Abstract 124: First-line serplulimab plus HLX04 and XELOX versus placebo plus bevacizumab and XELOX in metastatic colorectal cancer: A phase 2/3 study

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Background

- Colorectal cancer (CRC) is one of the most common malignant cancers globally. Over 1.9 million newly diagnosed cases and more than 900,000 deaths were estimated in 2020.[1]
- The standard of care for metastatic CRC (mCRC) involves the combination of vascular endothelial growth factor (VEGF) inhibitor, such as bevacizumab and systemic chemotherapy.[2-4] However, sustained efficacy and prognosis remains to be improved.
- Several PD-1 inhibitors were shown to confer significant survival benefits for advanced CRC patients with a deficient mismatch repair (dMMR)/microsatellite instability high (MSI-H) molecular phenotype.[5,6] However, the efficacy of adding immunotherapy to standard-of-care for proficient mismatch repair or microsatellite stable (pMMR/MSS) mCRC remains unclear.

Methods

- Here, we report the phase 2 part of our randomized, double-blind, phase 2/3 study that evaluates the efficacy of combining serplulimab and HLX04 plus chemotherapy versus bevacizumab plus chemotherapy as first-line treatment for mCRC (Figure 1).
- Serplulimab is a novel monoclonal antibody targeting PD-1; HLX04 is an approved biosimilar for bevacizumab. Eligible patients were randomized in a 1:1 ratio to receive serplulimab in combination with HLX04 and chemotherapy or placebo in combination with bevacizumab and chemotherapy.
- Tumor imaging by computed tomography or magnetic resonance imaging was scheduled at baseline, every 6 weeks for the first 48 weeks, and every 12 weeks thereafter. Tumor response was assessed by the IRRC and by investigators per RECIST v1.1.

Figure 1. Study design

Key inclusion criteria:

- Age 18–75 years; ECOG PS 0 or 1;
- Histopathologically confirmed unresectable metastatic/recurrent colorectal adenocarcinoma;
- Have not received any previous systemic anti-tumor drug treatment for metastatic/recurrent colorectal adenocarcinoma;
- At least one measurable lesion as assessed by the study site according to RECIST v1.1, which should not have received local treatment such as radiotherapy;

Group A Q3W
- Serplulimab[a], IV, 300 mg
- HLX04[a], IV, 7.5 mg/kg
- XELOX[b] (oxaliplatin[c]+capecitabine[a])

Group B Q3W
- Serplulimab placebo, IV, 300 mg
- Bevacizumab[a], IV, 7.5 mg/kg
- XELOX[b] (oxaliplatin[c]+capecitabine[a])

Primary endpoints:
PFS assessed by IRRC per RECIST v1.1

Secondary endpoints:
- OS
- PFS assessed by investigator
- ORR
- DCR
- Quality of life
- Safety
- Pharmacokinetics
- Immunogenicity
- Relation between PD-L1 and efficacy
- Biomarker explorations

[a] *Up to 2 years;* [b] *IV oxaliplatin + oral capecitabine;* [c] *Up to 8 cycles.*
DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IRRC, independent radiological review committee; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival; Q3W: every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Results

- Between July 16, 2021 and January 20, 2022, 114 patients (ITT) were enrolled and randomly assigned to group A (n = 57) or group B (n = 57), with a median age of 61.0 and 58.0 years, respectively. 44 (77.2%) patients in group A and 39 (68.4%) patients in group B were male.
- As of June 1, 2023 (data cutoff), median follow-up duration was 17.7 months.

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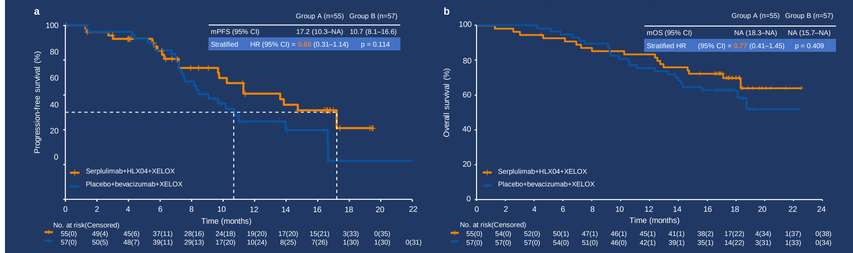
Serplulimab plus HLX04 and XELOX improved PFS and other efficacy endpoints compared to placebo plus bevacizumab and XELOX in patients with mCRC.

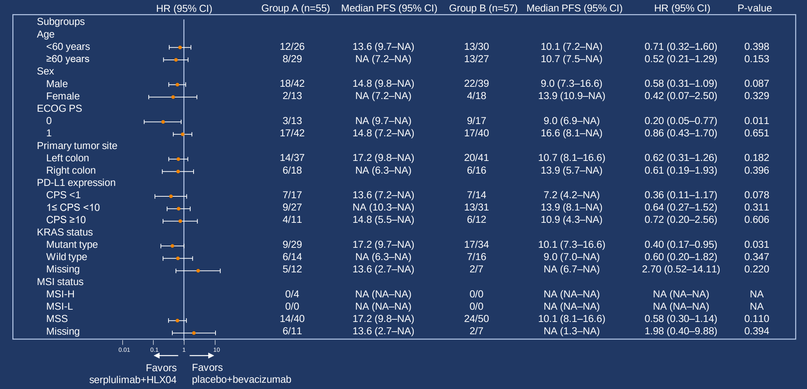
Efficacy

Figure 2. Kaplan–Meier curves of PFS as assessed by IRRC (a) and OS (b)[a]



[a] *Two patients in group A who did not receive any treatment were excluded.*
CI, confidence interval; HR, hazard ratio; IRRC, independent radiological review committee; m, median; NA, not available; PFS, progression-free survival; OS, overall survival; XELOX, oxaliplatin+capecitabine.

Figure 3. Forest plot analysis of progression-free survival as assessed by IRRC per RECIST v1.1[a]



[a] *Two patients in group A who did not receive any treatment were excluded.*
CI, confidence interval; HR, hazard ratio; IRRC, independent radiological review committee; NA, not available; PFS, progression-free survival.

Table 2. Tumor response[a,b] assessed by IRRC per RECIST v1.1

	Group A (n = 55)	Group B (n = 57)
ORR, % (95% CI)	**65.5 (51.4, 77.8)**	**66.7 (53.0, 78.6)**
DCR, % (95% CI)	**85.5 (73.3, 93.5)**	**84.2 (72.1, 92.5)**
CR, n (%)	1 (1.8)	2 (3.5)
PR, n (%)	35 (63.6)	36 (63.2)
Non-CR/Non-PD	1 (1.8)	1 (1.8)
SD, n (%)	11 (20.0)	10 (17.5)
PD, n (%)	2 (3.6)	2 (3.5)
NE, n (%)	5 (9.1)	6 (10.5)
DOR, months (95% CI)	15.9 (11.3–NA)	12.6 (5.8–15.3)
Stratified HR (95% CI) = 0.27 (0.10–0.74)		p = 0.007

- PFS benefit was observed with the serplulimab+HLX04+XELOX treatment in both the main and subgroup analysis.
- OS was not reached in both groups (HR=0.77).
- Tumor responses were similar between the two treatment groups.
- DOR was prolonged with the treatment of serplulimab+HLX04+XELOX.

[a] *Confirmed tumor response;* [b] *Two patients in group A who did not receive any treatment were excluded.*
CI, confidence interval; CR, complete response; DOR, duration of response; DCR, disease control rate; IRRC, independent radiological review committee, NA, not available; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

- Baseline demographics and characteristics of group A and group B are shown in Table 1.

Table 1. Patient demographics and baseline characteristics

	Group A (n = 57)	Group B (n = 57)
Median age (range), years	61.0 (25–74)	58.0 (26–73)
Male, n (%)	44 (77.2)	39 (68.4)
Race, Asian, n (%)	57 (100)	57 (100)
ECOG PS, n (%)		
0	13 (22.8)	17 (29.8)
1	44 (77.2)	40 (70.2)
Primary tumor site, n (%)		
Left colon	39 (68.4)	41 (71.9)
Right colon	18 (31.6)	16 (28.1)
Stage at study entry, n (%)		
IVA	19 (33.3)	20 (35.1)
IVB	27 (47.4)	24 (42.1)
IVC	11 (19.3)	13 (22.8)
PD-L1 expression, n (%)		
CPS < 1	17 (29.8)	14 (24.6)
1 ≤ CPS < 50	39 (68.4)	43 (75.4)
CPS ≥ 50	1 (1.8)	0
MSI status, n (%)		
MSI-H	4 (7.0)	0
MSI-L	0	0
MSS	40 (70.2)	50 (87.7)
Missing	13 (22.8)	7 (12.3)
KRAS mutation, n (%)		
Wild type	14 (24.6)	16 (28.1)
Mutant type	29 (50.9)	34 (59.6)
Missing	14 (24.6)	7 (12.3)

Safety

- TEAEs occurred in all of the patients in both groups (Table 3), most commonly anemia, platelet count decreased, neutrophil count decreased, white blood cell decreased, increased aspartate aminotransferase, decreased appetite, and nausea (Table 4).
- The incidences of Grade ≥ 3 TEAEs and TRAEs were similar between the two treatment groups. Grade ≥ 3 TEAEs related to serplulimab/placebo occurred in 41.8% of the patients in group A, and 33.3% of the patients in group B, most commonly neutrophil count decreased, platelet count decreased, and white blood cell count decreased.
- Treatment-related deaths occurred in 4 (7.3%) patients in group A, and 3 (5.3%) patients in group B.

Table 3. Summary of adverse events

n (%)	Group A[a] (n = 55)	Group B (n = 57)
Any TEAEs	55 (100.0)	57 (100.0)
Grade ≥3	39 (70.9)	38 (66.7)
Grade 5	7 (12.7)	7 (12.3)
Leading to Tx discontinuation	14 (25.5)	12 (21.1)
AESIs	34 (61.8)	32 (56.1)
IRR	8 (14.5)	7 (12.3)
irAEs	15 (27.3)	13 (22.8)
AESI for HLX04/bevacizumab	25 (45.5)	19 (33.3)
Any TRAEs	54 (98.2)	57 (100.0)
Grade ≥ 3	36 (65.5)	32 (56.1)
Grade 5	4 (7.3)	3 (5.3)
Related to serplulimab/placebo	47 (85.5)	53 (93.0)
Grade ≥3	23 (41.8)	19 (33.3)
Related to HLX04/bevacizumab	51 (92.7)	51 (89.5)
Grade ≥3	24 (43.6)	19 (33.3)

Table 4. Most common TEAEs (≥ 30%)[b]

n (%)	Group A[a] (n = 55)	Group B (n = 57)
Anemia	39 (70.9)	36 (63.2)
Platelet count decreased	33 (60.0)	31 (54.4)
Neutrophil count decreased	30 (54.5)	22 (38.6)
White blood cell count decreased	26 (47.3)	21 (36.8)
AST increased	25 (45.5)	31 (54.4)
Decreased appetite	23 (41.8)	24 (42.1)
Nausea	22 (40.0)	28 (49.1)
ALT increased	21 (38.2)	22 (38.6)
Proteinuria	21 (38.2)	18 (31.6)
Vomiting	19 (34.5)	21 (36.8)
Diarrhea	19 (34.5)	18 (31.6)
Hypoalbuminemia	19 (34.5)	26 (45.6)
Blood bilirubin increased	17 (30.9)	21 (36.8)

[a] *Two patients in group A who did not receive any treatment were excluded;* [b] ≥ 30% in either group.
AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; irAE, immune-related adverse event; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; Tx, treatment.

Acknowledgments and Disclosures

- The authors would like to acknowledge the participants in this study and their families, the investigators and staff at all clinical sites and the members of the Independent Data Monitoring Committee.
- This study was funded by Shanghai Henlius Biotech, Inc. Editorial support was provided by Zhi Hao Kwok and Chen Hu from Shanghai Henlius Biotech, Inc.
- Qingyu Wang, Jing Li, and Jun Zhu are employees of Shanghai Henlius Biotech, Inc. Dr. Rui-Hua Xu reported receiving speaker fees from Bristol Myers Squibb, Roche, Merck Serono, Hutchison, Hengrui, Junshi, Qilu, CPPC, Henlius, and participating on advisory board for Astellas, MSD, AstraZeneca, Junshi, Hengrui, BeiGene, Innovent, CPPC, and Keymed. All other authors have no competing interests to declare.

2024 American Society of Clinical Oncology Gastrointestinal (ASCO GI) Cancers Symposium, Jan. 18 – 20, 2024