WCLC 2024 Presentation Materials

- **Tropion-Lung01**
  - Sands, J. et al., WCLC 2024 OA08.03. (Oral)
- **Quantitative Continuous Scoring (QCS)**
  - Garassino, M.C. et al., WCLC 2024 PL02.11. (Oral)
- **NeoCOAST-2**
  - Cascone, T. et al., WCLC 2024 PL02.07. (Oral)
- **DESTINY-Lung03**
  - Planchard, D. et al., WCLC 2024 OA16.05. (Oral)
- **IDeate-Lung01**
  - Rudin, C. M. et al., WCLC 2024 OA04.03. (Oral)

This document does not cover all the company related topics presented at WCLC 2024.

Datopotamab Deruxtecan vs Docetaxel in Patients with Non-Small Cell Lung Cancer: Final Overall Survival from TROPION-Lung01

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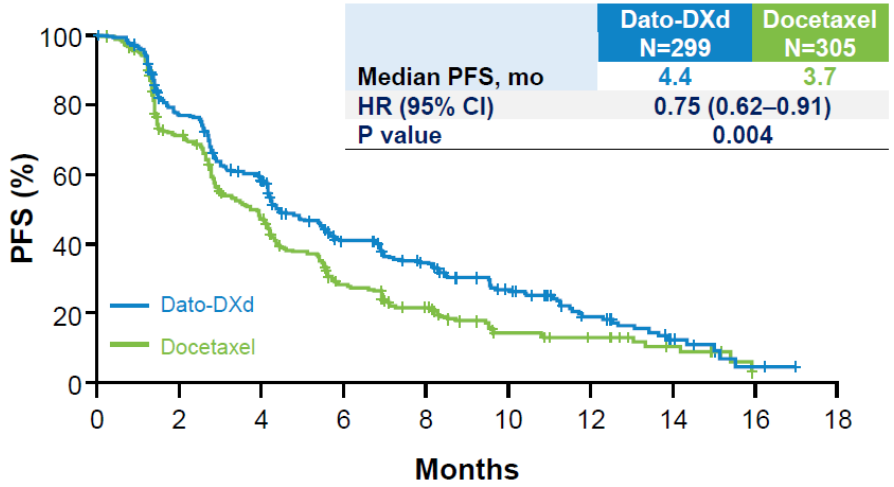
Background

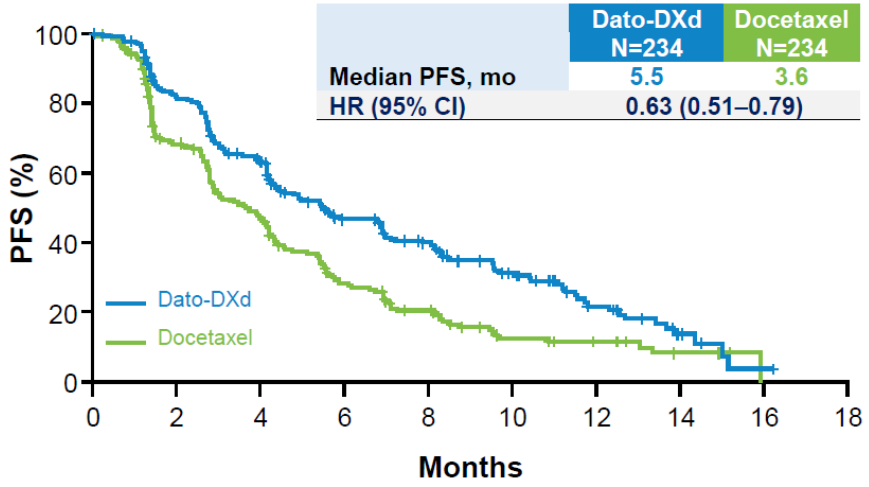
- Survival outcomes for patients with advanced NSCLC on docetaxel-based regimens in the second-line setting and beyond remain poor, and multiple trials of novel treatment regimens have failed in this setting, underscoring a high unmet need[1,2]
- **TROPION-Lung01** met its dual primary endpoint of **PFS with a statistically significant improvement** in favor of **datopotamab deruxtecan** (**Dato-DXd**) vs docetaxel[3]; a 37% reduction in relative risk of progression and more than doubling of response rate were seen in the NSQ subgroup[4]

ITT



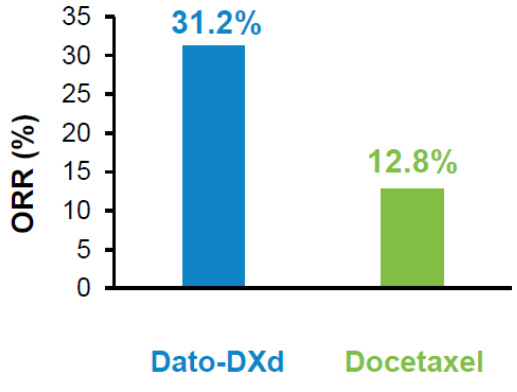
	Dato-DXd N=299	Docetaxel N=305
Median PFS, mo	4.4	3.7
HR (95% CI)	0.75 (0.62–0.91)	
P value	0.004	

NSQ



	Dato-DXd N=234	Docetaxel N=234
Median PFS, mo	5.5	3.6
HR (95% CI)	0.63 (0.51–0.79)	

	Dato-DXd N=234	Docetaxel N=234
Median DOR, mo	7.7	5.6



- Differential PFS outcomes by histology for Dato-DXd have been independently reported in two other NSCLC trials[5,6]

Here, we report the final analysis of the dual primary endpoint of overall survival for TROPION-Lung01

1. Fossella FV, et al. *J Clin Oncol* 18:2354-2362, 2000; 2. Reck M, et al. *Lancet Oncol* 15:143-155, 2014; 3. Ahn M-J, et al. Presented at ESMO 2023, Madrid, Spain, October 20–24, 2023 (Abstract 509MO);
4. Girard N, et al. Presented at ELCC 2024, Prague, Czech Republic, March 20–23, 2024 (Poster 59P); 5. Planchard D, et al. *J Clin Oncol* 42:8501, 2024; 6. Sun Y, et al. *J Clin Oncol* 42:8548, 2024.
CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DOR, duration of response; HR, hazard ratio; ITT, intention to treat; mo, months; NSCLC, non-small cell lung cancer; NSQ, nonsquamous; ORR, objective response rate; PFS, progression-free survival.

Study Design

Randomized, Phase 3, Open-Label, Global Study (NCT04656652)

Key eligibility criteria

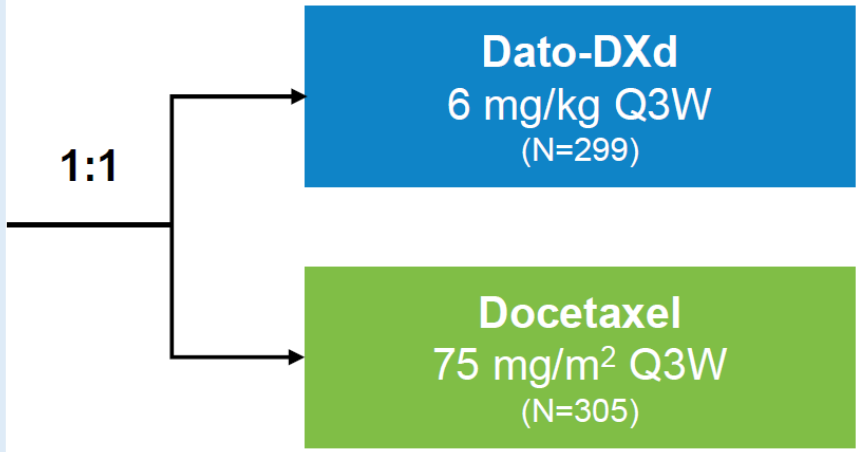
- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0–1
- No prior docetaxel

Without actionable genomic alterations

- One to two prior lines, including platinum-based CT and anti–PD-(L)1 mAb therapy

With actionable genomic alterations

- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
- One to two prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb



Dual primary endpoints

- PFS by BICR[a]
- OS

Secondary endpoints

- ORR[a]
- DOR[a]
- Safety and tolerability

Stratified by histology (nonsquamous vs squamous), actionable genomic alteration status,[b] anti–PD-(L)1 mAb included in most recent prior therapy, and geography[c]

Statistical considerations: Study deemed positive if either of the dual primary endpoints (PFS by BICR or OS) were statistically significant; the pre-specified P-value boundary for the OS analysis was α=0.045

[a]Evaluated per RECIST v1.1. [b]Presence vs absence. [c]United States/Japan/Western Europe vs rest of world.
BICR, blinded independent central review; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; mAb, monoclonal antibody; OS, overall survival; PD-(L)1, programmed cell death 1 (ligand 1); Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours.

Demographics and Baseline Characteristics

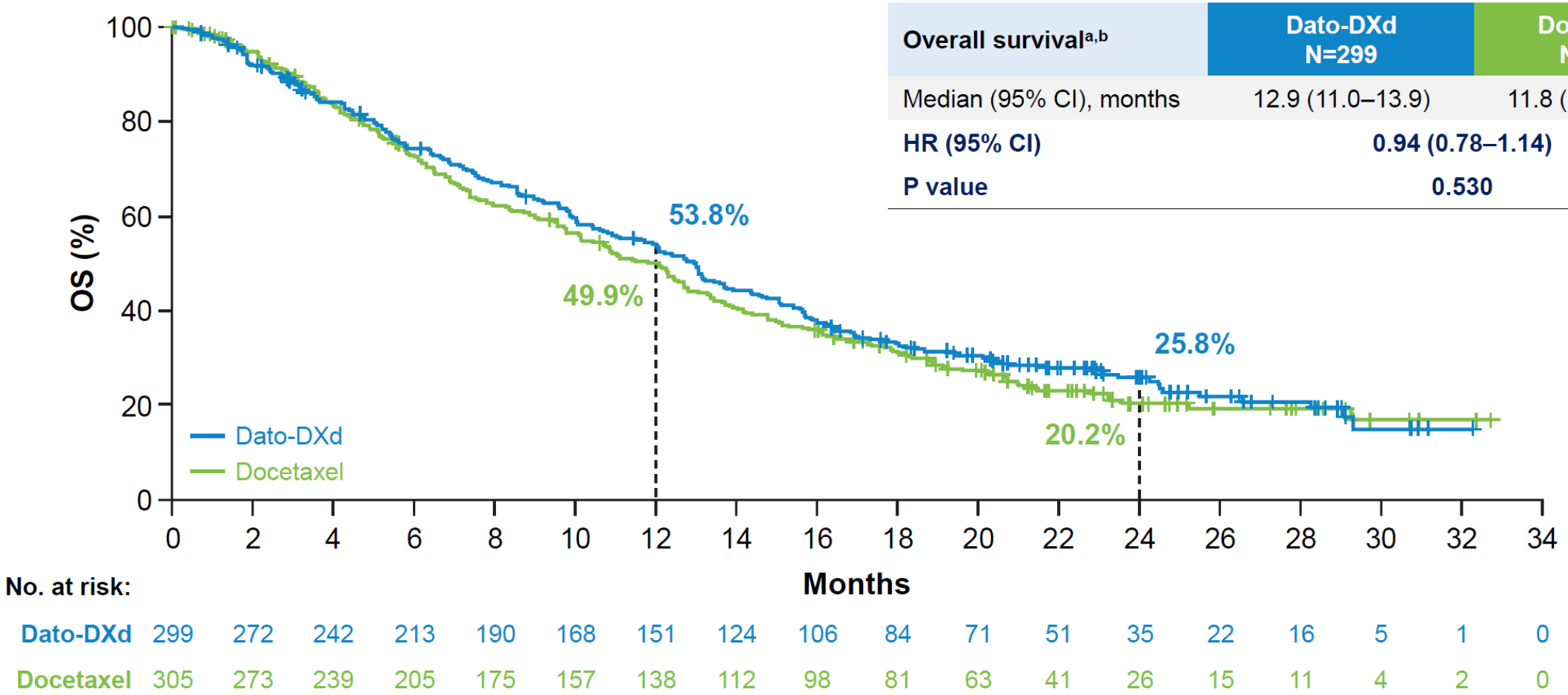
Characteristic, n (%)		Dato-DXd N=299	Docetaxel N=305
Age, years [median (range)]		63 (26–84)	64 (24–88)
Sex, male		183 (61)	210 (69)
Race	Asian	119 (40)	120 (39)
	White	123 (41)	126 (41)
	Black or African American	6 (2)	4 (1)
	Other/missing	51 (17)	55 (18)
ECOG PS[a]	0	89 (30)	94 (31)
	1	210 (70)	211 (69)
Histology	Nonsquamous	234 (78)	234 (77)
	Squamous	65 (22)	71 (23)

Characteristic, n (%)		Dato-DXd N=299	Docetaxel N=305
Current or former smoker		238 (80)	251 (82)
Actionable genomic alterations present		50 (17)	51 (17)
Brain metastasis at baseline[b]		79 (26)	91 (30)
Prior lines of therapy[c]	1	167 (56)	174 (57)
	2	108 (36)	102 (33)
	3	17 (6)	23 (8)
	≥4	5 (2)	5 (2)
Previous systemic therapy	Platinum containing	297 (99)	305 (100)
	Anti–PD-(L)1	263 (88)	268 (88)
	Targeted	46 (15)	50 (16)

[a]Screening score. [b]Patients with clinically stable brain metastases could be included. Clinically stable defined as asymptomatic, previously treated, or untreated. [c]Two patients in the Dato-DXd treatment group and one patient in the docetaxel treatment group had no prior lines of systemic therapy in the advanced/metastatic setting.
Per investigator reporting, these patients received prior systemic anti-cancer therapy in settings other than the advanced/metastatic setting.

Overall Survival: ITT

Overall survival[a,b]	Dato-DXd N=299	Docetaxel N=305
Median (95% CI), months	12.9 (11.0–13.9)	11.8 (10.0–12.8)
HR (95% CI)	**0.94 (0.78–1.14)**	
P value	**0.530**	



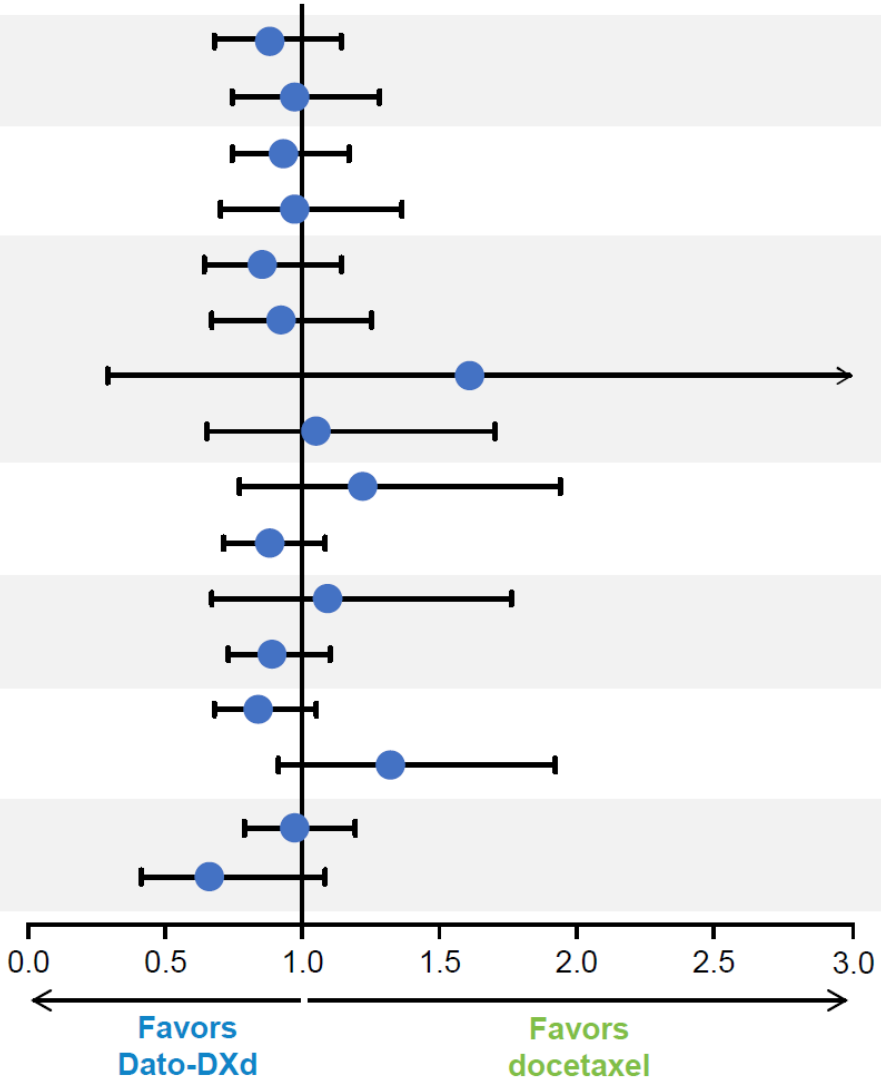
No. at risk:

Dato-DXd	299	272	242	213	190	168	151	124	106	84	71	51	35	22	16	5	1	0
Docetaxel	305	273	239	205	175	157	138	112	98	81	63	41	26	15	11	4	2	0

[a]Median (95% CI) OS follow-up was 23.1 (22.0, 24.8) months for Dato-DXd and 23.1 (21.7, 24.2) months for docetaxel. [b]At primary OS analysis (data cutoff: March 1, 2024), 433 OS events (IF) were observed.
IF, information fraction.

Overall Survival: Subgroup Analyses

		No. of events/No. of patients		HR
		Dato-DXd	Docetaxel	
Age at randomization	<65 years	117/162	112/155	0.88
	≥65 years	98/137	106/150	0.97
Sex	Male	136/183	156/210	0.93
	Female	79/116	62/95	0.97
Race	White	90/123	95/126	0.85
	Asian	83/121	79/120	0.92
	Black/African American	4/6	2/4	1.61
	Other	33/43	35/47	1.05
Smoking status	Never	43/60	31/52	1.22
	Former/current	172/239	186/251	0.88
Brain metastases at baseline	With	37/50	31/47	1.09
	Without	178/249	187/258	0.89
Histology	Nonsquamous	160/234	163/234	0.84
	Squamous	55/65	55/71	1.32
Actionable genomic alterations[a]	Absent	182/249	185/254	0.97
	Present	33/50	33/51	0.66

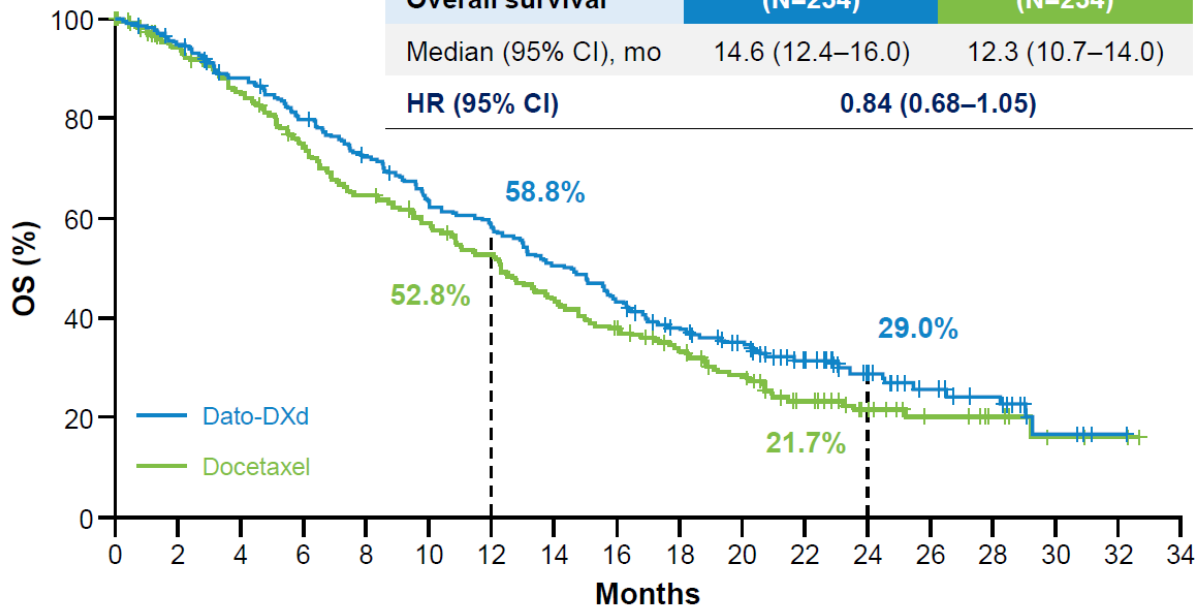


Data cutoff: March 1, 2024.
[a]Regardless of histology.

Overall Survival by Histology

Nonsquamous

Overall survival	Dato-DXd (N=234)	Docetaxel (N=234)
Median (95% CI), mo	14.6 (12.4–16.0)	12.3 (10.7–14.0)
HR (95% CI)	0.84 (0.68–1.05)	

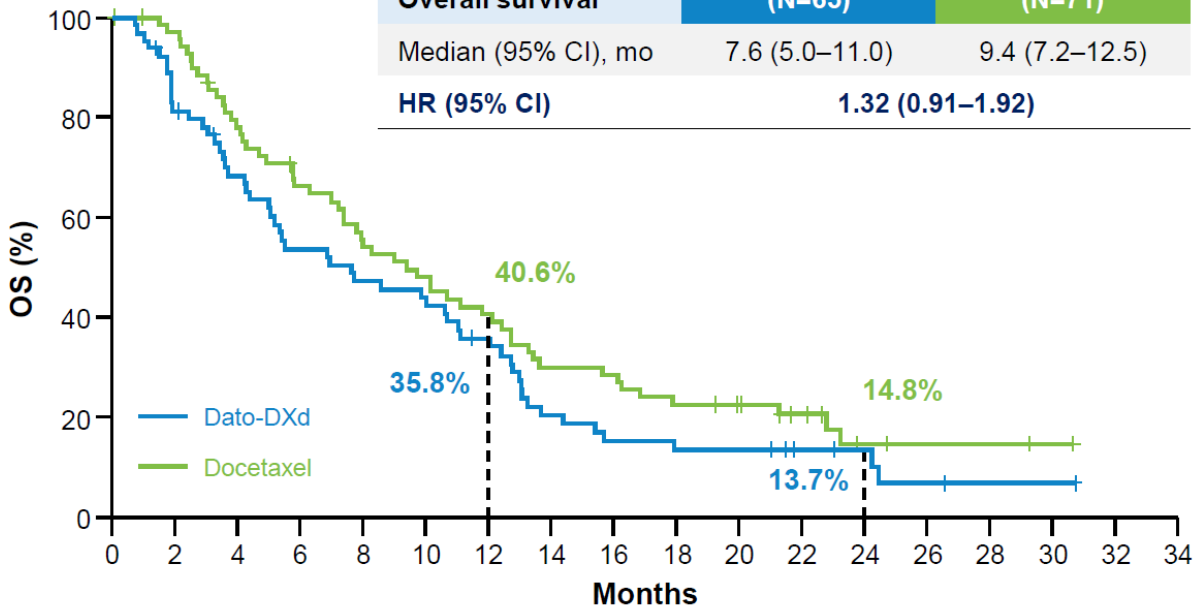


No. at risk:

Dato-DXd	234	220	200	180	161	141	130	112	97	76	63	46	31	20	15	4	1	0
Docetaxel	234	206	186	161	139	125	111	92	79	66	50	32	22	12	8	3	2	0

Squamous

Overall survival	Dato-DXd (N=65)	Docetaxel (N=71)
Median (95% CI), mo	7.6 (5.0–11.0)	9.4 (7.2–12.5)
HR (95% CI)	1.32 (0.91–1.92)	



	65	52	42	33	29	27	21	12	9	8	8	5	4	2	1	1	0	0
	71	67	53	44	36	32	27	20	19	15	13	9	4	3	3	1	0	0

- In patients with NSQ histology, 16% risk reduction for death and 2.3-month improvement in median OS with Dato-DXd
- OS improvements in the NSQ subset were seen regardless of actionable genomic alteration status[a]:
  - **Present**: 15.6 vs 9.8 months (HR [95% CI], 0.65 [0.40–1.08]); **Absent:** 13.6 vs 12.3 months (HR [95% CI], 0.89 [0.70–1.13])

Data cutoff: March 1, 2024.
[a]Based on the number of patients in the respective actionable genomic alteration subsets. Values were calculated based on patient data in the electronic case report forms.

Subsequent Anti-cancer Therapy

- In the NSQ patient population, **no meaningful impact** on OS by:
  - Removing the effect of subsequent use of docetaxel in the Dato-DXd arm after failure of therapy
  - Removing the effect of all post-treatment anti-cancer therapies in both arms

NSQ population	Dato-DXd (N=234)	Docetaxel (N=234)
Patients receiving any post-treatment anti-cancer therapy, n (%)	125 (**53.4**)	132 (**56.4**)
Median OS (95% CI), months	14.6 (12.4–16.0)	12.3 (10.7–14.0)
HR	0.84 (0.68–1.05)	
Sensitivity analysis[a]: Docetaxel in Dato-DXd arm		
Median OS (95% CI), months	14.8 (12.1–16.9)	12.3 (10.7–14.0)
HR	0.84 (0.66–1.07)	
Sensitivity analysis[a]: All post-treatment anti-cancer therapies in both arms		
Median OS (95% CI), months	12.1 (7.5–17.3)	9.6 (7.5–13.0)
HR	0.79 (0.54–1.15)	

Data cutoff: March 1, 2024.
[a]Analysis was performed using inverse-probability-of-censoring weighting.

Safety Summary: All Treated Patients

TRAEs, n (%)	Dato-DXd N=297	Docetaxel N=290
Any	260 (88)	252 (87)
Grade ≥3	76 (26)	122 (42)
Associated with:		
Dose reduction	60 (20)	86 (30)
Treatment discontinuation	24 (8)	35 (12)
Death[a]	3 (1)	2 (<1)
Serious	33 (11)	37 (13)
Grade ≥3	28 (9)	34 (12)

- Compared with the prior PFS data cutoff, with an additional ~11 months follow-up:
  - Overall safety profile was consistent
  - No late-onset toxicities were observed
- Fewer grade ≥3 TRAEs were observed with Dato-DXd compared with docetaxel
- Fewer TRAEs leading to dose reductions or discontinuations were seen with Dato-DXd compared with docetaxel

The median treatment durations for Dato-DXd and docetaxel were 4.2 and 2.8 months, respectively

Data cutoff: March 1, 2024.
[a]Two cases of ILD/pneumonitis and one of sepsis (Dato-DXd), and one case of ILD/pneumonitis and one of septic shock (docetaxel).
ILD, interstitial lung disease; TRAE, treatment-related adverse event.

TRAEs ≥15% and Adjudicated Drug-Related ILD

TRAEs,[a] n (%)	Dato-DXd (N=297)		Docetaxel (N=290)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Stomatitis	141 (47)[b]	20 (7)	45 (16)	3 (1)
Nausea	101 (34)	7 (2)	48 (17)	3 (1)
Alopecia	95 (32)	0	101 (35)	1 (<1)[c]
Decreased appetite	68 (23)	1 (<1)	46 (16)	1 (<1)
Asthenia	56 (19)	8 (3)	56 (19)	5 (2)
Anemia[d]	44 (15)	12 (4)	60 (21)	12 (4)
Diarrhea	30 (10)	1 (<1)	55 (19)	4 (1)
Neutropenia[e]	14 (5)	2 (1)	76 (26)	68 (23)
Leukopenia[f]	9 (3)	0	45 (16)	38 (13)
Adjudicated drug-related ILD or pneumonitis	26 (9)[g]	11 (4)	12 (4)	4 (1)

- Stomatitis events, the most common TRAE with Dato-DXd, were primarily grade 1 (23%) or grade 2 (18%)
- Hematologic toxicities, including neutropenia and febrile neutropenia[h], were more common with docetaxel
- No new adjudicated drug-related ILD events or deaths occurred since the PFS database lock
- Similar safety profiles were seen for the full safety analysis set and the NSQ subgroup

Data cutoff: March 1, 2024.
[a]Occurring in ≥15% of patients in either treatment group, plus all events of adjudicated drug-related ILD or pneumonitis. [b]Due to rounding, summed rates may not reflect total percentage of TRAEs. [c]Includes an event incorrectly reported as grade 3. [d]Grouped preferred terms of anemia, hemoglobin decreased, and red blood cell count decreased. [e]Grouped preferred terms of neutropenia and neutrophil count decreased. [f]Grouped preferred terms of leukopenia and white blood cell count decreased. [g]Includes one patient in the Dato-DXd group who experienced a grade 2 event that was adjudicated to be drug-related ILD by the adjudication committee. The investigator attributed the event to disease progression and removed the patient from the clinical database. [h]0.3% vs 6.9% for Dato-DXd and docetaxel, respectively.

Conclusions

- TROPION-Lung01 **met its dual primary endpoint of PFS** with a statistically significant improvement for Dato-DXd over docetaxel in the overall population
- The dual primary endpoint of **OS showed a numerical improvement** but **was not statistically significant**
- Consistent benefit seen with Dato-DXd across all efficacy endpoints in patients with **NSQ histology**
- The tolerability profile remains manageable and **no new safety signals** were identified
- TROP2 normalized membrane ratio as measured by quantitative continuous scoring has been shown to predict clinical response to Dato-DXd in an exploratory TROPION-Lung01 analysis[1]

The results of TROPION-Lung01 support the use of Dato-DXd as a potential new therapeutic option for patients with previously treated NSQ NSCLC eligible for subsequent therapy

1. Garassino M, et al. Presented at WCLC 2024, San Diego, CA, USA, September 7–10, 2024 (Abstract PL02.11).

Normalized Membrane Ratio of TROP2 by Quantitative Continuous Scoring is Predictive of Clinical Outcomes in TROPION-Lung01

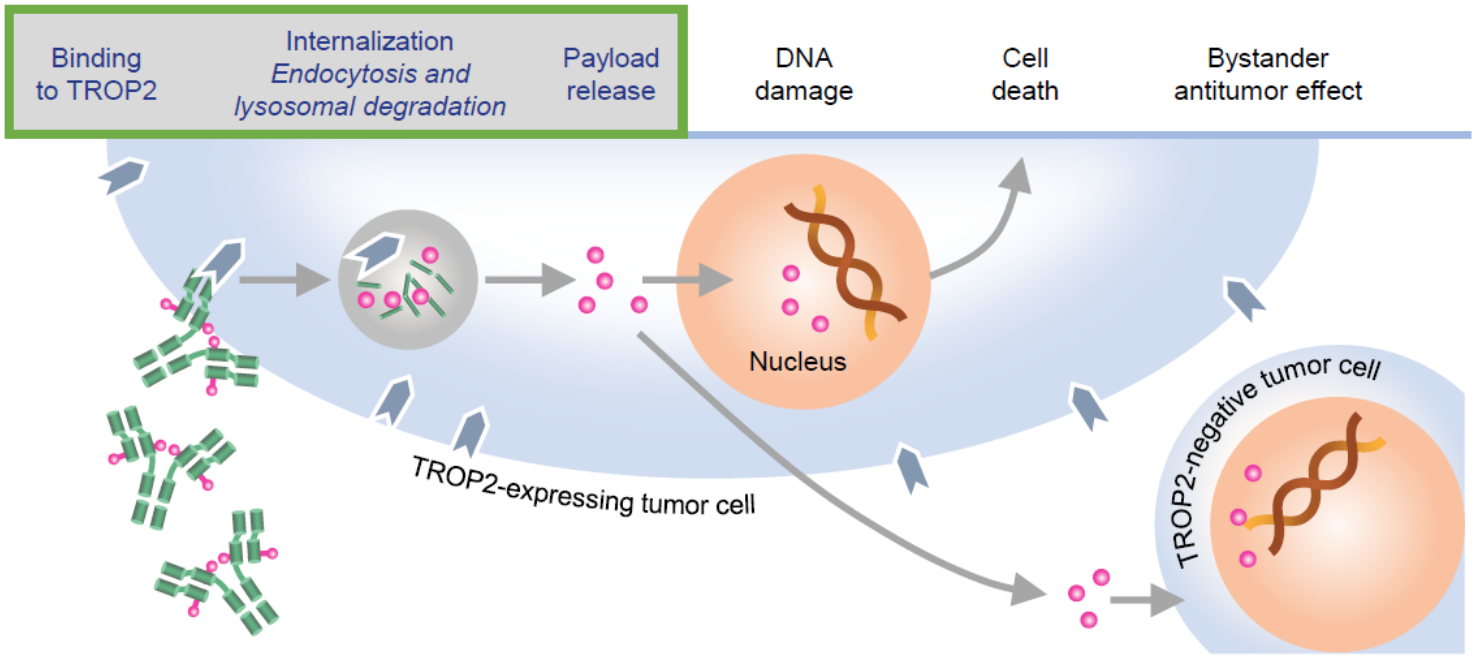
Marina Chiara Garassino,[1] Jacob Sands,[2] Luis Paz-Ares,[3] Aaron Lisberg,[4] Melissa Johnson,[5] Maurice Pérol,[6] Danielle Carroll,[7] Ansh Kapil,[8] Vincent Haddad,[7] Deise Uema,[9] Hadassah Sade,[8] Myung-Ju Ahn,[10]

[1]The University of Chicago, Chicago, IL, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]Universidad Complutense & CiberOnc, Hospital Universitario 12 de Octubre, Madrid, Spain; [4]Jonsson Comprehensive Cancer Center at UCLA, Los Angeles, CA, USA; [5]Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN, USA; [6]Léon-Bérard Cancer Center, Lyon, France; [7]AstraZeneca, Cambridge, UK; [8]AstraZeneca, Munich, Germany; [9]Daiichi Sankyo, Basking Ridge, NJ, USA; [10]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Background

- Datopotamab deruxtecan (Dato-DXd) is a TROP2-directed ADC with a plasma-stable linker[1,2]
- Dato-DXd must bind to membrane TROP2 and be internalized to release the cytotoxic payload[2]
- Dato-DXd has demonstrated statistically significant PFS improvement vs docetaxel in patients with advanced/metastatic NSCLC[3]
- Conventional IHC scoring has not predicted response to TROP2-directed ADCs in patients with NSCLC[4,5]
- Initial biomarker discovery was conducted on samples from patients with NSCLC in the TROPION-PanTumor01 study[6]

Dato-DXd mechanism of action[2]



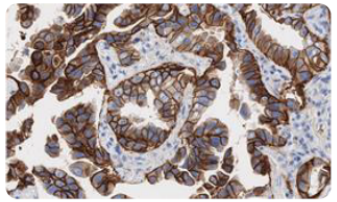
We hypothesized that a more precise and quantitative assessment of TROP2 expression **on the cell membrane and in the cytoplasm** may predict efficacy of Dato-DXd in patients with NSCLC

1. Okajima D, et al. Mol Cancer Ther 2021;20:2329–40; 2. Dent R, et al. Future Oncol 2023;19;2349–59;
3. Ahn MJ, et al. Oral presentation at ESMO 2023 (Abstract LBA12); 4. Shimizu T, et al. J Clin Oncol 2023;41:4678–87;
5. Heist RS, et al. J Clin Oncol 2017;35:2790–7; 6. Spitzmueller A, et al, 2023; International Patent Application No. PCT/IB2023/052428.
ADC, antibody-drug conjugate; Dato-DXd, datopotamab deruxtecan; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; PFS, progression-free survival; TROP2, trophoblast cell-surface antigen 2.

TROP2 Normalized Membrane Ratio (NMR) measured by Quantitative Continuous Scoring (QCS)

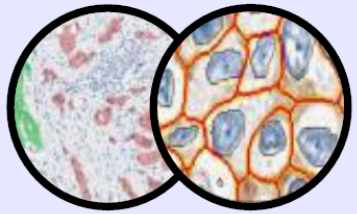
QCS is a novel, fully-supervised computational pathology approach that precisely quantifies and locates targets like TROP2

1 IHC with TROP2 Assay



2 Whole Slide Imaging

3 Automated Image Analysis (QCS)

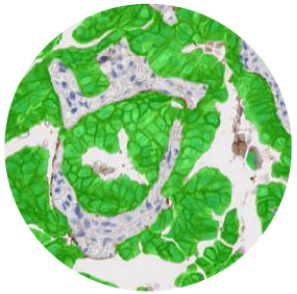


4 Patient Biomarker Status Determination

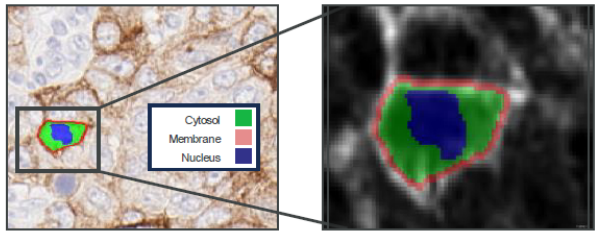
\+ ≥75% of tumor cells with TROP2 NMR ≤0.56

\- <75% of tumor cells with TROP2 NMR ≤0.56*

Differentiates tumor from non-tumor



Measures OD in each tumor cell



Membrane and cytoplasm optical density (OD)

Calculates TROP2 NMR for every tumor cell

$$\frac{\text{Membrane OD}}{\text{Membrane OD + Cytoplasm OD}}$$

Lower NMR → higher cytoplasm proportion

OD, optical density (a measure of staining intensity).
*Or >25% of cells with an NMR >0.56

TROPION-Lung01

Study Design (NCT04656652)[1]

Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

Without AGA*
- 1 or 2 prior lines, including platinum CT and anti–PD-(L)1 mAb therapy

With AGA
- Positive for *EGFR*, *ALK*, *NTRK*, *BRAF*, *ROS1*, *MET* exon 14 skipping, or *RET*
- 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb

R 1:1

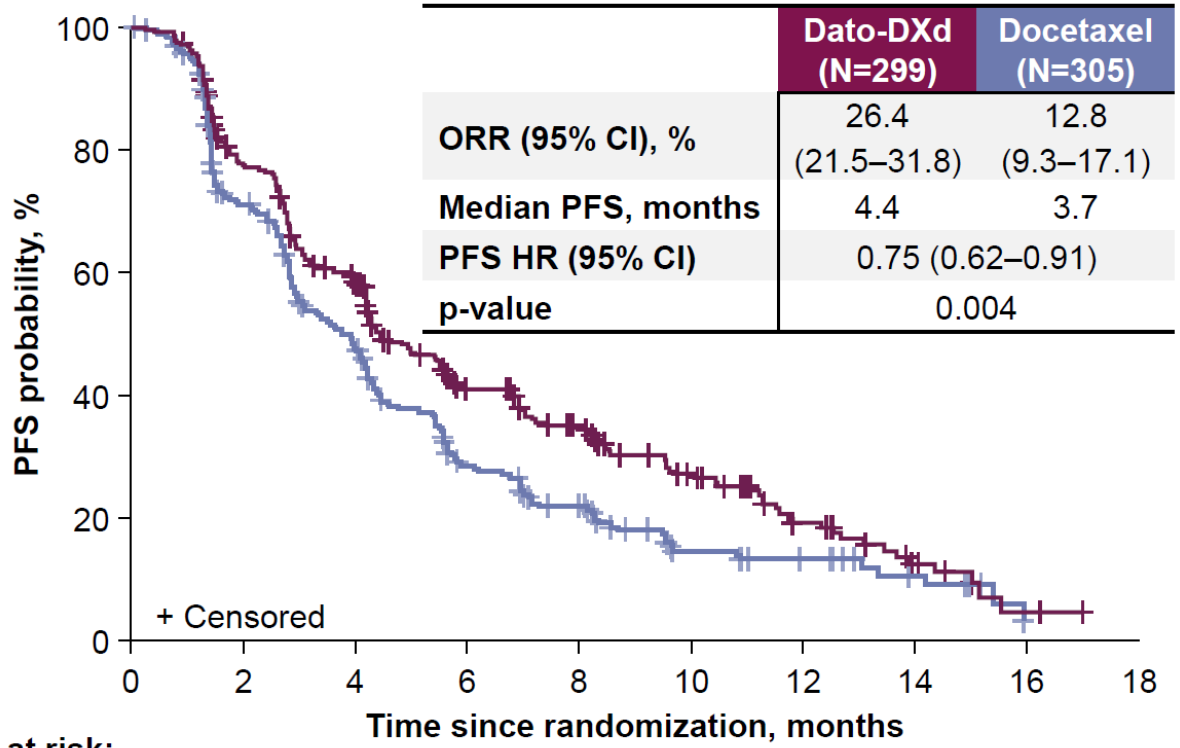
Dato-DXd
6 mg/kg q3w
N=299

Docetaxel
75 mg/m² q3w
N=305

Stratified by:
Histology†, AGA‡, anti–PD-(L)1 mAb included in most recent prior therapy, geography§

Dual Primary Endpoints: PFS by BICR; OS
Secondary Endpoints: ORR by BICR; DOR by BICR; Safety

PFS by BICR and ORR[1]



	Dato-DXd (N=299)	Docetaxel (N=305)
ORR (95% CI), %	26.4 (21.5–31.8)	12.8 (9.3–17.1)
Median PFS, months	4.4	3.7
PFS HR (95% CI)	0.75 (0.62–0.91)	
p-value	0.004	

No. at risk:

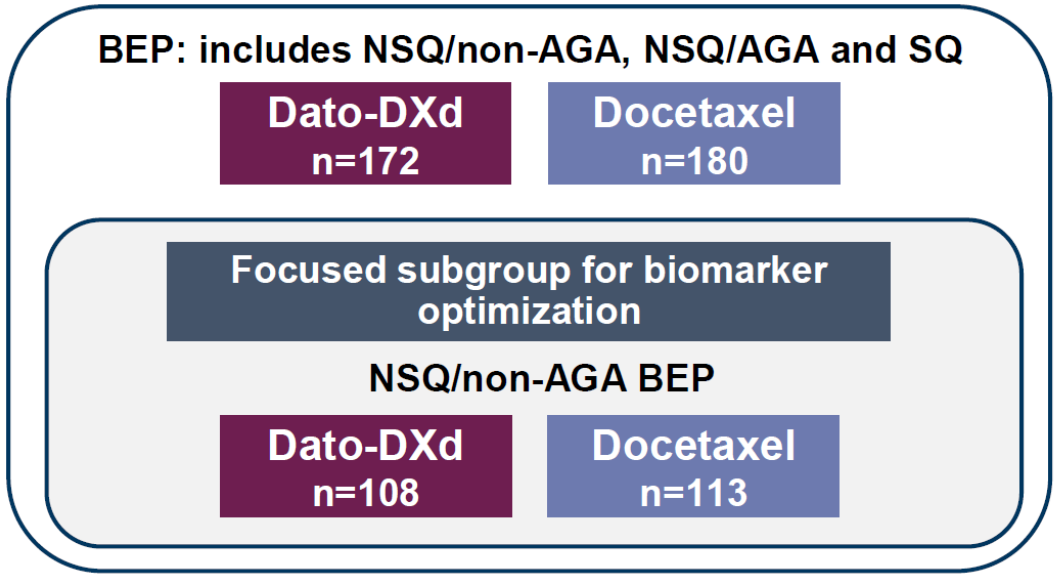
Dato-DXd	299	216	156	96	74	46	24	10	2	0
Docetaxel	305	186	120	63	42	19	14	7	0	0

1. Ahn MJ, et al. Oral presentation at ESMO 2023 (Abstract LBA12).
Enrollment period: February 19, 2021, to November 7, 2022. Data cutoff: March 29, 2023.
AGA, actionable genomic alterations; BICR, blinded independent central review; CI, confidence interval; CT, chemotherapy; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mAb, monoclonal antibody; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death (ligand) 1; q3w, every 3 weeks; R, randomized.
*Patients with *KRAS* mutations in the absence of known actionable genomic alterations are eligible; must meet prior therapy requirements for patients without actionable genomic alterations. †Squamous vs non-squamous. ‡Presence vs absence. §United States/Japan/Western Europe vs other geographic regions.

TROP2 QCS-NMR in TROPION-Lung01

Population and Methods

- Biomarker evaluable population (BEP) are those patients with available tissue samples for QCS determination
- Biomarker cut-points were optimized for PFS in NSQ/non-AGA patients from TROPION-Lung01
- Cut-points were confirmed through a robust statistical analysis plan (including bootstrapping, cross validation, and sensitivity analyses) and replication



Prevalence

Histology subgroup	Prevalence of TROP2 QCS-NMR+, % (n)
Biomarker-evaluable population, n=352	
NSQ	66% (179/272)
NSQ/non-AGA	63% (140/221)
NSQ/AGA	76% (39/51)
SQ	44% (35/80)

NSQ, non-squamous; SQ, squamous.

Baseline Characteristics by TROP2 QCS-NMR Status

Baseline characteristic		ITT population (N=604)[1]		Biomarker-evaluable population					
				Overall (n=352)		TROP2 QCS-NMR+ (n=214)		TROP2 QCS-NMR– (n=138)	
		Dato-DXd (N=299)	Docetaxel (N=305)	Dato-DXd (N=172)	Docetaxel (N=180)	Dato-DXd n=107	Docetaxel n=107	Dato-DXd n=65	Docetaxel n=73
Age, median (range), years		63 (26–84)	64 (24–88)	62 (26–84)	64.5 (24–88)	64 (26–84)	64 (24–88)	61 (33–77)	65 (30–79)
Male, %		61	69	59	66	56	64	65	68
Race, %	Asian	40	39	34	39	36	39	31	38
	White	41	41	47	39	44	36	52	44
	Black or African American	2	1	1	1	2	–	–	1
	Other/missing	17	18	18	22	19	25	17	16
ECOG PS 1, %		70	69	72	67	70	69	74	64
Current or former smoker, %		80	82	82	82	77	79	91	86
Brain metastasis at baseline, %*		17	15	16	15	14	17	18	12
≥3 prior lines of therapy, %		7	9	4	9	7	12	–	5
Histology, %	NSQ	78	77	76	78	81	86	68	67
	NSQ/non-AGA	61	60	62	62	64	67	62	56
	NSQ/AGA	17	17	14	16	18	19	6	11
	SQ	22	23	24	22	19	14	32	33

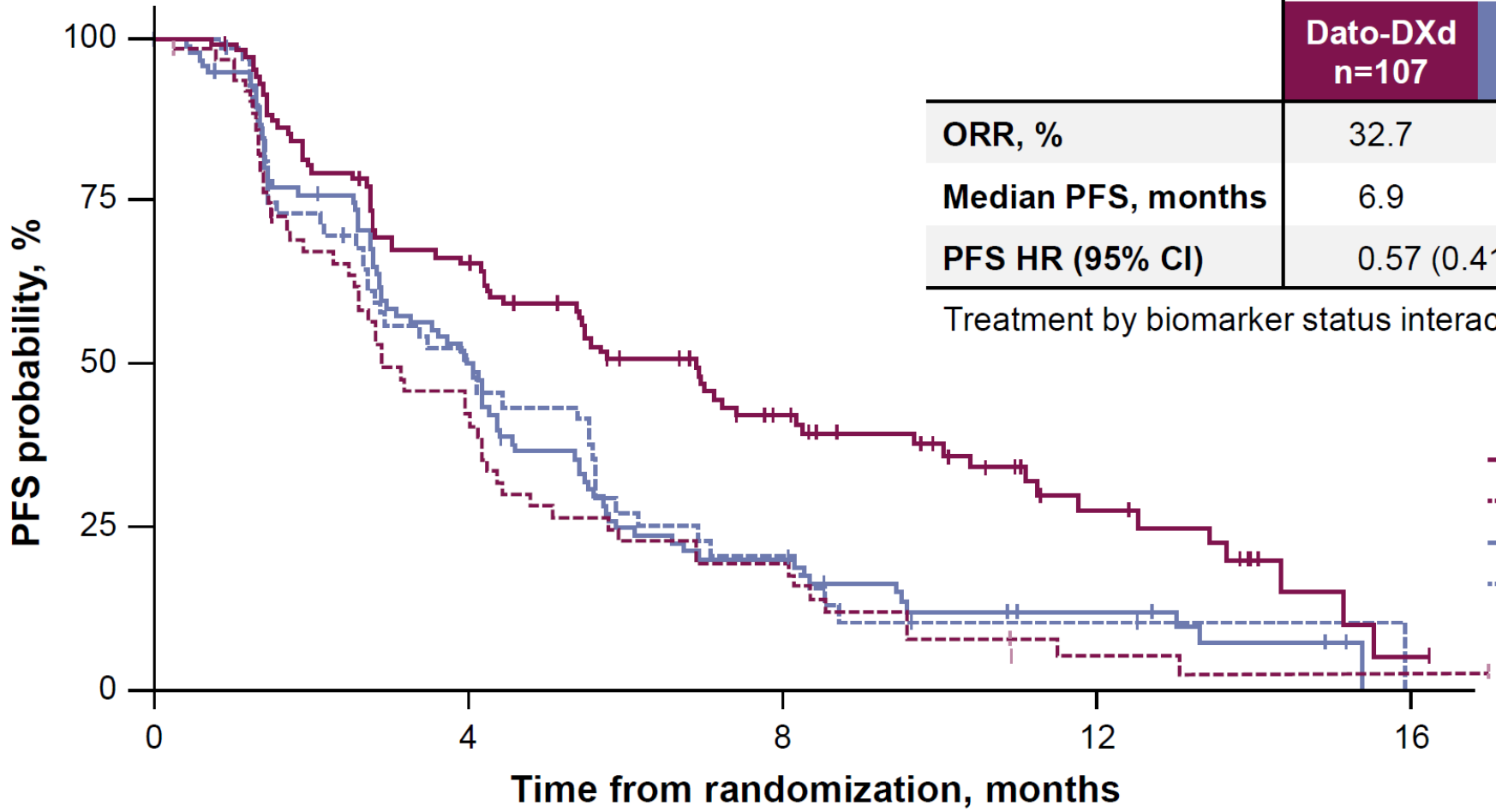
1. Ahn MJ, et al. Oral presentation at ESMO 2023 (Abstract LBA12).

*Patients who are no longer symptomatic and who require no treatment with corticosteroids and anticonvulsants and have recovered from acute toxic effects of radiation.

Overall BEP: Efficacy by TROP2 QCS-NMR Status

TROP2 QCS-NMR positivity is predictive for longer PFS with Dato-DXd in the biomarker-evaluable population

Biomarker-evaluable population, n=352



	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=107	Docetaxel n=107	Dato-DXd n=65	Docetaxel n=73
ORR, %	32.7	10.3	16.9	15.1
Median PFS, months	6.9	4.1	2.9	4.0
PFS HR (95% CI)	0.57 (0.41–0.79)		1.16 (0.79–1.70)	

Treatment by biomarker status interaction: p=0.0063

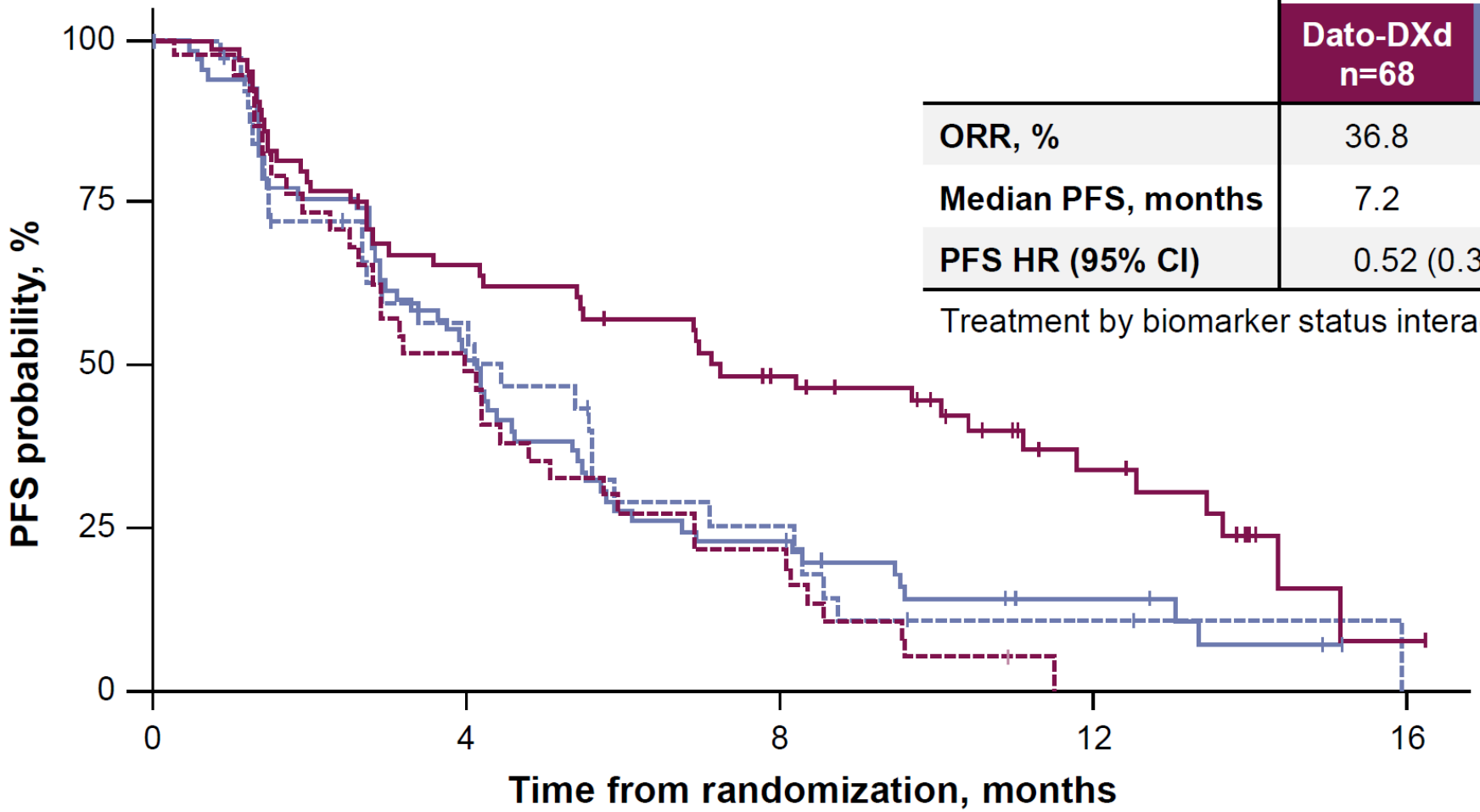
Data cutoff: March 29 2023

PFS HR (95% CI) by TROP2 QCS-NMR status (+ vs -) within treatment: Dato-DXd: 0.48 [0.33-0.69]; Docetaxel:0.97 [0.68-1.39]

NSQ/non-AGA BEP: Efficacy by TROP2 QCS-NMR Status

TROP2 QCS-NMR positivity is predictive for longer PFS with Dato-DXd in the NSQ/non-AGA biomarker-evaluable population

NSQ/non-AGA BEP, n=221



	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=68	Docetaxel n=72	Dato-DXd n=40	Docetaxel n=41
ORR, %	36.8	15.3	22.5	12.2
Median PFS, months	7.2	4.1	4.0	4.4
PFS HR (95% CI)	0.52 (0.35–0.78)		1.22 (0.74–2.00)	

Treatment by biomarker status interaction: p=0.0098

Data cutoff: March 29 2023

PFS HR (95% CI) by TROP2 QCS-NMR status (+ vs -) within treatment: Dato-DXd: 0.40 [0.25-0.64]; Docetaxel:0.94 [0.60-1.49]

Safety by TROP2 QCS-NMR Status

Treatment-related adverse events (TRAEs), n (%)		Biomarker-evaluable population (n=344*)			
		TROP2 QCS-NMR+		TROP2 QCS-NMR–	
		Dato-DXd n=106	Docetaxel n=102	Dato-DXd n=65	Docetaxel n=71
Any TRAE	All grades	92 (87)	94 (92)	56 (86)	58 (82)
	Grade ≥3	31 (29)	47 (46)	14 (22)	19 (27)
Treatment-related AESIs					
Stomatitis	All grades	57 (54)	23 (23)	29 (45)	10 (14)
	Grade ≥3	7 (7)	3 (3)	2 (3)	–
Ocular surface events	All grades	27 (25)	6 (6)	7 (11)	6 (8)
	Grade ≥3	3 (3)	–	1 (2)	–
Adjudicated ILD†	All grades	8 (8)	3 (3)	4 (6)	1 (1)
	Grade ≥3	3 (3)	1 (1)	1 (2)	–

Data cutoff: March 29 2023.
*Biomarker-evaluable population in safety analysis excludes patients who were randomized but did not receive treatment.
†ILD includes events that were adjudicated as ILD and related to use of Dato-DXd or docetaxel (includes cases of potential ILD/pneumonitis based on MedDRA v26.0 for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and preferred terms of respiratory failure and acute respiratory failure).
AESIs, adverse event of special interest; ILD interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized MedDRA query.

Conclusions

- TROP2 normalized membrane ratio (NMR) as measured by QCS reflects the expression of TROP2 in the membrane relative to total TROP2 (membrane and cytoplasm) and predicts outcomes in an exploratory TROPION-Lung01 analysis:
  - TROP2 QCS-NMR+ was more prevalent in patients with NSQ vs SQ histology (66% vs 44%)
  - Patients receiving Dato-DXd who were TROP2 QCS-NMR+ had a higher ORR and longer PFS compared with those who were TROP2 QCS-NMR–
  - Overall/grade 3+ adverse event rates with Dato-DXd were similar regardless of TROP2 QCS-NMR status
- Further investigation of this promising biomarker is ongoing in the first-line advanced/metastatic NSCLC trials AVANZAR (NCT05687266) and TROPION-Lung 10 (NCT06357533)

TROP2 QCS-NMR has the potential to be the first TROP2 biomarker and the first computational pathology biomarker for predicting clinical response to Dato-DXd in NSCLC

NeoCOAST-2: Efficacy and Safety of Neoadjuvant Durvalumab (D) + Novel Anticancer Agents + CT and Adjuvant D ± Novel Agents in Resectable NSCLC

Tina Cascone,[1] Florian Guisier,[2] Laura Bonanno,[3,4] Moishe Liberman,[5,6] Olivier Bylicki,[7] Amelia Insa,[8] Lorenzo Livi,[9] Romain Corre,[10] Thomas Egenod,[11] Agata Bielska,[12] Alula Yohannes,[13] Ray Mager,[13] Yun He,[12] Adam Dowson,[14] Lara McGrath,[12] Rakesh Kumar,[13] Italia Grenga,[12] Jonathan Spicer,[15] Patrick Forde[16]

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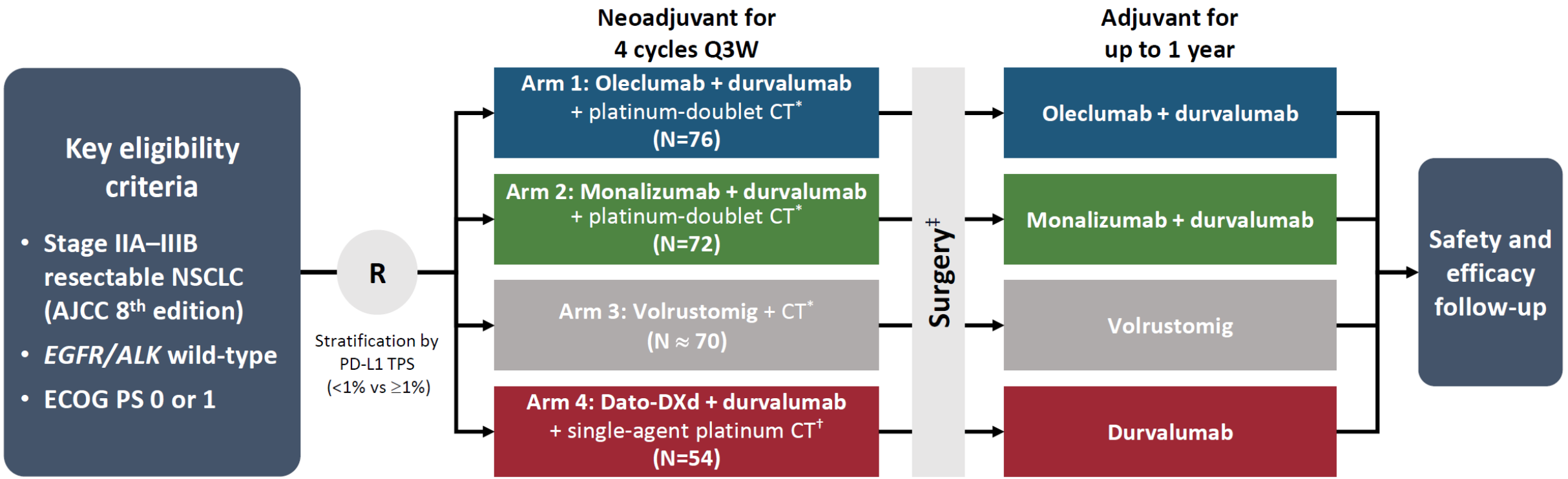
Background

- Durvalumab + oleclumab (anti-CD73) or monalizumab (anti-NKG2A) have demonstrated improved efficacy in COAST and NeoCOAST, two phase 2 studies in patients with early-phase NSCLC.[1,2]
- Datopotamab deruxtecan (Dato-DXd), a TROP2-directed antibody-drug conjugate, significantly improved PFS versus docetaxel in patients with locally advanced or metastatic NSCLC in the phase 3 TROPION-Lung01 study.[3]
- Perioperative anti-PD-(L)1 therapies + neoadjuvant CT have demonstrated improvements in EFS and pCR rates compared with CT alone, as reported by the phase 3 studies AEGEAN, KEYNOTE-671 and Checkmate 77T.[4–6]
- The phase 2 NeoCOAST-2 platform study (NCT05061550) is evaluating the efficacy and tolerability of novel perioperative treatment combinations in patients with resectable NSCLC.

1. Herbst RS, et al. *J Clin Oncol* 2022;40:3383–93; 2. Cascone T, et al. *Cancer Discov* 2023;13;2394–411; 3. Ahn M-J, et al. *Ann Oncol* 2023;34;S1305–6; 4. Heymach JV, et al. *N Engl J Med* 2023;389;1672–84; 5. Wakelee H, et al. *N Engl J Med* 2023;389:491–503; 6. Cascone T, et al. *N Engl J Med* 2024;390:1756–69.
CT, chemotherapy; EFS, event-free survival; pCR, pathological complete response; NSCLC, non-small-cell lung cancer; PD-(L)1, programmed cell death (ligand) 1; PFS, progression-free survival; TROP2, trophoblast cell surface antigen 2.

NeoCOAST-2: Open-label, multi-arm platform study in perioperative NSCLC



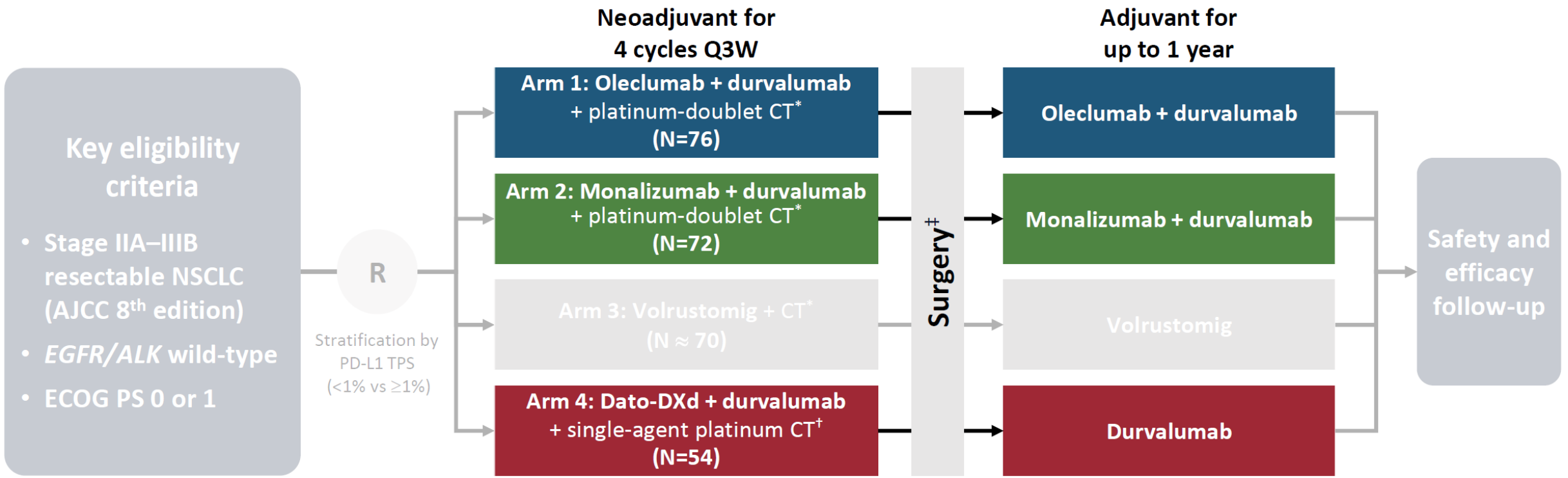
Primary endpoints
- pCR rate§
- Safety and tolerability

Key secondary endpoints
- mPR rate§ and EFS
- Feasibility of surgery

Statistical considerations
- This study was not powered to make direct statistical comparisons between arms.
- Descriptive statistics are summarised and presented.
- The primary intent was to look for preliminary efficacy signals by calculating pCR rates.

*Carboplatin + paclitaxel for squamous tumour histology, pemetrexed + cisplatin or carboplatin for non-squamous tumour histology. †Physician's choice of carboplatin or cisplatin. ‡Within 40 days of the last dose of neoadjuvant treatment. §Proportion of patients with no viable tumour cells and ≤10% residual viable tumour cells, respectively, in resected tumour specimen and sampled nodes at surgery. CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; EFS, event-free survival; mPR, major pathological response; NSCLC, non-small-cell lung cancer; pCR, pathological complete response; PD-L1, programmed cell death ligand-1; Q3W, every 3 weeks; R, randomised; TPS, tumour proportion score.

NeoCOAST-2: Open-label, multi-arm platform study in perioperative NSCLC



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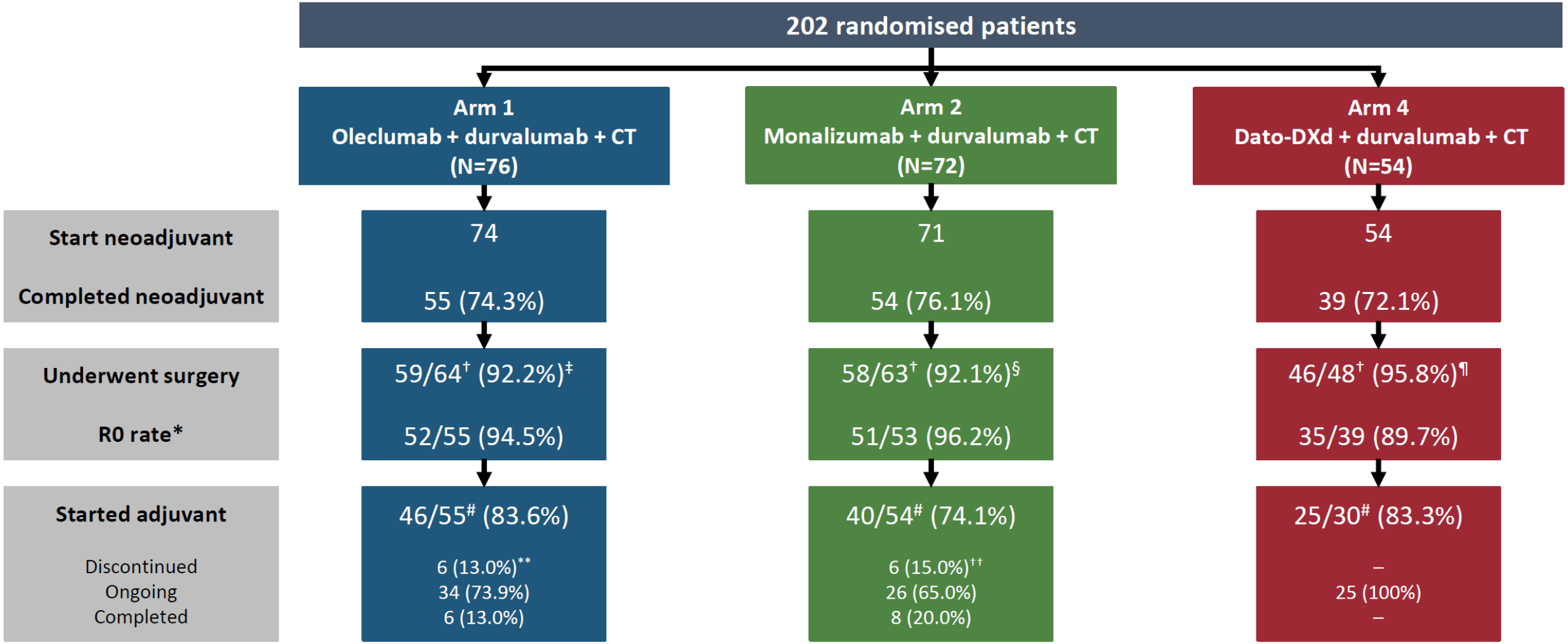
Baseline patient characteristics were well balanced across arms

	Arm 1 Oleclumab + durvalumab + CT N=76	Arm 2 Monalizumab + durvalumab + CT N=72	Arm 4 Dato-DXd + durvalumab + CT N=54
Median age, years (range)	66.5 (30–79)	66.0 (48–83)	65.0 (38–81)
Female/Male, n (%)	29 (38.2)/47 (61.8)	29 (40.3)/43 (59.7)	22 (40.7)/32 (59.3)
Race, n (%)			
Asian	7 (9.2)	5 (6.9)	5 (9.3)
Black or African American	1 (1.3)	0	0
White	48 (63.2)	43 (59.7)	37 (68.5)
Not reported	20 (26.3)	24 (33.3)	12 (22.2)
ECOG PS 0/1, n (%)	45 (61.6)/28 (38.4)*	49 (69.0)/22 (31.0)†	36 (66.7)/18 (33.3)
PD-L1 <1%/PD-L1 ≥1% TPS, n (%)	24 (31.6)/52 (68.4)	24 (33.3)/48 (66.7)	13 (24.1)/41 (75.9)
Stage, n (%)‡			
IIA	7 (9.2)	7 (9.7)	2 (3.8)
IIB	16 (21.1)	19 (26.4)	13 (24.5)
IIIA	40 (52.6)	33 (45.8)	27 (50.9)
IIIB	13 (17.1)	13 (18.1)	11 (20.8)
Histology, n (%)			
Adenocarcinoma	50 (65.8)	46 (63.9)	33 (61.1)
Squamous cell carcinoma	24 (31.6)	20 (27.8)	17 (31.5)
Other	2 (2.6)	6 (8.3)	4 (7.4)

- Consistent with real-world practice, the majority of patients received carboplatin compared with cisplatin: 72%, 77%, and 87% of patients received carboplatin vs cisplatin in Arms 1, 2, and 4, respectively.

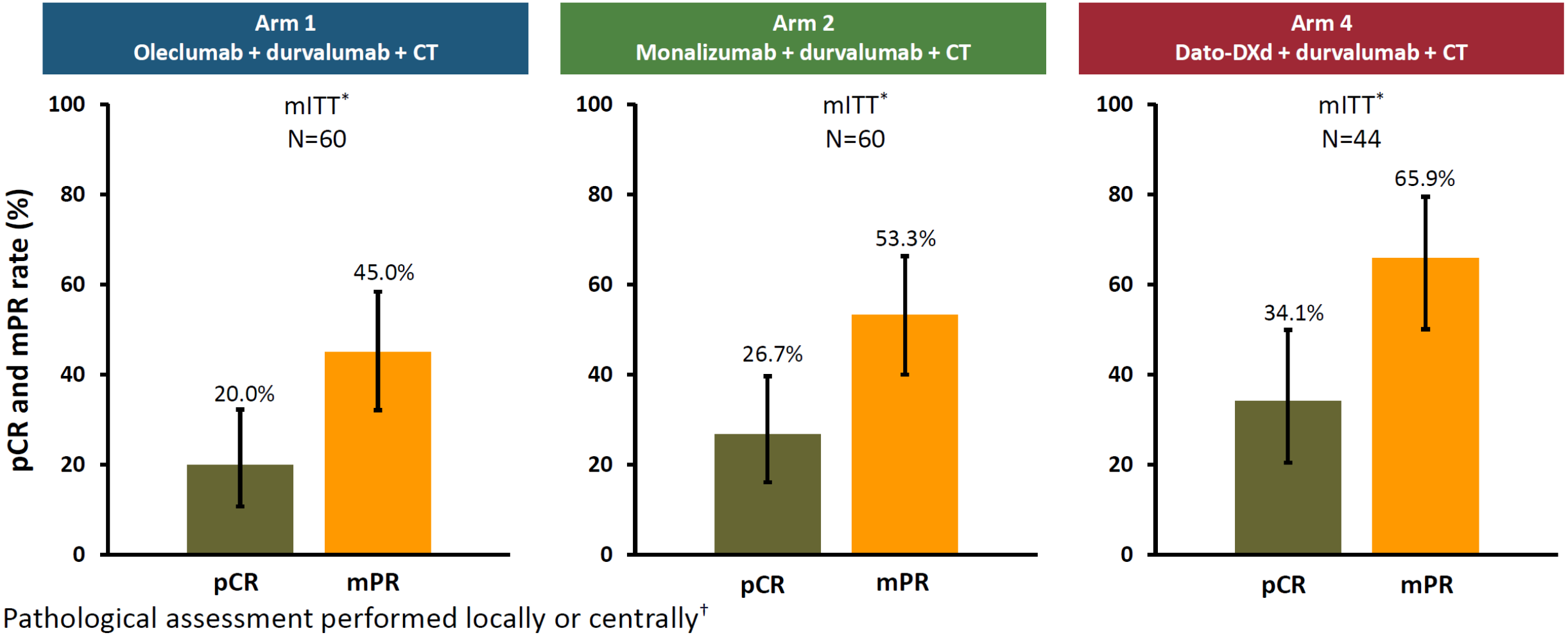
Data cut-off: 17 June 2024. *Data missing for 3 patients; †Data missing for 1 patient; ‡Data missing for 1 patient in Arm 4. CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death ligand 1; TPS, tumour proportion score.

Summary of treatment disposition and surgery



Data cut-off: 17 June 2024. Median (range) of number of adjuvant cycles completed in Arm 1, 2, and 4 are 6 (1–12), 7.5 (1–12) and 2 (1–6), respectively. *Margins are calculated from patients who completed surgery and had data available at data cut-off. †Denominator includes patients who underwent surgery or were ineligible for surgery at data cut-off. ‡No surgery: AE=1, PD=2, other=2. §No surgery: AE=2, other=3. ¶No surgery: investigator decision=1, other=1. #Denominator includes patients who underwent surgery and had enough follow-up time to start adjuvant treatment. **Reason for discontinuation of IP: AE=2, PD=3, other=1. ††Reason for discontinuation of IP: AE=3, PD=2, other=1.
AE, adverse event; CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; IP, investigational product; PD, progressive disease.

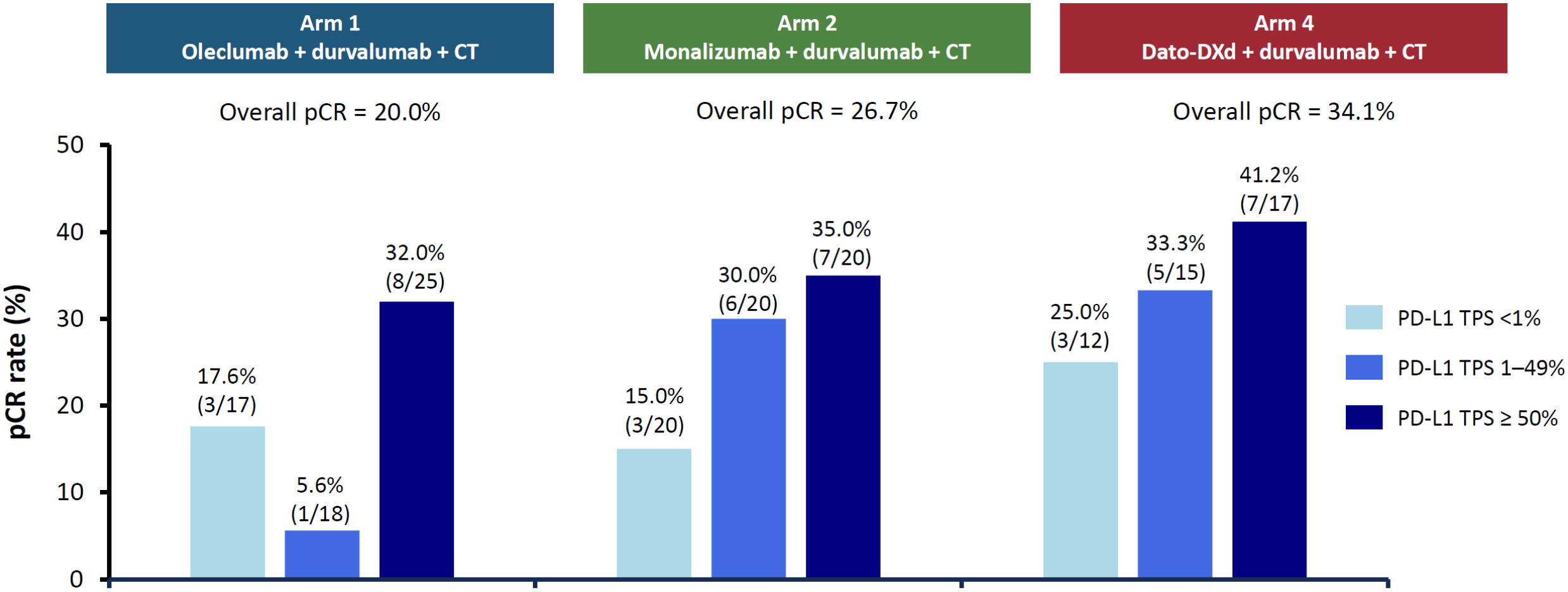
NeoCOAST-2: pCR and mPR rates across treatment arms



Pathological assessment performed locally or centrally†

Data cut-off: 17 June 2024. Error bars represent 95% confidence intervals.
*The mITT population includes all randomised patients with confirmed NSCLC histology who received at least 1 dose of study treatment and had central or local data available at the data cut-off, including those who were unable to receive or complete surgery. Some patients who underwent surgery did not have pathology results available at data cut-off. †Blind independent pathological review was used where available; proportion of local results were Arm 1: 9/55 (16.3%); Arm 2: 6/55 (11%); Arm 4: 16/41 (39%). Denominator includes only those patients who had surgery. CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; mITT, modified intention-to-treat population; mPR, major pathological response; NSCLC, non-small-cell lung cancer; pCR, pathological complete response.

pCR rates across baseline PD-L1 expression subgroups

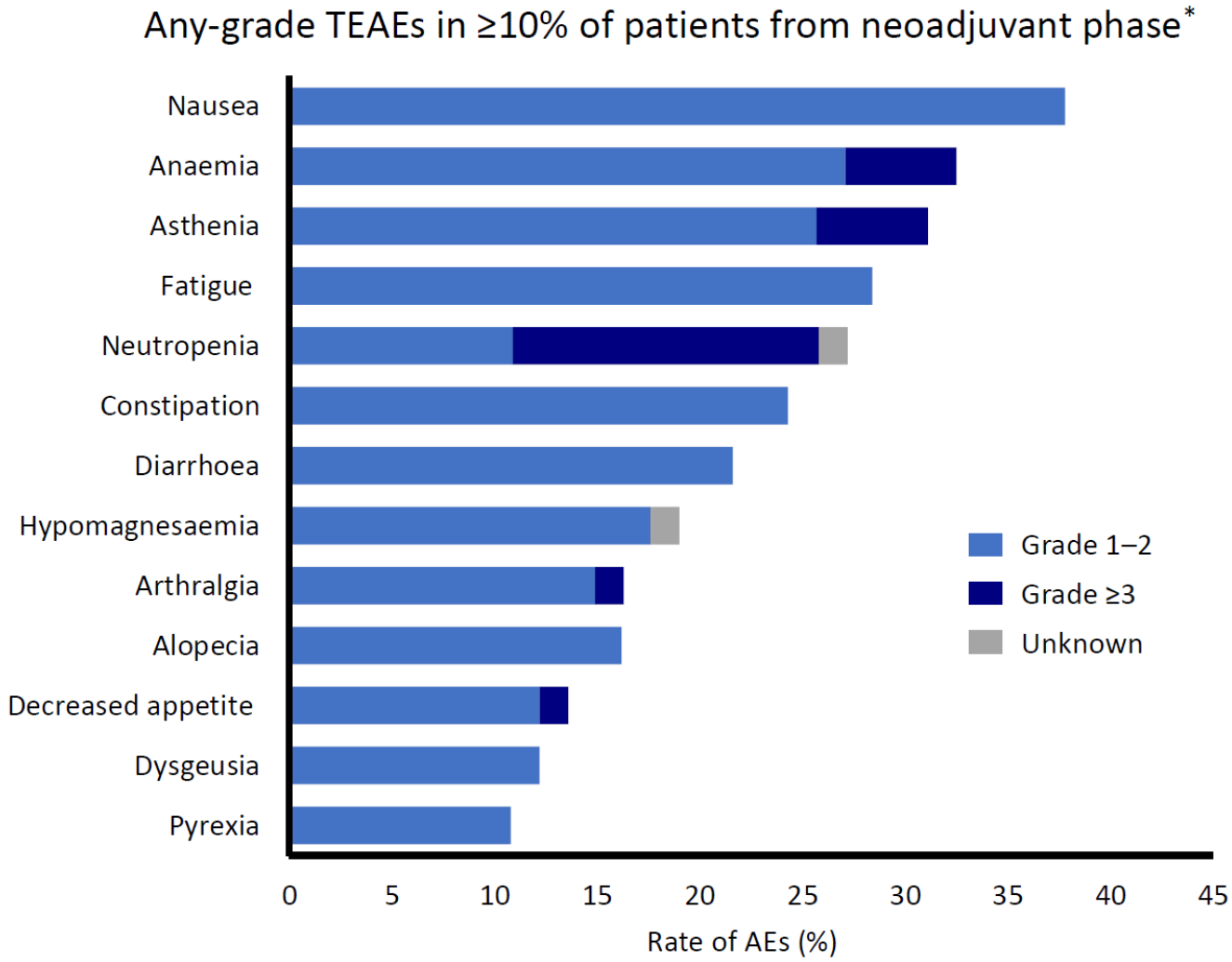


Data cut-off: 17 June 2024. Based on the modified intention-to-treat population which includes all randomised patients with confirmed NSCLC histology who received at least 1 dose of study treatment and had data available at data cut-off, including those who were unable to receive or complete surgery.
Baseline PD-L1 status is assessed using central (Ventana SP263) or local testing (Ventana SP263, pharmDx 28-8, or pharmDx 22C3). Proportion of central results were Arm 1: 12/60 (20%); Arm 2: 18/60 (30%); Arm 4: 13/44 (30%). Local results are reported for all other patients. CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; NSCLC, non-small-cell lung cancer; pCR, pathological complete response; PD-L1, programmed cell death ligand 1; TPS, tumour proportion score.

Safety profile of Arm 1: Oleclumab + durvalumab + CT

n (%)	Neoadjuvant N=74	Post-surgery N=59	Adjuvant N=46
Any TEAE	72 (97.3)	33 (55.9)	36 (78.3)
Any TRAE	70 (94.6)	3 (5.1)	29 (63.0)
Grade ≥3 TEAE	26 (35.1)	14 (23.7)	4 (8.7)
Grade ≥3 TRAE	23 (31.1)	0	2 (4.3)
AE leading to discontinuation	6 (8.1)	1 (1.7)	3 (6.5)
SAE	12 (16.2)	9 (15.3)	3 (6.5)
Any SAE with outcome of death	1 (1.4)[a]	2 (3.4)[b]	0

[a]Due to intestinal ischaemia related to chemotherapy (carboplatin and paclitaxel).
[b]Both due to respiratory failure related to surgery; both patients had a lobectomy.

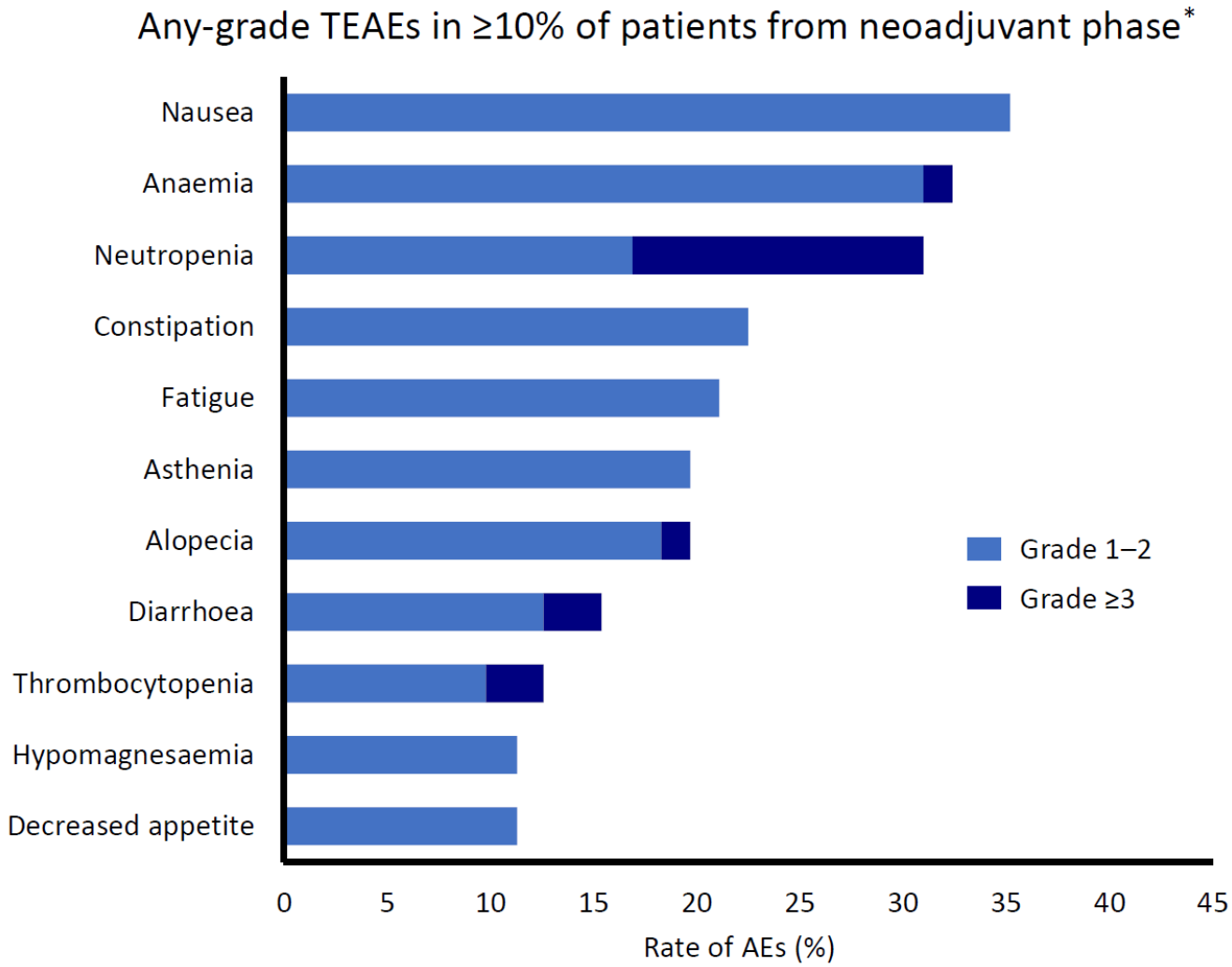


Data cut-off: 17 June 2024. The median (range) of number of adjuvant cycles completed per protocol in Arm 1 is 6 (1–12) as of data cut-off.
*Only neoadjuvant phase shown due to maturity of the data.
Patients with multiple occurrences in the same category are counted once per category regardless of the number of occurrences.
AE, adverse event; CT, chemotherapy; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Safety profile of Arm 2: Monalizumab + durvalumab + CT

n (%)	Neoadjuvant N=71	Post-surgery N=58	Adjuvant N=40
Any TEAE	70 (98.6)	36 (62.1)	29 (72.5)
Any TRAE	64 (90.1)	9 (15.5)	16 (40.0)
Grade ≥3 TEAE	29 (40.8)	14 (24.1)	8 (20.0)
Grade ≥3 TRAE	21 (29.6)	1 (1.7)	5 (12.5)
AE leading to discontinuation	9 (12.7)	0	3 (7.5)
SAE	12 (16.9)	14 (24.1)	5 (12.5)
Any SAE with outcome of death	0	3 (5.2)[a]	1 (2.5)[b]

[a]Due to sepsis (related to pneumonectomy), septic shock (related to lobectomy) and renal failure (related to bilobectomy).
[b]Due to cardiorespiratory arrest related to durvalumab and monalizumab.

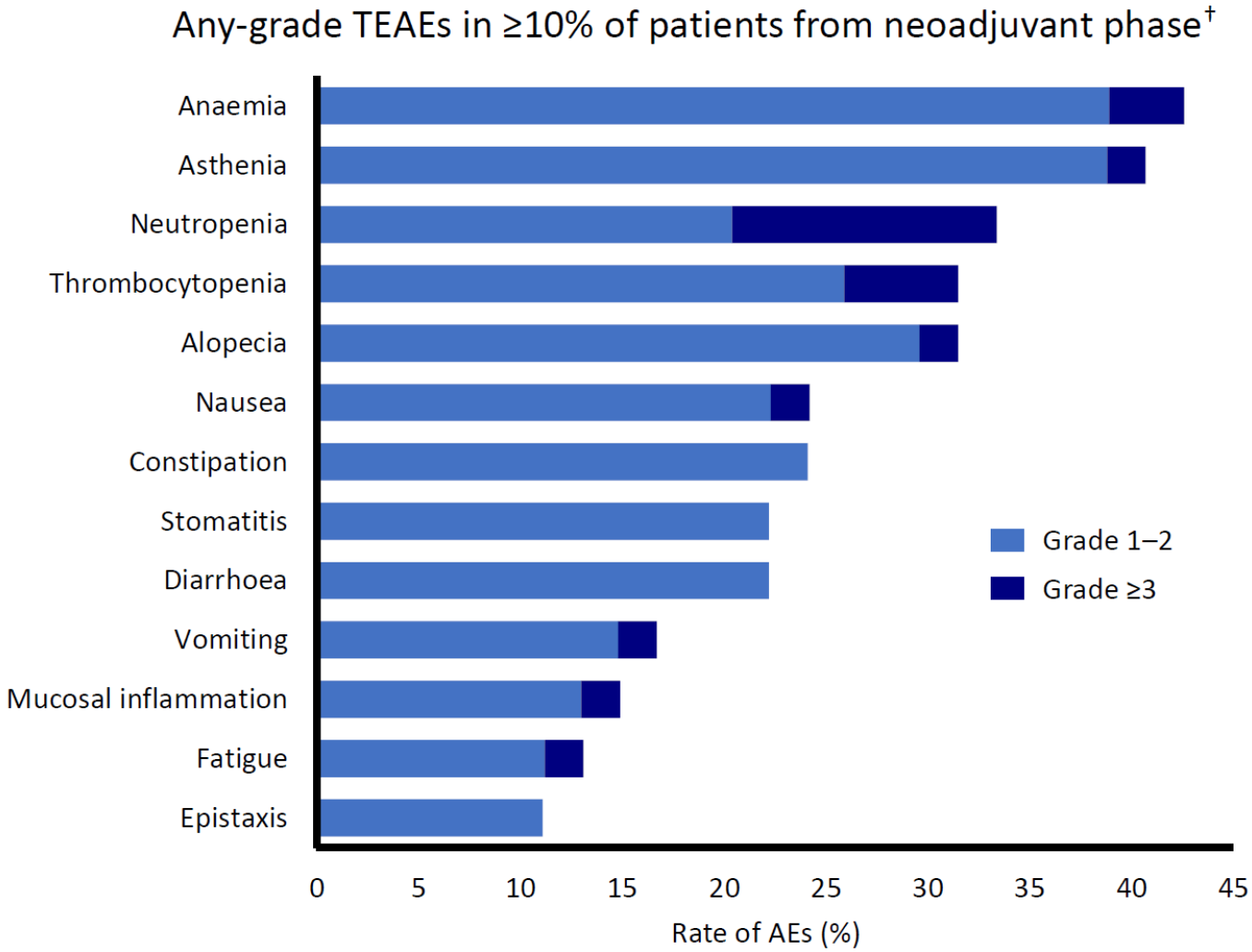


Data cut-off: 17 June 2024. The median (range) of number of adjuvant cycles completed per protocol in Arm 2 is 7.5 (1–12) as of data cut-off.
*Only neoadjuvant phase shown due to maturity of the data.
Patients with multiple occurrences in the same category are counted once per category regardless of the number of occurrences.
AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Safety profile of Arm 4: Dato-DXd + durvalumab + CT

n (%)	Neoadjuvant N=54	Post-surgery N=46	Adjuvant N=25
Any TEAE	53 (98.1)	24 (52.2)	11 (44.0)
Any TRAE	52 (96.3)	6 (13.0)	5 (20.0)
Grade ≥3 TEAE	13 (24.1)	4 (8.7)	1 (4.0)
Grade ≥3 TRAE	10 (18.5)	0	0
AE leading to discontinuation	4 (7.4)	0	0
SAE	10 (18.5)	7 (15.2)	1 (4.0)
Any SAE with outcome of death	0	1 (2.2)[a]	0

[a]Due to idiopathic pulmonary fibrosis unrelated to treatment.*



Data cut-off: 17 June 2024. The median (range) of number of adjuvant cycles completed per protocol in Arm 4 is 2 (1–6) as of data cut-off.
*Unrelated per principal investigator, independent adjudication is pending.
†Only neoadjuvant phase shown due to maturity of the data.
Patients with multiple occurrences in the same category are counted once per category regardless of the number of occurrences.
AE, adverse event; Dato-DXd, datopotamab deruxtecan; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Conclusions

- In perioperative NSCLC, novel combinations demonstrated promising efficacy, with numerically higher pCR and/or mPR rates compared to historical benchmarks.
  - Oleclumab + durvalumab + CT: pCR rate 20.0%; mPR rate 45.0%
  - Monalizumab + durvalumab + CT: pCR rate 26.7%; mPR rate 53.3%
  - Dato-DXd + durvalumab + CT: pCR rate 34.1%; mPR rate 65.9%

- Treatments in all arms demonstrated a manageable safety profile and surgical rates comparable to currently approved regimens.[1–3]

- **This is the first global phase 2 study showing encouraging efficacy and manageable safety profile of an antibody-drug conjugate in the neoadjuvant setting for patients with resectable NSCLC.**

1. Wakelee H, et al. *N Engl J Med* 2023;389;491–503; 2. Forde PM, et al. *N Engl J Med* 2022;386;1973–85;
3. Heymach JV, et al. *N Engl J Med* 2023;389:1672–84.
CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; mPR, major pathological response; NSCLC, non-small-cell lung cancer; pCR, pathological complete response.

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

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On behalf of the DESTINY-Lung03 investigators

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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 HER2-OE NSCLC
- T-DXd (5.4 mg/kg) is approved in several regions including the US and EU for previously treated HER2 (ERBB2)-mutant unresectable or metastatic NSCLC, and in the US for previously treated unresectable or metastatic HER2-positive (IHC 3+) solid tumors with no alternative therapies[8–10]
  - The approval in HER2-positive solid tumors was supported by DESTINY-Lung01 cohort 1a results; ORRs of 34.1% (overall) and 52.9% (IHC 3+ subgroup) were reported for T-DXd-treated patients with HER2-OE NSCLC[8,11,12]
- DESTINY-Lung03 (NCT04686305) is evaluating the safety and efficacy of T-DXd-based regimens in HER2-OE NSCLC
  - Here, we report results from Part 1 arm 1D, which evaluated T-DXd monotherapy (5.4 mg/kg) 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

1. Uzunparmak B, et al. *Ann Oncol*. 2023;34:1035–1046; 2. Heinmöller P, et al. *Clin Cancer Res*. 2003;9:5238–5243; 3. Zinner RG, et al. *Lung Cancer*. 2004;44:99–110; 4. Takenaka M, et al. *Anticancer Res*. 2011;31:4631–4636; 5. Lui L, et al. *J Thorac Oncol*. 2010;5:1922–1932; 6. Kim EK, et al. *PLoS One*. 2017;12:e0171280; 7. Ren S, et al. *ESMO Open*. 2022;7:100395; 8. Enhertu (fam-trastuzumab deruxtecan-nxki): highlights of prescribing information. 2024. Available from: www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s028lbl.pdf (Accessed August 6, 2024); 9. Enhertu (trastuzumab deruxtecan): summary of product characteristics. 2024. Available from: https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf (Accessed August 6, 2024); 10. AstraZeneca. Press release. October 23, 2023. Available from: https://www.astrazeneca.com/media-centre/press-releases/2023/enhertu-approved-in-the-eu-as-the-first-her2-directed-therapy-for-patients-with-her2-mutant-advanced-non-small-cell-lung-cancer.html (Accessed August 6, 2024); 11. Smit EF, et al. *Lancet Oncol*. 2024;25:439–454; 12. Smit EF, et al. *Lancet Oncol*. 2024;25:439–454 (Supplementary Information)

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

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

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)

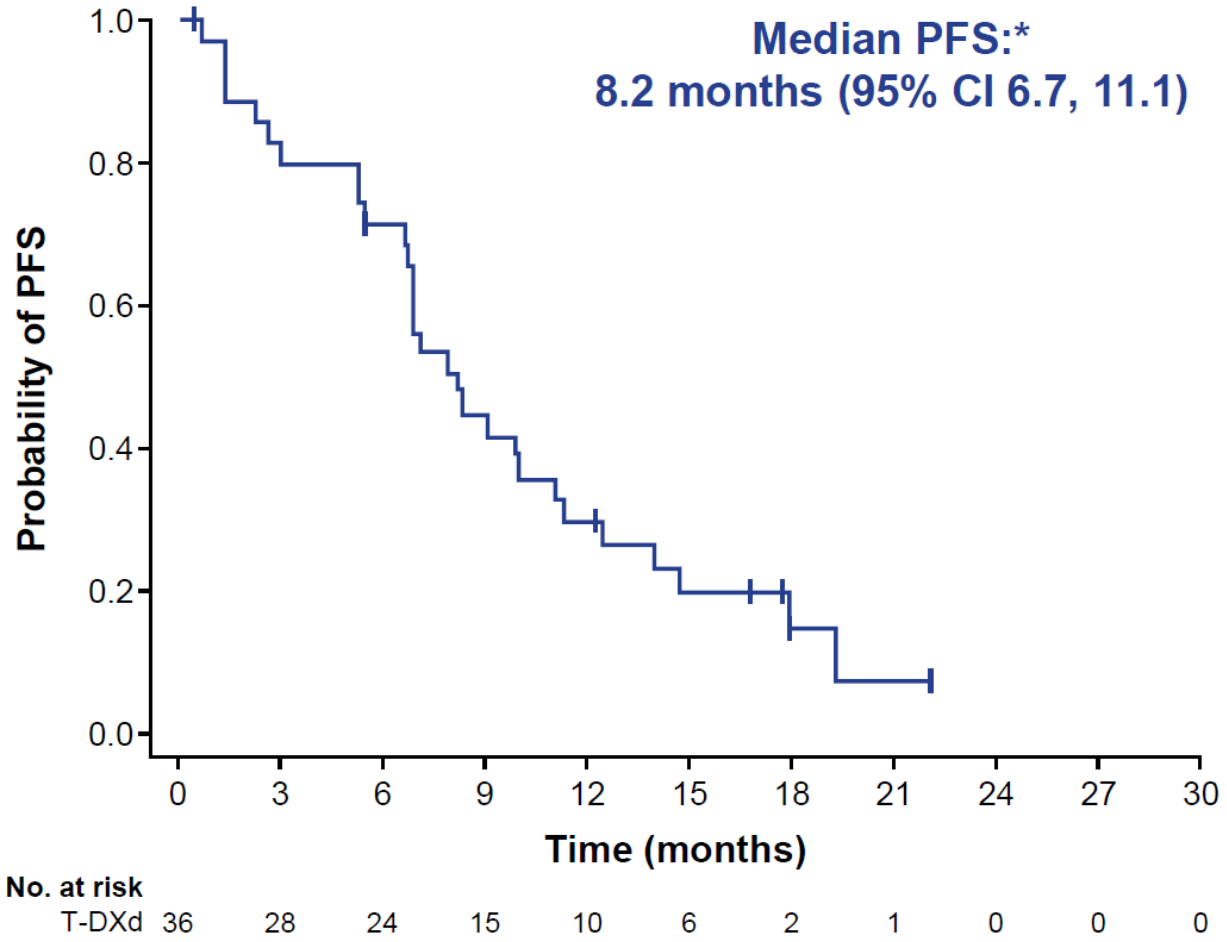
CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PD-L1, programmed cell death ligand 1; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor

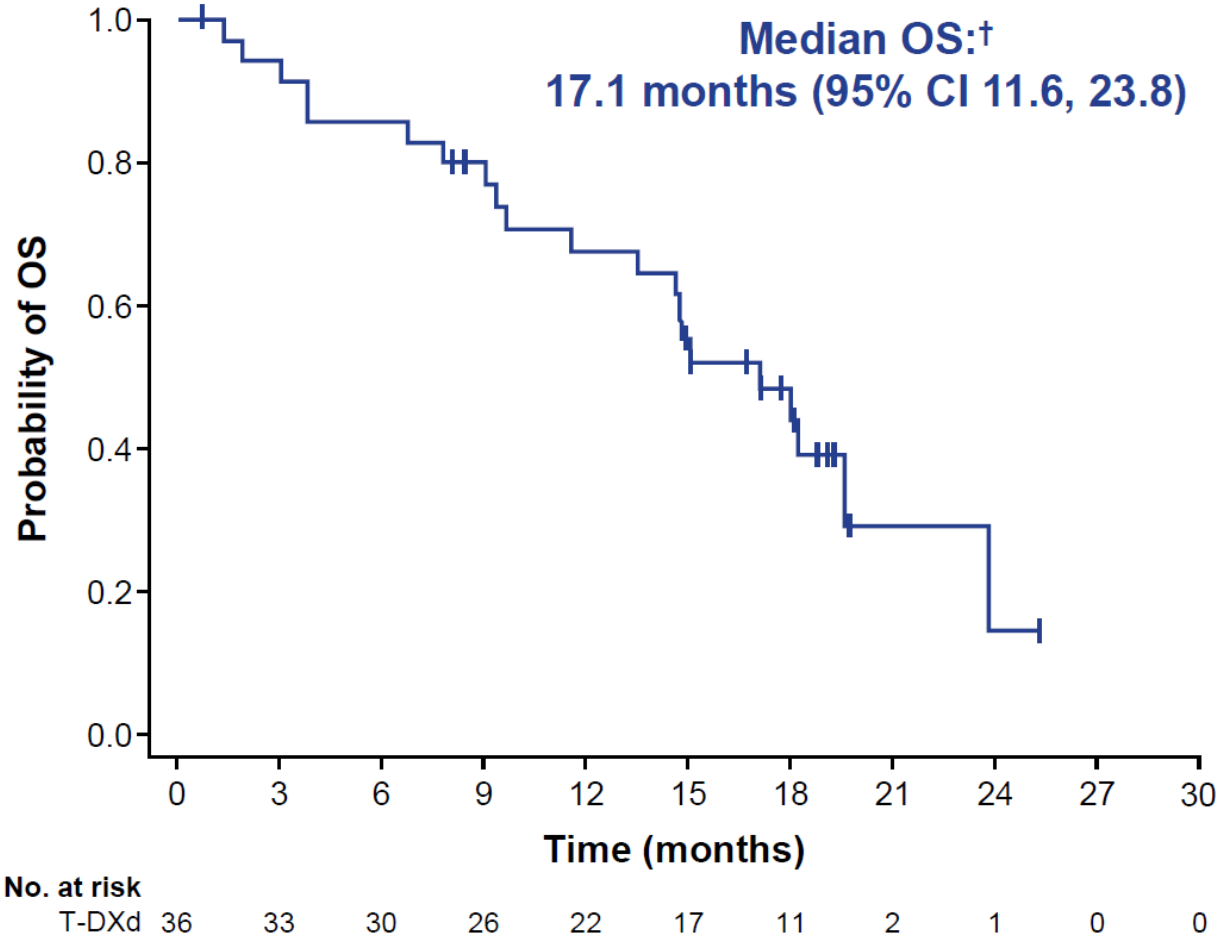
Response outcomes: ORR, DOR, and DCR

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

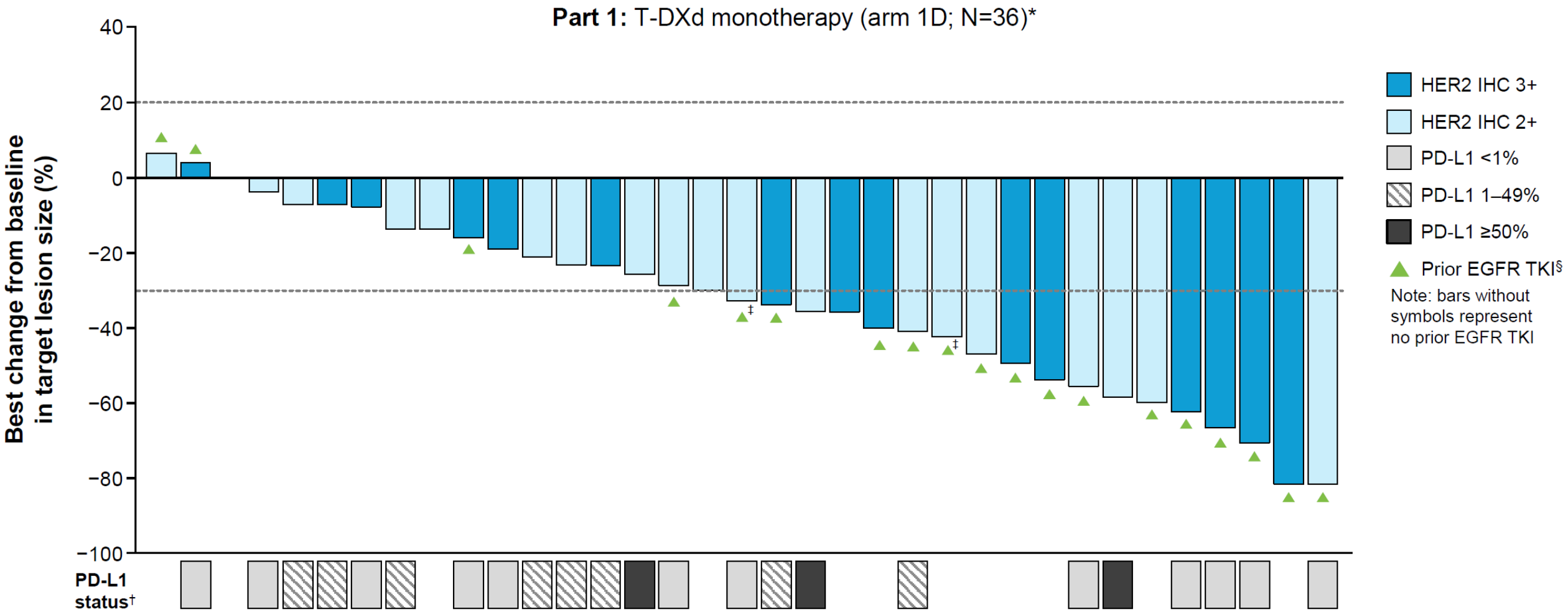




Symbols indicate a censored observation; PFS was assessed by investigator using RECIST v1.1. *Patients without disease progression or who had died, or who had disease progression or died after two or more missed visits, were censored at the last evaluable RECIST v1.1 assessment, or at the date of first 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



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

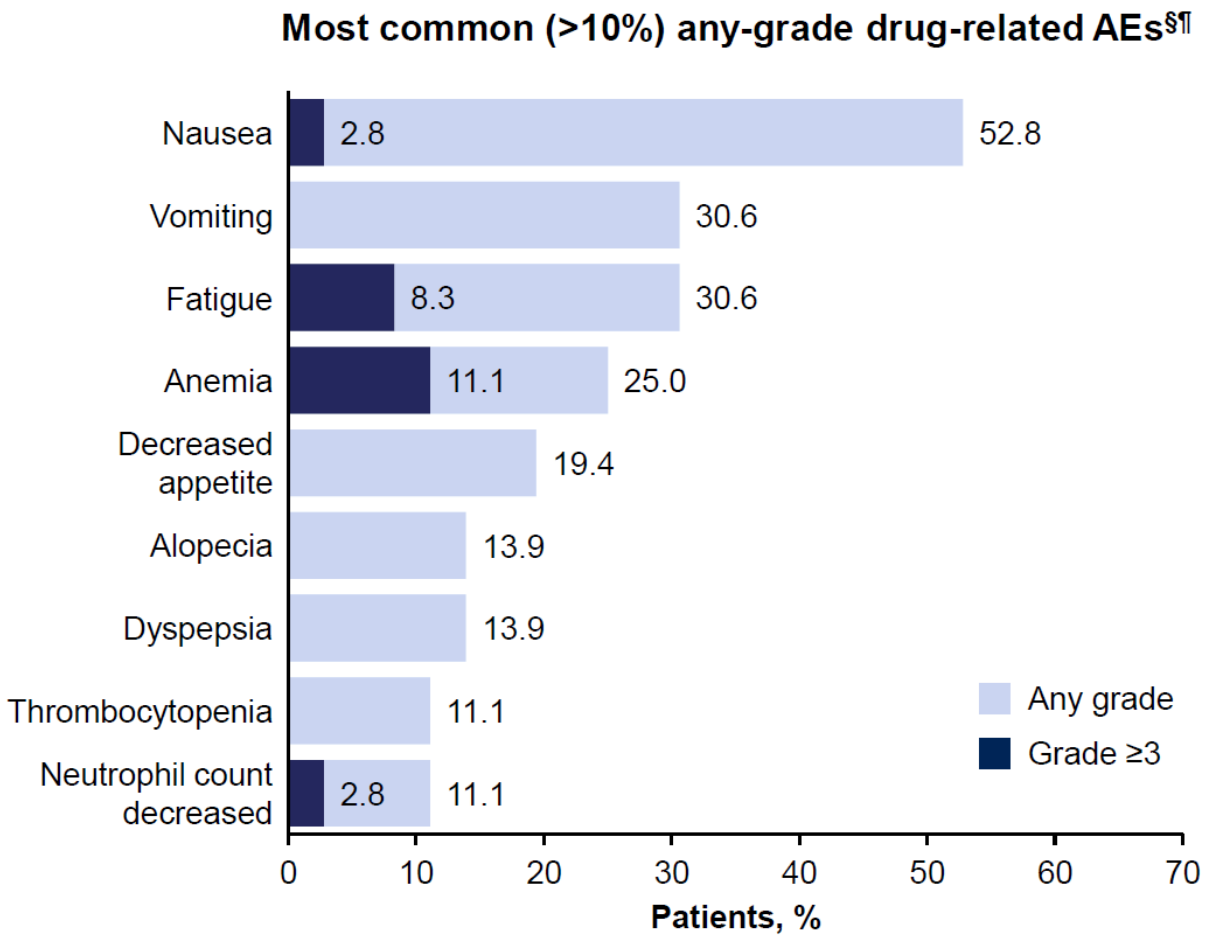
Exploratory analyses: efficacy outcomes by HER2 IHC status and prior EGFR TKI exposure

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, building on DESTINY-Lung01 cohort 1a results[1]**
  - Exploratory analyses showed promising activity in HER2-OE (IHC 3+ and IHC 2+) NSCLC, including in patients with and without prior EGFR TKI:
    - 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 treatment-naïve 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

Ifinatamab deruxtecan (I-DXd) in extensive-stage small cell lung cancer (ES-SCLC): interim analysis of IDeate-Lung01

Charles M. Rudin,[1] Myung-Ju Ahn,[2] Melissa Johnson,[3] Christine L. Hann,[4] Nicolas Girard,[5] Makoto Nishio,[6] Ying Cheng,[7] Hidetoshi Hayashi,[8] Yu Jung Kim,[9] Alejandro Navarro,[10] Yuanbin Chen,[11] Tetsuya Sakai,[12] Meng Qian,[13] Juliette Godard,[14] Mei Tang,[13] Jasmeet Singh,[13] Luis Paz-Ares[15]

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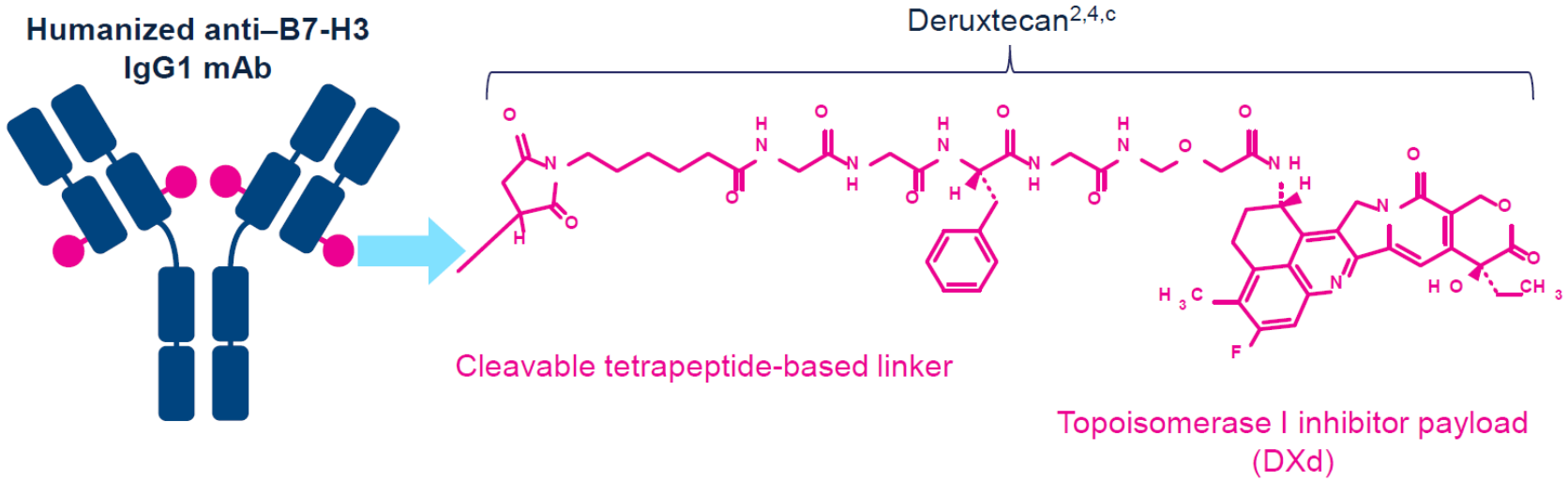
Ifinatamab deruxtecan (I-DXd) was designed with 7 key attributes

I-DXd is a B7-H3 (CD276)–directed ADC with 3 components[1–4]:

- A humanized anti–B7-H3 IgG1 mAb
- A tetrapeptide-based cleavable linker that covalently bonds antibody and payload
- A topoisomerase I inhibitor payload (an exatecan derivative, DXd)



The **mAb** directs the DXd ADC to the tumor cell.

1. Optimized drug-to-antibody ratio ≈4[4,a,b]

The **linker** binds the mAb to the payload.

2. Plasma-stable linker-payload[4,a]
3. Tumor-selective cleavable linker[4,a]

The **payload** induces cell death when delivered to the tumor.

4. Topoisomerase I inhibitor[2,4,a]
5. High potency[4,a]
6. Short systemic half-life[4,a,b]
7. Bystander antitumor effect[2,5,a]

[a]The clinical relevance of these features is under investigation. [b]Based on animal data. [c]Refers to the linker and payload.
ADC, antibody–drug conjugate; B7-H3, B7 homolog 3; CD276, cluster of differentiation 276; IgG1, immunoglobulin G1; mAb, monoclonal antibody.
1. Okajima D, et al. *Mol Cancer Ther*. 2021;20:2329–2340. 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. Yamato M, et al. *Mol Cancer Ther*. 2022;21:635–646.
5. Ogitani Y, et al. *Cancer Sci*. 2016;107:1039–1046.

Phase 2 IDeate-Lung01 study (NCT05280470)

Patient eligibility:

- Histologically or cytologically documented ES-SCLC
- Age ≥18 years[a]
- ≥1 prior line of PBC and ≤3 prior lines of systemic therapy
- Radiologically documented PD on or after most recent prior systemic therapy
- ECOG PS 0–1
- ≥1 measurable lesion per RECIST 1.1[b]
- Patients with asymptomatic brain metastases (untreated or previously treated) are eligible

R 1:1

Arm 1: I-DXd 8 mg/kg Q3W (n≈40)

Arm 2: I-DXd 12 mg/kg Q3W (n≈40)

Extended enrollment at RP3D (n≈70 3L+)

Stratification:

- 2L CTFI <90 days, 2L CTFI ≥90 days, 3L or 4L
- Prior anti–PD-(L)1 treatment (yes or no)

Primary endpoint:

- ORR by BICR[c]

Secondary endpoints:

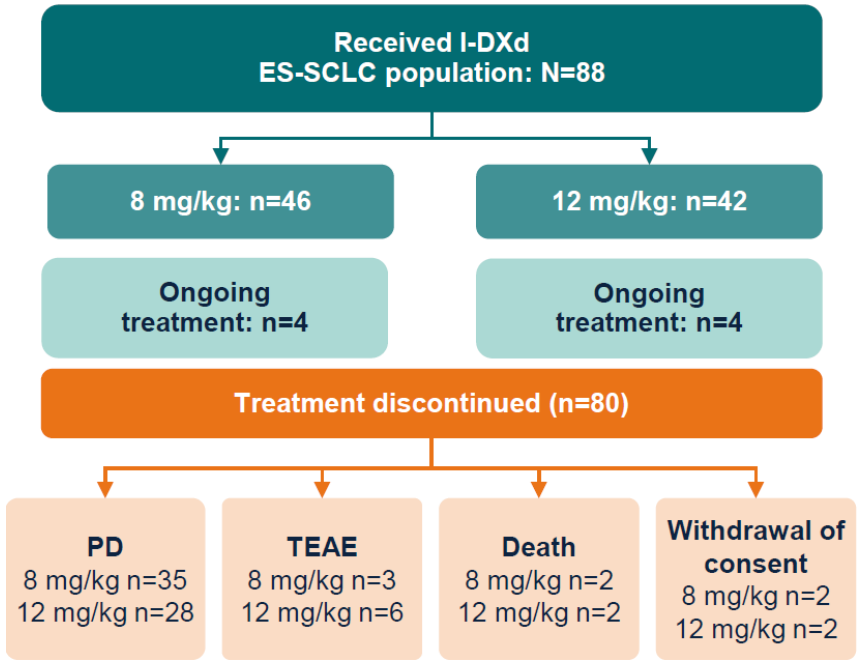
- DOR by BICR and inv[c]
- PFS by BICR and inv[c]
- OS
- DCR[c]
- TTR by BICR and inv[c]
- ORR by inv[c]
- Safety
- Pharmacokinetics
- Immmunogenicity

Exploratory analysis:

- Intracranial ORR by BICR[d]

[a]Or local legal age of consent. [b]Patients must also have ≥1 lesion that has not been irradiated and is amenable to biopsy. [c]Per RECIST 1.1. [d]Per CNS RECIST.
2L, second-line; 3L+, third-line and beyond; 4L, fourth-line; BICR, blinded independent central review; CTFI, chemotherapy treatment-free interval; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive-stage small cell lung cancer; inv, investigator; ORR, objective response rate; OS, overall survival; PBC, platinum-based chemotherapy; PD, progressive disease; PD-(L)1; programmed death (ligand) 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; RP3D, recommended Phase 3 dose; TTR, time to response.

Patient demographics and baseline characteristics



- Median treatment duration: 8 mg/kg, 3.5 months (range, 0.03–13.9); 12 mg/kg, 4.7 months (range, 0.03–15.2)
- Median follow-up: 8 mg/kg, 14.6 months (range, 0.6–17.0); 12 mg/kg, 15.3 months (range, 0.8–20.3)

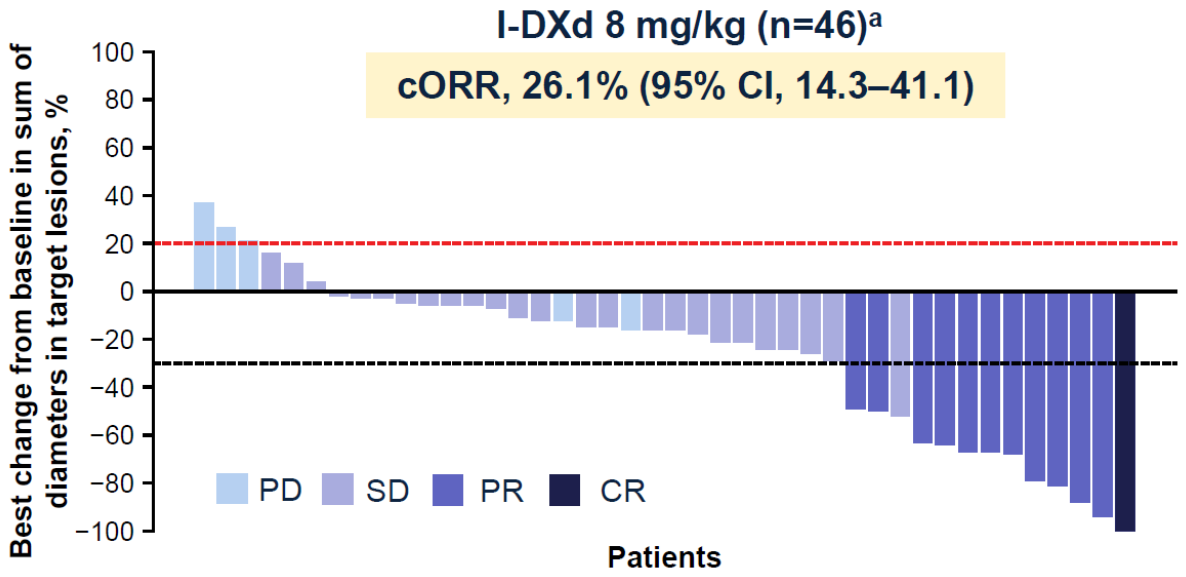
	I-DXd 8 mg/kg n=46	I-DXd 12 mg/kg n=42	Total N=88
Age, median (range)	64 (42–85)	64 (34–79)	64 (34–85)
Male, n (%)	30 (65.2)	33 (78.6)	63 (71.6)
ECOG PS, n (%)			
0	13 (28.3)	6 (14.3)	19 (21.6)
1	33 (71.7)	36 (85.7)	69 (78.4)
ES-SCLC at diagnosis, n (%)	32 (69.6)[a]	35 (83.3)	67 (76.1)
Patients with brain metastasis at baseline, n (%)	19 (41.3)	18 (42.9)	37 (42.0)
Number of prior lines of systemic therapy, n (%)			
1	13 (28.3)	12 (28.6)	25 (28.4)
2	22 (47.8)	22 (52.4)	44 (50.0)
3	11 (23.9)	8 (19.0)	19 (21.6)
Chemotherapy-free interval[b]			
<90 days	22 (47.8)	23 (54.8)	45 (51.1)
≥90 days	22 (47.8)	19 (45.2)	41 (46.6)
Select prior anticancer therapy received, n (%)			
Lurbinectedin	11 (23.9)	3 (7.1)	14 (15.9)
Irinotecan or topotecan	14 (30.4)	17 (40.5)	31 (35.2)
Tarlatamab	4 (8.7)	2 (4.8)	6 (6.8)
Amrubicin	3 (6.5)	3 (7.1)	6 (6.8)
Prior anti–PD-(L)1 therapy received,[c] n (%)	35 (76.1)	32 (76.2)	67 (76.1)

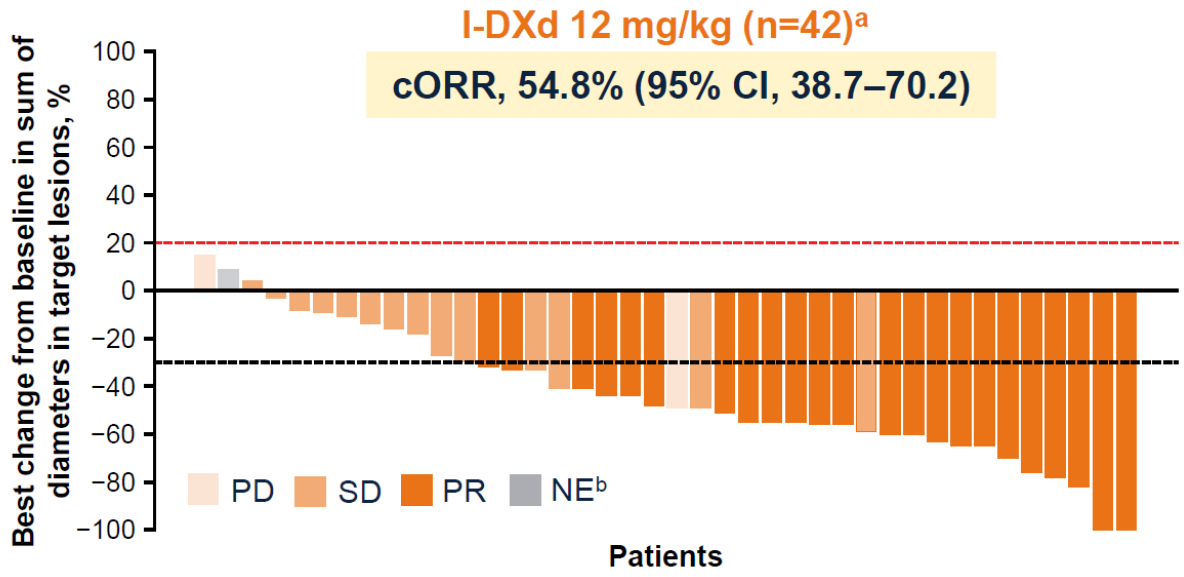
Data cutoff: April 25, 2024.

[a]One patient had missing data. [b]Two patients had missing data in the 8-mg/kg cohort. [c]Three patients (8 mg/kg, n=2; 12 mg/kg n=1) were previously treated in a blinded randomized clinical trial; information regarding patients' prior PD-(L)1 therapy was not available.

BICR, blinded central review; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive-stage small cell lung cancer; PD-(L)1; programmed death (ligand) 1; TEAE, treatment-emergent adverse event.

I-DXd has promising antitumor activity; patients treated with 12 mg/kg had a higher ORR than those treated with 8 mg/kg





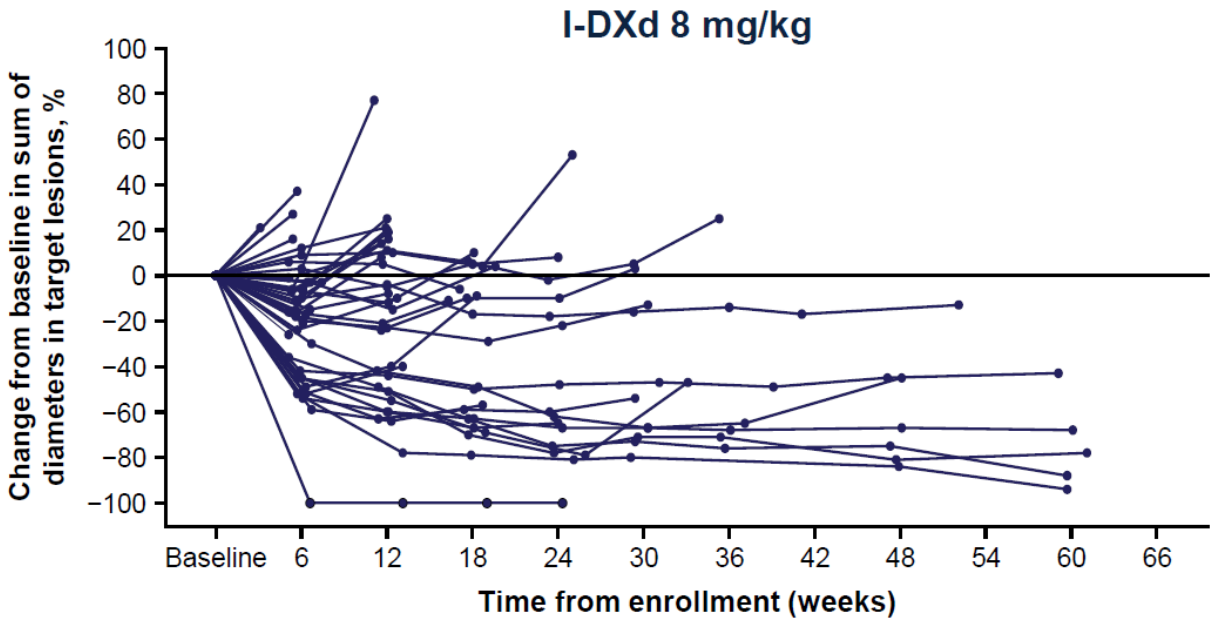
Confirmed response by BICR[c]	I-DXd 8 mg/kg n=46	I-DXd 12 mg/kg n=42
ORR, % (95% CI)	26.1 (14.3–41.1)	54.8 (38.7–70.2)
CR, n (%)	1 (2.2)	0
PR, n (%)	11 (23.9)	23 (54.8)
DCR, % (95% CI)	80.4 (66.1–90.6)	90.5 (77.4–97.3)

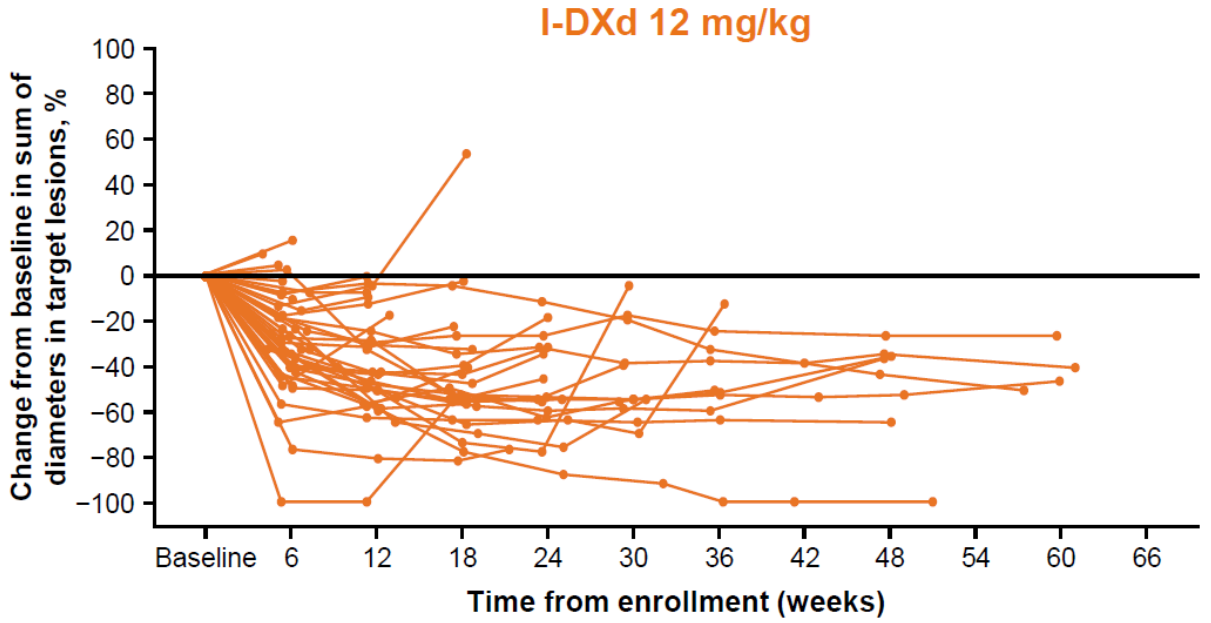
Data cutoff: April 25, 2024. The median follow-up for 8-mg/kg and 12-mg/kg cohorts was 14.6 months (range, 0.6–17.0) and 15.3 months (range, 0.8–20.3) respectively.

[a]Only patients with measurable disease at baseline and ≥1 post-baseline tumor scan were included in the waterfall plot: in the I-DXd 8-mg/kg cohort, n=42; 2 patients died and 2 patients withdrew consent before the Week 6 assessment; in the 12-mg/kg cohort, n=40; 1 patient died before the Week 6 assessment and 1 patient did not have target lesions at baseline. [b]This patient has a BOR of NE because the only post-baseline tumor scan was conducted outside the designated time window; the timepoint response was SD. [c]Per RECIST 1.1.

BICR, blinded independent central review; BOR, best overall response; cORR, confirmed ORR; CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SD, stable disease.

I-DXd treatment was associated with rapid responses at both doses





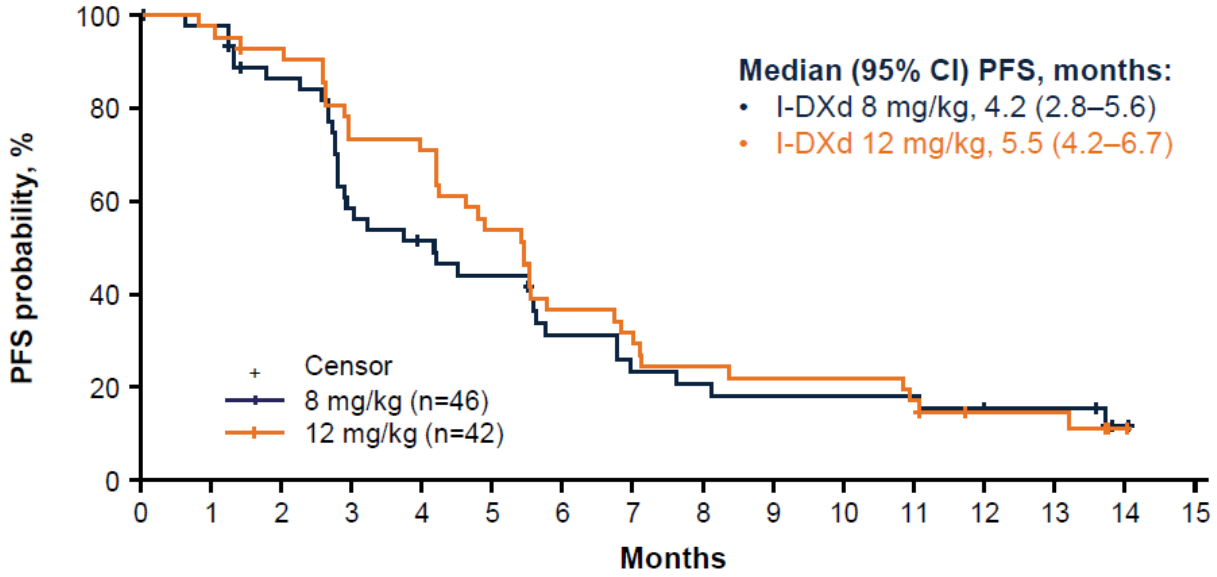
	I-DXd 8 mg/kg n=46	I-DXd 12 mg/kg n=42
Median (range) TTR,[a] months	1.4 (1.2–1.5)	1.4 (1.0–8.1)
Median (95% CI) DOR,[a,b] months	7.9 (4.1–NE)	4.2 (3.5–7.0)

Data cutoff: April 25, 2024. The median follow-up for 8-mg/kg and 12-mg/kg cohorts was 14.6 months (range, 0.6–17.0) and 15.3 months (range, 0.8–20.3) respectively.

[a]By BICR per RECIST 1.1. [b]Median DOR was longer in the 8-mg/kg cohort than in the 12-mg/kg cohort, possibly due to the higher proportion of 2L responders in the 8-mg/kg cohort.

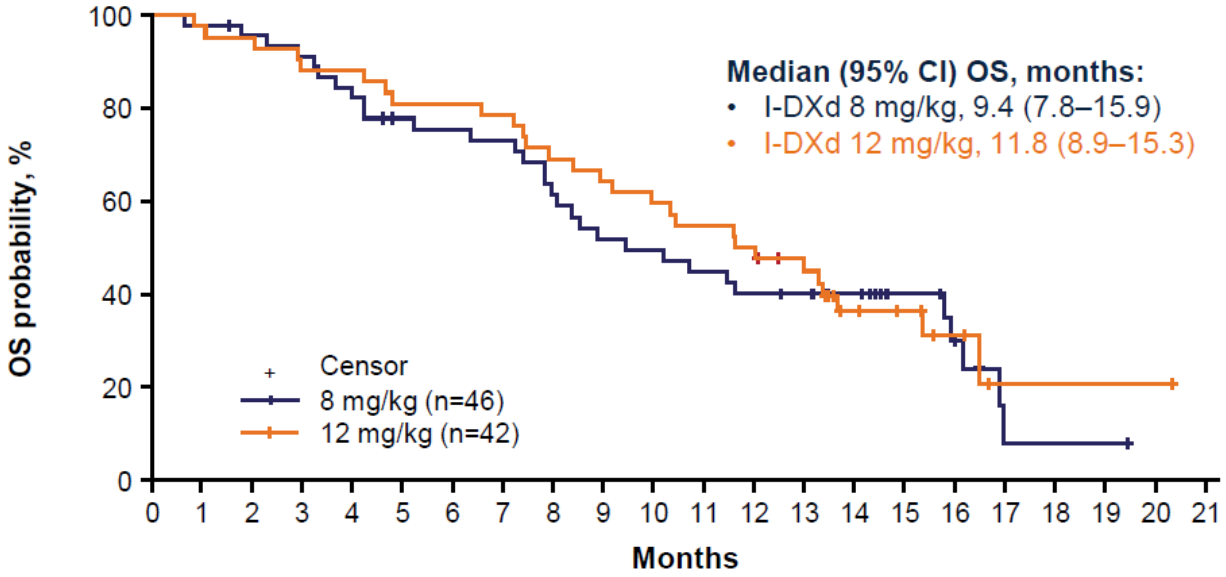
2L, second-line; BICR, blinded independent central review; DOR, duration of response; NE, not estimable; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; TTR, time to response.

PFS and OS were similar between study arms, numerically favoring the I-DXd 12-mg/kg dose



Number of patients still at risk

8 mg/kg	46	44	37	25	21	18	12	9	8	7	7	7	5	5	1	0
12 mg/kg	42	41	38	30	29	22	15	12	10	9	9	7	4	4	1	0



Number of patients still at risk

8 mg/kg	46	45	43	41	37	33	32	31	26	22	21	19	17	16	14	9	5	1	1	1	0	0
12 mg/kg	42	41	40	37	37	34	34	33	29	27	25	23	20	17	10	8	5	1	1	1	1	0

Data cutoff: April 25, 2024. The median follow-up for 8-mg/kg and 12-mg/kg cohorts was 14.6 months (range, 0.6–17.0) and 15.3 months (range, 0.8–20.3) respectively.

OS, overall survival; PFS, progression-free survival.

Efficacy summary in patients with brain metastases at baseline and in a subset of patients with brain target lesions at baseline

	Patients with brain metastases at baseline		Patients with brain target lesions at baseline			
	Systemic response[a]		Systemic response[a]		Intracranial response[b]	
	I-DXd 8 mg/kg n=19	I-DXd 12 mg/kg n=18	I-DXd 8 mg/kg n=6	I-DXd 12 mg/kg n=10	I-DXd 8 mg/kg n=6	I-DXd 12 mg/kg n=10
Confirmed ORR,[a] % (95% CI)	26.3 (9.1–51.2)	61.1 (35.7–82.7)	16.7 (0.4–64.1)	60.0 (26.2–87.8)	66.7 (22.3–95.7)	50.0 (18.7–81.3)
Best overall response,[a] n (%)						
CR	1 (5.3)	0	1 (16.7)	0	2 (33.3)	2 (20.0)
PR	4 (21.1)	11 (61.1)	0	6 (60.0)	2 (33.3)	3 (30.0)
SD	11 (57.9)	5 (27.8)	3 (50.0)	3 (30.0)	2 (33.3)	5 (50.0)
PD	2 (10.5)	2 (11.1)	2 (33.3)	1 (10.0)	0	0
NE	1 (5.3)	0	0	0	0	0

Data cutoff: April 25, 2024. The median follow-up for 8-mg/kg and 12-mg/kg cohorts was 14.6 months (range, 0.6–17.0) and 15.3 months (range, 0.8–20.3) respectively.

[a]By BICR per RECIST 1.1. [b]By BICR per CNS RECIST.

BICR, blinded independent central review; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; SD, stable disease.

Safety summary: I-DXd was well tolerated at both dose Data

	I-DXd 8 mg/kg n=46	I-DXd 12 mg/kg n=42
Median treatment duration, months (range)	3.5 (0.03–13.9)	4.7 (0.03–15.2)
Median cycles, n (range)	6.0 (1.0–21.0)	7.5 (1.0–23.0)
Any TEAE, n (%)	44 (95.7)	41 (97.6)
TEAE with CTCAE Grade ≥3, n (%)	20 (43.5)	21 (50.0)
TEAE associated with drug discontinuation, n (%)	3 (6.5)	7 (16.7)[a]
TEAE associated with dose delay, n (%)	10 (21.7)	15 (35.7)
TEAE associated with dose reduction, n (%)	4 (8.7)	6 (14.3)
TEAE associated with an outcome of death, n (%)	3 (6.5)	6 (14.3)

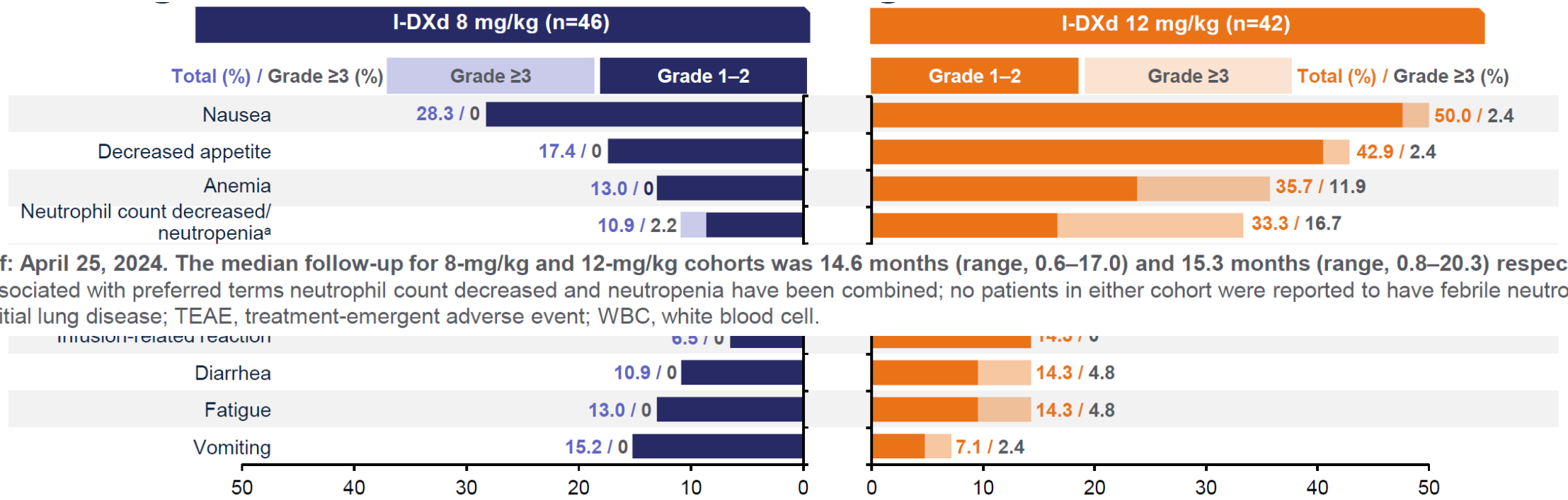
- Treatment discontinuations were:
  - In the 8-mg/kg cohort: pneumonia (Grade 3, n=1), pneumonitis (Grade 2, n=1) and pulmonary embolism (Grade 4, n=1)
  - In the 12-mg/kg cohort: pneumonia (Grade 1, n=1; Grade 3,[b] n=1), pneumonitis (Grade 2, n=1), ILD (Grade 2, n=1), *Pneumocystis jirovecii* pneumonia (Grade 3,[c] n=1), radiation pneumonitis (Grade 4, n=1), and septic shock (Grade 5, n=1)
- TEAEs associated with an outcome of death were:
  - In the 8-mg/kg cohort: disease progression (n=2) and sepsis (n=1); none were considered as related to study treatment
  - In the 12-mg/kg cohort: septic shock (n=2), disease progression (n=1), multiple organ dysfunction (n=1), pneumonia (n=1), and *Pneumocystis jirovecii* pneumonia (n=1), only the case of *Pneumocystis jirovecii* pneumonia was considered as related to study treatment

Data cutoff: April 25, 2024. The median follow-up for 8-mg/kg and 12-mg/kg cohorts was 14.6 months (range, 0.6–17.0) and 15.3 months (range, 0.8–20.3) respectively.

[a]Includes one patient for whom death was the primary reason for treatment discontinuation, but who was also recorded as having a TEAE (pneumonia) on the date of death. [b]Following Grade 3 pneumonia (unrelated to study treatment), the patient discontinued study treatment, and ultimately (1 day after study drug withdrawal), the patient was reported to have Grade 5 pneumonia. [c]Following Grade 3 *pneumocystis jirovecii* pneumonia, the patient discontinued study treatment; however, the patient never recovered and was reported to have Grade 5 *pneumocystis jirovecii* pneumonia 24 days later.

CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.

The most common treatment-related TEAEs (≥10% total population) were gastrointestinal and hematologic



Data cutoff: April 25, 2024. The median follow-up for 8-mg/kg and 12-mg/kg cohorts was 14.6 months (range, 0.6–17.0) and 15.3 months (range, 0.8–20.3) respectively.
[a]TEAEs associated with preferred terms neutrophil count decreased and neutropenia have been combined; no patients in either cohort were reported to have febrile neutropenia.
ILD, interstitial lung disease; TEAE, treatment-emergent adverse event; WBC, white blood cell.

ILD/pneumonitis adjudicated as treatment-related was reported in:

- Four (8.7%) patients in the 8-mg/kg cohort (Grade 2, n=3; Grade 5, n=1)
- Five (11.9%) patients in the 12-mg/kg cohort (Grade, 1 n=1; Grade 2, n=3; Grade 3, n=1)
- No ILD events were pending adjudication at the time of data cutoff

Data cutoff: April 25, 2024. The median follow-up for 8-mg/kg and 12-mg/kg cohorts was 14.6 months (range, 0.6–17.0) and 15.3 months (range, 0.8–20.3) respectively.
[a]TEAEs associated with preferred terms neutrophil count decreased and neutropenia have been combined; no patients in either cohort were reported to have febrile neutropenia.
ILD, interstitial lung disease; TEAE, treatment-emergent adverse event; WBC, white blood cell.

Summary

- I-DXd demonstrated promising efficacy in patients with pretreated ES-SCLC; I-DXd 12 mg/kg had improved efficacy compared with the 8-mg/kg dose:
  - ORR was 54.8% vs 26.1%
  - Median PFS was 5.5 months vs 4.2 months
  - Median OS was 11.8 months vs 9.4 months
- The observed safety profile was generally manageable and I-DXd was well tolerated, with a higher frequency of TEAEs in the 12-mg/kg cohort than in the 8-mg/kg cohort; the safety profile was consistent with previous reports[1,2]
  - The most common treatment-related TEAEs were gastrointestinal and hematologic (most commonly nausea, decreased appetite, anemia, and decreased neutrophil count or neutropenia)
  - Patients receiving I-DXd 12 mg/kg had a longer treatment duration than those receiving 8 mg/kg (4.7 vs 3.5 months)
  - The majority of cases of adjudicated drug-related ILD were Grade 1 or 2
- I-DXd showed intracranial and systemic activity in a small subset of patients with brain target lesions at baseline; a full analysis of the subgroup of patients with brain metastases at baseline will be presented at the ESMO Congress 2024
- I-DXd 12 mg/kg has been selected as the RP3D for further clinical development, including in an ongoing Phase 3 study in patients with relapsed SCLC following only 1 prior line of therapy (IDeate-Lung02; NCT06203210)

Data cutoff: April 25, 2024. The median follow-up for 8-mg/kg and 12-mg/kg cohorts was 14.6 months (range, 0.6–17.0) and 15.3 months (range, 0.8–20.3) respectively.

ESMO, European Society for Medical Oncology; ES-SCLC, extensive-stage small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RP3D, recommended Phase 3 dose; SCLC, small cell lung cancer; TEAE, treatment-emergent adverse event.

1. Johnson M, et al. Presented at the World Conference on Lung Cancer 2023. September 9–12, 2023. Singapore. Abstract 3258. 2. Patel MR, et al. Presented at the European Society for Medical Oncology Congress 2023. October 20–24, 2023. Madrid, Spain. Abstract 690P.