ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Patients With HER2-Overexpressing NSCLC: Results From Part 1 of the Open-Label, Multicenter, Phase 1b DESTINY-Lung03 Trial

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ABSTRACT

Introduction: HER2-directed treatments for HER2-overexpressing (HER2-OE; immunohistochemistry [IHC] 3+/2+) NSCLC are needed.

Methods: DESTINY-Lung03 is an open-label, multi-arm, phase 1b study. Part 1 evaluated trastuzumab deruxtecan (T-DXd, 4.4 or 5.4 mg/kg) plus durvalumab (1120 mg) and cisplatin (60 or 75 mg/m^2; Arm 1A)/carboplatin (area under the plasma concentration–time curve [AUC] 4 or 5; Arm 1B) or T-DXd 5.4 mg/kg monotherapy (Arm 1D) in pretreated metastatic HER2-OE NSCLC. Primary end points: dose-limiting toxicities (DLTs) and adverse events (AEs: Arms 1A and 1B). Secondary end points: safety (Arm 1D) and efficacy (all arms).

Results: At data cutoff (April 1, 2024), 11, 24, and 36 patients received treatment in Arms 1A, 1B, and 1D, respectively. DLTs reported in Arm 1A: febrile neutropenia (n = 1; grade [G] 5; 4.4 mg/kg/1120 mg/60 mg/m^2 doses); decreased platelet count (n = 2; G4 and G5; 5.4 mg/kg/1120 mg/75 mg/m^2 doses). DLTs reported in Arm 1B: febrile neutropenia (n = 1; G3; 4.4 mg/kg/1120 mg/AUC 5 doses; n = 1; G4; 4.4 mg/kg/1120 mg/AUC 4 doses); decreased platelet count (n = 1; G4; 5.4 mg/kg/1120 mg/AUC 5 doses). Drug-related serious AEs occurred in 63.6%, 37.5%, and 16.7% of Arms 1A, 1B, and 1D, respectively. Confirmed objective response rate (95% confidence interval) per investigator: 37.5% (18.8–59.4; Arm 1B) and 44.4% (27.9–61.9; Arm 1D).

Conclusions: Data confirm the activity of T-DXd monotherapy in pretreated HER2-OE NSCLC but do not support T-DXd plus durvalumab and platinum chemotherapy use in this population.

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Keywords: HER2-directed therapy; HER2-overexpressing; Non–small cell lung cancer; Trastuzumab deruxtecan

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide; approximately 85% of lung malignancies are NSCLC.[1,2] Assessing clinically relevant biomarkers and use of targeted therapy have revolutionized the NSCLC treatment landscape.[3–5] However, there remains a need for HER2-directed therapies in patients with HER2 overexpression (immunohistochemistry [IHC] 3+/IHC 2+), reported in 3% to 20% of NSCLC cases.[6–9] Current second-line treatment options for HER2-overexpressing (HER2-OE) NSCLC are generally the same as those recommended for an all-comer NSCLC population and include docetaxel or docetaxel with ramucirumab[10]; patients with NSCLC have poor prognosis (median overall survival [OS] of ≤1 y), despite treatment with these regimens.[11–15]

Trastuzumab deruxtecan (T-DXd; 5.4 mg/kg), a HER2-directed antibody–drug conjugate, is approved in multiple countries, including the United States, for unresectable or metastatic HER2-positive (IHC 3+) solid tumors after prior treatment and/or without alternative treatment options.[16–18] This approval was partly supported by results from DESTINY-Lung01 cohort 1a; confirmed objective response rates (ORRs) of 34.1% (HER2 IHC 3+/2+ overall cohort) and 52.9% (HER2 IHC 3+ subgroup) were reported in patients with advanced HER2-OE NSCLC treated with T-DXd.[16,19] Although notable antitumor activity has been observed with T-DXd monotherapy,[19] data from preclinical and phase 1b/2 clinical trials suggest that combining T-DXd with other agents could further improve clinical outcomes in HER2-OE NSCLC.[20–23] Of note, in an interim analysis of the U106 study, T-DXd plus pembrolizumab demonstrated an ORR of 54.5% and median progression-free survival (PFS) of 15.1 months in immunotherapy-naive HER2-expressing (IHC 1+/2+/3+) NSCLC.[23]

DESTINY-Lung03 (NCT04686305) is an independent multi-arm, phase 1b study that aims to evaluate T-DXd–based regimens in patients with HER2-OE (IHC 3+/2+) NSCLC; such studies are important to inform future clinical studies and treatment decisions in clinical practice. Here, we report results from Part 1 of the study, which assessed the safety and efficacy of T-DXd combined with durvalumab plus platinum chemotherapy, and T-DXd monotherapy in previously treated patients with HER2-OE NSCLC.

Materials and Methods

Study Design

DESTINY-Lung03 is an open-label, multicenter, independent multi-arm, phase 1b study evaluating T-DXd–based regimens in patients with HER2-OE (IHC 3+/2+) NSCLC. Part 1 assessed T-DXd plus durvalumab in combination

with cisplatin or carboplatin (dose-escalation combination therapy Arms 1A and 1B, respectively) and T-DXd monotherapy (fixed-dose Arm 1D) in patients with pretreated HER2-OE NSCLC. Part 1 Arm 1C assessing T-DXd plus durvalumab and pemetrexed was planned but not initiated.

Patients

In Part 1, adult patients had histologically documented HER2-OE locally advanced and unresectable or metastatic nonsquamous NSCLC; disease progression on or after one or two lines of therapy; at least one measurable lesion by Response Evaluation Criteria in Solid Tumours (RECIST) 1.1; and WHO/Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. HER2 overexpression was centrally assessed using the DAKO HER2Low assay (investigational use only) before enrollment using a formalin-fixed, paraffin-embedded tumor sample obtained when locally advanced or metastatic disease was diagnosed, or using a newly acquired biopsy if an existing sample was unavailable. During the study period, a repeat biopsy at disease progression was encouraged but not required. HER2 overexpression was defined as at least 25% tumor cells exhibiting acceptable partial or complete membrane staining patterns with a 2+ stain intensity or greater; any partial membrane staining pattern except luminal- or basal-only staining was accepted. Patients with therapy-targetable alterations who had received prior appropriate targeted therapy and those with stable baseline brain metastases (asymptomatic, not requiring treatment with corticosteroids [for $\geq$4 wk before receiving study treatment] or anticonvulsants) were also eligible for inclusion in Part 1. Key exclusion criteria included known *HER2* activating mutations, a history of non-infectious interstitial lung disease (ILD)/pneumonitis requiring steroids, and current ILD/pneumonitis (or if ILD/pneumonitis could not be ruled out by imaging at screening). Additional eligibility criteria are available in the Supplementary Methods.

Study Oversight

The study protocol was approved by the institutional review board and/or independent ethics committee at each site and conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and local regulations relating to the conduct of clinical research. All patients provided written, informed consent before participation in the study.

Procedures

In Part 1 Arm 1A, patients could receive one of three doses of T-DXd (3.2 mg/kg, 4.4 mg/kg [starting dose], and 5.4 mg/kg intravenously [IV] every 3 wk), durvalumab (1120 mg IV every 3 wk), and one of two doses of cisplatin (60 mg/m^2 [starting dose] and 75 mg/m^2 IV every 3 wk). In Part 1 Arm 1B, patients could receive one of three doses of T-DXd (3.2 mg/kg, 4.4 mg/kg [starting dose], and 5.4 mg/kg IV every 3 wk), durvalumab (1120 mg IV every 3 wk), and one of two doses of carboplatin (area under the plasma concentration–time curve [AUC] 4 [starting dose] and AUC 5 IV every 3 wk). A minimum of three dose-limiting toxicity (DLT)-assessable patients were assessed at each dose unless unacceptable toxicity was observed in the first two patients before a third was treated. Patients were considered DLT assessable if they had received one full prescribed dose of T-DXd, at least 75% of the prescribed dose of other study interventions, and either had completed the first 21-day cycle or had a DLT during the first 21-day cycle. DLTs were defined as any prespecified treatment-emergent adverse event (AE) not attributable to disease or disease-related processes that occurred during the DLT evaluation period (days 1–21 of cycle 1) that were grade 3 or higher (unless otherwise specified) according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. The decision to escalate or de-escalate doses of T-DXd or chemotherapy followed the modified Toxicity Probability Interval 2 (mTPI-2) algorithm, as assessed by the safety review committee; a dose level was considered unsafe if it had an estimated 95% or more probability of exceeding the maximum acceptable DLT rate of 30% (Supplementary Methods and Supplementary Fig. 1). Enrollment to Arms 1A and 1B occurred concurrently; participants were assigned to each treatment based on their suitability for cisplatin therapy as assessed by the investigator and the number of open slots available. In Part 1 Arm 1D, patients were enrolled if no open slots were available in Arms 1A and B and received T-DXd monotherapy (5.4 mg/kg IV every 3 wk).

T-DXd and durvalumab treatment were continued until documented disease progression per RECIST 1.1, unacceptable toxicity, withdrawal of consent, or investigator decision, whichever came first. Image-based tumor assessments were performed by computed tomography or magnetic resonance imaging at screening and every 6 weeks (±1 wk) until RECIST 1.1–defined objective disease progression or withdrawal of consent.

End Points

Safety. Primary end points included DLTs, AEs, serious AEs (SAEs), and AEs of special interest (AESIs; including ILD/pneumonitis and left ventricular ejection fraction [LVEF] decrease) in the T-DXd plus durvalumab and platinum chemotherapy treatment arms. AEs were coded using the Medical Dictionary for Regulatory Activities version 26.1 and graded according to the National Cancer Institute Common Terminology Criteria

for Adverse Events version 5.0. Potential ILD/pneumonitis events were evaluated by an independent ILD adjudication committee; for suspected ILD/pneumonitis events, treatment was interrupted pending further evaluation, and all events regardless of severity were followed until resolution. AEs, SAEs, and AESIs were secondary end points for the T-DXd monotherapy arm.

Efficacy. Confirmed ORR, duration of response (DOR), disease control rate (DCR), PFS, all by investigator assessment per RECIST 1.1, and OS were secondary end points in Part 1 treatment arms. Exploratory end points included subgroup analyses by HER2 status (IHC 3+ and 2+), prior EGFR tyrosine kinase inhibitor (TKI) exposure, and *EGFR* mutation status (retrospectively assessed using the GuardantOMNI assay [Guardant Health] in plasma circulating tumor DNA [ctDNA] obtained during screening or at cycle 1 day 1).

Statistical Methods

Sample size calculations are described in the Supplementary Methods. Safety was assessed in all patients who received at least one dose of T-DXd. Efficacy end points were assessed in all patients who were assigned to treatment and received at least one dose of any study treatment. ORR and DCR and their exact 95% confidence intervals (CIs) were calculated using the Clopper-Pearson method. Median DOR, PFS, and OS were estimated using the Kaplan-Meier method, and corresponding 95% CIs were calculated using the Brookmeyer-Crowley method. SAS version 9.4 or higher was used for all analyses; no formal statistical assessments were conducted.

Results

Patient Disposition

Of 72 patients assigned to treatment in Part 1 between March, 2021, and April, 2024, 71 received at least one dose of study treatment; 11 patients received T-DXd plus durvalumab and cisplatin, 24 received T-DXd plus durvalumab and carboplatin, and 36 received T-DXd monotherapy (5.4 mg/kg; Supplementary Fig. 2). At data cutoff (DCO; April 1, 2024), ten (90.9%), 20 (83.3%), and 33 (91.7%) patients had discontinued T-DXd plus durvalumab and cisplatin, T-DXd plus durvalumab and carboplatin, and T-DXd monotherapy, respectively. Reasons for treatment discontinuation are in Supplementary Figure 2.

Patient Demographics and Baseline Disease Characteristics

Overall median age was 63.0 (range, 31–80) years; 88.7% of patients were from Asia, 62.0% had an ECOG performance status of 1, 36.6% had brain/central nervous system (CNS) metastases at baseline, 49.3% received one prior line of therapy, and 46.5% received two prior lines of therapy (additional data by treatment arm are found in Table 1). The most common prior treatment received was targeted therapy (which included EGFR TKIs) across all treatment arms.

Safety

T-DXd Plus Durvalumab and Cisplatin (Arm 1A). The median total duration of treatment for both T-DXd and durvalumab was 3.5 (range, 0.3–24.8) months; a median of four (range, 1–4) cycles of cisplatin were received. A total of three DLTs occurred: grade 5 febrile neutropenia in one patient (T-DXd 4.4 mg/kg plus durvalumab 1120 mg and cisplatin 60 mg/m^2) and decreased platelet count in two patients (one grade 4 and one grade 5; T-DXd 5.4 mg/kg plus durvalumab 1120 mg and cisplatin 75 mg/m^2). Across the overall treatment arm, drug-related AEs, drug-related AEs of grade 3 or higher, and drug-related SAEs were reported in 11 (100%), 11 (100%), and seven (63.6%) patients, respectively (Table 2). Drug-related AEs led to discontinuation in one patient (9.1%), and two patients (18.2%) died due to drug-related AEs (febrile neutropenia [n = 1] and platelet count decreased [n = 1]). There were no reports of adjudicated drug-related ILD/pneumonitis or LVEF decrease. Given the toxicity observed with T-DXd plus durvalumab and cisplatin, treatment was discontinued and enrollment to this arm was closed.

T-DXd Plus Durvalumab and Carboplatin (Arm 1B). The median total duration of treatment for both T-DXd and durvalumab was 7.2 (range, 0.1–28.0) months; a median of four (range, 1–4) cycles of carboplatin were received. Three DLTs occurred: febrile neutropenia in two patients (one grade 3 and one grade 4; T-DXd 4.4 mg/kg plus durvalumab 1120 mg and carboplatin AUC 5, and T-DXd 4.4 mg/kg plus durvalumab 1120 mg and carboplatin AUC 4, respectively) and grade 4 decreased platelet count in one patient (T-DXd 5.4 mg/kg plus durvalumab 1120 mg and carboplatin AUC 5). In the overall treatment arm, drug-related AEs, drug-related AEs of grade 3 or higher, and drug-related SAEs were observed in 23 (95.8%), 20 (83.3%), and nine (37.5%) patients, respectively (Table 2). Drug-related AEs led to discontinuation in four patients (16.7%), and two patients (8.3%) died due to drug-related AEs (febrile neutropenia [n = 1] and ILD/pneumonitis [n = 1]). Adjudicated drug-related ILD/pneumonitis was reported in three patients (12.5%; one grade 2 and two grade 5) and LVEF decrease occurred in one patient (4.2%; grade 2). T-DXd 5.4 mg/kg plus durvalumab 1120 mg and

Table 1. Patient Demographics and Baseline Characteristics

Patient Characteristic	Part 1 Arm 1A				Part 1 Arm 1B				Part 1 Arm 1D
	T-DXd 4.4 mg/kg + Durvalumab[a] + Cisplatin 60 mg/m^2 (n = 5)	T-DXd 4.4 mg/kg + Durvalumab[a] + Cisplatin 75 mg/m^2 (n = 3)	T-DXd 5.4 mg/kg + Durvalumab[a] + Cisplatin 75 mg/m^2 (n = 3)	Overall (n = 11)	T-DXd 4.4 mg/kg + Durvalumab[a] + Carboplatin AUC 4 (n = 9)	T-DXd 4.4 mg/kg + Durvalumab[a] + Carboplatin AUC 5 (n = 7)	T-DXd 5.4 mg/kg + Durvalumab[a] + Carboplatin AUC 5 (n = 8)	Overall (n = 24)	T-DXd 5.4 mg/kg (n = 36)
Median age, y (range)	64.0 (52-68)	54.0 (54-72)	52.0 (31-54)	54.0 (31-72)	59.0 (52-79)	65.0 (44-70)	60.0 (47-75)	61.5 (44-79)	66.5 (47-80)
Sex, n (%)									
Male	3 (60.0)	1 (33.3)	1 (33.3)	5 (45.5)	5 (55.6)	4 (57.1)	4 (50.0)	13 (54.2)	14 (38.9)
Female	2 (40.0)	2 (66.7)	2 (66.7)	6 (54.5)	4 (44.4)	3 (42.9)	4 (50.0)	11 (45.8)	22 (61.1)
Region, n (%)									
Europe	1 (20.0)	2 (66.7)	0	3 (27.3)	1 (11.1)	0	0	1 (4.2)	3 (8.3)
Asia	4 (80.0)	1 (33.3)	3 (100)	8 (72.7)	8 (88.9)	7 (100)	8 (100)	23 (95.8)	32 (88.9)
US/South America	0	0	0	0	0	0	0	0	1 (2.8)
Smoking history, n (%)									
Current	0	0	0	0	0	0	0	0	3 (8.3)
Former	3 (60.0)	2 (66.7)	1 (33.3)	6 (54.5)	5 (55.6)	3 (42.9)	1 (12.5)	9 (37.5)	10 (27.8)
Never	2 (40.0)	1 (33.3)	2 (66.7)	5 (45.5)	4 (44.4)	4 (57.1)	7 (87.5)	15 (62.5)	23 (63.9)
Stage of disease, n (%)[b]									
III	2 (40.0)	0	0	2 (18.2)	0	0	1 (12.5)	1 (4.2)	3 (8.3)
IV	3 (60.0)	3 (100)	3 (100)	9 (81.8)	8 (88.9)	7 (100)	7 (87.5)	22 (91.7)	31 (86.1)
ECOG performance status, n (%)									
0	3 (60.0)	1 (33.3)	2 (66.7)	6 (54.5)	3 (33.3)	1 (14.3)	5 (62.5)	9 (37.5)	12 (33.3)
1	2 (40.0)	2 (66.7)	1 (33.3)	5 (45.5)	6 (66.7)	6 (85.7)	3 (37.5)	15 (62.5)	24 (66.7)
CNS metastases present at baseline, n (%)	0	1 (33.3)	2 (66.7)	3 (27.3)	6 (66.7)	4 (57.1)	2 (25.0)	12 (50.0)	11 (30.6)
Centrally confirmed HER2 IHC status, n (%)									
IHC 3+	3 (60.0)	0	1 (33.3)	4 (36.4)	5 (55.6)	3 (42.9)	5 (62.5)	13 (54.2)	16 (44.4)
IHC 2+	2 (40.0)	3 (100)	2 (66.7)	7 (63.6)	4 (44.4)	4 (57.1)	3 (37.5)	11 (45.8)	20 (55.6)
EGFR mutation status, n (%)[c]									
EGFRm	2 (40.0)	2 (66.7)	0	4 (36.4)	3 (33.3)	2 (28.6)	4 (50.0)	9 (37.5)	17 (47.2)
EGFRwt	2 (40.0)	1 (33.3)	2 (66.7)	5 (45.5)	4 (44.4)	0	3 (37.5)	7 (29.2)	14 (38.9)
EGFR low shedder[d]	1 (20.0)	0	1 (33.3)	2 (18.2)	1 (11.1)	3 (42.9)	1 (12.5)	5 (20.8)	4 (11.1)
PD-L1 status, n (%)									
<1%	3 (60.0)	0	1 (33.3)	4 (36.4)	6 (66.7)	4 (57.1)	2 (25.0)	12 (50.0)	12 (33.3)
1%-49%	1 (20.0)	2 (66.7)	1 (33.3)	4 (36.4)	1 (11.1)	1 (14.3)	2 (25.0)	4 (16.7)	9 (25.0)
≥50%	0	1 (33.3)	0	1 (9.1)	0	0	0	0	3 (8.3)
Unknown/not tested	1 (20.0)	0	1 (33.3)	2 (18.2)	2 (22.2)	2 (28.6)	4 (50.0)	8 (33.3)	12 (33.3)

(continued)

Table 1. Continued

Patient Characteristic	Part 1 Arm 1A				Part 1 Arm 1B				Part 1 Arm 1D
	T-DXd 4.4 mg/kg + Durvalumab[a] + Cisplatin 60 mg/m^2 (n = 5)	T-DXd 4.4 mg/kg + Durvalumab[a] + Cisplatin 75 mg/m^2 (n = 3)	T-DXd 5.4 mg/kg + Durvalumab[a] + Cisplatin 75 mg/m^2 (n = 3)	Overall (n = 11)	T-DXd 4.4 mg/kg + Durvalumab[a] + Carboplatin AUC 4 (n = 9)	T-DXd 4.4 mg/kg + Durvalumab[a] + Carboplatin AUC 5 (n = 7)	T-DXd 5.4 mg/kg + Durvalumab[a] + Carboplatin AUC 5 (n = 8)	Overall (n = 24)	T-DXd 5.4 mg/kg (n = 36)
Prior lines of therapy, n (%)[e]									
1	-	-	-	5 (45.5)	-	-	-	11 (45.8)	19 (52.8)
2	-	-	-	5 (45.5)	-	-	-	13 (54.2)	15 (41.7)
3	-	-	-	1 (9.1)	-	-	-	0	2 (5.6)
Prior therapies, n (%)[f]									
Targeted therapy	2 (40.0)	2 (66.7)	2 (66.7)	6 (54.5)	5 (55.6)	6 (85.7)	3 (37.5)	14 (58.3)	21 (58.3)
EGFR TKI[g]	2 (40.0)	2 (66.7)	0	4 (36.4)	4 (44.4)	5 (71.4)	4 (50.0)	13 (54.2)	19 (52.8)
Immunotherapy	0	1 (33.3)	1 (33.3)	2 (18.2)	1 (11.1)	3 (42.9)	4 (50.0)	8 (33.3)	8 (22.2)
Platinum chemotherapy	2 (40.0)	0	1 (33.3)	3 (27.3)	2 (22.2)	3 (42.9)	1 (12.5)	6 (25.0)	14 (38.9)
Taxane chemotherapy	0	0	0	0	0	0	1 (12.5)	1 (4.2)	3 (8.3)

AUC, area under the plasma concentration−time curve; CNS, central nervous system; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; EGFRm, *EGFR* mutant; EGFRwt, *EGFR* wild type; IHC, immunohistochemistry; PD-L1, programmed cell death ligand 1; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor.

[a]1120 mg.

[b]Stage of disease was unknown in one patient (11.1%) in the T-DXd 4.4 mg/kg + durvalumab + carboplatin AUC 4 arm and two patients (5.6%) in the T-DXd 5.4 mg/kg arm.

[c]*EGFR* mutation status was unknown/not tested in one patient (11.1%) in the T-DXd 4.4 mg/kg + durvalumab + carboplatin AUC 4 arm, two patients (28.6%) in the T-DXd 4.4 mg/kg + durvalumab + carboplatin AUC 5 arm, and one patient (2.8%) in the T-DXd 5.4 mg/kg arm.

[d]Tumor samples were considered to be shedders of ctDNA if ≥1 somatic alteration (single nucleotide variation or an oncogene amplification) was detected; where this criterion was not met, tumors were considered to be "low shedders". False-negative results may have occurred owing to low ctDNA shedding by the tumor.

[e]Number of prior lines of therapy was not provided directly by the investigator; results were manually derived by clinical review of the individual prior treatments reported.

[f]Treatment categories listed are not exhaustive or mutually exclusive.

[g]Included afatinib, alectinib, erlotinib, gefitinib, lazertinib, and osimertinib.

Table 2. Summary of Drug-Related Adverse Events[a]

Event, n (%)	Part 1 Arm 1A				Part 1 Arm 1B				Part 1 Arm 1D
	T-DXd 4.4 mg/kg + Durvalumab[b] + Cisplatin 60 mg/m^2 (n = 5)	T-DXd 4.4 mg/kg + Durvalumab[b] + Cisplatin 75 mg/m^2 (n = 3)	T-DXd 5.4 mg/kg + Durvalumab[b] + Cisplatin 75 mg/m^2 (n = 3)	Overall (n = 11)	T-DXd 4.4 mg/kg + Durvalumab[b] + Carboplatin AUC 4 (n = 9)	T-DXd 4.4 mg/kg + Durvalumab[b] + Carboplatin AUC 5 (n = 7)	T-DXd 5.4 mg/kg + Durvalumab[b] + Carboplatin AUC 5 (n = 8)	Overall (n = 24)	T-DXd 5.4 mg/kg (n = 36)
Drug-related AEs[c]	5 (100)	3 (100)	3 (100)	11 (100)	9 (100)	7 (100)	7 (87.5)	23 (95.8)	34 (94.4)
Grade ≥3	5 (100)	3 (100)	3 (100)	11 (100)	8 (88.9)	6 (85.7)	6 (75.0)	20 (83.3)	15 (41.7)
SAEs	3 (60.0)	1 (33.3)	3 (100)	7 (63.6)	2 (22.2)	3 (42.9)	4 (50.0)	9 (37.5)	6 (16.7)
Leading to dose interruption	3 (60.0)	0	2 (66.7)	5 (45.5)	6 (66.7)	2 (28.6)	4 (50.0)	12 (50.0)	5 (13.9)
Leading to dose reduction[d]	2 (40.0)	2 (66.7)	2 (66.7)	6 (54.5)	3 (33.3)	6 (85.7)	4 (50.0)	13 (54.2)	7 (19.4)
Leading to discontinuation	0	0	1 (33.3)	1 (9.1)	0	1 (14.3)	3 (37.5)	4 (16.7)	3 (8.3)
Associated with death[e]	1 (20.0)	0	1 (33.3)	2 (18.2)	1 (11.1)	0	1 (12.5)	2 (8.3)	1 (2.8)
Adjudicated drug-related ILD/ pneumonitis[f]									
Any grade	0	0	0	0	0	1 (14.3)	2 (25.0)	3 (12.5)	2 (5.6)
Grade 2	0	0	0	0	0	0	1 (12.5)	1 (4.2)	2 (5.6)
Grade 5	0	0	0	0	0	1 (14.3)	1 (12.5)	2 (8.3)	0
Drug-related LVEF decrease									
Any grade	0	0	0	0	1 (11.1)	0	0	1 (4.2)	1 (2.8)
Grade 2	0	0	0	0	1 (11.1)	0	0	1 (4.2)	1 (2.8)

AE, adverse event; AUC, area under the plasma concentration−time curve; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; SAE, serious adverse event; T-DXd, trastuzumab deruxtecan.

[a]Safety analysis set includes all patients who received ≥1 dose of T-DXd.

[b]1120 mg.

[c]Includes any AE related to any investigational product in the study.

[d]No patients had a protocol-defined dose de-escalation.

[e]Adverse events associated with death included: febrile neutropenia (n = 1) and platelet count decreased (n = 1) in the T-DXd plus durvalumab and cisplatin arm; febrile neutropenia (n = 1) and ILD/pneumonitis (n = 1) in the T-DXd plus durvalumab and carboplatin arm; and neutropenic colitis (n = 1) in the T-DXd monotherapy (5.4 mg/kg) arm.

[f]Assessed by the ILD adjudication committee.

Table 3. Response Outcomes: ORR, BOR, Median DOR, and DCR[a]

	Part 1 Arm 1B				Part 1 Arm 1D
Response Outcome	T-DXd 4.4 mg/kg + Durvalumab[b] + Carboplatin AUC 4 (n = 9)	T-DXd 4.4 mg/kg + Durvalumab[b] + Carboplatin AUC 5 (n = 7)	T-DXd 5.4 mg/kg + Durvalumab[b] + Carboplatin AUC 5 (n = 8)	Overall (n = 24)	T-DXd 5.4 mg/kg (n = 36)
Confirmed ORR, % (n)[c]	44.4 (4)	28.6 (2)	37.5 (3)	37.5 (9)	44.4 (16)
95% CI	13.7-78.8	3.7-71.0	8.5-75.5	18.8-59.4	27.9-61.9
BOR, n (%)					
Complete response	0	0	0	0	0
Partial response	4 (44.4)	2 (28.6)	3 (37.5)	9 (37.5)	16 (44.4)
Stable disease	5 (55.6)	5 (71.4)	3 (37.5)	13 (54.2)	15 (41.7)
Disease progression[d]	0	0	2 (25.0)	2 (8.3)	4 (11.1)
Not evaluable	0	0	0	0	1 (2.8)
DCR at 12 wk, %[e]	66.7	71.4	62.5	66.7	77.8
95% CI	29.9-92.5	29.0-96.3	24.5-91.5	44.7-84.4	60.9-89.9
Median DOR, mo[f]	22.0	7.7	7.2	7.7	11.0
95% CI	4.3-NE	7.0-NE	7.2-NE	4.3-22.0	5.5-16.7

AUC, area under the plasma concentration–time curve; BOR, best overall response; CI, confidence interval; DCR, disease control rate; DOR, duration of response; NE, not estimable; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan.
[a]Investigator-assessed by RECIST 1.1 in all patients who were assigned to and received ≥1 dose of study treatment (T-DXd, durvalumab, or carboplatin).
[b]1120 mg.
[c]Confirmed ORR, defined as the best objective response of complete or partial responses, required confirmation after at least 4 weeks.
[d]Includes RECIST-defined disease progression or death.
[e]DCR was defined as the best objective response of complete or partial response, or stable disease (without subsequent cancer therapy), for at least 11 weeks after first dose.
[f]DOR was defined as the time from the first documentation of complete or partial response (which was subsequently confirmed) until the date of progression, or death in the absence of disease progression.

carboplatin AUC 5 was selected as the recommended phase 2 dose.

T-DXd Monotherapy (Arm 1D). The median total duration of treatment was 7.2 (range, 0.7–23.3) months. Drug-related AEs, drug-related AEs of grade 3 or higher, and drug-related SAEs were reported in 34 (94.4%), 15 (41.7%), and six (16.7%) patients, respectively (Table 2). Drug-related AEs led to discontinuation in three patients (8.3%), and one patient (2.8%) died due to a drug-related AE (neutropenic colitis). There were two cases (5.6%) of adjudicated drug-related ILD/pneumonitis (both grade 2), and LVEF decrease occurred in one patient (2.8%; grade 2).

Additional safety data can be found in Supplementary Tables 1 and 2.

Efficacy

T-DXd Plus Durvalumab and Carboplatin (Arm 1B) and T-DXd Monotherapy (Arm 1D). The median (range) duration of follow-up was 14.4 (0.1–28.0) months in the T-DXd plus durvalumab and carboplatin arm and 14.9 (0.7–25.3) months in the T-DXd monotherapy (5.4 mg/kg) arm. Efficacy data for the T-DXd plus durvalumab and cisplatin arm are not reported given the low number of patients enrolled (n = 11) and short median duration of follow-up (5.0 [range, 0.3–26.6] mo). The confirmed ORR by investigator was 37.5% (95% CI: 18.8–59.4) in the overall T-DXd plus durvalumab and carboplatin arm and 44.4% (95% CI: 27.9–61.9) in the T-DXd monotherapy arm (Table 3). Investigator-assessed median DOR in the overall T-DXd plus durvalumab and carboplatin arm was 7.7 (95% CI: 4.3–22.0) months and in the T-DXd monotherapy arm was 11.0 (95% CI: 5.5–16.7) months. Median (range) best percentage change in target lesion size from baseline was −36.37% (n = 22; −75.9 to 0) and −33.72% (n = 35; −81.4 to 6.9) in the overall T-DXd plus durvalumab and carboplatin and T-DXd monotherapy arms, respectively (Fig. 1*A* and *B*). Median PFS by investigator assessment was 9.0 (95% CI: 2.7–10.6) months and 8.2 (95% CI: 6.7–11.1) months in the overall T-DXd plus durvalumab and carboplatin and T-DXd monotherapy arms, respectively (Fig. 2*A* and *B*). Median OS in the overall T-DXd plus durvalumab and carboplatin arm was 14.4 (95% CI: 8.6–not estimable [NE]) months and in the T-DXd monotherapy arm was 17.1 (95% CI: 11.6–23.8) months (Fig. 2*C* and *D*). Of the patients who discontinued treatment due to disease progression in the T-DXd plus durvalumab and carboplatin arm (n = 11) and T-DXd monotherapy arm (n = 27), 63.6% and 66.7%, respectively, received subsequent anticancer therapy (Supplementary Table 3);

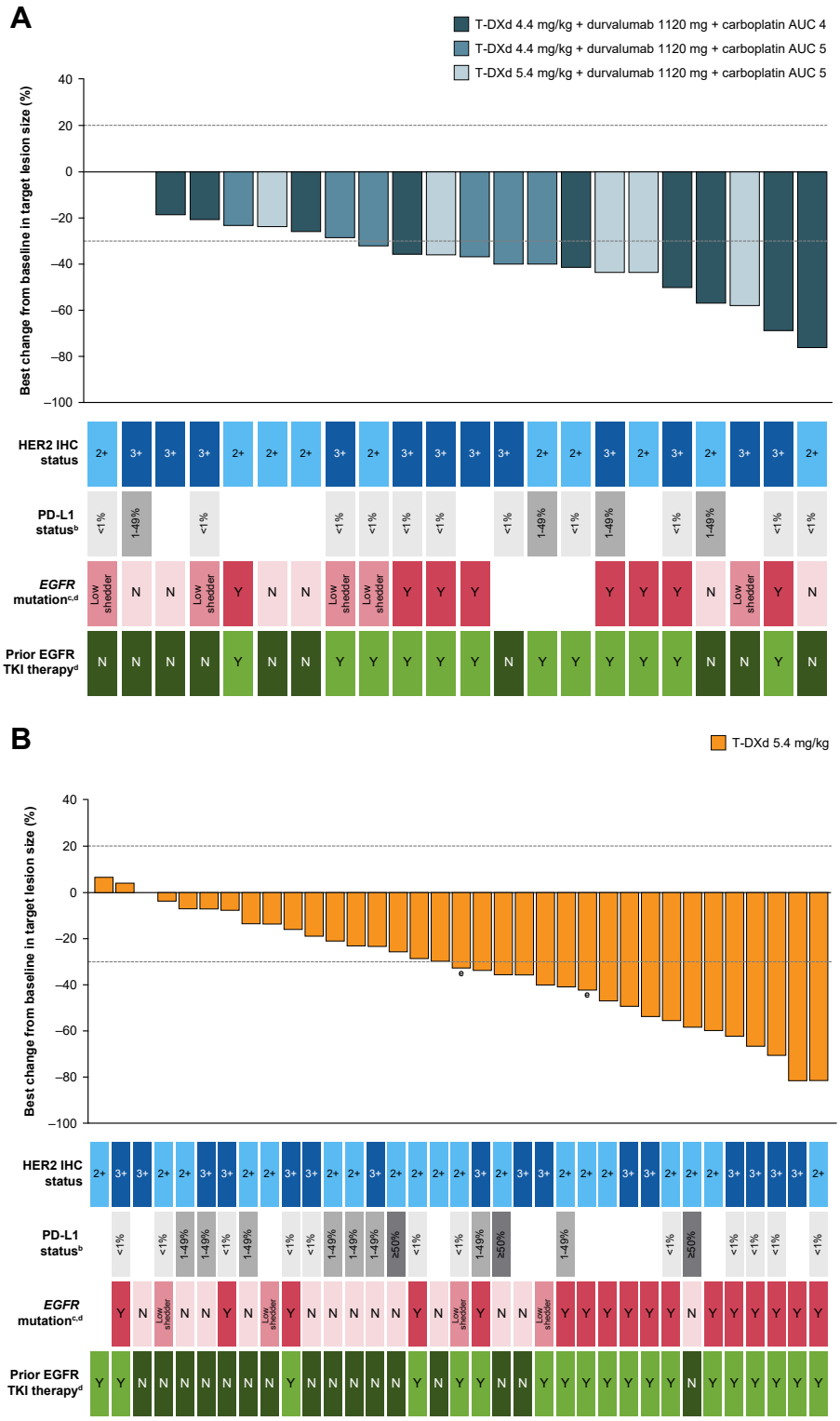

Figure 1. Best percentage change in target lesion size from baseline in the T-DXd plus durvalumab and carboplatin arm (*A*)[a] and T-DXd monotherapy arm (*B*).[a] Best percentage change in target lesion size is the maximum reduction from baseline or minimum increase from baseline in the absence of a reduction. Each bar in the waterfall plot represents a single patient in the T-DXd plus durvalumab and carboplatin arm and T-DXd monotherapy arm. The dashed line at −30% and 20% change in target lesion size indicates the threshold for partial response and progressive disease, respectively. [a]Two patients in the T-DXd plus durvalumab and carboplatin arm and one patient in the T-DXd monotherapy arm were not evaluable. [b]Patients with unknown PD-L1 status or for whom PD-L1 was not tested (A: n = 8; B: n = 12) are represented by white spaces. [c]*EGFR* mutation status was retrospectively assessed by ctDNA. [d]Patients had HER2-OE (IHC 3+/2+) NSCLC. [e]Unconfirmed response. AUC, area under the plasma concentration-time curve; IHC, immunohistochemistry; OE, overexpressing; PD-L1, programmed cell death-ligand 1; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase receptor.

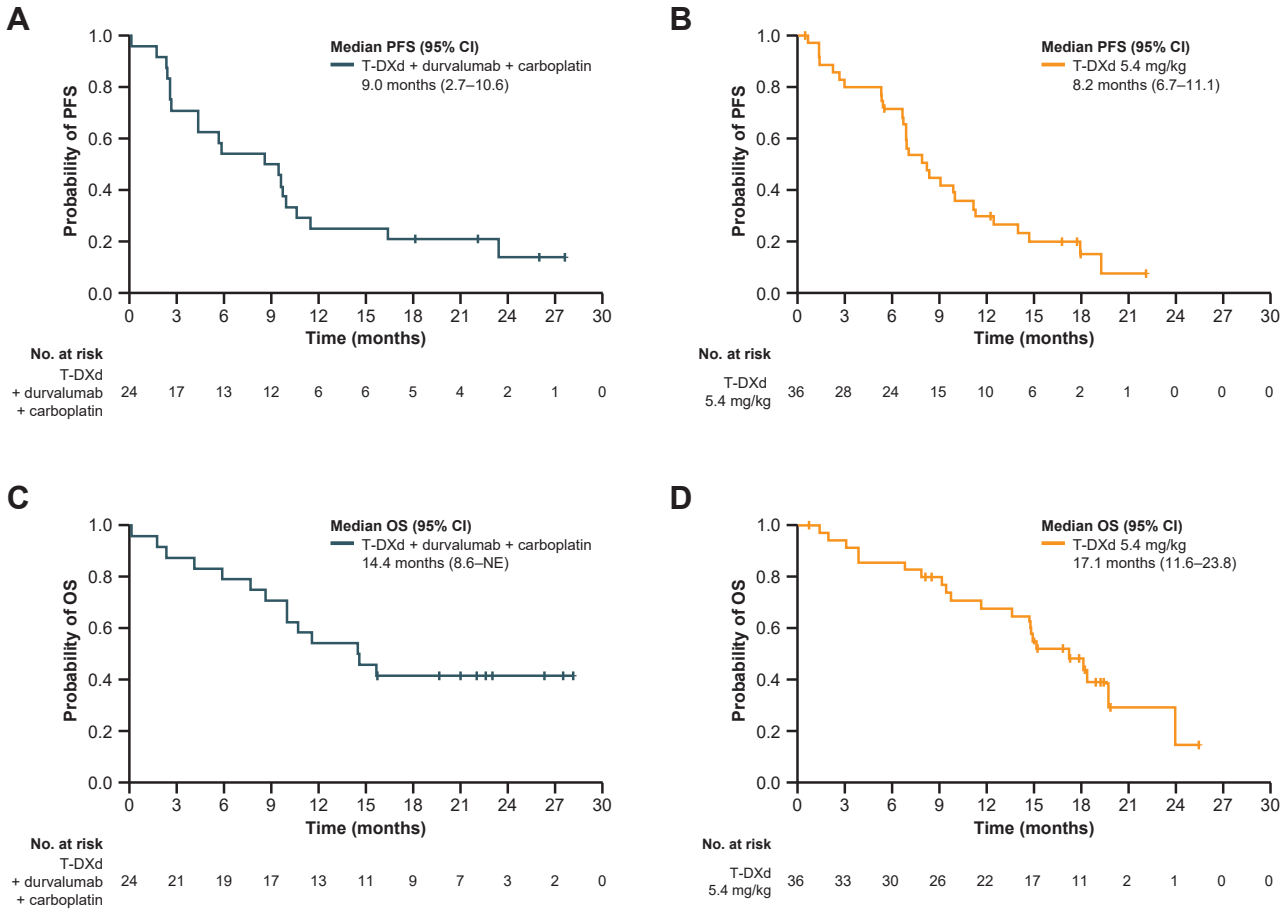

Figure 2. Investigator-assessed PFS[a] in the overall T-DXd plus durvalumab and chemotherapy arm (*A*)[b] and T-DXd monotherapy arm (*B*) and OS[c] in the overall T-DXd plus durvalumab and chemotherapy arm (*C*)[b] and T-DXd monotherapy arm (*D*). Assessed in all patients who were assigned to and received at least one dose of study treatment (T-DXd, durvalumab, or carboplatin). Symbols (+) indicate a censored observation. [a]Defined as the time from the date of first dose until the date of objective disease progression or death by any cause in the absence of disease progression; patients without disease progression or who had died, or who had disease progression or died after two or more missed visits, were censored at the last RECIST 1.1 evaluable assessment, or at the date of first dose if there were no evaluable visits or no baseline assessment (unless the patient died within 13 wk of baseline). [b]Data reported are a summary of the three dose levels in the T-DXd plus durvalumab and carboplatin arm; T-DXd 4.4 mg/kg + durvalumab 1120 mg + carboplatin AUC 4, T-DXd 4.4 mg/kg + durvalumab 1120 mg + carboplatin AUC 5, and T-DXd 5.4 mg/kg + durvalumab 1120 mg + carboplatin AUC 5. [c]Defined as the time from the date of first dose until death due to any cause; any patient not known to have died at data cutoff was censored on the recorded last date on which the patient was known to be alive; if the date of death occurred after the data cutoff date, the patient was censored at the date of data cutoff. AUC, area under the plasma concentration—time curve; CI, confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan.

one patient in the T-DXd monotherapy arm who discontinued treatment due to an AE received subsequent cisplatin and etoposide treatment.

T-DXd Monotherapy (Arm 1D): Exploratory Subgroup Analyses. In patients with HER2 IHC 3+ NSCLC and IHC 2+ NSCLC, the confirmed ORR by investigator was 56.3% (95% CI: 29.9–80.3) and 35.0% (95% CI: 15.4–59.2), respectively. Median PFS by investigator assessment was 6.9 (95% CI: 5.3–17.9) months in patients with HER2 IHC 3+ NSCLC and 8.2 (95% CI: 5.4–10.0) months in those with HER2 IHC 2+ NSCLC. Median OS was 16.4 (95% CI: 6.8–NE) months and 17.1 (95% CI: 9.4–23.8) months, respectively (Table 4 and Supplementary Figs. 3 and 4). Activity with T-DXd monotherapy was also observed in patients with and without prior EGFR TKI exposure; confirmed ORR was 68.4% (95% CI: 43.5–87.4) and 17.6% (95% CI: 3.8–43.4), respectively. Median PFS by investigator assessment was 8.2 (95% CI: 6.7–19.3) months in patients with prior EGFR TKI exposure and 7.1 (95% CI: 1.4–10.0) months in patients without prior EGFR TKI exposure. Median OS was 19.6 (95% CI: 13.5–NE) months and 14.7 (95% CI: 3.9–18.0) months,

Table 4. Efficacy Outcomes by HER2 IHC Status and Prior Exposure to EGFR TKI Therapy

	Part 1 Arm 1D			
	T-DXd 5.4 mg/kg			
Efficacy Outcome	HER2 IHC 3+ (n = 16)	HER2 IHC 2+ (n = 20)	Prior EGFR TKI (n = 19)	No Prior EGFR TKI (n = 17)
Confirmed ORR, % (n)[a,b]	56.3 (9)	35.0 (7)	68.4 (13)	17.6 (3)
95% CI	29.9-80.3	15.4-59.2	43.5-87.4	3.8-43.4
DCR at 12 wk, %[a,c]	81.3	75.0	84.2	70.6
95% CI	54.4-96.0	50.9-91.3	60.4-96.6	44.0-89.7
Median DOR, mo[a,d]	12.5	6.6	11.7	4.6
95% CI	5.5-NE	4.5-11.0	5.5-NE	4.5-NE
Median PFS, mo[a,e]	6.9	8.2	8.2	7.1
95% CI	5.3-17.9	5.4-10.0	6.7-19.3	1.4-10.0
Median OS, mo[f]	16.4	17.1	19.6	14.7
95% CI	6.8-NE	9.4-23.8	13.5-NE	3.9-18.0

Note: The study was not designed/powered to compare efficacy between subgroups. Exploratory efficacy outcomes were assessed in all patients who were assigned to and received ≥1 dose of T-DXd. Exploratory analyses are not reported for the T-DXd plus durvalumab and carboplatin arm owing to the low number of patients at each dose level. Of the 19 patients who had prior EGFR TKI exposure, 16 patients had *EGFR* mutations, two patients had low shedding tumors, and one patient was unknown. Of the 17 patients who had no prior EGFR TKI exposure, 14 patients were *EGFR* wild type, two patients had low shedding tumors, and one patient had an *EGFR* mutation.

CI, confidence interval; DCR, disease control rate; DOR, duration of response; HER2-OE, HER2-overexpressing; IHC, immunohistochemistry; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor.

[a]Investigator-assessed per RECIST 1.1.

[b]Confirmed ORR, defined as the best objective response of complete or partial responses, required confirmation after at least 4 weeks.

[c]DCR was defined as the best objective response of complete or partial response, or stable disease (without subsequent cancer therapy), for at least 11 weeks after first dose.

[d]DOR was defined as the time from the first documentation of complete or partial response (which was subsequently confirmed) until the date of progression, or death in the absence of disease progression.

[e]PFS was defined as the time from the date of first dose until the date of objective disease progression, or death by any cause in the absence of disease progression; patients without disease progression or who had died, or who had disease progression or died after two or more missed visits, were censored at the last evaluable RECIST 1.1 assessment, or at the date of first dose if there were no evaluable visits or no baseline assessment (unless the patient died within 13 weeks of baseline).

[f]OS was defined as the time from the date of first dose until death due to any cause; any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive; if the date of death occurred after the data cutoff date, the patient was censored at the date of data cutoff.

respectively (Table 4). Similar results were observed in patients with confirmed *EGFR*-mutant (EGFRm) and *EGFR*-wild type (EGFRwt) NSCLC (Supplementary Table 4).

Discussion

DESTINY-Lung03 Part 1 is one of the first studies to assess T-DXd–based regimens in previously treated patients with metastatic HER2-OE (IHC 3+/2+) NSCLC. Data from this study do not support further investigation of T-DXd plus durvalumab and cisplatin (Arm 1A) or T-DXd plus durvalumab and carboplatin (Arm 1B) in this patient population, as both regimens had unacceptable safety profiles. However, clinical benefit with T-DXd monotherapy (5.4 mg/kg; Arm 1D) was observed (ORR: 44.4%; median PFS: 8.2 mo; median OS: 17.1 mo) and no new safety signals were reported; adjudicated ILD/pneumonitis events were of low grade and the overall incidence (5.6%) was consistent with previous studies.[19,24,25]

Importantly, results from this study confirm the findings from DESTINY-Lung01 cohort 1a, which supported the approval of T-DXd (5.4 mg/kg) for the treatment of unresectable or metastatic HER2-positive (IHC 3+) solid tumors after prior treatment and/or without alternative treatment options in the United States and other countries.[16–19] Furthermore, exploratory analyses reported here revealed promising activity with T-DXd monotherapy in key subgroups. ORRs of 56% and 35% were reported in patients with HER2 IHC 3+ and IHC 2+ NSCLC, respectively, and survival outcomes were generally similar between these patient subgroups (HER2 IHC 3+: median PFS, 6.9 mo; median OS, 16.4 mo; and HER2 IHC 2+: median PFS, 8.2 mo; median OS: 17.1 mo). These findings, alongside the responses and survival outcomes reported in patients with HER2 IHC 3+ and IHC 2+ NSCLC treated with T-DXd (5.4 mg/kg) in DESTINY-Lung01 cohort 1a,[19] support the use of T-DXd in pretreated HER2 IHC 3+ NSCLC and provide evidence for the potential use of

T-DXd in HER2 IHC 2+ NSCLC. Activity with T-DXd monotherapy was also observed in patients with HER2-OE (IHC 3+/2+) NSCLC with and without prior EGFR TKI exposure and in those with EGFRm and EGFRwt disease. Interestingly, although ORRs with T-DXd monotherapy numerically differed between subgroups of patients with prior EGFR TKI therapy/*EGFR* mutations and those without prior EGFR TKI therapy/*EGFR* mutations, disease control and survival benefit with T-DXd were generally similar across these subgroups. However, the small number of patients in the subgroups should be considered when interpreting these results. In DESTINY-Lung01 cohort 1a, activity with T-DXd in patients with HER2-OE (IHC 3+/2+) NSCLC was observed regardless of prior EGFR TKI exposure, or some of the activating mutations assessed (including *EGFR*).[19] This is consistent with other studies that have revealed antitumor activity with antibody–drug conjugates in patients with NSCLC with and without known oncogenic alterations.[11,26–28] Interestingly, *HER2* amplification has been associated with acquired resistance to first-line EGFR TKIs in 1% to 2% of patients with EGFRm NSCLC in other studies[29–31]; as such, it may be possible that other *HER2* aberrations, including HER2 overexpression (as assessed by IHC), could have a similar role in EGFRm NSCLC resistance mechanisms, although further investigation is needed to confirm this. Taken together, these findings highlight the need for routine HER2 IHC assessment in NSCLC diagnostic workup to help inform treatment decisions in all patients with HER2-OE NSCLC.

Although cross-trial comparisons should be interpreted with caution, it is worth noting that benefit with T-DXd in HER2-OE NSCLC was observed in both DESTINY-Lung03 Part 1 Arm 1D and DESTINY-Lung01 cohort 1a despite differences in the study designs. For instance, in this study, a higher proportion of patients were from Asia and had received prior targeted therapy, including EGFR TKIs, compared with patients included in DESTINY-Lung01 cohort 1a.[19] In addition, the duration of treatment exposure and the assays used to assess HER2 overexpression (the DAKO HER2Low assay in this study and the PATHWAY HER2 (4B5) assay [Roche Diagnostic Solutions, Tucson, AZ] in DESTINY-Lung01) varied.[19] Indeed, some of the differences across the trials may reflect the variability of real-world clinical settings, including the absence of standardized methods to assess HER2 overexpression in NSCLC. Furthermore, given the patient population presenting with NSCLC is diverse (as reflected by all-comer populations in NSCLC trials in the second-line setting[11–15]), it is important to demonstrate the activity of T-DXd monotherapy in a broad population of patients with HER2-OE NSCLC, as found in DESTINY-Lung 01 cohort 1a and DESTINY-Lung03 Part 1,[19] to allow clinicians across regions to apply these findings to their clinical practice.

Treatment options currently recommended for previously treated HER2-OE (IHC 3+/2+) NSCLC include docetaxel or docetaxel with ramucirumab,[10] similar to an all-comer patient population, and platinum-based chemotherapy for those with *EGFR* mutations[3]; a median PFS of 3.6 to 5.4 months and a median OS of 9.4 to 15.9 months have been previously demonstrated with these regimens in pretreated metastatic nonsquamous NSCLC with or without *EGFR* mutations.[11–13,32–35] In this study, median PFS and median OS of 8.2 months and 17.1 months, respectively, were reported with T-DXd monotherapy in pretreated patients (approximately 50% had received at least two prior lines of therapy) with HER2-OE NSCLC. Combined with findings from DESTINY-Lung01 cohort 1a, where promising survival outcomes were also reported with T-DXd in pretreated patients (median lines of therapy, 3 [range, 2–4]) with HER2-OE NSCLC,[19] these results further demonstrate the potential survival benefit of T-DXd in this patient population. Notably, in DESTINY-Lung03 Part 1 Arm 1D, approximately one-third of patients had baseline brain/CNS metastases, which have been previously associated with poor prognosis in patients with NSCLC.[36] Given the CNS activity reported with T-DXd in previous studies,[19,37,38] further investigation of T-DXd in patients with HER2-OE NSCLC and CNS metastases may be warranted.

Overall, T-DXd plus durvalumab and carboplatin had antitumor activity in pretreated patients with HER2-OE (IHC 3+/2+) NSCLC, but both T-DXd–based triplet combination regimens assessed here had an unacceptable safety profile. Multiple factors might explain the limited additional activity observed with T-DXd plus durvalumab and carboplatin. For example, exposure to prior therapy may have affected patients' ability to tolerate triplet combination therapy; indeed, 50.0% to 54.2% of patients treated with T-DXd plus durvalumab and carboplatin had drug-related dose interruptions and/or reductions compared with less than 20% of those who received T-DXd monotherapy. Furthermore, some patients may have had disease refractory or with acquired resistance to components of the triplet regimens assessed.[33,39–42] However, there remains a need for additional HER2-directed treatment options for HER2-OE NSCLC, and several studies are ongoing to assess T-DXd–based regimens in this patient population. The U106 study cohort 3 is evaluating T-DXd plus pembrolizumab in patients with immunotherapy- and HER2-directed therapy-naive HER2-expressing (IHC 3+/2+/1+) locally advanced/metastatic NSCLC[43]; an ORR of 54.5% was reported at the interim analysis.[23] T-DXd with pembrolizumab versus pembrolizumab with

platinum-based chemotherapy are being assessed in the first-line setting in patients with HER2-OE NSCLC in the randomized phase 3 DESTINY-Lung06 study.[44] Furthermore, T-DXd plus volrustomig and T-DXd plus rilvegostomig are being assessed in the first-line setting in DESTINY-Lung03 Parts 3 and 4, respectively.[45]

Limitations of this study have already been briefly discussed and include the small sample size, which limits interpretation of results; the use of archival tumor tissue samples for assessment of HER2 IHC status and lack of repeat biopsy at disease progression (HER2 expression levels may change after treatment[46,47]); and the use of retrospective liquid biopsy-based detection of *EGFR* mutations, which has been associated with lower sensitivity compared with tissue biopsy-based detection.[48,49]

In conclusion, results from DESTINY-Lung03 Part 1 Arm 1D support the use of T-DXd in HER2-positive (IHC 3+) NSCLC and provide further evidence of antitumor activity in HER2 IHC 2+ NSCLC, building on results from DESTINY-Lung01 cohort 1a[19]; data also further demonstrate the manageable safety profile of T-DXd in patients with previously treated HER2-OE (IHC 3+/2+) NSCLC.[19] These findings also reinforce HER2 overexpression as an actionable biomarker in NSCLC and support routine HER2 IHC testing in NSCLC diagnostic workup. Safety and efficacy data do not support further investigation of T-DXd plus durvalumab and platinum chemotherapy in previously treated HER2-OE (IHC 3+/2+) NSCLC; however, the potential clinical benefit of novel T-DXd combination therapies is being further evaluated in the first- and second-line settings in this population.[43–45]

CRediT Authorship Contribution Statement

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Ji-Youn Han: Formal analysis, Investigation, Resources, Validation, Writing - original draft, Writing - review & editing.

Jens Samol: Formal analysis, Investigation, Resources, Validation, Writing - original draft, Writing - review & editing.

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James CH Yang: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Validation, Writing - original draft, Writing - review & editing.

Disclosure

Professor Planchard reported receiving personal fees for speaker engagements and/or advisory boards from AbbVie, AstraZeneca, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Gilead, Janssen (Johnson & Johnson), Merck, Novartis, Peer CME Review, Pfizer, Pierre Fabre, prIME Oncology, Roche, Samsung, and Seagen; and institutional grants from AbbVie, AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Janssen (Johnson & Johnson), Merck, Novartis, Pfizer, Pierre Fabre, Roche, and Sanofi-Aventis; all outside the submitted work. Professor Kim reported receiving clinical trial funding to their institution from AbbVie, ABL Bio, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Boryung, Bristol Myers Squibb, F. Hoffmann-La Roche Ltd./Genentech, Inc., Hanmi, Genmab, GlaxoSmithKline, Merck & Co. 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Doctor Li reported receiving payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Amgen, AstraZeneca, Eisai, Eli Lilly and Company, and Roche, all outside the submitted work. Professor Cortinovis reported receiving personal fees from participation on a data safety monitoring or advisory board with Amgen, AstraZeneca, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, CatalYm, Johnson & Johnson, Merck Sharp & Dohme, and Pfizer; all outside the submitted work. Doctor Han reported receiving consulting fees from AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Daewoong Pharma, Daiichi Sankyo, Janssen (Johnson & Johnson), Lantern Pharma, LG Chem, Novartis, Oncovix, ONO Pharmaceutical, Pfizer, Roche, and Takeda; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, Janssen (Johnson & Johnson), Merck Sharp & Dohme, Novartis, Pfizer, Roche, Takeda, and Yuhan; and participation on a data safety monitoring or advisory board with AstraZeneca and Janssen (Johnson & Johnson); all outside the submitted work. Assistant Professor Samol reported receiving payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Amgen, Astellas Pharma, AstraZeneca, BeiGene, Bristol Myers Squibb, Daiichi Sankyo, DKSH, Eisai, Ipsen, Johnson & Johnson, Merck Sharp & Dohme, Taiho Pharmaceutical, and Top Alliance; all outside the submitted work. Doctor Runglodvatana reported receiving payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, ATB Therapeutics, Eisai, Merck Sharp & Dohme, Novartis, and Roche; and travel support from Eisai and Merck Sharp & Dohme; all outside the submitted work. Professor K-Y Lee reported receiving payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Janssen (Johnson & Johnson), Lotus, Merck, Merck Sharp & Dohme, ONO Pharmaceutical, Pfizer, Roche, and Takeda; travel support from Lotus and Pfizer; and participation on a data safety monitoring or advisory board with OBI Pharma; all outside the submitted work. Doctor G-C Chang reported receiving payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly and Company, Merck Sharp & Dohme, Novartis, ONO Pharmaceutical, Pfizer, Roche, and Takeda; all outside the submitted work. Professor Kowalski reported having participation on an advisory board with Amgen, AstraZeneca, Bristol Myers Squibb, Genmab, Johnson & Johnson, Medison, Merck Sharp & Dohme, Pfizer, Roche, and Takeda; all outside the submitted work. Doctor Saw reported receiving grants or contracts from AstraZeneca; consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, and Pfizer; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AstraZeneca, Bristol Myers Squibb, Daiichi Sankyo, Merck Sharp & Dohme, Pfizer, Roche, and Takeda; travel support from AstraZeneca and Merck Sharp & Dohme; and participation on a data safety monitoring or advisory board with AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, and Pfizer; all outside

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Data-Sharing Statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://www.astrazenecaclinicaltrials.com/our-transparency-commitments/. Data for studies directly listed on Vivli can be requested through Vivli at https://vivli.org/. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at http://doi.org/10.1016/j.jtho.2025.12.080.

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