Trastuzumab Deruxtecan Monotherapy in Pretreated HER2-overexpressing Nonsquamous Non-small Cell Lung Cancer: DESTINY-Lung03 Part 1

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Background

- HER2 overexpression (IHC 3+/2+), identified in 3–20% of NSCLC tumors,[1–4] is associated with a poor prognosis;[5–7] currently, there are limited HER2-directed treatment options for patients with HER2-OE NSCLC
- T-DXd (5.4 mg/kg), a HER2-directed antibody-drug conjugate, is approved in several regions including the US and EU for patients with *HER2* (*ERBB2*)-mutant unresectable or metastatic NSCLC who have received prior therapy[8–10]
- T-DXd (5.4 mg/kg) is also approved in the US for patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have progressed after prior treatment and have no alternative therapies[8]
  - This approval was supported by results from DESTINY-Lung01 cohort 1a; ORRs of 34.1% (overall) and 52.9% (IHC 3+ subgroup) were reported in patients with HER2-OE NSCLC treated with T-DXd[8,11,12]
- DESTINY-Lung03 (NCT04686305) is evaluating the safety and efficacy of T-DXd-based regimens in patients with HER2-OE NSCLC
  - Here, we report efficacy and safety data for Part 1 T-DXd monotherapy (5.4 mg/kg; arm 1D) in patients with HER2-OE NSCLC who had disease progression following prior therapy

HER2, human epidermal growth factor receptor 2; HER2-OE, HER2-overexpressing; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; ORR, objective response rate; T-DXd, trastuzumab deruxtecan

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DESTINY-Lung03: Phase 1b, multicenter, open-label, dose-escalation study of T-DXd in HER2-OE NSCLC

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Patient population

- Aged ≥18 years
- Centrally assessed HER2-OE (IHC 3+/2+)* unresectable, locally advanced or metastatic nonsquamous NSCLC
- Measurable disease per RECIST v1.1
- WHO/ECOG performance status 0–1
- Patients in Part 1 had one or two prior lines of therapy; those with therapy-targetable alterations must have had prior appropriate targeted therapy

Part 1: dose escalation† (enrollment complete)

Arm 1A: T-DXd + durvalumab + cisplatin
Arm 1B: T-DXd + durvalumab + carboplatin

Part 1: T-DXd monotherapy (enrollment complete)

Arm 1D: T-DXd 5.4 mg/kg IV Q3W (N=36)

Part 3: dose confirmation and expansion (currently recruiting)

T-DXd + volrustomig ± carboplatin

Part 4: safety run-in and expansion (currently recruiting)

T-DXd + rilvegostomig ± carboplatin

Key endpoints: T-DXd monotherapy (arm 1D)

Secondary:

- ORR
- DOR
- DCR
- PFS

(Investigator assessed)

- OS
- Safety and tolerability

Exploratory:

- Efficacy outcomes by:
  - HER2 IHC status
  - Prior EGFR TKI exposure‡

Data cutoff for the Part 1 T-DXd monotherapy arm results was April 1, 2024.§ Part 2 of the study was not initiated owing to a strategic decision by the study sponsor.
*HER2 overexpression was defined as ≥25% of tumor cells with IHC 3+ or 2+ by central testing using the Dako HER2-low IHC assay; †arm 1C: T-DXd + durvalumab + pemetrexed treatment was planned but not initiated; ‡patients had HER2-OE (IHC 3+/2+) NSCLC; §the corresponding abstract reported data from the October 23, 2023 data cutoff
DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HER2-OE, HER2-overexpressing; IHC, immunohistochemistry; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; WHO, World Health Organization

Patient disposition

	Part 1: T-DXd monotherapy (arm 1D)
Patients assigned to treatment, n	36
Patients who received treatment, n (%)	36 (100)
Patients with treatment ongoing at data cutoff, n (%)	3 (8.3)
Discontinued treatment, n (%)	33 (91.7)
Objective disease progression*	16 (44.4)
Subjective disease progression	11 (30.6)
Adverse event	3 (8.3)
Patient decision	1 (2.8)
Other	2 (5.6)
Median duration of T-DXd treatment, months (range)	7.2 (0.7–23.3)
Median duration of follow up, months (range)	14.9 (0.7–25.3)

*RECIST-defined disease progression
RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan

Patient demographics and clinical characteristics

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Part 1: T-DXd monotherapy (arm 1D)		N=36
Median age, years (range)		66.5 (47–80)
Sex, n (%)	Male	14 (38.9)
	Female	22 (61.1)
Region, n (%)	Europe	3 (8.3)
	Asia	32 (88.9)
	US / South America	1 (2.8)
Smoking history, n (%)	Current	3 (8.3)
	Former	10 (27.8)
	Never	23 (63.9)
Stage of disease, n (%)	III	3 (8.3)
	IV	31 (86.1)
	Missing	2 (5.6)
ECOG performance status, n (%)	0	12 (33.3)
	1	24 (66.7)

Part 1: T-DXd monotherapy (arm 1D)		N=36
Brain / CNS metastases present at baseline, n (%)		11 (30.6)
Centrally confirmed HER2 IHC status, n (%)	IHC 3+	16 (44.4)
	IHC 2+	20 (55.6)
PD-L1 status, n (%)	<1%	12 (33.3)
	1–49%	9 (25.0)
	≥50%	3 (8.3)
	Unknown	12 (33.3)
Prior therapies, n (%)	Targeted therapy	21 (58.3)
	EGFR TKI	19 (52.8)
	Platinum chemotherapy	14 (38.9)
	Immunotherapy	8 (22.2)
	Taxane chemotherapy	3 (8.3)

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PD-L1, programmed cell death ligand 1; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor

Response outcomes: ORR, DOR, and DCR

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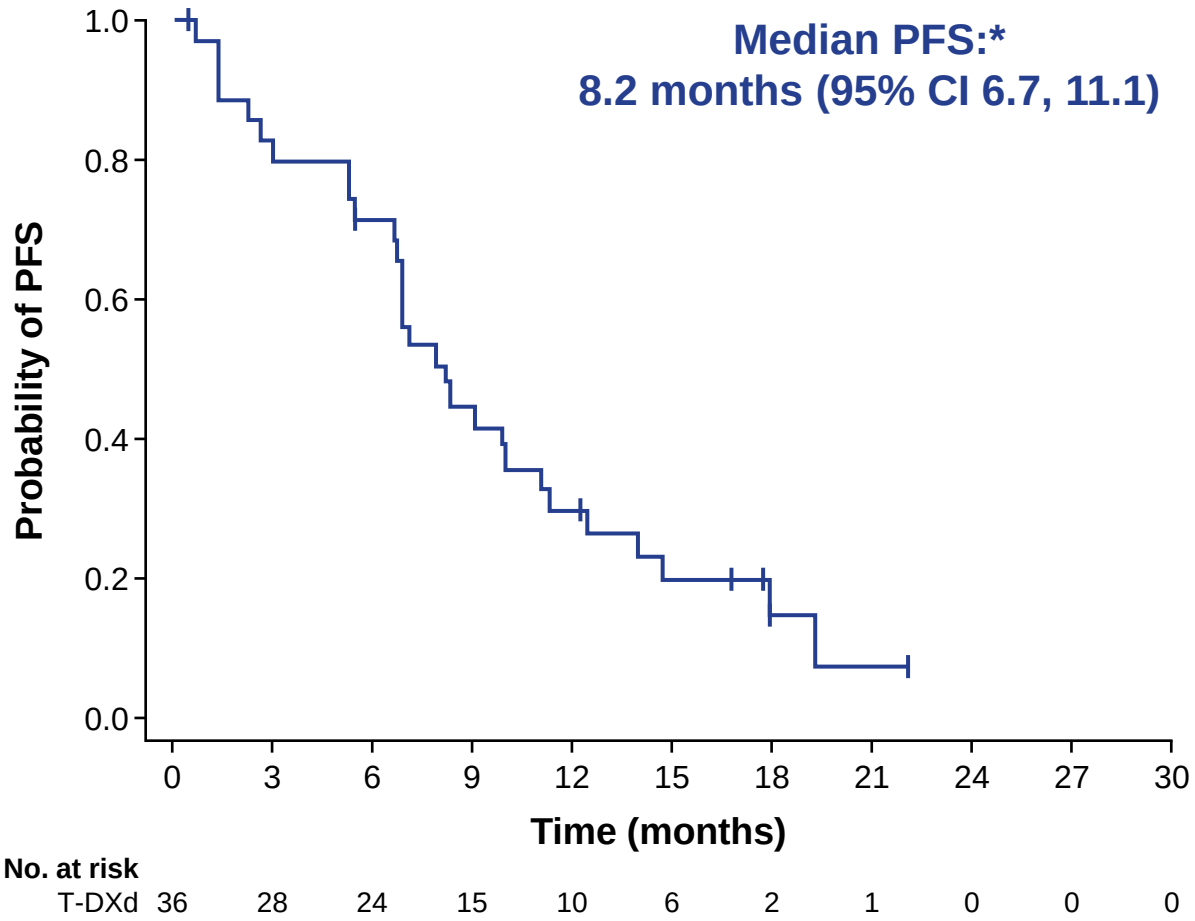
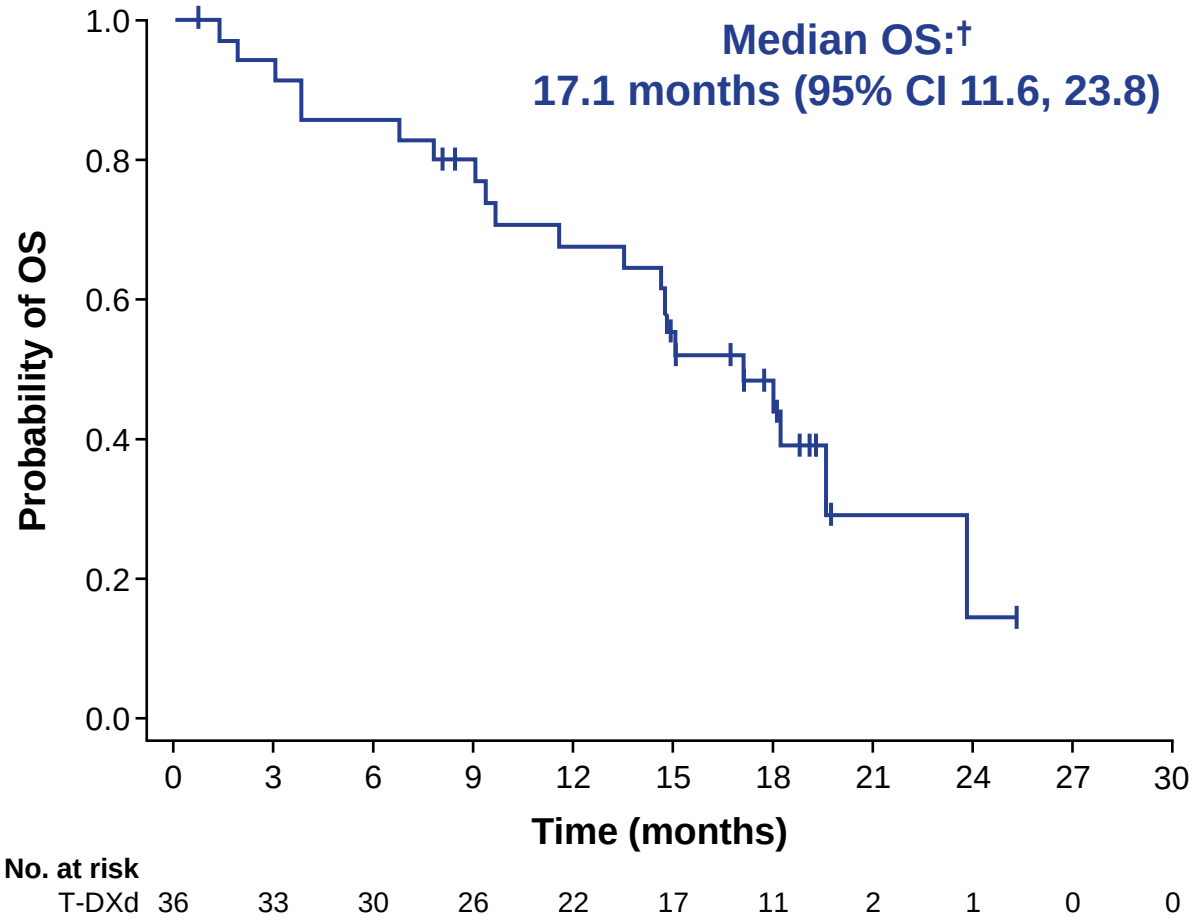
Part 1: T-DXd monotherapy (arm 1D)	N=36
Confirmed ORR, % (n)*	**44.4 (16)**
95% CI	**27.9, 61.9**
Best objective response, n (%)*	
Complete response	0
Partial response	16 (44.4)
Stable disease ≥5 weeks	15 (41.7)
Disease progression†	4 (11.1)
Not evaluable	1 (2.8)
DCR at 12 weeks, % (95% CI)*	**77.8 (60.9, 89.9)**
Median DOR, months (95% CI)*	**11.0 (5.5, 16.7)**

Confirmed ORR, defined as the best objective response of complete or partial responses, required confirmation after at least 4 weeks. 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. 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. Patients without progression or who had died were censored at their progression-free survival censoring date.
*Investigator assessed per RECIST v1.1; †including RECIST-defined disease progression or death
CI, confidence interval; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumours; RECIST v1.1, RECIST version 1.1; T-DXd, trastuzumab deruxtecan

Survival outcomes: PFS and OS





Symbols indicate a censored observation; PFS was assessed by investigator using RECIST v1.1. *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 v1.1 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); †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

CI, confidence interval; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan

Best percentage change from baseline in target lesion size

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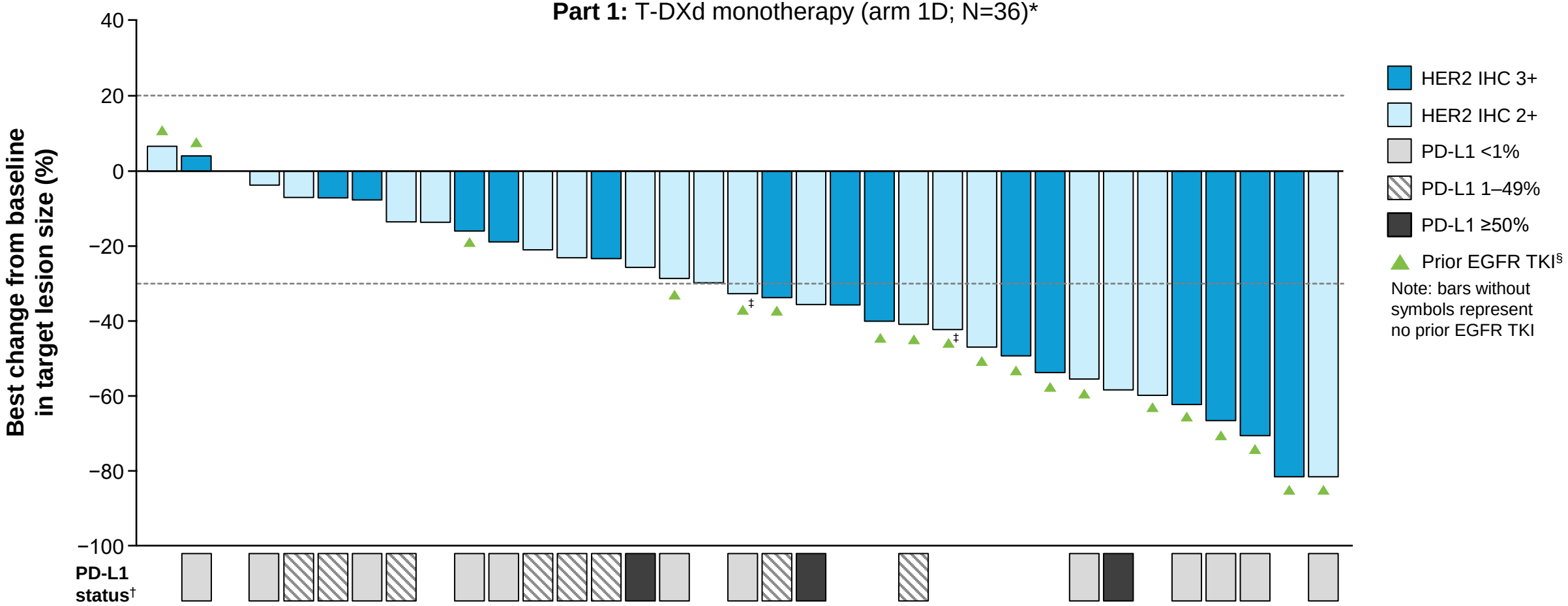
Part 1: T-DXd monotherapy (arm 1D; N=36)*



Investigator assessed per RECIST v1.1. Best percentage change is the maximum reduction or minimum increase from baseline in the target lesion size; the dashed lines at −30% and 20% change in target lesion size indicate the thresholds for partial response and progressive disease, respectively. The study was not designed/powered to compare efficacy between subgroups.
*One patient was not evaluable; †patients with unknown PD-L1 status (n=12) are represented by white spaces; ‡unconfirmed response; §patients had HER2-OE (IHC 3+/2+) NSCLC
EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HER2-OE, HER2-overexpressing; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor

Exploratory analyses: efficacy outcomes by HER2 IHC status and prior EGFR TKI exposure

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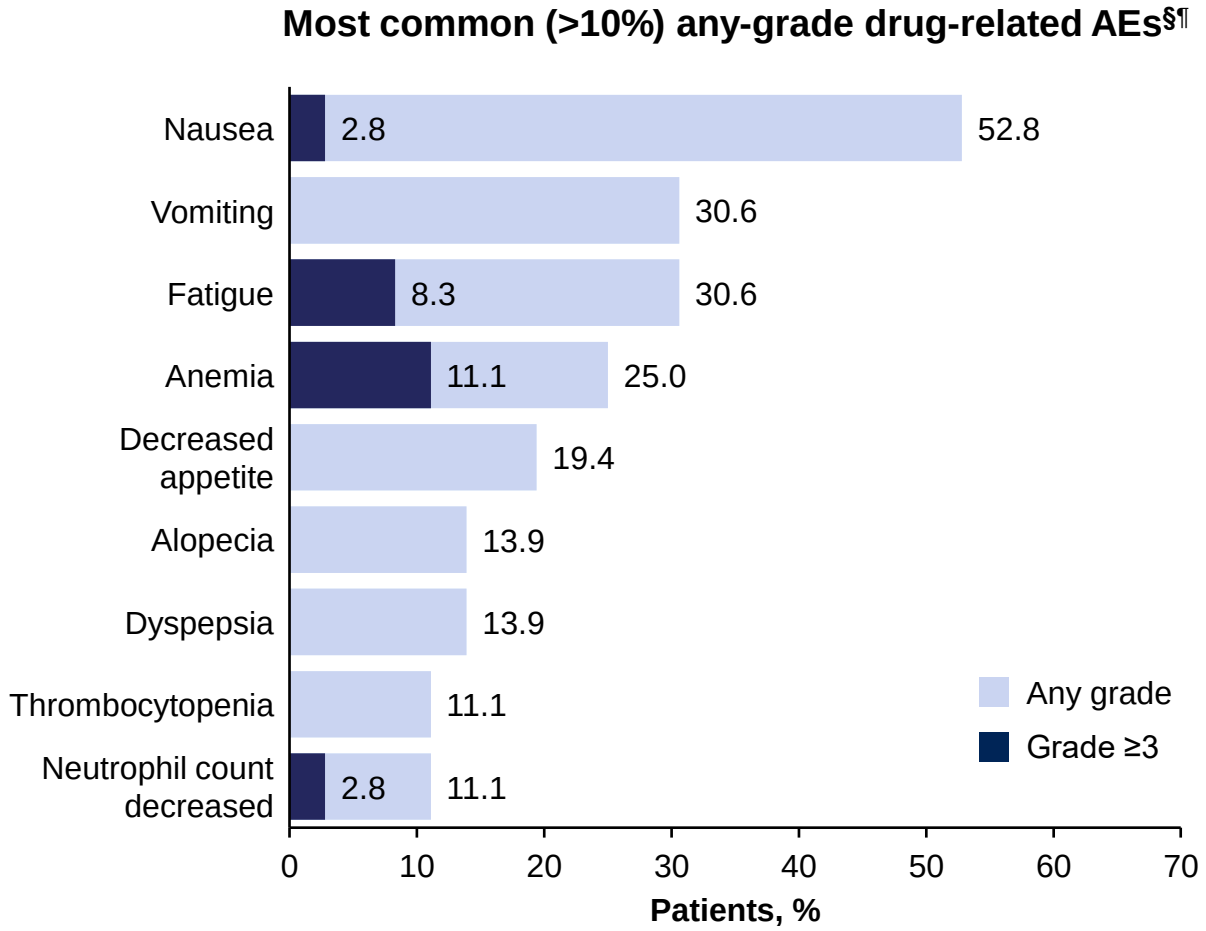
Part 1: T-DXd monotherapy (arm 1D)	HER2 IHC 3+ (n=16)	HER2 IHC 2+ (n=20)	Prior EGFR TKI (n=19)**	No prior EGFR TKI (n=17)**
Confirmed ORR, % (n)*† 95% CI	56.3 (9) 29.9, 80.3	35.0 (7) 15.4, 59.2	68.4 (13) 43.5, 87.4	17.6 (3) 3.8, 43.4
DCR at 12 weeks, % (95% CI)*‡	81.3 (54.4, 96.0)	75.0 (50.9, 91.3)	84.2 (60.4, 96.6)	70.6 (44.0, 89.7)
Median DOR, months (95% CI)*§	12.5 (5.5, NE)	6.6 (4.5, 11.0)	11.7 (5.5, NE)	4.6 (4.5, NE)
Median PFS, months (95% CI)*¶	6.9 (5.3, 17.9)	8.2 (5.4, 10.0)	8.2 (6.7, 19.3)	7.1 (1.4, 10.0)
Median OS, months (95% CI)‖	16.4 (6.8, NE)	17.1 (9.4, 23.8)	19.6 (13.5, NE)	14.7 (3.9, 18.0)

The study was not designed/powered to compare efficacy between subgroups. *Investigator assessed per RECIST v1.1; †confirmed ORR, defined as the best objective response of complete or partial responses, required confirmation after at least 4 weeks; ‡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; §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; ¶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 v1.1 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); ‖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; **patients had HER2-OE (IHC 3+/2+) NSCLC
CI, confidence interval; DCR, disease control rate; DOR, duration of response; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HER2-OE, HER2-overexpressing; IHC, immunohistochemistry; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; TKI, tyrosine kinase inhibitor

Safety summary

Part 1: T-DXd monotherapy (arm 1D) n (%) of patients		N=36
Drug-related AEs		34 (94.4)
Drug-related Grade ≥3 AEs		15 (41.7)
Drug-related serious AEs		6 (16.7)
Drug-related AEs leading to discontinuations		3 (8.3)
Drug-related AEs leading to dose reductions		7 (19.4)
Drug-related AEs leading to dose interruptions		5 (13.9)
Drug-related AEs with outcome of death		1 (2.8)*
Adjudicated drug-related ILD/pneumonitis†	Any grade	2 (5.6)
	Grade 2	2 (5.6)
Drug-related left ventricular dysfunction	Any grade	1 (2.8)‡
	Grade 2	1 (2.8)‡



Assessed by investigator (unless specified otherwise) in patients who received ≥1 dose of T-DXd. *Neutropenic colitis; †assessed by the ILD adjudication committee; ‡ejection fraction decreased; §graded according to CTCAE version 5; ¶individual preferred term; patients with multiple events in the same preferred term are counted only once in that preferred term and patients with events in more than one preferred term are counted once in each of those preferred terms

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan

Conclusions

- **Results from DESTINY-Lung03 Part 1 confirm the clinical benefit of T-DXd monotherapy (5.4 mg/kg; arm 1D) in pretreated HER2-OE (IHC 3+/2+) metastatic NSCLC (ORR: 44.4%; median PFS: 8.2 months; median OS: 17.1 months), building on DESTINY-Lung01 cohort 1a results[1]**
  - Exploratory analyses showed promising activity in patients with HER2-OE (IHC 3+/2+) NSCLC, including those with and without prior EGFR TKI exposure, as follows:
    - HER2 IHC 3+ (ORR: 56.3%; median PFS: 6.9 months; median OS: 16.4 months) and HER2 IHC 2+ (ORR: 35.0%; median PFS: 8.2 months; median OS: 17.1 months) subgroups
    - Prior EGFR TKI (ORR: 68.4%; median PFS: 8.2 months; median OS: 19.6 months) and no prior EGFR TKI (ORR: 17.6%; median PFS: 7.1 months; median OS: 14.7 months) subgroups
- These data suggest that T-DXd is associated with improved outcomes over current 2L SOC for metastatic HER2-OE NSCLC[2]
- **No new safety signals were identified, and the safety profile was consistent with the known profile of T-DXd**
- DESTINY-Lung03 is ongoing; Parts 3 and 4 are assessing T-DXd-based regimens in patients with previously untreated HER2-OE metastatic NSCLC

These results reinforce HER2 expression as an actionable biomarker in NSCLC and highlight the need for HER2 IHC testing in routine NSCLC diagnostic work up

2L, second-line; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HER2-OE, HER2-overexpressing; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SOC, standard of care; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor

1. Smit EF, et al. *Lancet Oncol*. 2024;25:439–454; 2. Garon EB, et al. *Lancet*. 2014;384:665–673

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Plain language summary

Why did we perform this research?

Some people with non-small cell lung cancer (NSCLC) have higher-than-normal levels of a protein called human epidermal growth factor receptor 2 (HER2); this is known as HER2-expressing NSCLC and is often associated with limited response to treatment.[1] Trastuzumab deruxtecan (T-DXd), a HER2-directed antibody-drug conjugate that kills HER2-altered cancer cells,[2,3] is approved as a treatment for people with HER2-expressing solid tumors (also known as HER2-positive or immunohistochemistry [IHC] 3+) that cannot be completely removed by surgery (unresectable), or have spread to other parts of the body (metastatic), and who have received prior treatment or have no alternative treatment options available.[4] Given there are limited HER2-directed treatment options available for people with HER2-expressing NSCLC, DESTINY-Lung03 is an ongoing clinical study designed to assess the use of T-DXd alone and in combination with other anticancer drugs for the treatment of people with HER2-expressing advanced (has spread to nearby tissues) or metastatic NSCLC.

How did we perform this research?

In this analysis, we evaluated how well T-DXd alone works as a treatment for people with HER2-expressing (IHC 3+ and IHC 2+) advanced or metastatic NSCLC who had received one or two prior anticancer treatments, and what side effects these people experienced with T-DXd treatment.

What were the findings of this research?

Overall, 16 out of 36 participants had a response to T-DXd (ie a reduction in the size or number of tumors): nine out of 16 participants with IHC 3+ tumors had a response. Responses were also observed in participants who had received a prior epidermal growth factor receptor tyrosine kinase inhibitor (a type of anticancer drug). The length of time that T-DXd stopped the cancer from growing or spreading in half of the participants with a response (median duration of response) was 11.0 months in all participants, and 12.5 months in those with IHC 3+ tumors. Side effects associated with T-DXd treatment that were experienced by at least one-quarter of participants included nausea (52.8%), vomiting (30.6%), fatigue (30.6%), and decreased red blood cells (known as anemia; 25.0%).

What are the implications of this research?

These results support the use of T-DXd as a treatment for people with HER2-expressing (IHC 3+) advanced or metastatic NSCLC who have received prior anticancer treatment.

Where can I access more information?

For more information about DESTINY-Lung03, please visit https://clinicaltrials.gov/study/NCT04686305. Please also reach out to Dr. Yang at chihyang@ntu.edu.tw

1. Ren S, et al. *ESMO Open*. 2022;7:100395; 2. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173–185; 3. Ogitani Y, et al. *Clin Cancer Res*. 2016;22:5097–5108; 4. Enhertu (fam-trastuzumab deruxtecan-nxki): highlights of prescribing information. 2024. Available from: www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s028lbl.pdf (Accessed August 5, 2024)