# 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)

#641P

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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, Agenus, 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 ≤1 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were safety and disease control rate (DCR) per RECIST 1.1, analysed when all pts completed 24 weeks or were prematurely withdrawn.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 result 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

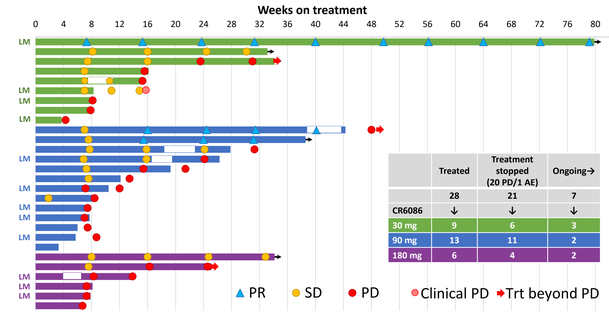
- According to the protocol, 28 pts were enrolled:
  - 9 at CR6086 30 mg bid + balstilimab,
  - 13 at CR6086 90 mg bid + balstilimab,
  - 6 at CR6086 180 mg bid + balstilimab.
- 21 pts discontinued (20 PD, 1 AE) and 7 pts were still on treatment at the 6-month cut-off date.
- CR6086 dose escalation proceeded as planned in the protocol (30, 90 and 180 mg bid).

**Table 1. Baseline characteristics**

| | Overall (N=28) | | Overall (N=28) |
|---|---|---|---|
| Age, median (range) | 59 (40-76) | Prior lines of therapy | |
| Sex, n (%) | | median (range) | 4 (2-10) |
| Male | 15 (54%) | Liver metastases, n (%) | |
| Female | 13 (46%) | Yes | 12 (43%) |
| ECOG PS at baseline, n (%) | | No | 16 (57%) |
| 0 | 20 (71%) | RAS status, n (%) | |
| 1 | 8 (29%) | Wild-type | 10 (36%) |
| CR6086 dose, n (%) | | Mutated | 18 (64%) |
| 30 mg bid + balstilimab Q2W | 9 (32%) | BRAF status, n (%) | |
| 90 mg bid + balstilimab Q2W | 13 (47%) | Wild-type | 26 (93%) |
| 180 mg bid + balstilimab Q2W | 6 (21%) | Mutated | 2 (7%) |
| Primary tumor site, n (%) | | Previous treatment, n (%)* | |
| Right colon | 7 (25%) | TAS-102 | 4 (14%) |
| Left colon | 11 (39%) | Regorafenib | 3 (11%) |
| Rectum | 10 (36%) | TAS-102 and regorafenib | 8 (29%) |

*All pts had prior exposure to fluoropyrimidines, oxaliplatin and irinotecan. All RAS WT pts had prior anti-EGFR treatment.

**Figure 1. Swimmer plot and disposition data**




| | Treated | Treatment stopped (20 PD/1 AE) | Ongoing→ |
|---|---|---|---|
| | 28 | 21 | 7 |
| CR6086 | ↓ | ↓ | ↓ |
| 30 mg | 9 | 6 | 3 |
| 90 mg | 13 | 11 | 2 |
| 180 mg | 6 | 4 | 2 |

LM=liver metastases
Uncoloured sections indicate study drugs temporary interruption.

## 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 the addition of prophylactic treatment with PPIs in all pts;
  - 1 balstilimab-related pneumonitis which was resolved with corticosteroids.
- There was no treatment-related death. 1 pt died due to a pulmonary embolism related to disease progression.

**Table 2. Overview of AEs**

| Overview of AEs | 30 mg +balstilimab (N=9) | 90 mg +balstilimab (N=13) | 180 mg +balstilimab (N=6) | Overall (N=28) |
|---|---|---|---|---|
| Number of DLTs | 0 | 0 | 0 | 0 |
| Grade ≥3 AEs | 2 (22%) | 4 (31%) | 1 (17%) | 7 (25%) |
| CR6086-related grade ≥3 AEs | 1 (11%) | 0 | 0 | 1 (4%) |
| Balstilimab-related grade ≥3 AEs | 0 | 1 (8%) | 0 | 1 (4%) |
| SAEs | 3 (33%) | 3 (23%) | 1 (17%) | 7 (25%) |
| CR6086-related SAEs | 1 (11%) | 0 | 0 | 1 (4%) |
| Balstilimab-related SAEs | 1 (11%) | 0 | 0 | 1 (4%) |
| AEs leading to drop out | 0 | 1* (8%) | 0 | 1 (4%) |
| Fatal AE | 0 | 1* (8%) | 0 | 1 (4%) |

The number (%) of pts experiencing AEs in each category are reported. *Pulmonary embolism related to disease progression

## Efficacy

- The trial met the designated primary endpoint, with a DCR of 50% associated with favourable safety results.
- A DCR of 25% was observed in the difficult to treat subgroup of pts with liver metastases.
- The overall ORR was 11%, with 3 pts having partial response (PR): one PR lasting >1 year at the cut-off date and the patient (with liver metastases at enrolment) is still ongoing; one PR lasted 7 months and the pt is now treated beyond PD (thanks to the clinical benefit); one PR lasted for at least 3.6 months and the patient is still ongoing after >6 months of treatment.
- Disease control for all the 11 pts with SD lasted at least 12 weeks, and for 5 pts lasted ≥ 24 weeks.
- At a median follow-up of 8 months (IQR 6.9-11.2), the median PFS and OS were 2.6 (CI 95% 1.7-3.6) and 13.7 (CI 95% 8.8-not reached) months, respectively. Translational analyses on tissue and blood biomarkers are ongoing.

**Table 3. Best overall response and DCR**

| Best overall response, n (%) | 30 mg +balstilimab (N=9) | 90 mg +balstilimab (N=13) | 180 mg +balstilimab (N=6) | Overall (N=28) | Pts with liver mets (N=12) |
|---|---|---|---|---|---|
| CR | 0 | 0 | 0 | 0 | 0 |
| PR | 1 (11%) | 2 (15%) | 0 | 3 (11%) | 1 (8%) |
| SD | 5 (56%) | 4 (31%) | 2 (33%) | 11 (39%) | 2 (17%) |
| PD | 3 (33%) | 6 (46%) | 4 (67%) | 13 (46%) | 9 (75%) |
| Not evaluable | 0 | 1 (8%) | 0 | 1 (4%) | 0 |
| DCR (CR+PR+SD), % | 67% | 46% | 33% | 50% | 25% |

**Figure 2. Waterfall plot**

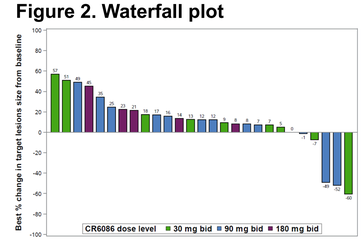



**Table 4. Responders**

| Characteristics | PID 1 | PID 2 | PID 3 |
|---|---|---|---|
| Max tumor reduction | 60% | 49% | 52% |
| Treatment ongoing/ Week | Y/80 | Y/48 | Y/38 |
| Gender | F | F | F |
| Age | 58 | 48 | 72 |
| Liver metastases | Y | N | N |
| Tumor site | Right | Left | Left |
| RAS/BRAF | WT | WT | WT |
| Prior lines of therapy | 3 | 3 | 4 |
| TMB (FoundationOne®CDx) | Low 2muts/Mb | Low 2muts/Mb | Low 0muts/Mb |

## References

[1] Take et al. Prostaglandin E Receptor 4 Antagonist in Cancer Immunotherapy: Mechanisms of Action. Front Immunol. 2020, 11:324
[2] Bonavita et al. Antagonistic inflammatory phenotypes dictate tumor fate and response to immune checkpoint blockade. Immunity 2020; 53: 1-15
[3] Caselli et al. Pharmacological characterisation of CR6086, a potent prostaglandin E2 receptor 4 antagonist, as a new potential disease-modifying anti-rheumatic drug. Arthr Res Ther 2018, 20:39
[4] Caselli et al. Combination of the EP4 antagonist CR6086 and anti-PD-1 monoclonal antibody inhibits tumor growth in a microsatellite stable colorectal cancer in mice. Cancer Res 2020; 80 (16_Supplement): 2208

## 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.

**Poster presented at ESMO Congress Madrid 2023**

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