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

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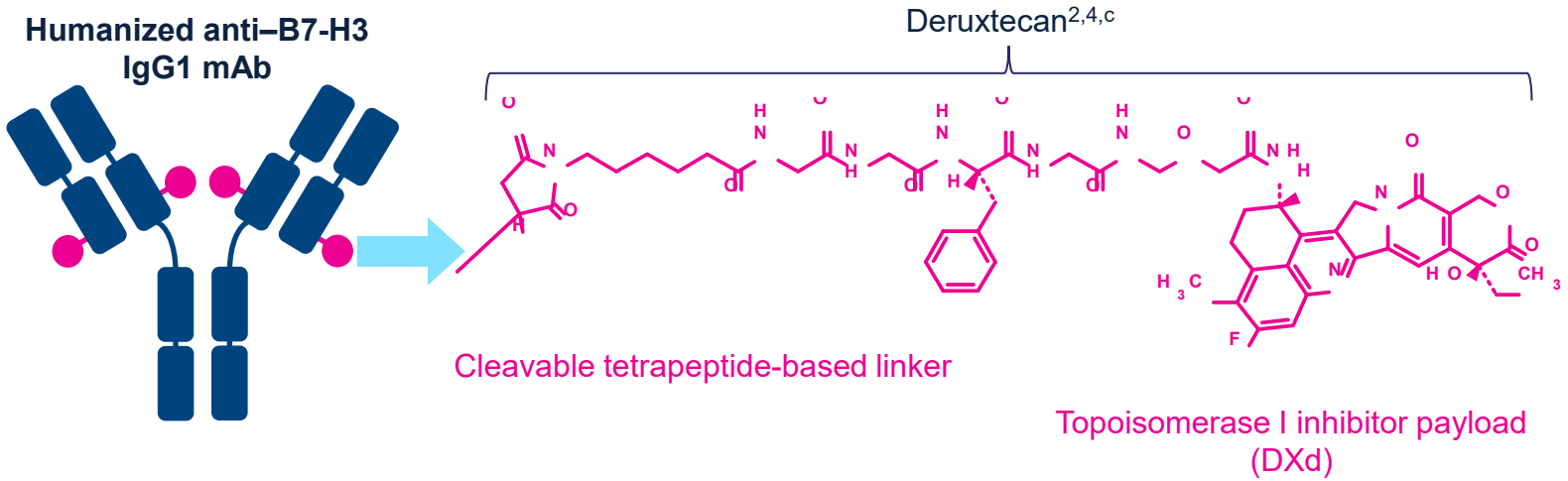
Ifinatamab deruxtecan (I-DXd) was designed with 7 key attributes

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

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



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

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

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

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

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

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

[a]The clinical relevance of these features is under investigation. [b]Based on animal data. [c]Refers to the linker and payload.
ADC, antibody–drug conjugate; B7-H3, B7 homolog 3; CD276, cluster of differentiation 276; IgG1, immunoglobulin G1; mAb, monoclonal antibody.
1. Okajima D, et al. *Mol Cancer Ther*. 2021;20:2329–2340. 2. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173–185. 3. Ogitani Y, et al. *Clin Cancer Res*. 2016;22:5097–5108. 4. Yamato M, et al. *Mol Cancer Ther*. 2022;21:635–646.
5. Ogitani Y, et al. *Cancer Sci*. 2016;107:1039–1046.

Phase 2 IDeate-Lung01 study (NCT05280470)

Patient eligibility:

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

R 1:1

Arm 1: I-DXd 8 mg/kg Q3W (n≈40)

Arm 2: I-DXd 12 mg/kg Q3W (n≈40)

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

Stratification:

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

Primary endpoint:

- ORR by BICR[c]

Secondary endpoints:

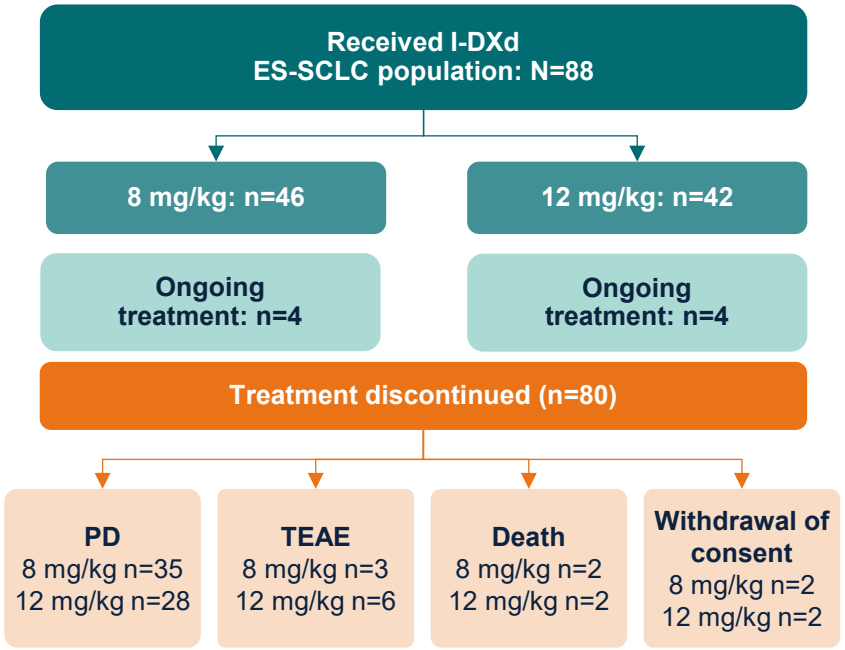
- DOR by BICR and inv[c]
- PFS by BICR and inv[c]
- OS
- DCR[c]
- TTR by BICR and inv[c]
- ORR by inv[c]
- Safety
- Pharmacokinetics
- Immmunogenicity

Exploratory analysis:

- Intracranial ORR by BICR[d]

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

Patient demographics and baseline characteristics



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

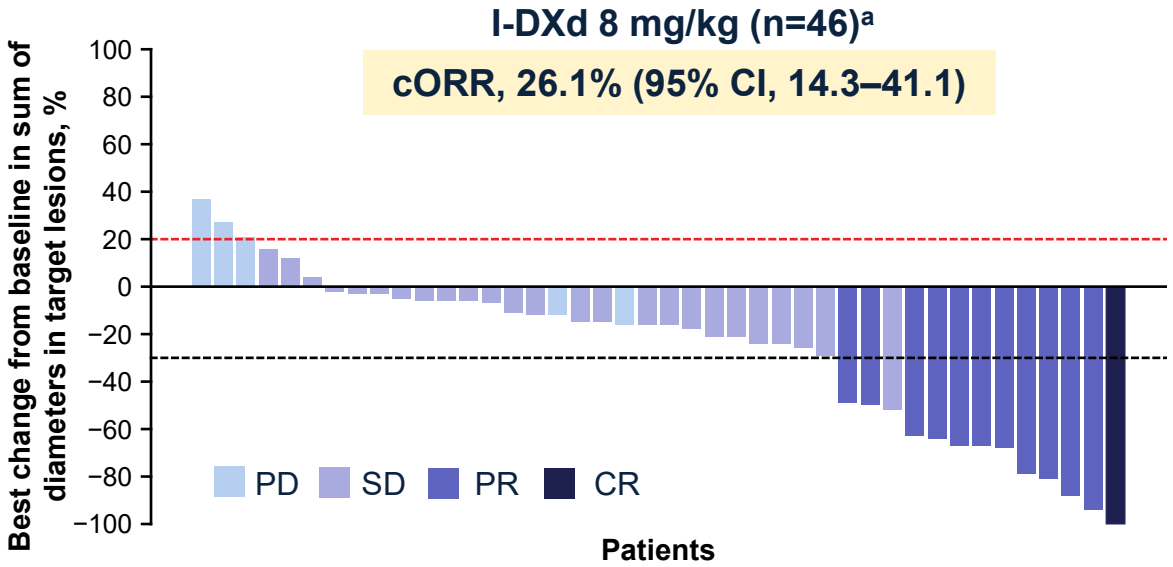
	I-DXd 8 mg/kg n=46	I-DXd 12 mg/kg n=42	Total N=88
Age, median (range)	64 (42–85)	64 (34–79)	64 (34–85)
Male, n (%)	30 (65.2)	33 (78.6)	63 (71.6)
ECOG PS, n (%)			
0	13 (28.3)	6 (14.3)	19 (21.6)
1	33 (71.7)	36 (85.7)	69 (78.4)
ES-SCLC at diagnosis, n (%)	32 (69.6)[a]	35 (83.3)	67 (76.1)
Patients with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

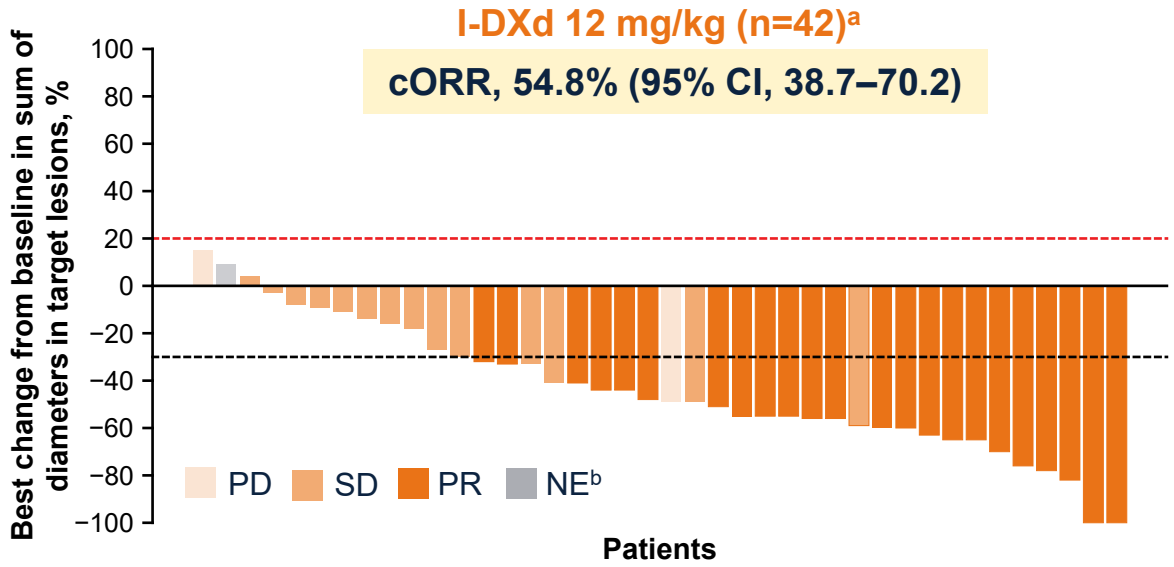
Data cutoff: April 25, 2024.

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

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

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





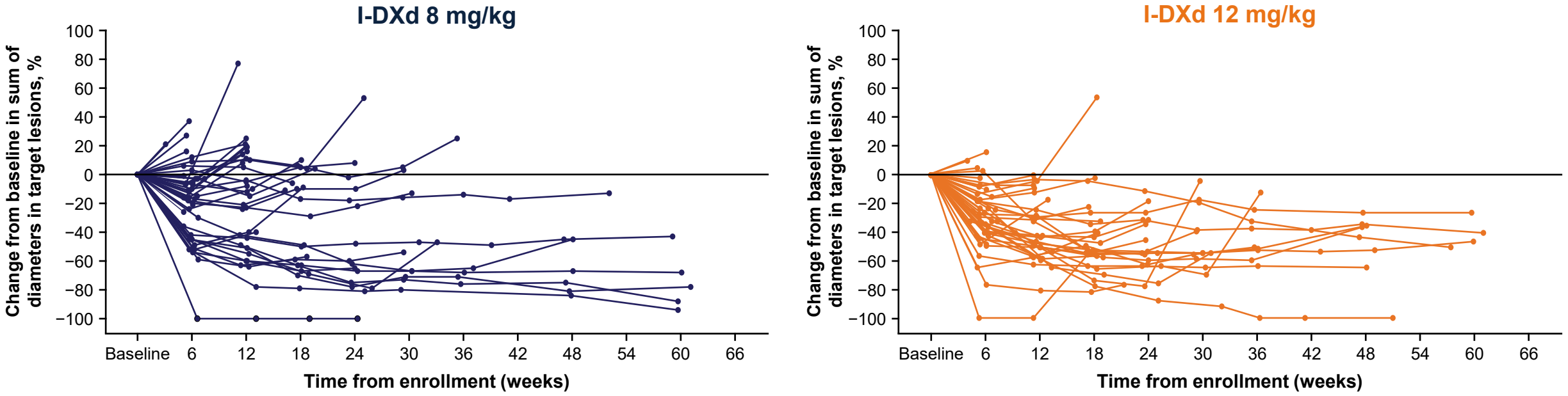
Confirmed response by BICR[c]	I-DXd 8 mg/kg n=46	I-DXd 12 mg/kg n=42
ORR, % (95% CI)	26.1 (14.3–41.1)	54.8 (38.7–70.2)
CR, n (%)	1 (2.2)	0
PR, n (%)	11 (23.9)	23 (54.8)
DCR, % (95% CI)	80.4 (66.1–90.6)	90.5 (77.4–97.3)

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

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

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

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



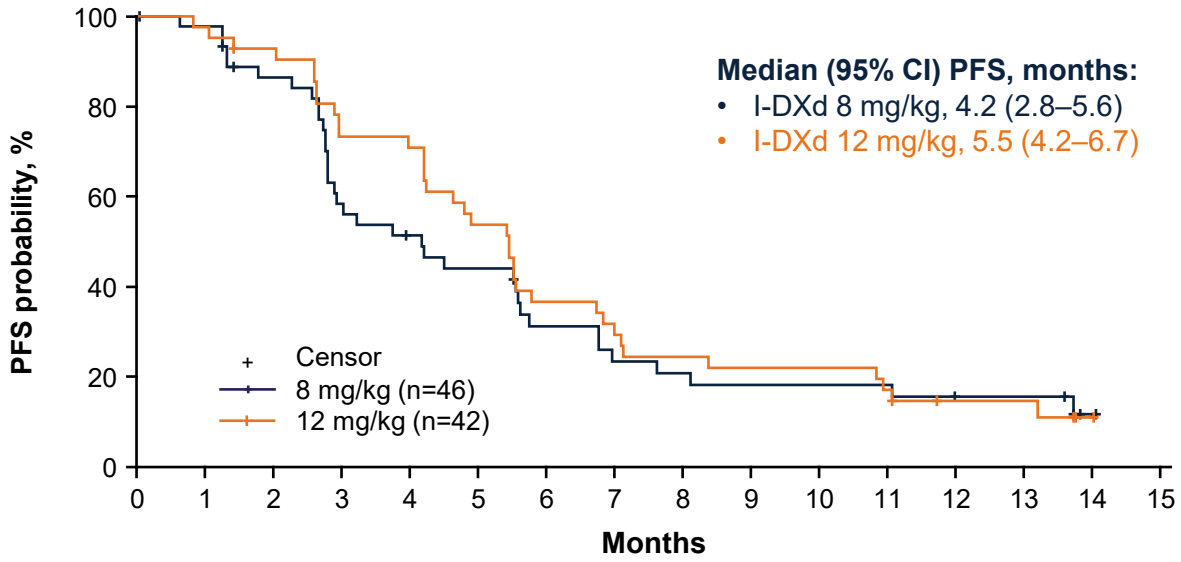
	I-DXd 8 mg/kg n=46	I-DXd 12 mg/kg n=42
Median (range) TTR,[a] months	1.4 (1.2–1.5)	1.4 (1.0–8.1)
Median (95% CI) DOR,[a,b] months	7.9 (4.1–NE)	4.2 (3.5–7.0)

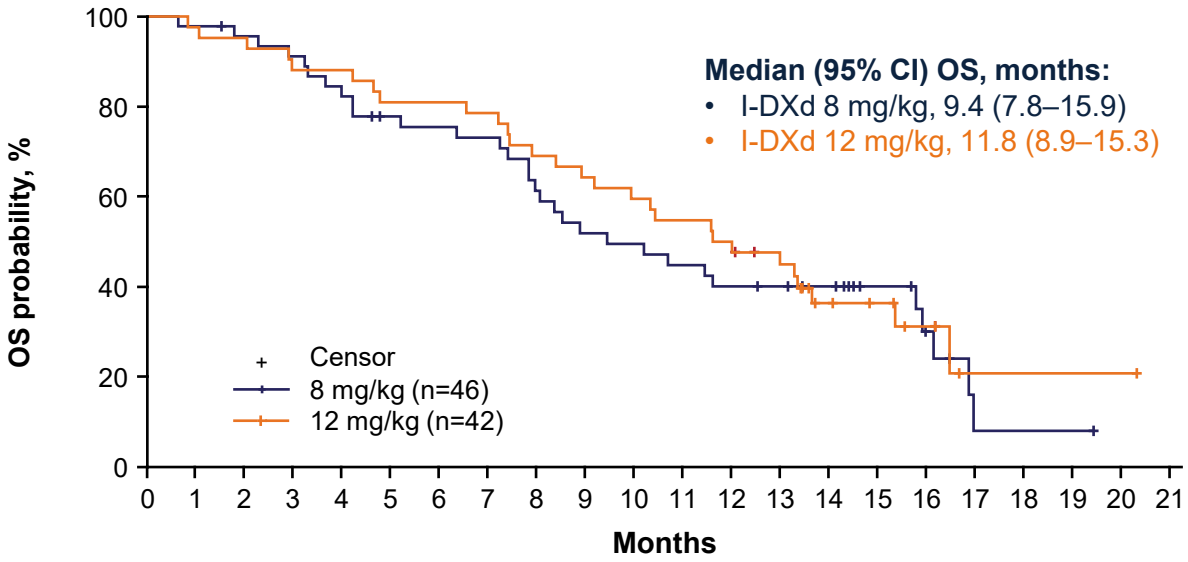
Data cutoff: April 25, 2024. The median follow-up for 8-mg/kg and 12-mg/kg cohorts was 14.6 months (range, 0.6–17.0) and 15.3 months (range, 0.8–20.3) respectively.

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

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

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





Number of patients still at risk

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

Number of patients still at risk

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

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

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

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

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

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

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

Safety summary: I-DXd was well tolerated at both doses

	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)

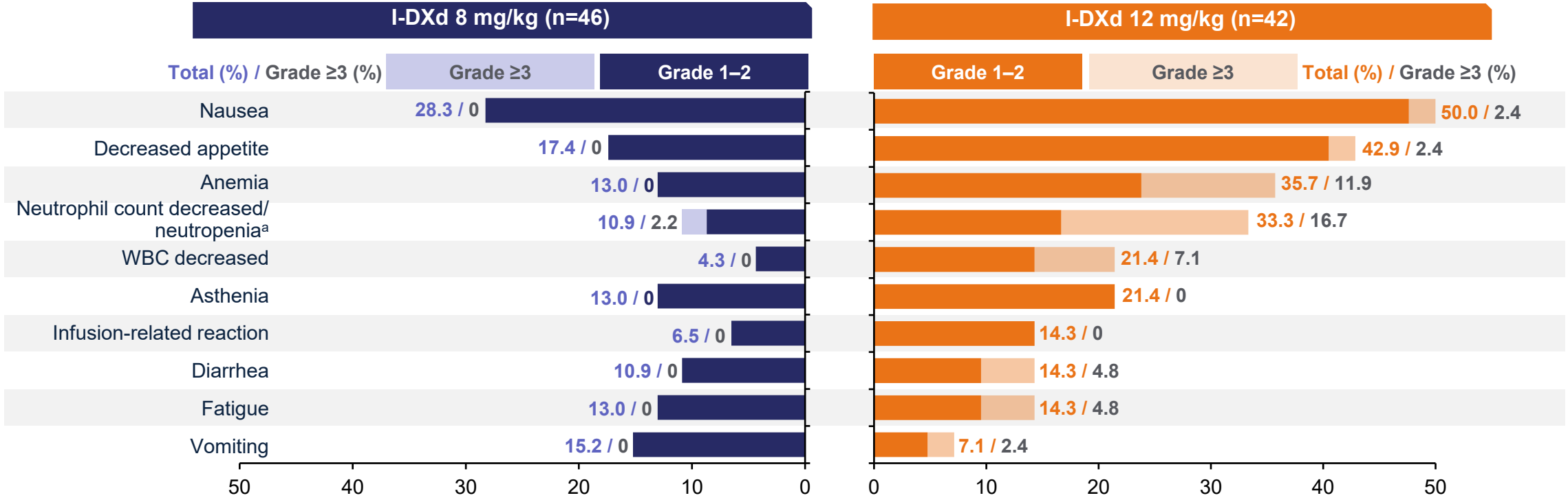
- Treatment discontinuations were:
  - In the 8-mg/kg cohort: pneumonia (Grade 3, n=1), pneumonitis (Grade 2, n=1) and pulmonary embolism (Grade 4, n=1)
  - In the 12-mg/kg cohort: pneumonia (Grade 1, n=1; Grade 3,[b] n=1), pneumonitis (Grade 2, n=1), ILD (Grade 2, n=1), *Pneumocystis jirovecii* pneumonia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

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