Poster #340

A Phase I Clinical Study to Evaluate the Safety, Tolerability, and Pharmacokinetic Characteristics of HLX43 (Anti-PD-L1 ADC) in Patients with Advanced/Metastatic Solid Tumors

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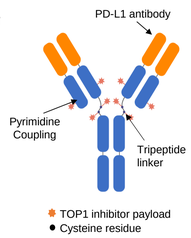
Background

- Programmed death-ligand 1 (PD-L1) is an immune checkpoint protein that is highly expressed in various tumor types but has limited expression in normal tissues, making it a promising target for antibody-drug conjugates (ADCs)[1].
- HLX43 is a novel ADC composed of an anti-PD-L1 antibody conjugated to topoisomerase 1 (TOP1) inhibitor payload via TMALIN® linker system, which enables both extracellular payload release within the tumor microenvironment and intracellular release upon ADC internalization[2].
- This study aimed to evaluate the safety, tolerability, and preliminary efficacy of HLX43 in patients with advanced/metastatic solid tumors.

Figure 1. Molecular components of HLX43



Key Features

- High PD-L1 binding affinity and internalizable humanized IgG1 with clinically proven safety
- Cleavable, tumor microenvironment-activatable tripeptide linker with high stability in circulation
- TOP1 inhibitor payload with high potency, short half-life and strong bystander killing effects.
- Drug antibody ratio of 8

Methods

- This is an open-label, first-in-human phase 1 clinical trial (NCT06115642) to evaluate the safety and tolerability, pharmacokinetic characteristics, and preliminary efficacy of HLX43 in patients with advanced/metastatic solid tumors. This study includes two parts: phase 1a dose escalation and phase 1b dose expansion part (**Figure 2**).
- Tumor imaging by enhanced computed tomography or magnetic resonance imaging was scheduled at baseline, every 6 weeks for 48 weeks from the first dose, and every 9 weeks thereafter.

Figure 2. Study design

Key inclusion criteria

- Age ≥18 years
- ECOG PS 0 or 1.
- For phase 1a, histologically or cytologically confirmed advanced/metastatic malignant solid tumors
- For phase 1b, histologically or cytologically confirmed advanced/metastatic NSCLC refractory or not amenable to standard therapy.
- Measurable disease according to RECIST v1.1.

Phase 1a dose escalation cohorts

HLX43
4.0 mg/kg
3.0 mg/kg
2.5 mg/kg
2.0 mg/kg
1.0 mg/kg
0.5 mg/kg
IV, Q3W

N = 3–6 for each cohort

Primary endpoints

- Proportion of patients with DLT
- MTD

Phase 1b dose expansion cohorts

Cohort 1	Cohort 2	Cohort 3
HLX43 2.0 mg/kg IV, Q3W	HLX43 2.5 mg/kg IV, Q3W	HLX43 3.0 mg/kg IV, Q3W
N=20	N=20	N=20

Primary endpoints

- RP2D
- ORR as assessed by BICR per RECIST v1.1

BICR, blinded independent central review; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MTD, maximum tolerable dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase II dose.

Conclusions

- HLX43 was well tolerated with no new safety signals across different doses and exhibited encouraging preliminary efficacy in patients with advanced solid tumors, particularly those with NSCLC, who had failed standard therapies.
- Further investigation of HLX43 is warranted.

Results

- As of the data cut-off date Mar 28, 2025, a total of 21 patients were enrolled in phase 1a to receive HLX43 at 0.5 mg/kg (n = 3), 1.0 mg/kg (n = 3), 2.0 mg/kg (n = 3), 2.5 mg/kg (n = 3), 3.0 mg/kg (n = 3), or 4.0 mg/kg (n = 6).
- In phase 1b, 21 patients with NSCLC (15 [71.4%] had squamous type and 6 [28.6%] had nonsquamous type) were enrolled to receive HLX43 at 2.0 mg/kg; enrolment of patients into the 2.5 and 3.0 mg/kg dose groups is ongoing. Hence, only the data from the 2.0 mg/kg group is presented here.
- Median follow-up duration was 9.7 months and 7.0 months for the two respective groups. Baseline demographics and characteristics are shown in **Table 1**. All patients in phase 1b 2.0 mg/kg group received platinum-based treatment previously.
- Investigator-assessed ORR for the phase 1a cohorts was 36.8% (**Table 2**); 3/4 patients with thymic squamous cell carcinoma achieved partial response (ORR = 75%) (**Figure 3**). Investigator-assessed ORR for the phase 1b 2.0 mg/kg cohort was 38.1% (**Table 2**). ORR among the squamous NSCLC patients was 40.0%. Subgroup analysis of tumor response in the phase 1b 2.0 mg/kg cohort is presented in **Table 3**. Best percentage change from baseline in target lesion size is provided in **Figure 3**.
- Duration of treatment for the patients in phase 1a and phase 1b 2.0 mg/kg cohorts is presented in **Figure 4**.
- Median PFS was 4.2 months for the phase 1a cohorts and 5.4 months for phase 1b 2.0 mg/kg cohort. Median OS was 8.9 months and not reached, respectively (**Table 2**).
- The summary of treatment-emergent adverse events (TEAEs) is listed in **Table 4**. One patient in the 4.0 mg/kg group in phase 1a experienced DLTs of febrile neutropenia and white blood cell count decreased; the MTD was 4.0 mg/kg. All patients in the 4.0 mg/kg group had their dose reduced to 2.0 mg/kg in treatment cycle 2 or 3.
- The most common TEAEs are listed in **Table 5**.

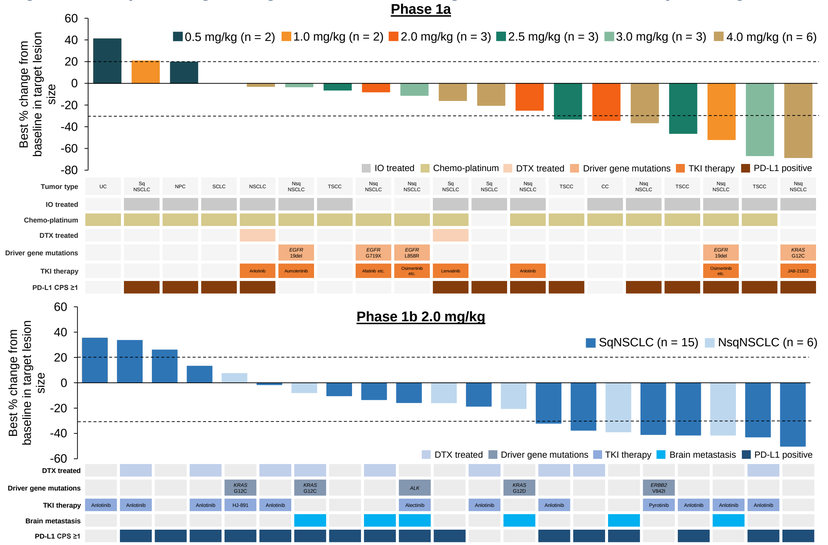
Table 1. Patient demographic and baseline characteristics

n (%)	Phase 1a (n = 21)	Phase 1b 2.0 mg/kg (n = 21)
Median age (range), years	52 (34–71)	56 (39–73)
Male	13 (61.9)	14 (66.7)
ECOG PS		
0	11 (52.4)	5 (23.8)
1	10 (47.6)	16 (76.2)
Prior anti-cancer therapy		
Chemotherapy+immunotherapy	16 (76.2)	16 (76.2)
Chemotherapy	11 (52.4)	11 (52.4)
Target therapy	10 (47.6)	9 (42.9)
Immunotherapy	6 (28.6)	5 (23.8)
Prior lines of therapy		
1	6 (28.6)	7 (33.3)
2	8 (38.1)	1 (4.8)
3	3 (14.3)	6 (28.6)
≥ 4	4 (19.0)	7 (33.3)
Median (range)	2.0 (1–6)	3.0 (1–7)

n (%)	Phase 1b 2.0 mg/kg (n = 21)
NSCLC subtype	
Squamous	15 (71.4)
EGFR wild type	100%
Nonsquamous	6 (28.6)
EGFR wild type	100%
Used docetaxel	
Yes	9 (42.9)
No	12 (57.1)
Brain metastasis	
Yes	6 (28.6)
No	15 (71.4)
Liver metastasis	
Yes	3 (14.3)
No	18 (85.7)
PD-L1 expression level*	
CPS ≥ 1	16 (76.2)
CPS < 1	5 (23.8)

*Detected with SP263. *CPS, combined positive score; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; MTD, maximum tolerable dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival, TEAE, treatment-emergent adverse event.*

Figure 3. Best percentage change from baseline in target lesion size assessed by investigator[a]



[a] In efficacy-evaluable patients. CC, cervical carcinoma; chemo, chemotherapy; CPS, combined positive score; DTX, docetaxel; EGFR, epidermal growth factor receptor; IO, immunotherapy; NPC, nasopharyngeal cancer; NSCLC, non-small cell lung cancer; nsqNSCLC, nonsquamous NSCLC; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; SCLC, small cell lung cancer; sqNSCLC, squamous NSCLC; TKI, tyrosine kinase inhibitor; TSCC, thymic squamous cell carcinoma; UC, uterine carcinosarcoma.

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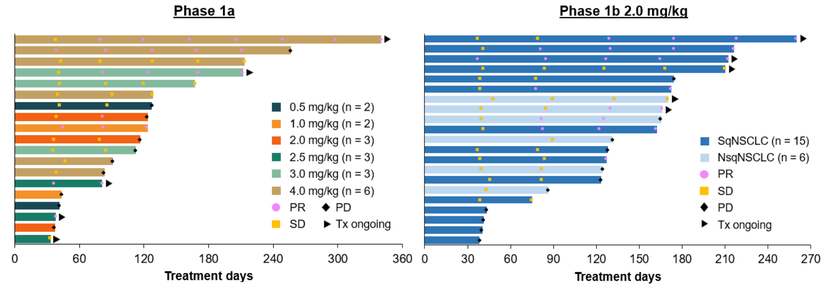
Figure 4. Swimmer plot of time to response and duration of study treatment[a]



[a] In efficacy-evaluable patients. nsqNSCLC, nonsquamous non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; sqNSCLC, squamous non-small cell lung cancer; Tx, treatment.

Table 2. Efficacy in efficacy-evaluable patients per RECIST v1.1[a]

	Phase 1a (n = 19)	Phase 1b 2.0 mg/kg (n = 21)
CR, n (%)	0	0
PR, n (%)	7 (36.8)	8 (38.1)
SD, n (%)	7 (36.8)	9 (42.9)
PD, n (%)	4 (21.1)	4 (19.0)
NE, n (%)	1 (5.3)	0
ORR, % (95% CI)	36.8 (16.3–61.6)	38.1 (18.1–61.6)
DCR, % (95% CI)	73.7 (48.8–90.9)	81.0 (58.1–94.6)
mDOR, months (95% CI)	7.2 (1.4–NE)	NR (1.4–NE)
mPFS, months (95% CI)	4.2 (2.7–8.4)	5.4 (4.0–6.3)
mOS, months (95% CI)	8.9 (6.0–NE)	NR (6.7–NE)

[a] Unconfirmed tumor response assessed by investigator. CI, confidence interval; CR, complete response; DCR, disease control rate; mDOR, median duration of response; mPFS, median progression-free survival; mOS, median overall survival; NE, not evaluable; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease.

Table 3. Subgroup analysis of tumor response in the phase 1b 2.0 mg/kg cohort per RECIST v1.1[a]

	ORR % (95% CI)	DCR % (95% CI)
NSCLC subtype		
Squamous (n = 15)	40.0 (16.3–67.7)	73.3 (44.9–92.2)
Nonsquamous (n = 6)	33.3 (4.3–77.7)	100 (54.1–100)
Used docetaxel		
Yes (n = 9)	33.3 (7.5–70.1)	77.8 (40.0–97.2)
No (n = 12)	41.7 (15.2–72.3)	83.3 (51.6–97.9)
Brain metastasis		
Yes (n = 6)	33.3 (4.3–77.7)	100 (54.1–100)
No (n = 15)	40.0 (16.3–67.7)	73.3 (44.9–92.2)
Liver metastasis		
Yes (n = 3)	33.3 (0.8–90.6)	66.7 (9.4–99.2)
No (n = 18)	38.9 (17.3–64.3)	83.3 (58.6–96.4)
PD-L1 expression		
CPS ≥ 1 (n = 16)	37.5 (15.2–64.6)	81.3 (54.4–96.0)
CPS < 1 (n = 5)	40.0 (5.3–85.3)	80.0 (28.4–99.5)

Table 4. Summary of adverse events

n (%)	Phase 1a (n = 21)	Phase 1b 2.0 mg/kg (n = 21)
Any TEAE	21 (100)	21 (100)
≥ Grade 3	10 (47.6)	11 (52.4)
≥ Grade 3 (≥ 10% in either group)		
Neutrophil count decreased	5 (23.8)	0
White blood cell count decreased	5 (23.8)	2 (9.5)
Anemia	3 (14.3)	3 (14.3)
Pneumonia	3 (14.3)	2 (9.5)
Lymphocyte count decreased	2 (9.5)	3 (14.3)
Serious	10 (47.6)	11 (52.4)
Any TRAE	20 (95.2)	21 (100)
≥ Grade 3	6 (28.6)	9 (42.9)
TEAE leading to Tx interruption	9 (42.9)	10 (47.6)
TEAE leading to Tx discontinuation	4 (19.0)	2 (9.5)
TEAE leading to dose reduction	8 (38.1)	0
TEAE leading to death	4 (19.0)	3 (14.3)

Table 5. Most common TEAEs (≥ 20%*)

n (%)	Phase 1a (n = 21)	Phase 1b 2.0 mg/kg (n = 21)
Anemia	16 (76.2)	16 (76.2)
Interleukin level increased	13 (61.9)	6 (28.6)
White blood cell count decreased	11 (52.4)	8 (38.1)
Neutrophil count decreased	10 (47.6)	8 (38.1)
Hyponatremia	10 (47.6)	7 (33.3)
Nausea	9 (42.9)	11 (52.4)
Hypoalbuminemia	9 (42.9)	8 (38.1)
Hyperuricemia	8 (38.1)	3 (14.3)
Aspartate aminotransferase increased	5 (23.8)	6 (28.6)
Lymphocyte count decreased	5 (23.8)	6 (28.6)
Hypochloremia	5 (23.8)	5 (23.8)
Constipation	4 (19.0)	7 (33.3)
Pneumonia	4 (19.0)	5 (23.8)
Decreased appetite	3 (14.3)	12 (57.1)
Vomiting	3 (14.3)	7 (33.3)
Hypertriglyceridemia	3 (14.3)	6 (28.6)
Alanine aminotransferase increased	2 (9.5)	6 (28.6)
Weight decreased	2 (9.5)	5 (23.8)
Proteinuria	1 (4.8)	5 (23.8)

≥20% in either group. TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; Tx, treatment.

References

1. O'Malley DP, et al. Mod Pathol. 2019;32(7):929-42.
2. Xue T, et al. Cancer Res 2024;84 (6_Supplement):4702.

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