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Ifinatamab Deruxtecan (I-DXd) in Extensive-Stage Small Cell Lung Cancer: Primary Analysis of the Phase 2 IDeate-Lung01 Study

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Introduction

- Despite recent advancements in treatment options beyond 1L for patients with ES-SCLC, outcomes remain poor, and there is still no globally accepted standard of care[1–5]
- I-DXd is a B7-H3–directed ADC designed to enhance selective tumor-cell death and reduce systemic exposure, comprising[6–9]:
  - A humanized anti–B7-H3 IgG1 mAb
  - A tetrapeptide-based cleavable linker that covalently bonds antibody and payload
  - A TOPO I inhibitor payload (an exatecan derivative, DXd)
- IDeate-Lung01 is a Phase 2, two-part trial (Part 1: dose optimization; Part 2: extension) designed to evaluate the efficacy and safety of I-DXd at doses of 8 and 12 mg/kg Q3W in previously treated ES-SCLC
  - Based on the overall benefit–risk assessment using pooled data from the interim analysis of Part 1 of IDeate-Lung01 and the Phase 1/2 trial,[10] the 12-mg/kg dose was selected for further investigation in Part 2

We present data from the primary analysis of IDeate-Lung01, with a focus on patients treated with I-DXd 12 mg/kg across both parts of the study

1L, first-line; ADC, antibody–drug conjugate; B7-H3, B7 homolog 3; ES-SCLC, extensive-stage small cell lung cancer; IgG1, immunoglobulin G1; mAb, monoclonal antibody; Q3W, every 3 weeks; TOPO I, topoisomerase I.

1. Trigo J, et al. *Lancet Oncol*. 2020;21:645–654. 2. Mountzios G, et al. *N Engl J Med*. 2025;393:349–361. 3. Shaw J, et al. *Oncologist*. 2024;29:1079–1089. 4. Borghaei H, et al. *Lung Cancer*. 2024;193:107819. 5. Steffens CC, et al. *Lung Cancer*. 2019;130:216–225. 6. Okajima D, et al. *Mol Cancer Ther*. 2021;20:2329–2340. 7. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173–185. 8. Ogitani Y, et al. *Clin Cancer Res*. 2016;22:5097–5108. 9. Yamato M, et al. *Mol Cancer Ther*. 2022;21:635–646. 10. Midde NM, et al. Poster presentation at the 2024 IASLC World Conference on Lung Cancer. September 7–10, 2024; San Diego, CA, USA. Presentation PT01.13.05.

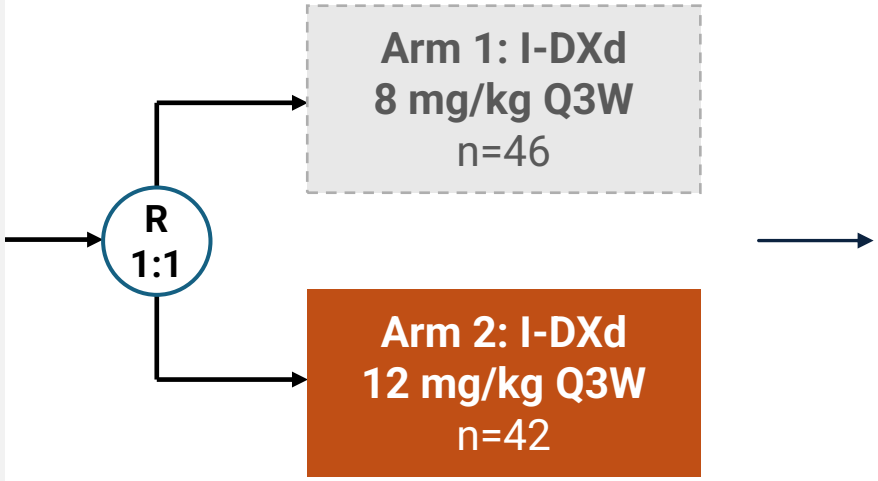
IDeate-Lung01 study design

Phase 2, multicenter, randomized, open-label 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) were eligible

Part 1: Dose optimization



Stratification factors:

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

Part 2: Extension

I-DXd 12 mg/kg Q3W
n=95

Primary endpoint

- ORR by BICR[c]

Secondary endpoints

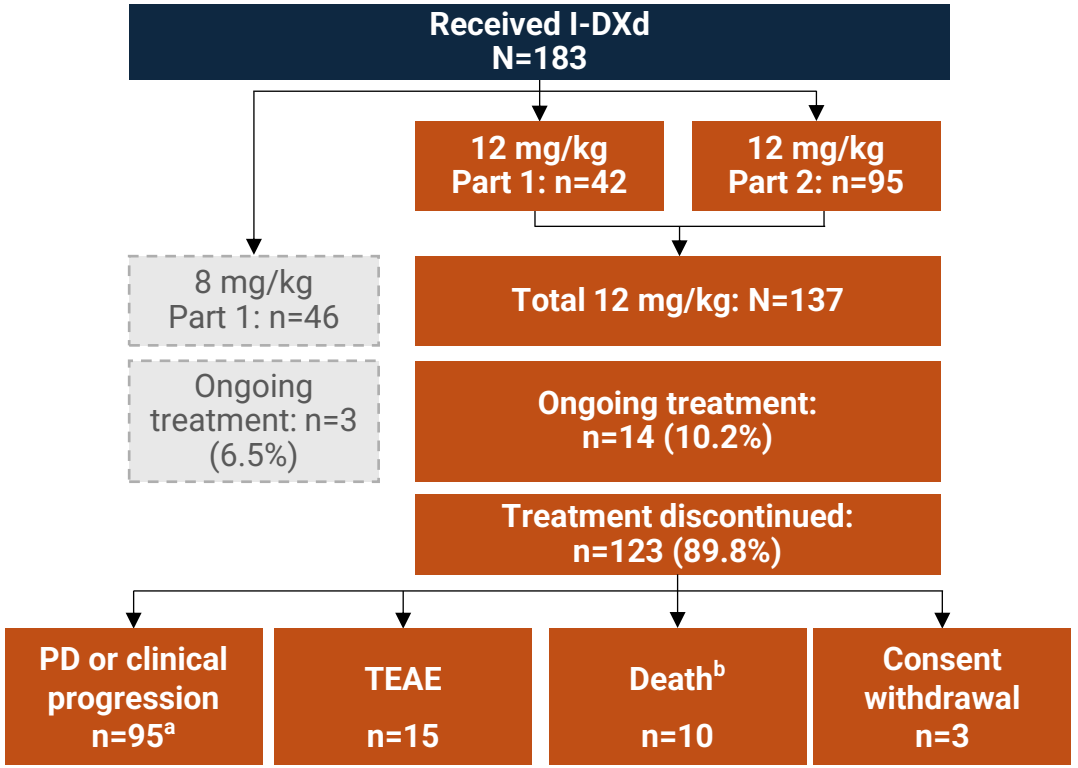
- DOR by BICR and inv[c]
- PFS by BICR and inv[c]
- OS
- DCR by BICR and inv[c]
- TTR by BICR and inv[c]
- ORR by inv[c]
- Safety
- Pharmacokinetics
- Immunogenicity

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]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; CNS, central nervous system; 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; TTR, time to response.

Patient disposition and baseline characteristics



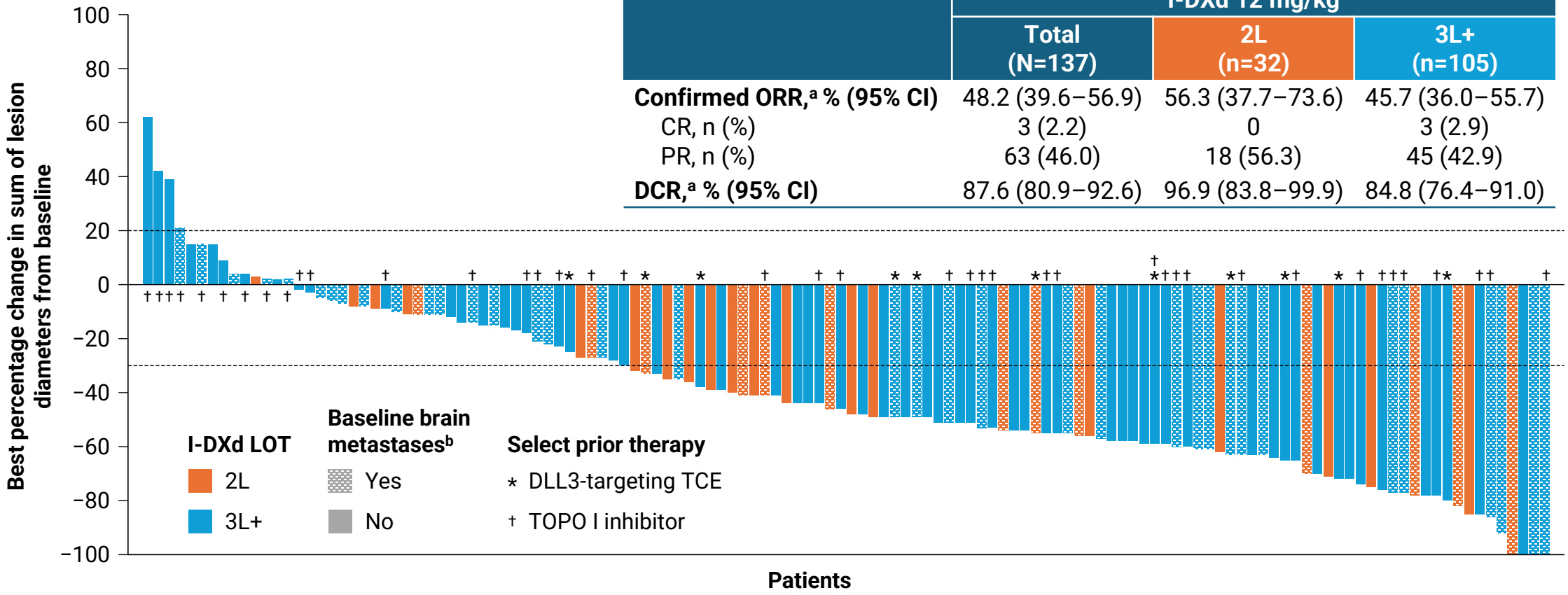
- Median treatment duration: total 12 mg/kg, 4.8 months (range, 0.7–22.7)
- Median follow-up: total 12 mg/kg, 12.8 months (95% CI, 12.2–13.1)[c]

Characteristic	Total I-DXd 12 mg/kg (N=137)
Age, median (range), years	63 (34–79)
Male, n (%)	90 (65.7)
Race, n (%)	
Asian / White / Other or multiple	67 (48.9) / 63 (46.0) / 7 (5.1)
Region, n (%)	
Asia / Europe / North America	66 (48.2) / 40 (29.2) / 31 (22.6)
ECOG PS 1, n (%)	106 (77.4)
ES-SCLC at diagnosis, n (%)	111 (81.0)
Brain / liver metastases at baseline,[d] n (%)	52 (38.0) / 55 (40.1)
CTFI, n (%)[e]	
≤30 days / >30 to <90 days / ≥90 days	18 (13.1) / 40 (29.2) / 72 (52.6)
Number of prior lines of systemic therapy, n (%)	
1 / 2 / 3	32 (23.4) / 75 (54.7) / 30 (21.9)
Select prior anticancer therapy, n (%)	
TOPO I inhibitor	44 (32.1)
Lurbinectedin	29 (21.2)
Amrubicin	12 (8.8)
DLL3-targeting TCE[f]	11 (8.0)
Prior anti–PD-(L)1 therapy, n (%)	111 (81.0)

Data cutoff: March 3, 2025.
[a]Included 8 patients with clinical progression. [b]Death due to any reason, not limited to TEAEs associated with death. [c]Median (95% CI) follow-up in Part 1: 26.4 months (22.3–NE); median follow-up in Part 2: 12.2 months (11.3–12.5). [d]By BICR. [e]Seven (5.1%) patients had missing CTFI data (based on a 90-day cutoff). [f]Seven patients received prior tarlatamab.
BICR, blinded independent central review; CI, confidence interval; CTFI, chemotherapy-free interval; DLL3, delta-like ligand 3; ECOG PS, Eastern Cooperative Oncology Group performance status; ES-SCLC, extensive-stage small cell lung cancer; NE, not estimable; PD, progressive disease; PD-(L)1, programmed death (ligand) 1; TCE, T-cell engager; TEAE, treatment-emergent adverse event; TOPO I, topoisomerase I.

I-DXd 12 mg/kg demonstrated promising antitumor activity

	I-DXd 12 mg/kg		
	Total (N=137)	2L (n=32)	3L+ (n=105)
Confirmed ORR,[a] % (95% CI)	48.2 (39.6–56.9)	56.3 (37.7–73.6)	45.7 (36.0–55.7)
CR, n (%)	3 (2.2)	0	3 (2.9)
PR, n (%)	63 (46.0)	18 (56.3)	45 (42.9)
DCR,[a] % (95% CI)	87.6 (80.9–92.6)	96.9 (83.8–99.9)	84.8 (76.4–91.0)

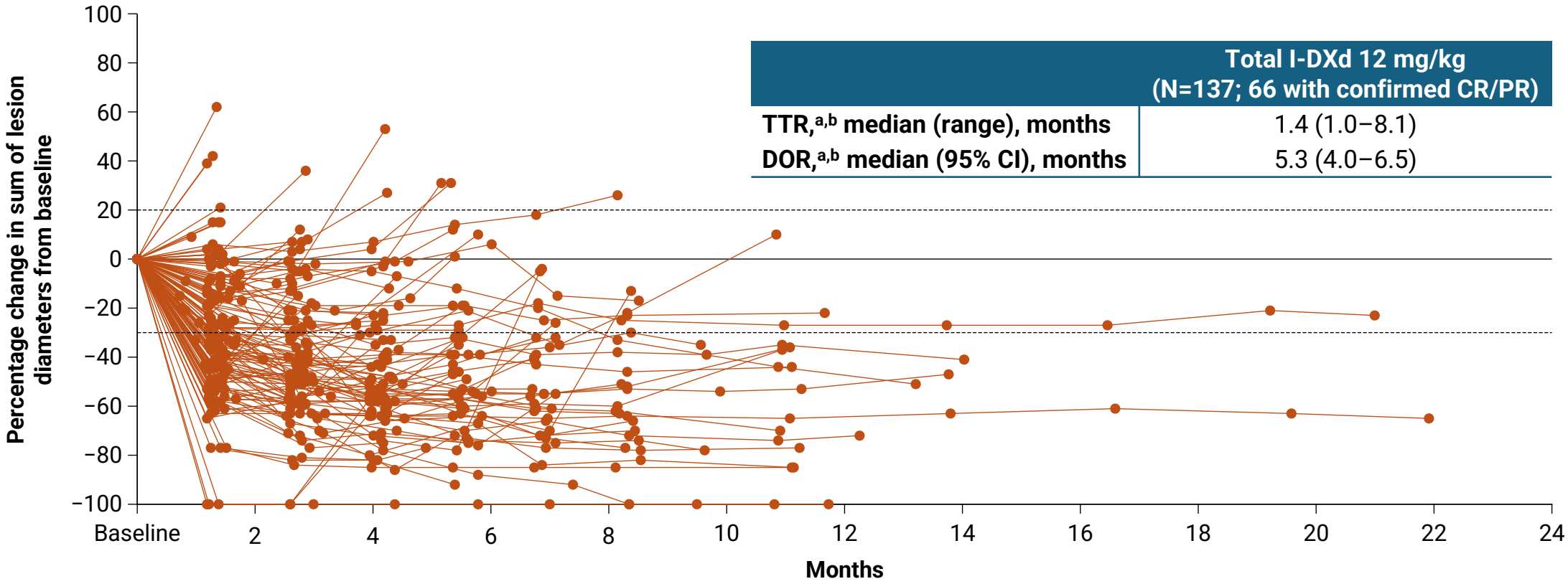


Data cutoff: March 3, 2025.

[a]Assessed by BICR per RECIST 1.1. [b]By BICR.

2L, second-line; 3L+, third-line and beyond; BICR, blinded independent central review; CI, confidence interval; CR, complete response; DCR, disease control rate; DLL3, delta-like ligand 3; LOT, line of therapy; ORR, objective response rate; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; TCE, T-cell engager; TOPO I, topoisomerase I.

Responses with I-DXd 12 mg/kg were rapid and durable



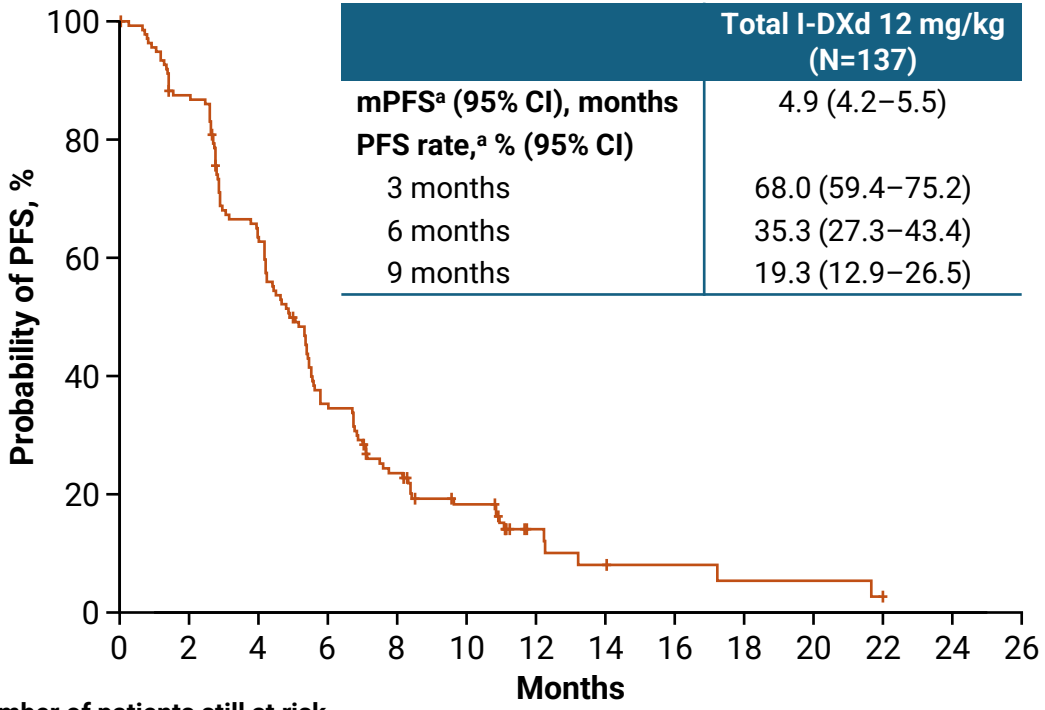
	Total I-DXd 12 mg/kg (N=137; 66 with confirmed CR/PR)
TTR,[a,b] median (range), months	1.4 (1.0–8.1)
DOR,[a,b] median (95% CI), months	5.3 (4.0–6.5)

Among patients who received I-DXd 12 mg/kg as 2L therapy (n=32), median TTR was 1.4 months (range, 1.2–4.0) and median DOR was 7.2 months (95% CI, 3.6–NE)

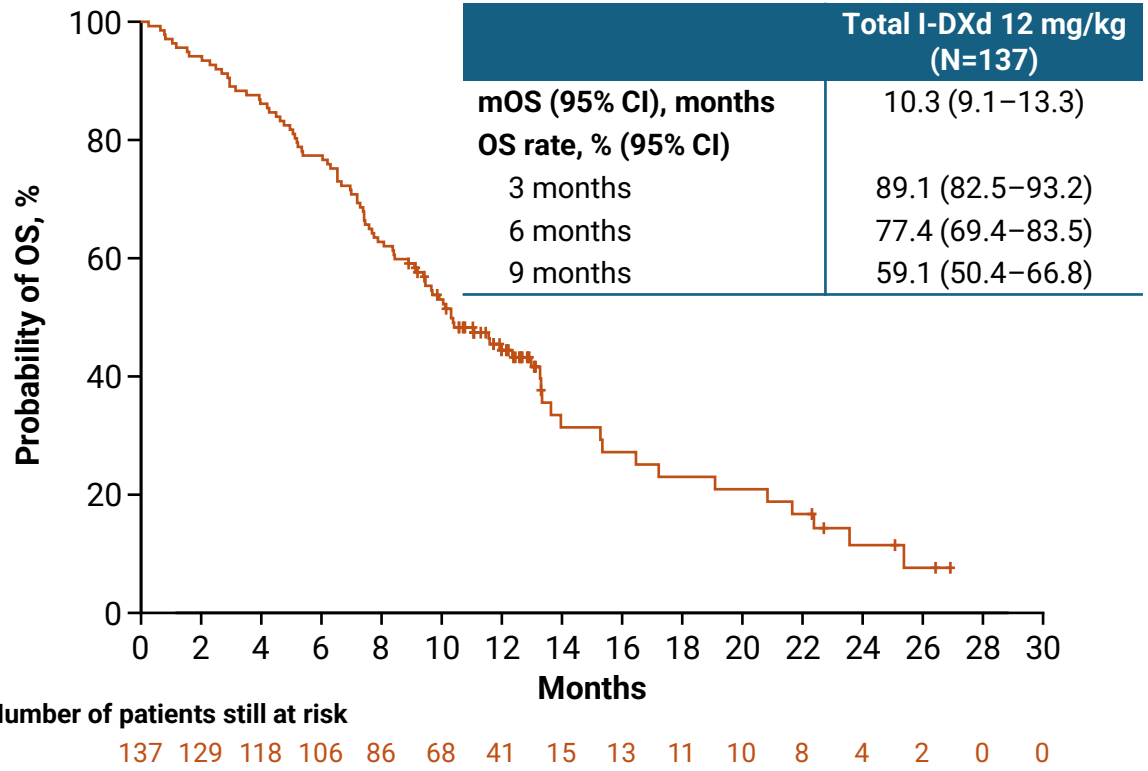
Data cutoff: March 3, 2025.
Tumor assessments were performed every 6 weeks (±7 days) in the first 36 weeks and every 12 weeks (±7 days) thereafter, until disease progression, death, loss to follow-up, or withdrawal of consent, whichever occurred first.
[a]Assessed by BICR per RECIST 1.1. [b]Patients with confirmed objective response.
2L, second-line; BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; NE, not estimable; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; TTR, time to response.

mPFS was 4.9 months and mOS was 10.3 months with I-DXd 12 mg/kg

	Total I-DXd 12 mg/kg (N=137)
mPFS[a] (95% CI), months	4.9 (4.2–5.5)
PFS rate,[a] % (95% CI)	
3 months	68.0 (59.4–75.2)
6 months	35.3 (27.3–43.4)
9 months	19.3 (12.9–26.5)



	Total I-DXd 12 mg/kg (N=137)
mOS (95% CI), months	10.3 (9.1–13.3)
OS rate, % (95% CI)	
3 months	89.1 (82.5–93.2)
6 months	77.4 (69.4–83.5)
9 months	59.1 (50.4–66.8)



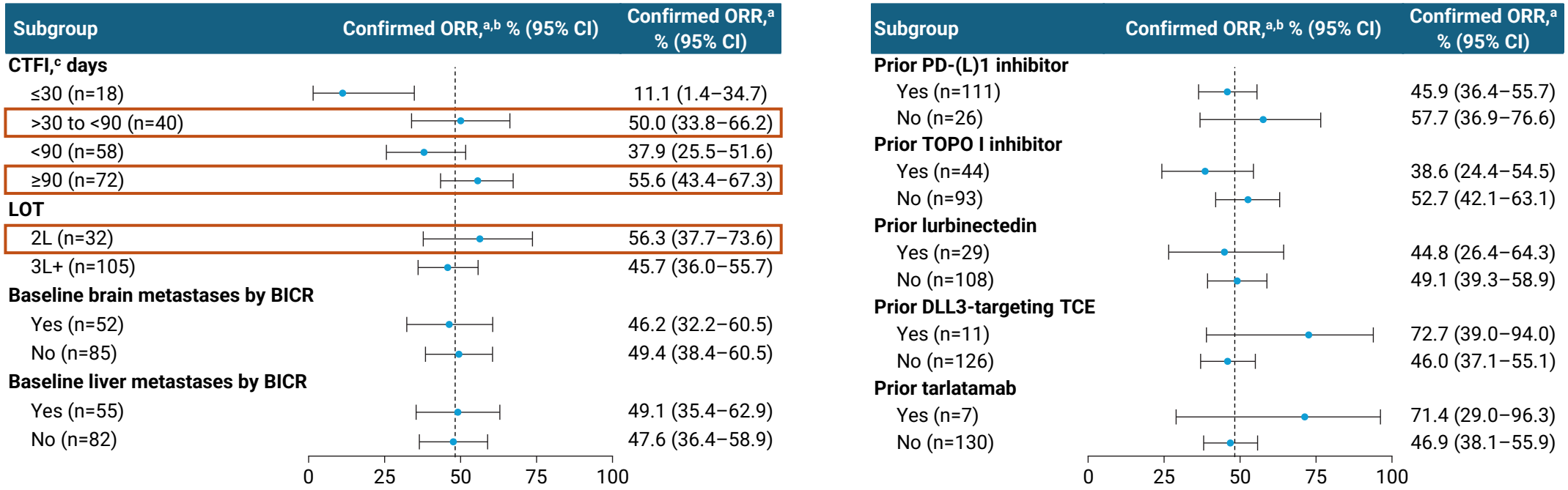
Among patients who received I-DXd 12 mg/kg as 2L therapy (n=32), mPFS was 5.6 months (95% CI, 3.9–8.1) and mOS was 12.0 months (95% CI, 7.3–19.1)

Data cutoff: March 3, 2025.

[a]Assessed by BICR per RECIST 1.1.

2L, second-line; BICR, blinded independent central review; CI, confidence interval; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1.

I-DXd demonstrated clinically meaningful benefit across subgroups of the total 12-mg/kg group



- The total 12-mg/kg population included 18 (13.1%) patients with CTFI ≤30 days; as expected, confirmed ORR was low in this population
- In 65 patients with baseline brain metastases identified using CNS BICR, CNS confirmed ORR was 46.2% (95% CI, 33.7–59.0)[d]

Data cutoff: March 3, 2025.
Median (95% CI) DOR,[a] months: CTFI ≤30 days, NE (NE–NE); **CTFI >30 to <90 days,** 3.7 (3.1–4.2); **CTFI <90 days,** 3.8 (3.1–4.4); **CTFI ≥90 days,** 6.5 (4.1–9.7); **2L,** 7.2 (3.6–NE); **3L+,** 4.3 (3.7–5.8); **baseline brain metastases by BICR "yes,"** 4.8 (3.0–8.3); **baseline brain metastases by BICR "no,"** 5.3 (4.1–7.0); **baseline liver metastases by BICR "yes,"** 5.3 (3.9–7.2); **baseline liver metastases by BICR "no,"** 4.9 (3.5–6.4); **prior PD-(L)1 inhibitor "yes,"** 4.5 (3.6–5.8); **prior PD-(L)1 inhibitor "no,"** 8.3 (3.9–NE); **prior TOPO I inhibitor "yes,"** 4.1 (3.0–9.8); **prior TOPO I inhibitor "no,"** 5.5 (3.9–6.5); **prior lurbinectedin "yes,"** 4.0 (2.6–5.5); **prior lurbinectedin "no,"** 5.8 (4.1–7.2); **prior DLL3-targeting TCE "yes,"** 5.1 (2.8–NE); **prior DLL3-targeting TCE "no,"** 5.3 (4.0–6.5); **prior tarlatamab "yes,"** 5.6 (2.8–NE); **prior tarlatamab "no,"** 5.1 (3.9–6.5).
[a]Assessed by BICR per RECIST 1.1. [b]Confirmed ORR for total I-DXd 12 mg/kg (N=137) was 48.2% (95% CI, 39.6–56.9) and is represented by the vertical dashed line. [c]Seven patients had missing CTFI data (based on a 90-day cutoff).
[d]Assessed using a version of RECIST 1.1 modified for assessment of CNS tumors.
2L, second-line; 3L+, third-line and beyond; BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CTFI, chemotherapy-free interval; DLL3, delta-like ligand 3; DOR, duration of response; LOT, line of therapy; NE, not estimable; ORR, objective response rate; PD-(L)1, programmed death (ligand) 1; RECIST (1.1), Response Evaluation Criteria in Solid Tumours (version 1.1); TCE, T-cell engager; TOPO I, topoisomerase I.

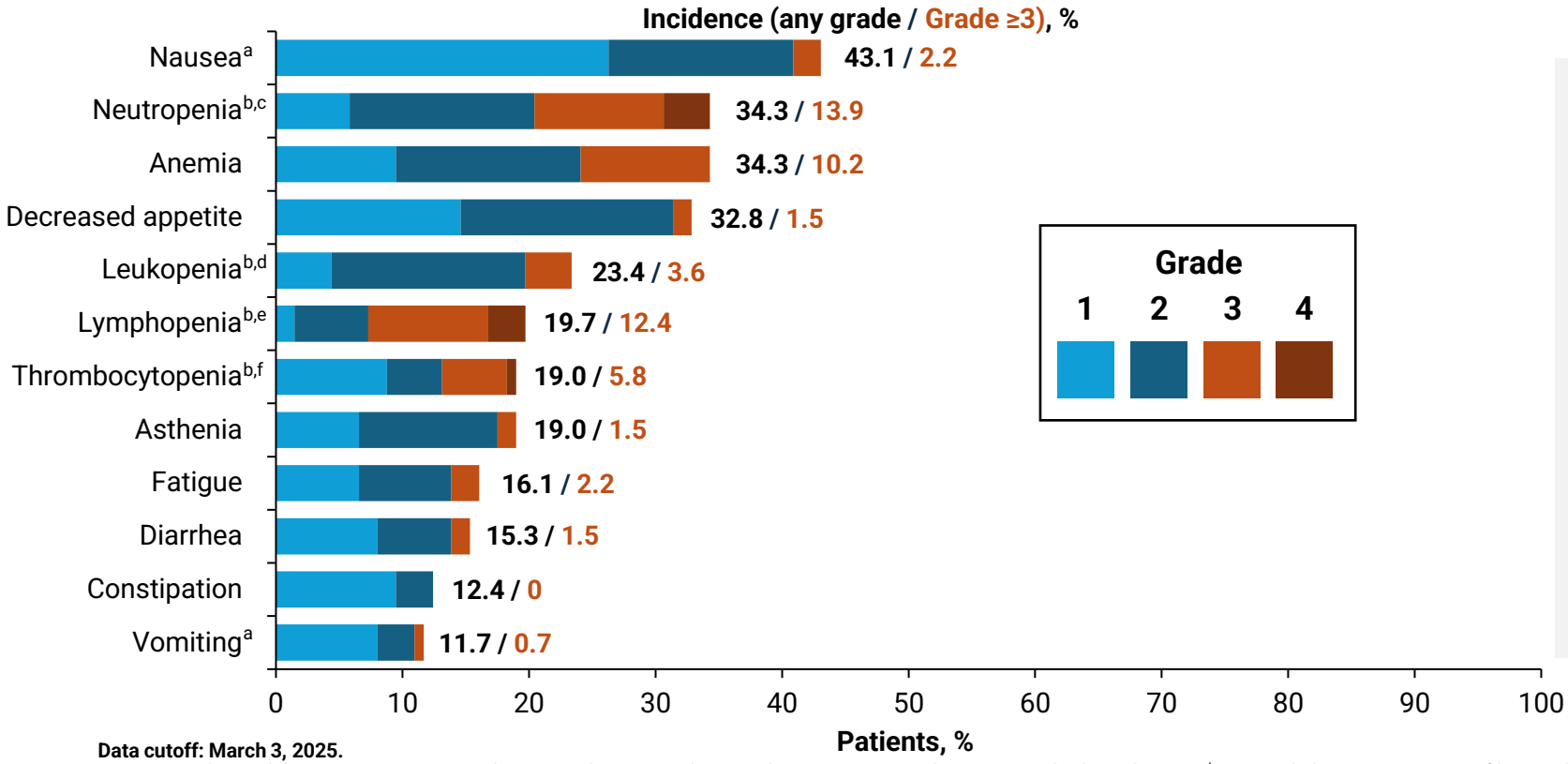
The safety profile of I-DXd 12 mg/kg was manageable

	Total I-DXd 12 mg/kg (N=137)
Median treatment duration,[a] months (range)	4.8 (0.7–22.7)
Median cycles, n (range)	7.0 (1.0–32.0)
Any-grade TRAEs, n (%)	123 (89.8)
Grade ≥3	50 (36.5)
Associated with dose delay	35 (25.5)
Associated with dose reduction	21 (15.3)
Associated with treatment discontinuation[b]	13 (9.5)
Associated with death[c]	6 (4.4)

Data cutoff: March 3, 2025.
[a]Treatment duration (months) is calculated as (date of the last dose − date of the first dose + 21 days) × 12 ÷ 365.25. For patients who were still on treatment at data cutoff, the last available date of dose prior to data cutoff was used.
[b]Grade 1: pneumonitis (n=1); Grade 2: ILD (n=3), pneumonitis (n=2), radiation pneumonitis (n=1), and fatigue (n=1); Grade 3: ILD (n=2), *Pneumocystis jirovecii* pneumonia (n=2), and nausea (n=1). [c]ILD/pneumonitis (n=3); *Pneumocystis jirovecii* pneumonia (n=2); pulmonary sepsis (n=1). Of the 3 treatment-related ILD/pneumonitis events associated with death per investigator, only 1 was subsequently adjudicated as treatment related by the ILD adjudication committee.
ILD, interstitial lung disease; TRAE, treatment-related adverse event.

The most common TRAEs were hematologic or gastrointestinal in nature, and fatigue

TRAEs reported in ≥10% of patients in the total I-DXd 12-mg/kg group (N=137)



- Among the most common TRAEs, the majority were Grade 1 or 2
- Adjudicated treatment-related ILD/pneumonitis was reported in 17 (12.4%) patients:
  - Grade 1 or 2, n=11 (8.0%)
  - Grade 3, n=4 (2.9%)
  - Grade 5, n=2 (1.5%)[g]
- No ILD events were pending adjudication at data cutoff

Data cutoff: March 3, 2025.

[a]Prior to each I-DXd dose, antiemetic premedication with a 2- or 3-drug combination was mandatory across both study parts. [b]For prophylaxis or treatment of hematologic toxicity, trilaciclib, hematopoietic growth factors, or transfusion of blood, red blood cells, and platelets could be administered. [c]Includes the preferred terms "neutrophil count decreased" and "neutropenia." [d]Includes the preferred terms "white blood cell count decreased" and "leukopenia." [e]Includes the preferred terms "lymphocyte count decreased" and "lymphopenia." [f]Includes the preferred terms "platelet count decreased" and "thrombocytopenia". [g]Both patients were deemed to have adjudicated Grade 5 treatment-related ILD by the ILD adjudication committee; however, only 1 of these patients also had treatment-related ILD associated with death per investigator.

ILD, interstitial lung disease; TRAE, treatment-related adverse event.

Conclusions

- I-DXd 12 mg/kg demonstrated remarkable efficacy in patients with previously treated ES-SCLC, particularly given the inclusion of populations often excluded from clinical trials
  - 18/137 with CTFI ≤30 days; 52/137 with asymptomatic untreated or previously treated brain metastases[a]
- Confirmed ORR was 48.2%, median DOR was 5.3 months, median PFS was 4.9 months, and median OS was 10.3 months
- Clinically meaningful benefit was observed regardless of platinum sensitivity or LOT, with confirmed ORRs of:
  - 55.6% (CTFI ≥90 days) and 50.0% (CTFI >30 to <90 days)
  - 56.3% (2L) and 45.7% (3L+)
- Meaningful intracranial efficacy was observed; a full subgroup analysis of patients with baseline brain metastases will be presented at ESMO 2025 (Abstract 2760MO)
- The safety profile of I-DXd 12 mg/kg was manageable and consistent with previous reports[1–3]
- The ongoing global Phase 3 IDeate-Lung02 trial (NCT06203210) is comparing I-DXd 12 mg/kg vs treatment of physician's choice (topotecan, amrubicin, or lurbinectedin) in patients with relapsed SCLC with only 1 prior line of systemic treatment, which must have included PBC

Data cutoff: March 3, 2025.

[a]By BICR.

2L, second-line; 3L+, third-line and beyond; BICR, blinded independent central review; CTFI, chemotherapy-free interval; DOR, duration of response; (ES)-SCLC, (extensive-stage) small cell lung cancer; LOT, line of therapy; ORR, objective response rate; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival.

1. Johnson M, et al. Oral presentation at the 2023 IASLC World Conference on Lung Cancer. September 9–12, 2023; Singapore. Presentation OA05.05. 2. Patel MR, et al. Poster presentation at the European Society for Medical Oncology Congress 2023. October 20–24, 2023; Madrid, Spain. Presentation 690P. 3. Rudin CM, et al. Oral presentation at the 2024 IASLC World Conference on Lung Cancer. September 7–10, 2024; San Diego, CA, USA. Presentation OA04.03.

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