IDeate-Lung01: A Phase 2 trial of ifinatamab deruxtecan (I-DXd) in extensive-stage small cell lung cancer

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

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

Presentation O12-4

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Declaration of interests

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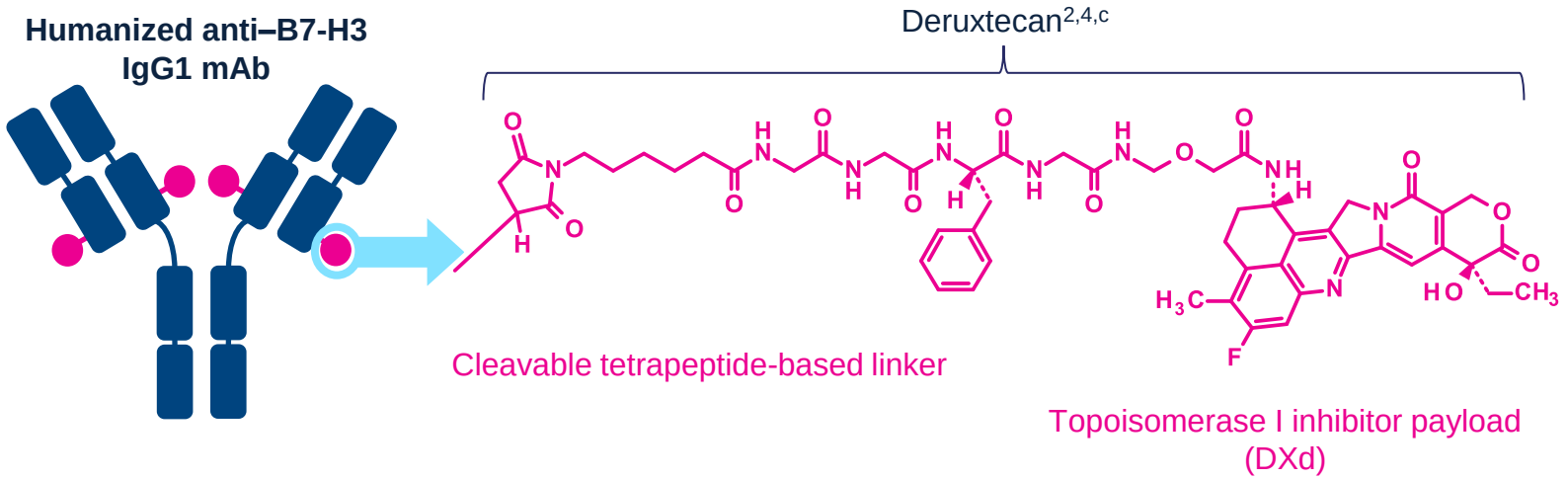
Representative of organization for clinical study receiving research expenses from company	X	

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.

IDeate-Lung01 (NCT05280470): Study design

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

Part 1: Dose-optimization (N=88)

R 1:1

Arm 1: I-DXd 8 mg/kg Q3W (n=46)

Arm 2: I-DXd 12 mg/kg Q3W (n=42)

Stratification

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

Part 2: Extended enrollment at RP3D

12 mg/kg Q3W

Patients who received ≥2 prior lines of therapy

(n≈70)

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]Assessed by RECIST 1.1. [d]Assessed using a version of RECIST 1.1 modified for assessment of CNS tumors.
2L, second-line; 3L, third-line; 4L, fourth-line; BICR, blinded independent central review; CTFI, chemotherapy-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 Tumours, version 1.1; RP3D, recommended Phase 3 dose; TTR, time to response.

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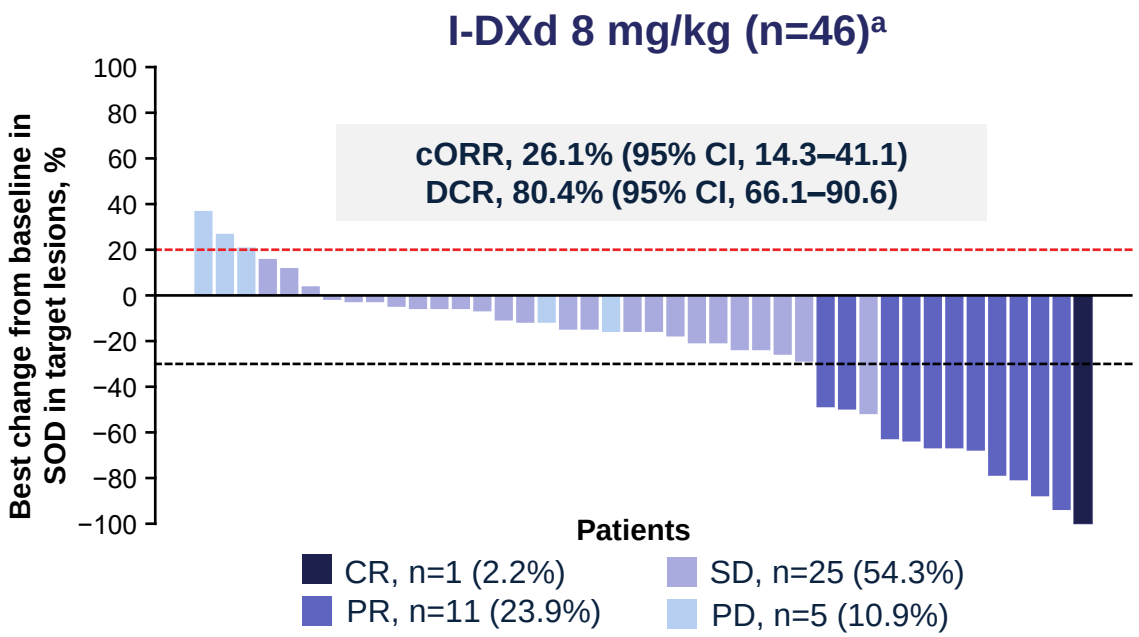
Baseline characteristics in the overall dose-optimization population

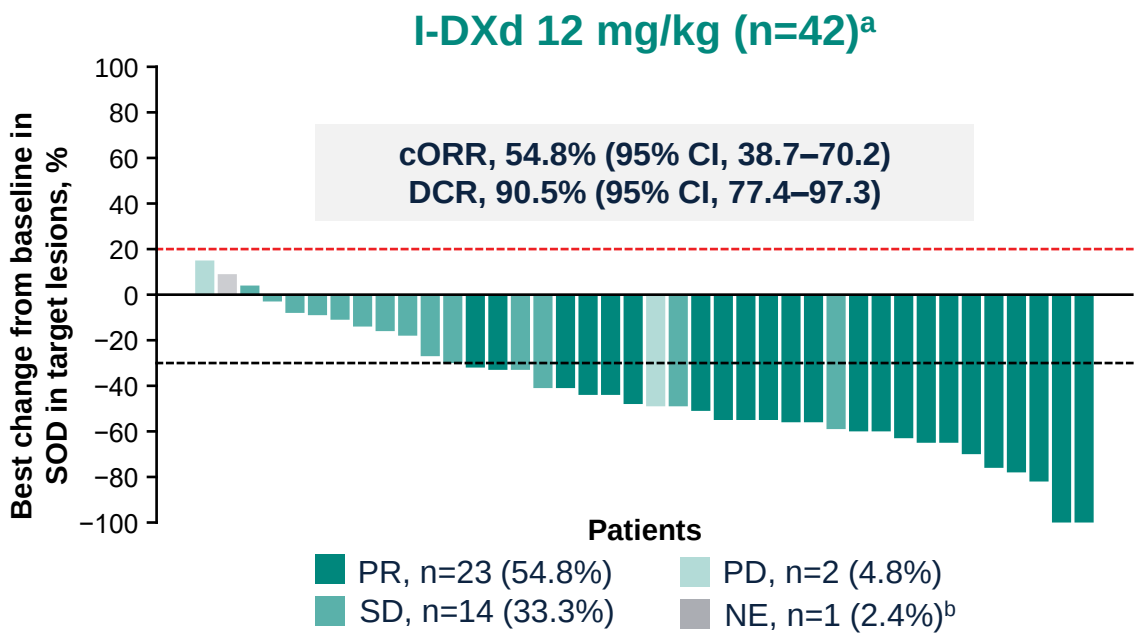
	I-DXd 8 mg/kg n=46	I-DXd 12 mg/kg n=42	Total N=88
Age, median (range), years	64 (42–85)	64 (34–79)	64 (34–85)
Male, n (%)	30 (65.2)	33 (78.6)	63 (71.6)
ECOG PS, n (%)			
0	13 (28.3)	6 (14.3)	19 (21.6)
1	33 (71.7)	36 (85.7)	69 (78.4)
ES-SCLC at diagnosis, n (%)	32 (69.6)[a]	35 (83.3)	67 (76.1)
ES-SCLC at study entry, n (%)	46 (100)	42 (100)	88 (100)
Patients with brain metastases at baseline, n (%)	19 (41.3)	18 (42.9)	37 (42.0)
Subset of patients with brain target lesions at baseline, n (%)	6 (13.0)	10 (23.8)	16 (18.2)
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] n (%)			
<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)
Received prior anti–PD-(L)1 therapy,[c] n (%)	35 (76.1)	32 (76.2)	67 (76.1)

- 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)

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 anti–PD-(L)1 therapy was not available.
ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive-stage small cell lung cancer; PD-(L)1; programmed death (ligand) 1.

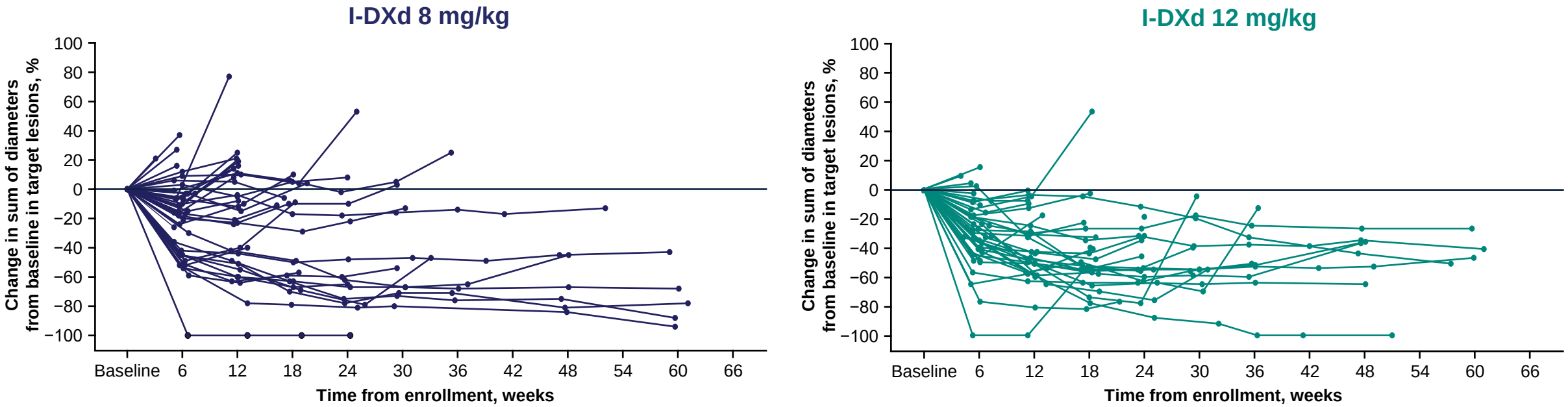
I-DXd demonstrated promising antitumor activity; confirmed ORR by BICR was higher in the 12-mg/kg cohort than in the 8-mg/kg cohort





Data cutoff: April 25, 2024. Median follow-up for the 8-mg/kg and 12-mg/kg cohorts was 14.6 (range, 0.6–17.0) months and 15.3 (range, 0.8–20.3) months, 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.
BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SOD, sum of diameters.

I-DXd treatment was associated with rapid responses at both doses in the overall dose-optimization population



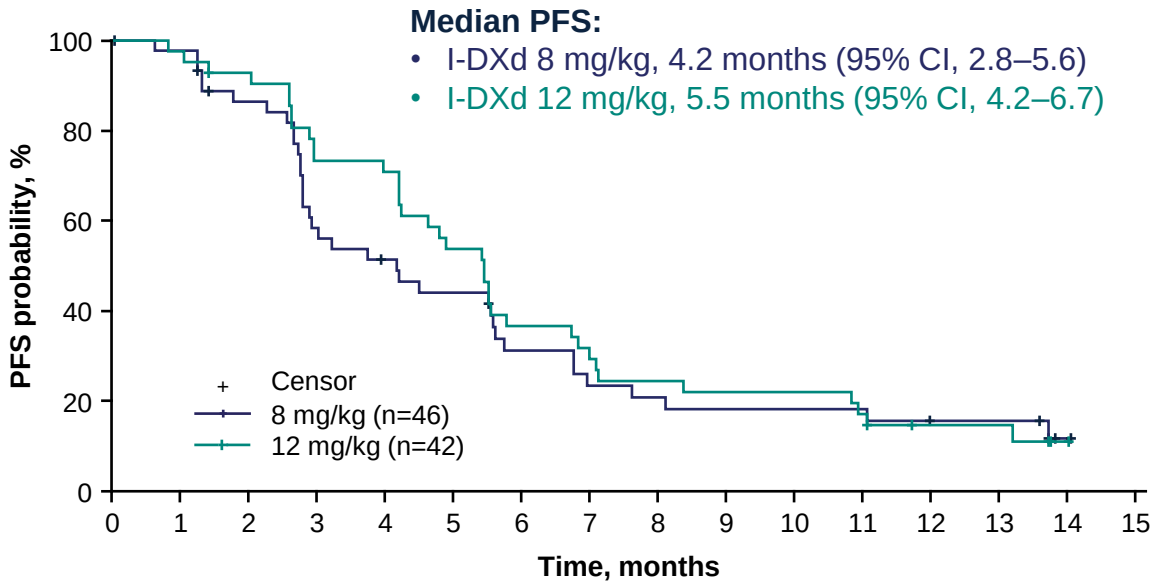
Patients with confirmed objective response

	I-DXd 8 mg/kg n=12	I-DXd 12 mg/kg n=23
TTR,[a] median (range), months	1.4 (1.2–1.5)	1.4 (1.0–8.1)
DOR,[a] median (95% CI), months[b]	7.9 (4.1–NE)	4.2 (3.5–7.0)

Data cutoff: April 25, 2024. Median follow-up for the 8-mg/kg and 12-mg/kg cohorts was 14.6 (range, 0.6–17.0) months and 15.3 (range, 0.8–20.3) months, respectively.
[a]By BICR per RECIST 1.1. [b]The higher proportion of second-line responders in the 8-mg/kg cohort may have contributed to the longer DOR observed in this cohort compared with the 12-mg/kg cohort.
BICR, blinded independent central review; CI, confidence interval; DOR, duration of response; NE, not estimable; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; TTR, time to response.

Median PFS and OS were numerically longer in the 12-mg/kg cohort than in the 8-mg/kg cohort in the overall dose-optimization population

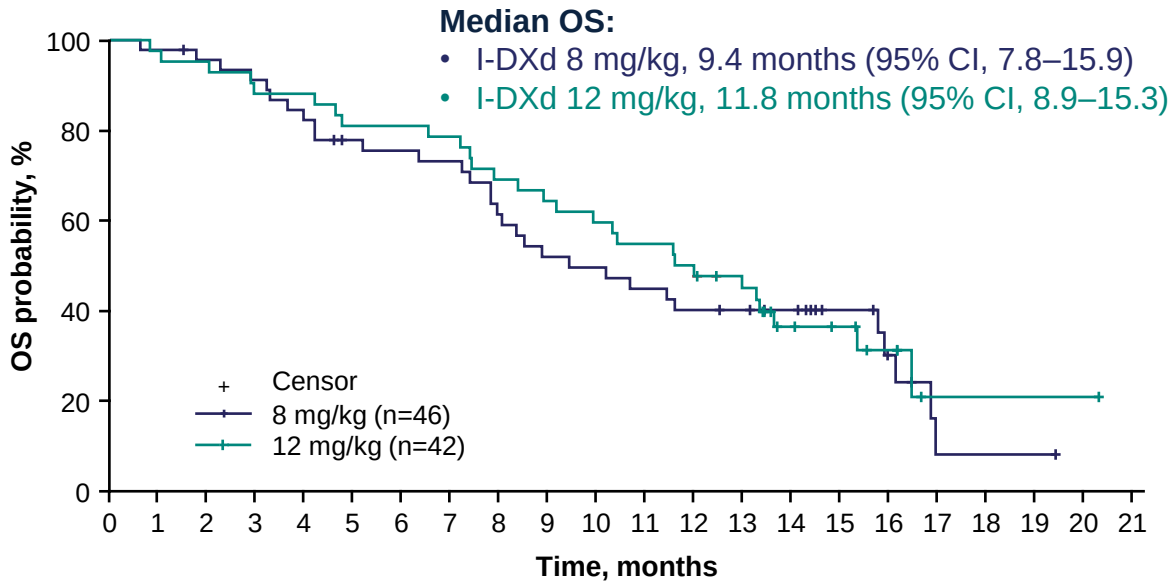
PFS



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

OS



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. Median follow-up for the 8-mg/kg and 12-mg/kg cohorts was 14.6 (range, 0.6–17.0) months and 15.3 (range, 0.8–20.3) months, respectively.
CI, confidence interval; OS, overall survival; PFS, progression-free survival.

I-DXd demonstrated promising intracranial activity in patients with brain metastases at baseline

	Patients with brain metastases at baseline		Subset of patients with brain target lesions	
	8 mg/kg (n=19)	12 mg/kg (n=18)	8 mg/kg (n=6)	12 mg/kg (n=10)
CNS efficacy				
CNS confirmed ORR,[a] % (95% CI)	36.8 (16.3–61.6)	38.9 (17.3–64.3)	66.7 (22.3–95.7)	50.0 (18.7–81.3)
CNS confirmed BOR,[a] n (%)				
CR	5 (26.3)	4 (22.2)	2 (33.3)	2 (20.0)
PR	2 (10.5)[b]	3 (16.7)[b]	2 (33.3)	3 (30.0)
SD or non-CR/non-PD[c]	8 (42.1)	10 (55.6)	2 (33.3)	5 (50.0)
PD	1 (5.3)	0	0	0
Not evaluable	3 (15.8)	1 (5.6)	0	0
CNS confirmed DCR,[a,d] % (95% CI)	78.9 (54.4–93.9)	94.4 (72.7–99.9)	100 (54.1–100.0)	100 (69.2–100.0)
CNS DOR, median (95% CI),[a] months	4.3 (3.3–NE)	7.4 (3.0–NE)	3.9 (3.3–NE)	6.5 (3.0–NE)
CNS TTR, median (range),[a] months	1.4 (1.2–1.5)	1.2 (0.9–2.8)	1.3 (1.2–1.4)	1.2 (0.9–2.8)
Systemic efficacy				
Systemic confirmed ORR,[e] % (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)
Concordance between systemic and CNS objective response,[f] %	78.9	77.8	NR	NR

Data cutoff: April 25, 2024.

[a]Assessed by BICR, using a version of RECIST 1.1 modified for assessment of CNS tumors. [b]All patients with PR had target lesions at baseline. [c]Only patients without baseline brain target lesions could have response classified as "non-CR/non-PD." [d]CR + PR + SD + non-CR/non-PD. [e]By BICR per RECIST 1.1. [f]Percentage of patients with both CNS and systemic objective response, and with neither CNS nor systemic objective response.

BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CNS, central nervous system; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not estimable; NR, not reported; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SD, stable disease; TTR, time to response.

Over 80% of patients with brain target lesions at baseline had both CNS and systemic disease control

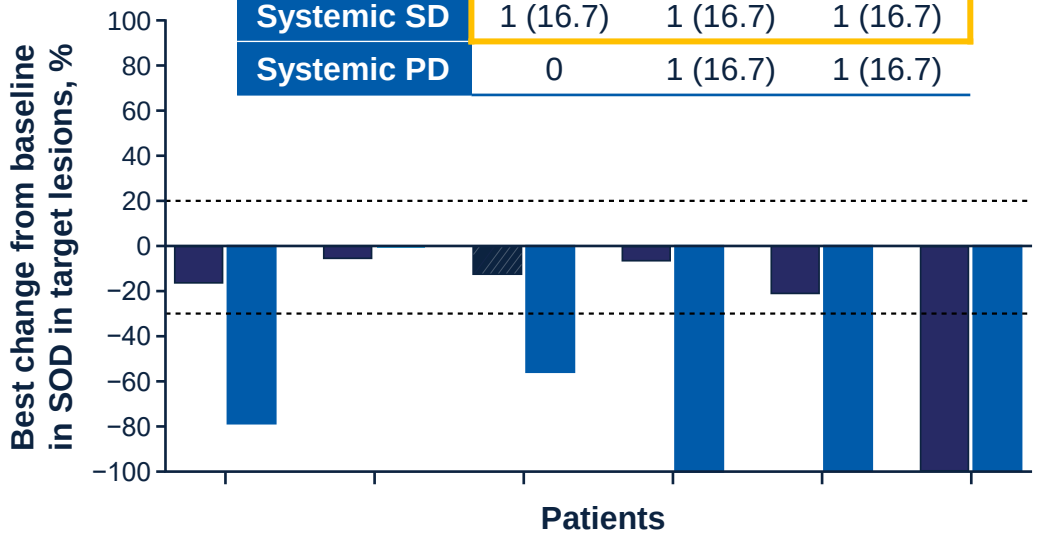
Systemic and intracranial change from baseline in SOD in target lesions

Change from baseline in SOD in target lesions

- Systemic
- CNS
- \+ Treatment ongoing at data cutoff

I-DXd 8 mg/kg (n=6)

	CNS CR	CNS PR	CNS SD
Systemic CR	1 (16.7)	0	0
Systemic PR	0	0	0
Systemic SD	1 (16.7)	1 (16.7)	1 (16.7)
Systemic PD	0	1 (16.7)	1 (16.7)

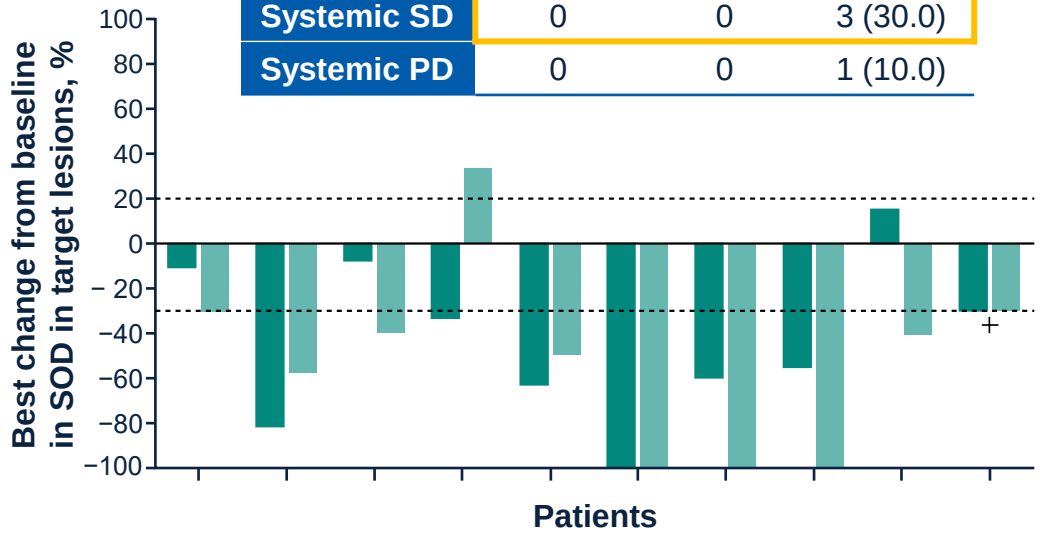


Time between last brain radiotherapy and start of study treatment, months

11.4 NA 16.6 NA NA NA

I-DXd 12 mg/kg (n=10)

	CNS CR	CNS PR	CNS SD
Systemic CR	0	0	0
Systemic PR	2 (20.0)	3 (30.0)	1 (10.0)
Systemic SD	0	0	3 (30.0)
Systemic PD	0	0	1 (10.0)



1.1 1.6 1.4 NA 11.8 NA 1.6 1.3 NA 19.7

Data cutoff: April 25, 2024.
CNS, central nervous system; CR, complete response; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease; SOD, sum of diameters.

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

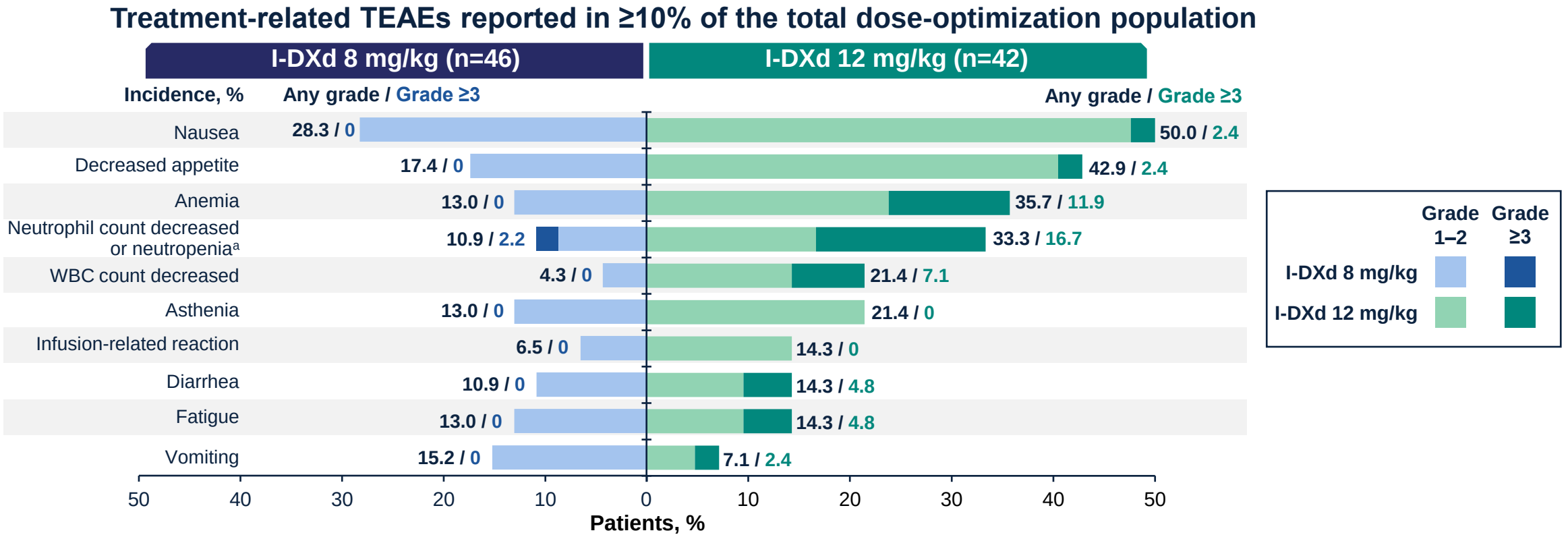
	I-DXd 8 mg/kg (n=46)	I-DXd 12 mg/kg (n=42)
Median treatment duration (range), months[a]	3.5 (0.03–13.9)	4.7 (0.03–15.2)
Median cycles (range), n	6.0 (1.0–21.0)	7.5 (1.0–23.0)
Any TEAE, n (%)	44 (95.7)	41 (97.6)
TEAEs with CTCAE Grade ≥3, n (%)	20 (43.5)	21 (50.0)
TEAEs associated with treatment discontinuation,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

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

The safety profile of I-DXd was generally comparable between patients with and without baseline brain metastases, and was consistent with the overall population

Data cutoff: April 25, 2024. The median follow-up for the 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]Treatment duration (months) is calculated as (date of the last dose − date of the first dose + 1 day) × 12 ÷ 365.25. For patients who are still on treatment at data cutoff, the last available date of dose prior to data cutoff is used. [b]Includes 1 patient whose primary reason for treatment discontinuation was death, but who was also recorded as having a TEAE (pneumonia) on the date of death. [c]This patient discontinued treatment following Grade 3 pneumonia (unrelated to study treatment) but was reported to have Grade 5 pneumonia 1 day after study-drug withdrawal. [d]Following Grade 3 *Pneumocystis jirovecii* pneumonia, the patient discontinued treatment but never recovered and was reported to have Grade 5 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 were gastrointestinal and hematologic



- ILD/pneumonitis adjudicated as treatment-related[b] was reported in:
  - Four (8.7%) of 46 patients in the **8-mg/kg** cohort (Grade 2, n=3; Grade 5, n=1)
  - Five (11.9%) of 42 patients in the **12-mg/kg** cohort (Grade 1, n=1; Grade 2, n=3; Grade 3, n=1)

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. [b]No ILD events are pending adjudication at the time of data cutoff.
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, with greater efficacy observed at the 12-mg/kg dose level compared with 8 mg/kg:
  - ORR, 54.8% vs 26.1%; median PFS, 5.5 months vs 4.2 months; median OS, 11.8 months vs 9.4 months
- I-DXd was generally well tolerated and demonstrated a manageable safety profile that was consistent with previous reports; the occurrence of TEAEs was dose-dependent, with a higher incidence reported in the 12-mg/kg cohort than in the 8-mg/kg cohort
  - 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
- Among the 37 patients with baseline brain metastases, CNS confirmed ORR was 37.8%; all 16 patients with brain target lesions at baseline achieved CNS disease control
- The safety profile of I-DXd was generally comparable between patients with and without baseline brain metastases, and was consistent with the overall population
- I-DXd 12 mg/kg has been selected as the RP3D for further clinical development, including in an ongoing Phase 3 trial in patients with relapsed SCLC who have received only 1 prior line of systemic treatment, which must have included PBC (IDeate-Lung02; NCT06203210)

Data cutoff: April 25, 2024.
CNS, central nervous system; ES-SCLC, extensive-stage small cell lung cancer; ILD, interstitial lung disease; ORR, objective response rate; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival; RP3D, recommended Phase 3 dose; SCLC, small cell lung cancer; TEAE, treatment-emergent adverse event.

IDeate-Lung02 study design (NCT06203210)

Further details of this study are presented at this congress (Poster P93-5)

A Phase 3, multicenter, randomized, open-label study of I-DXd vs treatment of physician's choice in patients with relapsed SCLC who have received only 1 prior line of platinum-based therapy

- Relapsed SCLC
- ECOG PS 0–1
- Received only 1 prior line of systemic treatment, which must have included PBC ± anti–PD-(L)1 therapy[a]
- N≈540

R 1:1

I-DXd 12 mg/kg Q3W
n≈270

TPC[b]
(topotecan, amrubicin, or lurbinectedin)
n≈270

Until PD, unacceptable toxicity, loss to follow-up, consent withdrawal, death, or other reason

Follow-up
Safety[c]

Long-term follow-up
Every 3 months[d]

Primary endpoints
- ORR (BICR)[e]
- OS

Secondary endpoints
- ORR (investigator)[e]
- PFS, DOR, DCR, and TTR (BICR and investigator)[e]
- Patient-reported outcomes (EORTC questionnaires)
- Safety[f]
- Immunogenicity
- Pharmacokinetics
- Relationship between B7-H3 expression and outcomes

Stratification
- Chemotherapy-free interval following 1L therapy (<90 vs ≥90 days)
- TPC (topotecan vs amrubicin vs lurbinectedin)
- Treatment with prior PD-(L)1 inhibitors (yes vs no)
- Presence or history of asymptomatic brain metastases (yes vs no)

[a]≥80% of patients are expected to have received prior anti–PD-(L)1 therapy. [b]Comparator treatments will only be utilized in countries where they are approved in second and subsequent lines of therapy for patients with SCLC who progressed on or after platinum-based therapy; ≥70% of patients in the comparator group will receive topotecan. [c]Safety follow-up visit will occur 40 days (+7 days) after the last dose. [d]Long-term follow-up will occur to assess survival; assess tumor progression until PD for patients discontinuing for reasons other than PD; and to collect information on further anticancer treatments, every 3 months (90 ±14 days) from study-drug discontinuation (end of treatment), withdrawal of consent, or from when a study-termination criterion is met. [e]Per RECIST 1.1. [e]TEAEs, deaths, serious TEAEs, adverse events of special interest, and TEAEs leading to dose modification or discontinuation.
1L, first-line; B7-H3, B7 homolog 3; BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC, European Organisation for Research and Treatment of Cancer; 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, randomized; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SCLC, small cell lung cancer; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice; TTR, time to response.

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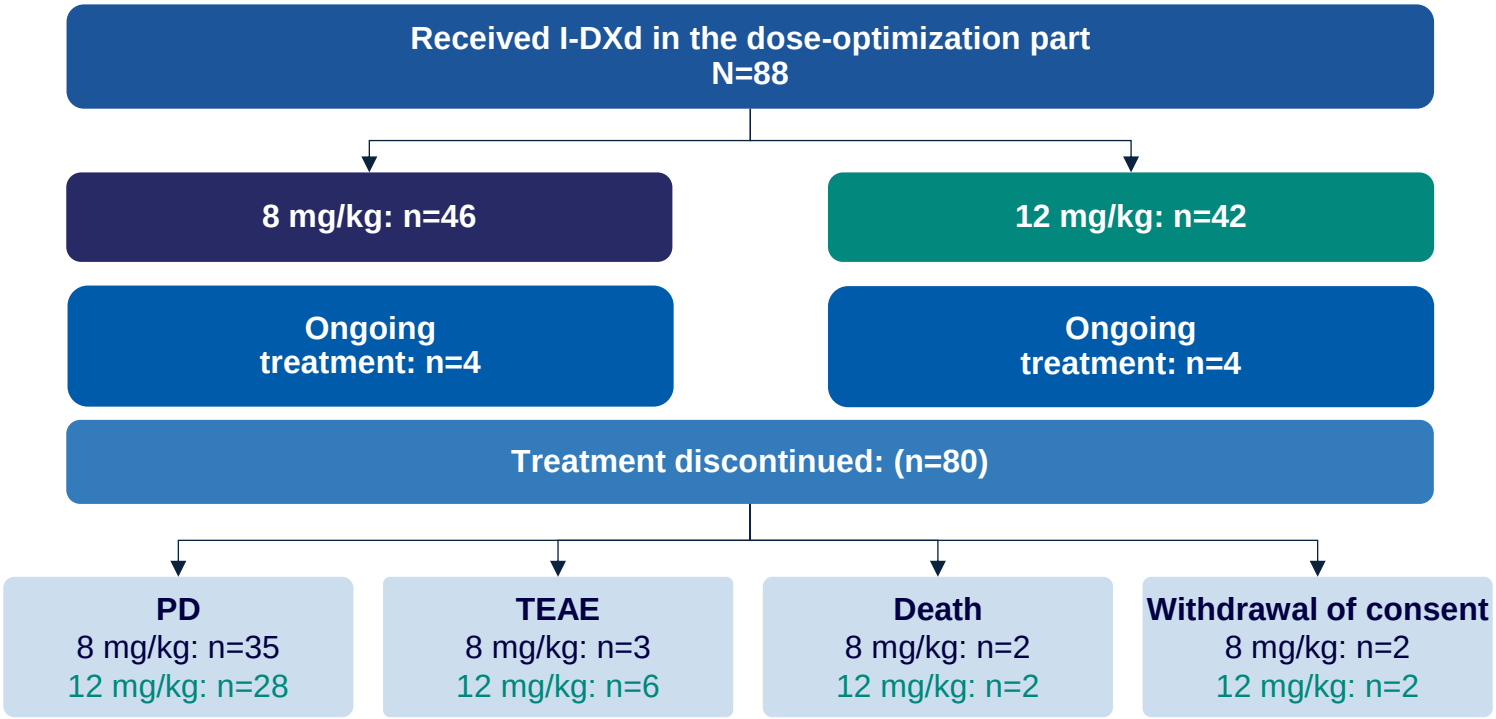
Patient disposition



Data cutoff: April 25, 2024.
PD, progressive disease; TEAE, treatment-emergent adverse event.

Baseline characteristics

	Dose-optimization population			Patients with brain metastases at baseline			Subset of patients with brain target lesions		
	I-DXd 8 mg/kg n=46	I-DXd 12 mg/kg n=42	Total N=88	I-DXd 8 mg/kg n=19	I-DXd 12 mg/kg n=18	Total n=37	I-DXd 8 mg/kg n=6	I-DXd 12 mg/kg n=10	Total n=16
Age, median (range), years	64 (42–85)	64 (34–79)	64 (34–85)	64.0 (42–79)	62.5 (46–76)	63.0 (42–79)	60.0 (42–79)	58.5 (46–70)	58.5 (42–79)
Male, n (%)	30 (65.2)	33 (78.6)	63 (71.6)	14 (73.7)	12 (66.7)	26 (70.3)	6 (100.0)	7 (70.0)	13 (81.3)
ECOG PS, n (%)									
0	13 (28.3)	6 (14.3)	19 (21.6)	8 (42.1)	3 (16.7)	11 (29.7)	2 (33.3)	1 (10.0)	3 (18.8)
1	33 (71.7)	36 (85.7)	69 (78.4)	11 (57.9)	15 (83.3)	26 (70.3)	4 (66.7)	9 (90.0)	13 (81.3)
ES-SCLC at diagnosis, n (%)	32 (69.6)[a]	35 (83.3)	67 (76.1)	15 (78.9)	16 (88.9)	31 (83.8)	5 (83.3)	8 (80.0)	13 (81.3)
Prior brain radiotherapy, n (%)	9 (19.6)	16 (38.1)	25 (28.4)	4 (21.1)	13 (72.2)	17 (45.9)	2 (33.3)	7 (70.0)	9 (56.3)
Number of prior lines of systemic therapy, n (%)									
1	13 (28.3)	12 (28.6)	25 (28.4)	7 (36.8)	7 (38.9)	14 (37.8)	2 (33.3)	3 (30.0)	5 (31.3)
2	22 (47.8)	22 (52.4)	44 (50.0)	7 (36.8)	8 (44.4)	15 (40.5)	3 (50.0)	4 (40.0)	7 (43.8)
3	11 (23.9)	8 (19.0)	19 (21.6)	5 (26.3)	3 (16.7)	8 (21.6)	1 (16.7)	3 (30.0)	4 (25.0)
Chemotherapy-free interval, n (%)									
<90 days	22 (47.8)[b]	23 (54.8)	45 (51.1)[b]	7 (36.8)	12 (66.7)	19 (51.4)	4 (66.7)	8 (80.0)	12 (75.0)
≥90 days	22 (47.8)[b]	19 (45.2)	41 (46.6)[b]	11 (57.9)	6 (33.3)	17 (45.9)	2 (33.3)	2 (20.0)	4 (25.0)
Select anticancer therapy received, n (%)									
Lurbinectedin	11 (23.9)	3 (7.1)	14 (15.9)	NR	NR	NR	NR	NR	NR
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, n (%)	35 (76.1)[c]	32 (76.2)[c]	67 (76.1)[c]	16 (84.2)[d]	17 (94.4)	33 (89.2)[d]	6 (100)	9 (90.0)	15 (93.8)

Data cutoff: April 25, 2024.

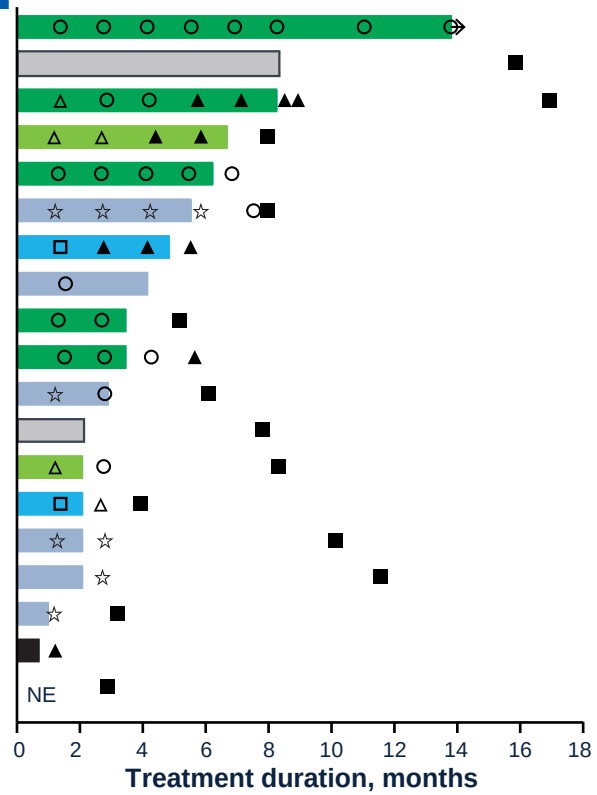
[a]One patient had missing data. [b]Two patients had missing data in the 8-mg/kg cohort. [c]Three patients (8 mg/kg, n=2; 12 mg/kg n=1) were previously treated in a blinded randomized clinical trial; information regarding patients' prior anti–PD-(L)1 therapy was not available.
[d]Information on prior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

ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive-stage small cell lung cancer; NR, not reported; PD-(L)1; programmed death (ligand) 1.

Intracranial response over time in patients with brain metastases at baseline

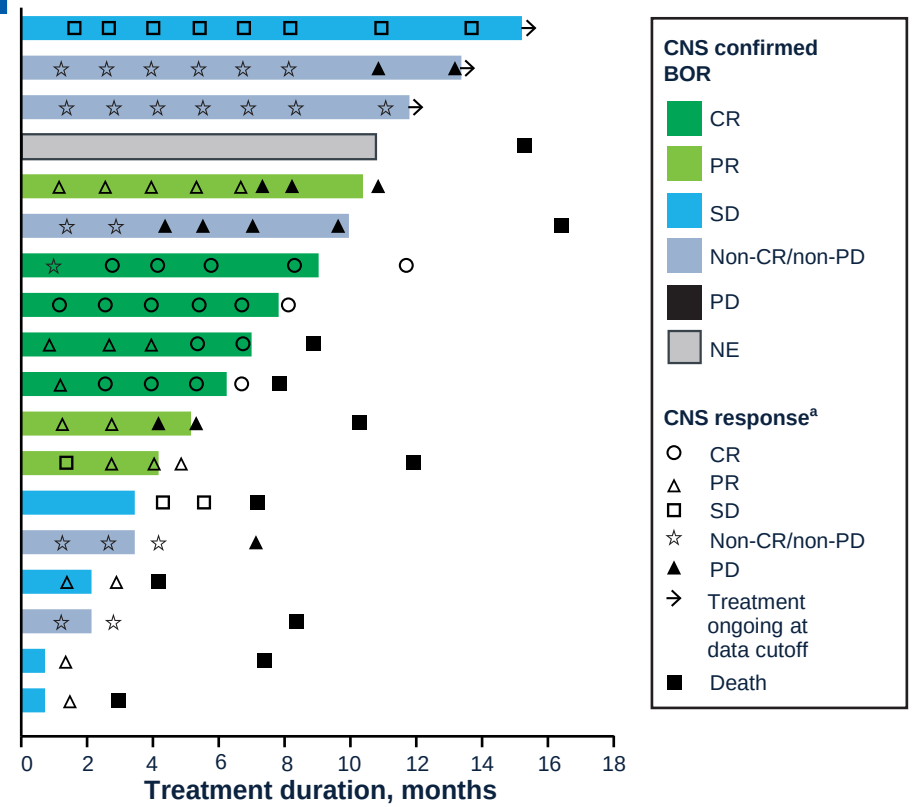
I-DXd 8 mg/kg CNS response (n=19)

Systemic confirmed BOR	Time between last brain radiotherapy and start of study treatment	Brain target lesion(s)
PR	31.5 months	No
SD	NA	No
CR	NA	Yes
PD	11.4 months	Yes
PR	NA	No
PR	NA	No
SD	NA	Yes
SD	NA	No
SD	NA	Yes
PR	NA	No
SD	7.4 months	No
SD	NA	No
SD	NA	Yes
PD	16.6 months	Yes
SD	NA	No
SD	NA	No
SD	NA	No
SD	NA	No
NE	NA	No



I-DXd 12 mg/kg CNS response (n=18)

Systemic confirmed BOR	Time between last brain radiotherapy and start of study treatment	Brain target lesion(s)
SD	19.7 months	Yes
PR	30.2 months	No
PR	1.4 months	No
PR	15.9 months	No
PR	11.8 months	Yes
PD	5.8 months	No
PR	NA	No
PR	NA	No
PR	1.3 months	Yes
PR	NA	Yes
PR	1.6 months	Yes
PR	1.6 months	Yes
PR	NA	Yes
SD	2.1 months	No
SD	1.4 months	Yes
SD	7.3 months	No
SD	1.1 months	Yes
PD	NA	Yes



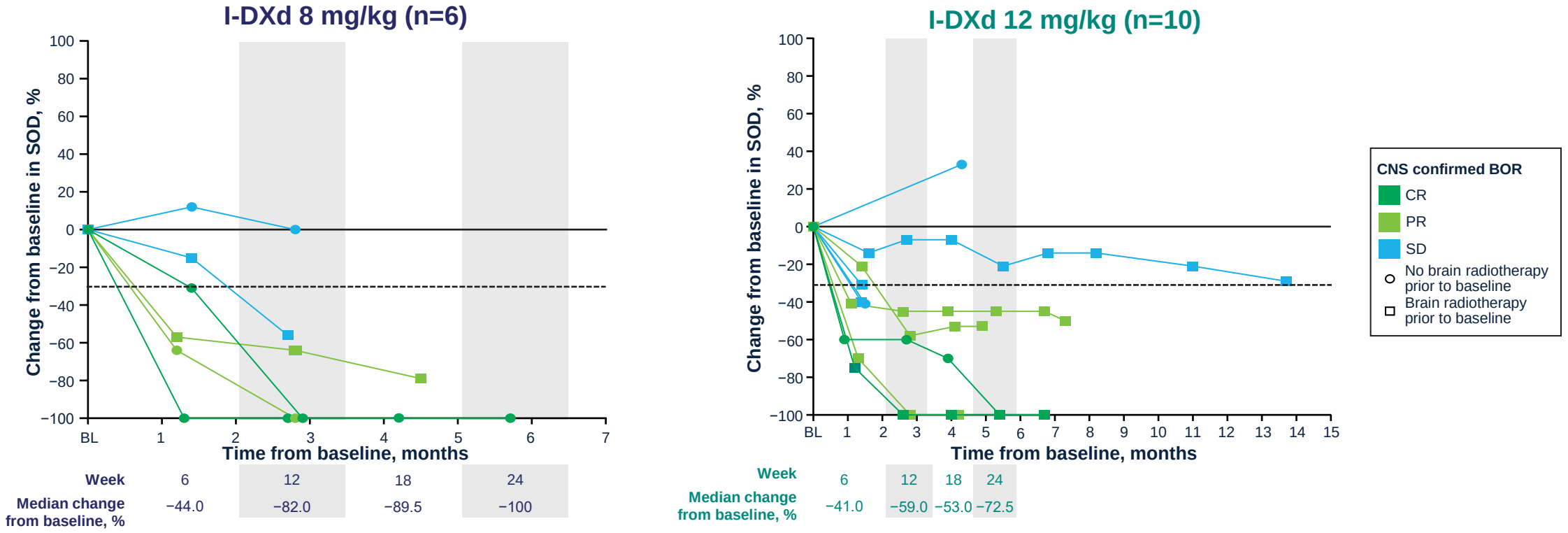
Data cutoff: April 25, 2024.

[a]Assessed by BICR, using a version of RECIST 1.1 modified for assessment of CNS tumors. CNS response denoted by these symbols includes both confirmed and unconfirmed responses.

BICR, blinded independent central review; BOR, best overall response; CNS, central nervous system; CR, complete response; NA, not applicable; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SD, stable disease.

Across both dose levels, >80% of patients had reductions in CNS target lesion volume ≥30%[a]

Change in CNS target-lesion volume



Week	6	12	18	24
Median change from baseline, %	−44.0	−82.0	−89.5	−100

Week	6	12	18	24
Median change from baseline, %	−41.0	−59.0	−53.0	−72.5

Among the 16 patients with brain target lesions at baseline, 13 (81.3%) had reductions in CNS target-lesion volume ≥30%, including 8 (80.0%) of the 10 patients treated with I-DXd 12 mg/kg

Data cutoff: April 25, 2024.
[a]Data are presented for tumor assessments collected before the first documented PD or before initiation of the next line of anticancer therapy.
BL, baseline; BOR, best overall response; CNS, central nervous system; CR, complete response; PR, partial response; SD, stable disease; SOD, sum of diameters.