Abstract 3569: 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

- Several PD-1 inhibitors conferred significant survival benefits for advanced colorectal cancer patients with a deficient mismatch repair (dMMR)/microsatellite instability high (MSI-H) molecular phenotype.[1,2] However, the efficacy of adding immunotherapy to standard-of-care (vascular endothelial growth factor [VEGF] inhibitor plus systemic chemotherapy) for proficient mismatch repair or microsatellite stable (pMMR/MSS) metastatic colorectal cancer (mCRC) remains unclear.
- Our previous interim analysis showed a trend of an improved survival for serplulimab (a novel anti-PD-1 antibody) plus HLX04 (an approved bevacizumab biosimilar) and XELOX compared to placebo plus bevacizumab and XELOX in MSS mCRC patients. Here we present the updated results with an extended follow-up duration of 24.4 months.

Methods

- This phase 2 part of our randomized, double-blind, phase 2/3 study evaluated the efficacy of combining serplulimab and HLX04 plus chemotherapy versus placebo plus bevacizumab plus chemotherapy as first-line treatment for mCRC (Figure 1).
- 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[a], IV, 300 mg
- Bevacizumab[a], IV, 7.5 mg/kg
- XELOX[b] (oxaliplatin[c]+capecitabine[a])

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

Secondary endpoints:
- OS
- PFS assessed by investigator
- ORR and DCR
- DOR
- 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-L1, programmed cell death ligand 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 enrolled patients (intent-to-treat) were 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.
- 38 (66.7%) patients in each group had liver metastasis. A vast majority of the patients had a MSS status (90.9% [40/44] in group A and 100.0% [50/50] in group B).
- As of December 15, 2023 (data cutoff), 112 patients (group A, n = 55; group B, n = 57) received the intended treatment regimen and were included in the efficacy and safety analysis. Median follow-up duration was 24.4 months.

References

1. Diaz, L. A., Jr. et al. Lancet Oncol 23, 659-670 (2022). 2. Lenz, H. J. et al. J Clin Oncol 40, 161-170 (2022).

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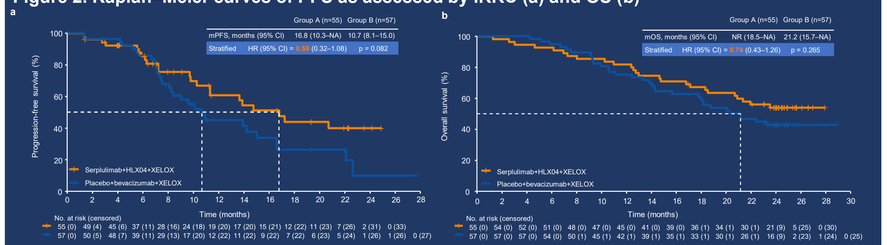
Trend of an improved PFS and other efficacy endpoints were maintained with serplulimab plus HLX04 and XELOX compared to placebo plus bevacizumab and XELOX in patients with mCRC.

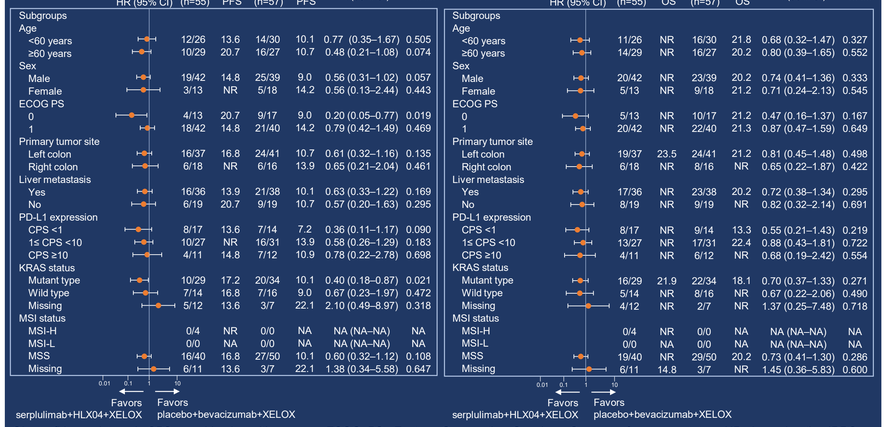
Efficacy

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



CI, confidence interval; HR, hazard ratio; IRRC, independent radiological review committee; m, median; NA, not available; NR, not reached; OS, overall survival; PFS, progression-free survival; XELOX, oxaliplatin+capecitabine.

Figure 3. Forest plot analysis of PFS as assessed by IRRC (a) and OS (b)



CI, confidence interval; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IRRC, independent radiological review committee; MSI, microsatellite instability; MSI-H/L, microsatellite instability high/low; MSS, microsatellite stable; NA, not available; NR, not reached; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; XELOX, oxaliplatin+capecitabine.

Table 2. Tumor response[a] 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 (52.9, 78.6)**
DCR, % (95% CI)	**85.5 (73.3, 93.5)**	**84.2 (72.1, 92.5)**
CR, n (%)	2 (3.6)	2 (3.5)
PR, n (%)	34 (61.8)	36 (63.2)
Non-CR/Non-PD, n (%)	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)
mDOR, months (95% CI)	19.4 (11.3–NA)	11.3 (5.8–15.2)
Stratified HR (95% CI)	0.31 (0.12–0.78)	p = 0.009

- A trend of an improved PFS and OS was observed for the serplulimab+HLX04+XELOX treatment arm in both the main and subgroup analysis.
- Tumor responses were similar between the two treatment groups; DOR was improved with serplulimab+HLX04+XELOX.

[a] *Confirmed tumor response.*
CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; HR, hazard ratio; IRRC, independent radiological review committee; m, median; 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)
Liver metastasis, n (%)		
Yes	38 (66.7)	38 (66.7)
No	19 (33.3)	19 (33.3)
Lung metastasis, n (%)		
Yes	26 (45.6)	20 (35.1)
No	31 (54.4)	37 (64.9)
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

- The incidence of grade ≥3 TEAEs was similar between the two treatment groups. Grade ≥3 TEAEs related to serplulimab/placebo occurred in 45.5% of the patients in group A, and 36.8% of the patients in group B (Table 3), most commonly neutrophil count decreased and platelet count decreased.
- 30.9% and 24.6% patients in group A and group B, respectively, reported irAEs. Most irAEs were mild (grade 1–2). Grade ≥3 irAEs occurred in 12.7% of the patients in group A, and 1.8% of the patients in group B.
- 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 (n = 55)	Group B (n = 57)
Any TEAEs	55 (100)	57 (100)
Grade ≥3	41 (74.5)	40 (70.2)
Grade 5	8 (14.5)	7 (12.3)
Leading to Tx discontinuation	14 (25.5)	11 (19.3)
AESIs	35 (63.6)	33 (57.9)
irAE	17 (30.9)	14 (24.6)
HLX04/bevacizumab related	26 (47.3)	20 (35.1)
IRR	8 (14.5)	8 (14.0)
Serplulimab/placebo related	4 (7.3)	5 (8.8)
Any TRAEs	54 (98.2)	57 (100)
Grade ≥3	38 (69.1)	34 (59.6)
Serplulimab/placebo related	48 (87.3)	54 (94.7)
Grade ≥3	25 (45.5)	21 (36.8)
HLX04/bevacizumab related	51 (92.7)	52 (91.2)
Grade ≥3	25 (45.5)	22 (38.6)

Table 4. Most common TEAEs (≥30%)[a]

n (%)	Group A (n = 55)	Group B (n = 57)
Anemia	38 (69.1)	37 (64.9)
Platelet count decreased	33 (60.0)	31 (54.4)
Neutrophil count decreased	30 (54.5)	22 (38.6)
AST increased	26 (47.3)	32 (56.1)
White blood cell count decreased	26 (47.3)	21 (36.8)
Decreased appetite	23 (41.8)	24 (42.1)
Nausea	22 (40.0)	28 (49.1)
ALT increased	22 (40.0)	22 (38.6)
Proteinuria	22 (40.0)	19 (33.3)
Hypoalbuminemia	21 (38.2)	27 (47.4)
Blood bilirubin increased	19 (34.5)	22 (38.6)
Vomiting	19 (34.5)	21 (36.8)
Diarrhea	19 (34.5)	18 (31.6)
Abdominal pain	19 (34.5)	10 (17.5)

[a] ≥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.

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