IASLC 2023 World Conference on Lung Cancer
SEPTEMBER 9-12, 2023 | SINGAPORE

Trastuzumab Deruxtecan in Patients With *HER2*-Mutant Metastatic Non–Small Cell Lung Cancer: Primary Results of DESTINY-Lung02

Pasi A. Jänne,[a] Yasushi Goto, Toshio Kubo, Kiichiro Ninomiya, Sang-We Kim, David Planchard, Myung-Ju Ahn, Egbert F. Smit, Adrianus Johannes de Langen, Maurice Pérol, Elvire Pons-Tostivint, Silvia Novello, Hidetoshi Hayashi, Junichi Shimizu, Dong-Wan Kim, Kaline Pereira, Fu-Chih Cheng, Ayumi Taguchi, Yingkai Cheng, and Koichi Goto

On behalf of the DESTINY-Lung02 investigators

[a]Dana-Farber Cancer Institute, Boston, MA, USA

DESTINY-Lung02

Blinded, randomized, multicenter, international, noncomparative, phase 2 trial (NCT04644237)

Background

- T-DXd 5.4 mg/kg and 6.4 mg/kg showed robust antitumor activity in multiple cancer types; however, T-DXd 5.4 mg/kg has not been evaluated in patients with previously treated *HER2*-mutant (*HER2*m) mNSCLC
- DESTINY-Lung02 assessed the efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg in patients with *HER2*m mNSCLC
  - In the interim analysis, T-DXd showed deep and durable responses and an acceptable and generally manageable safety profile[1]
- Herein, we report the **primary analysis results** of DESTINY-Lung02

Statistical considerations

- Statistical hypothesis testing for the primary analysis was performed by comparing the lower limit of the 95% Clopper-Pearson CI of confirmed ORR of a T-DXd dose with the benchmark ORR of 26.4% (upper limit of the ORR 95% CI in the ramucirumab plus docetaxel arm of the REVEL trial)[2]
- The study was not powered to statistically compare between arms

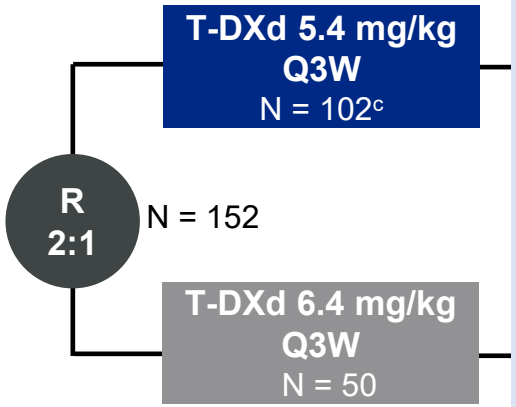
Key Eligibility Criteria[a]

- Metastatic *HER2*m[b] NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1

Stratification Factor:

- Prior anti–PD-(L)1 treatment

Study Design



Primary Endpoint

- Confirmed ORR by BICR

Secondary Endpoints

- Confirmed ORR by INV
- DoR by BICR and INV
- DCR by BICR and INV
- PFS by BICR and INV
- OS
- Safety

Patients and investigators were blinded to the dose level

Primary analysis data cutoff: 23 December 2022

BICR, blinded independent central review; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator assessment; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed death (ligand) 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan.
[a]Patients with stable baseline brain metastases (asymptomatic; not requiring corticosteroid or anticonvulsant treatment) were eligible. [b]Activating *HER2* mutation documented from an archival or fresh tumor tissue sample by certified local laboratory assessment. [c]1 patient randomly assigned to the T-DXd 5.4 mg/kg arm did not receive treatment as the patient discontinued due to COVID-19 before cycle 1 day 1.

1. Goto K et al. *Annals of Oncol*. 2022;33 (suppl_7): S808-S869 2. Garon EB et al. *Lancet*. 2014;384:665-73.

Baseline Characteristics and Efficacy Summary

Baseline Characteristics

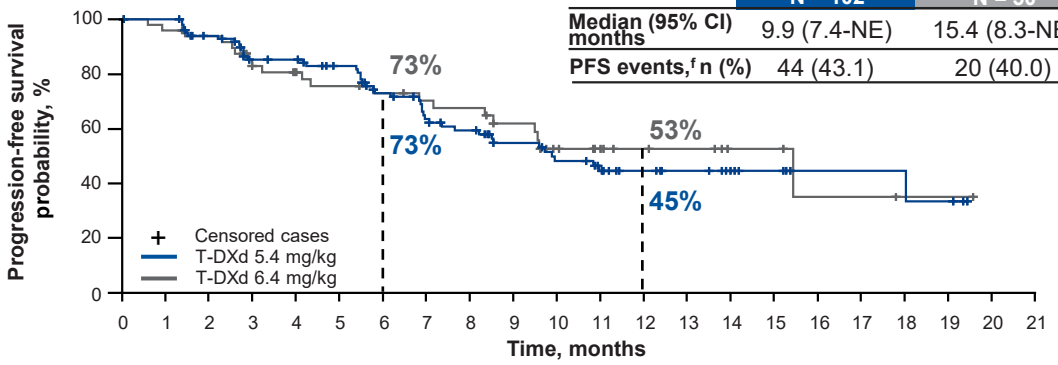
In the T-DXd 5.4 mg/kg and 6.4 mg/kg arms, respectively:

- **Median age** was 59.4 years (range, 31-84) and 61.3 years (range, 28-86)
- Most patients were **female** (63.7% and 68.0%), **from Asia** (61.8% and 60.0%), had **never smoked** (53.9% and 58.0%), and **received prior anti–PD-(L)1 therapy** (73.5% and 78.0%)
- *HER2* mutations were primarily in the **kinase domain** (97.1% and 100%)
- **Baseline CNS metastasis** was present in 34.3% and 44.0% of patients
- **Median prior lines of treatment** was 2 (range, 1-12) and 2 (range, 1-7)

Efficacy summary	T-DXd 5.4 mg/kg N = 102	T-DXd 6.4 mg/kg N = 50
Confirmed ORR,[a] n (%) [95% CI]	**50 (49.0)** [39.0-59.1]	**28 (56.0)** [41.3-70.0]
CR | PR	1 (1.0) | 49 (48.0)	2 (4.0) | 26 (52.0)
SD | PD	45 (44.1) | 4 (3.9)	18 (36.0) | 2 (4.0)
Non-evaluable[b]	3 (2.9)	2 (4.0)
DCR,[c] n (%) [95% CI]	95 (93.1) [86.4-97.2]	46 (92.0) [80.8-97.8]
Median DoR,[d,e] months (95% CI)	16.8 (6.4-NE)	NE (8.3-NE)
Median TTIR,[d] months (range)	1.8 (1.2-7.0)	1.6 (1.2-11.2)
Median follow-up, months (range)	11.5 (1.1-20.6)	11.8 (0.6-21.0)

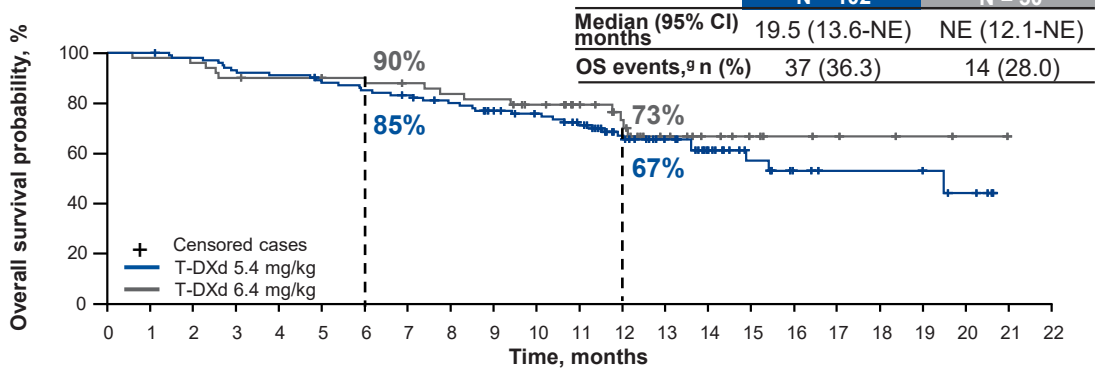
PFS

	T-DXd 5.4 mg/kg N = 102	T-DXd 6.4 mg/kg N = 50
Median (95% CI) months	9.9 (7.4-NE)	15.4 (8.3-NE)
PFS events,[f] n (%)	44 (43.1)	20 (40.0)



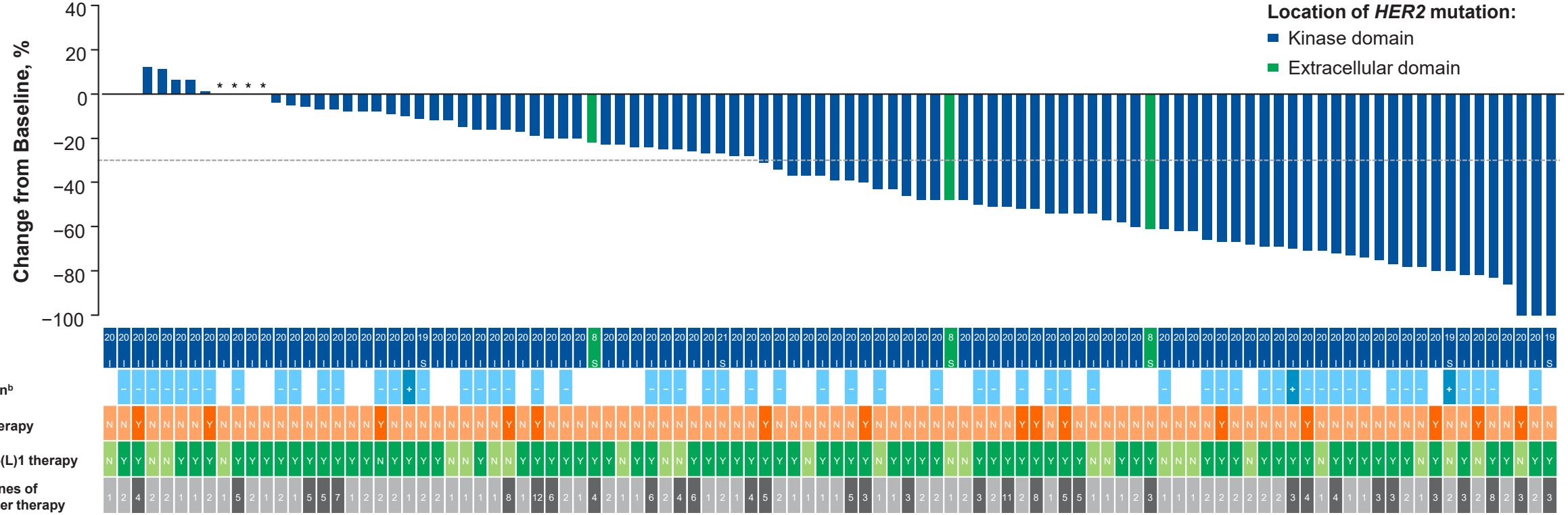
OS

	T-DXd 5.4 mg/kg N = 102	T-DXd 6.4 mg/kg N = 50
Median (95% CI) months	19.5 (13.6-NE)	NE (12.1-NE)
OS events,[g] n (%)	37 (36.3)	14 (28.0)



BICR, blinded independent central review; CNS, central nervous system; CR, complete response; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; NE, not estimable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease; T-DXd, trastuzumab deruxtecan; TTIR, time to initial response. [a]Proportion of patients with confirmed CR or PR assessed by BICR per RECIST v1.1. [b]3 patients were non-evaluable at 5.4 mg/kg (1 patient never received treatment due to COVID-19; 2 patients discontinued before first tumor assessment); 2 patients were non-evaluable at 6.4 mg/kg (discontinued due to adverse event before first tumor assessment). [c]Proportion of patients with confirmed CR, PR, or SD assessed by BICR. [d]Assessed by BICR. [e]60.0% and 75.0% of patients in the 5.4 mg/kg and 6.4 mg/kg arms were censored. [f]56.9% and 60.0% of patients in the 5.4 mg/kg and 6.4 mg/kg arms were censored. [g]63.7% and 72.0% of patients in the 5.4 mg/kg and 6.4 mg/kg arms were censored.

Best Percentage Change in Tumor Size by BICR With T-DXd 5.4 mg/kg (N = 102)

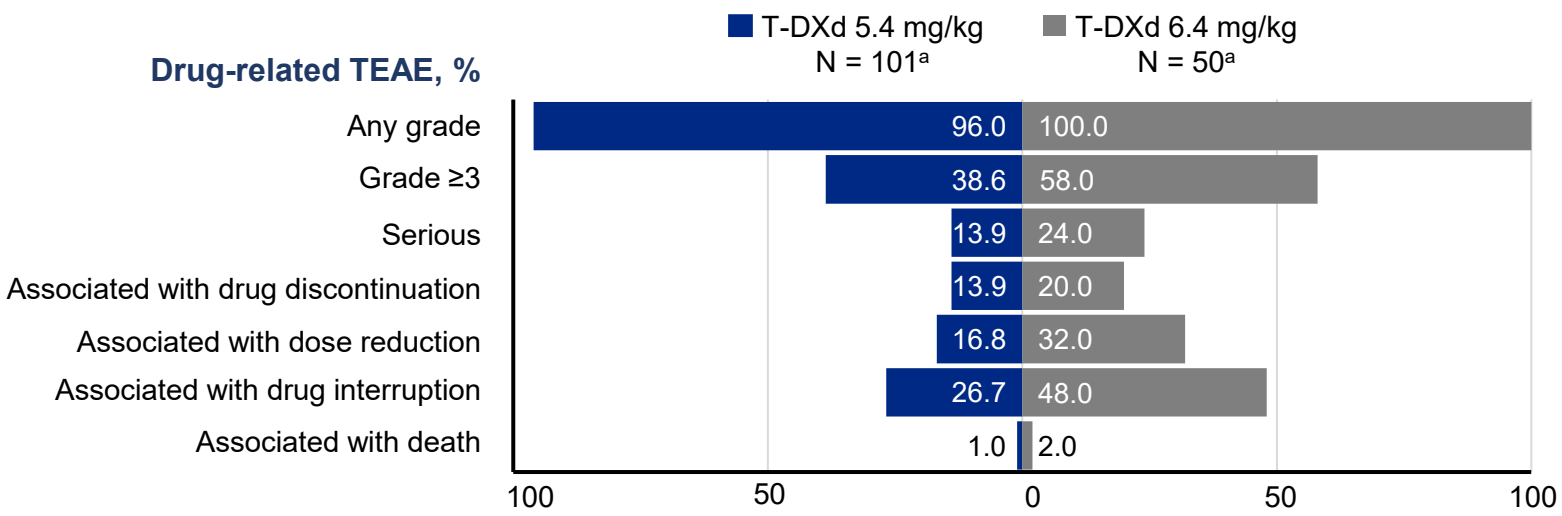


Responses were observed regardless of *HER2* mutation type, *HER2* amplification status, and number or type of prior therapies

BICR, blinded independent central review; I, insertion; HER2, human epidermal growth factor receptor 2; N, no; PD-(L)1, programmed death (ligand)1; S, substitution; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; Y, yes. The line at −30% indicates a partial response. *Indicates the patient had 0 best percentage change from baseline in the sum of diameters for all target lesions. Numbers in the *HER2* mutation row indicate in which exon the mutation occurred (8, 19, or 20). *HER2* amplification was only assessed in patients who received T-DXd 5.4 mg/kg. [a]Activating *HER2* mutation documented from an archival or fresh tumor tissue sample by certified local laboratory assessment. [b]*HER2* amplification status was evaluated using an exploratory Oncomine DX Target test copy number algorithm on NSCLC formalin-fixed paraffin-embedded tissue samples. Thermo Fisher Scientific and its affiliates are not endorsing, recommending, or promoting any use or application of Thermo Fisher Scientific products presented by third parties during this seminar. Information and materials presented or provided by third parties are provided as-is and without warranty of any kind, including regarding intellectual property rights and reported results. Parties presenting images, text and material represent they have the rights to do so.

Overall Safety Summary

Overall Safety



Adjudicated Drug-Related ILD

Adjudicated as drug-related ILD	T-DXd 5.4 mg/kg N = 101[a]	T-DXd 6.4 mg/kg N = 50[a]
Any grade, n (%)	**13 (12.9)**	**14 (28.0)**
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

- **Median treatment duration** was 7.7 months (range, 0.7-20.8) with T-DXd 5.4 mg/kg and 8.3 months (range, 0.7-20.3) with T-DXd 6.4 mg/kg
- The **most common any-grade TEAEs** in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms included **nausea** (67.3% and 82.0%), **neutropenia** (42.6% and 56.0%), and **fatigue** (44.6% and 50.0%)
- The **most common grade ≥3 TEAEs** in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms included **neutropenia** (18.8% and 36.0%) and **anemia** (10.9% and 16.0%)

ILD, interstitial lung disease; TEAE, treatment emergent adverse event; T-DXd, trastuzumab deruxtecan.
[a]The safety analysis set included all randomly assigned patients who received ≥1 dose of study drug.

Conclusions

- **T-DXd** demonstrated **deep and durable responses** at **both the 5.4 mg/kg and 6.4 mg/kg dose**
  - The lower limit of the ORR 95% CI of both doses exceeded the benchmark of 26.4%
  - Responses were consistent regardless of *HER2* mutation type, *HER2* amplification status, and prior systemic anticancer therapy

- The **safety profile** was **acceptable and generally manageable at both doses** and **favored the 5.4 mg/kg dose**
  - The observed safety profile was consistent with previous studies and no new safety signals were observed
  - Lower incidence of drug-related grade ≥3 TEAEs, serious TEAEs, and TEAEs associated with study drug discontinuations, dose reductions, and drug interruptions were observed with the 5.4 mg/kg dose
  - Adjudicated drug-related ILD rate was lower in the T-DXd 5.4 mg/kg arm than in the 6.4 mg/kg arm

Primary analysis results of DESTINY-Lung02 support the use of T-DXd 5.4 mg/kg for patients with previously treated *HER2*m NSCLC and reinforce T-DXd as the standard of care in this population

HER2, human epidermal growth factor receptor 2; HER2m, human epidermal growth factor receptor 2-mutant; ILD, interstitial lung disease; NSCLC, non–small cell lung cancer; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TEAEs, treatment-emergent adverse events.

Acknowledgements

We thank:

The patients, their families,
and caregivers for their participation

&

the study site staff for their contributions

This study was sponsored and designed by
Daiichi Sankyo in collaboration with AstraZeneca

Medical writing and editorial support was provided by
Caylin Bosch, PhD, and Cindy M. Rigby, PhD of ApotheCom
and was funded by Daiichi Sankyo

Accompanying Manuscript Published in the *Journal of Clinical Oncology*