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Ifinatamab deruxtecan (I-DXd; DS-7300) in patients with refractory SCLC: a subgroup analysis of a phase 1/2 study

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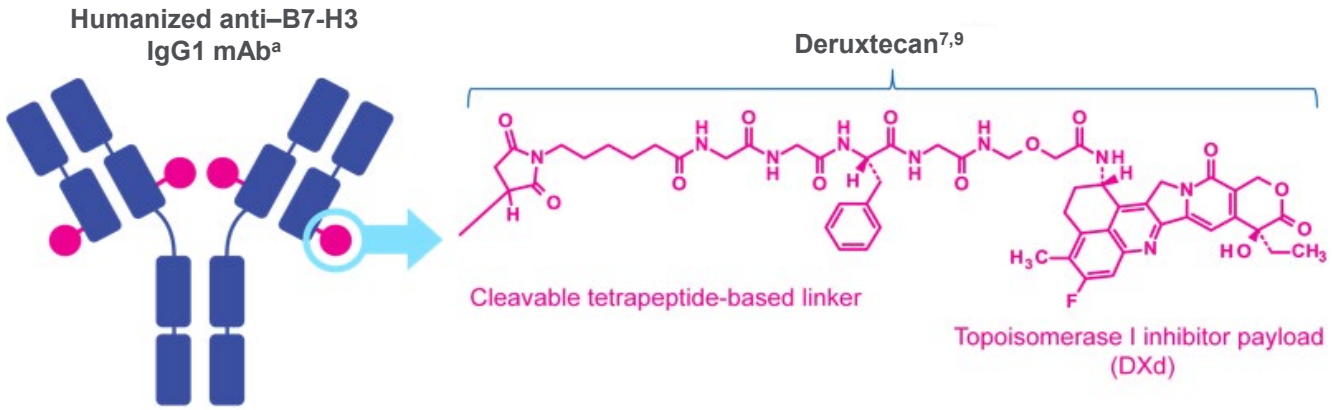
Ifinatamab Deruxtecan (I-DXd; DS-7300) Was Designed With 7 Key Attributes

- B7-H3 is overexpressed in a wide range of cancer types and is associated with disease progression and lower survival[1–5]
- I-DXd is a B7-H3 (CD276)-directed ADC composed of 3 parts:[6–9,11]
  - A humanized anti–B7-H3 IgG1 monoclonal antibody[9,11]
  - A topoisomerase I inhibitor payload (an exatecan derivative, DXd)
  - A tetrapeptide-based cleavable linker that covalently bonds the other 2 components

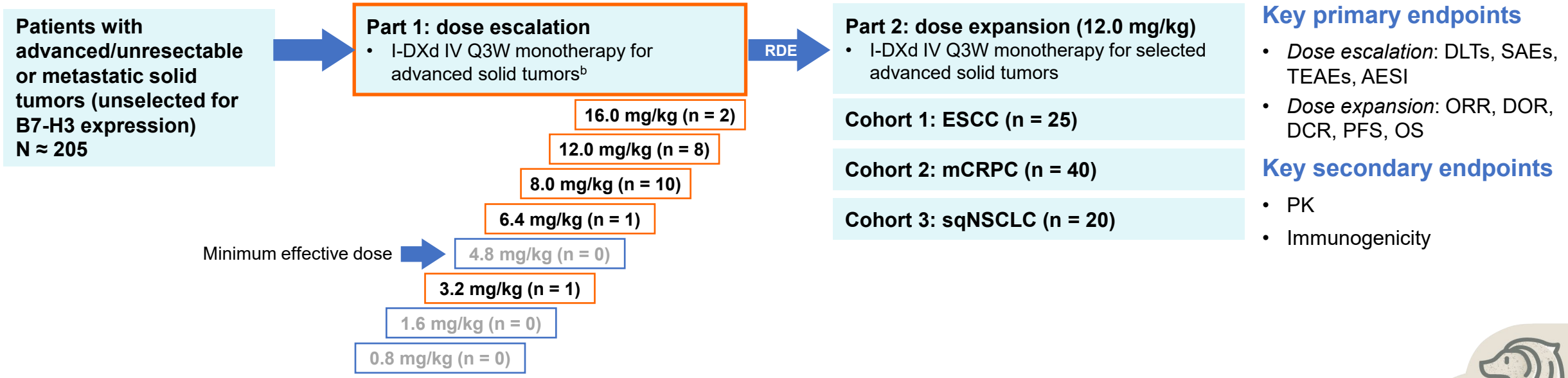


Payload mechanism of action: topoisomerase I inhibitor[7,9,11,b]
High potency of payload[9,11,b]
Optimized drug-to-antibody ratio ≈ 4[6–8,10,b]
Payload with short systemic half-life[9,11,b,c]
Stable linker-payload[9,11,b]
Tumor-selective cleavable linker[9,11,b]
Bystander antitumor effect[7,10,11,b]

[a]Image is for illustrative purposes only; actual drug positions may vary. [b]The clinical relevance of these features is under investigation. [c]Based on animal data.
ADC, antibody–drug conjugate; B7-H3, B7 homolog 3; CD276, cluster of differentiation 276; DXd, deruxtecan; IgG1, immunoglobulin G1; mAb, monoclonal antibody.
1. Yamato M, et al. AACR-NCI-EORTC 2020. Abstract 28. 2. Dong P, et al. *Front Oncol*. 2018;8:264. 3. Picarda E, et al. *Clin Cancer Res*. 2016;22(14):3425–3431. 4. Bendell JC, et al. *J Clin Oncol*. 2020;39(15 suppl 1). Abstract TPS3646.
5. Kontos F, et al. *Clin Cancer Res*. 2021;27(5):1227–1235. 6. Okajima D, et al. *Mol Cancer Ther*. 2021;20(12):2329–2340. 7. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173–185. 8. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097–5108.
9. Yamato M, et al. *Mol Cancer Ther*. 2022;21(4):635–646.10. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039–1046. 11. Daiichi Sankyo. Data on file.

DS7300-A-J101 Study Design (NCT04145622)

- I-DXd is generally well tolerated with early signs of antitumor activity[1,2]
- **We present a subgroup analysis of patients with SCLC (N = 22[a]) from part 1 treated with I-DXd at all doses studied**
  - Patients dosed at ≥6.4 mg/kg (n = 21) were evaluable for efficacy
  - Baseline tumor biopsies were retrospectively examined for B7-H3 protein level by IHC and used for correlative analysis in biomarker-evaluable patients dosed at ≥6.4 mg/kg (n = 17)



Key primary endpoints

- *Dose escalation*: DLTs, SAEs, TEAEs, AESI
- *Dose expansion*: ORR, DOR, DCR, PFS, OS

Key secondary endpoints

- PK
- Immunogenicity

[a]Number of patients with SCLC in parentheses of each dose cohort. [b]Tumor types included advanced/unresectable or metastatic HNSCC, ESCC, mCRPC, sqNSCLC, SCLC, bladder cancer, sarcoma, endometrial cancer, melanoma, and breast cancer. AESI, adverse event of special interest; B7-H3, B7 homolog 3; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ESCC, esophageal squamous cell carcinoma; IHC, immunohistochemistry; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; RDE, recommended dose for expansion; SAE, serious adverse event;; SCLC, small cell lung cancer; sqNSCLC, squamous non-small cell lung cancer; TEAE, treatment-emergent adverse event. 1. Johnson ML, et al. ESMO. 2021. Abstract 513O. 2. Doi T, et al. ESMO. 2022. Abstract 453O.

Patient Demographics and Baseline Characteristics

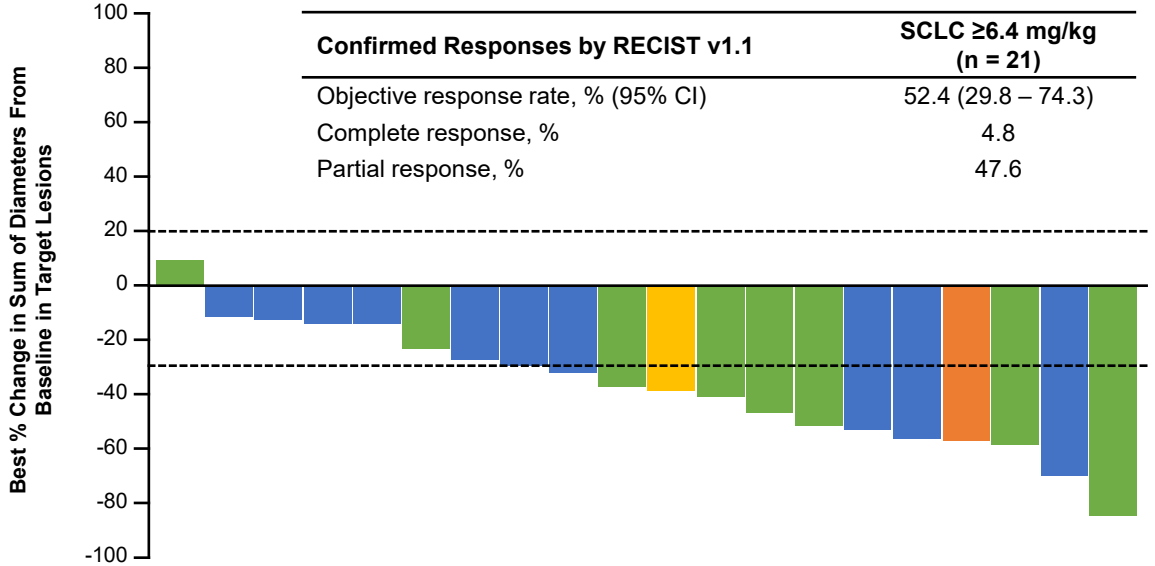
- As of 31 January 2023, 22 patients with SCLC received I-DXd at doses of 3.2 mg/kg to 16.0 mg/kg

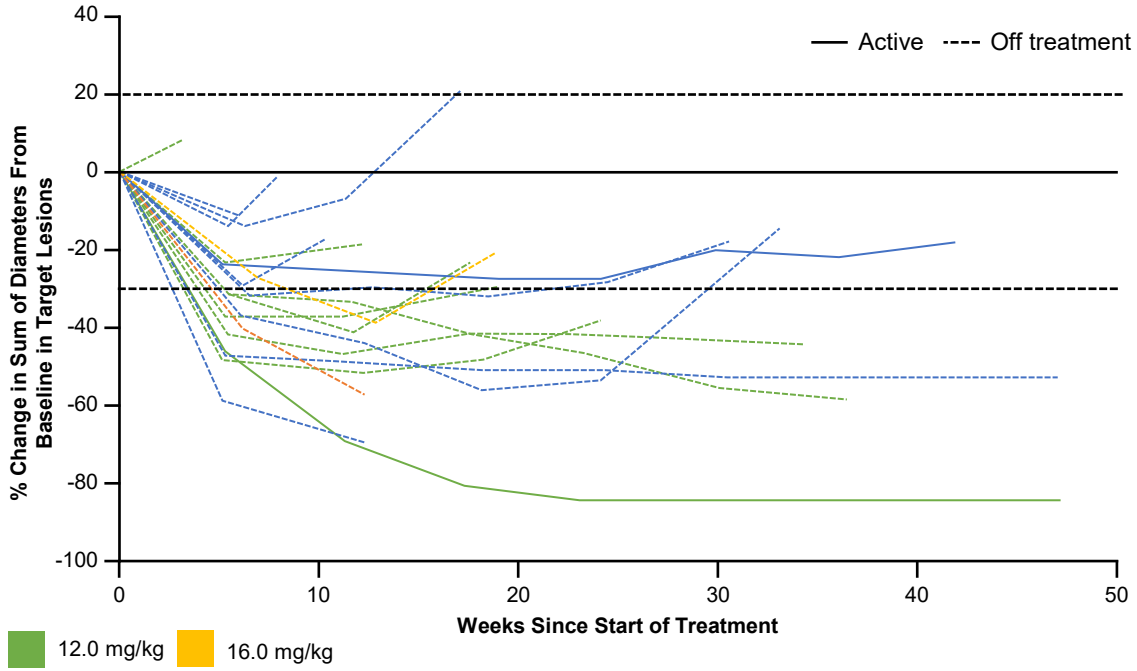
Patient or Disease Characteristic	SCLC (N = 22)
Age, median (range)	61 (40 – 84)
Male, n (%)	14 (63.6)
ECOG PS, n (%)	
0	7 (31.8)
1	15 (68.2)
Brain metastasis at baseline, n (%)	2 (9.1)
Number of prior systemic regimens, median (range)	2 (1 – 7)
Prior anticancer therapy received, n (%)	
Platinum-based chemotherapy	22 (100)
Immuno-oncology	18 (81.8)
Taxane	5 (22.7)
Irinotecan or topotecan	5 (22.7)[a]
Region of enrollment, n (%)	
United States	17 (77.3)
Japan	5 (22.7)

[a]1 patient received both.
ECOG PS, Eastern Cooperative Oncology Group performance status; SCLC, small cell lung cancer.

Antitumor Activity[a]

Confirmed Responses by RECIST v1.1	SCLC ≥6.4 mg/kg (n = 21)
Objective response rate, % (95% CI)	52.4 (29.8 – 74.3)
Complete response, %	4.8
Partial response, %	47.6





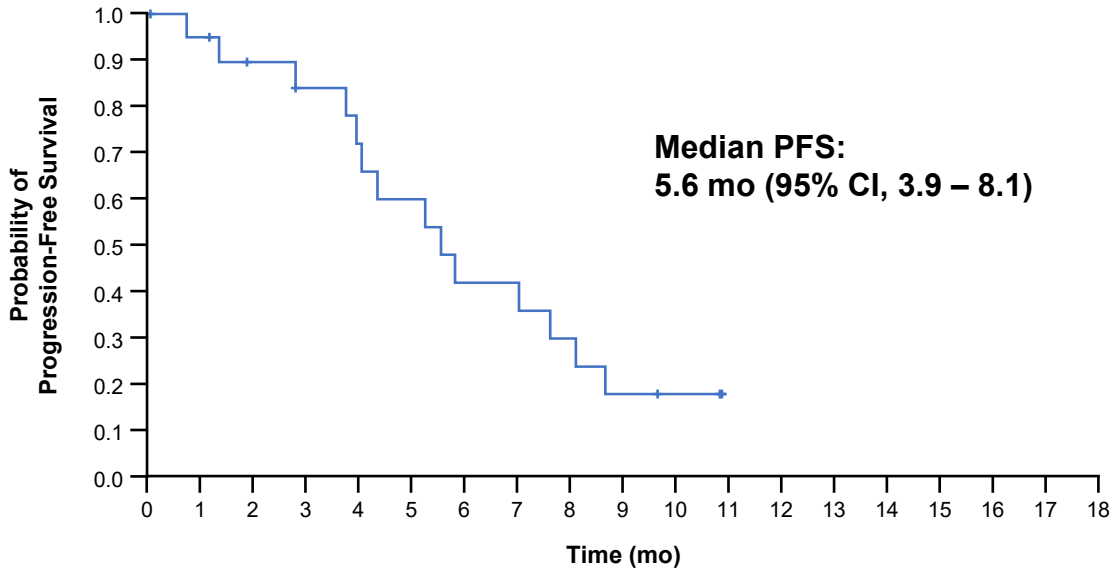
Starting Dose Level: 6.4 mg/kg; 8.0 mg/kg; 12.0 mg/kg; 16.0 mg/kg

- Nearly all patients with post-baseline scans had a reduction in target lesions
- Median time to response was 1.2 months (95% CI, 1.2 – 1.4)
- Median duration of response was 5.9 months (95% CI, 2.8 – 7.5); two patients remain on treatment
- Median follow-up was 11.7 months (95% CI, 4.63 – 12.88)

Data cutoff: January 31, 2023.
[a]Patients with SCLC from dose-escalation with measurable disease at baseline and ≥2 post-baseline tumor scans and/or discontinued the treatment at data cutoff are included in best overall response calculations.
1 patient did not have post-baseline tumor scans and is not included in the waterfall or spider plots.
CI, confidence interval; RECIST, Response Evaluation Criteria in Solid Tumors; SCLC, small cell lung cancer.

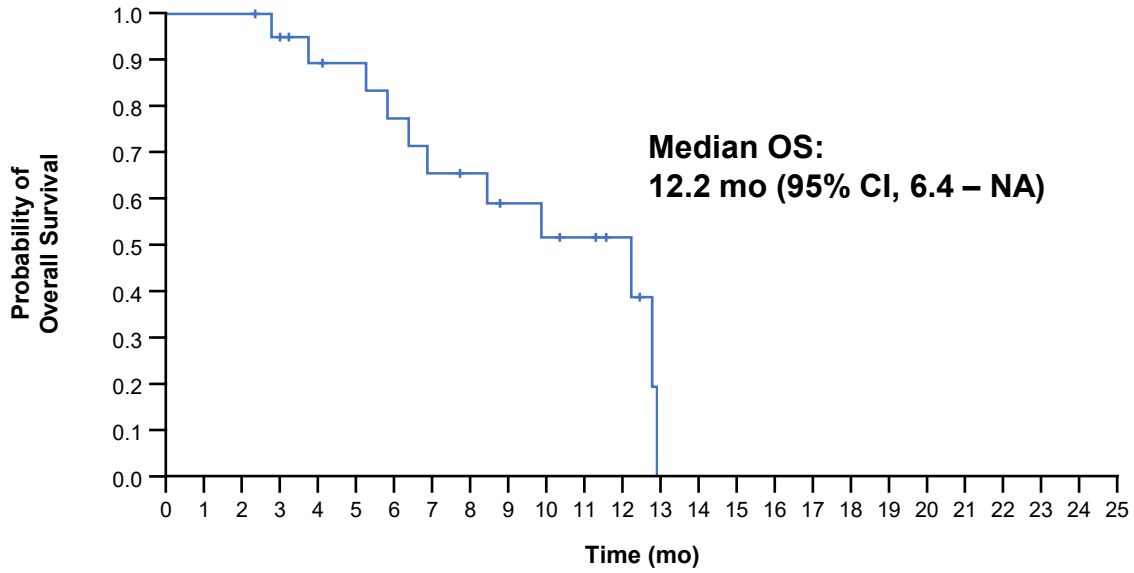
Progression-Free and Overall Survival

Progression-Free Survival — **SCLC ≥6.4 mg/kg (n = 21)**



Number of Patients at Risk:	21	19	16	14	12	10	7	7	5	3	2	0	0	0	0	0	0	0	0

Overall Survival — **SCLC ≥6.4 mg/kg (n = 21)**



Number of Patients at Risk:	21	21	21	18	16	15	13	11	10	8	7	6	4	0	0	0	0	0	0	0	0	0	0	0	0	0

Data cutoff: January 31, 2023.
CI, confidence interval; NA, not applicable; mo, months; OS, overall survival; PFS, progression-free survival; SCLC, small cell lung cancer.

Safety Summary

	SCLC (N = 22)
Treatment duration, median (range), months	3.9 (0.03 – 12.5)
Median cycles, number (range)	6.5 (1.0 – 18.0)
Any TEAE, n (%)	22 (100)
TEAE with CTCAE Gr ≥3, n (%)	8 (36.4)
TEAE associated with drug discontinuation, n (%)	5 (22.7)
TEAE associated with dose delay, n (%)	3 (13.6)
TEAE associated with dose reduction, n (%)	3 (13.6)
TEAE associated with death, n (%)	1 (4.5)[a]

- The safety profile is consistent with previous reports in overall population[1,2]
- Five patients discontinued treatment due to TEAEs, including one patient each with ILD (Gr 1, 8.0 mg/kg), pneumonitis (Gr 2, 8.0 mg/kg), cardiac failure (Gr 3, 16.0 mg/kg), embolism (Gr 3, 8.0 mg/kg) and COVID-19 pneumonia[a] (Gr 5, 12.0 mg/kg)

Data cutoff: January 31, 2023.
[a]Grade 5 COVID-19 pneumonia that was determined not to be treatment-related.
COVID-19, coronavirus disease 2019; CTCAE, Common Terminology Criteria for Adverse Events; Gr, grade; ILD, interstitial lung disease; SCLC, small cell lung cancer; TEAE, treatment-emergent adverse event.
1. Johnson ML, et al. ESMO. 2021. Abstract 513O. 2. Doi T, et al. ESMO. 2022. Abstract 453O.

Most Common (≥10%) All-Grade TEAEs Regardless of Causality

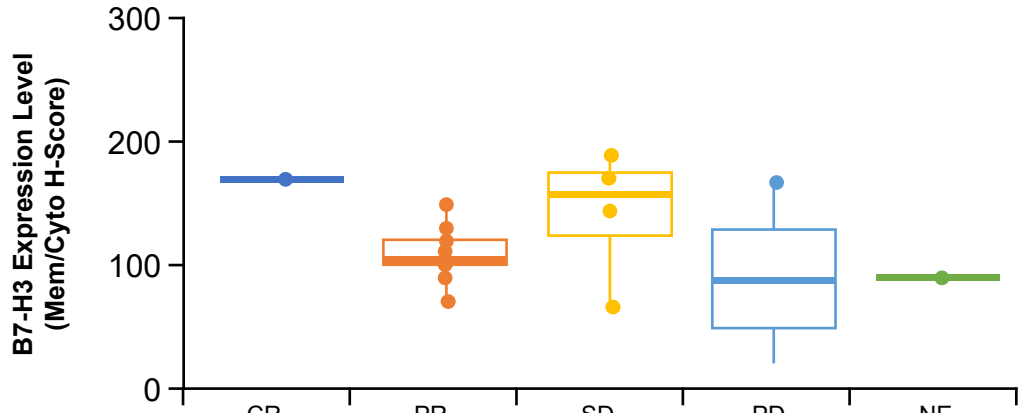
System Organ Class Preferred Term, n (%)	SCLC (N = 22)	
	Any Grade	Grade ≥3
Nausea	13 (59.1)	1 (4.5)
Fatigue	11 (50.0)	0 (0.0)
Anemia	6 (27.3)	1 (4.5)
Vomiting	6 (27.3)	0 (0.0)
Decreased appetite	5 (22.7)	1 (4.5)
Pyrexia	4 (18.2)	0 (0.0)
Constipation	4 (18.2)	1 (4.5)
IRR	3 (13.6)	0 (0.0)
Diarrhea	3 (13.6)	0 (0.0)
Dehydration	3 (13.6)	0 (0.0)
Dyspnea	3 (13.6)	0 (0.0)
Platelet count decreased	3 (13.6)	0 (0.0)
Arthralgia	3 (13.6)	0 (0.0)
Hyponatremia	3 (13.6)	0 (0.0)

- A total of three patients (13.6%) experienced an ILD or pneumonitis event (two Gr 1, one Gr 2)
  - All events were adjudicated by the ILD adjudication committee, of which one was adjudicated as drug-related ILD (Gr 2, 8.0 mg/kg) and discontinued treatment per protocol[a]
- Prophylactic premedication for nausea, vomiting, and IRR were not permitted for primary prophylaxis during cycle 1 of dose escalation

Data cutoff: January 31, 2023.
[a]Outcome was reported as "not recovered" for two events (Gr 1, Gr 2) and "recovered" for one event (Gr 1).
Gr, grade; ILD, interstitial lung disease; IRR, infusion-related reaction; SCLC, small cell lung cancer; TEAE, treatment-emergent adverse event.

B7-H3 Correlative Results for SCLC Cohort[a]

B7-H3 Level by BOR Status for Evaluable Patients



	CR	PR	SD	PD	NE
	n = 1	n = 9	n = 4	n = 2	n = 1
Median H-Score	170	105	157.5	89	90
H-Score Range	170	70 – 150	66 – 190	10 – 168	90

Efficacy Parameters by Median B7-H3 Level (n = 17)

B7-H3 mem/cyto H-Score at Baseline, Median (Range)	115 (10 – 190)

	B7-H3 Parameters	
	< median (n = 8)	**≥ median (n = 9)**
H-Score Range	10 – 105	115 – 190
Objective Response Rate	62.5%	55.6%
Median PFS, mo (95% CI)	5.8 (0.7 – NA)	5.3 (1.4 – NA)
Median OS, mo (95% CI)	12.2 (5.8 – NA)	6.9 (2.8 – NA)

- No trend of correlation of B7-H3 combined membrane/cytosol H-score with BOR, PFS, or OS was observed
- The correlative relationship between B7-H3 level and clinical efficacy will be further evaluated in future I-DXd studies

Data cutoff: January 31, 2023.
[a]SCLC tumor cell biopsy samples were retrospectively examined for B7-H3 protein level by IHC in biomarker-evaluable patients dosed at ≥6.4 mg/kg (n = 17). H-score of the combined membrane/cytosol staining was used for the correlative analysis to reflect the unique staining pattern of B7-H3 in SCLC tumor cells.
B7-H3, B7-homolog 3; BOR, best overall response; CI, confidence interval; CR, complete response; cyto, cytosol; IHC, immunohistochemistry; mem, membrane; NA, not applicable; NE, non-evaluable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response, SCLC, small cell lung cancer; SD, stable disease.

Conclusions

- I-DXd, a novel B7-H3–directed DXd-ADC, continues to demonstrate robust and durable efficacy in patients with heavily pretreated SCLC
  - Including 52% ORR, 5.9 months mDOR, 5.6 months mPFS, and 12.2 months mOS
- I-DXd was generally well tolerated; no new safety signals were observed, and the safety profile was consistent with previous reports[1,2]
  - Nausea was the most common TEAE, and antiemetic prophylaxis is now required for all I-DXd studies
- No apparent trend of correlation was observed between B7-H3 level and clinical efficacy parameters in the SCLC cohort
- These data support further clinical development of I-DXd, including a phase 2 study of patients with extensive stage SCLC following 1 – 3 prior lines of therapy (IDeate-1; NCT05280470)
  - TiP Poster #1561 at this meeting describes the design of this study

ADC, antibody–drug conjugate; B7-H3, B7 homolog 3; DXd, deruxtecan; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; SCLC, small cell lung cancer; TEAE, treatment-emergent adverse event; TiP, trial in progress.

1. Johnson ML, et al. ESMO. 2021. Abstract 513O. 2. Doi T, et al. ESMO. 2022. Abstract 453O.

Acknowledgments

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