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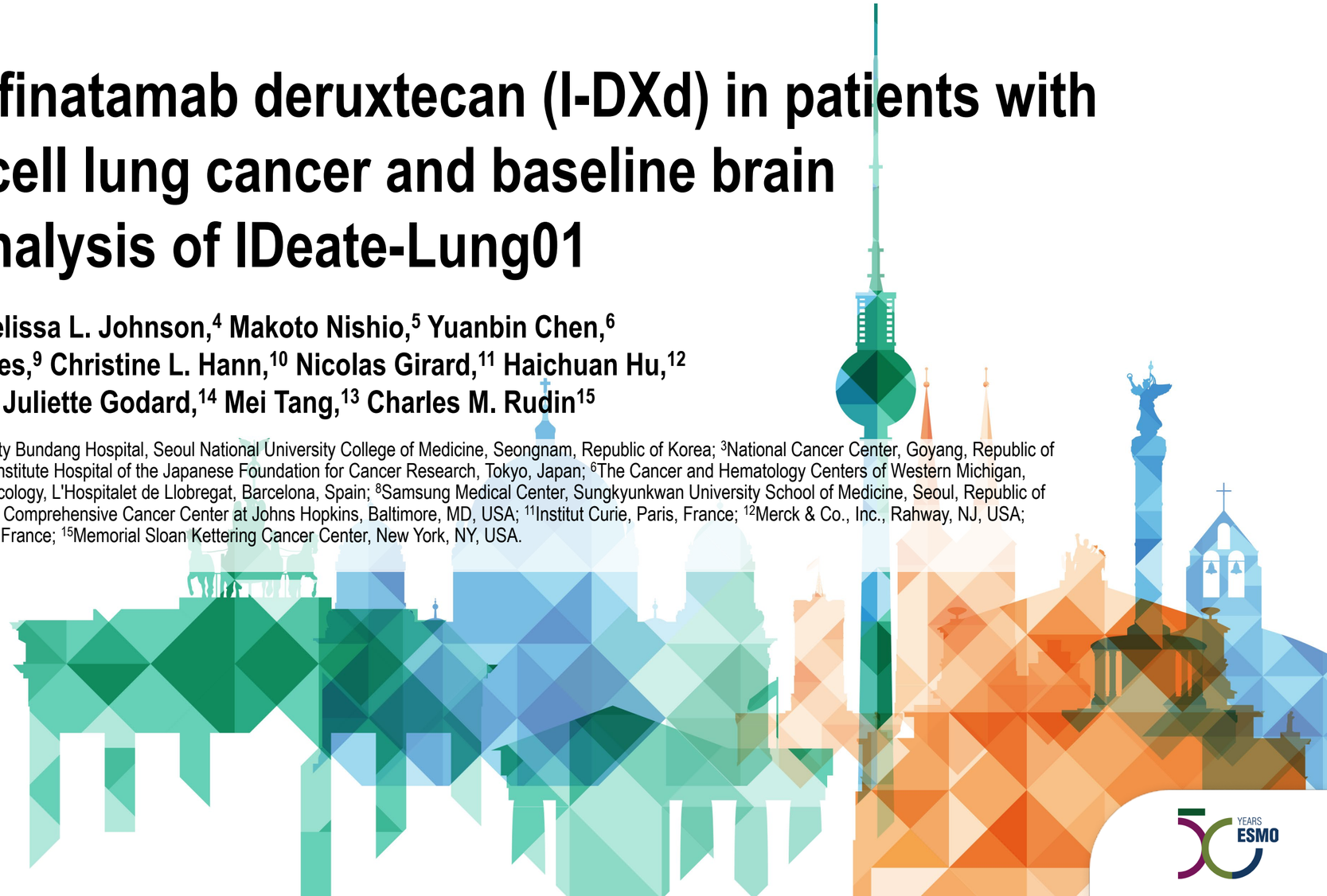
Intracranial activity of ifinatamab deruxtecan (I-DXd) in patients with extensive-stage small cell lung cancer and baseline brain metastases: Primary analysis of IDeate-Lung01

Pedro Rocha,[1] **Yu Jung Kim**,[2] **Ji-Youn Han**,[3] **Melissa L. Johnson**,[4] **Makoto Nishio**,[5] **Yuanbin Chen**,[6] **Ramón Palmero**,[7] **Myung-Ju Ahn**,[8] **Luis Paz-Ares**,[9] **Christine L. Hann**,[10] **Nicolas Girard**,[11] **Haichuan Hu**,[12] **David Leung**,[13] **Meng Qian**,[13] **Jasmeet Singh**,[13] **Juliette Godard**,[14] **Mei Tang**,[13] **Charles M. Rudin**[15]

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



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Declaration of interests

Pedro Rocha

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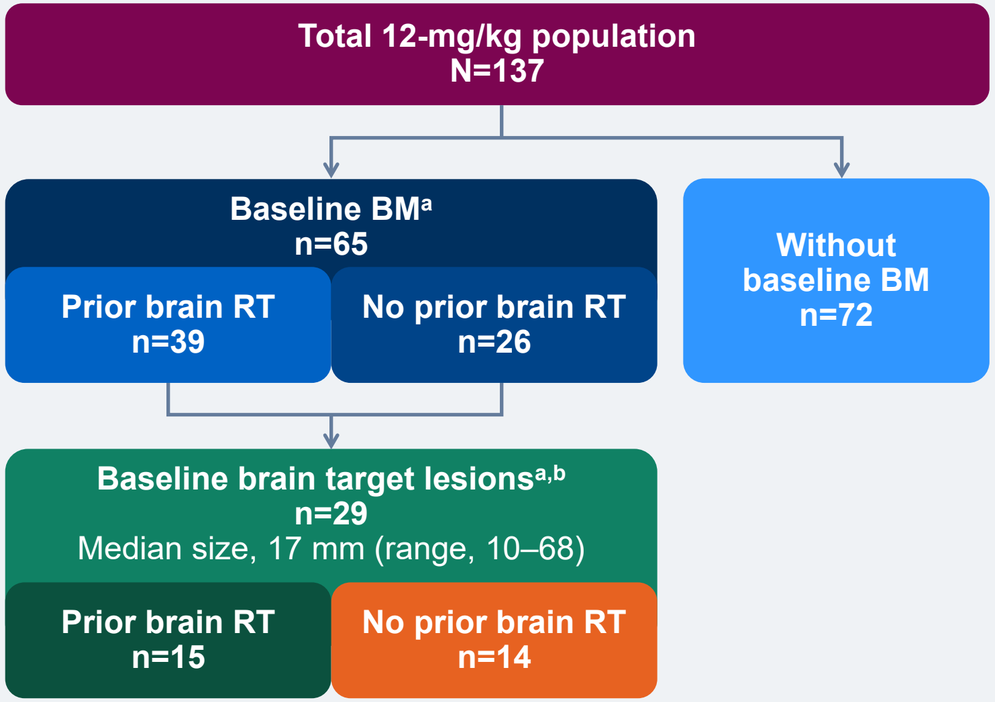
Background, patient population, and baseline characteristics

- Approximately 10–20% of patients with SCLC have brain metastases (BM) at diagnosis, increasing to 80% after ~2 years[1–7]
  - For patients with BM at baseline, median OS from time of diagnosis is ~5 months, with a 3-year survival rate of 3.0%[2]
- In the primary analysis of IDeate-Lung01 (Phase 2; NCT05280470), I-DXd 12 mg/kg Q3W demonstrated a systemic cORR of 48.2%, mDOR of 5.3 months, and mPFS of 4.9 months in 137 patients with previously treated ES-SCLC[8]
- We report a subgroup analysis of patients with asymptomatic (previously treated or untreated) BM identified by CNS BICR at study baseline[a]
- Brain CT/MRI was performed at baseline for all patients and, for those with investigator-determined BM, Q6W for 36 weeks and Q12W thereafter



Baseline characteristics of patients with baseline BM:

- Median age, 61.0 years (range, 39.0–76.0)
- ECOG PS 0, 20.0% / ECOG PS 1, 80.0%
- Median prior lines of systemic therapy, 2 (range, 1–3)

[a]Identified by CNS BICR, detectable by CT/MRI brain scan at baseline. Intracranial response was assessed by CNS BICR using a version of RECIST 1.1 modified for assessment of CNS tumors. [b]Defined as ≥1 CNS target lesion with a longest diameter of ≥10 mm or twice the slice thickness by CT/MRI scan, whichever was larger.

BICR, blinded independent central review; BM, brain metastases; CNS, central nervous system; cORR, confirmed objective response rate; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; (ES-)SCLC, (extensive-stage) small cell lung cancer; mDOR, median duration of response; mPFS, median progression-free survival; MRI, magnetic resonance imaging; OS, overall survival; QXW, every X weeks; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; RT, radiotherapy.

1. Rudin CM, et al. *Nat Rev Dis Primers*. 2021;7:3. 2. Zhou G, et al. *Cancer Med*. 2023;12:1195–1203. 3. Kromer C, et al. *J Neurooncol*. 2017;134:55–64. 4. Korfel A, et al. *Eur J Cancer*. 2002;38:1724–1729. 5. Hirsch FR, et al. *Cancer*. 1982;50:2433–2437. 6. Lekic M, et al. *Radiol Oncol*. 2012;46:54–59. 7. Nugent JL, et al. *Cancer*. 1979;44:1885–1893. 8. Ahn M-J, et al. Oral presentation at the IASLC 2025 World Conference on Lung Cancer. September 6–9, 2025; Barcelona, Spain. Presentation OA06.03.

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I-DXd demonstrated promising systemic and intracranial efficacy in patients with baseline BM

	With baseline BM (n=65)		Without baseline BM (n=72)
	Intracranial	Systemic	Systemic
cORR,[a] % (95% CI)	46.2% (33.7–59.0)	46.2% (33.7–59.0)	50.0% (38.0–62.0)
cBOR,[a] n (%)			
CR	20 (30.8%)	1 (1.5%)	2 (2.8%)
PR	10 (15.4%)	29 (44.6%)	34 (47.2%)
SD	29 (44.6%)	28 (43.1%)	26 (36.1%)
PD	1 (1.5%)	5 (7.7%)	5 (6.9%)
NE	5 (7.7%)[b]	2 (3.1%)[c]	5 (6.9%)[d]
cDCR,[a] % (95% CI)	90.8% (81.0–96.5)	89.2% (79.1–95.6)	86.1% (75.9–93.1)
DOR,[a] median (95% CI), months	6.2 (4.0–7.9)	4.3 (3.0–5.8)	5.9 (4.0–8.3)
TTR,[a] median (range), months	1.4 (0.9–8.5)	1.4 (1.0–8.1)	1.4 (1.2–4.0)
PFS,[a] median (95% CI), months	—	4.5 (4.0–5.4)	5.4 (4.2–6.7)
OS, median (95% CI), months	—	10.4 (7.9–15.3)	10.1 (8.4–13.3)

- **Concordance** between systemic and CNS **objective response: 75.4%**
- **Concordance** between systemic and CNS **disease control: 86.2%**

- OS and PFS were similar for patients with and without baseline BM

Data cutoff: March 3, 2025.

[a]By CNS BICR using a version of RECIST 1.1 modified for assessment of CNS tumors for intracranial response and by BICR per RECIST 1.1 for systemic response. [b]Reason for NE was no adequate post-baseline assessment (n=5). [c]Reason for NE was no adequate post-baseline assessment (n=2). [d]Reason for NE was no adequate post-baseline assessment (n=3) or SD too early (n=2).

BICR, blinded independent central review; BM, brain metastases; cBOR, confirmed best overall response; cDCR, confirmed disease control rate; CI, confidence interval; CNS, central nervous system; cORR, confirmed objective response rate; CR, complete response; DOR, duration of response; NE, not evaluable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; SD, stable disease; TTR, time to response.

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I-DXd demonstrated promising intracranial efficacy regardless of prior treatment for baseline BM

Intracranial cORR in patients with or without prior RT to the brain for baseline BM

	cORR,[a] % (95% CI)
With baseline BM (n=65)	46.2% (33.7–59.0)
No prior RT (n=26)	57.7% (36.9–76.6)
Prior RT (n=39)	38.5% (23.4–55.4)
<6 months before study[b] (n=28)	39.3% (21.5–59.4)
≥6 months before study[b] (n=11)	36.4% (10.9–69.2)

Data cutoff: March 3, 2025.

[a]By CNS BICR using a version of RECIST 1.1 modified for assessment of CNS tumors. [b]Time from last RT of brain until first dose of study treatment.

BICR, blinded independent central review; BM, brain metastases; CI, confidence interval; CNS, central nervous system; cORR, confirmed objective response rate; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; RT, radiotherapy.

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Progression in the brain was uncommon, suggesting that I-DXd may prevent BM

Patients with site of progression in the brain per CNS BICR

	Progression in the brain, n (%)
With baseline BM (n=65)	**23 (35.4%)**
No prior RT (n=26)	6 (23.1%)
Prior RT (n=39)	17 (43.6%)
Without baseline BM (n=72)	**9 (12.5%)**

Data cutoff: March 3, 2025.

BICR, blinded independent central review; BM, brain metastases; CNS, central nervous system; RT, radiotherapy.

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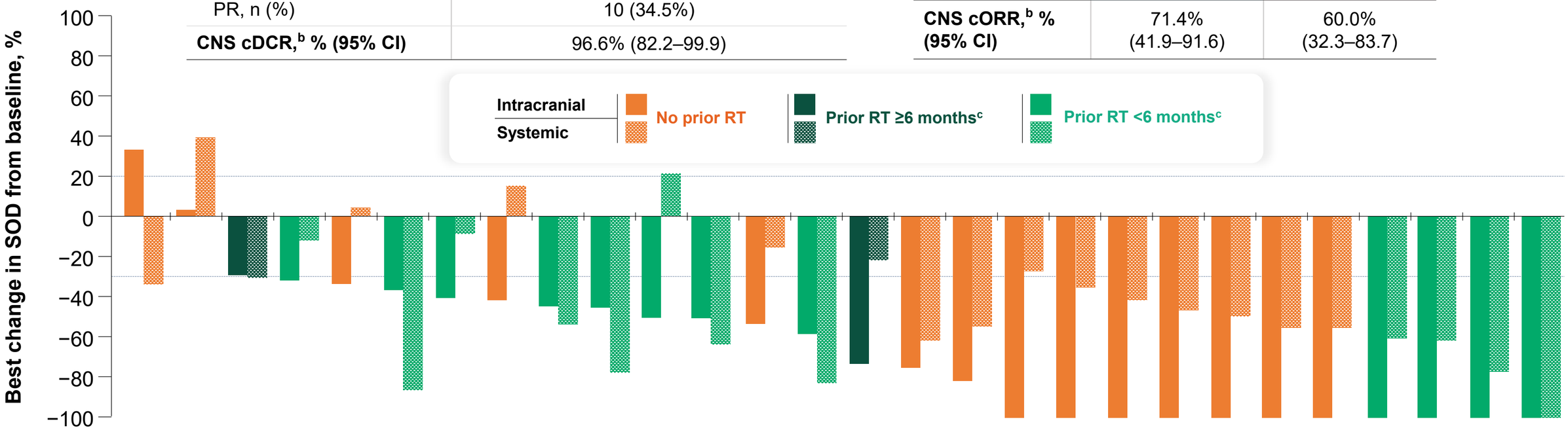
I-DXd demonstrated promising responses in patients with brain target lesions[a]

	With baseline brain target lesions (n=29)
CNS cORR,[b] % (95% CI)	65.5% (45.7–82.1)
CR, n (%)	9 (31.0%)
PR, n (%)	10 (34.5%)
CNS cDCR,[b] % (95% CI)	96.6% (82.2–99.9)

	No prior RT (n=14)	With prior RT (n=15)
CNS cORR,[b] % (95% CI)	71.4% (41.9–91.6)	60.0% (32.3–83.7)



Concordance between systemic and CNS **objective response: 69.0%**

Data cutoff: March 3, 2025.

[a]Only patients with measurable disease at baseline and ≥1 post-baseline assessment are included in the plot (n=28); 1 patient was excluded due to a lack of post-baseline assessment. [b]By CNS BICR using a version of RECIST 1.1 modified for assessment of CNS tumors. [c]Time from last RT of brain until first dose of study treatment.

BICR, blinded independent central review; cDCR, confirmed disease control rate; CI, confidence interval; CNS, central nervous system; cORR, confirmed objective response rate; CR, complete response; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; RT, radiotherapy; SOD, sum of diameters.

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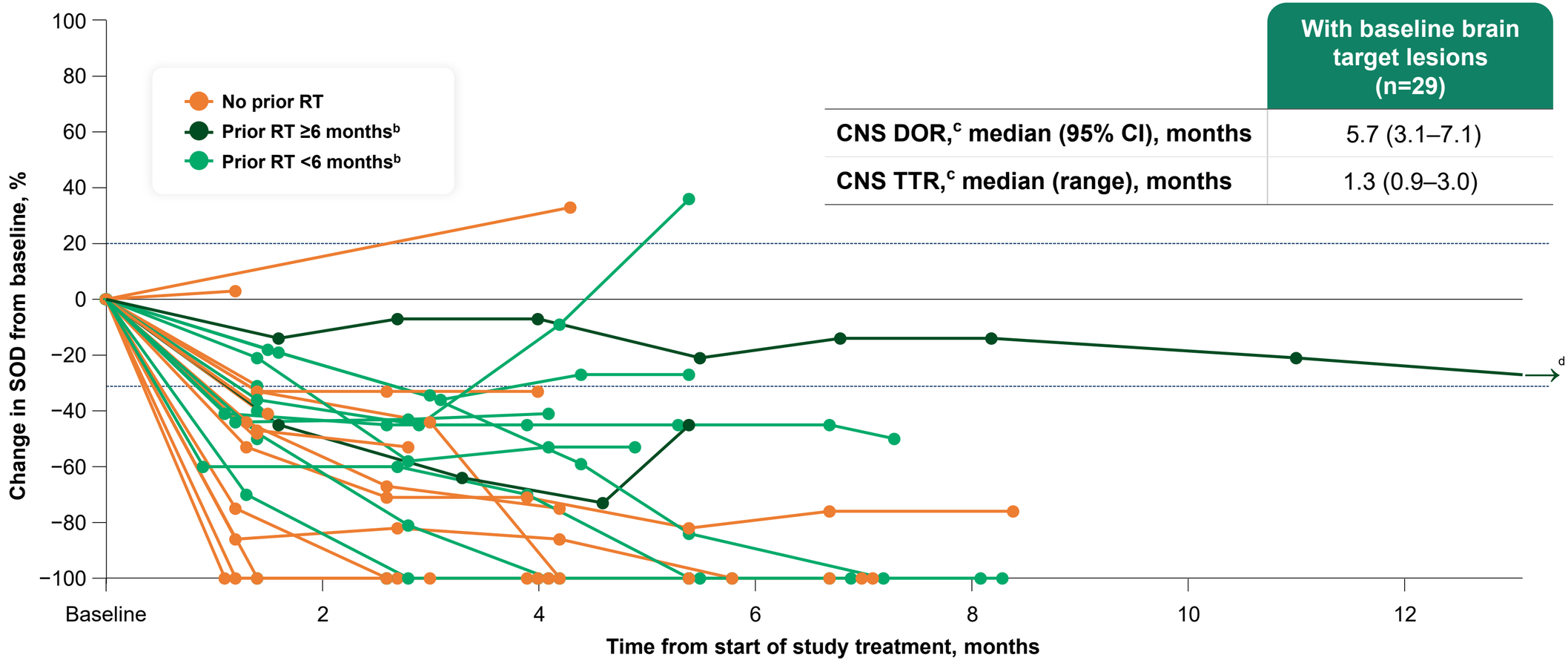
I-DXd demonstrated rapid and durable responses in patients with brain target lesions[a]



	With baseline brain target lesions (n=29)
CNS DOR,[c] median (95% CI), months	5.7 (3.1–7.1)
CNS TTR,[c] median (range), months	1.3 (0.9–3.0)

Data cutoff: March 3, 2025.

[a]Only patients with measurable disease at baseline and ≥1 post-baseline assessment are included in the plot (n=28); 1 patient was excluded due to a lack of post-baseline assessment. [b]Time from last RT of brain until first dose of study treatment. [c]By CNS BICR using a version of RECIST 1.1 modified for assessment of CNS tumors. [d]Duration of treatment was ~21 months at data cutoff.

BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; DOR, duration of response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours, version 1.1; RT, radiotherapy; SOD, sum of diameters; TTR, time to response.

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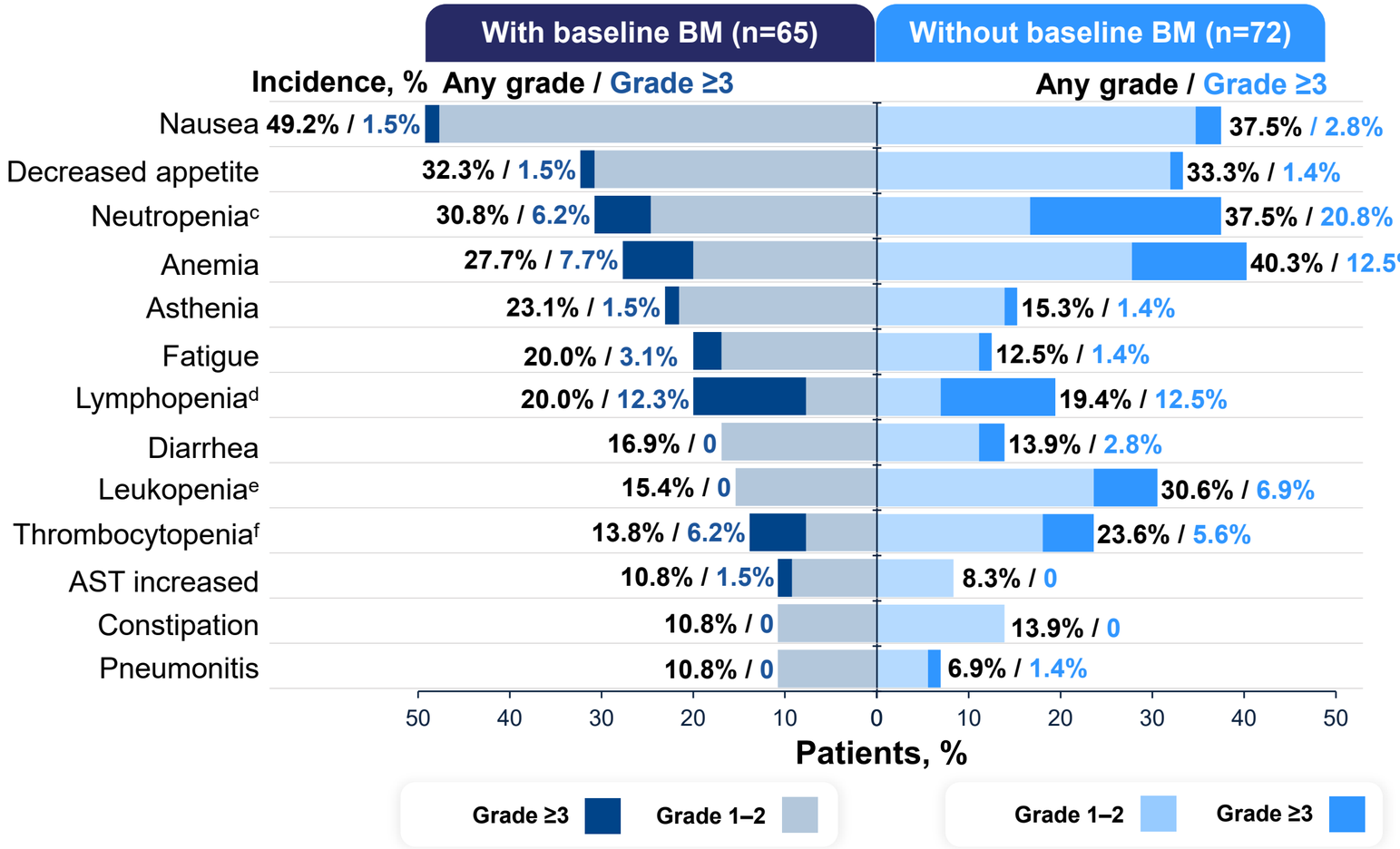
No new safety signals were identified in patients with baseline BM

Summary of TRAEs

TRAEs, n (%)	With baseline BM (n=65)	Without baseline BM (n=72)
Any grade	57 (87.7%)	66 (91.7%)
Grade ≥3	20 (30.8%)	30 (41.7%)
Serious	7 (10.8%)	18 (25.0%)
Associated with:		
Dose delay	15 (23.1%)	20 (27.8%)
Dose reduction	10 (15.4%)	11 (15.3%)
Treatment discontinuation	5 (7.7%)	8 (11.1%)
Death as outcome	1 (1.5%)[a]	5 (6.9%)[b]

- The safety profile of I-DXd was similar between patients with and without baseline BM
- There were no new safety signals identified compared with the total 12-mg/kg population

TRAEs reported in ≥10% of patients with baseline BM



Data cutoff: March 3, 2025.

[a]*Pneumocystis jirovecii* pneumonia (n=1). [b]ILD/pneumonitis (n=3; of 3 treatment-related ILD/pneumonitis events associated with death per investigator, only 1 was subsequently adjudicated as treatment related by the ILD adjudication committee), *Pneumocystis jirovecii* pneumonia (n=1), and pulmonary sepsis (n=1). [c]Includes "neutropenia" and "neutrophil count decreased." [d]Includes "lymphopenia" and "lymphocyte count decreased." [e]Includes "leukopenia" and "white blood cell count decreased." [f]Includes "thrombocytopenia" and "platelet count decreased."

AST, aspartate aminotransferase; BM, brain metastases; ILD, interstitial lung disease; TRAE, treatment-related adverse event.

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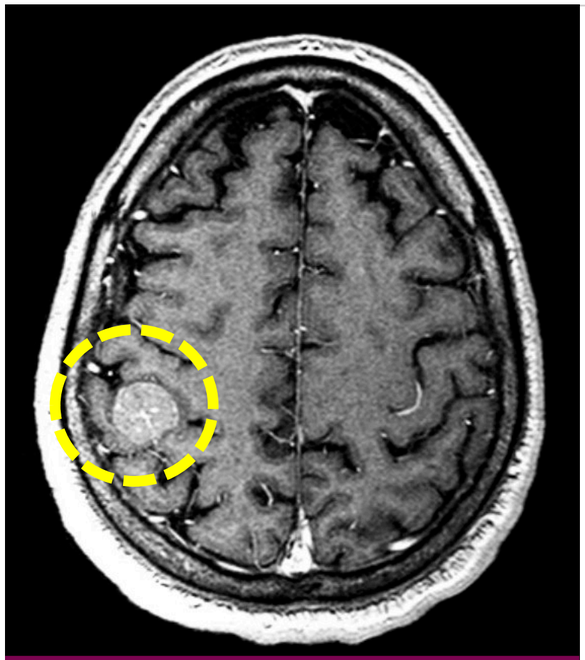
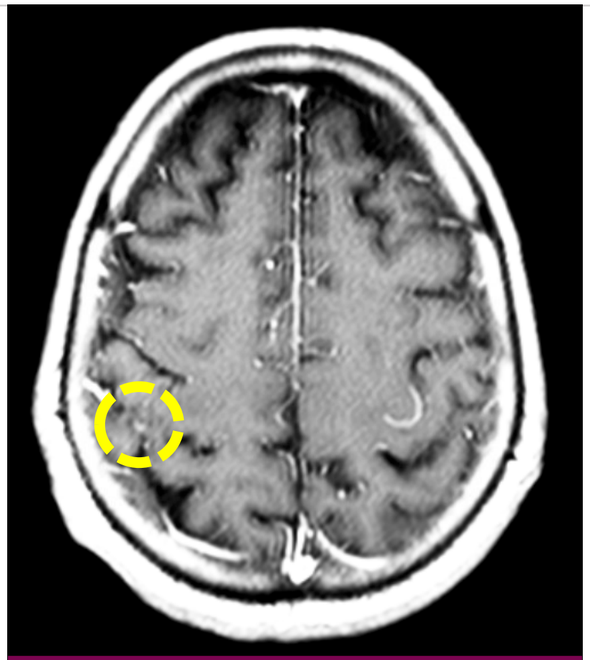
Patient case

60-year-old male patient with ES-SCLC without prior brain RT; received I-DXd in 3L setting

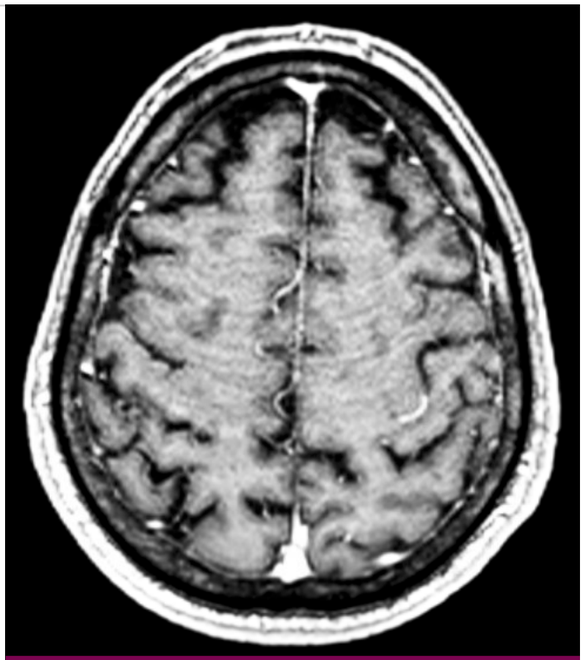
Case summary	
Previous anticancer therapy	1L: carboplatin/etoposide + atezolizumab; BOR: PR 2L: lurbinectedin + atezolizumab; BOR: PR
CTFI	78 days (platinum resistant)



Baseline



Week 6



Week 30

1/2/3L, first/second/third line; BOR, best overall response; CTFI, chemotherapy-free interval; ES-SCLC, extensive-stage small cell lung cancer; PR, partial response; RT, radiotherapy.

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Conclusions

- Intracranial efficacy with I-DXd 12 mg/kg was promising, with 30.8% of patients achieving an intracranial CR, contributing to an intracranial cORR of 46.2% and DCR of 90.8%
  - Intracranial cORR was 57.7% among 26 patients who had not received prior brain RT for baseline BM
  - In 29 patients with baseline brain target lesions, intracranial cORR was 65.5% (9 CR, 10 PR), and almost all patients experienced intracranial disease control (96.6%)
- In 72 patients without baseline BM, progression in the brain was uncommon (12.5%)
- The safety profile for patients with and without baseline BM was consistent with the overall I-DXd 12-mg/kg population[1]
- The intracranial activity of I-DXd will be investigated further in the ongoing Phase 3 IDeate-Lung02 study (NCT06203210), which is comparing I-DXd with treatment of physician's choice (topotecan, amrubicin, or lurbinectedin) in patients with relapsed SCLC[2]

Data cutoff: March 3, 2025.

BM, brain metastases; cORR, confirmed objective response rate; CR, confirmed response; DCR, disease control rate; PR, partial response; RT, radiotherapy; SCLC, small cell lung cancer.

1. Ahn M-J, et al. Oral presentation at IASLC 2025 World Conference on Lung Cancer. September 6–9, 2025; Barcelona, Spain. Presentation OA06.03. 2. Owonikoko TK, et al. Poster presented at the 2024 American Society of Clinical Oncology Annual Meeting. May 31–June 4, 2024; Chicago, IL, USA. Presentation TPS8126.

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