# Phase I/II study of the EP4 antagonist vorbipiprant combined with anti-PD-1 immunotherapy: safety and efficacy results in metastatic gastrointestinal non-colorectal cancers

#2608

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## Background

- Novel combination strategies are being explored to enhance the effectiveness of immune checkpoint inhibitors (ICIs).
- Prostaglandin E2, through its receptor 4 (EP4), is a major contributor to immunosuppression in the tumor microenvironment.
- Vorbipiprant (CR6086), acting as EP4 antagonist, is supposed to restore the cancer-immunity cycle, enhancing ICI efficacy in immune-excluded tumors [1,2].
- In the concluded dose-response part of this phase I/II study (NCT05205330), vorbipiprant combined with PD-1 blockade (balstilimab, Agenus, Inc.) was well tolerated and showed promising efficacy in refractory mismatch-repair-proficient/microsatellite stable (pMMR/MSS) metastatic colorectal cancer (mCRC) [3].
- The study was extended to non-colorectal metastatic gastrointestinal (GI) cancers, to explore the combination further potential activity.

## Methods

- This was a phase Ib/IIa prospective, open label, single-arm trial conducted at one site in Italy.
- Adult patients (pts) with non-colorectal metastatic gastrointestinal (GI) cancers, ECOG PS ≤1 and failure of at least one prior treatment, were to be included in 3 cohorts (9 pts each): gastric cancer (GC) with PD-L1 Combined Positive Score (CPS) ≥5 (cohort A), GC with PD-L1 CPS<5 (cohort B), and GI cancers other than CRC and GC (cohort C). Pts received oral vorbipiprant (90 mg twice daily) plus iv balstilimab (3 mg/kg every 2 weeks) until disease progression, 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were safety and disease control rate (DCR) per RECIST 1.1, analysed when all pts completed 24 weeks or were prematurely withdrawn.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 15% DCR associated with an acceptable safety profile in patients with gastric cancer, was considered a result meeting the primary endpoint; no predefined endpoint was foreseen for non-colorectal/non-gastric GI cancer patients.
- Secondary endpoints included objective response rate (ORR), duration of response, progression-free and overall survival (PFS, OS). Exploratory endpoints include tissue and blood biomarkers.

## 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] Pietrantonio et al. The Prostaglandin EP4 Antagonist Vorbipiprant Combined with PD-1 Blockade for Refractory Microsatellite-Stable Metastatic Colorectal Cancer: A Phase Ib/IIa Trial. Clin Cancer Res 2025;31:649–58

## Results

**Table 1. Baseline characteristics**

| | Cohort A mGC PDL-1 CPS ≥5 (n=9) | Cohort B mGC PDL-1 CPS <5 (n=9) | Cohort C mBiliary/pancreatic cancer (N=9) | Overall (N=27) |
|---|---|---|---|---|
| Age, median (range) | 61 (57-64) | 57 (55-65) | 65 (61-74) | 61 (55-68) |
| Sex M/F, n (%) | 8 (89%) | 6 (67%) | 5 (56%) | 19 (70%) |
| ECOG PS at baseline, n (%) | | | | |
| 0 | 4 (44%) | 5 (56%) | 3 (33%) | 12 (44%) |
| 1 | 5 (56%) | 4 (44%) | 6 (67%) | 15 (56%) |
| Primary tumor site, n (%) | | | | |
| Stomach | 3 (33%) | 5 (56%) | - | - |
| GEJ | 6 (67%) | 4 (44%) | - | - |
| Pancreas | - | - | 2 (22%) | - |
| Biliary tract | - | - | 5 (56%) | - |
| Vater ampulla | - | - | 2 (22%) | - |
| Number of metastatic sites, n (%) | | | | |
| 1 | 4 (44%) | 3 (33%) | 4 (44%) | 11 (41%) |
| ≥ 2 | 5 (56%) | 6 (67%) | 5 (56%) | 16 (59%) |
| Site of metastases, n (%) | | | | |
| Liver | 5 (56%) | 6 (67%) | 5 (56%) | 16 (59%) |
| Limphonode | 8 (89%) | 4 (44%) | 3 (33%) | 15 (56%) |
| Peritoneum | 2 (22%) | 3 (33%) | 4 (44%) | 9 (33%) |
| Lung | 2 (22%) | 1 (11%) | 4 (44%) | 7 (26%) |
| Bone | 0 | 2 (22%) | 0 | 2 (7%) |
| Pleura | 0 | 0 | 1 (11%) | 1 (4%) |
| Prior lines, median (range) | 3 (2-4) | 3 (2-3) | 2 (2-3) | 3 (2-4) |
| Prior immunotherapy, n (%) | 4 (44%) | 2 (22%) | 1 (11%) | 7 (26%) |
| MS/MMR Status, n (%) | | | | |
| MSS/pMMR | 5 (56%) | 6 (67%) | 6 (67%) | 17 (63%) |
| MSI/dMMR | 2 (22%) | 0 | 2 (22%) | 4 (14%) |
| Unknown | 2 (22%) | 3 (33%) | 1 (11%) | 6 (22%) |

## Safety

- Study drugs very well tolerated.
- No vorbipiprant-related AE grade ≥3.
- 5 pts had SAE, all not related to study drugs, but 1 immune-mediated pneumonitis related to balstilimab.
- 2 pts dropped out for AE not related to study drugs.

**Table 2. Overview of AEs**

| Overview of AEs n (%) of pts | Cohort A mGC PDL-1 CPS ≥5 (n=9) | Cohort B mGC PDL-1 CPS <5 (n=9) | Cohort C mBiliary/pancreatic cancer (N=9) | Overall (N=27) |
|---|---|---|---|---|
| Grade (G) ≥3 AEs | 2 (22%) | 3 (33%) | 1 (11%) | 6 (22%) |
| Vorbipiprant-related G≥3 AEs | 0 | 0 | 0 | 0 |
| Balstilimab-related G≥3 AEs | 1 (11%) | 1 (11%) | 1 (11%) | 3 (11%) |
| SAEs | 3 (33%) | 1 (11%) | 1 (11%) | 5 (19%) |
| Vorbipiprant-related SAEs | 0 | 0 | 0 | 0 |
| Balstilimab-related SAEs | 0 | 0 | 1 (11%) | 1 (4%) |
| AEs leading to drop out | 1 (11%) | 1 (11%) | 0 | 2 (7%) |

## Patient disposition

- Enrolment is completed. 27 pts were treated with vorbipiprant 90 mg bid in combination with an immune checkpoint inhibitor (ICI), 9 patients in each cohort.
- 25 pts discontinued treatment (23 for disease progression and 2 for AE) and 2 pts were still on treatment after 10 and 15 months.
- Overall, median age was 61 (IQR: 55-68) years, similar among cohorts; 70% were men, with a slightly higher prevalence in Cohort A
- The median number of prior treatment lines was 3 (IQR: 2-4) overall and in gastric cohorts, and 2 (IQR: 2-3) in other GI cancers cohort.
- Prior ICIs were administered in 44%, 22% and 11% in Cohort A, B and C, respectively.
- Microsatellite status was stable for the majority of patients.

## Efficacy

- The primary endpoint in gastric cancer pts was met, with a 44% DCR and no safety issues. In cohort A, 3 pts had a partial response (PR), 2 of them still ongoing and all lasting more than 6 months; in addition, 1 pt had stable disease (SD). In cohort B, 4 pts had SD, 2 of them lasting more than 6 months. Lastly, in cohort C, 1 pt with pancreatic cancer had a PR, lasting 7 months and 1 BTC patient had SD.
- For GC pts, at a median follow-up of 6.8 months, the median PFS and OS were 2.0 and 9,7 months respectively, while in cohort C, at a median follow-up of 5.7 months, the median PFS and OS were 2.0 and 10,2 months respectively.
- Responses in GC occurred irrespective of MSI/MMR status and prior exposure to ICIs.
- Translational analyses on tissue and blood biomarkers are ongoing.

**Table 3. DCR/ORR and PFS/OS**

| Best overall response, n (%) | Cohort A mGC PDL-1 CPS ≥5 (n=9) | Cohort B mGC PDL-1 CPS <5 (n=9) | Overall mGC (N=18) | Cohort C mBiliary/pancreatic cancer (N=9) |
|---|---|---|---|---|
| CR | 0 | 0 | 0 | 0 |
| PR | 3 (33%) | 0 | 3 (17%) | 1 (11%) |
| SD | 1 (11%) | 4 (44%) | 5 (28%) | 1 (11%) |
| PD | 5 (56%) | 5 (56%) | 10 (56%) | 7 (78%) |
| **DCR (CR+PR+SD), %** | **44%** | **44%** | **44%** | **22%** |
| **ORR (CR+PR), %** | **33%** | **0%** | **17%** | **11%** |
| **PFS median (95% CI)** | **2.0 (1.0-8.6)** | **1.8 (0.8-9.3)** | **2.0 (1.8-4.5)** | **2,0 (1.8-NR)** |
| **OS median (95% CI)** | **9.7 (2.4-NR)** | **6.8 (2.0-NR)** | **9.7 (4.3-NR)** | **10.2 (4.0-NR)** |
| **FU median (IQR)** | 8.3 (4.0-9.7) | 6.8 (3.7-14.1) | 6.8 (4.0-11.5) | 5.7 (4.3-10.2) |

**Figure 1. Swimmer plot**

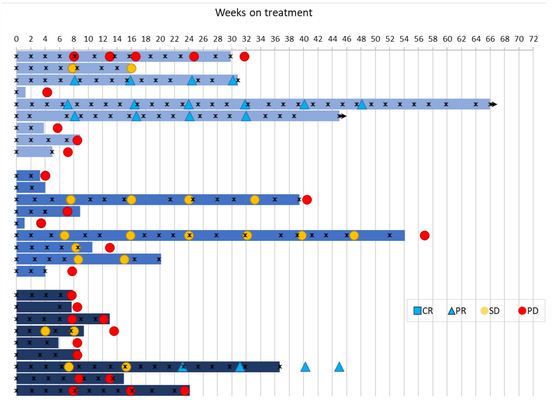
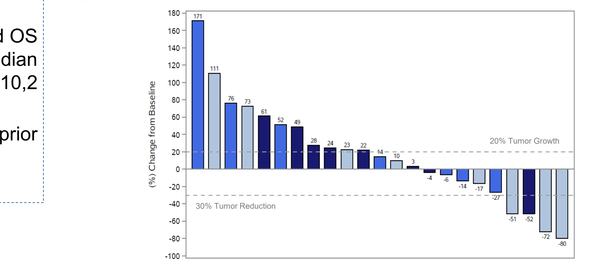
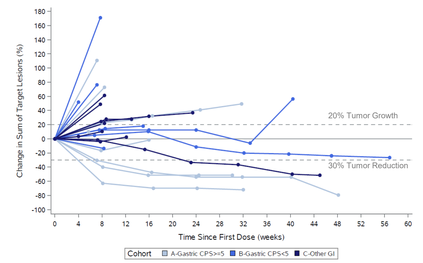



**Figure 2. Waterfall and Spider plot by best overall response**




**Conclusions** **Vorbipiprant combined with PD-1 blockade was well tolerated and showed signs of activity in non-colorectal GI cancers, thus confirming a broader spectrum of activity, on top of the results obtained in MSS mCRC. To further confirm preliminary positive results, a Phase II expansion in both MSS mCRC and GC patients is planned.**

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