Updated results and subgroup analysis by presence of liver metastases of a phase I/II study of the EP4 antagonist vorbipiprant 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

- Novel combination strategies are being explored to enhance the effectiveness of immune checkpoint inhibitors (ICIs) in pMMR/MSS mCRC.
- Prostaglandin E2, 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 ICIs [1, 2].
- Vorbipiprant (CR6086) is a potent and selective EP4 antagonist [3] that significantly enhanced the activity of PD-1 blockade in MSS preclinical models [4].
- Preliminary analysis of a phase I/II clinical trial of vorbipiprant added to the anti-PD-1 balstilimab (Agenus Inc.) in pMMR/MSS chemorefractory mCRC showed promising efficacy and acceptable safety of the recommended doses of this combination [5]. Here we report updated results and subgroup analyses of efficacy outcomes including by presence of liver metastases (LM) (data cutoff April 21, 2024).

Methods

- This was a phase Ib/IIa prospective, open label, single-arm trial conducted at one site in Italy (NCT05205330).
- Adult patients (pts) with pMMR/MSS mCRC, ECOG PS ≤1 and prior exposure to fluoropyrimidines, oxaliplatin and irinotecan, received oral treatment with vorbipiprant (30, 90 or 180 mg twice daily, bid) plus balstilimab (3 mg/kg intravenous every 2 weeks) until progressive disease (PD), unacceptable toxicity or death.
- 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were safety and disease control rate (DCR) per RECIST 1.1, analysed when all pts completed 24 weeks or were prematurely withdrawn.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 (PFS) and overall survival (OS). Ongoing exploratory endpoints include tissue and blood biomarkers.
- Efficacy outcomes are presented here by presence or absence of LM at enrollment.

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

[5] Pietrantonio et al. 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). *Ann Oncol* 2023; 34 (suppl 2): S452-S453

Results

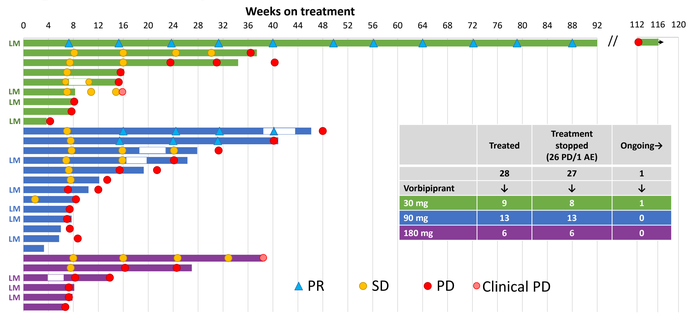
- 28 pts were enrolled and treated:
  - 9 at vorbipiprant 30 mg bid + balstilimab,
  - 13 at vorbipiprant 90 mg bid + balstilimab,
  - 6 at vorbipiprant 180 mg bid + balstilimab.
- All pts discontinued treatment (26 due to PD, 1 due to a not drug-related adverse event) except for 1 pt who had a durable response which lasted >24 months.
- 12 pts (43%) had LM at enrollment.
- Safety data were favorable and in line with previous update.

Table 1. Baseline characteristics

	Pts with LM (N=12)	Pts without LM (N=16)	Overall (N=28)
Age, median (range)	58 (40-76)	59.5 (48-72)	59 (40-76)
Sex, n (%)			
Male	7 (58%)	8 (50%)	15 (54%)
Female	5 (42%)	8 (50%)	13 (46%)
ECOG PS at baseline, n (%)			
0	7 (58%)	13 (81%)	20 (71%)
1	5 (42%)	3 (19%)	8 (29%)
Primary tumor site, n (%)			
Right colon	4 (33%)	3 (19%)	7 (25%)
Left colon	5 (42%)	6 (37%)	11 (39%)
Rectum	3 (25%)	7 (44%)	10 (36%)
Prior lines of therapy			
median (range)	3 (2-8)	4 (3-10)	4 (2-10)
RAS status, n (%)			
Wild-type	5 (42%)	5 (31%)	10 (36%)
Mutated	7 (58%)	11 (69%)	18 (64%)
BRAF status, n (%)			
Wild-type	12 (100%)	14 (88%)	26 (93%)
Mutated	0	2 (12%)	2 (7%)
Previous treatment, n (%)*			
TAS-102	1 (8%)	3 (19%)	4 (14%)
Regorafenib	1 (8%)	2 (12%)	3 (11%)
TAS-102 and regorafenib	3 (25%)	5 (31%)	8 (29%)

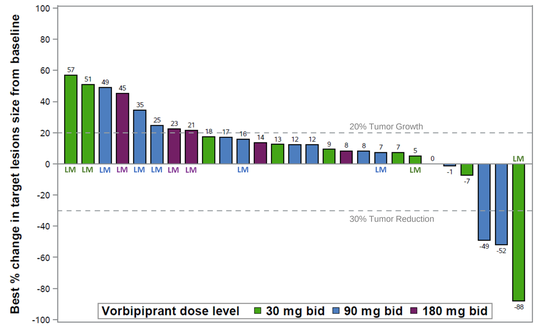
LM: pts with liver metastases at enrollment; NLM: pts without liver metastases at enrollment. ECOG PS: Eastern Cooperative Oncology Group Performance Status.
*All pts had prior exposure to fluoropyrimidines, oxaliplatin and irinotecan. All RAS WT pts had prior anti-EGFR treatment.

Figure 1. Swimmer plot and disposition data



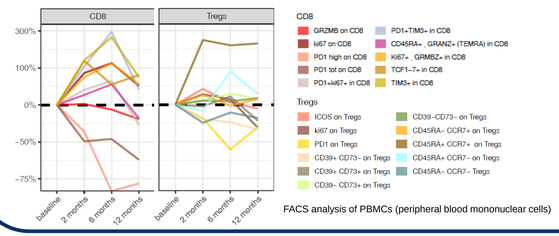
Uncoloured sections indicate study drugs temporary interruption.

Figure 2. Waterfall plot



- The trial met the designated primary endpoint, with a DCR of 50% associated with favorable safety results.
- Overall, 3 pts had partial response and 11 had stable disease, leading to an ORR of 11% and a DCR of 50%.
- At a median follow-up of 12.5 months (interquartile range 8.9-14.7 months), median PFS was 2.6 months (95% CI 1.7-3.6 months), and median OS was 13.7 months (95% CI 10.6-not reached).
- In pts with LM, ORR was 8% and DCR was 25%; median PFS was 1.8 months (95% CI 1.6-3.5 months), and median OS was 13.7 months (95% CI 5.5-not reached). To note, 1 pt had a durable partial response exceeding 24 months; then, she experienced oligoprogression at a single lesion and successfully underwent resection; the decision to restart treatments is now under evaluation.
- In pts without LM, ORR was 13% and DCR was 69%; median PFS was 3.6 months (95% CI 1.8-7.2 months), and median OS was not reached (95% CI 10.6-not reached).

Figure 3. Signs of activated immune status from PBMCs of the patient with LM and durable partial response



FACS analysis of PBMCs (peripheral blood mononuclear cells)

Table 2. Best overall response and DCR

Best overall response, n (%)	Pts with LM (N=12)	Pts without LM (N=16)	Overall (N=28)
CR	0	0	0
PR	1 (8%)	2 (13%)	3 (11%)
SD	2 (17%)	9 (56%)	11 (39%)
PD	9 (75%)	4 (25%)	13 (46%)
Not evaluable	0	1 (6%)	1 (4%)
DCR (CR+PR+SD), %	25%	69%	50%

Figure 4. Kaplan Meier plot for PFS

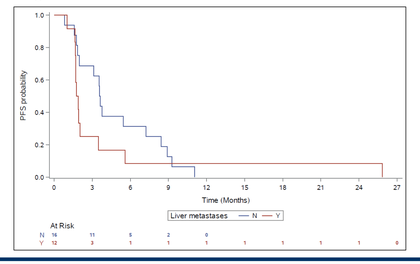
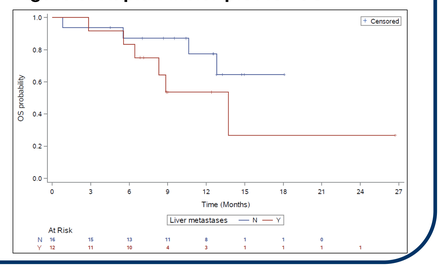


Figure 5. Kaplan Meier plot for OS



Conclusions

Vorbipiprant combined with an anti-PD-1 (balstilimab) showed promising efficacy in this phase I/II study. Encouraging results were observed in pts with LM. This finding deserves particular attention given that the presence of LM is considered an immune resistance factor and is associated with poor outcomes of treatment with ICIs.

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