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Trastuzumab Deruxtecan in Patients With *HER2*-Mutant Metastatic Non–Small-Cell Lung Cancer: Primary Results From the Randomized, Phase II DESTINY-Lung02 Trial

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ABSTRACT

PURPOSE Trastuzumab deruxtecan (T-DXd) 5.4 and 6.4 mg/kg showed robust antitumor activity in multiple cancer indications; however, T-DXd 5.4 mg/kg has not been evaluated in patients with previously treated human epidermal growth factor receptor 2–mutant (*HER2*m; defined as single-nucleotide variants and exon 20 insertions) metastatic non–small-cell lung cancer (mNSCLC).

METHODS DESTINY-Lung02, a blinded, multicenter, phase II study, investigated T-DXd 5.4 mg/kg once every 3 weeks for the first time in previously treated (platinum-containing therapy) patients with *HER2*m mNSCLC and further assessed T-DXd 6.4 mg/kg once every 3 weeks in this population. The primary end point was confirmed objective response rate (ORR) per RECIST v1.1 by blinded independent central review.

RESULTS One hundred fifty-two patients were randomly assigned 2:1 to T-DXd 5.4 or 6.4 mg/kg once every 3 weeks. As of December 23, 2022, the median duration of follow-up was 11.5 months (range, 1.1-20.6) with 5.4 mg/kg and 11.8 months (range, 0.6-21.0) with 6.4 mg/kg. Confirmed ORR was 49.0% (95% CI, 39.0 to 59.1) and 56.0% (95% CI, 41.3 to 70.0) and median duration of response was 16.8 months (95% CI, 6.4 to not estimable [NE]) and NE (95% CI, 8.3 to NE) with 5.4 and 6.4 mg/kg, respectively. Median treatment duration was 7.7 months (range, 0.7-20.8) with 5.4 mg/kg and 8.3 months (range, 0.7-20.3) with 6.4 mg/kg. Grade ≥ 3 drug-related treatment-emergent adverse events occurred in 39 of 101 (38.6%) and 29 of 50 (58.0%) patients with 5.4 and 6.4 mg/kg, respectively. 13 of 101 (12.9%) and 14 of 50 (28.0%) patients had adjudicated drug-related interstitial lung disease (2.0% grade ≥ 3 in each arm) with 5.4 and 6.4 mg/kg, respectively.

CONCLUSION T-DXd demonstrated clinically meaningful responses at both doses. Safety profile was acceptable and generally manageable, favoring T-DXd 5.4 mg/kg.

ACCOMPANYING CONTENT

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Data Supplement

Protocol

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INTRODUCTION

Approximately 2%-4% of nonsquamous non–small-cell lung cancer (NSCLC) is driven by human epidermal growth factor receptor 2 (*HER2*; *ERBB2*) mutations.[1] Chemotherapy and immunotherapy have limited efficacy, and other HER2-targeted therapies have demonstrated inconsistent results in patients with *HER2*-mutant (*HER2*m) metastatic NSCLC (mNSCLC) in the second-line setting.[2-6] Therefore, effective HER2-targeted therapies are urgently needed in this patient population.[7]

Trastuzumab deruxtecan (T-DXd) is the first and only approved HER2-directed therapy for patients with previously treated *HER2*m mNSCLC in several countries. The clinical benefit of T-DXd 6.4 mg/kg was demonstrated in the phase II DESTINY-Lung01 trial, in which patients with *HER2*m mNSCLC achieved a confirmed objective response rate (ORR) of 54.9%, median duration of response (DoR) of 10.6 months, median progression-free survival (PFS) of 8.2 months, and median overall survival (OS) of 18.6 months.[8,9] The incidence of drug-related interstitial lung disease (ILD)/pneumonitis was 27.5% in the *HER2*m cohort,[9]

CONTEXT

Key Objective

What is the efficacy and safety of trastuzumab deruxtecan (T-DXd) 5.4 mg/kg and 6.4 mg/kg once every 3 weeks in patients with previously treated human epidermal growth factor receptor 2 (*HER2*)–mutant metastatic non–small-cell lung cancer?

Knowledge Generated

Both T-DXd 5.4 and 6.4 mg/kg once every 3 weeks demonstrated deep and durable responses that were consistent regardless of *HER2* mutation type and amplification status, baseline CNS metastasis, and prior treatment; safety at both doses was acceptable and generally manageable. T-DXd 5.4 mg/kg was associated with a more favorable safety profile and lower rates of adjudicated drug-related interstitial lung disease versus T-DXd 6.4 mg/kg.

Relevance *(T.E. Stinchcombe)*

This randomized phase II study established the dose of T-DXd for clinical care, and illustrates the importance of determining the optimal dose of agents as part of the drug development process.*

*Relevance section written by *JCO* Associate Editor Thomas E. Stinchcombe, MD.

warranting evaluation of a lower dose of T-DXd in patients with *HER2*m mNSCLC.

DESTINY-Lung02 is a phase II trial evaluating the efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg once every 3 weeks in patients with *HER2*m (single-nucleotide variants [SNVs] and exon 20 insertions) mNSCLC, thereby characterizing the benefit/risk profile of T-DXd in this patient population. Interim analysis of DESTINY-Lung02 (data cutoff [DCO]: March 24, 2022) provided the first clinical data of T-DXd 5.4 mg/kg in patients with *HER2*m mNSCLC[10] and served as the basis for accelerated approval of T-DXd 5.4 mg/kg in the United States as the first HER2-directed treatment for patients with unresectable NSCLC or mNSCLC with activating *HER2* (*ERRB2*) mutations, as detected by a US Food and Drug Administration (FDA)–approved test and who have received a prior systemic therapy.[11] We report primary results from DESTINY-Lung02 (DCO: December 23, 2022).

METHODS

Study Design and Participants

DESTINY-Lung02 is a randomized, multicenter, blinded, 2-cohort, phase II study (ClinicalTrials.gov identifier: NCT04644237) conducted at 47 sites across North America, Asia, Europe, and Australia evaluating the efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg once every 3 weeks in patients with previously treated *HER2*m mNSCLC.

Patients were eligible if they were 18 years or older; had mNSCLC with a known activating *HER2* mutation (Data Supplement, Table A1 [online only]) documented from an archival or fresh tumor tissue sample by certified local laboratory assessment; had received ≥1 previous treatment (platinum-based chemotherapy) in the metastatic/locally advanced setting; were not amenable to curative surgery or radiation; and had ≥1 measurable lesion by blinded independent central review (BICR) on the basis of RECIST version 1.1 (RECIST v1.1).[12]

Patients were excluded if they had known driver mutations in *EGFR*, *BRAF*, or *MET* exon 14 gene or known *ALK*/*ROS1*/*RET*/*NTRK* fusions and if they had spinal cord compression or clinically active brain metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants. However, patients with stable baseline brain metastases (asymptomatic; not requiring corticosteroid or anticonvulsant treatment) were allowed to enroll. Patients were also excluded if they had a history of noninfectious ILD requiring steroids or had current or suspected ILD, which could not be ruled out by imaging at screening. Additional eligibility criteria are provided in the Data Supplement (Supplementary Methods).

The study Protocol (online only) was approved by the institutional review board at each site and was conducted in accordance with the International Conference on Harmonization Good Clinical Practice, the Declaration of Helsinki, and local regulations on the conduct of clinical research. All patients provided written informed consent before study participation.

Procedures

Eligible patients were randomly assigned 2:1 to T-DXd 5.4 mg/kg once every 3 weeks or 6.4 mg/kg once every 3 weeks, respectively. Random assignment was stratified by patients who received prior anti–PD-(L)1 treatment. All patients, investigators, site staff (except the pharmacist and other staff members deemed necessary for site operations to maintain blinding), central imaging readers, and the ILD adjudication committee were blinded to the dose level.

T-DXd 5.4 mg/kg or 6.4 mg/kg was administered intravenously once every 3 weeks. Two dose reductions were permitted in each arm (additional details in the Data Supplement, Supplementary Methods).

Tumor assessments were performed in all patients at baseline and every 6 weeks from cycle 1, day 1. Biomarker assessment was performed in patients with activating *HER2* mutations detected in archival or fresh tumor tissue samples. The Oncomine Dx Target Test (Thermo Fisher Scientific, Frederick, MD) was used for retrospective central confirmation of *HER2* SNVs and exon 20 insertion mutation type. *HER2* amplification status was evaluated using an exploratory Oncomine Dx Target Test copy number algorithm on NSCLC formalin-fixed paraffin-embedded tissue samples. Copy number gain was defined as the lower limit of the copy number 95% CI > 4.[13] Immunohistochemistry analysis was not performed because of the limited availability of suitable tissue samples.

End Points

The primary end point was confirmed ORR, defined as the sum of the confirmed complete response (CR) rate and partial response (PR) rate, as assessed by BICR per RECIST v1.1. Secondary efficacy end points included confirmed ORR by investigator assessment, disease control rate (DCR; defined as the sum of CR, PR, or stable disease [SD] rates) by BICR and investigator, DoR (defined as the time from date of initial response [CR or PR] to the date of disease progression or death due to any cause for patients with a confirmed CR or PR) by BICR and investigator, PFS (defined as the time from the date of random assignment to the earliest date of the first objective documentation of radiographic disease progression or death due to any cause) by BICR and investigator, and OS (defined as the time from the date of random assignment to the date of death due to any cause). Exploratory end points included time to response, best percentage change in the sum of diameters of target lesions, and biomarkers.

Safety end points, which included treatment-emergent adverse events (TEAEs), serious adverse events, and adverse events of special interest (including ILD/pneumonitis and left ventricular [LV] dysfunction), were coded using the Medical Dictionary for Drug Regulatory Activities version 25.1 and graded on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. The seriousness, severity, and relationship of adverse events to the study drug were determined by the investigator. All cases of potential ILD/pneumonitis were evaluated by an independent ILD adjudication committee and managed according to protocol-defined ILD management guidelines (Data Supplement, Supplementary Methods).

Statistical Analysis

A sample size of 150 patients was originally planned for this study on the basis of the probability evaluation that the 95% Clopper-Pearson CI exceeded and excluded the ORR benchmark of 26.4%. This benchmark was the upper limit of the 95% CI (ORR, 22.9%; 95% CI, 19.7 to 26.4%) in the ramucirumab plus docetaxel arm of the REVEL trial, which was investigated as a second-line treatment for patients with advanced NSCLC after platinum-based therapy.[14]

Efficacy end points and biomarkers were assessed in all patients randomly assigned to receive study treatment (including those who were randomly assigned but not treated). Safety was assessed in all randomly assigned patients who received at least one dose of study treatment. ORR by BICR and investigator assessment was estimated using 2-sided Clopper-Pearson 95% CIs. DoR, PFS, and OS were analyzed using the Kaplan-Meier method, with 2-sided 95% CIs calculated using the Brookmeyer-Crowley method. This study was not powered to statistically compare treatment arms. All statistical analyses were performed using SAS version 9.3 or higher (additional details in the Data Supplement).

RESULTS

Patients

One hundred fifty-two patients were enrolled between March 2021 and March 2022, of whom 102 patients were randomly assigned to T-DXd 5.4 mg/kg once every 3 weeks and 50 patients to T-DXd 6.4 mg/kg once every 3 weeks. One patient randomly assigned to the T-DXd 5.4 mg/kg arm did not receive treatment. At DCO (December 23, 2022), 27 patients (26.7%) in the 5.4 mg/kg arm and 14 patients (28.0%) in the 6.4 mg/kg arm were continuing treatment and 47 (46.5%) and 19 patients (38.0%), respectively, had discontinued treatment because of disease progression (Data Supplement, Fig A1).

In the 5.4 mg/kg once every 3 weeks and 6.4 mg/kg once every 3 weeks arms, *HER2* mutations predominated in the kinase domain (n = 99 [97.1%] and n = 50 [100%]; Table 1). In the 5.4 and 6.4 mg/kg arms, 55 (53.9%) and 29 patients (58.0%), respectively, were never-smokers, and 35 (34.3%) and 22 patients (44.0%) had stable CNS metastases at baseline. Patients in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms received a median of two prior therapy regimens (range, 1-12 and 1-7); all patients received prior platinum-based chemotherapy, and most patients (73.5% and 78.0%, respectively) received anti–PD-(L)1 treatment.

Efficacy

In the T-DXd 5.4 mg/kg once every 3 weeks arm, confirmed ORR by BICR was 49.0% (95% CI, 39.0 to 59.1; 50 patients; DCO, December 23, 2022), with one patient (1.0%) and 49 patients (48.0%) achieving CR and PR, respectively (Table 2). In the T-DXd 6.4 mg/kg once every 3 weeks arm, confirmed ORR was 56.0% (95% CI, 41.3 to 70.0; 28 patients), with two (4.0%) and 26 patients (52.0%) achieving CR and PR, respectively. Responses were observed across treatment arms regardless of the number or type of prior systemic anticancer therapy and baseline CNS metastasis (Fig 1; Data

TABLE 1. Patient Baseline Characteristics and Prior Therapies

Baseline Characteristic	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 102)	T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50)
Age, years, median (range)	59.4 (31-84)	61.3 (28-86)
Sex, No. (%)		
Male	37 (36.3)	16 (32.0)
Female	65 (63.7)	34 (68.0)
Race, No. (%)		
Asian	65 (63.7)	31 (62.0)
White	23 (22.5)	5 (10.0)
Others	14 (13.7)	12 (24.0)
Region, No. (%)		
Asia	63 (61.8)	30 (60.0)
North America	4 (3.9)	2 (4.0)
Europe	33 (32.4)	17 (34.0)
Australia	2 (2.0)	1 (2.0)
ECOG PS, No. (%)		
0	29 (28.4)	19 (38.0)
1	73 (71.6)	31 (62.0)
Histology, No. (%)		
Adenocarcinoma	100 (98.0)	50 (100.0)
Squamous	1 (1.0)	0
Others	1 (1.0)	0
HER2 mutations, No. (%)		
Kinase domain	99 (97.1)	50 (100.0)
Extracellular domain	3 (2.9)	0
CNS metastasis at baseline,[a] No. (%)	35 (34.3)	22 (44.0)
History of prior lung resection, No. (%)	22 (21.6)	12 (24.0)
Renal function at baseline,[b] No. (%)		
Normal renal function	38 (37.3)	16 (32.0)
Mild renal impairment	41 (40.2)	29 (58.0)
Moderate renal impairment	23 (22.5)	5 (10.0)
Hepatic function at baseline, No. (%)		
Normal hepatic function[c]	76 (74.5)	39 (78.0)
Mild hepatic impairment[d]	26 (25.5)	11 (22.0)
Smoking history, No. (%)		
Former	47 (46.1)	21 (42.0)
Never	55 (53.9)	29 (58.0)
Any prior systemic anticancer therapy, No. (%)		
Yes	102 (100.0)	50 (100.0)
No. of prior therapy regimens, No. (%)		
≤2	65 (63.7)	31 (62.0)
>2	37 (36.3)	19 (38.0)
Median (range)	2 (1-12)	2 (1-7)
Previous systemic anticancer therapy, No. (%)		
Platinum-based therapy	102 (100.0)	50 (100.0)
Anti–PD-(L)1	75 (73.5)	39 (78.0)
Platinum and anti–PD-(L)1 (in combination)	51 (50.0)	29 (58.0)
Platinum and anti–PD-(L)1 (not in combination)	24 (23.5)	10 (20.0)
Docetaxel	30 (29.4)	17 (34.0)
Prior radiation therapy, No. (%)	58 (56.9)	25 (50.0)
Prior cancer surgery, No. (%)	25 (24.5)	13 (26.0)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; T-DXd, trastuzumab deruxtecan; ULN, upper limit of normal.
[a]Only stable (asymptomatic; not requiring corticosteroid or anticonvulsant treatment) CNS metastasis were allowed.
[b]Renal function status as determined by baseline creatinine clearance, where normal renal function is a serum creatinine clearance of ≥90 mL/min; mild renal impairment is a serum creatinine clearance of ≥60, <90 mL/min; and moderate renal impairment is a serum creatinine clearance of ≥30 but <60 mL/min.
[c]Defined as total bilirubin ≤ULN and (AST ≤ ULN) except for patients with Gilbert syndrome or total bilirubin ≤3.0 × ULN and (AST ≤ ULN) for patients with Gilbert syndrome.
[d]Defined as total bilirubin >ULN, ≤1.5 × ULN and any AST except for patients with Gilbert syndrome; total bilirubin >ULN, ≤3.0 × ULN and (AST > ULN) for patients with Gilbert syndrome; or total bilirubin ≤ULN and (AST > ULN) regardless of Gilbert syndrome.

Supplement, Fig A2). At both doses, patients had a reduction in tumor size from baseline (Fig 1) that was sustained over time (Data Supplement, Fig A3). The median DoR was 16.8 months (95% CI, 6.4 to not estimable [NE]; Data Supplement, Fig A4), and the median time to initial response (TTIR) was 1.8 months (range, 1.2-7.0) with T-DXd 5.4 mg/kg. With T-DXd 6.4 mg/kg, the median DoR was NE (95% CI, 8.3 to NE), and the median TTIR was 1.6 months (range, 1.2-11.2; Table 2). The estimated proportion of responders maintaining a response at 12 months was 54.4% (95% CI, 37.6 to 68.5) with T-DXd 5.4 mg/kg and 64.1% (95% CI, 38.2 to 81.4) with T-DXd 6.4 mg/kg. Investigator-assessed ORR and DCR were consistent with the BICR assessments (Data Supplement, Table A2).

At DCO, the median duration of follow-up was 11.5 months (range, 1.1-20.6) in the T-DXd 5.4 mg/kg once every 3 weeks arm and 11.8 months (range, 0.6-21.0) in the 6.4 mg/kg once every 3 weeks arm. In the 5.4 mg/kg and 6.4 mg/kg arms, the median PFS by BICR was 9.9 months (95% CI, 7.4 to NE) and 15.4 months (95% CI, 8.3 to NE), respectively (Figs 2A and 2B). At 12 months, the estimated PFS rate as determined by BICR was 45% (95% CI, 33 to 56) with T-DXd 5.4 mg/kg and

TABLE 2. Response to T-DXd in Patients With *HER2*-Mutant mNSCLC

Response Assessment by BICR	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 102)	T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50)
Confirmed ORR, No. (%)	50 (49.0)	28 (56.0)
95% CI	39.0 to 59.1	41.3 to 70.0
Best confirmed overall response, No. (%)		
CR	1 (1.0)	2 (4.0)
PR	49 (48.0)	26 (52.0)
SD	45 (44.1)	18 (36.0)
PD	4 (3.9)	2 (4.0)
Nonevaluable[a]	3 (2.9)	2 (4.0)
DCR, No. (%)	95 (93.1)	46 (92.0)
95% CI	86.4 to 97.2	80.8 to 97.8
DoR, months, median (95% CI)	16.8 (6.4 to NE)	NE (8.3 to NE)
TTIR, months, median (range)	1.8 (1.2-7.0)	1.6 (1.2-11.2)
Follow-up, months, median (range)	11.5 (1.1-20.6)	11.8 (0.6-21.0)

Abbreviations: BICR, blinded independent central review; CR, complete response; DCR, disease control rate; DoR, duration of response; mNSCLC, metastatic non–small-cell lung cancer; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan; TTIR, time to initial response.
[a]Three patients were nonevaluable at 5.4 mg/kg (one patient never received treatment because of COVID-19; two patients discontinued before first tumor assessment); two patients were nonevaluable at 6.4 mg/kg (discontinued because of adverse event before first tumor assessment).

53% (95% CI, 36 to 67) with T-DXd 6.4 mg/kg. The median OS was 19.5 months (95% CI, 13.6 to NE) and NE (95% CI, 12.1 to NE) in the 5.4 and 6.4 mg/kg arms, respectively (Figs 2C and 2D). The estimated 12-month OS rate was 67% (95% CI, 56 to 76) and 73% (95% CI, 57 to 84) with T-DXd 5.4 and 6.4 mg/kg, respectively.

Safety

The median treatment duration was 7.7 months (range, 0.7-20.8) and 8.3 months (range, 0.7-20.3) in the T-DXd 5.4 mg/kg and 6.4 mg/kg once every 3 weeks arms, respectively. Any-grade TEAEs were reported in all patients across treatment arms; the most common in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms were nausea (67.3% and 82.0%, respectively), neutropenia (42.6% and 56.0%), fatigue (44.6% and 50.0%), and decreased appetite (39.6% and 50.0%); the most common grade ≥3 TEAEs were neutropenia (18.8% and 36.0%) and anemia (10.9% and 16.0%; Table 3).

Drug-related any-grade TEAEs occurred in 97 patients (96.0%) and 50 patients (100%) in the 5.4 mg/kg and 6.4 mg/kg once every 3 weeks arms, respectively, with drug-related grade ≥3 TEAEs occurring in 38.6% (95% CI, 29.1 to 48.8) and 58.0% (95% CI, 43.2 to 71.8) of patients (Table 4). Among patients receiving T-DXd 5.4 mg/kg, drug-related TEAEs led to drug discontinuation in 13.9% of patients, dose reduction in 16.8% of patients, and drug interruption in 26.7% of patients. At the 6.4 mg/kg dose, drug-related TEAEs were associated with drug discontinuation in 20.0% of patients, dose reduction in 32.0% of patients, and drug interruption in 48.0% of patients. Drug-related TEAEs most commonly associated with drug discontinuation, as reported by the investigator, were ILD (5.9% and 8.0%) and pneumonitis (5.0% and 4.0%) in the 5.4 mg/kg and 6.4 mg/kg arms, respectively. Drug-related TEAEs were associated with death in one patient in each arm; the cause of both deaths was adjudicated drug-related ILD.

At DCO, all potential cases of ILD/pneumonitis were adjudicated by the adjudication committee, with no pending cases. Adjudicated drug-related ILD occurred in 13 patients (12.9% [95% CI, 7.0 to 21.0]; four grade 1, seven grade 2, one grade 3, and one grade 5) receiving T-DXd 5.4 mg/kg once every 3 weeks and 14 patients (28.0% [95% CI, 16.2 to 42.5]; four grade 1, nine grade 2, and one grade 5) receiving T-DXd 6.4 mg/kg once every 3 weeks (Table 4). In the T-DXd 5.4 and 6.4 mg/kg arms, 14.9% (11 of 74) and 28.2% (11 of 39) of patients who received prior anti–PD-(L)1 treatment had adjudicated drug-related ILD/pneumonitis, whereas in patients who did not receive prior anti–PD-(L)1 treatment, rates were 7.4% (2 of 27) and 27.3% (3 of 11), respectively. In the T-DXd 5.4 mg/kg arm, 7 of 13 patients with ILD had a history of smoking, 9 of 13 patients had prior radiotherapy (any location), and 2 of 13 patients had prior chest/lung radiotherapy. In the T-DXd 6.4 mg/kg arm, 7 of 14 patients with ILD had a history of smoking, 4 of 14 patients had prior radiotherapy (any location), and 2 of 14 patients had prior chest/lung radiotherapy. The median time to onset of adjudicated drug-related ILD in all patients was 88.0 days (range, 40-421) with T-DXd 5.4 mg/kg and 83.5 days (range, 36-386) with T-DXd 6.4 mg/kg. In the T-DXd 5.4 and 6.4 mg/kg arms, 84.6% (11 of 13) and 71.4% (10 of 14) of patients, respectively, received steroid treatment. In the T-DXd 5.4 mg/kg and 6.4 mg/kg arms, eight (61.5%; three grade 1, four grade 2, and one grade 3) and eight (57.1%; three grade 1 and five grade 2) patients had recovered and three (23.1%) and four (28.6%) patients had not recovered at the time of DCO. None of the patients with grade 1 ILD in the T-DXd 5.4 mg/kg arm were retreated with T-DXd. Two of the three patients with grade 1 ILD in the 6.4 mg/kg arm were retreated with T-DXd, both with negative rechallenge (no recurrence of ILD/pneumonitis after retreatment with T-DXd).

LV dysfunction was reported in one (1%) patient in the T-DXd 5.4 mg/kg once every 3 weeks arm (grade 1; ejection fraction decreased) and in no patients in the T-DXd 6.4 mg/kg once every 3 weeks arm. Other cardiovascular events reported included myocarditis (two patients [2.0%] and zero; not confirmed by endomyocardial biopsy) and

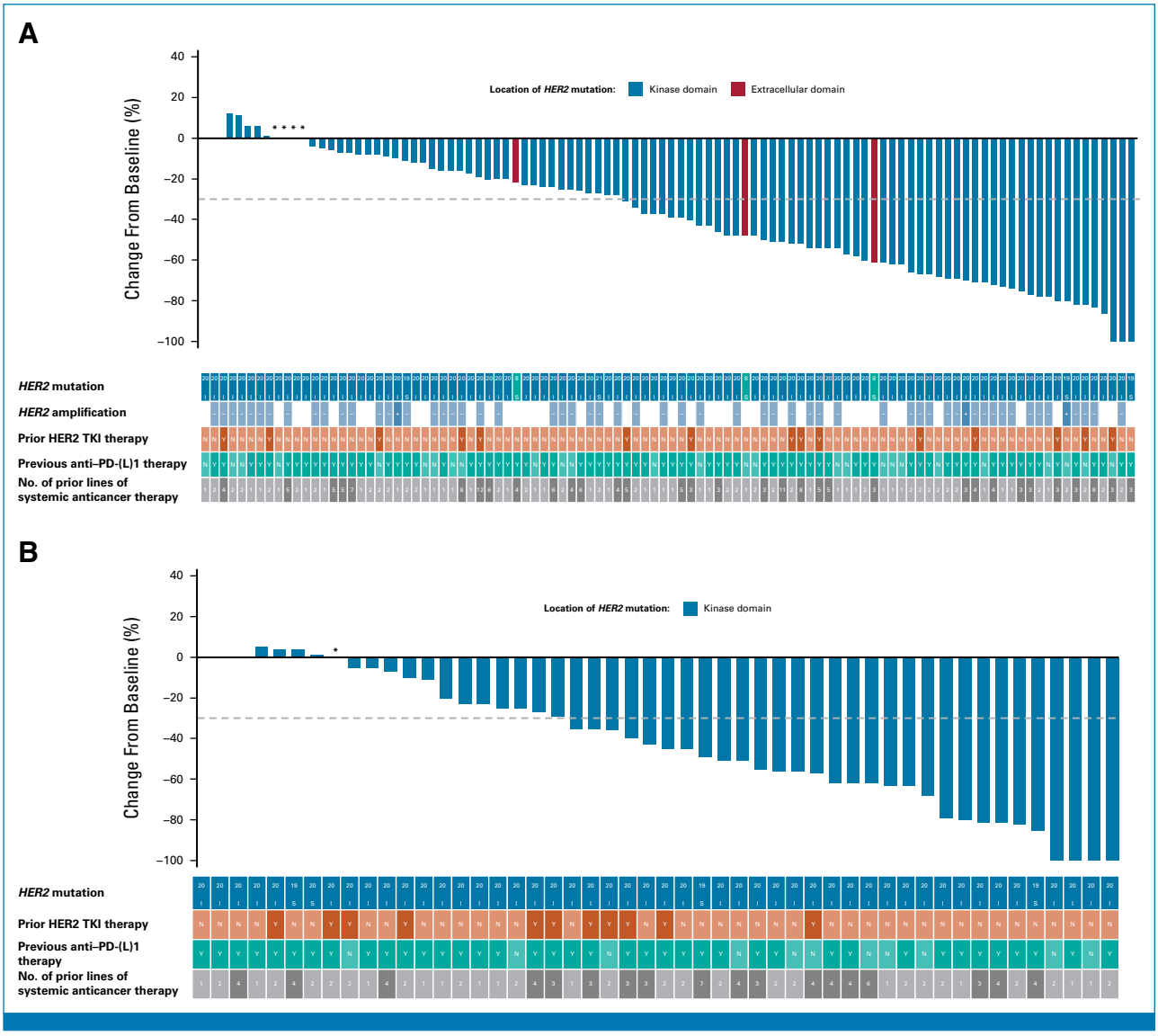

FIG 1. Antitumor activity of T-DXd in patients with *HER2*-mutant metastatic non–small-cell lung cancer by *HER2* mutation status and prior therapy. Best (minimum) percent change from baseline in the sum of diameters for all target lesions in (A) the T-DXd 5.4 mg/kg once every 3 weeks arm and (B) the T-DXd 6.4 mg/kg once every 3 weeks arm. The line at −30% indicates a partial response. Patients who had zero best percentage change from baseline in the sum of diameters for all target lesions are indicated with an asterisk (*). Numbers in the *HER2* mutation row indicate in which exon the mutation occurred (8, 19, or 20). *HER2* amplification was only assessed in patients who received T-DXd 5.4 mg/kg. HER2, human epidermal growth factor receptor 2; I, insertion; N, no; S, substitution; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; Y, yes.

hypertension (one patient [1.0%] and two patients [4.0%]) in the 5.4 and 6.4 mg/kg arms, respectively.

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 T-DXd doses, tumor reduction was observed regardless of *HER2* mutation type and *HER2* amplification status in the T-DXd 5.4 mg/kg once every 3 weeks arm (Data Supplement, Table A3).

DISCUSSION

DESTINY-Lung02 was the first and only randomized, blinded phase II trial assessing the efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg once every 3 weeks in patients with *HER2*m mNSCLC. T-DXd demonstrated deep and durable antitumor responses at both doses. The primary end point of confirmed ORR by BICR was met and exceeded the statistical hypothesis (49.0% [5.4 mg/kg] and 56.0% [6.4 mg/kg]). Responses were consistent regardless of *HER2* mutation type and amplification status and presence or absence of baseline CNS metastases and prior treatment.

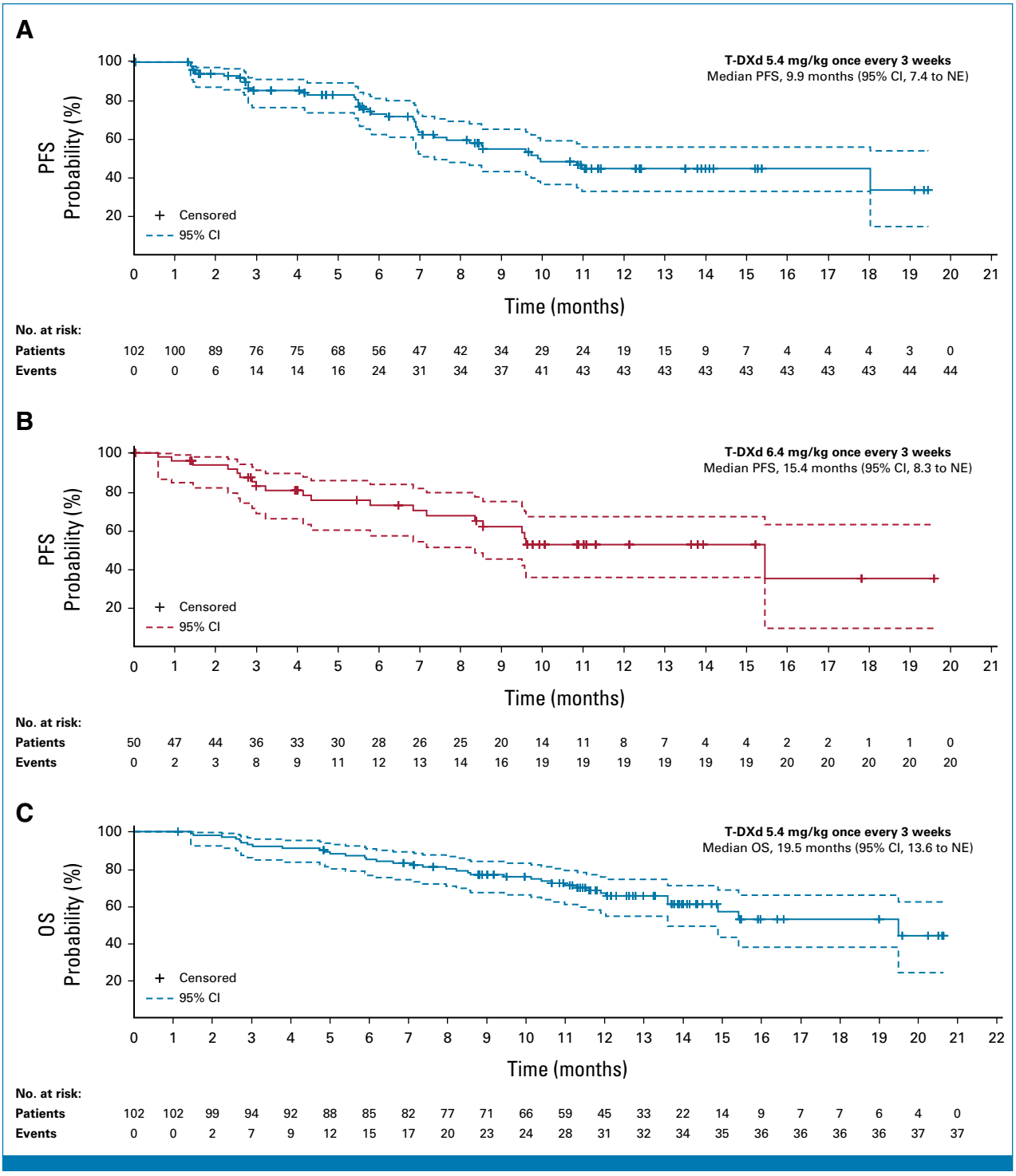

FIG 2. PFS and OS in patients with human epidermal growth factor receptor 2–mutant metastatic non–small cell lung cancer receiving T-DXd. Kaplan-Meier curve and estimated median PFS for patients receiving (A) T-DXd 5.4 mg/kg once every 3 weeks and (B) T-DXd 6.4 mg/kg once every 3 weeks and Kaplan-Meier curve and estimated median OS for patients receiving (C) T-DXd 5.4 mg/kg and (D) T-DXd 6.4 mg/kg. PFS was assessed by blinded independent central review per RECIST version 1.1. Patients who were alive without objective documentation of radiographic disease progression by the PFS DCO date were censored at their last evaluable tumor assessment. For OS, if there was no death reported for a patient before the DCO, OS was censored at the last contact date at which the patient was known to be alive. DCO, data cutoff; NE, not estimable; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan. (continued on following page)

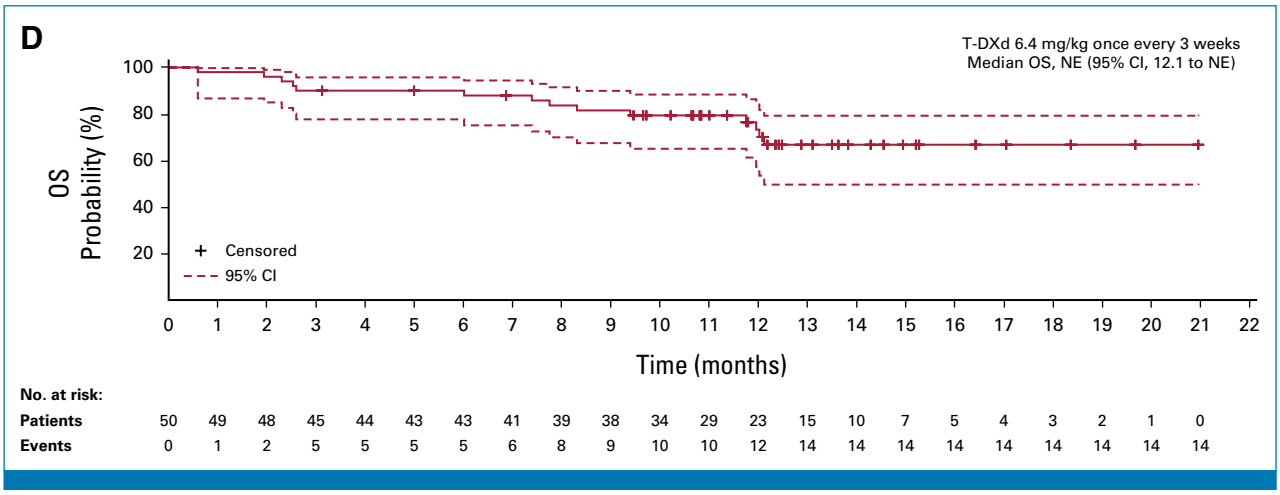

FIG 2. (Continued).

These primary results were generally consistent with the interim analysis of DESTINY-Lung02 (DCO, March 24, 2022) that led to the FDA approval of T-DXd 5.4 mg/kg for previously treated *HER2*m mNSCLC and support the therapeutic benefit of T-DXd in this patient population.[10]

T-DXd is the preferred recommended therapy for patients with previously treated *HER2*m mNSCLC.[15] In our study, the efficacy results were comparable with those reported for T-DXd 6.4 mg/kg in DESTINY-Lung01[8]; however, because of the large number of patients without events of disease progression or death by the primary analysis DCO, additional analyses with longer follow-up are needed to better establish estimates of median PFS and OS at the 5.4 mg/kg dose. Trastuzumab emtansine (T-DM1) is another recommended therapy for this patient population.[15] In a phase II basket trial, patients receiving T-DM1 showed promising treatment responses (ORR, 44%; 14 of 28); however, the response duration was limited to 4.4 months, and the median PFS was 5.0 months.[16] Other HER2-targeting agents, such as pyrotinib, poziotinib, and afatinib, have shown mixed results

TABLE 3. Most Common (≥20% of patients) Treatment-Emergent Adverse Events in Patients With Human Epidermal Growth Factor Receptor 2–Mutant Metastatic Non–Small-Cell Lung Cancer Treated With T-DXd

	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 101),[a] No. (%)		T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50),[a] No. (%)	
Preferred Term	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Nausea	68 (67.3)	4 (4.0)	41 (82.0)	3 (6.0)
Neutropenia[b]	43 (42.6)	19 (18.8)	28 (56.0)	18 (36.0)
Fatigue[b]	45 (44.6)	8 (7.9)	25 (50.0)	5 (10.0)
Decreased appetite	40 (39.6)	2 (2.0)	25 (50.0)	2 (4.0)
Anemia[b]	37 (36.6)	11 (10.9)	26 (52.0)	8 (16.0)
Vomiting	32 (31.7)	3 (3.0)	22 (44.0)	1 (2.0)
Constipation	37 (36.6)	1 (1.0)	16 (32.0)	0
Leukopenia[b]	29 (28.7)	5 (5.0)	17 (34.0)	8 (16.0)
Thrombocytopenia[b]	28 (27.7)	6 (5.9)	14 (28.0)	5 (10.0)
Diarrhea	23 (22.8)	1 (1.0)	18 (36.0)	2 (4.0)
Alopecia	22 (21.8)	0	17 (34.0)	0
Transaminases increased[b]	22 (21.8)	3 (3.0)	10 (20.0)	0

NOTE. Data for adjudicated drug-related interstitial lung disease are presented separately.
Abbreviation: T-DXd, trastuzumab deruxtecan.
[a]The safety analysis set includes all randomly assigned patients who received ≥1 dose of study drug.
[b]Grouped terms include neutropenia (neutrophil count decreased, neutropenia), fatigue (fatigue, asthenia, malaise, lethargy), anemia (hemoglobin decreased, RBC decreased, anemia, hematocrit decreased), leukopenia (WBC decreased, leukopenia), thrombocytopenia (platelet count decreased, thrombocytopenia), and transaminases increased (transaminases increased, AST increased, ALT increased, gamma-glutamyl transferase increased, liver function test abnormal, hepatic function test abnormal, liver function test increased, hypertransaminasemia).

TABLE 4. Overall Safety Summary and Adjudicated Drug-Related ILD

Type of AE	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 101),[a] No. (%)	T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50),[a] No. (%)
Any-grade TEAEs	101 (100.0)	50 (100.0)
Drug-related	97 (96.0)	50 (100.0)
Grade ≥ 3 TEAEs	53 (52.5)	33 (66.0)
Drug-related	39 (38.6)	29 (58.0)
Serious TEAEs	37 (36.6)	20 (40.0)
Drug-related	14 (13.9)	12 (24.0)
TEAEs associated with drug discontinuation	15 (14.9)	13 (26.0)
Drug-related	14 (13.9)	10 (20.0)
TEAEs associated with dose reduction	18 (17.8)	16 (32.0)
Drug-related	17 (16.8)	16 (32.0)
TEAEs associated with drug interruption	45 (44.6)	31 (62.0)
Drug-related	27 (26.7)	24 (48.0)
TEAEs associated with an outcome of death	6 (5.9)[b]	2 (4.0)[c]
Drug-related	1 (1.0)	1 (2.0)
Adjudicated drug-related ILD[d]		
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)
Total (95% CI)	13 (12.9) (7.0 to 21.0)	14 (28.0) (16.2 to 42.5)

Adjudicated Drug-Related ILD in Patients With Prior Anti–PD-(L)1 Therapy	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 74), No. (%)	T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 39), No. (%)
Grade 1	4 (5.4)	2 (5.1)
Grade 2	5 (6.8)	9 (23.1)
Grade 3	1 (1.4)	0
Grade 4	0	0
Grade 5	1 (1.4)	0
Total	11 (14.9)	11 (28.2)

Adjudicated Drug-Related ILD in Patients Without Prior Anti–PD-(L)1 Therapy	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 27), No. (%)	T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 11), No. (%)
Grade 1	0	2 (18.2)
Grade 2	2 (7.4)	0
Grade 3	0	0
Grade 4	0	0
Grade 5	0	1 (9.1)
Total	2 (7.4)	3 (27.3)

Abbreviations: AE, adverse event; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]The safety analysis set included all randomly assigned patients who received ≥1 dose of study drug.
[b]TEAEs associated with death were malignant lung neoplasm in two patients, malignant neoplasm progression in two patients, cerebrovascular incident in one patient, and pneumonitis in one patient.
[c]TEAEs associated with death were abnormal general physical condition in one patient and ILD in one patient.
[d]All cases of potential ILD/pneumonitis were adjudicated by the data cutoff.

(ORR, 19%-30%) and have not demonstrated the same antitumor efficacy observed with T-DXd in this study; however, cross-trial comparisons should be observed with caution.[4-6]

Responses were observed in patients with different *HER2* mutation types. HER2 receptor internalization and intracellular uptake of the HER2 antibody-drug conjugate complex has been shown to be enhanced in the presence of

activating *HER2* mutations,[3,17] which may have contributed to the efficacy benefit observed with T-DXd in the *HER2*m mNSCLC population of our study.

The safety profile of T-DXd was acceptable and generally manageable with both doses, and no new safety signals were observed. Although patients in the T-DXd 6.4 mg/kg once every 3 weeks arm were slightly older and had a higher percentage of CNS metastasis at baseline compared with those in the 5.4 mg/kg once every 3 weeks arm, trends appeared to favor the T-DXd 5.4 mg/kg dose across multiple safety end points. Patients receiving T-DXd 5.4 mg/kg had a lower incidence of drug-related grade ≥3 TEAEs (38.6%) than patients receiving 6.4 mg/kg (58.0%). Furthermore, the incidences of drug-related TEAEs associated with drug discontinuation, dose reduction, and drug interruption were lower with T-DXd 5.4 mg/kg than 6.4 mg/kg. Overall, the most common TEAEs occurring in ≥20% of patients were gastrointestinal and hematologic events and fatigue consistent with the results from DESTINY-Lung01.[8] Low rates of cardiovascular events, including LV dysfunction and suspected myocarditis, were reported; however, there was no supportive evidence to indicate a causal association of myocarditis with T-DXd treatment.

ILD/pneumonitis remains an important risk associated with T-DXd treatment. In the T-DXd 5.4 mg/kg once every 3 weeks arm, adjudicated drug-related ILD incidence was lower than the 6.4 mg/kg once every 3 weeks arm (12.9% and 28.0%, respectively), and most cases were low-grade, with one grade 5 event occurring in each arm. Adjudicated drug-related ILD rates in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms were comparable with those previously reported for T-DXd 5.4 mg/kg in breast cancer and for T-DXd 6.4 mg/kg in DESTINY-Lung01.[8,18,19] Notably, the incidence of grade ≥3 events in our study was lower than DESTINY-Lung01, which may be attributed to the implementation of ILD management guidelines that aid physician detection and treatment of ILD/pneumonitis symptoms, potentially reducing the severity of these events. Adjudicated drug-related ILD rates were similar between patients with and without prior anti–PD-(L)1 therapy in the T-DXd 6.4 mg/kg arm, whereas in the 5.4 mg/kg arm, patients with prior anti–PD-(L)1 therapy had higher ILD rates than those without. However, these numeric differences in adjudicated drug-related ILD rates were not controlled for by potential confounding factors, and the number of patients who did not receive prior anti–PD-(L)1 therapy was small.

The incidence of adjudicated drug-related ILD/pneumonitis in the T-DXd 6.4 mg/kg once every 3 weeks arm was higher than incidences in gastric and colorectal cancers at the same dose.[20-22] The higher incidence in lung cancers may be attributable to existing lung damage in patients with NSCLC, such as those caused by smoking, prior lung surgery, and prior radiation therapy, which may predispose patients to T-DXd–related pulmonary toxicity and hinder the resolution of ILD/pneumonitis[23]; however, prior chest/lung radiotherapy was not identified as a potential risk factor for T-DXd–related ILD/pneumonitis, and smoking history was not examined in a previous pooled analyses. Besides lung comorbidities, other potential risk factors for T-DXd–related ILD/pneumonitis may include low oxygen saturation, moderate or severe renal impairment, younger than 65 years, receiving treatment in Japan (*v* other regions), and time since disease diagnosis.[24] In addition, distinguishing between cancer-related respiratory symptoms and computed tomography scan lung abnormalities and those associated with ILD is a challenge unique to patients with lung cancer and could potentially contribute to the higher ILD/pneumonitis diagnostic rates observed in patients with NSCLC.

An inherent limitation of our study was the absence of a non–T-DXd comparator arm. Current second-line treatments in this patient population have very limited therapeutic benefit compared with T-DXd; therefore, a comparator arm was not used.[3-6,8] However, the efficacy of T-DXd 5.4 mg/kg monotherapy versus chemotherapy plus pembrolizumab is currently being investigated in the first-line setting in the phase III DESTINY-Lung04 trial in patients with *HER2*m mNSCLC.

T-DXd 5.4 mg/kg and 6.4 mg/kg once every 3 weeks demonstrated strong and durable responses in patients with previously treated *HER2*m mNSCLC in DESTINY-Lung02. The safety profile was acceptable and generally manageable with both doses; however, a lower incidence of drug-related TEAEs and ILD/pneumonitis was observed with the lower dose. In conclusion, the more favorable benefit/risk profile observed with T-DXd 5.4 mg/kg supports the use of this dose for patients with previously treated *HER2*m mNSCLC and reinforces T-DXd as the standard of care in this population.

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DATA SHARING STATEMENT

Anonymized individual participant data on completed studies and applicable supporting clinical study documents may be available on request at https://vivli.org/. In cases where clinical study data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo Companies will continue to protect the privacy of company and our clinical study participants. The details on data sharing criteria and the procedure for requesting access can be found at this web address: https://vivli.org/ourmember/daiichi-sankyo/.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Trastuzumab Deruxtecan in Patients With *HER2*-Mutant Metastatic Non–Small-Cell Lung Cancer: Primary Results From the Randomized, Phase II DESTINY-Lung02 Trial

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Consulting or Advisory Role: Pfizer, Boehringer Ingelheim, AstraZeneca, Merrimack, Chugai Pharma, Roche/Genentech, Loxo, Mirati Therapeutics, Araxes Pharma, Ignyta, Lilly, Takeda, Novartis, Biocartis, Voronoi Health Analytics, SFJ Pharmaceuticals Group, Sanofi, Daiichi Sankyo, Silicon Therapeutics, Nuvalent Inc, Eisai, Bayer, Syndax, AbbVie, Allorion Therapeutics, Accutar Biotech, Transcenta, Monte Rosa Therapeutics, Scorpion Therapeutics, Merus, Frontier Medicines, Hongyun Biotech, Duality Biologics
Research Funding: AstraZeneca (Inst), Astellas Pharma (Inst), Daiichi Sankyo (Inst), Lilly (Inst), Boehringer Ingelheim (Inst), Puma Biotechnology (Inst), Takeda (Inst), Revolution Medicines (Inst)
Patents, Royalties, Other Intellectual Property: I am a co-inventor on a DFCI owned patent on EGFR mutations licensed to Lab Corp. I receive post-marketing royalties from this invention

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