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# 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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# DECLARATION OF INTERESTS

**Dr. Yanhong Deng** declares no conflict of interest.

**Dr. Jianwei Zhang** declares no conflict of interest.

# 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.<sup>1,2</sup>
- 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<sup>1,2</sup>, however, demonstrate limited activity as monotherapy in patients with MSS or pMMR mCRC.<sup>3,4</sup>
- 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.<sup>5,6</sup> 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.

# Study Design (NCT05382442)

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

## Key Eligibility Criteria

- No prior systemic therapy for recurrent or metastatic CRC
- Not suitable for surgical resection or local therapy
- ECOG PS 0 or 1
- Measurable disease per RECIST v1.1
- Patients with known MSI-high or dMMR tumors were excluded

R  
1:1

Ivonescimab<sup>a</sup>  
+FOLFOXIRI<sup>b</sup>  
for 8 cycles

Ivonescimab<sup>a</sup> + 5-FU/LV<sup>d</sup>  
until loss of benefit,  
unacceptable toxicity, or  
withdraw

Ivonescimab<sup>a</sup>  
+Ligufalimab<sup>c</sup>  
+ FOLFOXIRI<sup>b</sup>  
for 8 cycles

Ivonescimab<sup>a</sup> +Ligufalimab<sup>c</sup>  
+5-FU/LV<sup>d</sup>  
until loss of benefit,  
unacceptable toxicity, or  
withdraw

## Primary endpoints

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

## Secondary endpoints

- DCR
- TTR
- OS
- DOR
- PFS

<sup>a</sup>Ivonescimab 20 mg/kg on day 1 Q2W, <sup>b</sup>5-FU 2400-2800 mg/m<sup>2</sup> as 46-48 h continuous IV infusion starting on day 1 Q2W + LV 400 mg/m<sup>2</sup> IV on day 1 Q2W + oxaliplatin 85 mg/m<sup>2</sup> IV on day 1 Q2W + irinotecan 150-165 mg/m<sup>2</sup> IV on day 1 Q2W.

<sup>c</sup>Ligufalimab 45 mg/kg on day 1 Q2W, <sup>d</sup>5-FU 2400-2800 mg/m<sup>2</sup> as 46-48 h continuous IV infusion starting on day 1 Q2W + LV 400 mg/m<sup>2</sup> 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.

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

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

<sup>a</sup>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.

# Efficacy Summary

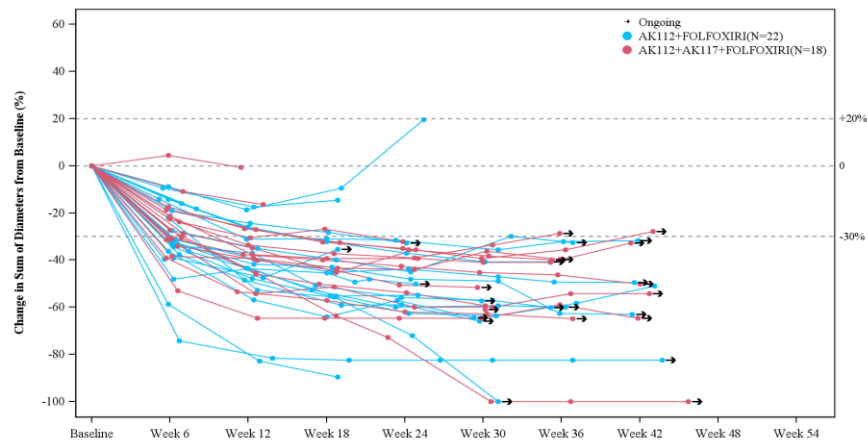
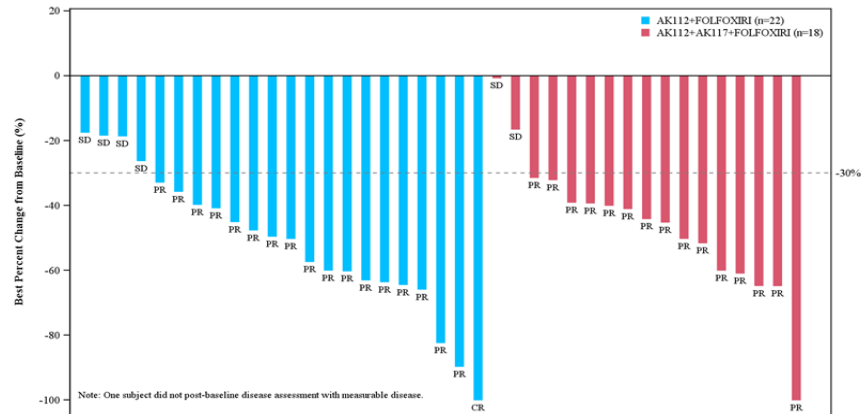
- ORR was 81.8% (18/22) with ivonescimab + FOLFOXIRI and 88.2% (15/17) with ivonescimab + ligufalimab + FOLFOXIRI.

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

<sup>a</sup> One patient had no post-baseline tumor assessment.

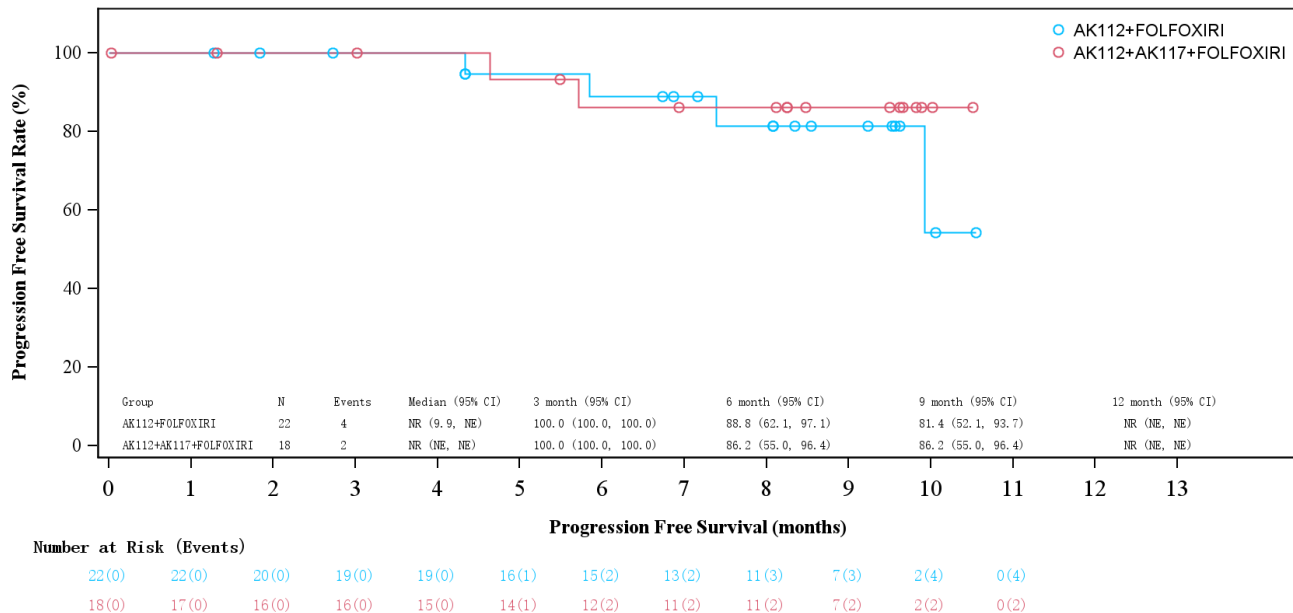
Abbreviation: CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, objective response rate; PR, partial response; SD, stable response.

Data cutoff date: Feb 29, 2024



# 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

# Safety Summary

- Grade  $\geq 3$  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  $\geq 3$  TRAEs, with a frequency of  $\geq 10\%$  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).

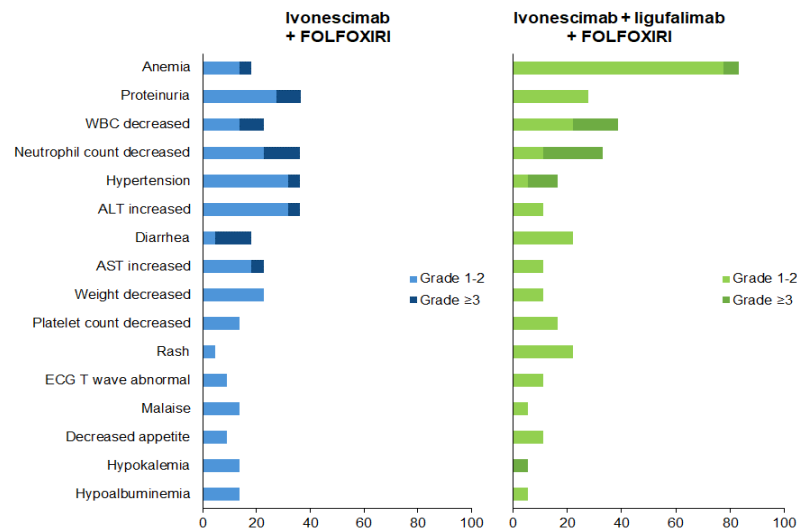
## Summary of AE Results

AE Category	Ivonescimab + FOLFOXIRI n = 22	Ivonescimab + Ligufalimab + FOLFOXIRI n = 18
TEAEs with Grade $\geq 3$	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 $\geq 3$	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 ( $\geq 10\%$ Overall)





# 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  $\geq 3$  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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