



Original Investigation | Oncology

Trastuzumab Deruxtecan for *ERBB2*-Mutant Metastatic Non–Small Cell Lung Cancer With or Without Brain Metastases

A Secondary Analysis of Randomized Clinical Trials

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Abstract

IMPORTANCE Brain metastases reduce overall survival rates of patients with non–small cell lung cancer (NSCLC); patients with epidermal growth factor receptor 2 (*ERBB2* [formerly *HER2*])–mutant NSCLC are more likely to have baseline brain metastases. Trastuzumab deruxtecan (T-DXd) is an approved *ERBB2*-directed treatment for previously treated unresectable or metastatic *ERBB2*-mutant NSCLC.

OBJECTIVE To assess the clinical effectiveness and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg doses in patients with previously treated *ERBB2*-mutant metastatic NSCLC with or without untreated or previously treated stable brain metastases.

DESIGN, SETTING, AND PARTICIPANTS This post hoc secondary analysis pooled patients from the DESTINY-Lung01 (data cutoff date: December 3, 2021) and DESTINY-Lung02 (data cutoff date: December 23, 2022) clinical trials by T-DXd dose (5.4 mg/kg and 6.4 mg/kg). DESTINY-Lung01 was a multicenter, open-label, 2-cohort, nonrandomized phase 2 study, while DESTINY-Lung02 was a dose-blinded, multicenter, 2-cohort, randomized phase 2 study. Participants had a previously treated *ERBB2*-mutant metastatic NSCLC with or without untreated or previously treated stable brain metastases at baseline. All statistical analyses were performed from April 2023 to October 2024.

INTERVENTION Patients received a T-DXd dose of either 5.4 mg/kg or 6.4 mg/kg intravenously every 3 weeks.

MAIN OUTCOME AND MEASURE Systemic and intracranial effectiveness by blinded independent central review using RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1, sites of progression, and safety.

RESULTS This analysis included 102 patients in the T-DXd 5.4-mg/kg dose group (65 females [64%]; median [range] age, 57.5 [37.0–83.0] years and 59.5 [30.0–79.0] years in patients with and without brain metastases, respectively) and 141 patients in the T-DXd 6.4-mg/kg dose group (94 females [67%]; median [range] age, 62.5 [29.0–88.0] years and 59.0 [27.0–83.0] years in patients with and without brain metastases, respectively). In each group, 31% (32 of 102) and 38% (54 of 141) of patients, respectively, had baseline brain metastases and 53% (17 of 32) and 44% (24 of 54), respectively, received prior brain metastasis treatment. In patients with and without brain metastases, systemic confirmed objective response rates (ORRs) were 47% (15 of 32; 95% CI, 29%–65%) and 50% (35 of 70; 95% CI, 38%–62%), respectively, with the T-DXd 5.4-mg/kg dose,

(continued)

Key Points

Question What is the effectiveness and safety of trastuzumab deruxtecan (T-DXd) 5.4-mg/kg and 6.4-mg/kg doses in patients with epidermal growth factor receptor 2 (*ERBB2* [formerly *HER2*])–mutant metastatic non–small cell lung cancer (NSCLC) with or without treated or untreated stable brain metastases?

Findings This secondary analysis included 243 participants in the DESTINY-Lung01 and DESTINY-Lung02 clinical trials. Patients with and without brain metastases who received the T-DXd 5.4-mg/kg dose had systemic confirmed objective response rates (ORRs) of 47% and 50%, respectively, and an intracranial confirmed ORR of 50%. With the T-DXd 6.4-mg/kg dose, systemic confirmed ORRs were 50% and 59% for patients with and without brain metastases, respectively, and the intracranial confirmed ORR was 30%.

Meaning These findings support T-DXd use in patients with previously treated *ERBB2*-mutant metastatic NSCLC with or without brain metastases.

+ Supplemental content

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Abstract (continued)

and 50% (27 of 54; 95% CI, 36%-64%) and 59% (51 of 87; 95% CI, 48%-69%) with the T-DXd 6.4-mg/kg dose. Median progression-free survival was 7.1 (95% CI, 5.5-9.7) months in the T-DXd 5.4-mg/kg dose group and 7.1 (95% CI, 4.5-9.6) months in the T-DXd 6.4-mg/kg dose group of patients with baseline brain metastases. Among patients with measurable baseline brain metastases, intracranial confirmed ORRs were 50% (7 of 14; 95% CI, 23%-77%) with the T-DXd 5.4-mg/kg dose and 30% (9 of 30; 95% CI, 15%-49%) with the T-DXd 6.4-mg/kg dose. At both doses, the safety profile of T-DXd was generally manageable, regardless of baseline brain metastases, favoring the T-DXd 5.4 mg/kg dose.

CONCLUSIONS AND RELEVANCE In this secondary analysis, T-DXd at the approved dose of 5.4 mg/kg showed antitumor activity in patients with previously treated *ERBB2*-mutant metastatic NSCLC with or without brain metastases. This finding supports T-DXd 5.4 mg/kg use in this population.

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Introduction

Epidermal growth factor receptor 2 (*ERBB2* [formerly *HER2*])–mutant non–small cell lung cancer (NSCLC) is a highly aggressive disease with poor estimated outcome.^{1,2} Brain metastases in *ERBB2*-mutant NSCLC remain a treatment challenge and are associated with poorer survival outcomes.³ In retrospective studies, approximately 14% to 20% of patients with *ERBB2*-mutant NSCLC have brain metastases at metastatic diagnosis and an additional 28% to 35% of patients develop brain metastases later.^{3–5} Notably, not all patients in these previous studies underwent baseline central nervous system (CNS) scans; therefore, the proportion of patients with brain metastases and *ERBB2*-mutant NSCLC may be underestimated.

Patients with *ERBB2*-mutant NSCLC may be at a higher risk of developing brain metastases due to increased expression of C-X-C motif chemokine receptor 4.^{3,6,7} Moreover, the estimated outcome of *ERBB2*-mutant NSCLC worsens when brain metastases are present; patients with brain metastases have substantially lower median overall survival (OS) than those without brain metastases (1.2 vs 2.5 years; hazard ratio, 2.8; $P = .01$).³

Current therapies for managing patients with NSCLC and brain metastases, including whole-brain radiotherapy (WBRT) alone or combinations of surgical resection and/or stereotactic radiosurgery with or without WBRT, raise concerns about neurologic deterioration.⁸ Targeted therapies with intracranial efficacy and an acceptable safety profile (eg, second- or third-generation tyrosine kinase inhibitors [TKIs]) show promise over cytotoxic chemotherapy in treating brain metastases associated with lung cancer with actionable oncogenic alterations⁹; therefore, targeted treatments could be key to managing brain metastases in this patient population.

Trastuzumab deruxtecan (T-DXd), an *ERBB2*-directed antibody-drug conjugate (ADC),^{10–12} is the first approved *ERBB2*-directed treatment for patients with previously treated unresectable or metastatic *ERBB2*-mutant NSCLC. In the DESTINY-Lung01 and DESTINY-Lung02 trials, the T-DXd 5.4-mg/kg and 6.4-mg/kg doses showed robust antitumor activity, leading to the approval of the T-DXd 5.4-mg/kg dose for previously treated *ERBB2*-mutant metastatic NSCLC in several countries.^{13–15}

In this exploratory pooled post hoc secondary analysis, we examined results from the DESTINY-Lung01 and DESTINY-Lung02 trials. Our objective was to assess the clinical effectiveness and safety of T-DXd 5.4-mg/kg and 6.4-mg/kg doses in patients with previously treated *ERBB2*-mutant metastatic NSCLC with or without baseline brain metastases.

Methods

Study Design

DESTINY-Lung01, with a data cutoff date of December 3, 2021, was a multicenter, 2-cohort, nonrandomized, phase 2 study that evaluated T-DXd 5.4-mg/kg or 6.4-mg/kg dose administered intravenously every 3 weeks in patients with *ERBB2*-overexpressing metastatic NSCLC and T-DXd 6.4-mg/kg dose in patients with *ERBB2*-mutant metastatic NSCLC. DESTINY-Lung02, with a data cutoff date of December 23, 2022, was a dose-blinded, multicenter, 2-cohort, phase 2 study in which patients with *ERBB2*-mutant, unresectable and/or metastatic NSCLC were randomly assigned 2:1 to receive either T-DXd 5.4-mg/kg or 6.4-mg/kg dose intravenously every 3 weeks.¹⁴ Patients whose disease had relapsed from or was refractory to standard treatment were included in DESTINY-Lung01, while patients with previously treated *ERBB2*-mutant metastatic NSCLC (≥ 1 prior anticancer therapy, including platinum-based chemotherapy) were included in DESTINY-Lung02. Details of the study designs have been described previously.^{14,15} In the present analysis, patients with *ERBB2*-mutant metastatic NSCLC from each trial were pooled by dose (T-DXd 5.4 mg/kg and 6.4 mg/kg). The institutional review board at each trial site approved DESTINY-Lung01 (conducted at 21 sites across the US, France, Japan, the Netherlands, and Spain) and DESTINY-Lung02 (conducted at 50 sites across the US, Australia, Canada, France, Italy, Japan, the Netherlands, South Korea, Spain, and Taiwan). The trial protocols are provided in [Supplement 1](#). Both trials were conducted in accordance with the International Council for Harmonisation Good Clinical Practice Guidelines, the Declaration of Helsinki,¹⁶ and local regulations on the conduct of clinical research. All participants provided written informed consent. Ethics approval and informed consent extended to this secondary analysis. We followed the Consolidated Standards of Reporting Trials ([CONSORT](#)) reporting guideline.

Patients

Patients included in this secondary analysis had a pathologically documented unresectable or metastatic *ERBB2*-mutant NSCLC per local testing, an Eastern Cooperative Oncology Group Performance Status score of 0 (indicating that the patient was fully active and able to carry on all predisease performance without restriction) or 1 (indicating that the patient was restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature), and at least 1 measurable lesion (≥ 10 mm in 1 dimension on computed tomography [CT] or magnetic resonance imaging [MRI]) per investigator assessment and the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.¹⁷ Patients were excluded if they were previously treated with *ERBB2*-targeted therapies in the DESTINY-Lung01 trial (except prior *ERBB2* TKIs, which were allowed in both studies) or had a history of or current interstitial lung disease or pneumonitis. In the DESTINY-Lung01 and DESTINY-Lung02 trials, all patients underwent contrast-enhanced CT or MRI brain scans at screening, regardless of prior history or suspicion of brain metastases. Additionally, patients with stable, asymptomatic brain metastases at baseline were eligible if they did not require ongoing corticosteroids or anticonvulsants, if they had recovered from acute radiotherapy toxic effects, and if at least 2 weeks had passed since their WBRT. Patients with measurable (≥ 10 mm) or nonmeasurable (< 10 mm) brain metastases or no brain metastases at baseline were included. The eligibility criteria for the DESTINY-Lung01 and DESTINY-Lung02 trials have been published elsewhere.^{14,15}

Effectiveness

In patients with or without baseline brain metastases, systemic effectiveness—evaluated by confirmed objective response rate (ORR) and duration of response (DOR)—and sites of progression were evaluated by blinded independent central review (BICR) using the RECIST version 1.1 guideline; brain metastases were included as target lesions in systemic response evaluation. In patients with measurable baseline brain metastases, intracranial ORR, DOR, and disease control rate were assessed by BICR using the RECIST version 1.1 criteria, regardless of whether patients had undergone prior

brain radiotherapy. Intracranial activity was evaluated by CT or MRI scans every 6 weeks from cycle 1, day 1; unless clinically indicated, those without baseline brain metastases required no serial imaging.

Safety

Safety was assessed based on the incidence and severity of treatment-emergent adverse events (TEAEs), serious adverse events, and adverse events of special interest in patients with or without baseline brain metastases. All adverse events were categorized using the Medical Dictionary for Regulatory Activities, version 25.1. Adverse events and abnormal laboratory test results, if applicable, were graded using the Common Terminology Criteria for Adverse Events, version 5.0.

Statistical Analysis

Systemic and intracranial confirmed ORRs—defined as the proportion of patients with confirmed complete response (CR) and partial response (PR), as assessed by BICR using RECIST version 1.1—were determined using descriptive statistics, including 2-sided exact 95% CI (Clopper-Pearson). Systemic and intracranial DOR, defined as the time from initial response (CR or PR) until documented tumor progression or death from any cause, was summarized using the Kaplan-Meier approach for each dose level. Systemic and intracranial disease control rates, defined as the proportion of patients with CR, PR, or stable disease, were based on BICR and investigator assessments. A best response of stable disease was assigned only after the patient had participated in the study for 35 days or more. If the patient's participation lasted fewer than 35 days, any tumor assessment indicating stable disease before this period was assigned a best response of not evaluable (NE) unless progressive disease was identified. Patients with missing assessments were considered NE. Progression-free survival (PFS; defined as time from randomization until first objective radiographic tumor progression or death from any cause) and OS (defined as time from randomization until death from any cause) were summarized using the Kaplan-Meier approach. Best percentage change from baseline in the sum of target lesion diameters was summarized descriptively by T-DXd dose level. All statistical analyses were performed from April 2023 to October 2024 using SAS, version 9.3 or higher (SAS Institute Inc).

Results

Patients with *ERBB2*-mutant NSCLC from DESTINY-Lung01 and DESTINY-Lung02 trials were pooled according to T-DXd doses of 5.4 mg/kg (n = 102; 65 females [64%] and 37 males [36%]; median [range] age, 57.5 [37.0-83.0] years and 59.5 [30.0-79.0] years in patients with and without brain metastases, respectively) and 6.4 mg/kg (n = 141; 94 females [67%] and 47 males [33%]; median [range] age, 62.5 [29.0-88.0] years and 59.0 [27.0-83.0] years in patients with and without brain metastases, respectively) (eFigure 1 in [Supplement 2](#); [Table 1](#)). In the T-DXd 5.4-mg/kg dose group, 31% (32 of 102) of patients had brain metastases and 69% (70 of 102) did not. In the T-DXd 6.4-mg/kg dose group, 38% (54 of 141) of patients had brain metastases and 62% (87 of 141) did not. In total, 59% (19 of 32) of patients with brain metastases and 66% (46 of 70) without brain metastases in the T-DXd 5.4-mg/kg dose group were female; 41% (13 of 32) and 34% (24 of 70) of patients, respectively, were male. In the T-DXd 6.4-mg/kg dose group, 59% (32 of 54) of patients with brain metastases and 71% (62 of 87) without brain metastases were female; 41% (22 of 54) and 29% (25 of 87) of patients, respectively, were male.

Approximately half of patients with baseline brain metastases (T-DXd 5.4 mg/kg: 53% [17 of 32]; T-DXd 6.4 mg/kg: 44% [24 of 54]) received prior treatment for brain metastases. Patients without baseline brain metastases may have previously had brain metastases that fully resolved before screening. In patients with brain metastases, imaging was performed via MRI in 47% (15 of 32) and 76% (41 of 54) of patients in the T-DXd 5.4-mg/kg and 6.4-mg/kg dose groups, respectively, and via CT in 53% (17 of 32) and 24% (13 of 54) of patients in these groups (Table 1).

Table 1. Baseline Patient Characteristics

Characteristic	Patients, No. (%) ^a		T-DXd 6.4 mg/kg-dose group pooled from DESTINY-Lung01 and DESTINY-Lung02 trials			
	T-DXd 5.4 mg/kg-dose group in DESTINY-Lung02 trial With measurable BMs (n = 14)	Without measurable BMs (n = 18)	With measurable BMs (n = 30)	Without measurable BMs (n = 24)	Without BMs (n = 87)	
Age, median (range), y	57.0 (37.0-77.0)	60.5 (40.0-83.0)	64.5 (41.0-85.0)	60.5 (29.0-88.0)	59.0 (27.0-83.0)	
Sex						
Female	8 (57)	11 (61)	16 (53)	16 (67)	62 (71)	
Male	6 (43)	7 (39)	14 (47)	8 (33)	25 (29)	
Region						
Europe	11 (79)	8 (44)	15 (50)	5 (21)	30 (34)	
Asia	3 (21)	9 (50)	9 (30)	8 (33)	36 (41)	
North America	0	1 (6)	6 (20)	11 (46)	20 (23)	
Rest of world	0	0	0	0	1 (1)	
Time from initial NSCLC diagnosis to randomization, median (range), mo	24.2 (6.9-39.3)	19.1 (3.2-63.0)	19.3 (1.7-51.8)	15.7 (1.9-125.9)	16.2 (3.3-151.9)	
ECOG PS score						
0	3 (21)	3 (17)	7 (23)	6 (25)	29 (33)	
1	11 (79)	15 (83)	23 (77)	18 (75)	58 (67)	
History of BMs						
Yes	12 (86)	17 (94)	30 (100)	15 (63)	15 (17)	
No	2 (14)	1 (6)	0	9 (38)	72 (83)	
Prior regimens in the metastatic setting						
≤2	10 (71)	13 (72)	16 (53)	17 (71)	60 (69)	
>2	4 (29)	5 (28)	14 (47)	7 (29)	27 (31)	
Intracranial progression on prior therapy						
Yes	5 (36)	5 (28)	9 (30)	4 (17)	2 (2)	
No	3 (21)	4 (22)	5 (17)	6 (25)	4 (5)	
Prior treatment of BMs						
Radiotherapy only	7 (50)	8 (44)	13 (43)	10 (42)	6 (7)	
Surgery only	0	0	0	0	0	
Radiotherapy and surgery	1 (7)	1 (6)	1 (3)	0	0	
None	6 (43)	9 (50)	16 (53)	14 (58)	81 (93)	
Time since prior radiotherapy, median (range), mo	7.9 (1.3-23.9)	10.0 (1.0-38.5)	1.6 (0.6-11.3)	2.3 (0.5-17.2)	13.6 (3.0-21.0)	
Baseline brain imaging						
MRI	5 (36)	10 (56)	20 (67)	21 (88)	NA	
CT	9 (64)	8 (44)	10 (33)	3 (13)	NA	
No. of BMs, median (range)	3.0 (2.0-11.0)	2.0 (1.0-6.0)	7.0 (2.0-18.0)	1.5 (1.0-7.0)	0	

Abbreviations: BM, brain metastasis; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MRI, magnetic resonance imaging; NA, not applicable; NSCLC, non-small cell lung cancer; T-DXd, trastuzumab deruxtecan.

^a Totals may not equal 100% due to rounding.

Systemic Effectiveness

In the T-DXd 5.4-mg/kg dose group, systemic confirmed ORRs were 47% (15 of 32; 95% CI, 29%-65%) in patients with brain metastases (all with PR); 64% (9 of 14; 95% CI, 35%-87%) and 33% (6 of 18; 95% CI, 13%-59%) in patients with measurable and nonmeasurable brain metastases, respectively; and 50% (35 of 70; 95% CI, 38%-62%) in patients without brain metastases (1% with CR, 49% with PR). In the T-DXd 6.4-mg/kg dose group, systemic confirmed ORRs were 50% (27 of 54; 95% CI, 36%-64%) in patients with brain metastases (all with PR); 43% (13 of 30; 95% CI, 26%-63%) and 58% (14 of 24; 95% CI, 37%-78%) in patients with measurable and nonmeasurable brain metastases, respectively; and 59% (51 of 87; 95% CI, 48%-69%) in patients without brain metastases (3% with CR, 55% with PR). Median DOR was shorter in patients with brain metastases than in those without brain metastases (T-DXd 5.4 mg/kg: 4.6 [95% CI, 4.2-9.5] months vs 16.8 [95% CI, 8.7-NE] months; T-DXd 6.4 mg/kg: 7.2 [95% CI, 5.3-NE] months vs 14.1 [95% CI, 9.3-NE] months) (Table 2).

Intracranial progression occurred in 14% (2 of 14) and 22% (4 of 18) of patients with measurable and nonmeasurable brain metastases in the T-DXd 5.4-mg/kg dose group, respectively, and in 20% (6 of 30) and 8% (2 of 24) of patients in the T-DXd 6.4-mg/kg dose group. In patients without baseline brain metastases, 4% (3 of 70) who received the T-DXd 5.4-mg/kg dose and 6% (5 of 87) who received the T-DXd 6.4-mg/kg dose experienced intracranial progression (Table 2). Rates may be underestimated due to nonmandatory serial brain imaging in patients without baseline brain metastases.

Patients with brain metastases experienced a shorter median PFS and OS (T-DXd 5.4 mg/kg: 7.1 [95% CI, 5.5-9.7] months and 13.6 [95% CI, 9.4-NE] months, respectively; T-DXd 6.4 mg/kg: 7.1 [95% CI, 4.5-9.6] months and 13.8 [95% CI, 11.1-19.5] months, respectively) compared with patients without brain metastases (T-DXd 5.4 mg/kg: 18.0 [95% CI, 8.5-NE] months and 19.5 [95% CI, 14.9-NE] months, respectively; T-DXd 6.4 mg/kg: 11.9 [95% CI, 7.2-16.1] months and 27.9 [95% CI, 17.8-NE] months, respectively) (Table 2; eFigure 2 in Supplement 2). PFS by brain metastases measurability is shown in eFigure 3 in Supplement 2.

Intracranial Confirmed ORR and Best Overall Response (Measurable Brain Metastases)

Among patients with measurable baseline brain metastases treated with T-DXd 5.4 mg/kg, intracranial confirmed ORR was 50% (7 of 14; 95% CI, 23%-77%; 21% [3 of 14] with CR). With T-DXd 6.4 mg/kg, intracranial confirmed ORR was 30% (9 of 30; 95% CI, 15%-49%; all with PR). Clinical images of a patient with CR are shown in eFigure 4 in Supplement 2. The median intracranial DOR was 9.5 (95% CI, 3.6-NE) months and 4.4 (95% CI, 2.9-10.2) months in the T-DXd 5.4-mg/kg and 6.4-mg/kg dose groups, respectively (Table 3). Among these patients, 86% (12 of 14) and 78% (21 of 27) of patients in the T-DXd 5.4-mg/kg and 6.4-mg/kg dose groups, respectively, experienced a reduction in brain lesion size (Figure).

Intracranial Response With and Without Prior Brain Metastases Treatment (Measurable Brain Metastases)

Among all patients with measurable brain metastases at baseline, intracranial confirmed ORRs were 32% (7 of 22; 95% CI, 14%-55%) and 41% (9 of 22; 95% CI, 21%-64%) with and without prior treatment for brain metastases, respectively. The combined median (range) time since prior brain radiotherapy in patients with intracranial response was 7.2 (0.6-23.9) months, while the median (range) time since prior brain radiotherapy was 9.2 (7.2-23.9) months with the T-DXd 5.4-mg/kg dose and 0.9 (0.6-0.9) months with the T-DXd 6.4-mg/kg dose. In the T-DXd 5.4-mg/kg dose group, intracranial confirmed ORRs were 50% (4 of 8; 95% CI, 16%-84%) among patients with prior brain metastasis treatment (all with PR) and 50% (3 of 6; 95% CI, 12%-88%) among patients without prior brain metastasis treatment (all with CR). In the T-DXd 6.4-mg/kg dose group, intracranial confirmed ORRs were 21% (3 of 14; 95% CI, 5%-51%; all with PR) and 38% (6 of 16; 95% CI, 15%-65%; all with

Table 2. Systemic Objective Response Rate

Response	Patients, No. (%)		T-DXd 5.4 mg/kg-dose group in DESTINY-Lung02 trial (n = 102)		T-DXd 6.4-mg/kg dose group pooled from DESTINY-Lung01 and DESTINY-Lung02 trials (n = 141)			
	With measurable BMs (n = 14)	With nonmeasurable BMs (n = 18)	Overall (n = 32)	Without BMs (n = 70)	With measurable BMs (n = 30)	With nonmeasurable BMs (n = 24)	Overall (n = 54)	Without BMs (n = 87)
Systemic confirmed objective response	9 (64)	6 (33)	15 (47)	35 (50)	13 (43)	14 (58)	27 (50)	51 (59)
Systemic confirmed ORR (95% CI), % ^{a,b}	64 (35-87)	33 (13-59)	47 (29-65)	50 (38-62)	43 (26-63)	58 (37-78)	50 (36-64)	59 (48-69)
CR	0	0	0	1 (1)	0	0	0	3 (3)
PR	9 (64)	6 (33)	15 (47)	34 (49)	13 (43)	14 (58)	27 (50)	48 (55)
SD	5 (36)	9 (50)	14 (44)	31 (44)	14 (47)	9 (38)	23 (43)	29 (33)
PD	0	2 (11)	2 (6)	2 (3)	1 (3)	1 (4)	2 (4)	3 (3)
NE	0	1 (6)	1 (3)	2 (3)	2 (7)	0	2 (4)	4 (5)
Missing data	0	0	0	2 (3)	0	0	0	4 (5)
Disease control	14 (100)	15 (83)	29 (91)	66 (94)	27 (90)	23 (96)	50 (93)	80 (92)
DCR (95% CI), % ^{a,b}	100 (77-100)	83 (59-96)	91 (75-98)	94 (86-98)	90 (74-98)	96 (79-100)	93 (82-98)	92 (84-97)
DOR, median (95% CI), mo ^c	5.0 (3.6-NE)	4.6 (2.8-NE)	4.6 (4.2-9.5)	16.8 (8.7-NE)	5.8 (4.6-NE)	NE (2.9-NE)	7.2 (5.3-NE)	14.1 (9.3-NE)
Sites of first systemic progression	5 (36)	9 (50)	14 (44)	21 (30)	13 (43)	10 (42)	23 (43)	38 (44)
Intracranial only	1 (7)	2 (11)	3 (9)	3 (4)	6 (20)	1 (4)	7 (13)	2 (2)
Extracranial only	3 (21)	5 (28)	8 (25)	18 (26)	7 (23)	6 (25)	13 (24)	32 (37)
Both	1 (7)	2 (11)	3 (9)	0	0	1 (4)	1 (2)	3 (3)
Missing data	0	0	0	0	0	2 (8)	2 (2)	1 (1)
PFS, median (95% CI), mo	7.1 (5.4-NE)	6.9 (5.5-9.7)	7.1 (5.5-9.7)	18.0 (8.5-NE)	6.4 (4.0-7.1)	8.5 (4.3-NE)	7.1 (4.5-9.6)	11.9 (7.2-16.1)
OS, median (95% CI), mo	13.6 (5.4-NE)	NE (6.2-NE)	13.6 (9.4-NE)	19.5 (14.9-NE)	11.2 (7.1-14.8)	21.1 (13.8-NE)	13.8 (11.1-19.5)	27.9 (17.8-NE)

Abbreviations: BM, brain metastasis; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan.

^a Denominator for percentages is the number of patients in the full analysis set with BM tumor assessment.

^b Based on Clopper-Pearson method for single proportion.

^c Calculated as time from first CR until progression.

Table 3. Intracranial Confirmed Objective Response Rate in Patients With Measurable Brain Metastases With or Without Prior Treatment

Response	Patients, No. (%)		T-DXd 6.4-mg/kg dose group pooled from DESTINY-Lung01 and DESTINY-Lung02 trials (n = 141)								Combined groups	
	T-DXd 5.4-mg/kg dose group in DESTINY-Lung02 trial (n = 102)											
	With measurable BMs (n = 14)	With prior treatment (n = 8)	Without prior treatment (n = 6)	With measurable BMs (n = 30)	With prior treatment (n = 14)	Without prior treatment (n = 16)	With prior treatment (n = 22)	Without prior treatment (n = 22)				
Intracranial confirmed objective response	7 (50)	4 (50)	3 (50)	9 (30)	3 (21)	6 (38)	7 (32)	9 (41)				
Intracranial confirmed ORR (95% CI), % ^{a,b}	50 (23-77)	50 (16-84)	50 (12-88)	30 (15-49)	21 (5-51)	38 (15-65)	32 (14-55)	41 (21-64)				
CR	3 (21)	0	3 (50)	0	0	0	0	3 (14)				
PR	4 (29)	4 (50)	0	9 (30)	3 (21)	6 (38)	7 (32)	6 (27)				
SD	6 (43)	3 (38)	3 (50)	13 (43)	7 (50)	6 (38)	10 (45)	9 (41)				
PD	1 (7)	1 (13)	0	4 (13)	3 (21)	1 (6)	4 (18)	1 (5)				
NE	0	0	0	2 (7)	0	2 (13)	0	2 (9)				
Missing data	0	0	0	2 (7)	1 (7)	1 (6)	1 (5)	1 (5)				
Intracranial disease control	13 (93)	7 (88)	6 (100)	22 (73)	10 (71)	12 (75)	17 (77)	18 (82)				
Intracranial DCR (95% CI), % ^{a,b}	93 (66-100)	88 (47-100)	100 (54-100)	73 (54-88)	71 (42-92)	75 (48-93)	77 (55-92)	82 (60-95)				
Intracranial DOR, median (95% CI), mo ^{c,d}	9.5 (3.6-NE)	7.1 (3.6-NE)	9.5 (NE-NE)	4.4 (2.9-10.2)	4.4 (2.9-NE)	5.6 (2.9-NE)	4.6 (2.9-NE)	6.8 (2.9-NE)				
Time to intracranial progression, median (range), mo	NA	2.8 (1.3-10.9)	NE (NE-NE)	NA	2.6 (1.2-6.9)	5.6 (0.6-14.0)	2.7 (1.2-10.9)	5.6 (0.6-14.0)				
Time since prior brain radiotherapy, median (range), mo ^e	NA	9.2 (7.2-23.9)	NA	NA	0.9 (0.6-0.9)	NA	7.2 (0.6-23.9)	NA				

Abbreviations: BM, brain metastasis; CR, complete response; DCR, disease control rate; DOR, duration of response; NA, not applicable; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan.

^a Denominator for percentage is the number of patients in the full analysis set who had at least 1 target lesion at baseline, per blinded independent central review.

^b Based on Clopper-Pearson method for single proportion.

^c Calculated as time from first response in brain until progression in brain.

^d Based on Kaplan-Meier analysis and computed with the Brookmeyer-Crowley method.

^e For patients with confirmed best overall response in brain (CR, PR).

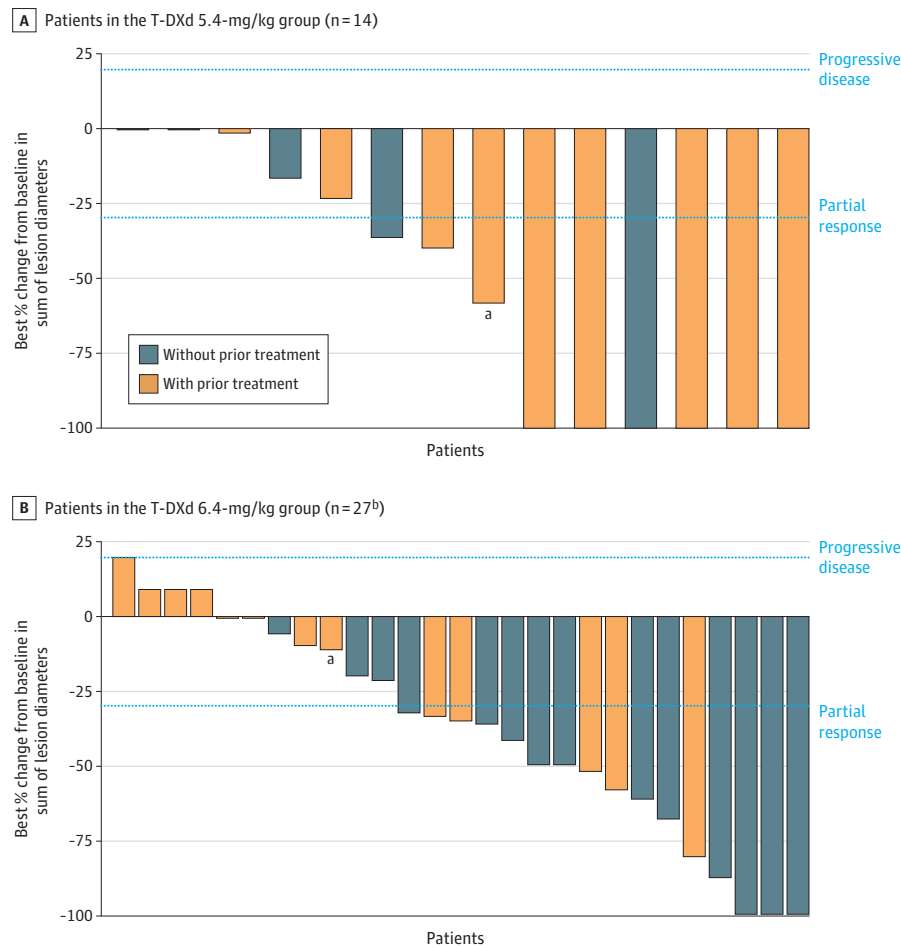
PR) with and without prior brain metastasis treatment, respectively. Intracranial DOR in both dose groups was comparable regardless of prior brain metastasis treatment (6.8 [95% CI, 2.9-NE] months vs 4.6 [95% CI, 2.9-NE] months) (Table 3).

Safety

In the T-DXd 5.4-mg/kg dose group, median (range) treatment duration was 5.8 (0.7-14.0) months in patients with baseline brain metastases and 8.3 (0.7-20.8) months in those without; in the T-DXd 6.4-mg/kg dose group, median (range) treatment duration was 5.6 (0.7-22.6) months and 8.5 (0.7-33.8) months, respectively. The overall safety profile of T-DXd in both treatment groups was generally manageable, consistent with the known T-DXd safety profile. Drug-related TEAE rates were generally lower with the T-DXd 5.4-mg/kg dose than the 6.4-mg/kg dose, regardless of brain metastasis status, particularly for drug-related TEAEs associated with drug discontinuation (5 [16%] and 9 [13%] for patients with and without brain metastases, respectively, compared with 12 [22%] and 22 [25%] for patients with and without brain metastases, respectively) and drug interruption (7 [23%] and 20 [29%] for patients with and without brain metastases, respectively, compared with 17 [31%] and 38 [44%] for patients with and without brain metastases, respectively) (Table 4).

The most common ($\geq 5\%$ in either cohort) grade 3 or higher TEAEs in patients with brain metastases were neutropenia, vomiting, decreased neutrophil count, and hypokalemia in the T-DXd 5.4-mg/kg dose group and decreased neutrophil count, anemia, and nausea in the T-DXd 6.4-mg/kg dose group (eTable 1 in Supplement 2). Grade 3 or higher CNS-related TEAEs were more frequent in

Figure. Best Overall Response in Patients With Measurable Brain Metastases



patients with brain metastases than those without (eTable 2 in Supplement 2). Adjudicated drug-related interstitial lung disease occurred in 16% (5 of 31) and 11% (8 of 70) of patients with and without brain metastases in the T-DXd 5.4-mg/kg dose group and in 20% (11 of 54) and 32% (28 of 87) of patients with and without brain metastases in the T-DXd 6.4-mg/kg dose group; most events were grade 1 or 2 (eTable 3 in Supplement 2).

Discussion

This secondary analysis of the DESTINY-Lung01 and DESTINY-Lung02 trials showed the effectiveness of T-DXd monotherapy in patients with previously treated *ERBB2*-mutant metastatic NSCLC, regardless of whether brain metastases were present at baseline. Additionally, T-DXd demonstrated intracranial effectiveness among patients with baseline brain metastases and reduced brain metastasis size in more than 78% of patients (per best overall response in measurable brain metastases). Intracranial effectiveness with T-DXd was similar in patients with and without prior brain metastasis treatment, suggesting that the intracranial responses observed were more likely due to T-DXd treatment rather than a residual effect of prior treatment. In patients with measurable brain metastases at baseline, the intracranial ORRs and disease control rates observed in our study provide encouraging evidence of T-DXd intracranial efficacy.

Patients in the T-DXd 5.4-mg/kg dose group showed no evidence of a lower level of intracranial response compared with those in the T-DXd 6.4-mg/kg dose group. Intracranial DOR was similar in patients with untreated baseline brain metastases vs previously treated brain metastases (6.8 months vs 4.6 months); however, due to the small sample size of the analysis, findings should be interpreted with caution. Given the longer time since previous brain radiotherapy in the T-DXd 5.4-mg/kg dose group, the intracranial responses in this group are more likely attributable to T-DXd treatment than delayed responses to the earlier radiotherapy.

The intracranial effectiveness of T-DXd in our study is comparable to findings from TROPION-Lung05 trial in which datopotamab deruxtecan, a TROP2 (trophoblastic cell surface antigen 2)-directed ADC, showed an intracranial ORR of 22% in patients with metastatic NSCLC with actionable genomic alterations.¹⁸ Similarly, in the HERTHENA-Lung01 trial, patritumab deruxtecan, an ERBB3-directed ADC with the same payload as T-DXd, demonstrated a confirmed CNS ORR of

Table 4. Overall Safety Summary

	Patients, No. (%)		T-DXd 6.4-mg/kg dose group pooled from DESTINY-Lung01 and DESTINY-Lung02 trials (n = 141)	
	T-DXd 5.4-mg/kg dose group in DESTINY-Lung02 trial (n = 102)		With BMs (n = 54)	Without BMs (n = 87)
	With BMs (n = 31)	Without BMs (n = 70)		
Treatment duration, median (range), mo	5.8 (0.7-14.0)	8.3 (0.7-20.8)	5.6 (0.7-22.6)	8.5 (0.7-33.8)
Any-grade TEAEs	31 (100)	70 (100)	54 (100)	87 (100)
Drug-related	28 (90)	69 (99)	54 (100)	84 (97)
Grade ≥3 TEAEs	20 (65)	33 (47)	41 (76)	55 (63)
Drug-related	12 (39)	27 (39)	32 (60)	39 (45)
Serious TEAEs	15 (48)	22 (31)	25 (46)	34 (39)
Drug-related	6 (19)	8 (11)	16 (30)	14 (16)
TEAEs associated with drug discontinuation	5 (16)	10 (14)	16 (30)	32 (37)
Drug-related	5 (16)	9 (13)	12 (22)	22 (25)
TEAEs associated with drug interruption	13 (42)	32 (46)	27 (50)	50 (57)
Drug-related	7 (23)	20 (29)	17 (31)	38 (44)
TEAEs associated with dose reduction	3 (10)	15 (21)	22 (41)	28 (32)
Drug-related	3 (10)	14 (20)	21 (39)	28 (32)
TEAEs associated with an outcome of death	2 (6)	4 (6)	6 (11)	9 (10)
Drug-related	1 (3)	0	1 (2)	1 (1)

Abbreviations: BM, brain metastasis; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

33% (10 of 30) in patients with nonirradiated baseline brain metastases and epidermal growth factor receptor-mutated NSCLC.¹⁹ Evidence of CNS penetration and intracranial activity by T-DXd, as observed in our study, may be bolstered by results from breast cancer trials such as ROSET-BM, DEBBRAH, TUXEDO-1, DESTINY-Breast07, and DESTINY-Breast12, and a pooled analysis of the DESTINY-Breast01/02/03 trials, in which T-DXd showed robust intracranial efficacy.²⁰⁻²⁷

On a systemic level, DOR, PFS, and OS were prolonged in patients without brain metastases as expected given the worst estimated outcome historically reported in patients with brain metastases.^{3,4} Although cross-trial comparisons should be interpreted with caution, in our study, T-DXd demonstrated improved systemic confirmed ORR compared with small-molecule TKIs such as pyrotinib, which showed an ORR of 25% in patients who had *ERBB2*-mutant NSCLC with brain metastases.²⁸ Our findings are also comparable with newer TKIs in development such as BAY 2927088 (which has shown robust systemic efficacy in patients with *ERBB2*-mutant NSCLC; trials evaluating intracranial efficacy are ongoing) and zongertinib (which has shown an intracranial ORR of 33% [9 of 27] in patients with *ERBB2*-mutant metastatic NSCLC).²⁹⁻³¹

In both dose groups, the safety profile of T-DXd was generally manageable in patients with and without brain metastases at baseline, favoring the T-DXd 5.4-mg/kg dose, and consistent with the established safety profile of T-DXd.²³ Patients with and without brain metastases exhibited comparable safety outcomes overall, although there was a tendency for occurrence of grade 3 or higher TEAEs in patients with vs without brain metastases, in contrast to results from breast cancer trials in which similar rates of grade 3 or higher TEAEs were reported in patients with and without brain metastases.^{23,26} Moreover, higher rates of grade 3 or higher CNS-related TEAEs were reported among patients with brain metastases compared with those without. Further analyses are needed to determine the underlying factors contributing to the increased rates of grade 3 or higher TEAEs observed in patients with baseline brain metastases.

In contrast to other studies conducted in patients with *ERBB2*-mutant NSCLC, all participants in the DESTINY-Lung01 and DESTINY-Lung02 trials underwent CNS screening (by MRI or CT) to provide a more accurate incidence of brain metastases at baseline, with 47% and 76% of patients with brain metastases in the T-DXd 5.4-mg/kg and 6.4-mg/kg dose groups, respectively, undergoing MRI scans, the preferred method of brain metastasis screening.³²⁻³⁴ The high number of patients identified as having baseline brain metastases in each dose group supports the high burden of CNS metastases in patients with *ERBB2*-mutant metastatic NSCLC, as described previously.³⁻⁵

The current standard of care for brain metastases—WBRT alone or combinations of surgical resection and/or stereotactic radiosurgery with or without WBRT—has shown poor intracranial control for patients with *ERBB2*-mutant NSCLC³; in our study, T-DXd demonstrated both systemic and intracranial effectiveness. The intracranial effectiveness of T-DXd observed in our study may be attributable to robust systemic efficacy of T-DXd coupled with the nature of brain metastases and ADCs.^{35,36} Although monoclonal antibodies are believed to not cross the blood-brain barrier, imaging of a radioisotope form of trastuzumab, [⁶⁴Cu] DOTA-trastuzumab, revealed localization in brain metastases of patients with *ERBB2*-positive metastatic breast cancer. Moreover, in brain metastases, the blood-brain barrier is disrupted and replaced by a blood-tumor barrier with higher endothelial fenestration, potentially allowing larger molecules to penetrate. As a homogeneous ADC, T-DXd has consistent conjugation patterns of cytotoxic molecules, populated in a drug to antibody ratio of approximately 8 molecules of payload per antibody.^{10,37} Compared with heterogeneous ADCs, homogeneous ADCs, such as T-DXd, have been shown to provide improved antitumor activity in the brain, dependent on homogeneity and payload loading rate.³⁵

Limitations

Study limitations include the exploratory, retrospective design; small sample size; and lack of a comparator arm, which may limit interpretation. Additionally, PFS was not assessed in patients based on prior brain radiotherapy status. The exclusion of patients with untreated and symptomatic brain metastases requiring corticosteroids or anticonvulsants may restrict the generalizability of our

findings to patients with less aggressive CNS disease. An additional study limitation was the lack of serial brain imaging in patients without baseline brain metastases, which may have resulted in an underestimation of intracranial progression, and the heterogeneity of prior local brain metastasis treatments complicates the attribution of benefits exclusively to T-DXd. Nevertheless, the clinically meaningful intracranial activity observed with T-DXd is encouraging, and further analyses are warranted to maximize intracranial efficacy.

Conclusions

In this exploratory post hoc secondary analysis of the DESTINY-Lung01 and DESTINY-Lung02 clinical trials, T-DXd at the approved dose of 5.4 mg/kg showed activity in patients with previously treated *ERBB2*-mutant metastatic NSCLC with or without brain metastases. This finding supports the use of T-DXd in these patients.

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SUPPLEMENT 1.

Trial Protocols

SUPPLEMENT 2.

eTable 1. Most Common ($\geq 5\%$ in Either Dose Group) Grade ≥ 3 TEAEs

eTable 2. Grade ≥ 3 CNS-Related TEAEs

eTable 3. Adjudicated Drug-Related ILD

eFigure 1. Exploratory Pooled Analysis Schema

eFigure 2. Progression-Free Survival of Patients With or Without Baseline BMs

eFigure 3. Progression-Free Survival of Patients With Measurable and Nonmeasurable Baseline BMs

eFigure 4. Intracranial Response to T-DXd. Brain Scans of a Patient in the T-DXd 5.4-mg/kg Group Who Achieved Complete Response as Assessed by BICR

eReferences

SUPPLEMENT 3.

Data Sharing Statement