Exposure–response analyses to support Phase 3 dose selection for ifinatamab deruxtecan (I-DXd) in patients with ES-SCLC

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OBJECTIVES

The objectives of this exposure–response (ER) analysis were to evaluate:

- Exposure–safety (ES) relationships in patients with advanced solid tumors (tumor agnostic)
- Exposure–efficacy (EE) relationships in patients with ES-SCLC
- Dose–response projections to support Phase 3 dose selection

CONCLUSIONS

- ES analyses identified a statistically significant relationship between exposure and 9 out of 11 safety endpoints that occurred at a rate of >10% (any-grade GI disorders; any Grade ≥3 TEAE; any serious TEAE; any-grade anemia; Grade ≥3 anemia; drug interruption; dose reduction; any-grade neutropenia; any-grade thrombocytopenia)
- EE analyses found a statistically significant relationship between I-DXd exposure and ORR, and between I-DXd exposure and BTR (best percentage change from baseline in sum of longest diameters of target lesions)
- EE analyses projected higher efficacy with increasing dose of I-DXd; both the 8 mg/kg and the 12 mg/kg doses showed manageable safety profiles
- Based on the overall risk–benefit assessment and ER analyses, I-DXd at 12 mg/kg IV Q3W was selected as the recommended dose for the extension part of the IDeate-Lung01 study and for the Phase 3, IDeate-Lung02 study

INTRODUCTION

- Ifinatamab deruxtecan (I-DXd) is an antibody–drug conjugate made up of 3 components: a humanized anti–B7-H3 immunoglobulin G1 monoclonal antibody, covalently linked to a potent topoisomerase I inhibitor payload via a stable tetrapeptide-based cleavable linker
- I-DXd showed promising efficacy at doses of ≥6.4 mg/kg in heavily pretreated patients with ES-SCLC in the ongoing Phase 1/2 IDeate-PanTumor01 study (NCT04145622)[1]
- I-DXd is also under clinical investigation in patients with ES-SCLC in the ongoing Phase 2 IDeate-Lung01 study (NCT05280470)[2] and Phase 3 IDeate-Lung02 study (NCT06203210)[3]

METHODS

- Baseline characteristics of the patient population included in the analyses are presented (**Table 1**)
- ER analyses were conducted with interim data when all patients (n=88) in Part 1 of the IDeate-Lung01 study had completed a minimum of 12 months of follow-up after the first dose

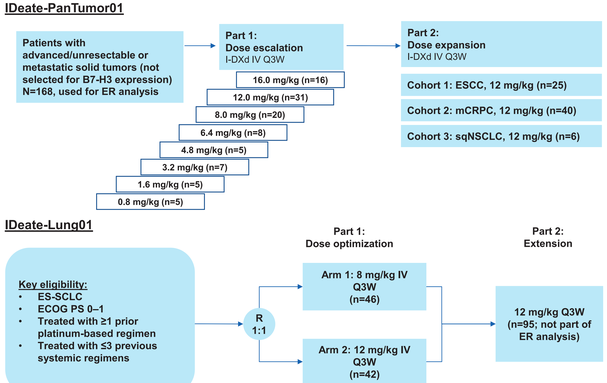
Endpoints prespecified in the analysis plan for ER analysis

- Safety endpoints (total 19):
  - Events with >10% rate (total 11): any-grade GI disorders; any Grade ≥3 TEAE; any serious TEAE; any-grade anemia; Grade ≥3 anemia; drug interruption (including dose delays); dose reduction; any-grade neutropenia; any-grade IRRs; any-grade thrombocytopenia; and any-grade decrease in LVEF
  - Events with <10% rate (total 8): Grade ≥3 GI disorders; Grade ≥3 neutropenia; Grade ≥3 thrombocytopenia; Grade ≥3 decrease in LVEF; any-grade ILD; Grade ≥3 ILD; Grade ≥3 IRR; and drug discontinuation – not included in the analyses
- Efficacy endpoints: ORR, BTR, DCR, PFS, DOR assessed by BICR per RECIST 1.1, and OS

Covariates prespecified in the analysis plan for ER analysis

- Age, sex, ECOG PS, race, geographic region, race-country, baseline B7-H3 membrane H-score (ES analysis), baseline B7-H3 membrane and cytoplasm H-score (EE analysis), prior anti-PD-(L)-1 therapy, tumor type, and line of therapy

Figure 1: Designs of studies used in ER analyses



IDeate-Lung01 stratification factors (Part 1): Prior anti-PD-(L)-1 therapy (yes or no), line of therapy (2nd line CTFI <90 days, 2nd line CTFI ≥90 days, 3L or 4L)

Table 1: Selected patient baseline characteristics

		ES population (N=256)		EE population (N=110)
		IDeate-PanTumor01 n=168	IDeate-Lung01 n=88	IDeate-PanTumor01 (n=22) + IDeate-Lung01 (n=88)
Weight (kg)	Median (range)	75.3 (42.8, 144)	70.5 (38.7, 121)	71.0 (38.7, 121)
Age (years)	Median (range)	66 (35, 84)	64 (34, 85)	64 (34, 85)
Sex	Male, n (%)	139 (82.7)	63 (71.6)	77 (70.0)
	Female, n (%)	29 (17.3)	25 (28.4)	33 (30.0)
ECOG PS	0, n (%)	65 (38.7)	19 (21.6)	26 (23.6)
	1, n (%)	103 (61.3)	69 (78.4)	84 (76.4)
Geographic region	Asian from Japan, n (%)	56 (33.3)	18 (20.5)	23 (23.9)
	Asian from China, n (%)	0	10 (11.4)	10 (9.1)
	Asian not from Japan/China, n (%)	1 (0.6)	22 (25.0)	22 (20.0)
	Non-Asian, n (%)	111 (66.1)	38 (43.2)	55 (50.0)
Tumor type	SCLC, n (%)	22 (13.1)	88 (100)	110 (100)
	mCRPC, n (%)	75 (44.6)	0	0
	ESCC, n (%)	29 (17.3)	0	0
	sqNSCLC, n (%)	12 (7.1)	0	0
	Other, n (%)	30 (17.9)	0	0
Prior lines of therapy	1 line (CTFI is missing), n (%)	5 (3.0)	0	0
	1 line, CTFI <90 days, n (%)	8 (4.8)	16 (18.2)	20 (18.2)
	1 line, CTFI ≥90 days, n (%)	1 (0.6)	9 (10.2)	9 (8.2)
	2–3 lines, n (%)	45 (26.8)	63 (71.6)	72 (65.5)
	≥4 lines, n (%)	102 (60.7)	0	5 (4.5)
	Missing, n (%)	7 (4.2)	0	4 (3.6)
Prior anti-PD-(L)-1 therapy	Yes, n (%)	104 (61.9)	67 (76.1)	87 (79.1)
	No, n (%)	64 (38.1)	18 (20.5)	18 (16.4)
	Missing, n (%)	0	3 (3.4)	5 (4.5)

RESULTS

Exposure–Safety Relationships

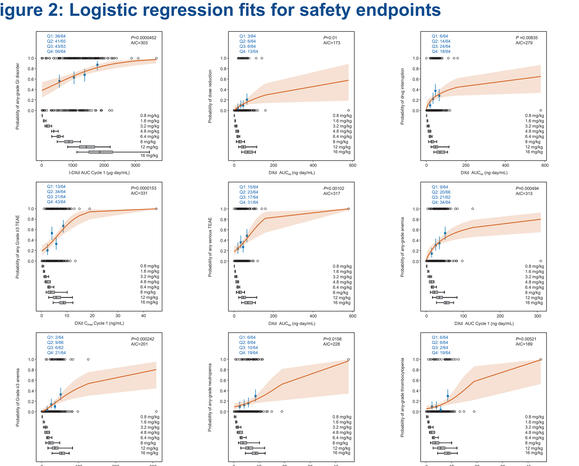
- Individual exposures (C_{max} Cycle 1, AUC Cycle 1, AUC_{ss}, C_{avg} at time of event [$C_{avg\ toe}$]) for I-DXd and DXd were derived using a population PK model based on the same patients' PK data
- Exploratory boxplots and univariate logistic regression were performed to investigate ES relationships, and only one exposure metric for each corresponding endpoint (**Figure 2**) was carried forward to perform multivariate analysis
- The single exposure metric was chosen based on low p-value and low Akaike information criterion. Pharmacological plausibility and experience with other ADCs with the same payload were also considered when choosing the exposure metric
- Significant ES relationships were identified for 9 of 11 selected safety endpoints that have observed event rates >10% (**Figure 2**). A summary of covariate effects is presented in **Table 2** and model-projected event rates for these endpoints are presented in **Figure 5**
- For ILD (preferred term: ILD/pneumonitis), the any-grade incidence rate was 7.8% (20/256), and the Grade ≥3 rate was 1.6% (4/256); ILD rates will be evaluated further when more mature data are available

Table 2: Summary of covariate effects on safety endpoints

Safety endpoint	Exposure variable	Significant covariates* (p<0.05)	Slope effect
Any-grade GI disorders	I-DXd Cycle 1 AUC	Tumor type not SCLC	+
Any Grade ≥3 TEAE	DXd Cycle 1 C_{max}	ECOG PS >0	+
Any serious TEAE	DXd AUC_{ss}	Age ≥64 years	+
Dose reduction	DXd AUC_{ss}	Age ≥64 years	+
Grade ≥3 anemia	DXd Cycle 1 AUC	Tumor type not SCLC	+

*Further evaluation is needed to confirm covariate effects once mature data are available from these studies.

Figure 2: Logistic regression fits for safety endpoints



Exposure–Efficacy Relationships

- A similar approach as in ES analysis was used to explore relationships between exposure (Cycle 1 AUC, $C_{min,ss}$, $C_{avg\ toe}$) and binary (ORR and DCR), continuous (BTR) or time-to-event (DOR, PFS, and OS) efficacy endpoints
- $C_{min,ss}$ was carried forward for covariate analysis and for event rate projections
- Significant EE relationships were identified for ORR and BTR (**Figures 3** and **4**). Model-projected ORR median event rates at 8 mg/kg and 12 mg/kg were 31.5% and 55.4% respectively (**Figure 5**). No covariates were identified to include in the model
- EE relationships for DCR, DOR, PFS and OS were not significant with current interim data and will be re-evaluated when more mature data are available

Figure 3: Logistic regression fits for ORR

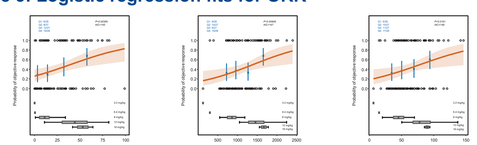


Figure 4: Linear regression fits for BTR

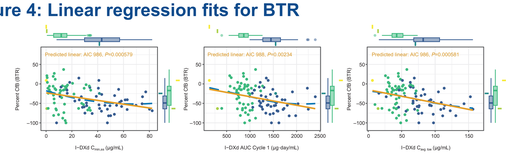
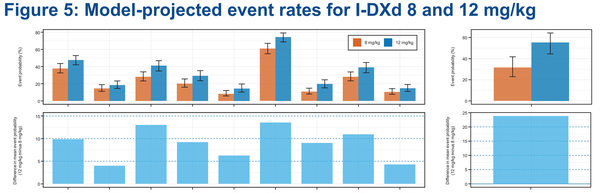


Figure 5: Model-projected event rates for I-DXd 8 and 12 mg/kg



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ABBREVIATIONS

ADC, antibody–drug conjugate; AIC, Akaike information criterion; AUC, area under the time–plasma concentration curve; AUC_{ss}, area under the time–plasma concentration curve at steady state; B7-H3, B7 homolog 3; BICR, blinded independent central reviews; BTR, best tumor response; $C_{avg\ toe}$, average plasma concentration at the time of event; CfB, change from baseline; C_{max}, maximum plasma concentration; $C_{min,ss}$, minimum plasma concentration at steady state; CTFI, chemotherapy-free interval; DCR, disease control rate; DOR, duration of response; DXd, deruxtecan; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EE, exposure–efficacy; ER, exposure–response; ES, exposure–safety; (ES-)SCLC, (extensive stage) small cell lung cancer; ESCC, esophageal squamous cell carcinoma; GI, gastrointestinal; I-DXd, ifinatamab deruxtecan; ILD, interstitial lung disease; IRR, infusion-related reaction; IV, intravenous; LVEF, left ventricular ejection fraction; mCRPC, metastatic castration-resistant prostate cancer; ORR, objective response rate; OS, overall survival; PD-(L)-1, programmed death (ligand)-1; PFS, progression-free survival; PK, pharmacokinetics; Q, quartile; Q3W, every 3 weeks; R, randomization; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; sqNSCLC, squamous non-small cell lung cancer; TEAE, treatment-emergent adverse event.

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