 (2%)	0
Neoplasm malignant	0	0	0	0	0	0	0	1 (2%)

Data are number of patients (%), for adverse events that occurred in at least 10% (grade 1–2) of patients by worst toxicity grade, and all grade 3–5 events, listed in decreasing order of grade 1–2 frequency for cohort 1. *Grouped terms: abdominal pain (abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain); anaemia (haemoglobin decreased, red blood cell count decreased, anaemia, haematocrit decreased); fatigue (fatigue, asthenia, malaise); leukopenia (white blood cell count decreased, leukopenia); lymphopenia (lymphocyte count decreased, lymphopenia); neutropenia (neutrophil count decreased, neutropenia); thrombocytopenia (platelet count decreased, thrombocytopenia); upper respiratory tract infection (influenza, influenza-like illness, upper respiratory tract infection); stomatitis (stomatitis, aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosal blistering). †Judged to be a drug-related death by the investigators, and subsequently adjudicated as drug-related grade 5 interstitial lung disease by the independent adjudication committee. ‡When a patient died from progressive disease with no other immediate causes, disease progression was reported as a serious adverse event.

Table 3: **Treatment-emergent adverse events by preferred terms or grouped terms* per investigator assessment, safety analysis set**

of 36% [95% CI 22·9–50·8], 18 of 50 patients, *vs* 41% [27·6–55·8], 21 of 51) in patients with HER2-positive NSCLC.[17] In that study, HER2-positive NSCLC was defined as immunohistochemistry 2+ status (complete, moderate membrane staining of >10% of tumour cells) or 3+ status (complete, intense membrane staining of ≥80% of tumour cells), assessed with the Dako HercepTest kit, or gene amplification (*HER2* to CEN17 ratio ≥2), assessed by FISH.[17] In the second trial, among previously treated patients with HER2-overexpressing NSCLC, clinical benefit was observed only in patients with HER2 immunohistochemistry 3+ status who were treated with trastuzumab emtansine (objective response rate 20% [95% CI 5·7–43·7] in patients with immunohistochemistry 3+ status [n=4 of 20]; objective response rate 0% [95% CI not reported], in patients with immunohistochemistry 2+ status [n=0 of 29]).[16] In that study, HER2 overexpression was assessed with the Ventana Pathway HER2 (4B5) immunohistochemistry assay from Ventana Medical Systems via central testing and defined as immunohistochemistry 2+ status (weak-to-moderate complete, basolateral, or lateral membranous reactivity in ≥10% of tumour cells) or 3+ status (strong complete, basolateral, or lateral membranous reactivity in ≥10% of tumour cells).[16] Of four patients with a response, one patient did not have *HER2* amplification or mutation, one patient had *HER2* amplification, and two patients had both *HER2* amplification and *HER2*

mutation; the three with *HER2*-amplified tumours were assessed by in situ hybridisation (*HER2* to CEN17 gene ratio ≥2) and the two patients with *HER2* mutations were detected by central next generation sequencing and the other by local next generation sequencing (Foundation Medicine).[16] The HER2 staining conditions and scoring criteria for immunohistochemistry 3+ or 2+ disease differed in these studies from assays used in other literature and the present study.

HER2 immunohistochemistry testing should be standardised across indications, including NSCLC, because patients with HER2-overexpressing NSCLC have worse prognosis than those without HER2 overexpression.[1,18] Furthermore, HER2 overexpression or amplification might contribute to EGFR tyrosine-kinase inhibitor resistance in patients with NSCLC.[3] However, in a phase 2 basket trial of trastuzumab emtansine in patients with *HER2*-amplified or *HER2*-mutant lung cancers, objective response rate was 51% (95% CI 36–66; 25 of 49 patients), and responses were observed with or without *HER2* co-mutation.[19] Further study of HER2-targeted antibody–drug conjugates is needed in this patient population.

A previous study showed that some patients with HER2-overexpressing NSCLC had co-occurring mutations in *EGFR* (one [17%] of six patients) or *KRAS* (two [33%] patients) via direct DNA sequencing of exons 18–21 in *EGFR* and codons 12 and 13 in *KRAS*.[18] In the present study, antitumour activity was observed with trastuzumab deruxtecan in patients with and without *EGFR* or *KRAS* mutations; however, patient numbers were small. Additional investigation is needed to assess the efficacy of trastuzumab deruxtecan in these populations.

No new safety signals were observed in the current study. The overall safety profile was acceptable, generally manageable, and consistent with the established safety profile of trastuzumab deruxtecan[6,10] and favoured the 5·4 mg/kg dose. Gastrointestinal and haematological events, and fatigue, alopecia, and cough were among the most common types of treatment-emergent adverse events with trastuzumab deruxtecan. Drug-related treatment-emergent adverse events associated with drug discontinuation, dose reduction, and drug interruption were numerically higher with the 6·4 mg/kg dose than the 5·4 mg/kg dose, which might have affected the response to trastuzumab deruxtecan at the 6·4 mg/kg dose. In addition, a slightly lower number of drug-related treatment-emergent adverse events were associated with death with the 5·4 mg/kg dose than the 6·4 mg/kg dose when including independently adjudicated drug-related grade 5 interstitial lung disease or pneumonitis events.

Interstitial lung disease or pneumonitis associated with trastuzumab deruxtecan treatment was an important risk to monitor. The incidence of all-grade adjudicated drug-related interstitial lung disease or pneumonitis appeared to be dose related, because fewer events occurred with the 5·4 mg/kg dose than with the 6·4 mg/kg dose (two [5%] patients *vs* ten [20%] patients), which is consistent with observations of trastuzumab deruxtecan in DESTINY-Lung02 and in patients with breast cancer and colorectal cancer.[7,20,21] Importantly, the lower dose (5·4 mg/kg) did not compromise activity, and was shown to have a numerically higher response rate than the 6·4 mg/kg dose. The rate of interstitial lung disease or pneumonitis observed with trastuzumab deruxtecan 6·4 mg/kg in the HER2-overexpressing cohort (cohort 1) was slightly lower than the rate observed in the *HER2*-mutant cohort (cohort 2) of DESTINY-Lung01 at the same dose (20% [median treatment duration, 4·1 months] *vs* 26% [median treatment duration, 6·9 months]).[6] Moderate or severe baseline renal impairment has been identified as a potential risk factor for interstitial lung disease or pneumonitis;[22] in DESTINY-Lung01, four (40%) of the ten patients in cohort 1 and no patients in cohort 1A with adjudicated drug-related interstitial lung disease or pneumonitis had moderate or severe renal impairment at baseline (data not shown); however, the patient number in our study was too small to evaluate whether this was a risk factor. Further investigation into the risk factors associated with interstitial lung disease or pneumonitis is warranted.

Sample size was a limitation of this study. Small numbers of patients were included in the subgroup analyses, limiting the conclusions that can be drawn from these analyses. HER2 testing was done on archival tissue for most patients, which could also be a potential limitation if HER2 expression levels changed during previous therapies. Only systemic activity was analysed in patients with CNS metastasis at baseline, and investigation into the intracranial efficacy of trastuzumab deruxtecan is needed.

Trastuzumab deruxtecan 5·4 mg/kg and 6·4 mg/kg showed antitumour activity in patients with HER2-overexpressing NSCLC. The safety profile was consistent with the established safety profile of trastuzumab deruxtecan and favoured the 5·4 mg/kg dose. Trastuzumab deruxtecan was granted breakthrough therapy designation in August, 2023, in the USA by the Food and Drug Administration for the treatment of adult patients with HER2-positive (immunohistochemistry 3+) solid tumours who have either progressed on previous treatment and have no standard alternatives, or for the treatment of patients with HER2-positive (immunohistochemistry 3+) metastatic colorectal cancer who have received two or more previous treatment regimens.[23] Ongoing phase 1 and 2 trials are investigating trastuzumab deruxtecan in HER2-overexpressing NSCLC. DESTINY-Lung03 (NCT04686305) is a phase 1b study evaluating the safety of trastuzumab deruxtecan in combination with immunotherapeutic agents (durvalumab or volrustomig) with or without chemotherapy in the first-line setting. In the phase 1b U106 trial (NCT04042701), trastuzumab deruxtecan is

being investigated in combination with pembrolizumab in a two-part dose escalation and dose expansion study in patients with HER2-expressing NSCLC who had not received any previous treatment with anti-PD-1, anti-PD-L1, or HER2 agents. In the phase 2 HUDSON trial (NCT03334617), trastuzumab deruxtecan in combination with durvalumab is being evaluated in patients who have progressed on an anti-PD-1 or anti-PD-L1 containing therapy. Results of the current trial support further exploration and development of trastuzumab deruxtecan as a potential treatment option for patients with HER2-overexpressing NSCLC.

Contributors

KP, AT, YC, QY, WF, ZT, and PAJ contributed to study conception. KP, AT, YC, QY, WF, ZT, BTL, DP, and PAJ contributed to study design. KP, AT, YC, QY, WF, ZT, and PAJ contributed intellectually to the development of the study protocol. EFS, EF, DU, MN, KN, LP-AR, JMP, BTL, DP, CB, YG, HM, AS, and PAJ were principal investigators and participated in data acquisition and quality control. All authors contributed to data interpretation. YC provided clinical safety and pharmacovigilance monitoring throughout the study. QY was responsible for biostatistics and data management, and developed the statistical rationale for the study. WF did the clinical biomarker analysis and managed the HER2 immunohistochemistry analysis at Ventana (now Roche Tissue Diagnostics). ZT performed clinical biomarker analysis. All authors had access to the data from the study and approved the manuscript and had final responsibility for the decision to submit for publication. AT and EFS accessed and verified the study data.

Declaration of interests

EFS has received provision of study materials (drug) and clinical trial funding (to their institution) from Daiichi Sankyo; consulting fees from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Janssen, MSD, Roche Sanofi, and Takeda; speaker payment or honoraria from Boehringer Ingelheim and Daiichi Sankyo; and participated on a data safety monitoring board for Daiichi Sankyo. 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Data sharing

Anonymised individual participant data (IPD) on completed studies and applicable supporting clinical study documents may be available upon request at the Vivli website (https://vivli.org). In cases where clinical study data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo will continue to protect the privacy of our clinical trial participants. Details on data sharing criteria and the procedure for requesting access can be found at this web address: https://vivli.org/ourmember/daiichi-sankyo. More information on data sharing is provided in the appendix (p 2).

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