A Phase 1 Study of Serplulimab (a Novel Anti-PD-1 Antibody) in Combination with HLX04 (an Anti-VEGF Antibody) in Patients with Advanced Solid Tumors

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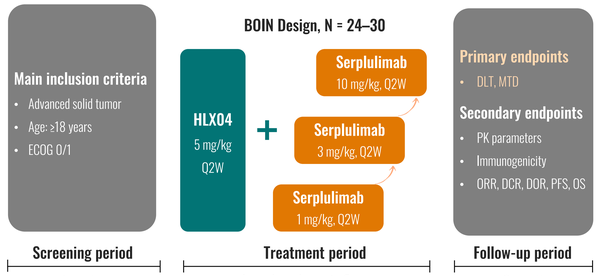
BACKGROUND

- According to GLOBOCAN 2020, 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020[1].
- In 2020, atezolizumab (anti-PD-L1) in combination with bevacizumab (anti-VEGF) was approved by FDA for the treatment of unresectable or metastatic hepatocellular carcinoma[2], suggesting that the combination of immune checkpoint inhibitors and angiogenesis inhibitors had synergistic anti-tumor effect.
- Serplulimab (HLX10, anti-PD-1) showed great efficacy in different types of tumors[3–4]. The New Drug Application (NDA) of serplulimab for the treatment of microsatellite instability-high (MSI-H) solid tumors and squamous non-small cell lung cancer were accepted by the National Medical Products Administration (NMPA) in April 2021 and September 2021, respectively[5].
- HLX04 (anti-VEGF), a biosimilar demonstrated to be highly similar to the reference bevacizumab[6–7], received NDA approval from the NMPA in December 2021[8].
- Here we report the safety results of the phase 1 study (NCT03757936, HLX10HLX04-001, serplulimab plus bevacizumab biosimilar HLX04).

METHODS

Figure 1. HLX10HLX04-001 study design



BOIN, Bayesian optimal interval; **DCR**, disease control rate; **DLT**, dose limiting toxicity; **DOR**, duration of response; **ECOG**, eastern cooperative oncology group; **MTD**, maximum tolerated dose; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **PK**, pharmacokinetics; **Q2W**, every two weeks;

- This open-label, dose-escalation phase 1 study aimed to determine the MTD and RP2D of serplulimab-HLX04 combination therapy in patients with advanced solid tumors who have failed standard therapy or had no standard of care. Safety, PK and efficacy were also evaluated.
- This study used BOIN design and the target toxicity was set as 30%. Eligible patients were enrolled to receive biweekly intravenous infusion of serplulimab and HLX04 at the assigned dose level in a 4-week cycle. DLT observation period was the first 4 weeks after the initial dose (Figure 1).

No DLT occurred in this study, demonstrating serplulimab-HLX04 combination therapy has manageable safety and tolerability profiles

Safety

Table 1. Summary of safety events

	Serplulimab 1 mg/kg HLX04 5 mg/kg (n=3)	Serplulimab 3 mg/kg HLX04 5 mg/kg (n=3)	Serplulimab 10 mg/kg HLX04 5 mg/kg (n=20)	Overall (N=26)
Any AE, n (%)	3 (100)	3 (100)	20 (100)	26 (100)
Any TEAE, n (%)	3 (100)	3 (100)	20 (100)	26 (100)
CTCAE grade 1	3 (100)	3 (100)	20 (100)	26 (100)
CTCAE grade 2	2 (66.7)	1 (33.3)	14 (70.0)	17 (65.4)
CTCAE grade 3	2 (66.7)	1 (33.3)	7 (35.0)	10 (38.5)
CTCAE grade ≥4	0	0	0	0
ADR, n (%)	3 (100)	3 (100)	18 (90.0)	24 (92.3)
SAE, n (%)	0	0	4 (20.0)	4 (15.4)
AEs leading to serplulimab or HLX04 discontinuation, n (%)	0	0	3 (15.0)	3 (11.5)
AEs leading to death, n (%)	0	0	0	0
DLT, n (%)	0	0	0	0

ADR, adverse drug reaction; **AE**, adverse event; **CTCAE**, Common Terminology Criteria for Adverse Events; **DLT**, dose limiting toxicity; **SAE**, serious AE; **TEAE**, treatment-emergent AE;

- All patients experienced TEAEs, most commonly proteinuria (50%), γ-glutamyltransferase increased (38.5%), alkaline phosphatase increased (34.6%) and amylase increased (30.8%).
- 10 (38.5%) patients experienced grade ≥3 TEAEs, most commonly hypertension (11.5%). Three patients (11.5%, all in serplulimab 10 mg/kg plus HLX04 5 mg/kg group) experienced TEAEs leading to drug discontinuation. No DLT or death due to TEAEs were reported.

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RESULTS

Demographics

- 26 eligible patients were enrolled and given at least one dose of serplulimab plus HLX04. All patients were included in the full analysis set, the safety set, and the pharmacokinetic analysis set.
- By December 3, 2020, 22 patients (84.6%) discontinued treatment mostly due to disease progression (11/22), patient withdrawal (7/22), and adverse events (3/22). 12 patients (46.2%) ended the study because of death (7/12), loss to follow-up (4/12), and patient withdrawal (1/12).
- Demographics and baseline characteristics are shown in Table 2.

Table 2. Demographics and baseline characteristics

Category		Serplulimab 1 mg/kg HLX04 5 mg/kg (n=3)	Serplulimab 3 mg/kg HLX04 5 mg/kg (n=3)	Serplulimab 10 mg/kg HLX04 5 mg/kg (n=20)	Overall (N=26)
Age, years	Mean (SD)	46.3 (13.3)	66.3 (11.0)	55.2 (8.9)	55.5 (10.4)
Race, n (%)	Asian	3 (100)	3 (100)	20 (100)	26 (100)
Sex, n (%)	Female	2 (66.7)	0	8 (40.0)	10 (38.5)
	Male	1 (33.3)	3 (100)	12 (60.0)	16 (61.5)
Primary lesion, n (%)	Colorectum	1 (33.3)	0	6 (30.0)	7 (26.9)
	Lung	0	0	4 (20.0)	4 (15.4)
	Pancreas	0	0	2 (10.0)	2 (7.7)
	Breast	1 (33.3)	0	1 (5.0)	2 (7.7)
	Other	1 (33.3)	3 (100)	7 (35.0)	11 (42.3)
TNM staging, n (%)	IV	3 (100)	3 (100)	20 (100)	26 (100)
Histological classification, n (%)	Adenocarcinoma	2 (66.7)	2 (66.7)	15 (75.0)	19 (73.1)
	HCC	0	0	1 (5.0)	1 (3.8)
	RCC	0	0	1 (5.0)	1 (3.8)
	Other	1 (33.3)	1 (33.3)	3 (15.0)	5 (19.2)
Treatment line, n (%)	First-line	0	0	1 (5.0)	1 (3.8)
Prior systemic therapies, n (%)	Oxaliplatin	1 (33.3)	2 (66.7)	7 (35.0)	10 (38.5)
	Irinotecan	1 (33.3)	0	8 (40.0)	9 (34.6)
	Capecitabine	2 (66.7)	0	6 (30.0)	8 (30.8)
	Bevacizumab	0	0	8 (40.0)	8 (30.8)
	Fluorouracil	1 (33.3)	1 (33.3)	5 (25.0)	7 (26.9)
	Tegafur	1 (33.3)	1 (33.3)	5 (25.0)	7 (26.9)

HCC, hepatocellular carcinoma; **RCC**, renal cell carcinoma; **SD**, standard deviation; **TNM**, TNM classification of malignant tumors;

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8. HLX04, NMPA approval

DISCLOSURES

- This study is sponsored by Shanghai Henlius Biotech, Inc.
- D. Peng, Q. Wang, and J. Zhu are employees of Shanghai Henlius Biotech, Inc. All other authors declare no conflict of interest.

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