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Daiichi-Sankyo

WCLC/ESMO Highlights 2024

DAIICHI SANKYO CO., LTD.

September 17th, 2024

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WCLC/ESMO Highlights 2024: IR conference call

Ken Takeshita
Head of Global R&D

Mark Rutstein
Head of Global Oncology Development

Agenda

1. Opening remarks
2. Highlights from WCLC & ESMO 2024
3. Q&A

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

Jacob Sands,[1] Aaron Lisberg,[2] Isamu Okamoto,[3] Luis Paz-Ares,[4] Robin Cornelissen,[5] Nicolas Girard,[6] Elvire Pons-Tostivint,[7] David Vicente Baz,[8] Shunichi Sugawara,[9] Manuel Cobo Dols,[10] Maurice Pérol,[11] Céline Mascaux,[12] Elena Poddubskaya,[13] Satoru Kitazono,[14] Hidetoshi Hayashi,[15] Min Hee Hong,[16] Enriqueta Felip,[17] Richard Hall,[18] Oscar Juan-Vidal,[19] Daniel Brungs,[20] Shun Lu,[21] Marina Garassino,[22] Ekaterine Alexandris,[23] Yong Zhang,[23] Paul Howarth,[23] Deise Uema,[23] Myung-Ju Ahn[24]

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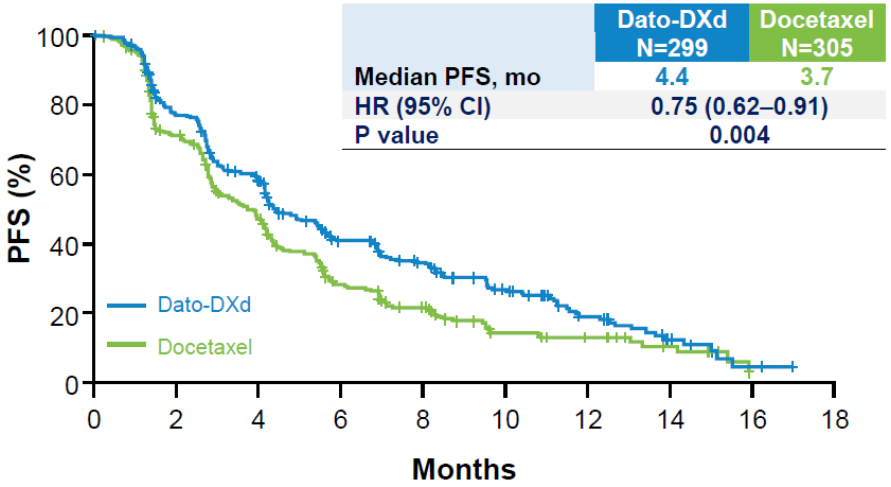
Background

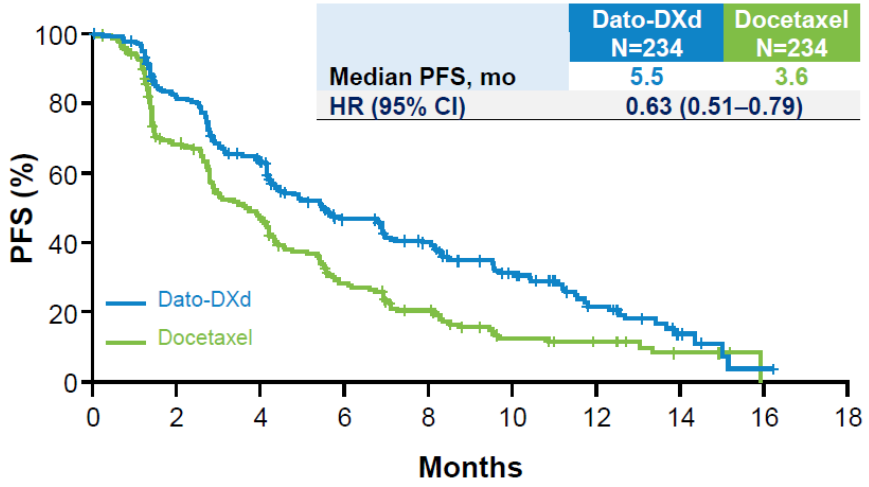
- Survival outcomes for patients with advanced NSCLC on docetaxel-based regimens in the second-line setting and beyond remain poor, and multiple trials of novel treatment regimens have failed in this setting, underscoring a high unmet need[1,2]
- **TROPION-Lung01** met its dual primary endpoint of **PFS 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



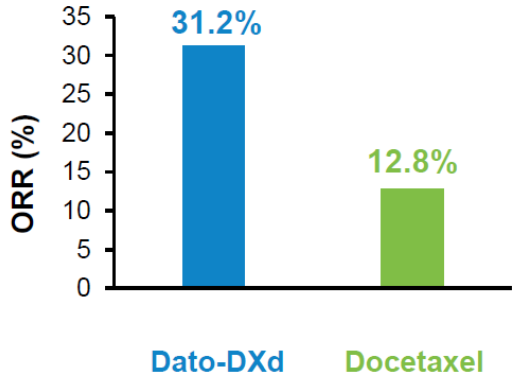
	Dato-DXd N=299	Docetaxel N=305
Median PFS, mo	4.4	3.7
HR (95% CI)	0.75 (0.62–0.91)	
P value	0.004	

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

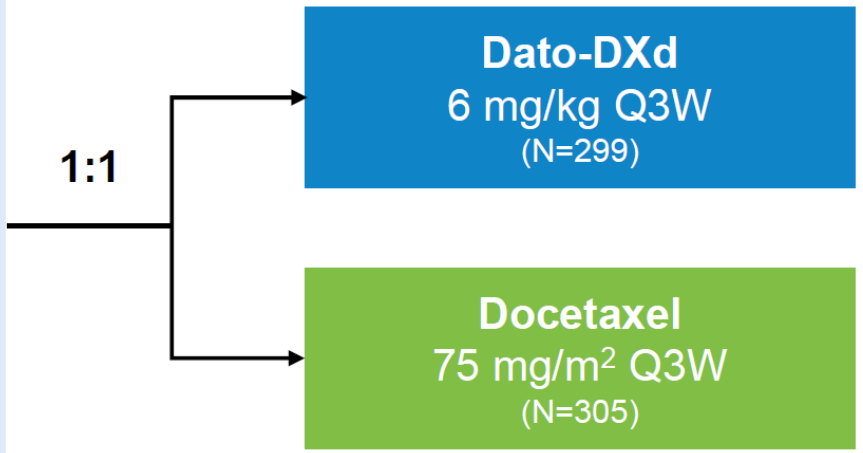
- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0–1
- No prior docetaxel

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

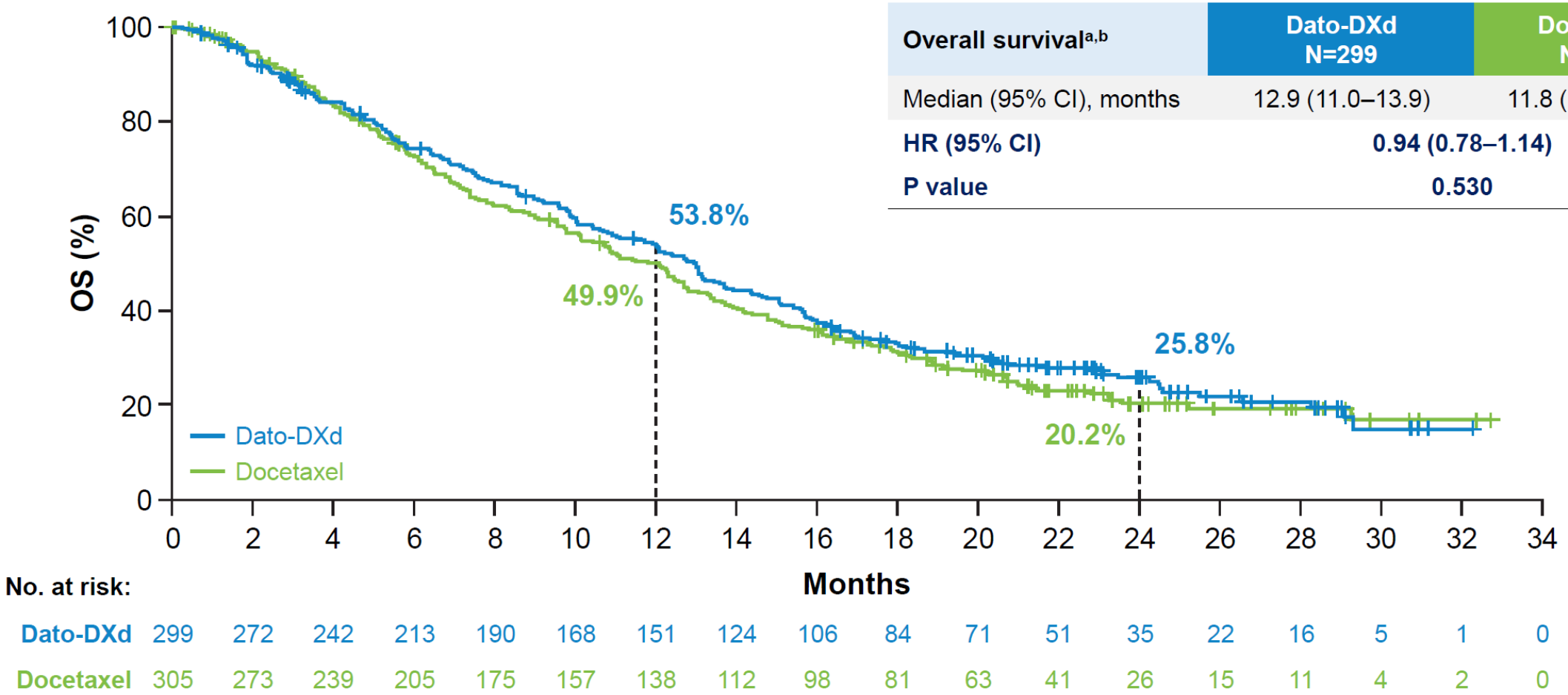
Characteristic, n (%)		Dato-DXd N=299	Docetaxel N=305
Age, years [median (range)]		63 (26–84)	64 (24–88)
Sex, male		183 (61)	210 (69)
Race	Asian	119 (40)	120 (39)
	White	123 (41)	126 (41)
	Black or African American	6 (2)	4 (1)
	Other/missing	51 (17)	55 (18)
ECOG PS[a]	0	89 (30)	94 (31)
	1	210 (70)	211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



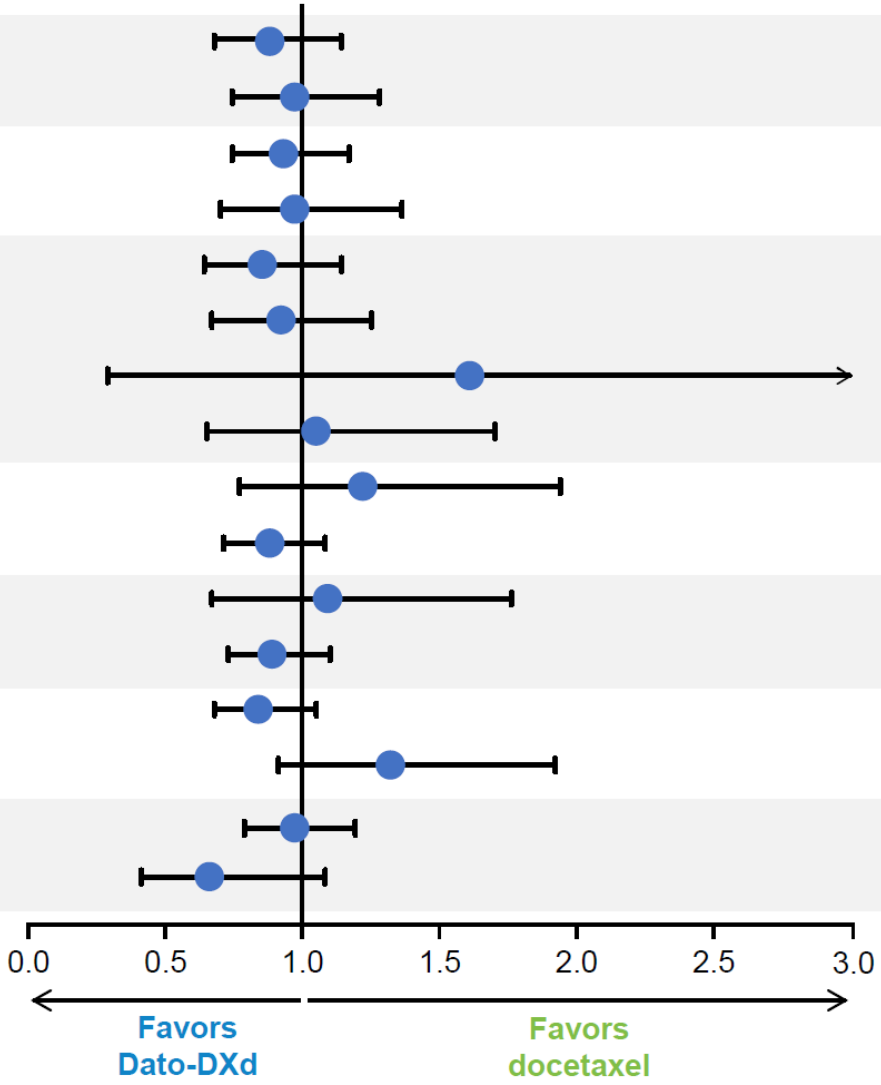
No. at risk:

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

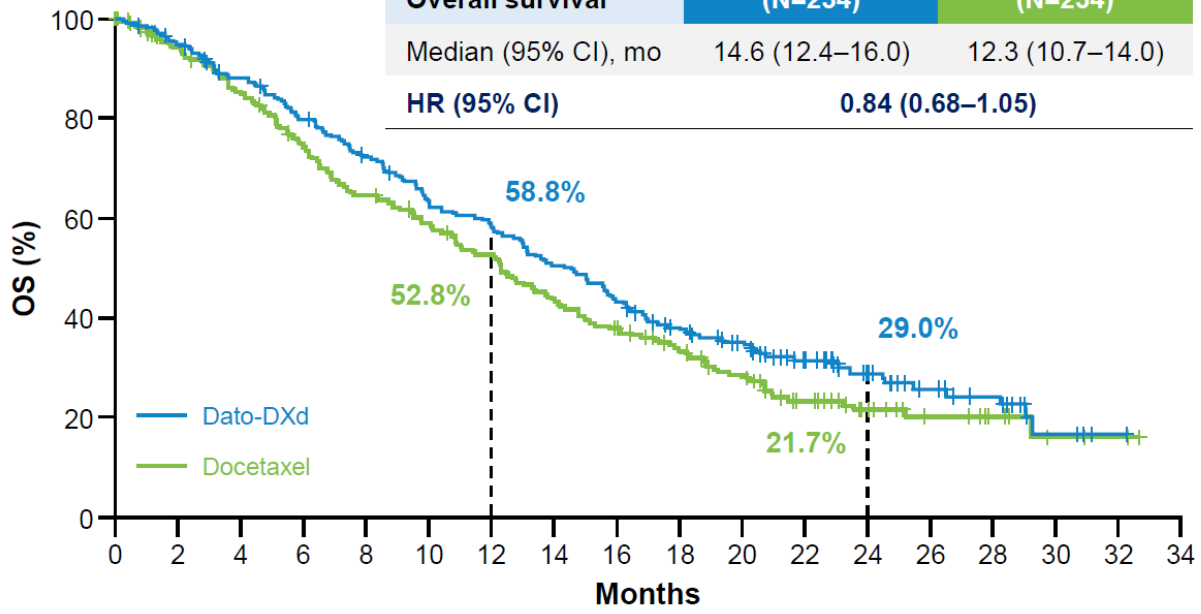


Data cutoff: March 1, 2024.
[a]Regardless of histology.

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)	

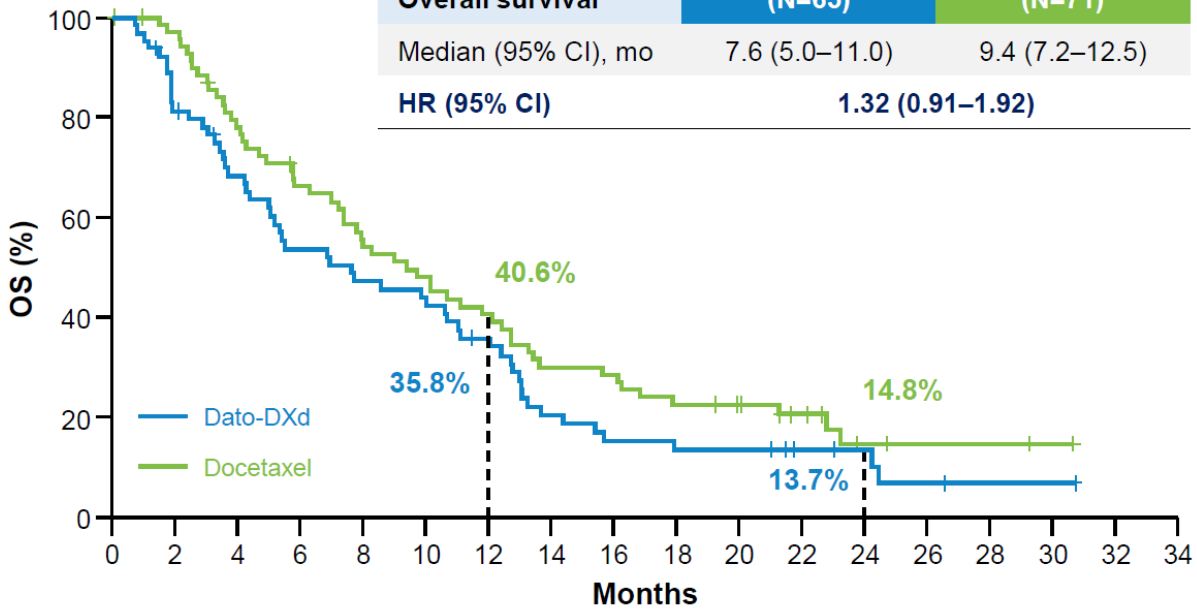


No. at risk:

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.

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

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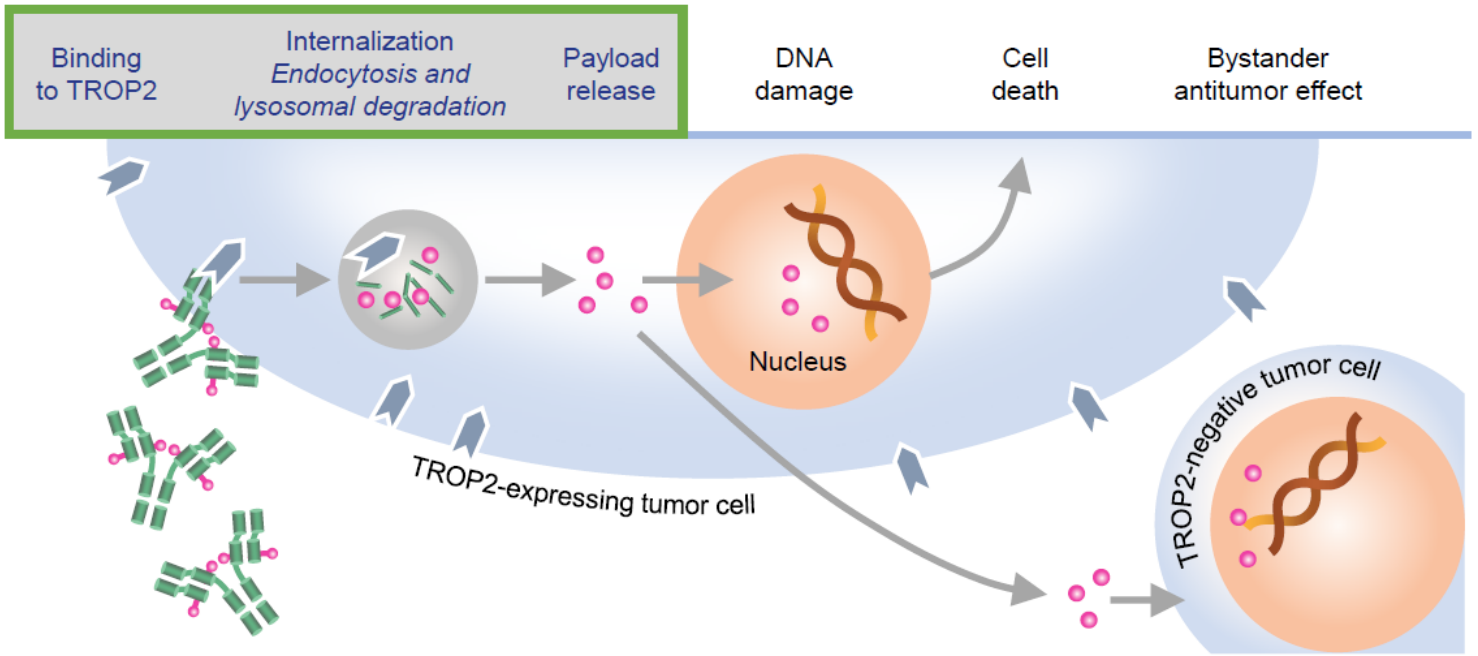
[1]The University of Chicago, Chicago, IL, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]Universidad Complutense & CiberOnc, Hospital Universitario 12 de Octubre, Madrid, Spain; [4]Jonsson Comprehensive Cancer Center at UCLA, Los Angeles, CA, USA; [5]Sarah Cannon Research Institute, Tennessee 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

WCLC 2024 PL02.11. (Oral)

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]



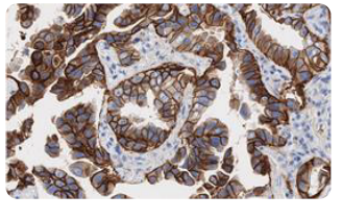
We hypothesized that a more precise and quantitative assessment of TROP2 expression **on the cell membrane and in the cytoplasm** may predict efficacy of Dato-DXd in patients with NSCLC

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)

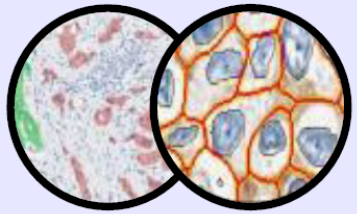
QCS is a novel, fully-supervised computational pathology approach that precisely quantifies and locates targets like TROP2

1 IHC with TROP2 Assay



2 Whole Slide Imaging

3 Automated Image Analysis (QCS)

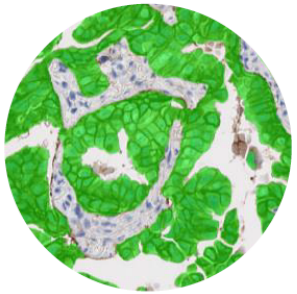


4 Patient Biomarker Status Determination

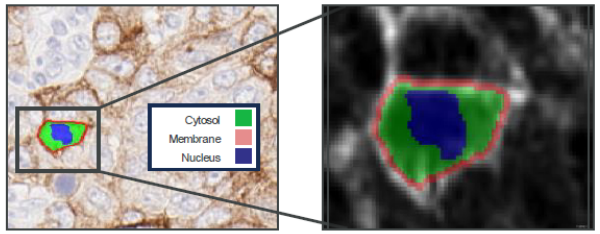
\+ ≥75% of tumor cells with TROP2 NMR ≤0.56

\- <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

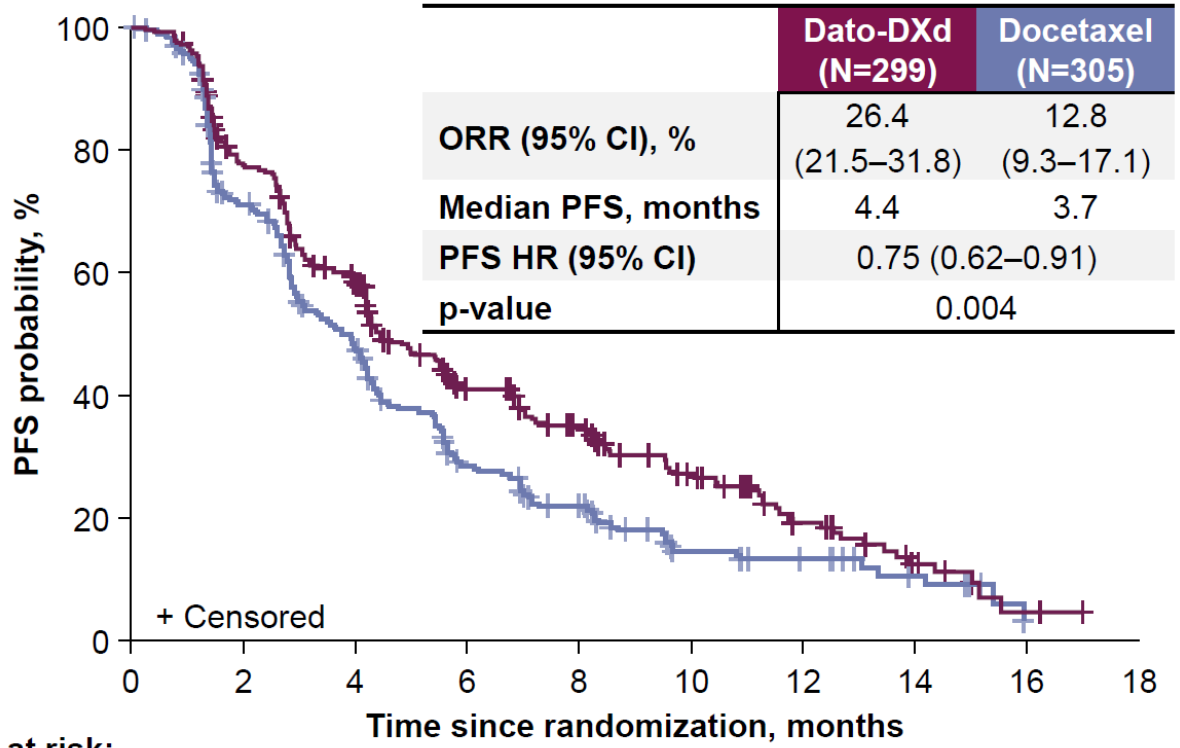
Dato-DXd
6 mg/kg q3w
N=299

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:

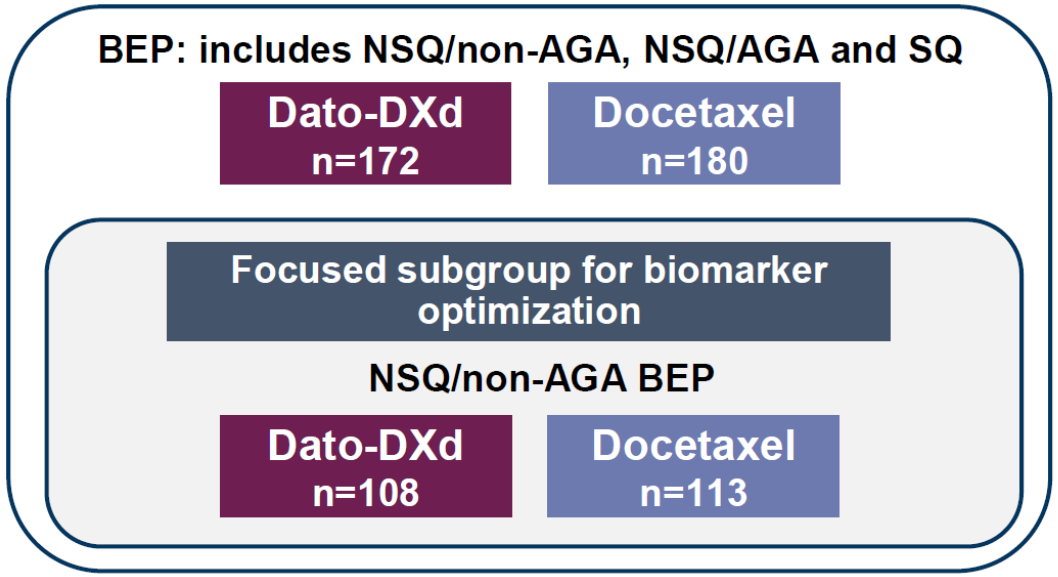
Dato-DXd	299	216	156	96	74	46	24	10	2	0
Docetaxel	305	186	120	63	42	19	14	7	0	0

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

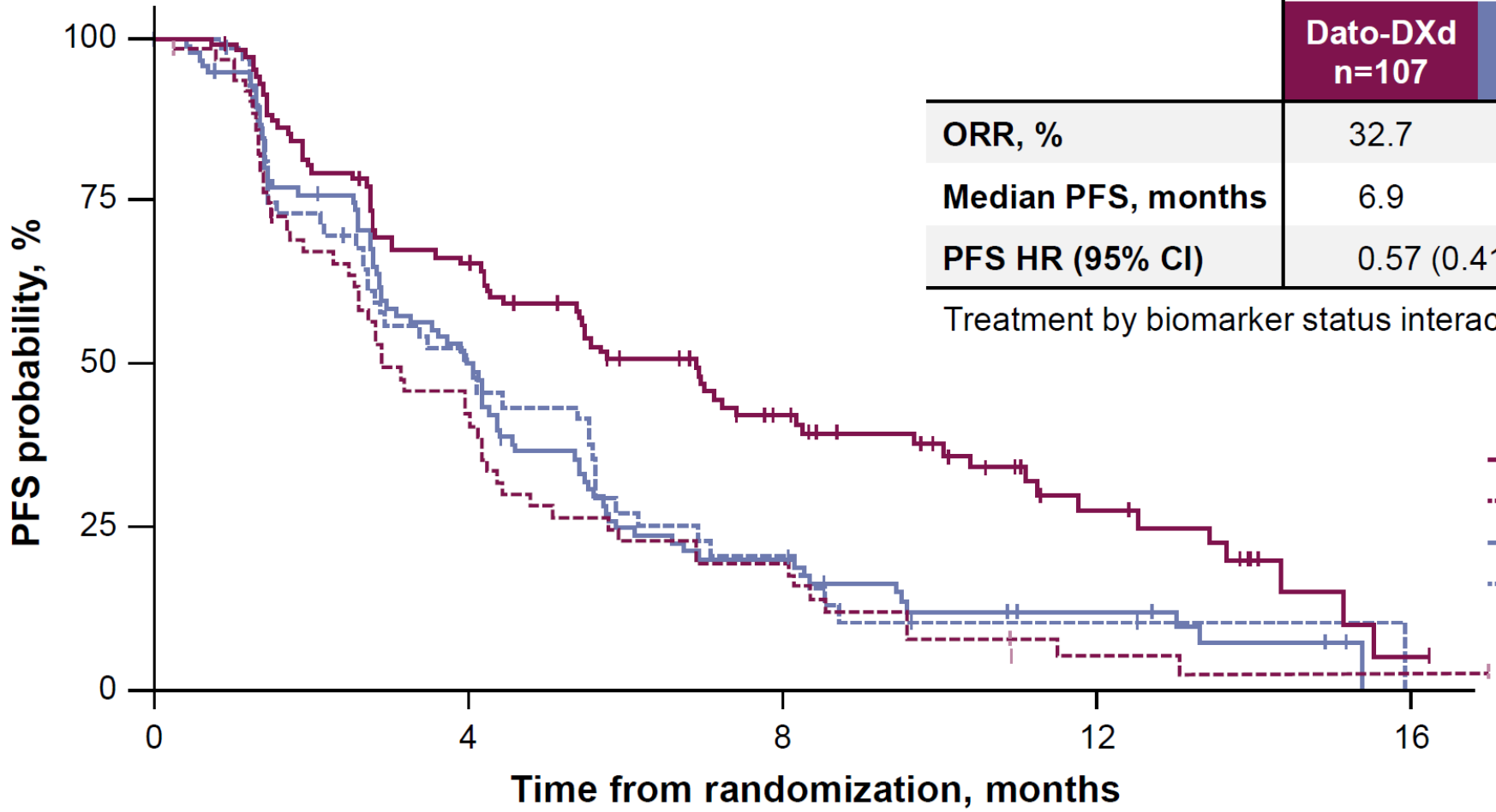
1. Ahn MJ, et al. Oral presentation at ESMO 2023 (Abstract LBA12).

*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

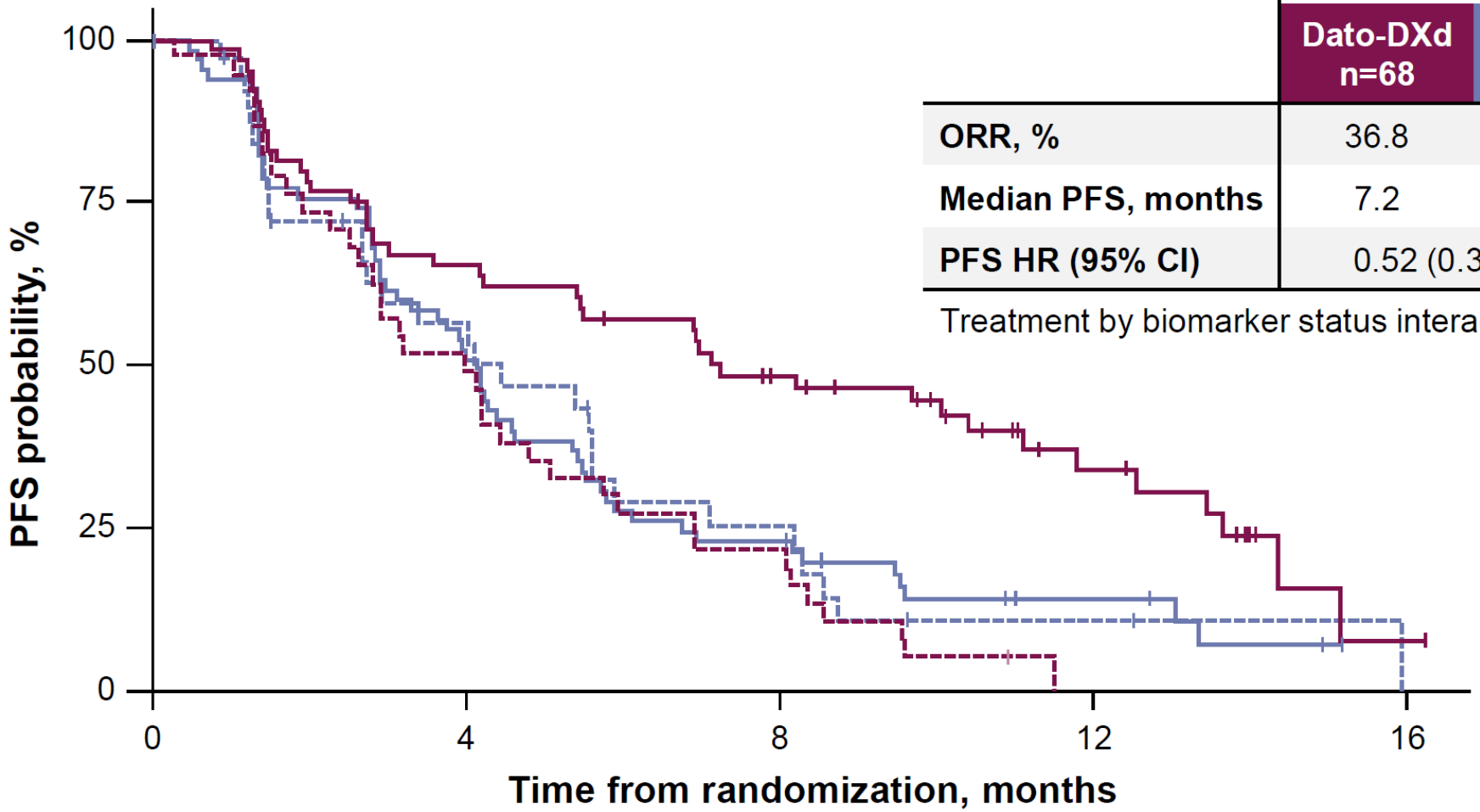
Data cutoff: March 29 2023

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)

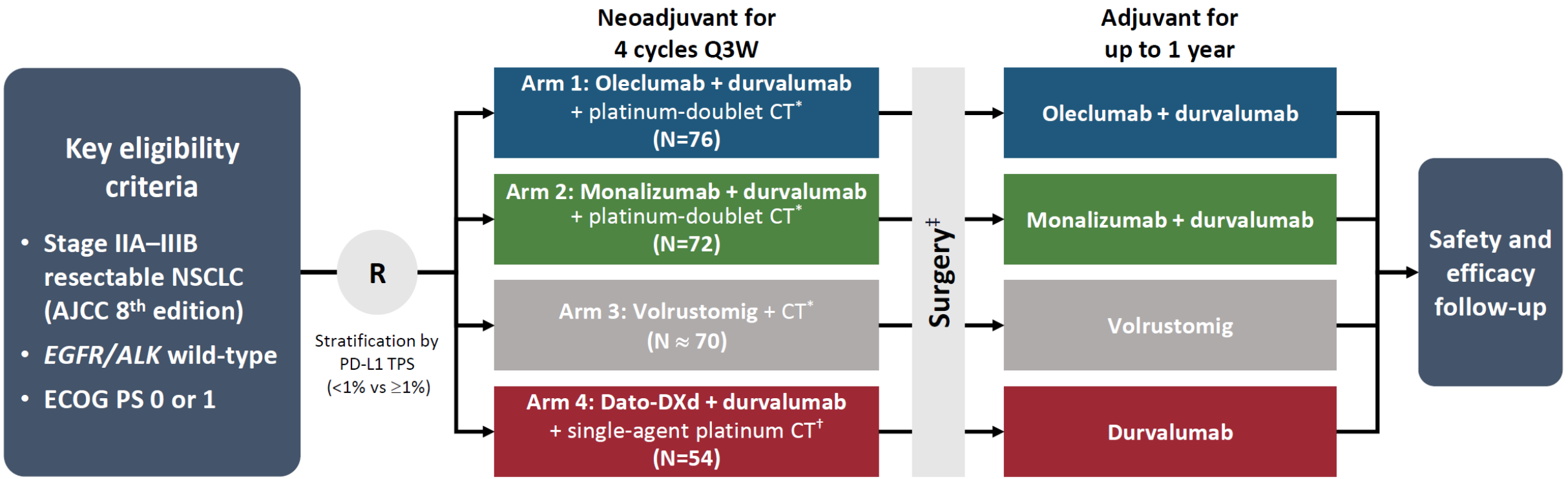
TROP2 QCS-NMR has the potential to be the first TROP2 biomarker and the first computational pathology biomarker for predicting clinical response to Dato-DXd in NSCLC

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]

[1]Department of Thoracic/Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Univ Rouen Normandie, LITIS Lab QuantIF team EA4108, CHU Rouen, Department of Pneumology and Inserm CIC-CRB 1404, F-76000 Rouen, France; [3]Department of Surgery, Oncology and Gastroenterology, University of Padova, Italy; [4]Medical Oncology 2, Istituto Oncologico Veneto IRCCS, Padova, Italy; [5]Division of Thoracic Surgery, University of Montréal, Montréal, Québec, Canada; [6]CETOC - CHUM Endoscopic Tracheobronchial and Oesophageal Center, Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada; [7]Respiratory Medicine Department, Hôpital d'Instruction des Armées Sainte-Anne, Toulon, France; [8]Medical Oncology Department, Hospital Clínico Universitario de Valencia, 46010 Valencia, Spain; [9]Department of Radiation Oncology, University of Florence, Florence, Italy; [10]Department of Medical Oncology, CH de Cornouaille, Quimper, France; [11]Department of Thoracic Oncology, Dupuytren University Hospital, Limoges, France; [12]AstraZeneca, Waltham, MA, USA; [13]AstraZeneca, Gaithersburg, MD, USA; [14]AstraZeneca, Cambridge, UK; [15]Department of Thoracic Surgery, McGill University, Montréal, Québec, Canada; [16]Bloomberg–Kimmel Institute for Cancer Immunotherapy, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA

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



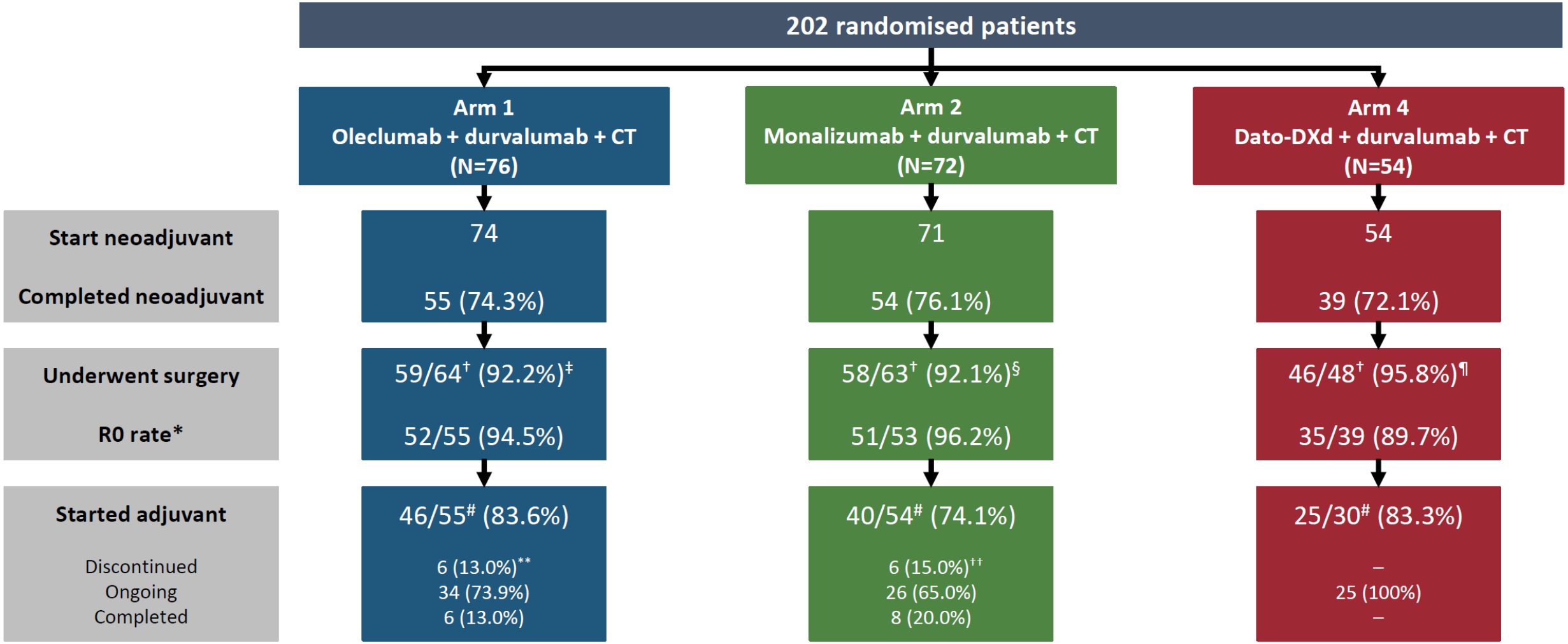
Primary endpoints
- pCR rate§
- Safety and tolerability

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.

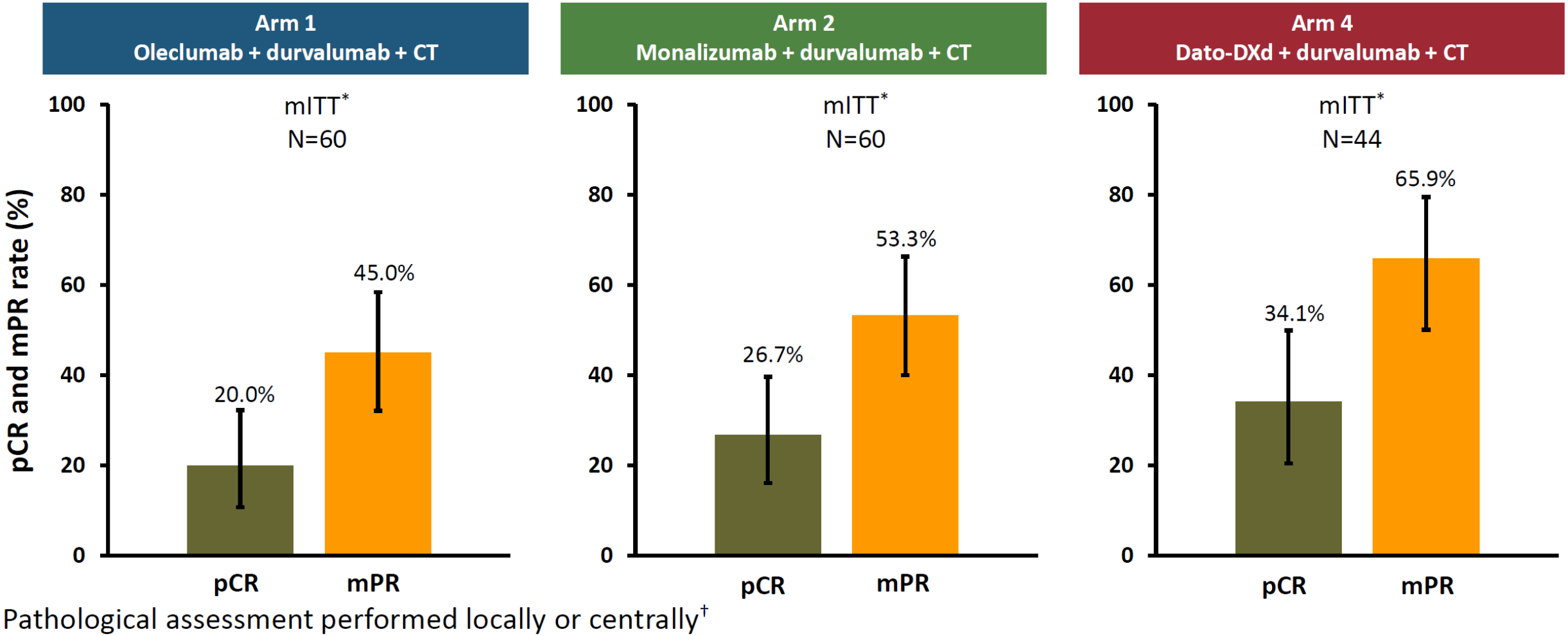
*Carboplatin + paclitaxel for squamous tumour histology, pemetrexed + cisplatin or carboplatin for non-squamous tumour histology. †Physician's choice of carboplatin or cisplatin. ‡Within 40 days of the last dose of neoadjuvant treatment. §Proportion of patients with no viable tumour cells and ≤10% residual 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.

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.

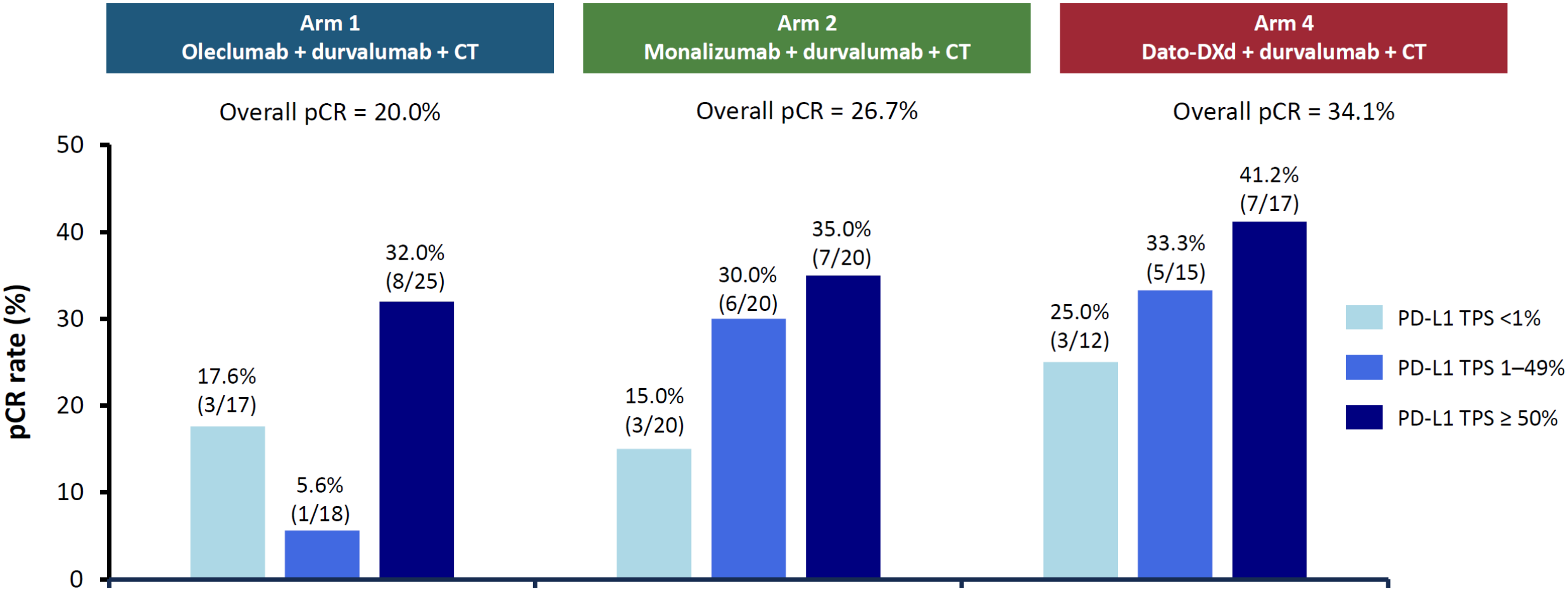
NeoCOAST-2: pCR and mPR rates across treatment arms



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

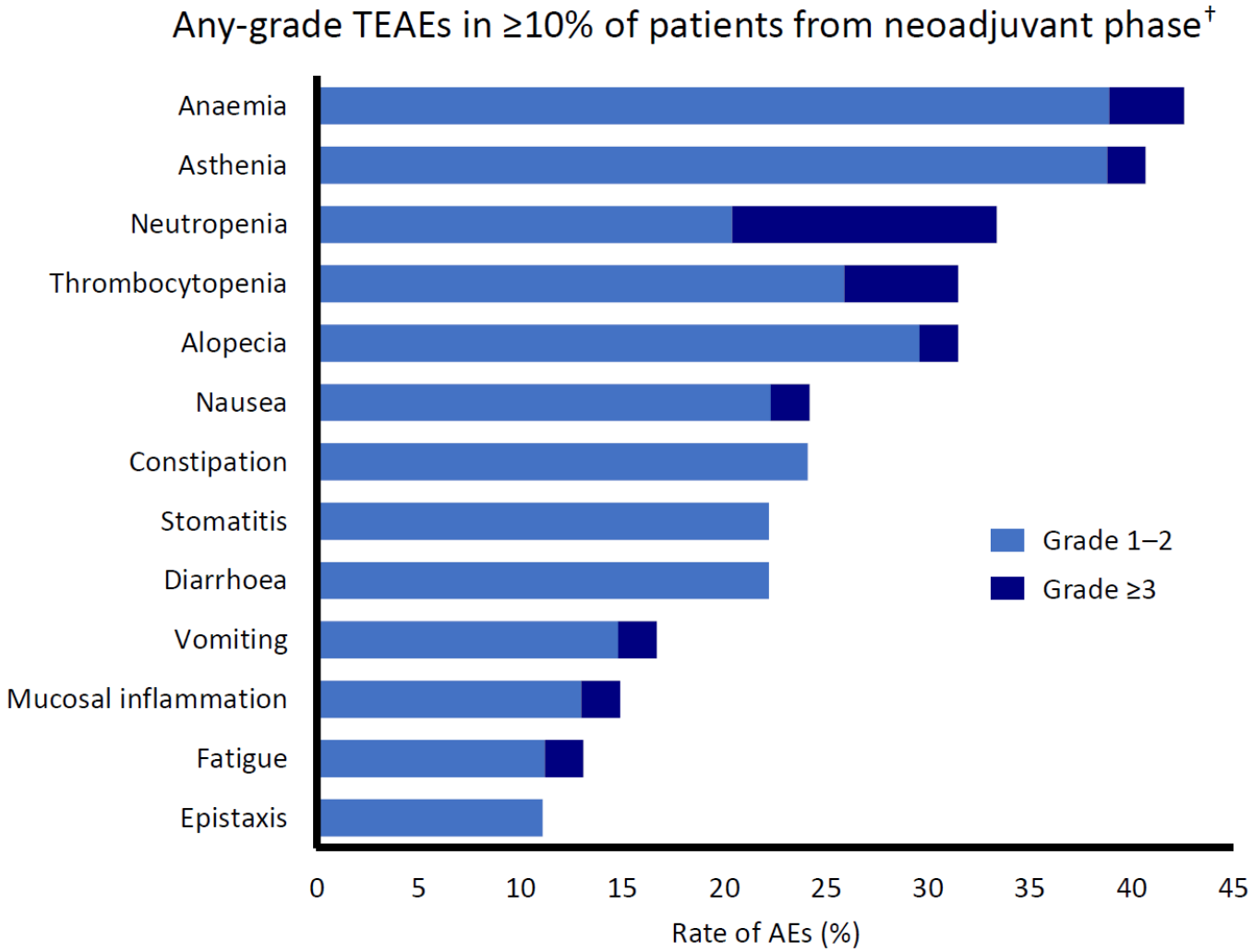


Data cut-off: 17 June 2024. Based on the modified intention-to-treat population which includes all randomised patients with confirmed NSCLC histology who received at least 1 dose of study treatment and had data available at data cut-off, including those who were unable to receive or complete surgery.
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 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.

Datopotamab deruxtecan (Dato-DXd) in patients with Ovarian or Endometrial Cancer: Results from the Phase 2 TROPION-PanTumor03 Study

Ana Oaknin,[1] Joo Ern Ang,[2] Sun Young Rha,[3] Kan Yonemori,[4] Rebecca Kristeleit,[5] Chia-Chi Lin,[6] Taroh Satoh,[7] Purificatión Estévez-Garcia,[8] Mehmet Ali Nahit Şendur,[9] Laura Medina Rodriquez,[10] Antoine Italiano,[11] Iwona Lugowska,[12] Isabelle Ray-Cocquard,[13] Amit Oza,[14] Jimmy L. Zhao,[15] Srikanth Gajavelli,[15] Justyna Filant,[16] Shamim Gharagoozloo,[17] Yelena Janjigian,[18] Funda Meric-Bernstam[19]

[1]Medical Oncology Service, Valld'Hebron Institute of Oncology, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [2]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK; [3]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [4]Department of Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; [5]Guy's and St Thomas' NHS Foundation Trust, London, UK; [6]National Taiwan University Hospital, Taipei, Taiwan; [7]Osaka University Hospital, Suita, Japan; [8]Hospital Universitario Virgen del Rocio, Seville, Spain; [9]Ankara YıldırımBeyazıtUniversity Faculty of Medicine and Ankara BilkentCity Hospital, Ankara, Türkiye; [10]Regional and Virgen de la Victoria University Hospitals, IBIMA, Malaga, Spain; [11]Institut Bergonié, Bordeaux, France; [12]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw,Poland; [13]Centre Leon Bérard, Lyon, France; [14]Princess Margaret Cancer Centre, Toronto, Canada; [15]AstraZeneca, New York, NY, USA; [16]AstraZeneca, Warsaw, Poland; [17]Biostatistics, AstraZeneca, Cambridge, UK; [18]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [19]MD Anderson Cancer Center, University of Texas, Houston, TX, USA

TROPION-PanTumor03 Study Design

A Phase 2, open-label, global study (NCT05489211) evaluating Dato-DXd as monotherapy and in combination with various anticancer agents across several tumour types

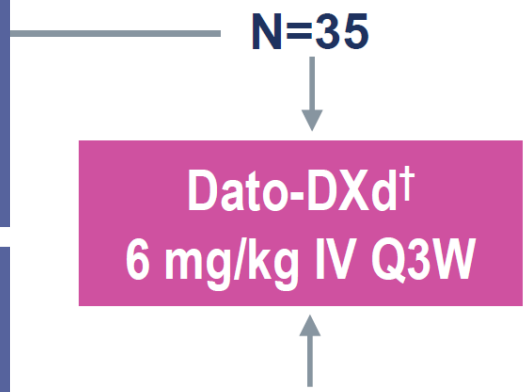
- Here, we present results of Dato-DXd monotherapy in the ovarian and endometrial cancer cohorts

Ovarian cancer (TROP2 expression unselected)

- High-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal carcinoma
- ECOG PS 0 or 1
- Progressed on ≥1 line of platinum chemotherapy but no more than 2 lines of therapy for advanced or metastatic disease; platinum-sensitive and resistant disease allowed*

Endometrial cancer (TROP2 expression unselected)

- Advanced/metastatic endometrial carcinoma
- All histologies (except sarcoma)
- ECOG PS 0 or 1
- Progressed on ≥1 line of platinum chemotherapy but no more than 2 lines of therapy for advanced or metastatic disease



Endpoints

Primary

- ORR by investigator per RECIST v1.1
- Safety & tolerability

Secondary

- PFS, DoR, DCR by investigator
- PK and immunogenicity

Exploratory

- OS
- Biomarker analyses

*Platinum-sensitive is defined as relapse/progression ≥6 months after completion of platinum-based chemotherapy; platinum-resistant is defined as progression <6 months of platinum-based therapy, including primary-refractory patients who progressed on or within 3 months of platinum-based chemotherapy (modified definition implemented by IMG); †Patients continued to receive treatment until they met one of the discontinuation criteria, including disease progression, unacceptable toxicity, withdrawal of consent, or study termination. Per protocol, a daily oral care protocol for stomatitis prophylaxis was provided to all patients prior to initiation of Dato-DXd; the use of a steroid-containing mouthwash was highly recommended.
DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IMG, International Medical Graduates; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; RECIST v1.1, Response evaluable criteria in solid tumours version 1.1.

Baseline Characteristics and Demographics

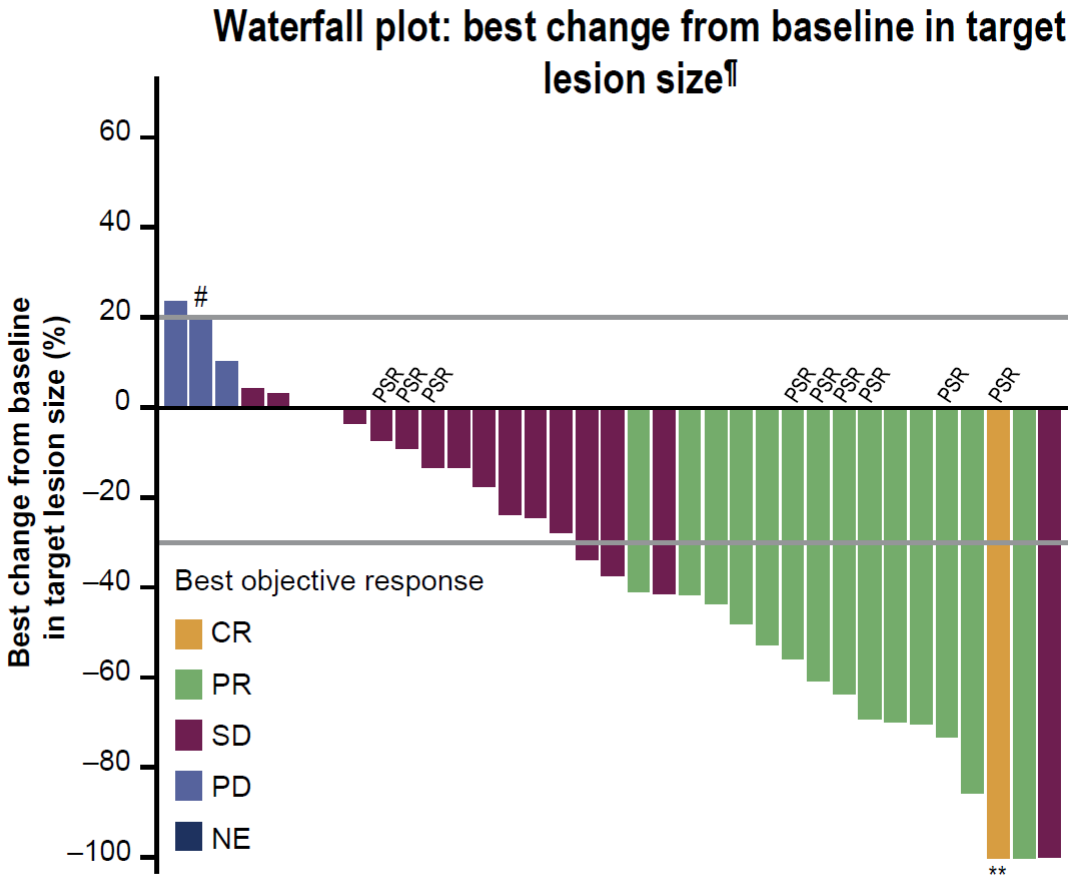
Characteristic		Ovarian (N=35)	Endometrial (N=40)
Age	Median (range), years	61.0 (35–80)	66.5 (48–78)
Race, n (%)	Asian	8 (22.9)	16 (40.0)
	White	23 (65.7)	18 (45.0)
	Other or not reported	4 (11.4)*	6 (15.0)†
ECOG PS, n (%)	0	21 (60.0)	25 (62.5)
	1	14 (40.0)	15 (37.5)
Major histology types, n (%)	High-grade endometrioid	0 (0.0)	11 (27.5)
	High-grade serous	27 (77.1)	10 (25.0)
	Low-grade endometrioid	0 (0.0)	7 (17.5)
	Clear cell	6 (17.1)	3 (7.5)
	Other‡	2 (5.7)	9 (22.5)
Previous lines of therapy, n (%)§	1	11 (31.4)	29 (72.5)
	≥2	24 (68.6)	11 (27.5)
Prior therapy, n (%)‖	Platinum therapy	35 (100)	40 (100)
	Bevacizumab/Lenvatinib	25 (71.4)	8 (20.0)
	PARP inhibitors	18 (51.4)	1 (2.5)
	Immunotherapy	2 (5.7)	9 (22.5)
	Hormone therapy	0 (0.0)	5 (12.5)
Platinum-sensitivity	Platinum-resistant¶	26 (74.3)	–
	Platinum-sensitive	9 (25.7)	–

*Including other (n=1), missing (n=1) and not reported (n=2); †Including American Indian or Alaska Native (n=1), Black or African American (n=1), not reported (n=3) and missing (n=1); ‡Including carcinosarcoma; §A patient who has received multiple lines of therapy is counted under the higher line of therapy only. No more than 2 previous lines of systemic therapy in the advanced or metastatic setting were allowed, neoadjuvant/adjuvant was counted as a line of therapy in the ovarian cohort; ‖A patient can be counted in multiple rows since more than one therapy can be taken. Within each row, a patient is counted only once; ¶Includes patients with platinum-refractory disease, defined as progression within 3 months of platinum therapy. PARP, Poly-ADP ribose polymerase.

Efficacy in Ovarian Cancer

- As of June 14, 2024, median duration of follow-up* was 14.5 months (range 10.4–15.4) in the ovarian cohort

	Ovarian		
	Total (N=35)	Platinum-sensitive (n=9)	Platinum-resistant (n=26)
Confirmed ORR, % (95% CI)	42.9 (26.3–60.6)	66.7 (29.9–92.5)	34.6 (17.2–55.7)
Best overall response, n (%)			
CR	1 (2.9)	1 (11.1)	0 (0.0)
PR	14 (40.0)	5 (55.6)	9 (34.6)
SD†	17 (48.6)	3 (33.3)	14 (53.8)
PD‡	3 (8.6)	0 (0.0)	3 (11.5)
NE§	0 (0.0)	0 (0.0)	0 (0.0)
Median time to response, months (range)	1.4 (1.2–8.2)	–	–
Median DoR, months (95% CI)	5.7 (2.9–NC)	8.5 (2.7–NC)	5.6 (2.9–NC)
DCR at 12 weeks,‖ % (80% CI)	85.7 (75.1–92.9)	100 (77.4–100.0)	80.8 (67.2–90.3)
Median PFS, months (95% CI)	5.6 (4.1–7.0)	–	–



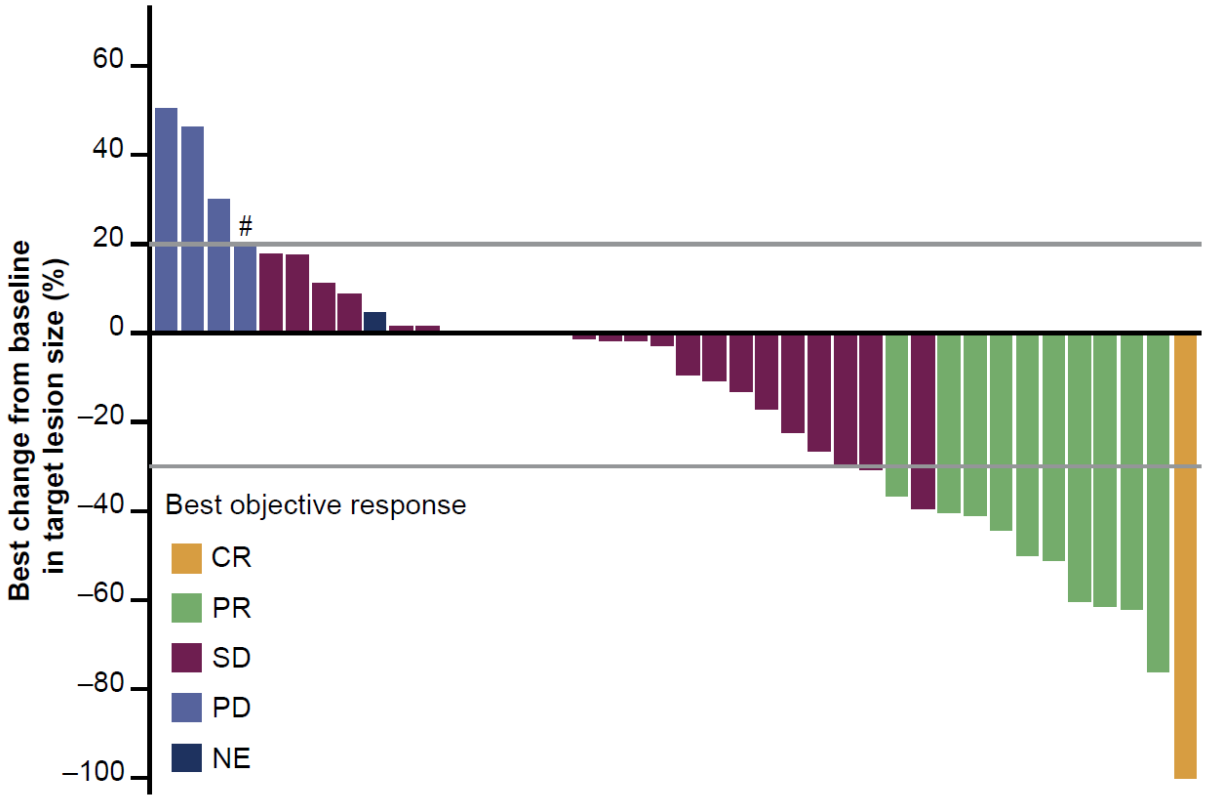
*Duration of follow-up calculated as the median time from randomisation to the date of censoring, in censored patients only; †Unconfirmed CR/PR, or SD ≥35 days; ‡RECIST progression or death ≤13 weeks; §SD <35 days, no valid baseline assessment or evaluable follow-up assessment; ‖Defined as the percentage of patients who achieved CR, PR or SD; ¶Best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction. Lines at -30% and 20% indicate thresholds for PR and PD, respectively. If best percentage change cannot be calculated due to missing data, +20% will be imputed as the best percentage change in the following situations (otherwise left as missing): patient has no post-baseline assessment, has died, has new lesions or progression of lesions, or has withdrawn due to PD and has no evaluable target lesion data. Patients with imputed values marked with #; **Patient had PR at the first visit (with a change from baseline in the target lesion of 100%) and PD at the subsequent two visits and was therefore an unconfirmed PR and classified as SD. CI, confidence interval; CR, complete response; NC, not calculable; NE, not evaluable; PD, progressive disease; PR, partial response; PSR, platinum-sensitive relapsed; SD, stable disease.

Efficacy in Endometrial Cancer

- As of June 14, 2024, median duration of follow-up* was 13.6 months (range 2.1–19.6) in the endometrial cohort

	Endometrial (N=40)
Confirmed ORR, % (95% CI)	27.5 (14.6–43.9)
Best overall response, n (%)	
CR	1 (2.5)
PR	10 (25.0)
SD†	23 (57.5)
PD‡	5 (12.5)
NE§	1 (2.5)
Median time to response, months (range)	2.8 (1.4–4.2)
Median DoR, months (95% CI)	16.4 (7.1–NC)
DCR at 12 weeks,‖ % (80% CI)	57.5 (46.1–68.3)
Median PFS, months (95% CI)	6.3 (2.8–NC)

Waterfall plot: best change from baseline in target lesion size¶



*Duration of follow-up calculated as the median time from randomisation to the date of censoring, in censored patients only; †Unconfirmed CR/PR, or SD ≥35 days; ‡RECIST progression or death ≤13 weeks; §SD <35 days, no valid baseline assessment or evaluable follow-up assessment; ‖Defined as the percentage of patients who achieved CR, PR or SD; ¶Best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction. Lines at -30% and 20% indicate thresholds for PR and PD, respectively. If best percentage change cannot be calculated due to missing data, +20% will be imputed as the best percentage change in the following situations (otherwise left as missing): patient has no post-baseline assessment, has died, has new lesions or progression of lesions, or has withdrawn due to PD and has no evaluable target lesion data. Patients with imputed values marked with #.

Exposure and Safety

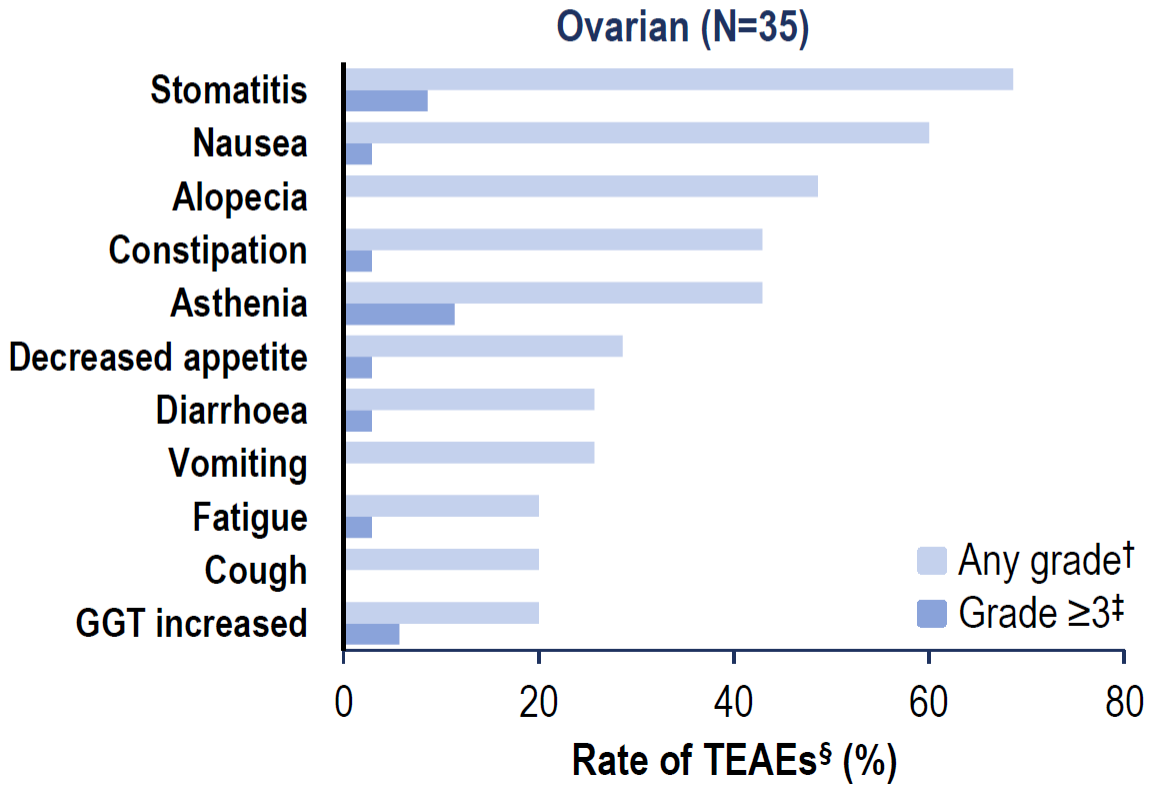
- The median treatment duration* for Dato-DXd was 5.6 months (range 1.4–14.8) in the ovarian cohort and 5.2 months (range 0.7–19.3) in the endometrial cohort

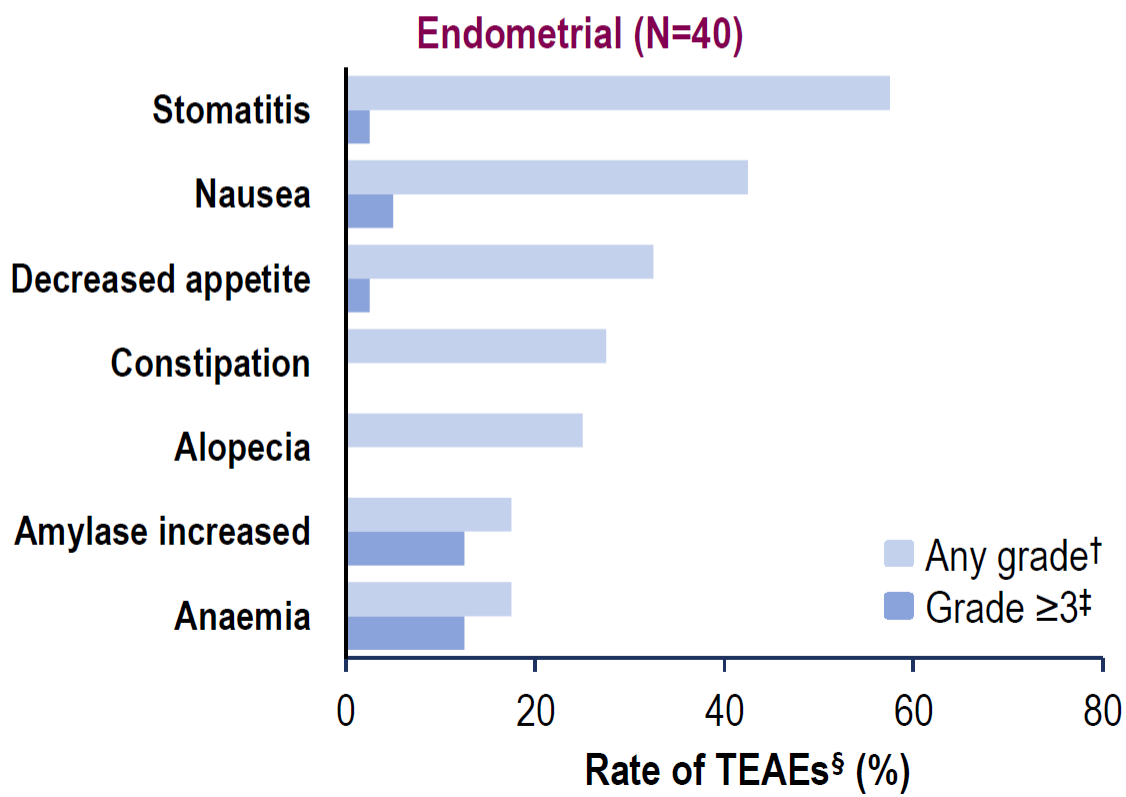
TEAEs, n (%)†	Ovarian (N=35)	Endometrial (N=40)
All grade	35 (100.0)	39 (97.5)
Grade ≥3‡	19 (54.3)	23 (57.5)
Serious	10 (28.6)	11 (27.5)
Leading to		
Dose reduction§	13 (37.1)	10 (25.0)
Dose interruption‖	16 (45.7)	14 (35.0)
Discontinuation¶	2 (5.7)	3 (7.5)
Death	0 (0)	0 (0)

*Actual treatment duration, defined as the total treatment duration (period from the first dose data of study drug to earliest of date of study discontinuation, date of death, data cutoff) minus the total duration of interruptions;
†Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories;
‡According to Common Terminology Criteria for Adverse Events (CTCAE) v5.0; §The most common reason for dose reduction in both cohorts was stomatitis (ovarian cohort: n=4; endometrial cohort: n=7); ‖The most common reasons for dose interruptions were punctate keratitis (n=2), vision blurred (n=2), and stomatitis (n=2) in the ovarian cohort and COVID-19 (n=2), keratitis (n=3) and amylase increased (n=2) in the endometrial cohort; ¶Reasons for discontinuation were pneumonitis (n=2) in the ovarian cohort and syncope (n=1), dry eye and ulcerative keratitis (n=1) and ILD (n=1) in the endometrial cohort. ILD, interstitial lung disease; TEAEs, treatment-emergent adverse events.

Most Frequent TEAEs

- The most common TEAEs in both cohorts were stomatitis* and nausea; the majority of cases were grade 1–2
- Adjudicated drug-related ILD* was reported in 1 patient in each cohort; both cases were grade 3
- Ocular surface events* were reported in 40.0% (grade 3: 0%) and 27.5% (grade 3: 5%) of patients in the ovarian and endometrial cohorts, respectively; there were no grade 4 or 5 events





*Adverse events of Special Interest. Ocular surface events and ILD are reported as group terms; †TEAEs that occurred at any grade in ≥20% of patients shown; ‡According to CTCAE v5.0; grade ≥3 AEs that occurred in ≥5 patients included; §Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
GGT, gamma-glutamyltransferase.

Conclusions

- **Dato-DXd monotherapy** demonstrated **encouraging efficacy** in patients with **advanced/metastatic ovarian and endometrial cancer** who had disease progression on prior platinum chemotherapy
  - In the ovarian cohort, ORR was 42.9% and median DoR was 5.7 (95% CI: 2.9–NC) months
    - In platinum-sensitive patients, ORR was 66.7% and median DoR was 8.5 (95% CI: 2.7–NC) months
    - In platinum-resistant patients, ORR was 34.6% and median DoR was 5.6 (95% CI: 2.9–NC) months
  - In the endometrial cohort, ORR was 27.5% and median DoR was 16.4 (95% CI: 7.1–NC) months

- The **safety profile** of Dato-DXd monotherapy was **manageable** and **consistent** with that of previous studies
  - Few TEAEs led to drug discontinuation and there were no TEAEs that led to death
  - The most common TEAEs were stomatitis and nausea; mostly grade 1/2
  - Rates of adjudicated drug-related ILD were low

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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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 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)

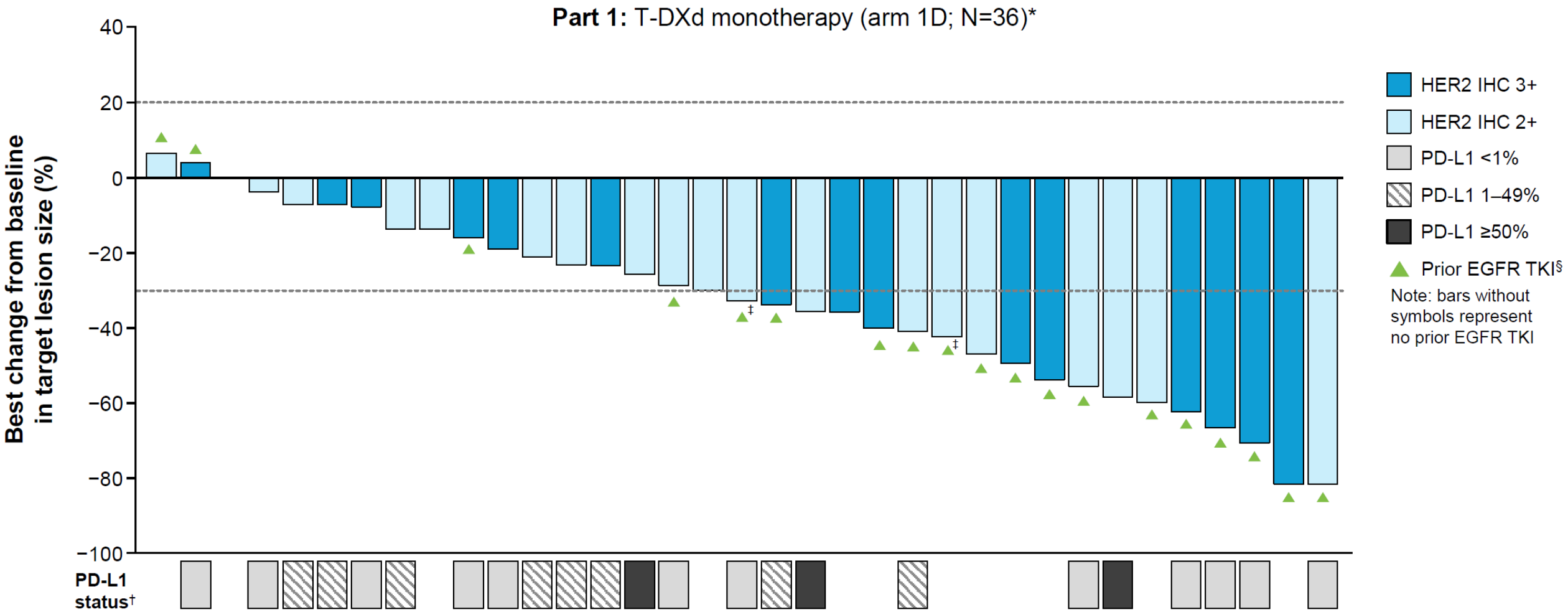
CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PD-L1, programmed cell death ligand 1; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor

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

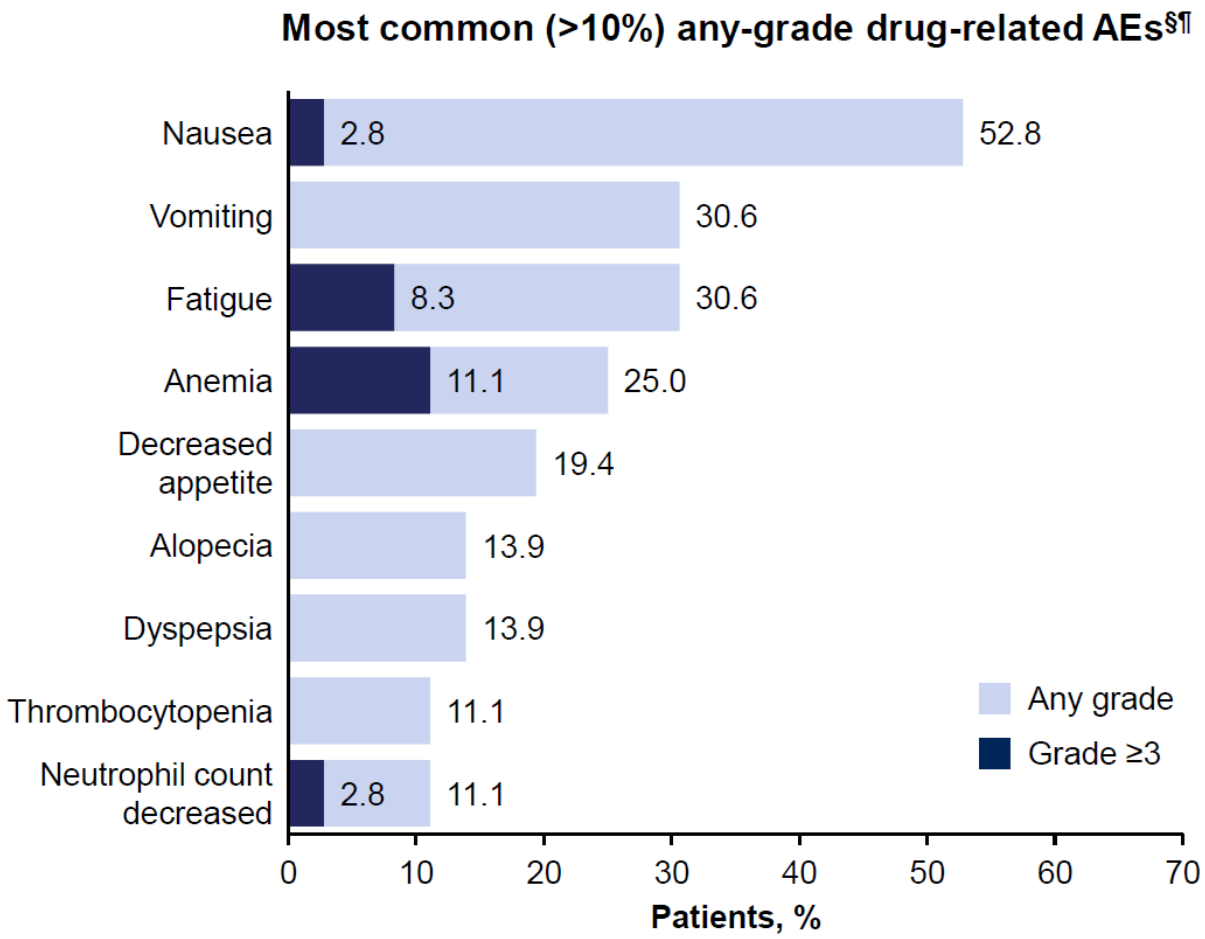
Best percentage change from baseline in target lesion size



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

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

Efficacy, safety and biomarker analysis of ICARUS-BREAST01: a phase 2 Study of Patritumab Deruxtecan (HER3-DXd) in patients with HR+/HER2 advanced breast cancer

B. Pistilli[1,15], L. Pierotti[2], M. Lacroix-Triki[3], C. Vicier[4], J.S. Frenel[5], V. D'Hondt[6], F. Dalenc[7], T. Bachelot[8], A. Ducoulombier[9], M.A Benderra[10], D. Loirat[11], D. Mayeur[12], G. Nachabeh[13], A. Sporchia[14], F.Suto[14], S.Michiels[2], N. Corcos[15], F. Mosele[1,16], F. André[1,16,17], G. Montagnac[15]

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ESMO 2024 340O (Oral)

ICARUS BREAST01: Study Design

Multi-center, single-arm, phase 2 study (NCT04965766)

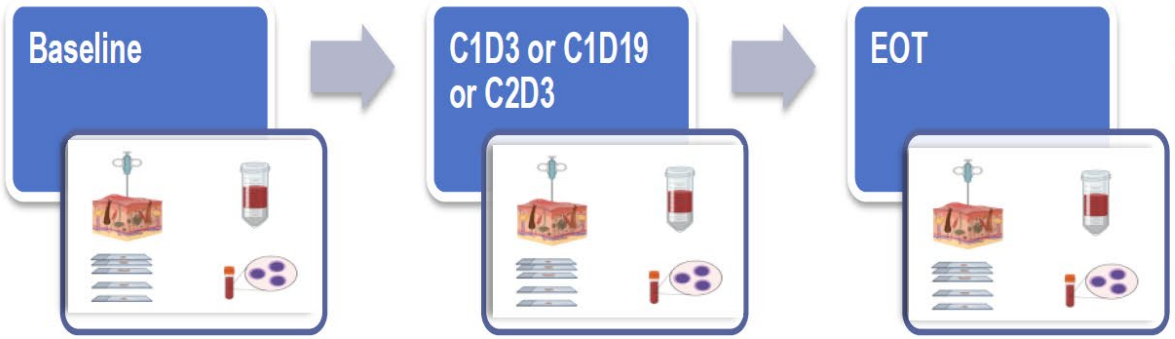
KEY ELIGIBILITY CRITERIA*:
-unresectable locally advanced/metastatic BC
-HR+/HER2-neg[a]
-progression on CDK4/6inh + ET
-progression on 1 prior chemotherapy for ABC
-prior PI3K/AKT/mTORinh allowed
-no prior T-DXd

HER3-DXd 5.6 mg/kg every 3 weeks until PD or unacceptable toxicity

Primary Endpoint:
- Investigator-assessed confirmed ORR

Secondary Endpoints:
- DOR, PFS, CBR, OS
- Safety and tolerability

Mandatory:
-tumor biopsy (1 frozen + 3 FFPE)
-blood (whole blood + serum)



Exploratory Endpoints:
- Predictors of response/resistance
- Dynamics of HER3 expression before and after treatment
- CTCs levels during treatment

***HER3-expression prescreening (75% of membrane positivity at 10x) was removed by amendment on April 21st 2022[b]**

a. Either IHC2+ and in situ hybridization [ISH] negative, or IHC1+ or IHC0+; b. The study was initially designed to include only patients with HER3-membrane expression ≥ 75% with 10x in tumor biopsies at baseline, however this inclusion criterion was deleted by amendment on 21st of April, 2022, after including the first 29 patients, and afterwards recruitment proceeded regardless of HER3 expression. This decision was taken because of the lack of a clear correlation between HER3 expression and response in other datasets. ABC: advanced breast cancer; CBR: clinical benefit rate; CTC: circulating tumor cells; DOR: duration of response; ET: endocrine therapy, T-DXd: Trastuzumab deruxtecan; ORR: objective response rate; OS: overall survival; PFS: progression-free survival;

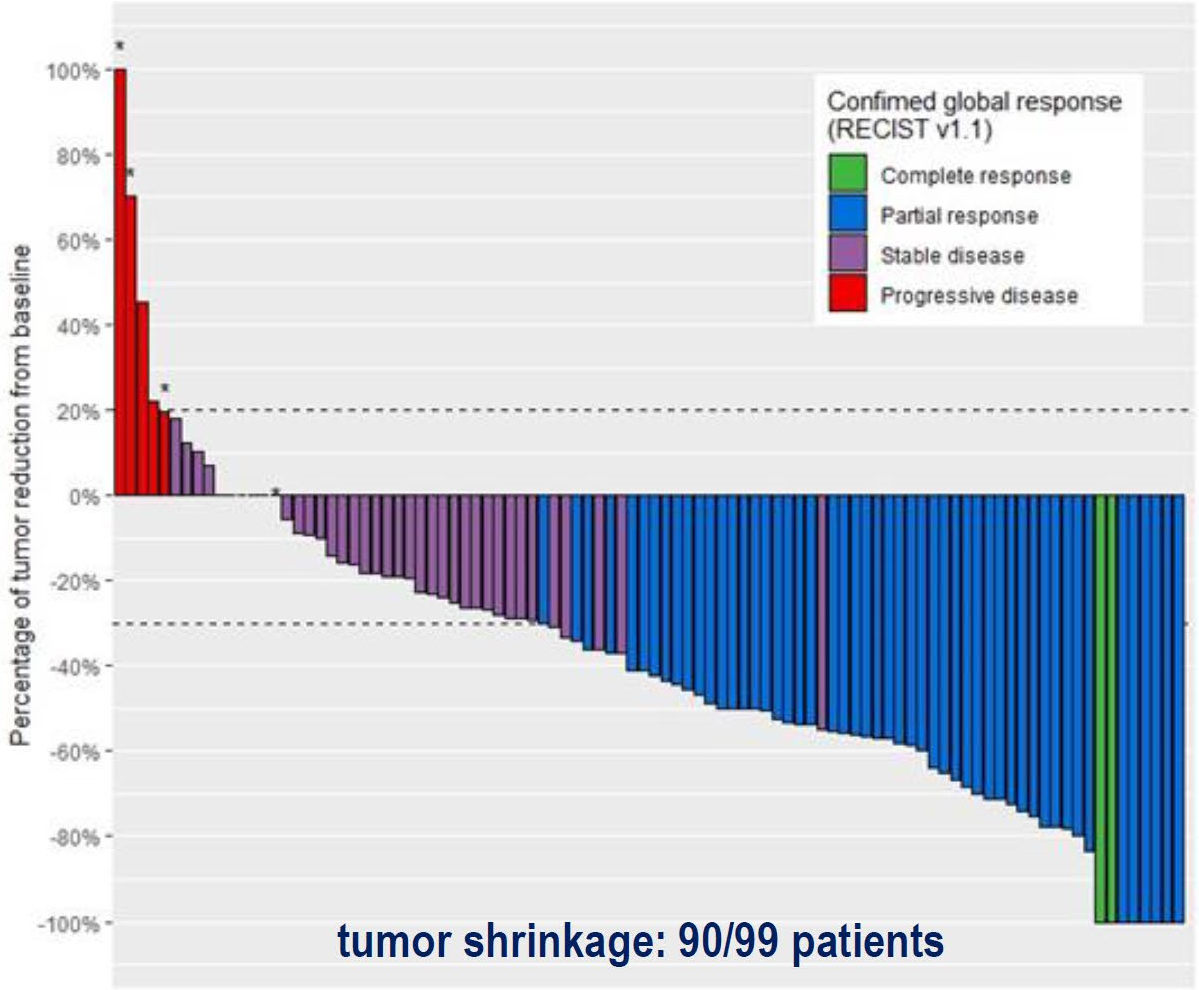
Demographics and baseline characteristics

PATIENTS N=99

Age	
Median [range], years	57.0 (48.0;66.0)
Sex, n (%)	
Female	99 (100.0)
HR status, n (%)[a]	
ER+	94 (94.9)
PR+	42 (42.4)
HER2 expression, n (%)[b]	
IHC 0*	39 (39.4)
IHC 1+	22 (22.2)
IHC 2+	7 (7.1)
IHC 3+	1 (1.0)
Unknown	30 (30.3)[c]
HER3 expression[b]	
Membrane H-score, median (IQR)	180 (144;215)
Overall membrane positivity at 10x, n (%):	
<25%	16 (16.2)
25-74%	7 (7.1)
≥75%	49 (49.4)
Unknown	27 (27.3)
Median number of systemic therapies for ABC, n [range]	2 [1;4]
Prior treatment with CDK4/6inh, n (%)	98 (99.0)[d]
Median duration, months [range]	13.7 [6.5;19.7][e]
Prior PI3K/AKT/mTOR inh for ABC, n (%)	35 (35.4)
Prior chemotherapy for ABC, n (%)[f]	99 (100.0)

a. As assessed on initial tumor biopsy at diagnosis; b. Centrally assessed on tumor biopsy at study entry; c. Insufficient tumor sample available; d. 96 patients had CDK4/6inh for ABC, 2 patients for early breast cancer; 1 patient was enrolled by mistake as did not receive any prior treatment with CDK4/6inh; e. assessed in 73 patients; f. only 1 line of chemotherapyr allowed; *20 with HER2 membrane staining 1-10 %

Confirmed Objective Response Rate

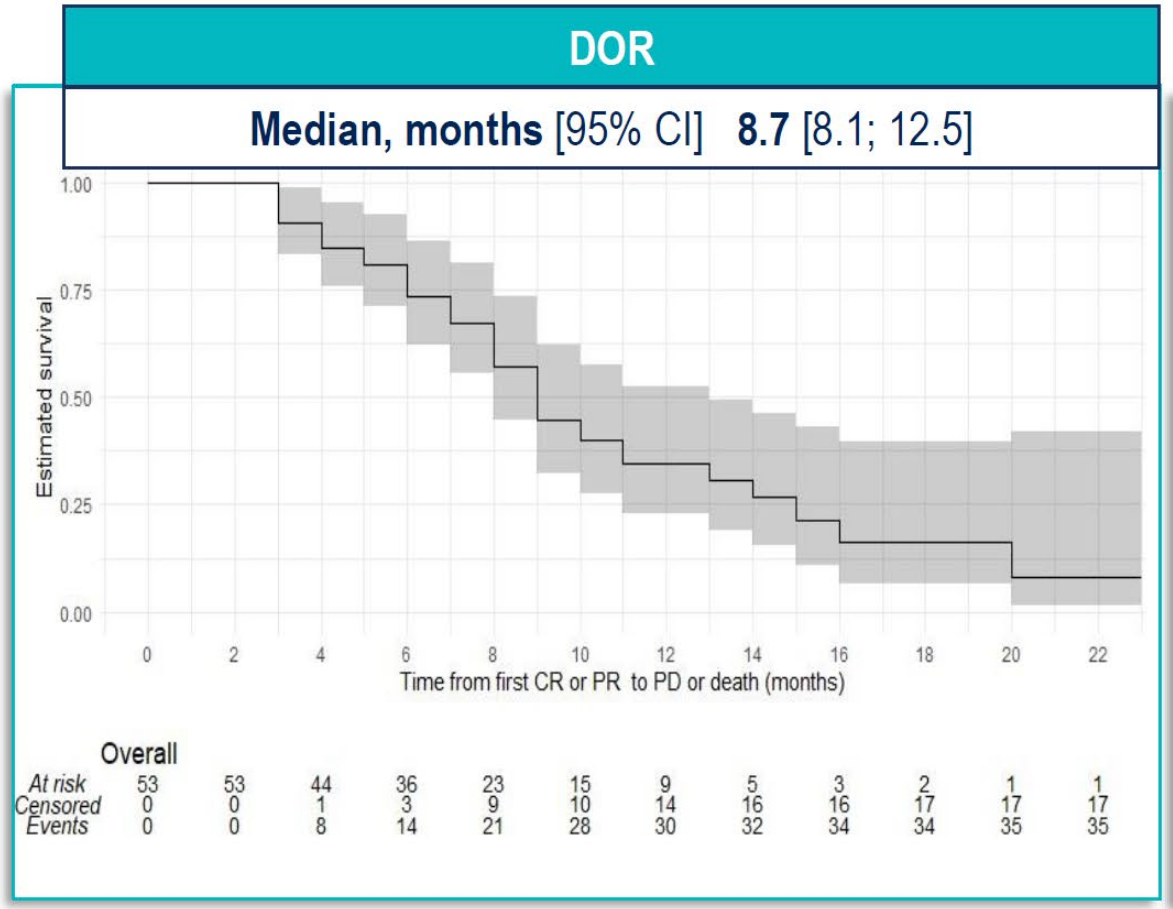


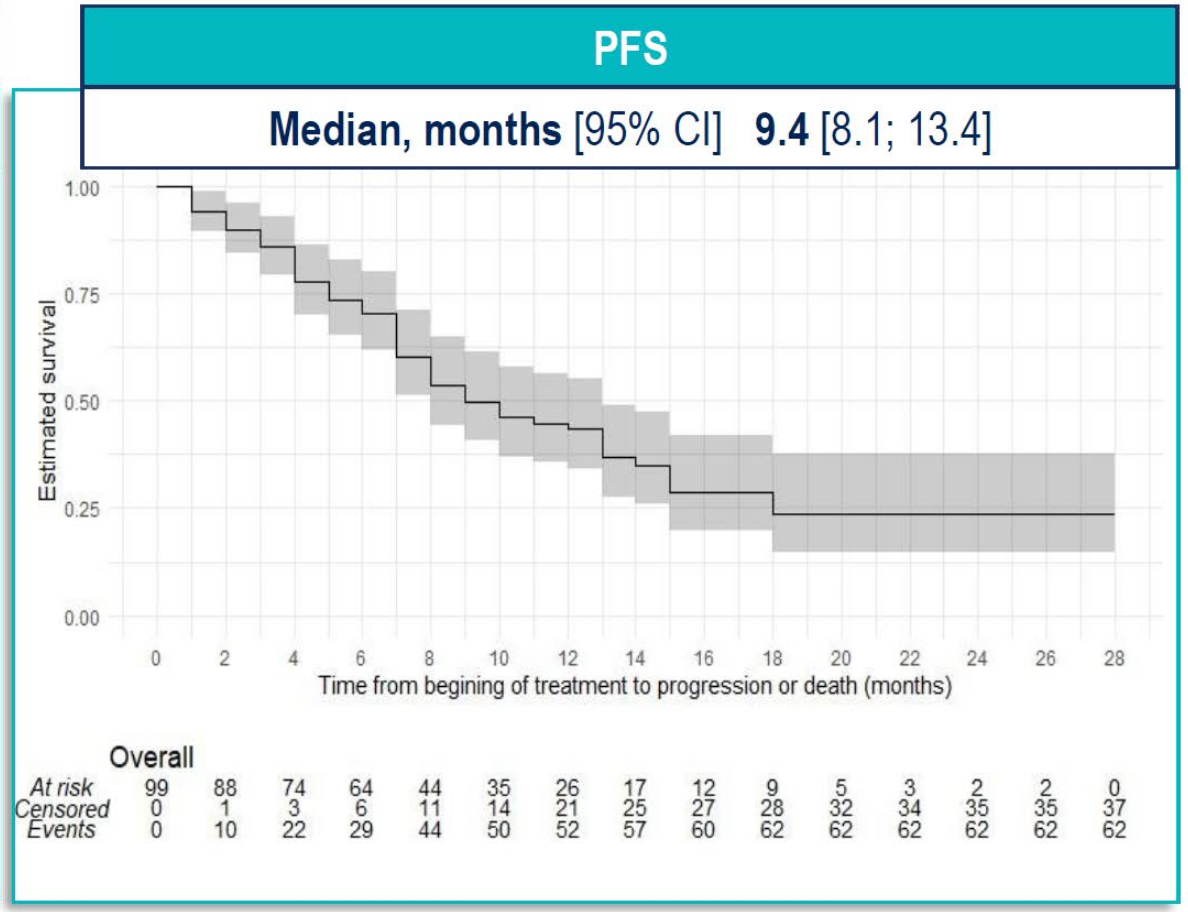
	N=99 n	% [95%CI][a]
Confirmed ORR[b]	**53**	**53.5** [43.2; 63.6]
CR	2	2.0 [0.2;7.1]
PR	51	51.5 [41.3; 61.7]
SD	37	37.4 [27.8; 47.7]
PD	7	7.1 [2.9; 14.0]
NE[c]	2	2.0 [0.2;7.1]
CBR[d]	**62**	**62.6** [52.3;72.1]

No significant association between HER2 expression and ORR (*p-value 0.8*)[e]

a. Clopper-Pearson (Exact) method was used for confidence interval; b. Confirmation of response must be demonstrated with a new tumor assessment 4 weeks or later from the initial response; c. 2 patients were not evaluable for ORR: one patient had only one tumor assessment with PR and then treatment discontinued due to clinical progression, a second patient had not evaluable as global response of target lesions. d. CBR is defined as the presence of at least a confirmed PR or CR, or a stable disease (SD) >6 months; e. logistic regression model was performed to estimate association between HER2 expression and ORR

Duration of Response and Progression-free Survival





Median follow-up: 15.3 months [95%CI 13.0;17.2]

No significant association between HER2 expression and PFS (*p-value 0.6*)[a]

a. Cox regression model was performed to estimate association between HER2 expression and PFS

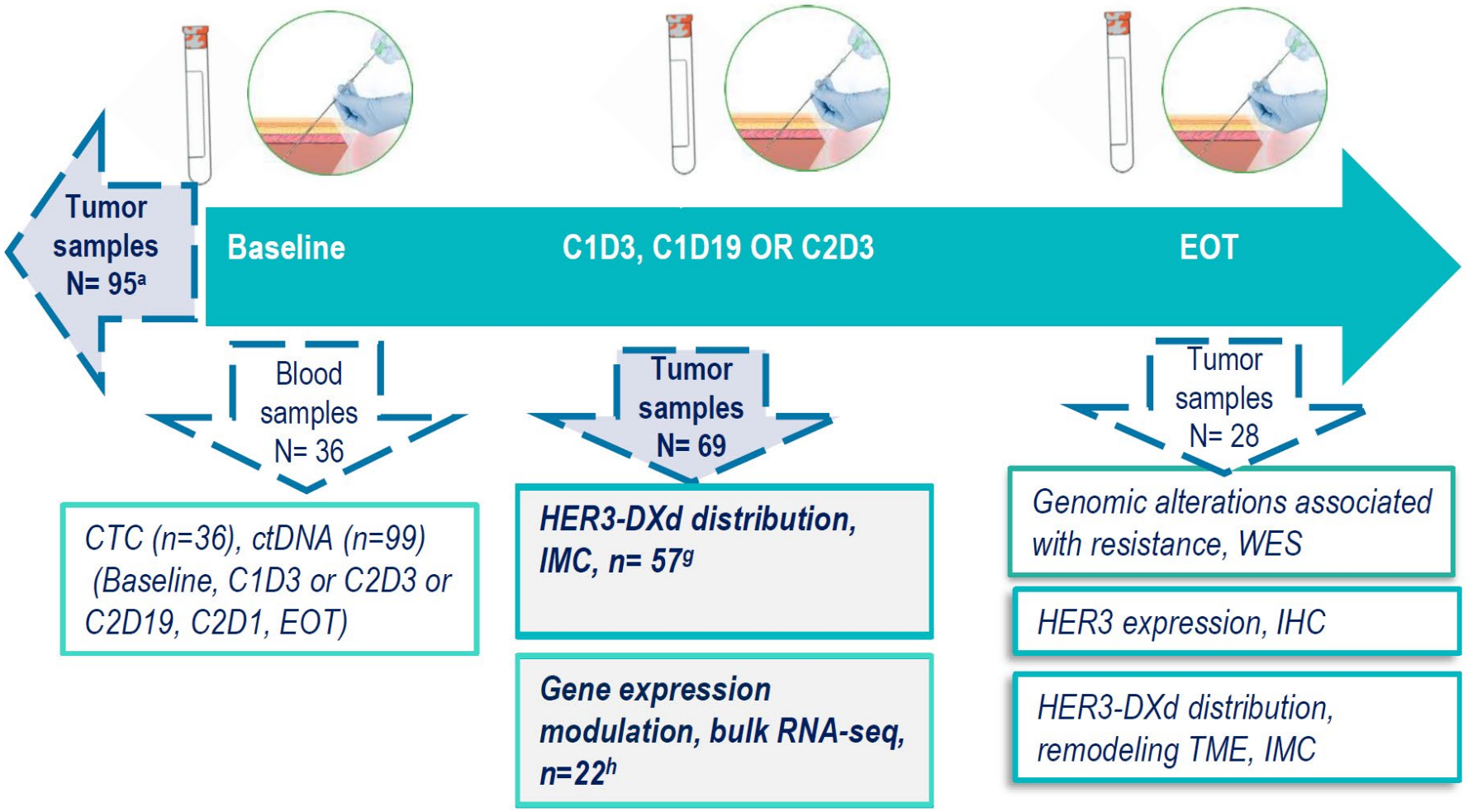
Overall safety data

Overall safety profile, n (%)	
• **Patients with any grade TEAEs**	**97 (98.0)**
Grade ≥3 TEAEs	**54 (54.5)**
• **Patients with any grade TRAEs**	**97 (98.0)**
Grade ≥3 TRAEs	**50 (50.1)**
• TEAEs leading to HER3-DXd discontinuation	11 (11.1)
• TEAEs leading to HER3-DXd interruption	26 (26.3)
• TEAEs leading to HER3-DXd dose reduction	20 (20.2)
• TEAEs leading to death	1 (1.0)[a]
• **Adjudicated treatment-related ILD**	**7 (7.1)[b]**
Grade 1	7

TRAEs occurring in ≥ 10% of patients	Any grade, n (%)	Grade ≥ 3, n (%)
Fatigue	82 (82.8)	10 (10.1)
Nausea	74 (74.7)	14 (14.1)
Diarrhea	52 (52.5)	10 (10.1)
Alopecia	40 (40.4)	0
Constipation	21 (21.2)	0
Vomiting	18 (18.2)	3 (3.0)
Anorexia	16 (16.2)	1 (1.0)
Neutrophil count decrease	14 (14.1)	12 (12.1)
Abdominal pain	11 (11.1)	0
Stomatitis	10 (10.1)	0
Anemia	10 (10.1)	0

TEAEs: Treatment-Emergent Adverse Events; ILD: Interstitial Lung Disease ; a. one patient died due to a massive pleural effusion not related to study treatment; b.Among the 13 cases identified as suspected during the treatment period, 7 case was adjudicated as HER3-DXd-related ILD, 2 of them led to treatment discontinuation

Exploratory biomarker analysis



a.4 biopsies not performed/collected; b. 23 samples < 10%; c.25 excluded after pathologist's review; d. 15 fresh biopsies not collected/provided by centers, 28 < 200 ng DNA or < 10% tumor cell; 13 failed quality control; e. 15 fresh biopsies not provided by centers, 28 < 200 ng RNA or < 30% tumor cell, 5 failed quality control, 29 did not have the matched on-T sample; f. 15 fresh biopsies were not provided centers, 28 < 200 ng RNA or < 30% tumor cell, 5 failed the quality control, 29 did not have matched on-T sample; g. 12 samples inadequate staining; h. 22 fresh biopsies not provided by centers, 39 < 200 ng RNA or < 30% tumor cell, 1 sample failed the quality control, 15 did not have matched BL sample;
IHC: Immunohistochemistry, RNAseq: RNA Sequencing, IMC: Imaging Mass Cytometry, WES: Whole Exome Sequencing; ML: machine learning; HER3 IHC: clone SP438

Conclusion and perspectives

- HER3-DXd showed clinically meaningful activity and manageable safety profile in patients with HR+/HER2- ABC progressing after 2 or more lines of therapy, including CDK4/6inh:
  ORR 53.5% [95%CI, 43.2; 63.6]; mDoR 8.7 [8.1; 12.5]; mPFS 9.4 mos [95%CI 8.1; 13.4]

- Activity of HER3-DXd was observed **across a range of tumor HER3 and HER2 membrane expression by IHC**

- Although with the limitations of the small sample size, exploratory biomarker analysis suggest that:
  -distribution of HER3-DXd in the tumor may play a role in determining a better treatment response
  -up-regulation of genes involved in immune response, particularly interferon alpha and gamma were significantly enriched in the entire cohort and among responders

- **Efficacy and safety profile of HER3-DXd make this ADC an optimal candidate for further larger trials in patients with HR+/HER2- ABC after failure of CDK4/6 inhibitors**

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

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[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]Sarah Cannon Research Institute, Nashville, TN, USA; [4]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [5]Institut Curie, Paris, France; [6]The Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan; [7]Jilin Cancer Hospital, Changchun, China; [8]Department of Medical Oncology, Kindai University, Osaka, Japan; [9]Seoul National University Bundang Hospital and Seoul National University College of Medicine, Seongnam, Republic of Korea; [10]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [11]Cancer and Hematology Centers, Grand Rapids, Michigan, MI, USA; [12]National Cancer Center Hospital East, Kashiwa, Japan; [13]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [14]Daiichi Sankyo, SAS, Paris, France; [15]Hospital Universitario 12 de Octubre, Madrid, Spain.

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:

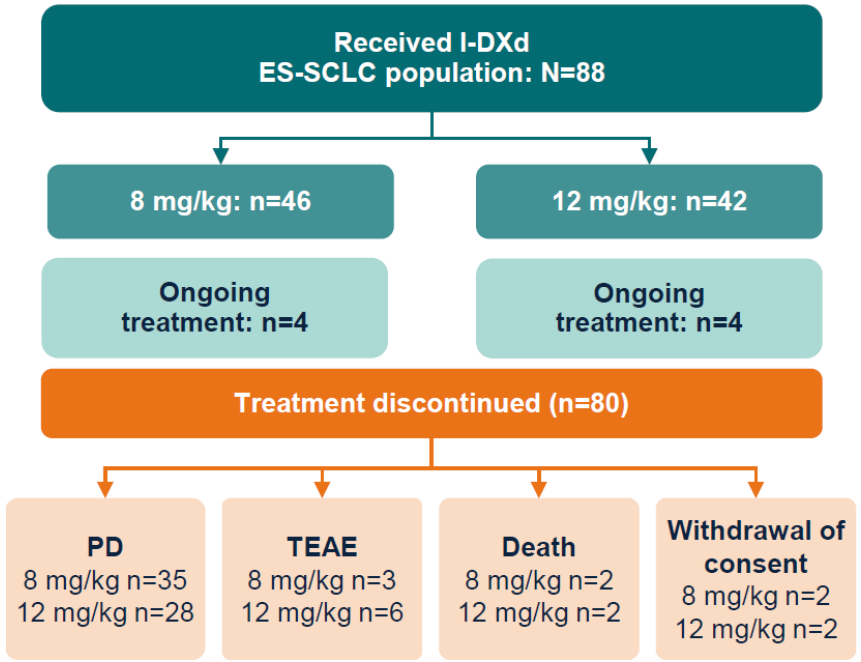
- DOR by BICR and inv[c]
- PFS by BICR and inv[c]
- OS
- DCR[c]
- TTR by BICR and inv[c]
- ORR by inv[c]
- Safety
- Pharmacokinetics
- Immmunogenicity

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)

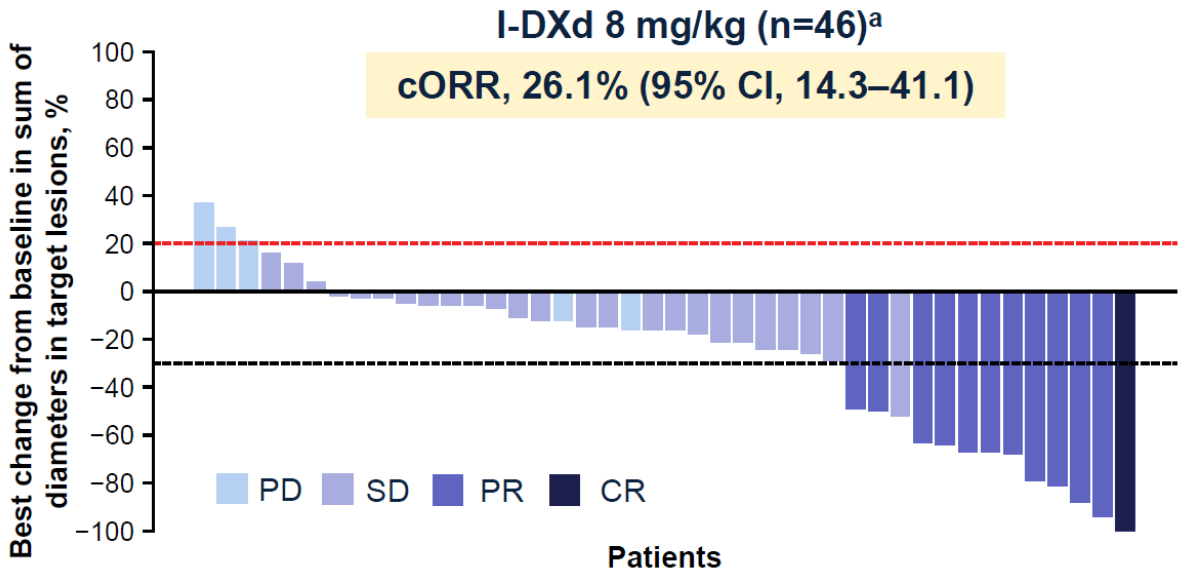
	I-DXd 8 mg/kg n=46	I-DXd 12 mg/kg n=42	Total N=88
Age, median (range)	64 (42–85)	64 (34–79)	64 (34–85)
Male, n (%)	30 (65.2)	33 (78.6)	63 (71.6)
ECOG PS, n (%)			
0	13 (28.3)	6 (14.3)	19 (21.6)
1	33 (71.7)	36 (85.7)	69 (78.4)
ES-SCLC at diagnosis, n (%)	32 (69.6)[a]	35 (83.3)	67 (76.1)
Patients with 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)

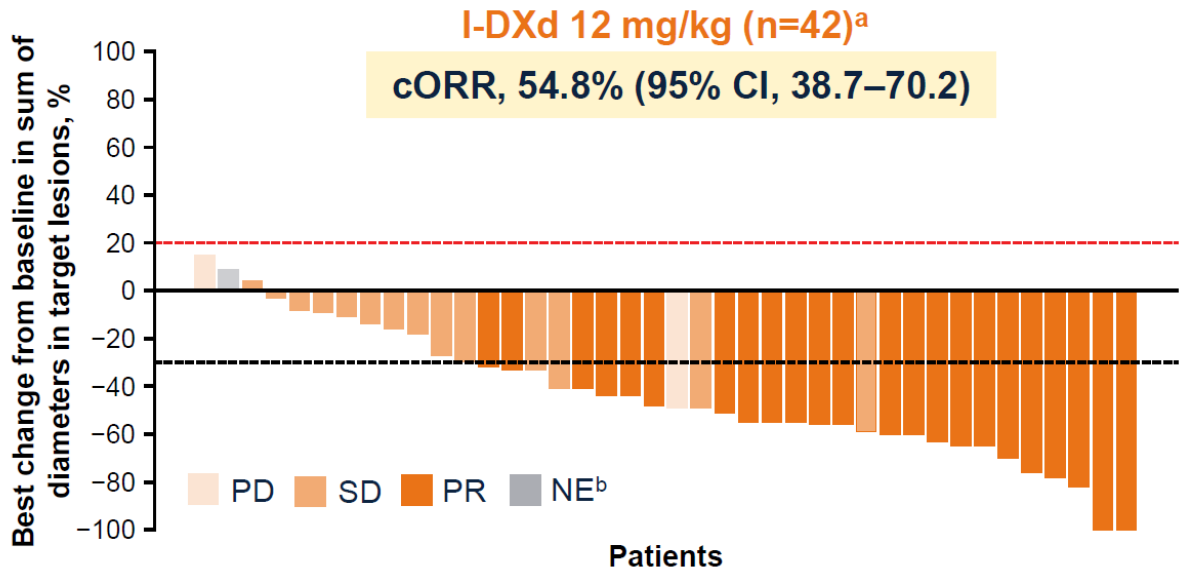
Data cutoff: April 25, 2024.

[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





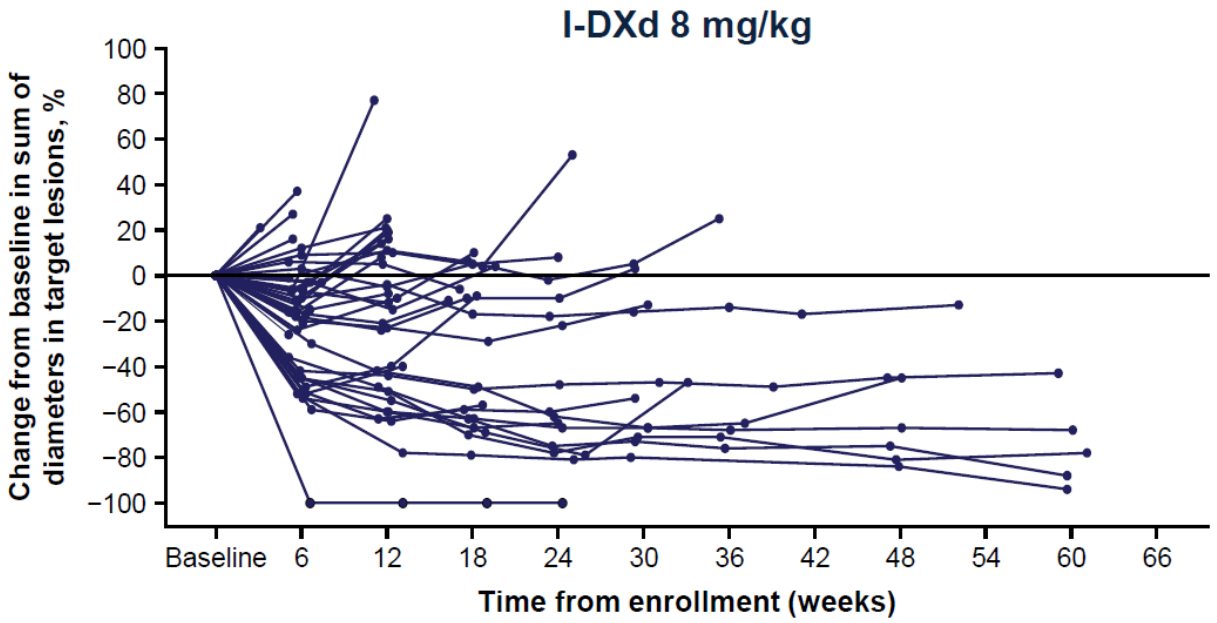
Confirmed response by BICR[c]	I-DXd 8 mg/kg n=46	I-DXd 12 mg/kg n=42
ORR, % (95% CI)	26.1 (14.3–41.1)	54.8 (38.7–70.2)
CR, n (%)	1 (2.2)	0
PR, n (%)	11 (23.9)	23 (54.8)
DCR, % (95% CI)	80.4 (66.1–90.6)	90.5 (77.4–97.3)

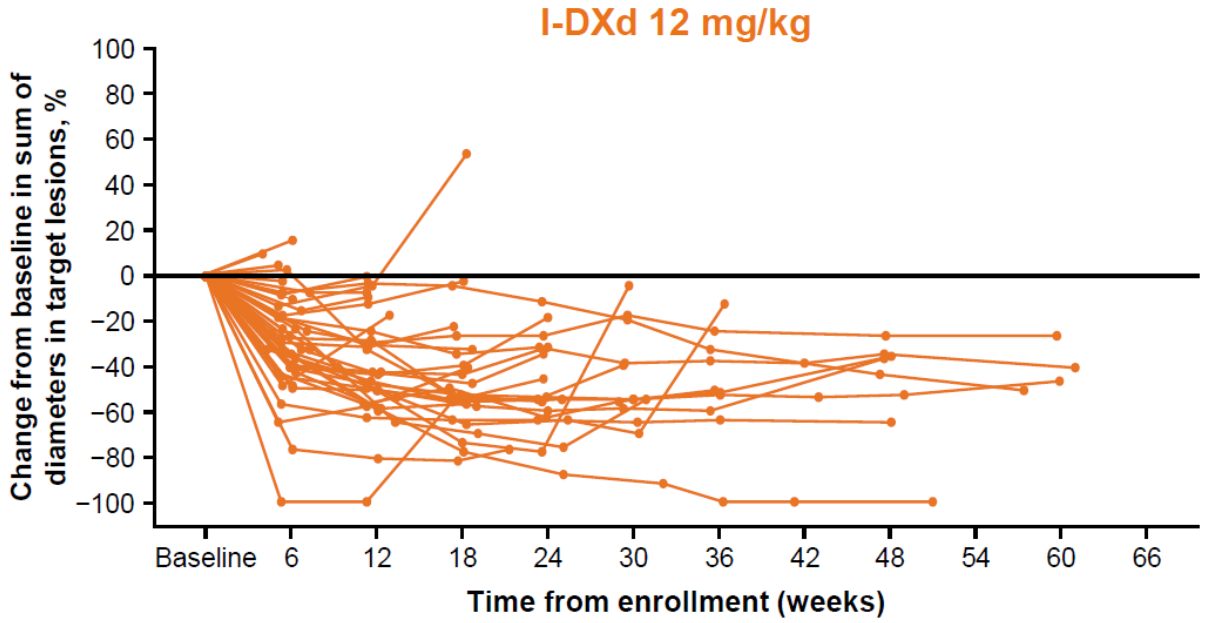
Data cutoff: April 25, 2024. The median follow-up for 8-mg/kg and 12-mg/kg cohorts was 14.6 months (range, 0.6–17.0) and 15.3 months (range, 0.8–20.3) respectively.

[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





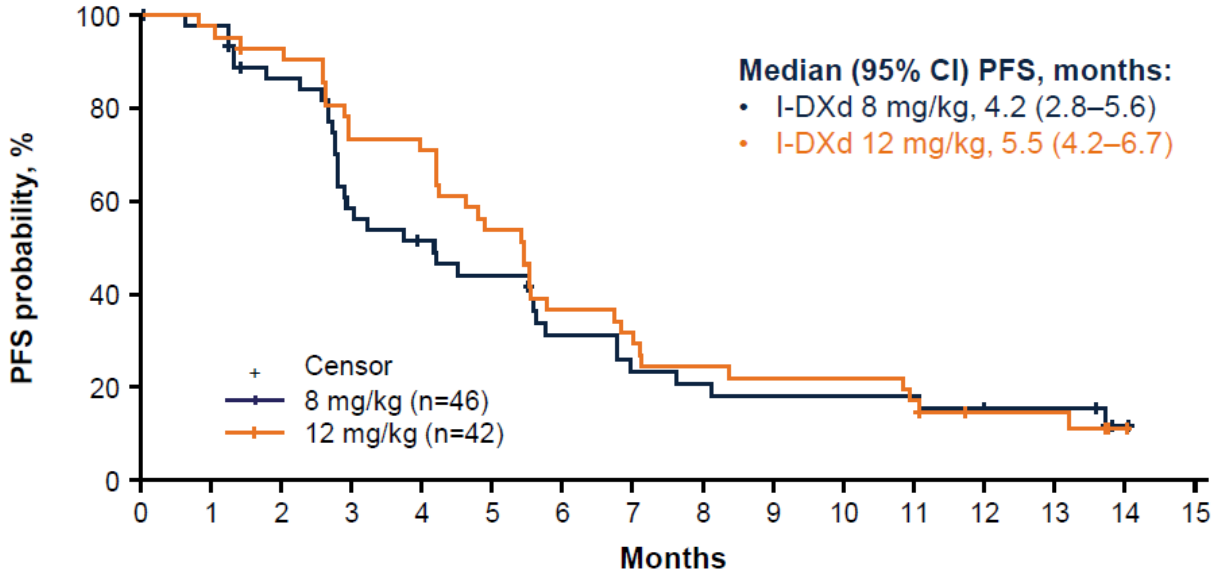
	I-DXd 8 mg/kg n=46	I-DXd 12 mg/kg n=42
Median (range) TTR,[a] months	1.4 (1.2–1.5)	1.4 (1.0–8.1)
Median (95% CI) DOR,[a,b] months	7.9 (4.1–NE)	4.2 (3.5–7.0)

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.

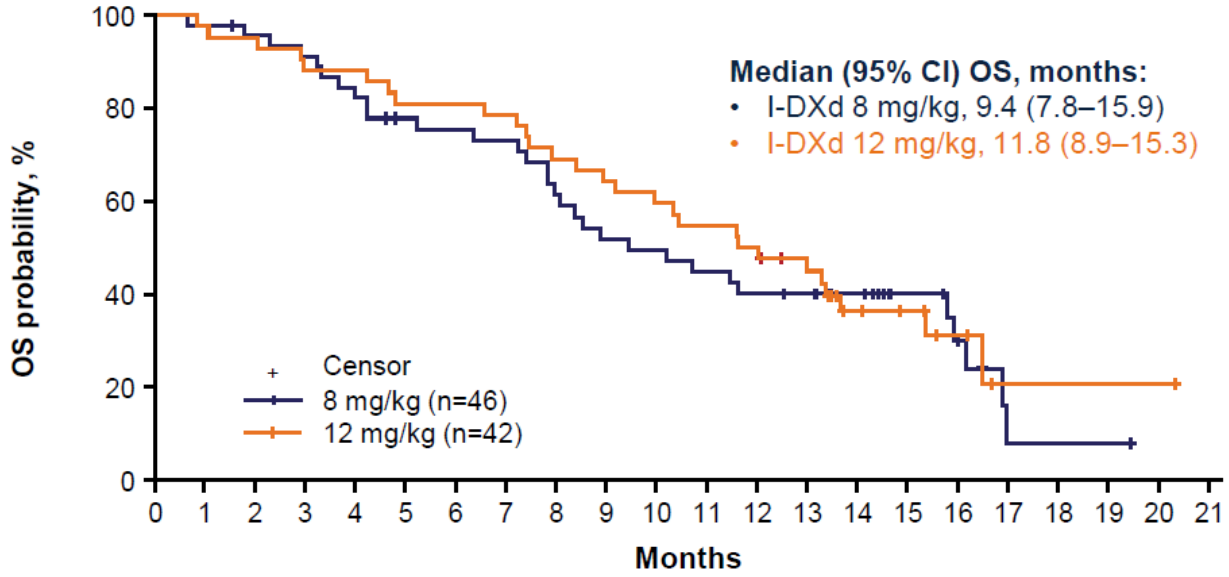
2L, second-line; BICR, blinded independent central review; DOR, duration of response; NE, not estimable; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; TTR, time to response.

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.

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)

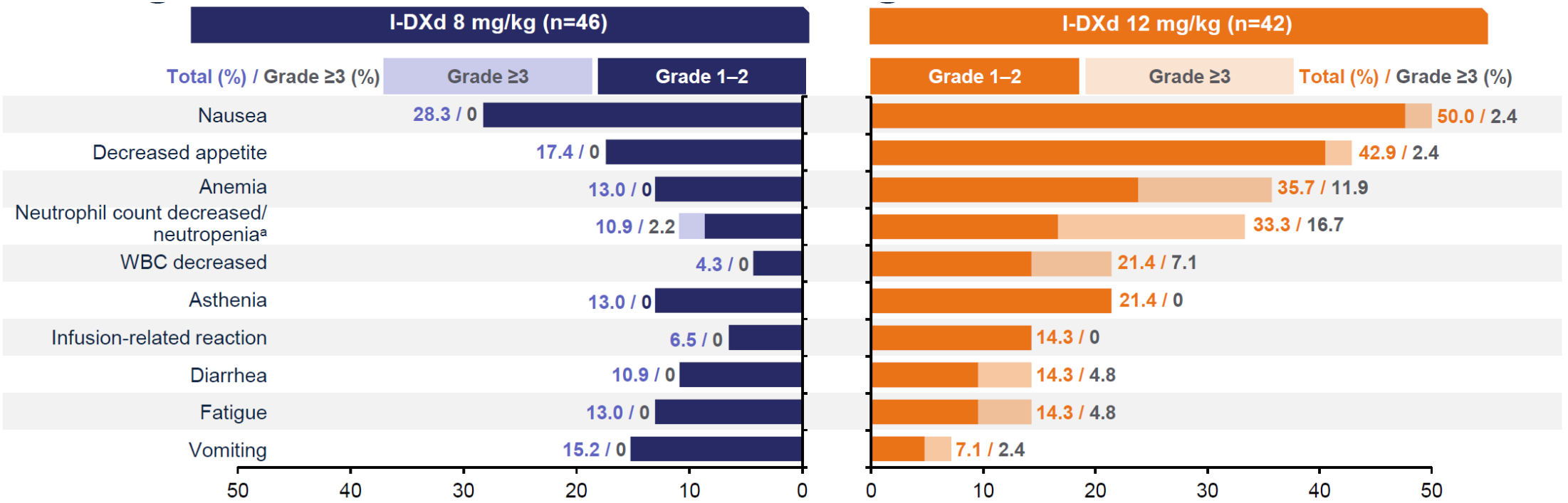
- Treatment discontinuations were:
  - In the 8-mg/kg cohort: pneumonia (Grade 3, n=1), pneumonitis (Grade 2, n=1) and pulmonary embolism (Grade 4, n=1)
  - In the 12-mg/kg cohort: pneumonia (Grade 1, n=1; Grade 3,[b] n=1), pneumonitis (Grade 2, n=1), ILD (Grade 2, n=1), *Pneumocystis jirovecii* pneumonia (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



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.

Preliminary results from a Phase 1, first-in-human study of DS-9606, a Claudin 6 (CLDN6)-directed antibody–drug conjugate, in patients with tumor types known to express CLDN6

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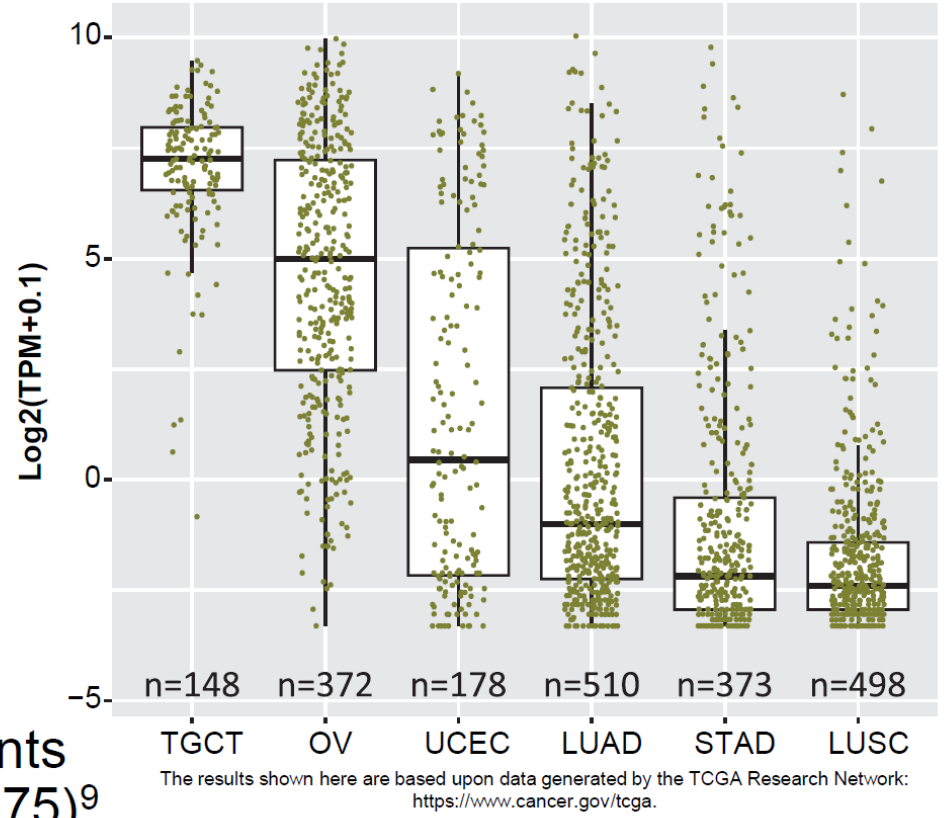
[1]Florida Cancer Specialists, Sarasota, FL, USA; [2]Sarah Cannon Research Institute, Nashville, TN, USA; [3]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]Sarah Cannon Research Institute, Denver, CO, USA; [5]Institute of Cancer Research and the Royal Marsden Hospital, London, UK; [6]Karmanos Cancer Institute, Detroit, MI, USA; [7]Daiichi Sankyo Inc., Basking Ridge, NJ, USA; [8]Sarah Cannon Research Institute, London, UK.

ESMO 2024 610O (Oral)

Background

- **DS-9606 is an ADC composed of[1]:**
  - Humanized anti-CLDN6 mAb
  - Cleavable linker
  - Modified PBD payload
- **CLDN6**
  - Important component of cell-to-cell tight junctions[2]
  - Plays a role in the regulation of epithelial and endothelial cell proliferation and differentiation[2]
  - Nearly absent in normal adult tissue but expressed in several tumor types, including ovarian, endometrial, and gastric cancers, GCTs, and NSCLC[3–8]
  - Can be associated with poor prognosis[7]
- First report from an ongoing Phase 1 trial of DS-9606 in patients with locally advanced or metastatic solid tumors (NCT05394675)[9]

CLDN6 expression in select solid tumors



The results shown here are based upon data generated by the TCGA Research Network: https://www.cancer.gov/tcga.

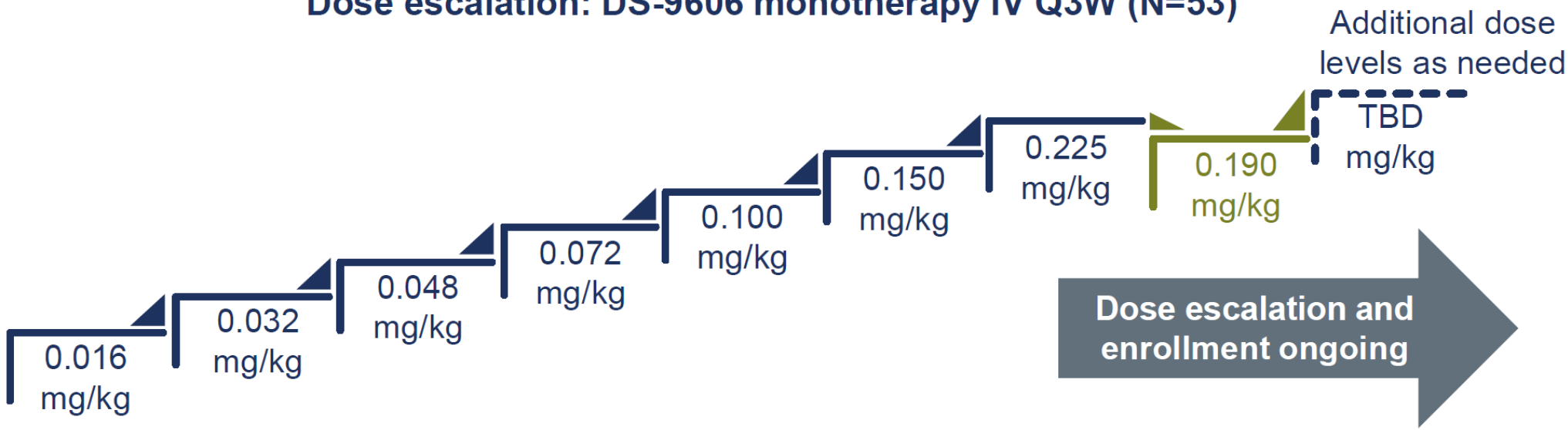
ADC, antibody–drug conjugate; CLDN6, Claudin 6; GCT, germ cell tumor; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; OV, ovarian serous cystadenocarcoma; PBD, pyrrolobenzodiazepine; STAD, stomach adenocarcinoma; TCGA, The Cancer Genome Atlas; TGCT, testicular GCT; TPM, transcripts per million; UCEC, uterine corpus endometrial carcinoma.

1. Data on file. Daiichi Sankyo, Inc. DS9606-137 protocol, version 6; 2023. 2. Du H, et al. *Mol Med Rep*. 2021;24:677. 3. Wang L, et al. *Diagn Pathol*. 2013;8:190. 4. Ushiku T, et al. *Histopathology*. 2012;61:1043–1056. 5. Kojima M, et al. *Cancers (Basel)*. 2020;12:2748. 6. Micke P, et al. *Int J Cancer*. 2014;135:2206–2214. 7. Zhang C, et al. *Front Cell Dev Biol*. 2021;9:726656. 8. Yu S, et al. *Cell Death Dis*. 2019;10:949. 9. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05394675. Accessed August 15, 2024.

First-in-human Phase 1 study of DS-9606[1,2]

Preliminary safety and efficacy analysis of dose-escalation

Dose escalation: DS-9606 monotherapy IV Q3W (N=53)



Key enrollment criteria:

- Adults with locally advanced or metastatic solid tumors known to express CLDN6 (CLDN6 expression was not required for selection[a])
- PD with SOC treatment for metastatic disease (any number of prior LOTs)
- ECOG PS 0–1
- No prior CLDN6-targeted agents or ADCs that deliver a PBD payload
- Adequate cardiac and pulmonary function, including no history of or current ILD/pneumonitis

Data cutoff: June 14, 2024

[a]Archived tumor tissue, or fresh tumor biopsy if archived tissue was not available, was tested retrospectively; patients with GCTs without archived tumor tissue may be allowed with medical monitor approval.

ADC, antibody–drug conjugate; CLDN6, Claudin 6; ECOG PS, Eastern Cooperative Oncology Group performance status; GCT, germ cell tumor; ILD, interstitial lung disease; IV, intravenous; LOT, line of therapy; PBD, pyrrolobenzodiazepine; PD, progressive disease; Q3W, every 3 weeks; SOC, standard-of-care; TBD, to be determined.

1. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05394675. Accessed August 15, 2024. 2. Data on file. Daiichi Sankyo, Inc. DS9606-137 protocol, version 6; 2023.

Baseline characteristics and disposition

Patients were heavily pretreated, and baseline characteristics were balanced across dose groups

DS-9606 dose, mg/kg	0.016 (n=3)	0.032 (n=7)	0.048 (n=7)	0.072 (n=6)	0.100 (n=7)	0.150 (n=14)	0.190 (n=3)	0.225 (n=6)	Total (N=53)
Age, median (range), years	67 (52–72)	52 (24–72)	63 (51–68)	48 (29–68)	63 (55–75)	58 (31–84)	65 (37–75)	54 (32–66)	58 (24–84)
Sex, n (%)									
Male	1 (33.3)	3 (42.9)	1 (14.3)	3 (50.0)	1 (14.3)	10 (71.4)	2 (66.7)	3 (50.0)	24 (45.3)
Female	2 (66.7)	4 (57.1)	6 (85.7)	3 (50.0)	6 (85.7)	4 (28.6)	1 (33.3)	3 (50.0)	29 (54.7)
ECOG PS, n (%)									
0	1 (33.3)	2 (28.6)	3 (42.9)	0	1 (14.3)	5 (35.7)	0	1 (16.7)	13 (24.5)
1	2 (66.7)	5 (71.4)	4 (57.1)	6 (100.0)	6 (85.7)	9 (64.3)	3 (100.0)	5 (83.3)	40 (75.5)
Primary diagnosis, n (%)									
Ovarian cancer[a]	1 (33.3)	2 (28.6)	5 (71.4)	2 (33.3)	5 (71.4)	2 (14.3)	0	2 (33.3)	19 (35.8)
GCT[b]	0	2 (28.6)	0	3 (50.0)	0	4 (28.6)	1 (33.3)	1 (16.7)	11 (20.8)
G/GEJ/E-AC[c]	0	0	0	0	1 (14.3)	3 (21.4)	0	3 (50.0)	7 (13.2)
NSCLC	0	0	0	0	0	5 (35.7)	2 (66.7)	0	7 (13.2)
Pancreatic cancer	1 (33.3)	2 (28.6)	2 (28.6)	0	0	0	0	0	5 (9.4)
Breast cancer	0	1 (14.3)	0	0	1 (14.3)	0	0	0	2 (3.8)
Endometrial cancer	1 (33.3)	0	0	1 (16.7)	0	0	0	0	2 (3.8)
No. prior LOT, median (range)	3.0 (3–3)	3.0 (2–8)	4.0 (1–8)	3.5 (1–8)	6.0 (3–9)	4.0 (1–9)[d]	3.0 (2–5)	5.5 (2–8)	4.0 (1–9)
Ongoing in study, n (%)	0	1 (14.3)	1 (14.3)	1 (16.7)	0	10 (71.4)	3 (100.0)	5 (83.3)	21 (39.6)

Data cutoff: June 14, 2024

[a]Includes ovarian cancer (n=18) and fallopian tube cancer (n=1). [b]Includes anterior mediastinal tumor (n=1), mediastinal GCT (n=1), embryonal cell carcinoma of the right testis (n=1), and testicular cancer (n=8). [c]Includes gastric cancer (n=1), stomach cancer (n=1), gastrointestinal carcinoid tumor (n=1), gastroesophageal junction cancer (n=2), and esophageal cancer (n=2). [d]Information on prior systemic anticancer therapy missing for one patient.

ECOG PS, Eastern Cooperative Oncology Group performance status; G/GEJ/E-AC, gastric/gastroesophageal junction/esophageal adenocarcinoma; GCT, germ cell tumor; LOT, line of therapy; NSCLC, non-small cell lung cancer.

Safety: Overview of TEAEs and related TEAEs

- 45 patients (84.9%) had TEAEs; 28 patients (52.8%) had related TEAEs
- No treatment withdrawals due to related TEAEs; related TESAEs occurred at the highest dose level
- No DLTs to date; MTD and RDE not yet determined

DS-9606 dose, mg/kg	0.016 (n=3)	0.032 (n=7)	0.048 (n=7)	0.072 (n=6)	0.100 (n=7)	0.150 (n=14)	0.190 (n=3)	0.225 (n=6)	Total (N=53)
TEAEs, n with event (%)									
Any grade	3 (100.0)	6 (85.7)	7 (100)[a]	6 (100)	5 (71.4)	13 (92.9)	1 (33.3)	4 (66.7)	45 (84.9)
Related	0	5 (71.4)	5 (71.4)[a]	4 (66.7)	2 (28.6)	8 (57.1)	0	4 (66.7)	28 (52.8)
Grade ≥3	1 (33.3)	2 (28.6)	3 (42.9)	2 (33.3)	2 (28.6)	4 (28.6)	0	2 (33.3)	16 (30.2)
Related	0	1 (14.3)	1 (14.3)	0	0	0	0	1 (16.7)	3 (5.7)
Serious[b]	1 (33.3)	1 (14.3)	3 (42.9)	2 (33.3)	2 (28.6)	4 (28.6)	0	3 (50.0)	16 (30.2)
Related	0	0	0	0	0	0	0	2 (33.3)	2 (3.8)
Associated with:									
Treatment interruption	0	2 (28.6)[c]	2 (28.6)	2 (33.3)	0	2 (14.3)	0	1 (16.7)	9 (17.0)
Related	0	0	0	0	0	0	0	1 (16.7)	1 (1.9)
Dose reduction	0	0	1 (14.3)[a]	0	0	1 (7.1)	0	1 (16.7)	3 (5.7)
Related	0	0	1 (14.3)[a]	0	0	1 (7.1)	0	1 (16.7)	3 (5.7)
Treatment withdrawal	0	0	0	0	0	1 (7.1)	0	0	1 (1.9)
Related	0	0	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0	0	0

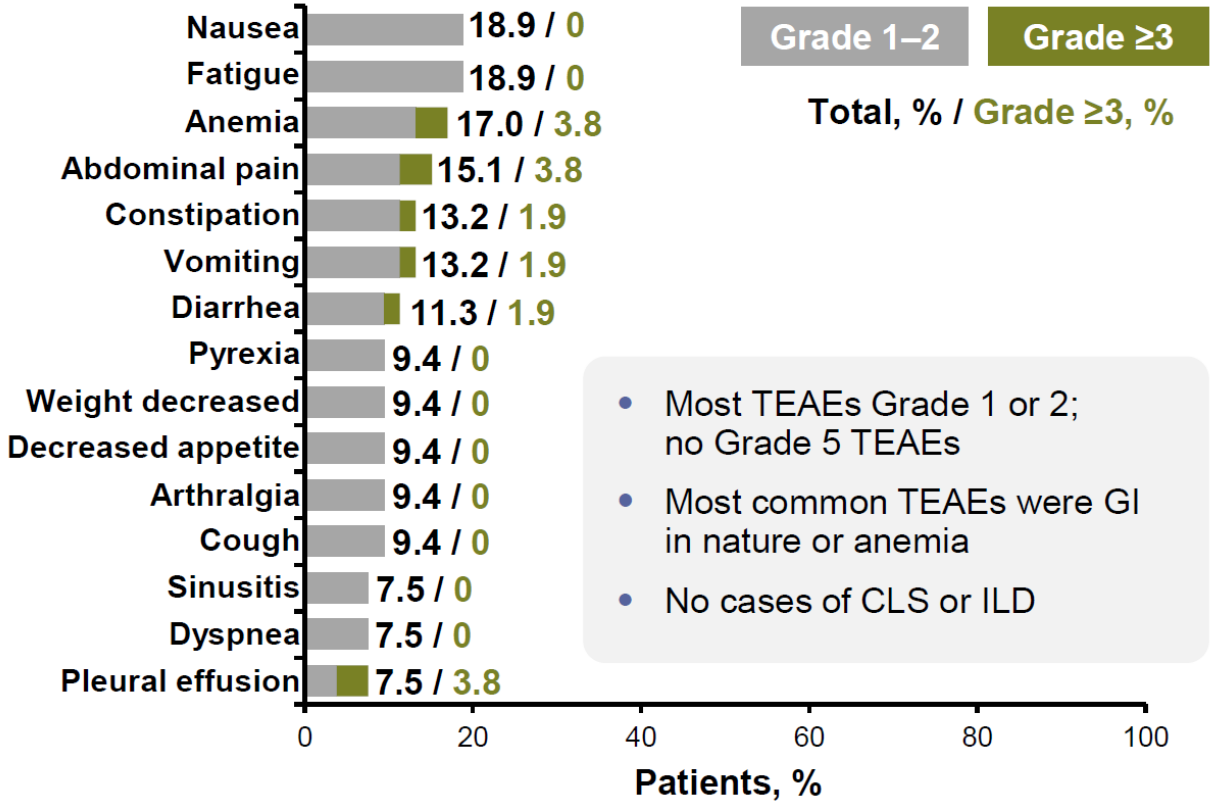
Data cutoff: June 14, 2024

[a]One intra-patient dose escalation (IPDE), with the patient receiving DS-9606 0.048 mg/kg from Cycle 1–10, 0.100 mg/kg from Cycle 11–14, and then 0.048 mg/kg from Cycle 15 through end of treatment. Dose reduction occurred at 0.100 mg/kg. Per the protocol, IPDE was allowed if the investigator determined IPDE was favorable from a benefit–risk standpoint; the patient had completed at least 6 cycles of treatment at the current dose level; no Grade ≥3 related TEAEs or any AE leading to dose reduction were observed at the current dose level; the totality of the patient's available data had been reviewed by the medical monitor; and the sponsor had granted approval. [b]Per the protocol, AEs were considered serious if they resulted in any of death, a life-threatening AE, inpatient hospitalization of ≥24 hours or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly/birth defect, or an important medical event. [c]Includes 1 IPDE, with the patient receiving DS-9606 0.032 mg/kg from Cycle 1–23, 0.048 mg/kg from Cycle 24–25, and 0.032 mg/kg from Cycle 26 through end of treatment. AE, adverse event; DLT, dose-limiting toxicity; IPDE, intra-patient dose escalation; MTD, maximum tolerated dose; RDE, recommended dose for expansion; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

Safety: Most common TEAEs and related TEAEs[a]

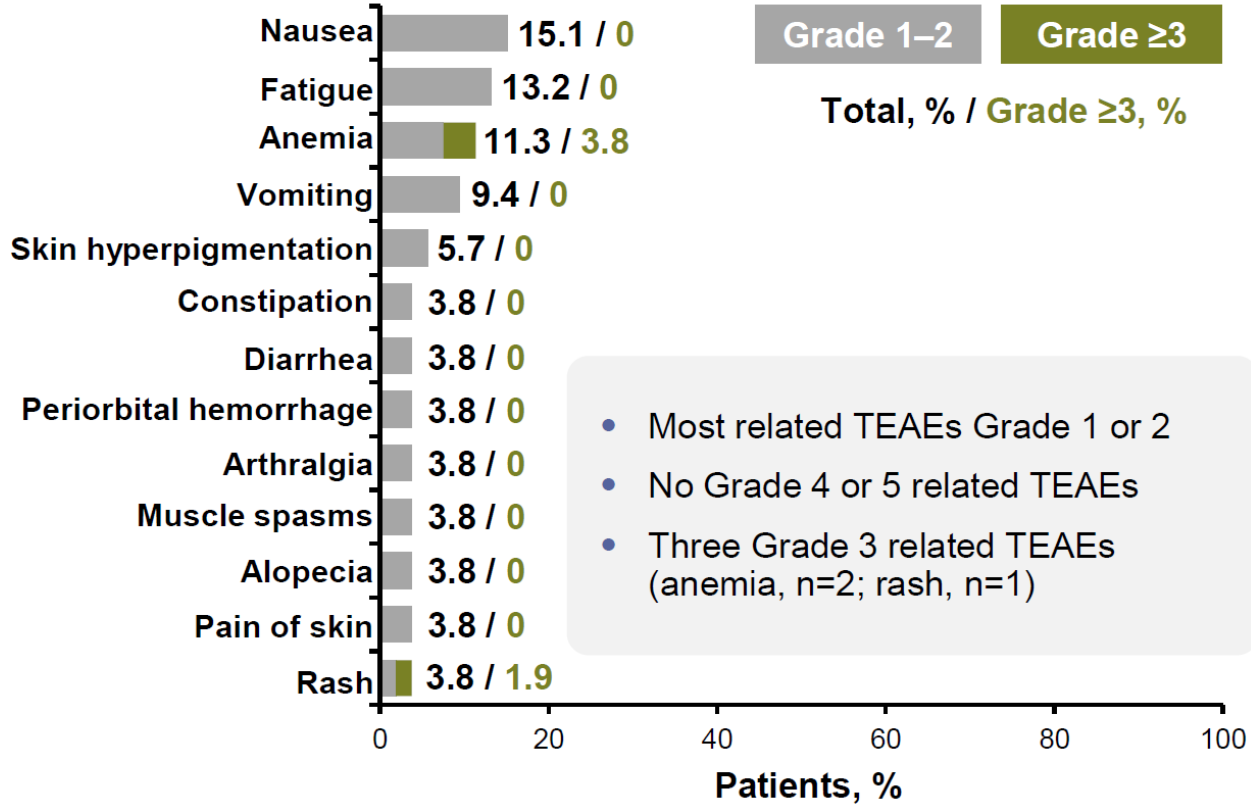
DS-9606 safety was manageable and tolerable

Any-grade TEAEs (≥7.5% of patients)[b]



- Most TEAEs Grade 1 or 2; no Grade 5 TEAEs
- Most common TEAEs were GI in nature or anemia
- No cases of CLS or ILD

Any-grade related TEAEs (≥3.8% of patients)



- Most related TEAEs Grade 1 or 2
- No Grade 4 or 5 related TEAEs
- Three Grade 3 related TEAEs (anemia, n=2; rash, n=1)

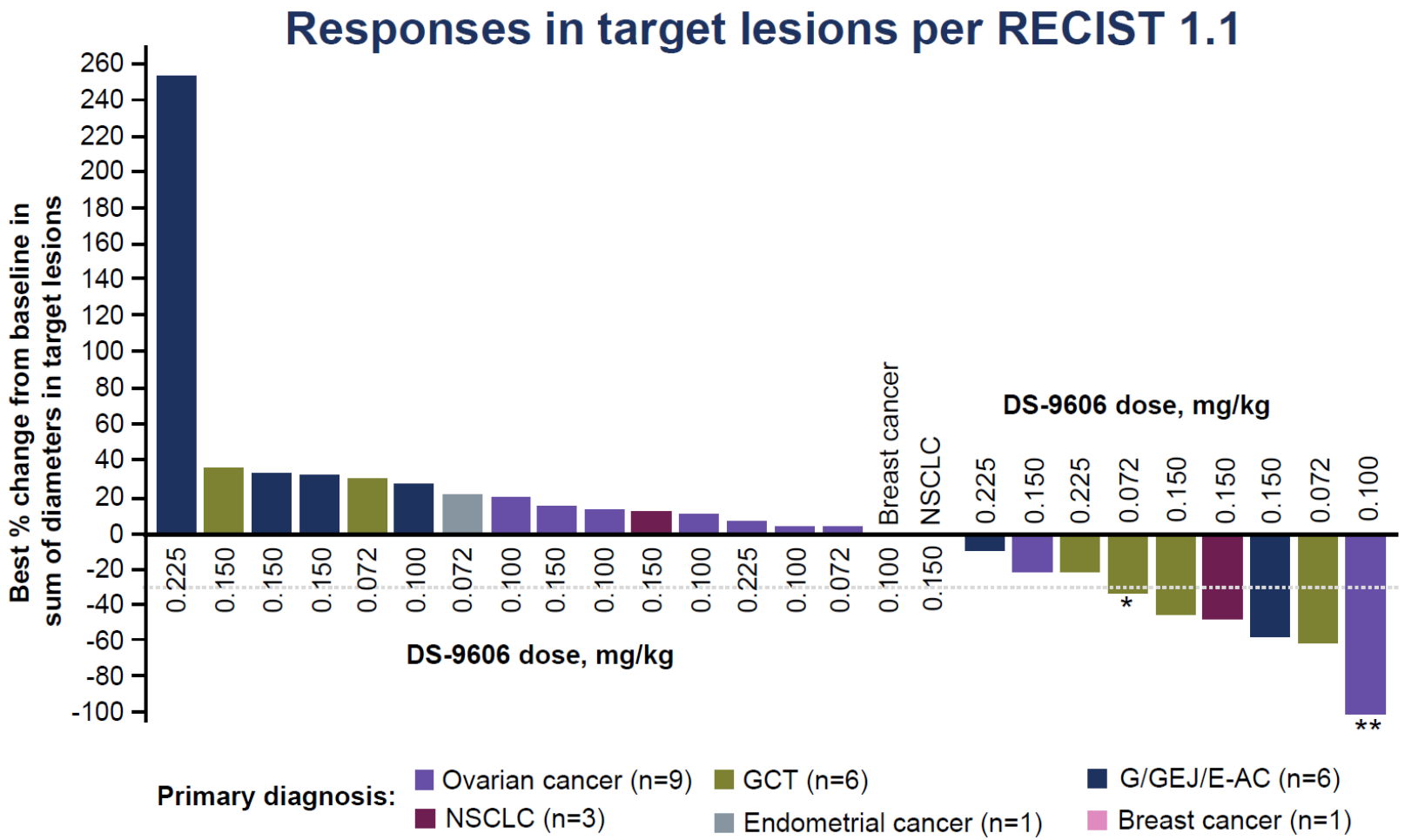
- When grouped, events of cutaneous toxicity (AESI) were the most common TEAEs and related TEAEs

Data cutoff: June 14, 2024

[a]Overall population (N=53). TEAEs occurring at any grade in ≥7.5% of patients and Grade ≥3 TEAEs occurring for those preferred terms. Related TEAEs occurring at any grade in ≥3.8% of patients and Grade ≥3 related TEAEs occurring for those preferred terms. [b]Five TEAEs in 4 patients were not coded at the data cutoff (all Grade 1 or 2).

AESI, adverse event of special interest; CLS, capillary leak syndrome; GI, gastrointestinal; ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.

Preliminary efficacy[a]: All tumor types



- Confirmed objective responses seen across tumor types (RECIST 1.1)
  - GCT, n=2
  - G/GEJ/E-AC, n=1
  - NSCLC, n=1
  - Response highest with 0.150 mg/kg (3/12[b] patients)

Data cutoff: June 14, 2024

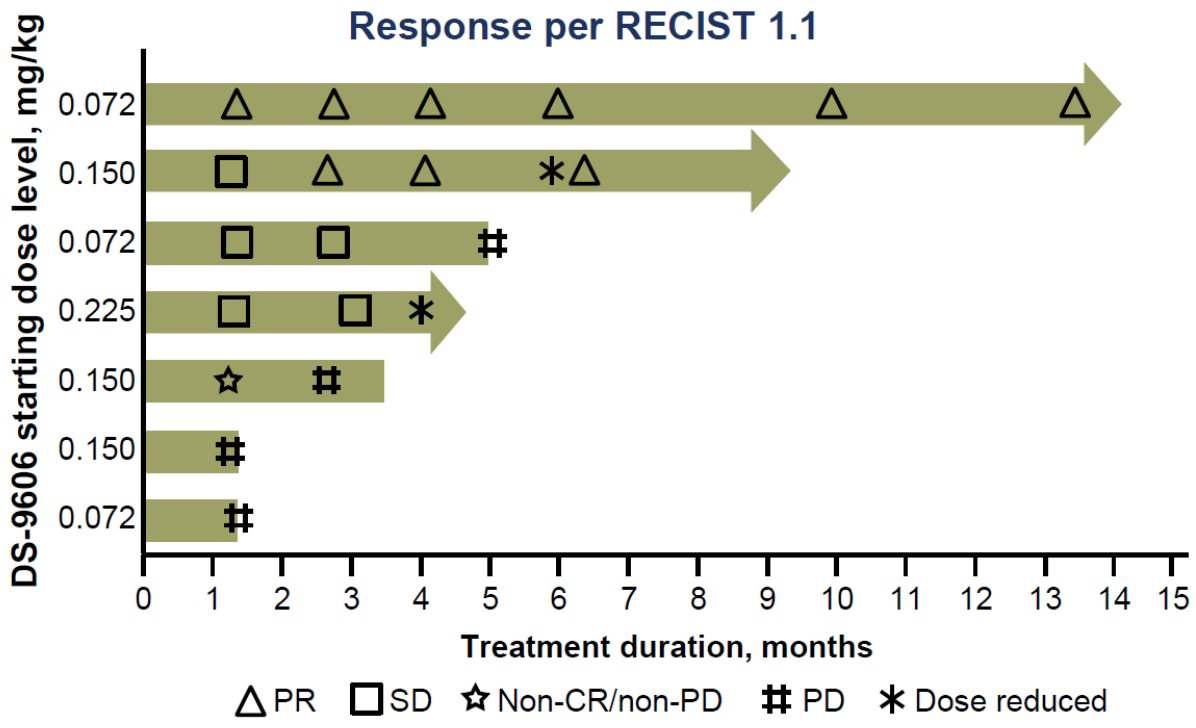
[a]DS-9606 doses ≥0.072 mg/kg, except 0.190 mg/kg due to immature data. [b]Includes only 12 of 14 patients; patients were included if they had ≥2 post-baseline scans and/or had discontinued treatment for any reason.
*Patient did not have confirmed PR due to new lesion observed at disease assessment. **Patient did not have a confirmed PR due to progression at subsequent assessment.

GCT, germ cell tumor; G/GEJ/E-AC, gastric/gastroesophageal junction/esophageal adenocarcinoma; NSCLC, non-small cell lung cancer; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1.

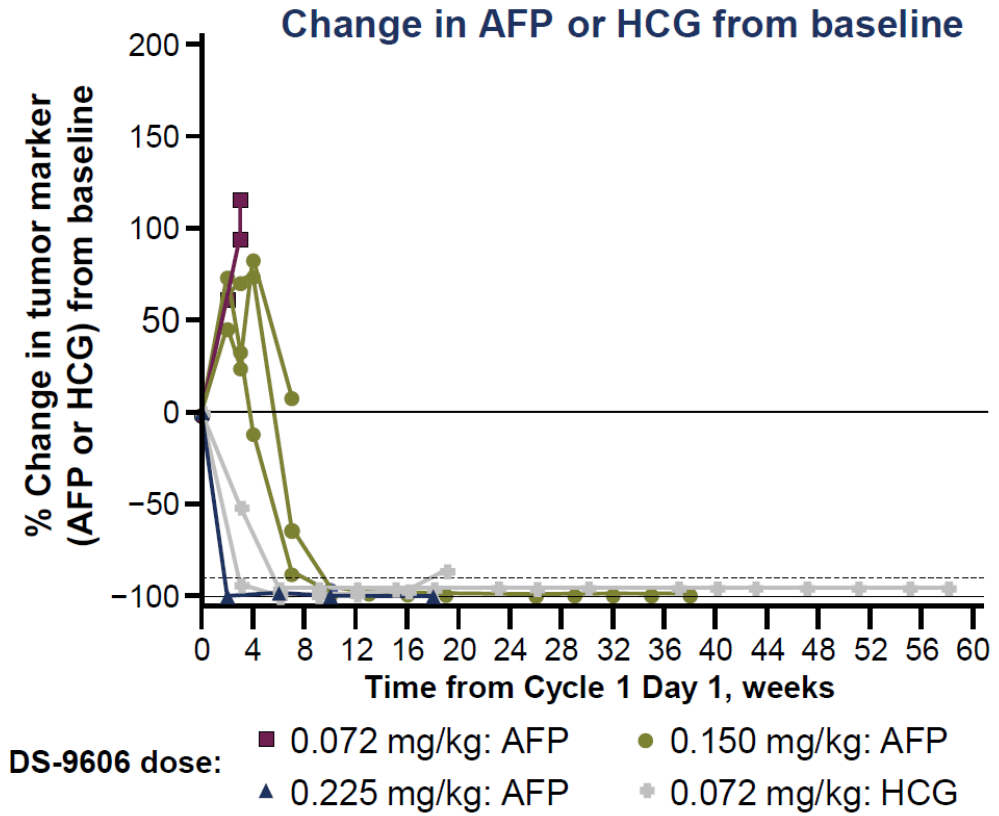
Preliminary efficacy[a]: GCT responses

Responses in patients with GCTs who were heavily pretreated/refractory to prior treatment

- 2/7 patients had PR as best response (RECIST 1.1) and remained on treatment >6 months



- 5/7 patients had ≥90% reduction in tumor markers



Data cutoff: June 14, 2024

[a]DS-9606 doses ≥0.072 mg/kg, excluding 0.190 mg/kg due to lack of efficacy data availability.

AFP, alpha-fetoprotein; CR, complete response, GCT, germ cell tumor; HCG, human chorionic gonadotropin; PD, progressive disease; PR, partial response; SD, stable disease.

Conclusions

- In this heavily pretreated population, interim data with DS-9606 show:
  - **Manageable and tolerable safety profile**
    - No DLTs or discontinuations due to related TEAEs. Most TEAEs and related TEAEs were Grade 1 or 2
    - No cases of CLS or ILD, and mostly low-grade cutaneous toxicity
  - **Promising preliminary efficacy,** with responses across tumor types
    - Encouraging efficacy in GCTs based on several tumor markers
- Enrollment and dose escalation are ongoing with MTD and RDE not yet determined

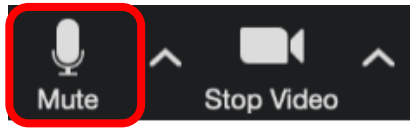
Data cutoff: June 14, 2024

CLS, capillary leak syndrome; DLT, dose-limiting toxicity; GCT, germ cell tumor; ILD, interstitial lung disease; MTD, maximum tolerated dose; RDE, recommended dose for expansion; TEAE, treatment-emergent adverse event.

Agenda

1. Opening remarks
2. Highlights from WCLC & ESMO
3. **Q&A**

Once Mic. is opened
発言許可次第



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