



2026 World Conference on Lung Cancer



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First-line trastuzumab deruxtecan (T-DXd) in metastatic *HER2*-mutant NSCLC: DESTINY-Lung04 primary results

Julia Rotow, MD

Dana-Farber Cancer Institute, Boston, MA, US

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Additional authors: Isamu Okamoto, Koichi Goto, Myung-Ju Ahn, Parneet Cheema, Julien Mazieres, Silvia Novello, Dongqing Lv, Yongchang Zhang, Antonio Passaro, Ernest Nadal, How-Wen Ko, Hai-Yan Tu, Nandini Menon, Emilio Bria, Jamie Chaft, Maximilian Hochmair, Mukesh Chaudhari, AJ van der Wekken, Pascale Tomasini, Sukhmani K Padda, William N William Jr, Ashwini Vishweswaramurthy, Yi-Ting Chang, Erica Schreffler, Bob Li, Yi-Long Wu

On behalf of the DESTINY-Lung04 investigators

Disclosures

Julia Rotow

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Background

- *HER2 (ERBB2)* mutations are detected in ~2–4% of nonsquamous NSCLCs,^{1–3} resulting in an aggressive disease characterized by poor prognosis⁴
- Globally, the 1L SOC is typically IO + platinum-based doublet chemo^{5,6}
 - Limited response rates and disease progression for many patients support the need for HER2-directed treatment options⁷
- T-DXd, a HER2-directed ADC, was the first targeted treatment to be approved globally for patients with unresectable/metastatic *HER2*-mutant NSCLC in the 2L setting^{5,6,8}
- DESTINY-Lung04 was designed to investigate T-DXd monotherapy as a 1L treatment for patients with *HER2*-mutant NSCLC and is the first global randomized Phase 3 trial of a HER2-directed therapy vs SOC pembro + platinum chemo + pemetrexed in this setting

ADC, antibody-drug conjugate; chemo, chemotherapy; T-DXd, trastuzumab deruxtecan

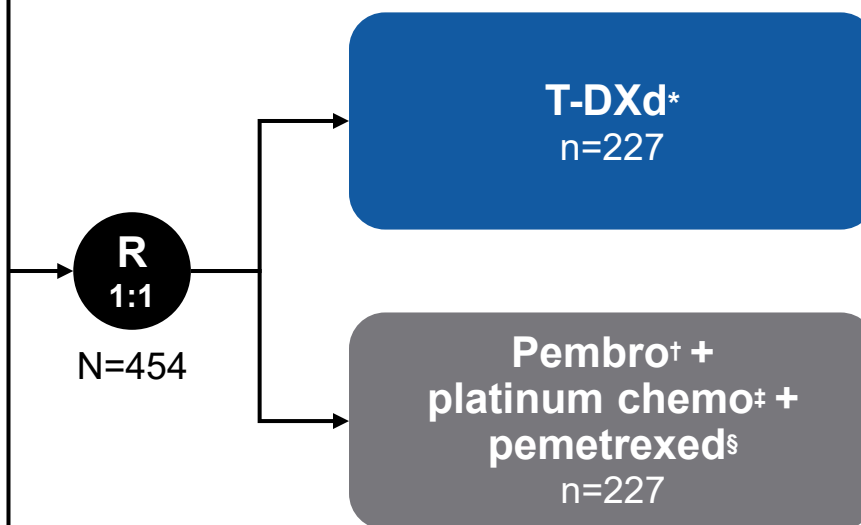
1. cBioPortal for Cancer Genomics. Available from: cbioportal.org (Accessed September 1, 2026); 2. Li BT, et al. *J Thorac Oncol.* 2016;11:414–493; 3. Yoshizawa A, et al. *Lung Cancer.* 2014;85:373–378; 4. Ren S, et al. *ESMO Open.* 2022;7:100395; 5. ESMO living guideline: oncogene-addicted metastatic non-small-cell lung cancer, v1.3 2026. Available from: <https://www.esmo.org/guidelines/living-guidelines/esmo-living-guideline-oncogene-addicted-metastatic-non-small-cell-lung-cancer/management-of-advanced-and-metastatic-disease/stage-iv-mnsc-lc-molecular-tests-positive-ntrk-met-ret-her2-kras-g12c-nrg1-c-met/stage-iv-mnsc-lc-molecular-tests-positive-for-her2> (Accessed September 1, 2026); 6. Lee SH, et al. *ESMO Open.* 2024;9:103996; 7. Saalfeld FC, et al. *J Thorac Oncol.* 2021;16:1952–1958; 8. Puri S, et al. *J Clin Oncol.* 2026;doi: 10.1200/JCO-26-01479: June 29 [Epub ahead of print]

DESTINY-Lung04 trial design

A randomized, open-label, multicenter, Phase 3 trial (NCT05048797)

Patients

- Unresectable locally advanced or metastatic nonsquamous NSCLC
- Treatment naïve for advanced disease
- *HER2* exon 19 or 20 mutation by central/local test
- ECOG PS 0 or 1
- Asymptomatic/stable/treated brain metastases permitted
- ≥1 measurable lesion per RECIST 1.1



Endpoints

Primary[¶]

- PFS (BICR)

Secondary

- OS^{||}
- ORR and DOR (BICR)
- PFS2 (investigator)
- Safety and tolerability

Stratification factors

- Presence/history of brain metastases (yes vs no)
- Smoking history status (ever vs never)

- Data cutoff for final PFS analysis / first OS interim analysis: **June 9, 2026**
 - Formal hypothesis testing for OS will be performed at second interim and final analyses only
- Median (range) duration of follow up: **21.6 months (0.4–51.1) with T-DXd** vs **20.4 months (0.1–52.0) with pembro + chemo**

PFS, ORR, and DOR all per RECIST 1.1. Participants with objective radiological CNS disease progression per RECIST 1.1 could continue with their assigned trial treatment if, in the investigator's opinion, they continued to receive clinical benefit and were without any discontinuation criteria. Treatment crossover was not permitted

*5.4 mg/kg IV Q3W until disease progression, unacceptable toxicity, or other discontinuation criteria; †200 mg IV Q3W until disease progression, unacceptable toxicity, or other discontinuation criteria; ‡investigator choice of cisplatin (75 mg/m²) or carboplatin (AUC 5) IV Q3W for up to four cycles; §500 mg/m² IV Q3W until disease progression, unacceptable toxicity, or other discontinuation criteria; ¶for the final PFS analysis, ~306 events provided 90% power to detect a hazard ratio of 0.69 with a two-sided significance level of 5%; ||the first OS interim analysis was conducted at the time of final PFS analysis; no formal hypothesis testing was planned

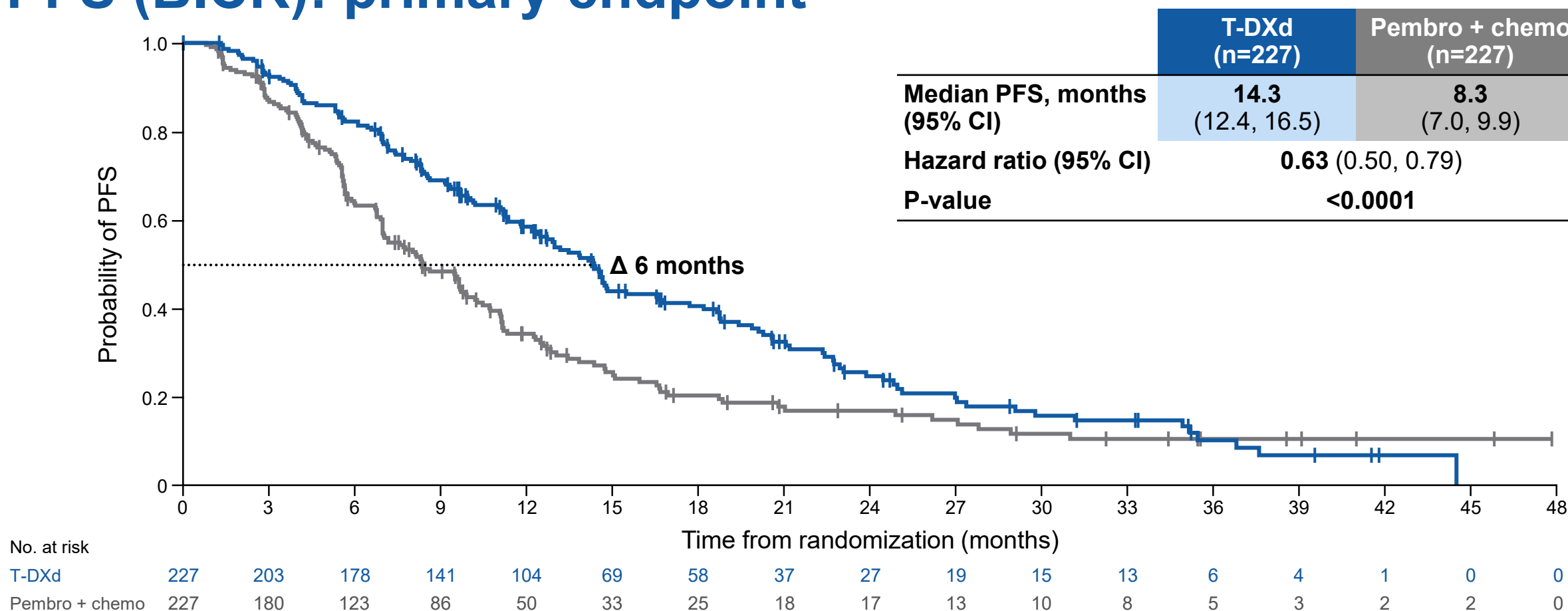
Demographics and baseline characteristics

		T-DXd (n=227)	Pembro + chemo (n=227)
Median age, years (range)		62 (26–85)	62 (31–85)
Age group, n (%)	<65 years	123 (54.2)	133 (58.6)
	≥65 years	104 (45.8)	94 (41.4)
Female sex, n (%)		133 (58.6)	131 (57.7)
Region, n (%)	Asia	105 (46.3)	120 (52.9)
	Europe	87 (38.3)	69 (30.4)
	North America	26 (11.5)	30 (13.2)
	Rest of World	9 (4.0)	8 (3.5)
ECOG PS, n (%)	0	107 (47.1)	108 (47.6)
	1	120 (52.9)	118 (52.0)
	Missing	–	1 (0.4)
Smoking status, n (%)	Ever	86 (37.9)	86 (37.9)
	Never	141 (62.1)	141 (62.1)

		T-DXd (n=227)	Pembro + chemo (n=227)
Liver metastases, n (%)		45 (19.8)	31 (13.7)
Brain metastases, n (%)*		52 (22.9)	55 (24.2)
Prior therapy for early-stage disease, n (%)	Prior radiotherapy	83 (36.6)	73 (32.2)
	Cytotoxic chemo	34 (15.0)	28 (12.3)
	Immunotherapy	5 (2.2)	2 (0.9)
	Targeted therapy	1 (0.4)	3 (1.3)
HER2 mutation, n (%)†	Exon 20	214 (94.3)	211 (93.0)
	Exon 19	10 (4.4)	15 (6.6)
PD-L1 status, n (%)‡	<1%	95 (41.9)	81 (35.7)
	1–49%	34 (15.0)	38 (16.7)
	≥50%	11 (4.8)	8 (3.5)
	Missing§	87 (38.3)	100 (44.1)
Disease status, n (%)	Recurrence/relapse	41 (18.1)	42 (18.5)
	De novo metastatic	172 (75.8)	177 (78.0)
	Unresectable, locally advanced	14 (6.2)	8 (3.5)

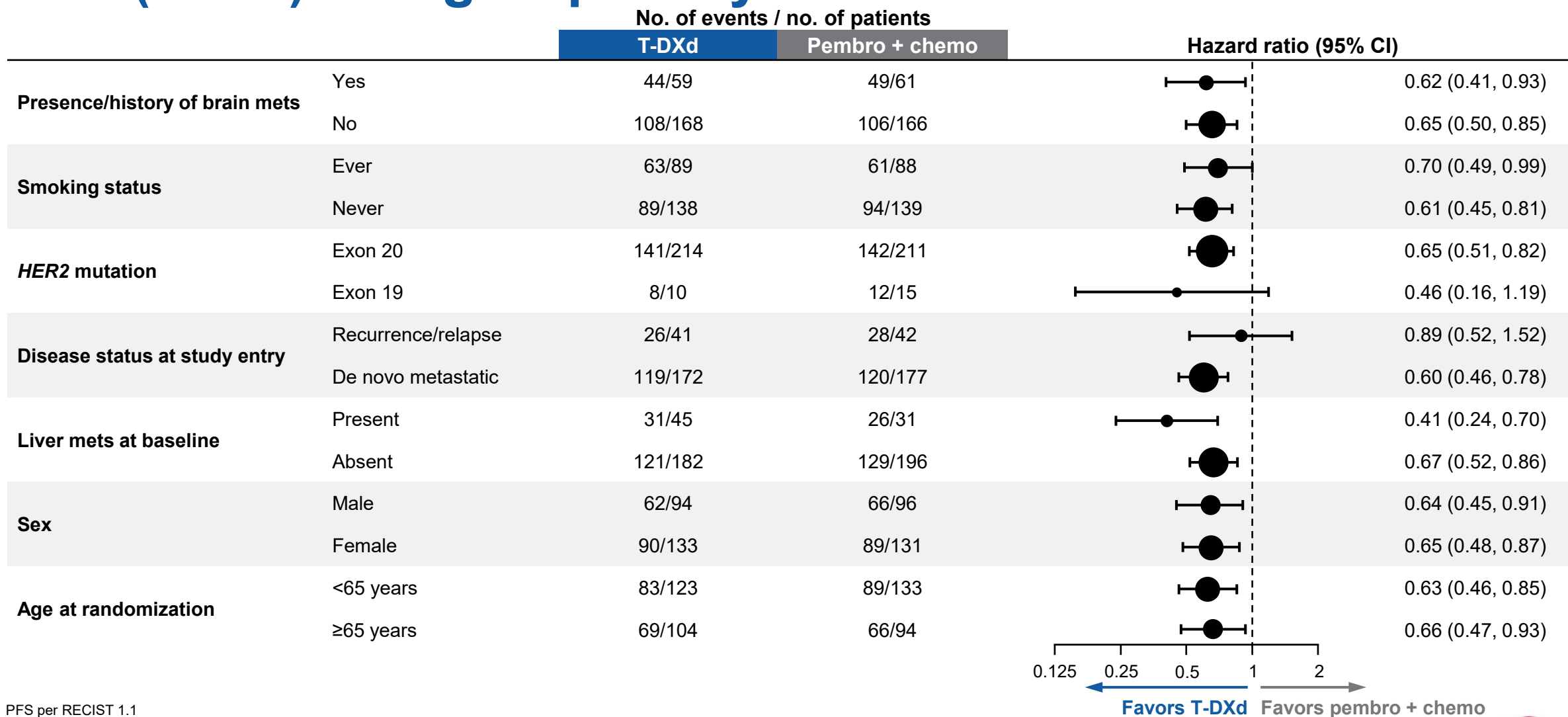
*All patients with brain metastases at baseline had received prior local therapy; †per local or central test. Three patients in the T-DXd arm and one patient in the pembro + chemo arm had NSCLC with a positive *HER2* activating mutation that was not exon 19 or 20; ‡per central test; §prospective testing was not mandated; central retrospective testing was completed when tissue was available

PFS (BICR): primary endpoint



T-DXd monotherapy demonstrated a statistically significant and clinically meaningful PFS improvement vs standard-of-care pembro + doublet chemo

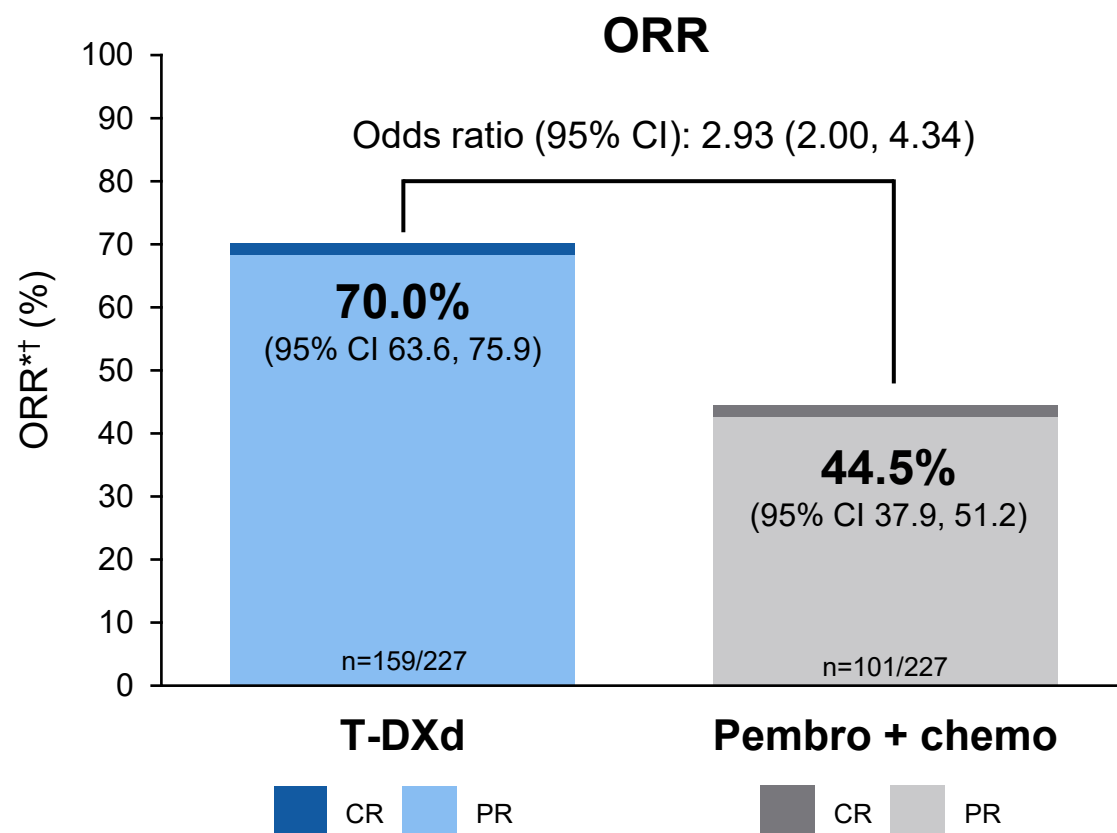
PFS (BICR): subgroup analysis



PFS per RECIST 1.1

Circles are proportional to the overall number of events

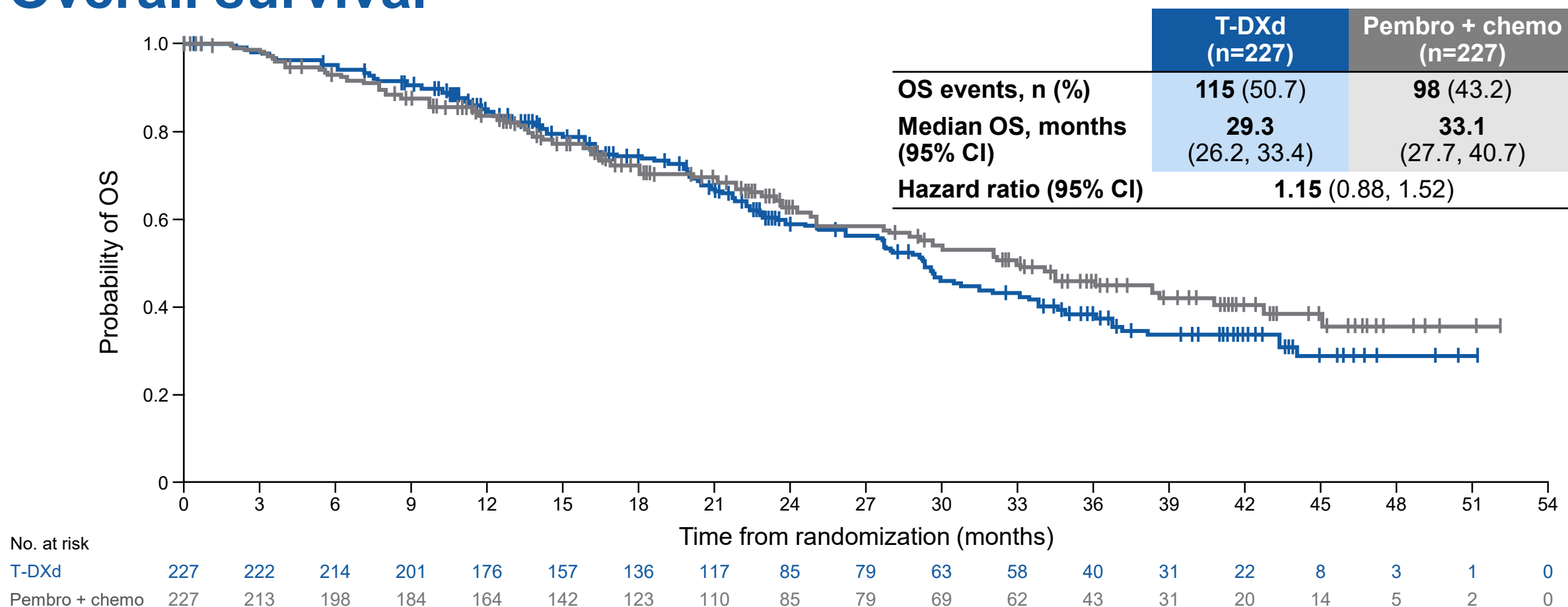
Secondary efficacy endpoints



	T-DXd (n=227)	Pembro + chemo (n=227)
Best overall response,*† n (%)		
Complete response	4 (1.8)	4 (1.8)
Partial response	155 (68.3)	97 (42.7)
Stable disease	61 (26.9)	98 (43.2)
Progressive disease‡	4 (1.8)	15 (6.6)
Non-evaluable‡	3 (1.3)	13 (5.7)
Median DOR,* months (95% CI)	13.4 (10.4, 17.2)	9.7 (7.0, 11.1)
Median PFS2,§ months (95% CI)	22.7 (20.3, 26.3)	17.3 (15.6, 21.8)
Hazard ratio (95% CI)	0.80 (0.62, 1.02)	

*By BICR per RECIST 1.1; †includes unconfirmed responses; ‡for patients who died with no evaluable RECIST assessments, best overall response was assigned as either progressive disease (if the death occurred ≤13 weeks after randomization) or non-evaluable (if the death occurred >13 weeks after randomization); §PFS2 was determined by investigator per RECIST 1.1 according to local standard clinical practice as the time from randomization to second progression (earliest progression event following first subsequent therapy) or death

Overall survival*

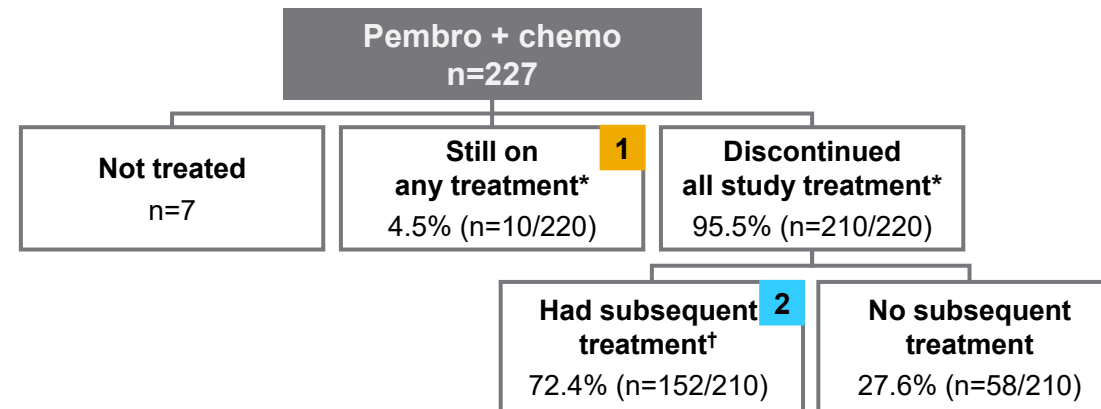
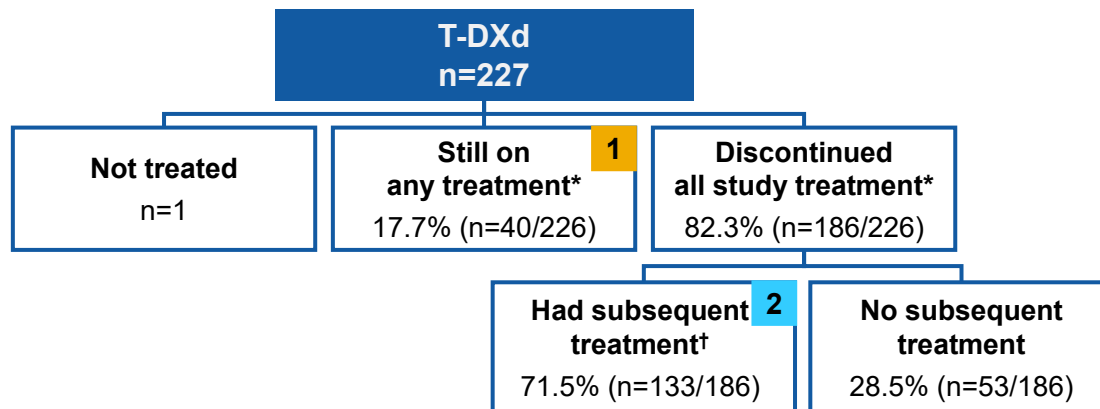


No OS benefit was observed with T-DXd; subsequent treatments may have impacted results

At data cutoff, overall data maturity for OS was 46.9%. Median follow up was 21.6 months (range 0.4–51.1) in the T-DXd arm and 20.4 months (range 0.1–52.0) in the pembro + chemo arm

*This administrative OS interim analysis was performed with a two-sided alpha-spend of 0.0001. **Formal hypothesis testing will be performed at the second interim analysis and final analysis**

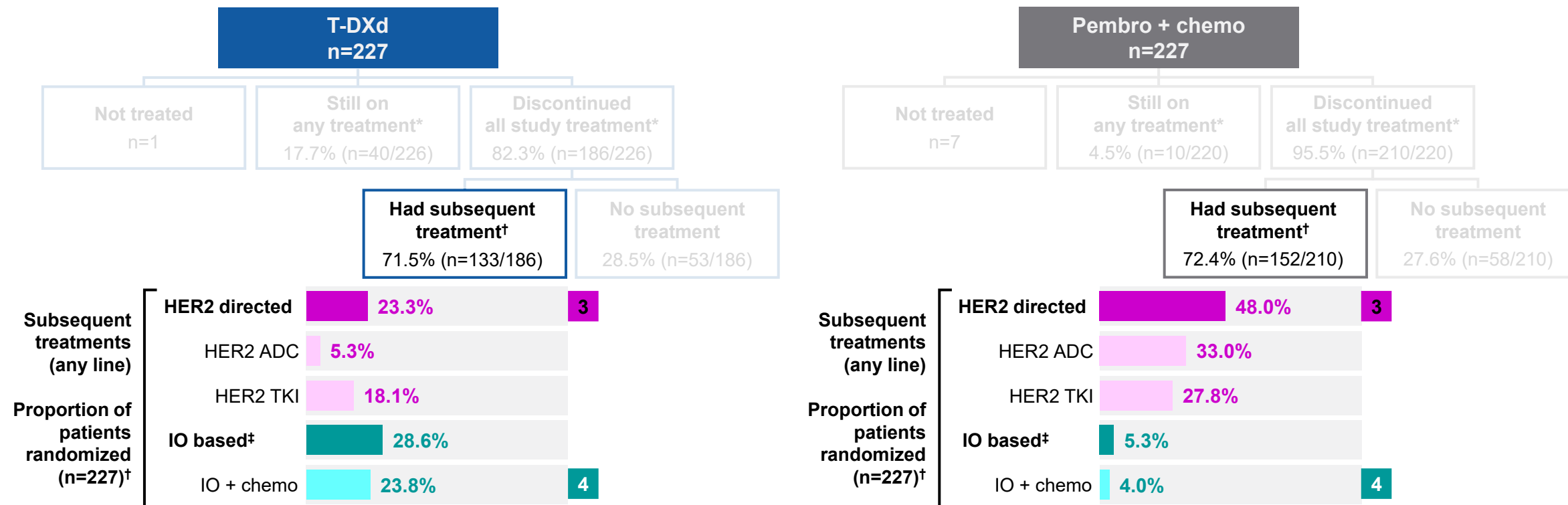
Imbalance in subsequent therapies



1 More patients remained on any study treatment at data cutoff in the T-DXd arm (**17.7%** vs **4.5%**)

2 Among patients who discontinued study treatment, subsequent anti-cancer therapy use was similar between arms: **71.5%** vs **72.4%**

Imbalance in subsequent therapies



3 More patients in the pembro + chemo arm subsequently received HER2-directed therapies: **48.0%** vs **23.3%**

4 Use of subsequent IO + chemo combination therapies in the T-DXd arm was limited (**23.8%**)

Imbalance in subsequent HER2-directed / IO + chemo therapies may have confounded interpretation of OS

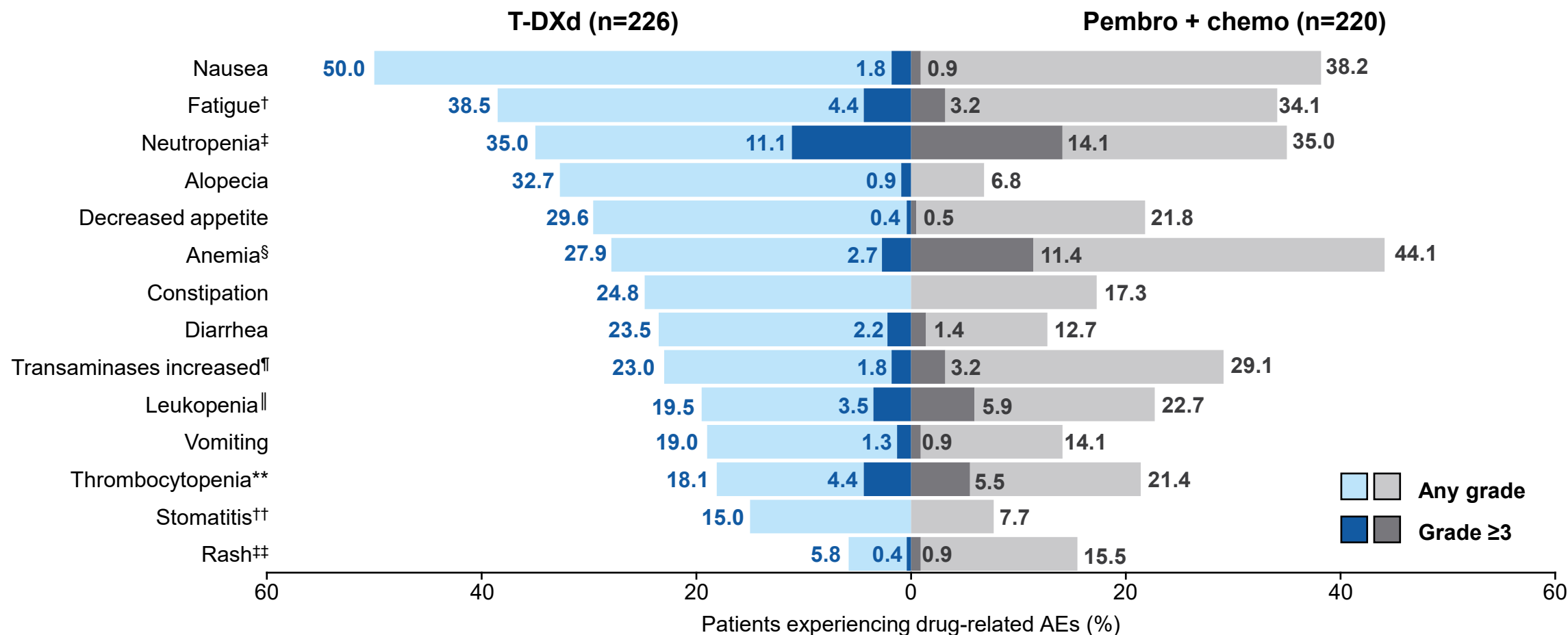
Therapies listed are not exhaustive or mutually exclusive. Values may not total 100%. *Proportions based on patients treated; †in any line; ‡IO-containing regimens other than IO + chemo: 5.3% (T-DXd) vs 1.8% (pembro + chemo)

Overall safety summary (investigator assessed)

	T-DXd (n=226)	Pembro + chemo (n=220)
Median (range) treatment duration	12.3 (0.7–44.8)	7.1 (0.7–49.1)
Drug-related AEs, n (%)		
Any grade	204 (90.3)	197 (89.5)
Grade ≥3	77 (34.1)	74 (33.6)
Serious	35 (15.5)	22 (10.0)
Associated with any drug discontinuation	36 (15.9)	35 (15.9)
Associated with dose reduction	40 (17.7)	35 (15.9)
Associated with death*	4 (1.8)	1 (0.5)

*Drug-related AEs associated with death were pneumonitis (n=4) in the T-DXd arm and sepsis (n=1) in the pembro + chemo arm

Most common ($\geq 15\%$)* drug-related AEs (investigator assessed)



*In either arm; †fatigue (grouped term): fatigue, asthenia, malaise, and lethargy; ‡neutropenia (grouped term): neutropenia and neutrophil count decreased; §anemia (grouped term): anemia, hemoglobin decreased, hematocrit decreased, and red blood cell count decreased; ¶transaminases increased (grouped term): transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal, hypertransaminasemia, and liver function test increased; ||leukopenia (grouped term): leukopenia and white blood cell count decreased; **thrombocytopenia (grouped term): platelet count decreased and thrombocytopenia; ††stomatitis (grouped term): aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosal blistering, oral mucosal eruption, and stomatitis; ‡‡rash (grouped term): rash, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular

Adverse events of special interest

n (%)		T-DXd (n=226)	Pembro + chemo (n=220)
Adjudicated drug-related ILD/pneumonitis*	Any grade	47 (20.8)	5 (2.3)
	Grade 1	7 (3.1)	1 (0.5)
	Grade 2	30 (13.3)	4 (1.8)
	Grade 3	5 (2.2) [†]	0
	Grade 4	1 (0.4)	0
	Grade 5	4 (1.8) [‡]	0
Left ventricular dysfunction§	Any grade	7 (3.1)	1 (0.5)
	Grade 1	0	1 (0.5)
	Grade 2	4 (1.8)	0
	Grade 3	3 (1.3)	0
	Grade 4	0	0
	Grade 5	0	0

In the T-DXd arm:

- Most cases of ILD were Grade 1/2 (78.7%) and resolved (66.0%)
- 16 of the 30 Grade 2 adjudicated ILD events were upgraded from Grade 1 (per investigator) because of use of steroids
- Delayed initiation and/or suboptimal steroid dosing was observed in 90% of all Grade ≥3 ILD cases, including all four Grade 5 cases
- Among patients with Grade ≤3 ILD who discontinued T-DXd, 64.1% received subsequent therapy, consistent with the overall T-DXd arm (71.5%)[¶]

ILD remains an important risk of T-DXd and should be monitored/managed appropriately

*An independent adjudication committee reviewed all potential cases of ILD/pneumonitis; [†]one patient had a Grade 3 ILD event after the 47-day safety follow-up period; [‡]all counts in this table reflect the locked clinical database (safety analysis set). One additional fatal event (preferred term: respiratory failure) occurred in the T-DXd arm and was subsequently adjudicated as drug-related Grade 5 ILD; [§]left ventricular ejection fraction decreased; [¶]n=25/39 patients with Grade ≤3 ILD who discontinued T-DXd received subsequent therapy / n=133/186 patients who discontinued T-DXd received subsequent therapy

Conclusions

- DESTINY-Lung04 met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in PFS (BICR) with **T-DXd** monotherapy vs SOC **pembro + doublet chemo**
 - Median **14.3** vs **8.3** months (HR 0.63; P<0.0001), an improvement of 6 months
- Response rates and durability favored **T-DXd** and supported the PFS benefit: ORR (BICR) of **70.0%** vs **44.5%**, with median DOR (BICR) of **13.4** vs **9.7** months
- OS in the T-DXd arm did not outperform the pembro + chemo arm, which may, in part, be due to imbalances in subsequent therapies
- Safety was generally consistent with the known profiles of each treatment^{1,2}

DESTINY-Lung04 is the first Phase 3 trial to show benefit with a HER2-directed therapy vs SOC, supporting T-DXd as a new 1L treatment option for patients with *HER2*-mutant NSCLC

1. Enhertu (fam-trastuzumab deruxtecan-nxki): highlights of prescribing information. 2026. Available from: <https://daiichisankyo.us/prescribing-information-portlet/getPIContent?productName=Enhertu&inline=true> (Accessed September 1, 2026); 2. Keytruda (pembrolizumab): highlights of prescribing information. 2024. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/125514s174lbl.pdf (Accessed September 1, 2026)

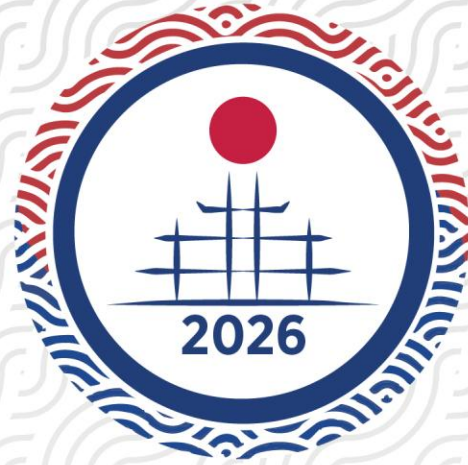
Acknowledgments

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Thank You.●

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Supplementary content

ILD narratives

Severity	n (%)	Outcome	ILD adjudication committee findings
Grade 3	5 (2.2)	3 recovered	4 of 5 cases had suboptimal steroid management - In 3 out of 5 cases, the ILD adjudication committee noted a start date earlier than PI-reported start dates
Grade 4	1 (0.4)	Not recovered / resolved	This case had suboptimal steroid management
Grade 5	4 (1.8)*	Fatal	All 4 cases had suboptimal steroid management; ILD adjudication committee noted that start dates were earlier than PI-reported start dates in 3 out of 4 cases

Outcomes

80% of patients with Grade 1–3 ILD were recovered/recovering

One patient had a Grade 4 event and had not recovered†

**Suboptimal steroid management
9 of 10 cases**

Steroid administration was not in accordance with treatment management guidelines in 90% of Grade ≥3 ILD cases

**Earlier action possible
6 of 10 cases**

ILD could have been detected 10–55 days earlier per adjudication committee in 60% of patients with Grade ≥3 ILD

Favorable outcomes predominated in adjudicated low-grade (Grade 1–3) ILD. Delayed detection and suboptimal management may have contributed to unfavorable outcomes in Grade 4–5 cases

*One additional fatal event (preferred term: respiratory failure) occurred in the T-DXd arm and was subsequently adjudicated as drug-related Grade 5 ILD; this patient also could have been detected earlier as per the ILD adjudication committee and did not receive steroids; †this patient withdrew consent; therefore, the outcome has not been updated since September 2022

Plain language summary

People in the T-DXd arm lived longer without their cancer growing, spreading, or getting worse than those in the pembrolizumab + chemotherapy arm, supporting potential use of T-DXd as a first-line treatment option for people with advanced/metastatic *HER2*-mutant NSCLC



Why did we perform this research?

Some people with non-small cell lung cancer (NSCLC) have tumors with a mutation in the human epidermal growth factor receptor 2 (*HER2*; also known as *ERBB2*) gene, leading to an aggressive disease. Currently, *HER2*-mutant NSCLC that cannot be removed with surgery and has spread to other parts of the body (known as advanced/metastatic disease) is initially treated with a combination of an immune therapy (eg pembrolizumab) and two chemotherapy drugs (eg a platinum agent and pemetrexed).^{1,2} However, for many people, the cancer gets worse despite this initial (first-line) treatment.³ Trastuzumab deruxtecan (T-DXd) is a *HER2*-directed antibody-drug conjugate, which is a chemotherapy with a linker (together called deruxtecan) joined to an antibody (trastuzumab), that kills *HER2*-altered cancer cells.^{4,5} At the moment, T-DXd can only be given to people with *HER2*-mutant NSCLC as a second-line treatment.^{1,2,6} This study aims to investigate whether T-DXd could also be beneficial to people when given as a first-line treatment.



How did we perform this research?

DESTINY-Lung04 is a global clinical study evaluating T-DXd versus pembrolizumab + chemotherapy (platinum and pemetrexed) as a treatment for people with advanced/metastatic *HER2*-mutant NSCLC who had not received prior treatment. The main aim was to determine whether people lived longer without their cancer growing, spreading, or getting worse. Other objectives included the response to treatment (at least a 30% decrease in the size, or complete disappearance, of tumors) and treatment side effects.



What were the findings of this research?

This study included 454 participants. The timepoint after randomization at which half of the participants were alive without their cancer growing, spreading, or getting worse was 14.3 months with T-DXd and 8.3 months with pembrolizumab + chemotherapy. Overall, 70.0% of participants in the T-DXd arm had a response to treatment compared with 44.5% of those in the pembrolizumab + chemotherapy arm. Side effects were as expected based on what was already known about each study drug.



What are the implications of this research?

These results support the potential use of T-DXd as a first-line treatment for people with advanced/metastatic *HER2*-mutant NSCLC.



Where can I access more information?

For more information about DESTINY-Lung04, please visit <https://clinicaltrials.gov/study/NCT05048797>.

1. ESMO living guideline: oncogene-addicted metastatic non-small-cell lung cancer, v1.3 2026. Available from: <https://www.esmo.org/guidelines/living-guidelines/esmo-living-guideline-oncogene-addicted-metastatic-non-small-cell-lung-cancer/management-of-advanced-and-metastatic-disease/stage-iv-mnslc-molecular-tests-positive-ntkr-met-ret-her2-kras-g12c-nrg1-c-met/stage-iv-mnslc-molecular-tests-positive-for-her2> (Accessed September 1, 2026);
2. Lee SH, et al. *ESMO Open*. 2024;9:103996; 3. Saalfeld FC, et al. *J Thorac Oncol*. 2021;16:1952–1958; 4. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173–185; 5. Ogitani Y, et al. *Clin Cancer Res*. 2016;22:5097–5108;
6. Puri S, et al. *J Clin Oncol*. 2026;doi 10.1200/JCO-26-01479: June 29 [Epub ahead of print]