Phase I/II study of the EP4 antagonist CR6086 combined with the anti-PD-1 balstilimab in mismatch-repair-proficient and microsatellite stable (pMMR/MSS) chemorefractory metastatic colorectal cancer (mCRC)

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Background

• Approved immune checkpoint inhibitors (ICI) have little to no benefit in patients (pts) with pMMR/MSS mCRC. Several combination strategies to overcome intrinsic resistance have failed.

• Prostaglandin E2 (PGE2), through its receptor 4 (EP4), is a major contributor to immunosuppression in the tumor microenvironment and blockade of this pathway may sensitize cold tumors to ICI [1, 2].

• CR6086 is a clinical stage EP4 receptor antagonist [3] acting as a targeted immunomodulator. In preclinical models, CR6086 significantly enhanced the activity of PD-1 blockade [4], prompting this ongoing phase I/II study of CR6086 with an anti-PD-1 (balstilimab, Agens, Inc.) in pMMR/MSS chemorefractory mCRC.

Methods

• This was a phase Ib/IIa prospective, open label, single-arm trial conducted at one site in Italy (NCT05205330).

• Adult pts with pMMR/MSS mCRC, ECOG PS ≤2 pts at 1 dose level (e.g., >15% in an overall population) and prior exposure to fluoropyrimidines, oxaliplatin and irinotecan, received oral treatment with CR6086 (twice daily) plus balstilimab (3 mg/kg IV every 2 weeks) until disease progression, unacceptable toxicity or death.

• The planned escalating CR6086 doses were: 30 mg bid, 90 mg bid and 180 mg bid. Intermediate doses could be explored, if needed.

• Primary endpoints were safety and disease control rate (DCR) per RECIST 1.1, analysed when all pts completed 24 weeks or were prematurely withdrawn.

• A DCR observed in ≥2 pts at 1 dose level (e.g.>15%) in an expanded cohort of 12 pts), associated with an acceptable safety profile, was considered a meeting the primary endpoint.

• Secondary endpoints included objective response rate (ORR), duration of response, progression-free and overall survival (PFS, OS). Exploratory endpoints include tissue and blood biomarkers.

Results

• According to the protocol, 28 pts were enrolled:
  - 9 at CR6086 30 mg bid + balstilimab,
  - 13 at CR6086 90 mg bid + balstilimab,
  - 6 at CR6086 180 mg bid + balstilimab.

• 21 pts discontinued (20 PD, 1 AE) and 7 pts were still on treatment at the 6-month cut-off date.

• CR6086 dose escalation proceeded as planned in the protocol (balstilimab dose was planned to be reduced from 3 mg/kg to 2 mg/kg for CR6086 180 mg bid in Q1 2024 and then to 1 mg/kg in Q2 2024).

• CR6086 dose escalation proceeded as planned in the protocol: 28 pts were enrolled:

  - 2 pts at 1 dose level (e.g.>15% in an overall population).

• There was no treatment-related death. 1 pt died due to a pulmonary embolism related to disease progression.

• No DLT were observed.

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Safety

• No DLT were observed.

• 7 pts had SAE. Of them, 2 pts had a drug-related SAE:
  - 1 CR6086-related duodenal ulcer haemorrhage which prompted treatment at the 6-month cut-off date.
  - 1 balstilimab-related pneumonitis which was resolved with treatment at the 6-month cut-off date.

Conclusions

CR6086 combined with an anti-PD-1 (balstilimab) was well tolerated and achieved durable responses in pMMR/MSS mCRC, with promising results observed also in pts with liver metastases. Expansion in other gastrointestinal tumors is ongoing and a randomized Phase II study in pMMR/MSS mCRC is planned in Q2 2024.

References


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Poster presented at ESMO Congress Madrid 2023

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