Poster #170

Updated efficacy and subgroup analysis of first-line serplulimab plus bevacizumab and XELOX versus placebo plus bevacizumab and XELOX in metastatic colorectal cancer: a phase 2/3 study

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Background

- This study evaluates the efficacy of serplulimab (a novel anti-PD-1 antibody) in combination with HLX04 (approved bevacizumab biosimilar, hereafter referred to as bevacizumab) and XELOX versus placebo plus bevacizumab and XELOX as a first-line treatment for metastatic colorectal cancer (mCRC).
- Our previous analysis showed a trend of an improved survival for serplulimab plus bevacizumab and XELOX compared to placebo plus bevacizumab and XELOX in mCRC patients, including those with a proficient mismatch repair or microsatellite stable (pMMR/MSS) status. Median duration of response (DOR) was similarly prolonged for the patients receiving serplulimab plus bevacizumab and XELOX.
- Here we present the updated efficacy and safety with an extended follow-up duration of 31.0 months.

Methods

- Eligible patients were randomized in a 1:1 ratio to receive serplulimab in combination with bevacizumab and chemotherapy or placebo in combination with bevacizumab and chemotherapy (**Figure 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 IRRC according to RECIST v1.1, which should not have received local treatment such as radiotherapy

Group A Q3W
- Serplulimab[a], IV, 300 mg
- Bevacizumab[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
- 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.

Conclusions

- The findings indicate a trend of survival and clinical benefits with serplulimab plus bevacizumab and XELOX as compared to placebo plus bevacizumab and XELOX for mCRC patients, including different patient subgroups. Safety profiles of the two treatment groups were comparable.
- Serplulimab plus bevacizumab and XELOX has promising potential to be an alternative first-line option in mCRC. The phase 3 part of this study conducted in patients with MSS mCRC is currently ongoing (NCT04547166).

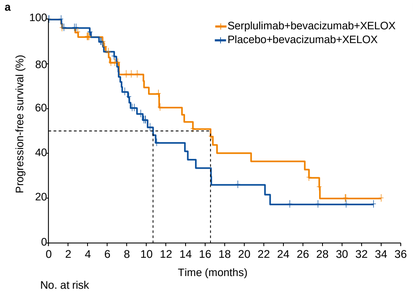
Results

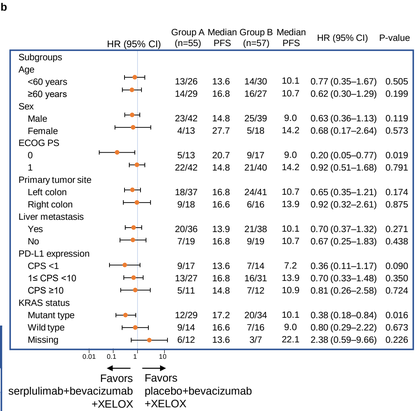
- Between July 16, 2021 and January 20, 2022, 114 enrolled patients (intent-to-treat) were randomly assigned to group A (n = 57) or group B (n = 57).
- 38 (66.7%) patients in each group had liver metastasis. A vast majority of the patients had a MSS status (90.9% [40/44] in group A and 100.0% [50/50] in group B) (**Table 1**).
- As of June 30, 2024 (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 analyses. The median follow-up duration was 31.0 months.
- A trend of an improved PFS was maintained for the serplulimab+bevacizumab+XELOX treatment arm in both the main and subgroup analysis (**Figure 2**), along with a sustained OS benefit.
- Similar survival benefits were also observed for the MSS subgroup (**Figure 3**);
- Subsequent antitumor therapies received by patients are listed in **Table 2**.
- Median DOR was improved with serplulimab+bevacizumab+XELOX (**Table 3**).
- 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 4**).
- Most common TEAEs reported in ≥30% of the patients in either group are listed in **Table 5**.
- 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.

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)

Figure 2. Kaplan-Meier curve (a) and subgroup analysis (b) of PFS as assessed by IRRC





	Group A[a] (n=55)	Group B (n=57)
mPFS, months (95% CI)	16.6 (10.3–26.2)	10.7 (8.1–15.0)
Stratified HR (95% CI)	0.66 (0.37–1.19)	p = 0.167

[a] *Two patients in group A who did not receive any study treatment were excluded.*
CI, confidence interval; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IRRC, independent radiological review committee; m, median; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; XELOX, oxaliplatin+capecitabine.

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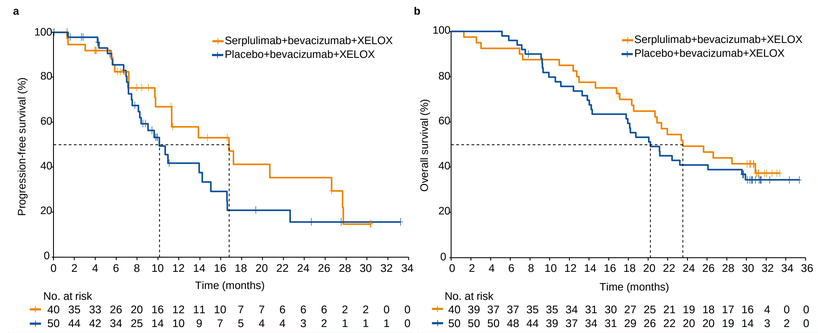
Figure 3. Kaplan-Meier curves of PFS (a) as assessed by IRRC and OS (b) for the MSS subgroup



	Group A (n=40)	Group B (n=50)
mPFS, months (95% CI)	16.8 (9.8–27.7)	10.1 (8.1–15.0)
Stratified HR (95% CI)	0.65 (0.33–1.29)	p = 0.211

	Group A (n=40)	Group B (n=50)
mOS, months (95% CI)	23.5 (18.5–NE)	20.2 (14.3–29.9)
Stratified HR (95% CI)	0.79 (0.45–1.38)	p = 0.399

CI, confidence interval; HR, hazard ratio; IRRC, independent radiological review committee; m, median; MSS, microsatellite stable; NE, not evaluable; OS, overall survival; PFS, progression-free survival; XELOX, oxaliplatin+capecitabine.

Table 2. Subsequent antitumor therapy

n (%)	Group A[a] (n = 55)	Group B (n = 57)
Any antitumor therapy	23 (41.8)	27 (47.4)
MSS subgroup	n = 40	n = 50
Any antitumor therapy	19 (47.5)	25 (50.0)
Pyrimidine analogues	16 (40.0)	19 (38.0)
Topoisomerase 1 inhibitors	15 (37.5)	18 (36.0)
Platinum compounds	2 (5.0)	5 (10.0)
VEGF/VEGFR inhibitors	12 (30.0)	14 (28.0)
VEGFR tyrosine kinase inhibitors	2 (5.0)	6 (12.0)
EGFR inhibitors	2 (5.0)	5 (10.0)
PD-1/PD-L1 inhibitors	3 (7.5)	2 (4.0)

Table 3. Confirmed tumor response[b]

	Group A[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 (%)	1 (1.8)	2 (3.5)
PR, n (%)	35 (63.6)	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)	17.7 (11.3–26.3)	11.3 (5.8–15.2)
Stratified HR (95% CI)	0.45 (0.20–0.98)	p = 0.041

[a] *Two patients in group A who did not receive any study treatment were excluded.* [b] *Assessed by the IRRC per RECIST v1.1.*
CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; EGFR, epidermal growth factor receptor; HR, hazard ratio; IRRC, independent radiological review committee; m, median; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PD-L1, programmed cell death 1; PD-L1, programmed cell death ligand 1; PR, partial response; SD, stable disease; TOP1, topoisomerase 1; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Table 4. Summary of adverse events

n (%)	Group A[a] (n = 55)	Group B (n = 57)
Any TEAEs	55 (100)	57 (100)
Grade ≥3	42 (76.4)	40 (70.2)
Grade 5[b]	9 (16.4)	7 (12.3)
Leading to Tx discontinuation	14 (25.5)	12 (21.1)
AESIs	36 (65.5)	33 (57.9)
irAE	17 (30.9)	14 (24.6)
Bevacizumab related	27 (49.1)	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	39 (70.9)	34 (59.6)
Serplulimab/placebo related	48 (87.3)	54 (94.7)
Grade ≥3	25 (45.5)	21 (36.8)
Bevacizumab related	51 (92.7)	52 (91.2)
Grade ≥3	26 (47.3)	22 (38.6)

Table 5. Most common TEAEs (≥30%)[c]

n (%)	Group A[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)	31 (54.4)
White blood cell count decreased	26 (47.3)	21 (36.8)
Decreased appetite	23 (41.8)	25 (43.9)
Proteinuria	23 (41.8)	19 (33.3)
Nausea	22 (40.0)	28 (49.1)
Hypoalbuminemia	22 (40.0)	27 (47.4)
ALT increased	22 (40.0)	22 (38.6)
Blood bilirubin increased	19 (34.5)	22 (38.6)
Vomiting	19 (34.5)	21 (36.8)
Diarrhea	19 (34.5)	19 (33.3)
Abdominal pain	19 (34.5)	10 (17.5)

[a] *Two patients in group A who did not receive any study treatment were excluded.* [b] *4 (7.3%) patients in group A and 4 (7.0%) in group B experienced a grade 5 TEAE of disease progression that led to death.* [c] ≥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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