The efficacy and safety of ivonescimab with or without ligufalimab in combination with FOLFOXIRI as first-line (1L) treatment for metastatic colorectal cancer (mCRC)

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Barcelona, Spain, 14 September 2024

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DECLARATION OF INTERESTS

Dr. Yanhong Deng declares no conflict of interest.

Dr. Jianwei Zhang declares no conflict of interest.

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Study Rationale

- Triplet combination chemotherapy with 5-fluorouracil (5-FU)/leucovorin (LV) + oxaliplatin + irinotecan (FOLFOXIRI) plus anti-vascular endothelial growth factor (VEGF) therapy with bevacizumab is a standard first-line (1L) treatment for patients with unresectable metastatic colorectal cancer (mCRC) and microsatellite stable (MSS) or mismatch repair proficient (pMMR) tumors.[1,2]
- Programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors are recommended as 1L treatment in patients with microsatellite instability (MSI)-high or mismatch repair deficient (dMMR) mCRC[1,2], however, demonstrate limited activity as monotherapy in patients with MSS or pMMR mCRC.[3,4]
- Ivonescimab, a tetrameric bispecific antibody targeting PD-1 and VEGF, has the potential to produce synergistic anti-tumor effects through both pathways via cooperative binding.
- Ligufalimab is a novel humanized IgG4 monoclonal antibody targeting CD47 that may enhance antitumor activity when combined with ivonescimab.
- The addition of PD-1/PD-L1 inhibitors to SOC in the 1L setting for mCRC has been reported in some studies in order to enhance the antitumoural effect of immune checkpoint inhibitors by increasing tumor immunogenicity.[5,6] In this study, we choose triplet combination chemotherapy.

1.Morris VK et al. J Clin Oncol. 2023;41:678-700. 2.Cervantes A et al. Ann Oncol. 2023;34:10-32. 3.Matteucci L et al. Cancers. 2023;15:5189. 4.Ros J et al. Front Oncol. 2023;13:1112276. 5.Heinz-Josef Let al.. J Immunother Cancer 2024;12(3):e008409. 6.Carlotta A et al.Lancet Oncol. 2022;23(7):876-887.

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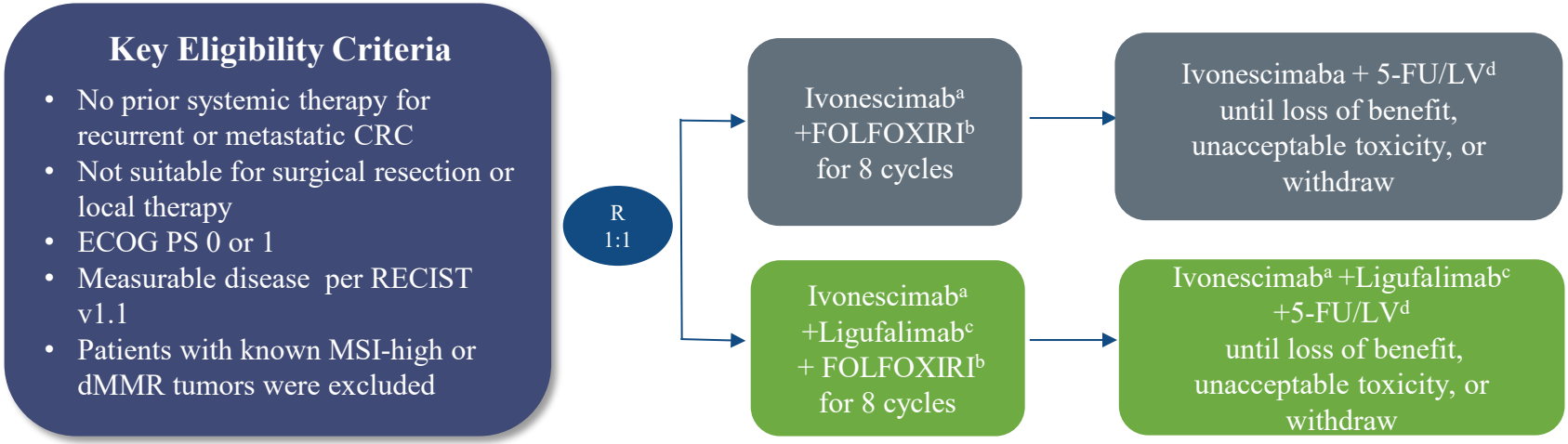
Study Design (NCT05382442)

We report preliminary results from a phase 2 trial of ivonescimab and ligufalimab plus chemotherapy in patients with previously untreated mCRC.



Primary endpoints

- ORR, as assessed by investigator per RECIST v1.1
- AE

Secondary endpoints

- DCR
- DOR
- TTR
- PFS
- OS

[a]Ivonescimab 20 mg/kg on day 1 Q2W，[b]5-FU 2400-2800 mg/m^2 as 46-48 h continuous IV infusion starting on day 1 Q2W + LV 400 mg/m^2 IV on day 1 Q2W + oxaliplatin 85 mg/m^2 IV on day 1 Q2W + irinotecan 150-165 mg/m^2 IV on day 1 Q2W，[c]Ligufalimab 45 mg/kg on day 1 Q2W，[d]5-FU 2400-2800 mg/m^2 as 46-48 h continuous IV infusion starting on day 1 Q2W + LV 400 mg/m^2 IV on day 1 Q2W.

Abbreviation: 5-FU, 5-fluorouracil; CRC, colorectal cancer; dMMR, mismatch repair deficient; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFOXIRI, 5-FU/LV + oxaliplatin + irinotecan; IV, intravenous; LV, leucovorin; MSI, microsatellite instability; Q2W, every 2 weeks; R, randomization; ORR, objective response rate; AE, adverse event; DCR, disease control rate; DOR, duration of response; TTR, time to response; PFS, progression-free survival; OS, overall survival.

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Baseline Characteristics

- As of Feb 29, 2024, a total of 40 patients randomized to 2 arms. The median follow-up was 9.0 months (range, 6.3-11.3) in the ivonescimab + FOLFOXIRI group and 9.6 months (range, 4.6-11.0) in the ivonescimab + ligufalimab + FOLFOXIRI group.
- The median age was 58 years (range, 30-72) and 50% of patients had an ECOG PS of 1 at baseline.

Characteristic	Ivonescimab + FOLFOXIRI n = 22	Ivonescimab + Ligufalimab + FOLFOXIRI n = 18
Age, years		
median, range	58.5 (30-72)	58.0 (34-70)
ECOG PS, n (%)		
0	11 (50.0)	9 (50.0)
1	11 (50.0)	9 (50.0)
Primary tumor site, n (%)		
Colon	13 (59.1)	10 (55.6)
Rectum	9 (40.9)	8 (44.4)
Liver disease, n (%)	18 (81.8)	15 (83.3)
Number of metastatic sites, n (%)		
<3	15 (68.2)	15 (83.3)
≥3	7 (31.8)	3 (16.7)
Time to metastasis, n (%)		
Synchronous	21 (95.5)	16 (88.9)
Metachronous	1 (4.5)	2 (11.1)

Characteristic	Ivonescimab + FOLFOXIRI n = 22	Ivonescimab + Ligufalimab + FOLFOXIRI n = 18
PD-L1 combined positive score [a], n (%)		
<1	12 (54.5)	10 (55.6)
≥1	9 (40.9)	8 (44.4)
MSI/MMR status, n (%)		
MSS/pMMR	21 (95.5)	18 (100.0)
Unknown	1 (4.5)	0
RAS mutation status [a], n (%)		
Mutated	8 (36.3)	8 (44.4)
Wild type	13 (59.1)	8 (44.4)
BRAF mutation status [a], n (%)		
Mutated	3 (13.6)	3 (16.7)
Wild type	18 (81.8)	13 (72.2)

[a] Patients with unknow status were not shown.
Abbreviation：ECOG PS, Eastern Cooperative Oncology Group performance status; MMR, mismatch repair; MSI, microsatellite instability; MSS, microsatellite stable; pMMR, mismatch repair proficient; PD-L1, programmed death-ligand 1.

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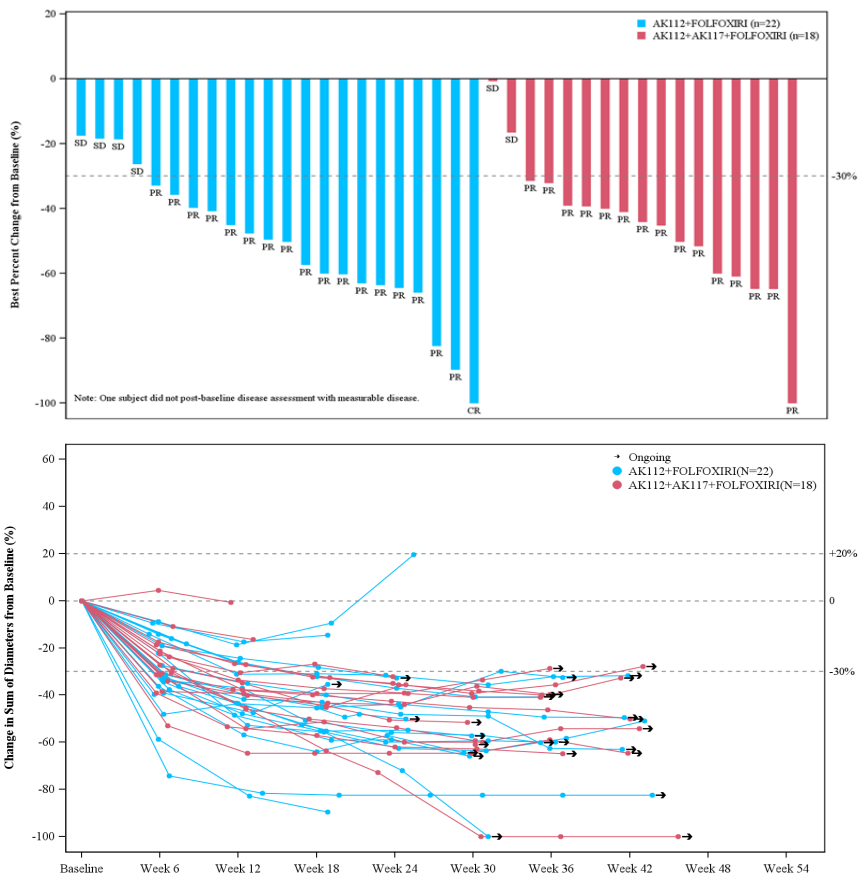
Efficacy Summary

- ORR was 81.8% (18/22) with ivonescimab + FOLFOXIRI and 88.2% (15/17) with ivonescimab + ligufalimab + FOLFOXIRI.

	Ivonescimab + FOLFOXIRI n = 22	Ivonescimab + Ligufalimab + FOLFOXIRI n = 17 [a]
Investigator-assessed objective response rate		
n	18	15
ORR (95% CI), %	81.8 (59.7-94.8)	88.2 (63.6-98.5)
Investigator-assessed disease control rate		
n	22	17
DCR (95% CI), %	100 (84.6-100)	100 (80.5-100)

[a] One patient had no post-baseline tumor assessment.
Abbreviation: CI, confidence interval; CR, complete response; DCR, disease control rate; ; ORR, objective response rate; PR, partial response; SD, stable response.
Data cutoff date: Feb 29, 2024



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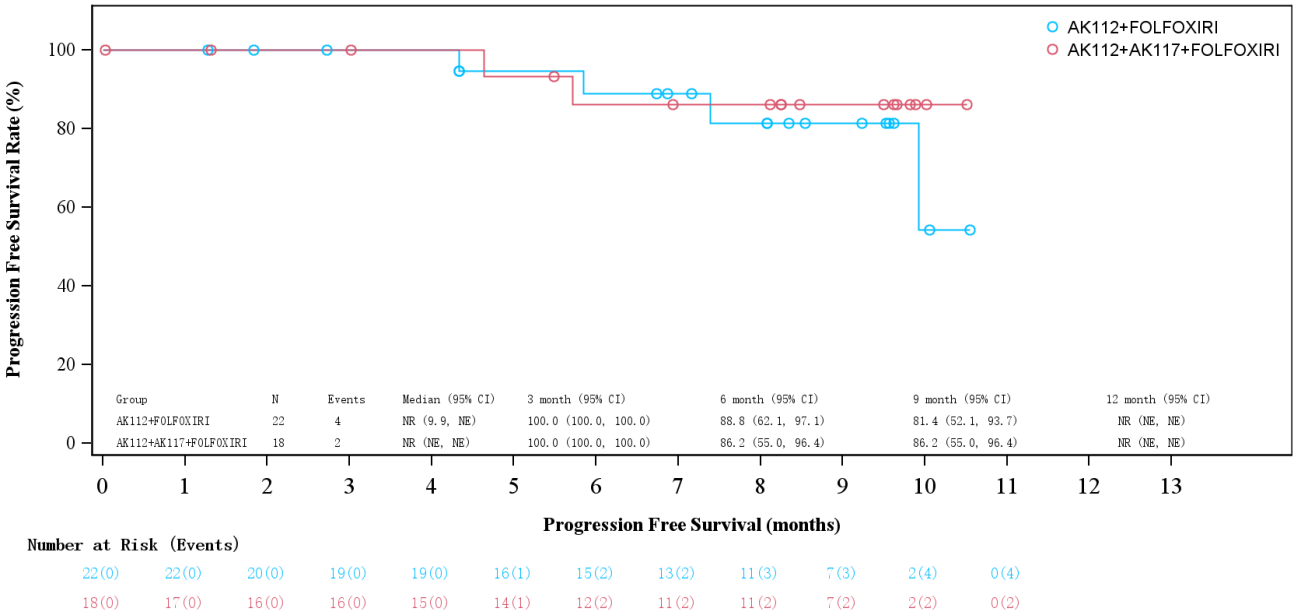
Efficacy of PFS

- At the time of analysis, median PFS had not been reached in either group
- Estimated 9-month PFS rates were 81.4% (95% CI, 52.1-93.7) with ivonescimab + FOLFOXIRI and 86.2% (95% CI, 55.0-96.4) with ivonescimab + ligufalimab + FOLFOXIRI.



Abbreviation: CI, confidence interval; PFS, progression-free survival;
Data cutoff date: Feb 29, 2024

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Safety Summary

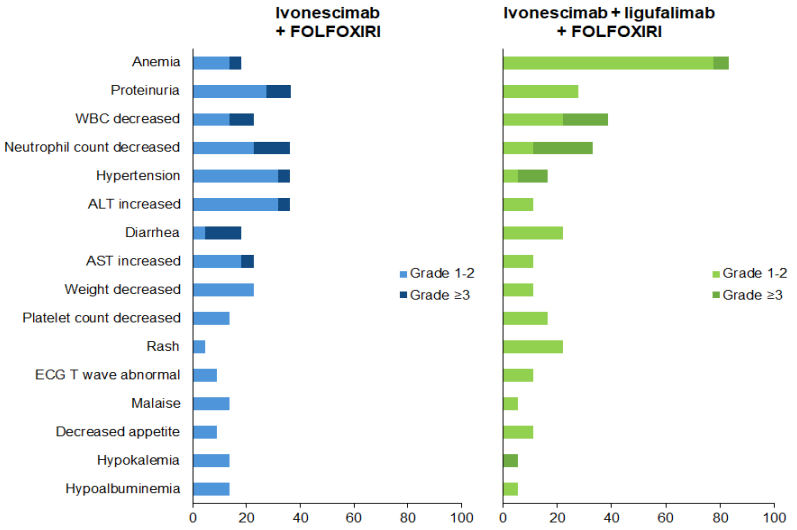
- Grade ≥3 treatment-related adverse events (TRAEs) were reported in 54.5% of patients in the ivonescimab + FOLFOXIRI group and 44.4% of patients in the ivonescimab + ligufalimab + FOLFOXIRI group.
- The most common grade ≥3 TRAEs, with a frequency of ≥10% overall, were neutrophil count decreased (13.6% and 22.2% in ivonescimab + FOLFOXIRI group and ivonescimab + ligufalimab + FOLFOXIRI group, respectively) and white blood cell (WBC) count decreased (9.1% and 16.7%, respectively).

Summary of AE Results

AE Category	Ivonescimab + FOLFOXIRI n = 22	Ivonescimab + Ligufalimab + FOLFOXIRI n = 18
TEAEs with Grade ≥3	15 (68.2)	12 (66.7)
TESAE	5 (22.7)	3 (16.7)
TEAEs Leading to Permanently Discontinued	0	1 (5.6)
TRAEs with Grade ≥3	12(54.5)	8 (44.4)
TRSAE	5 (22.7)	2 (11.1)
TRAEs Leading to Permanently Discontinued	0	1 (5.6)

Abbreviation: TEAE:treatment-emergent adverse event;TESAE: Serious TEAE; TRAE: treatment-related adverse event; TRSAE: Serious TRAE; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; WBC, white blood cell.
Data cutoff date: Feb 29, 2024

Most common TRAEs (≥10% Overall)



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Conclusions

- Ivonescimab +/- ligufalimab in combination with FOLFOXIRI showed promising anti-tumor activity as 1L treatment of recurrent or metastatic CRC.
  - Ivonescimab + FOLFOXIRI group: ORR was 81.8%, DCR was 100%, 9-month PFS was 81.4%.
  - Ivonescimab + ligufalimab + FOLFOXIRI group: ORR was 88.2%, DCR was 100%, 9-month PFS was 86.2%.
- Ivonescimab +/- ligufalimab in combination with FOLFOXIRI showed manageable safety profile in recurrent or metastatic CRC
  - The most common grade ≥3 TRAEs were hematologic toxicity, including neutrophil count decreased and WBC count decreased
- Results of this analysis support further evaluation of ivonescimab +/- ligufalimab plus chemotherapy for the 1L treatment of recurrent or metastatic CRC.

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Acknowledgments

We sincerely thank all:

- Participating patients and their family members.
- Investigators from all centers in this study, and the staff for their involvement and support.

This study is sponsored by Akeso Biopharma, Inc.

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