PRESS RELEASE

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Vorbipiprant combined with PD-1 blockade for refractory microsatellite stable metastatic colorectal cancer phase I/II trial results published in Clinical Cancer Research

Monza (Italy) – Rottapharm Biotech announces that results from the phase I/II study of the EP4 antagonist vorbipiprant (CR6086) with an anti-PD-1 antibody (balstilimab, Agenus Inc, Nasdaq: AGEN) in mismatch-repair-proficient/microsatellite stable (pMMR/MSS) chemorefractory metastatic colorectal cancer (mCRC) have been published online in Clinical Cancer Research, one of the leading journals in cancer research.

The study was performed at the National Cancer Institute (Istituto Nazionale Tumori) in Milano, Italy, by the Gastroenterological Oncology Unit led by Dr. Filippo Pietrantonio, within the Department of Medical Oncology.

This was a phase 1b/2a prospective single-arm trial following a dose escalation/optimization design (28 patients, receiving oral vorbipiprant 30, 90, or 180 mg b.i.d.). No dose-limiting toxicities were observed, and the combination was well-tolerated across doses. The combination achieved a disease control rate (DCR) of 50% across the entire cohort, and a notable DCR of 25% in the subgroup of patients with liver metastases, that are usually refractory to immunotherapy approaches. The overall response rate (ORR) was 11% with a median duration of response of 7.4 months. Median overall survival (OS) was 14.2 months. Dose optimization led to the selection of 90 mg b.i.d. as the vorbipiprant dose for further development.

While providing the proof-of-concept that vorbipiprant can convert immune-resistant mCRC into a tumor responsive to anti-PD-1 inhibition, the extensive translational analyses in tumor and blood samples of enrolled patients suggested that vorbipiprant may boost response to anti-PD-1 in patients with partially immunogenic tumors, where the effects of immune-checkpoint inhibitors can be effectively activated.

"*We all know that the one-size-fits-all strategy is not reasonable for microsatellite stable advanced refractory CRC patients, and rational development of immunotherapy combinations is necessary.*" commented Lucio Rovati, MD, Chief Scientific Officer at Rottapharm Biotech. "*The combination of vorbipiprant and a PD-1 inhibitor yielded promising activity in refractory pMMR/MSS mCRC, worth of confirmation in future clinical trials in*

biomarker-enriched populations. Indeed, vorbipiprant performed particularly well in immune-enriched MSS tumors."

He also added: "*Patient selection will be key to advance immunotherapy in MSS mCRC and vorbipiprant plus anti-PD-1 therapy may be a well-tolerated immunotherapy backbone to be investigated in future trials in molecularly selected subgroups. We want to pursue this specific signal, and we are now expanding the study to consolidate these data, enriching the study population and the translational analyses.*"

The publication
"*The Prostaglandin EP4 Antagonist Vorbipiprant Combined with PD-1 Blockade for Refractory Microsatellite Stable Metastatic Colorectal Cancer: A Phase 1b/2a Trial*" by Pietrantonio F, et al. Clinical Cancer Research 2024
https://doi.org/10.1158/1078-0432.CCR-24-2611

The open access paper can be downloaded at the link in the reference above.

About CR6086 (vorbipiprant)
CR6086 (vorbipiprant) is a novel targeted immunomodulator acting as an antagonist at the prostaglandin E2 (PGE2) receptor EP4 subtype. EP4 receptors have an important role in the altered immune response observed in autoimmune diseases. PGE2-EP4 signalling plays a major immunosuppressive role in the tumour microenvironment, and as such it favours cancer immune escape and tumour progression. Consistently, experimental evidence suggests that EP4 receptor antagonists may improve the response to immune checkpoint inhibitors (ICIs).
A Phase I/II clinical trial to evaluate the safety and efficacy of CR6086 in combination with the PD-1 inhibitor balstilimab in patients with pretreated mismatch-repair-proficient and microsatellite stable metastatic colorectal cancer, and other metastatic GI cancers, provided promising results.

About Rottapharm Biotech
Rottapharm Biotech is a research company dedicated to the discovery and development of innovative drugs. It is located in Monza (Italy). The company expertise in research and development includes medicinal/computational chemistry for small molecules, development of biologics and advanced therapies, new targets validation, pharmacological and pharmacokinetic characterization of new drug candidates, original formulations, and design of innovative clinical trials. The company strategy is to develop its own pipeline independently and then seek partnerships with pharmaceutical companies, as well as investing in alliances on innovative projects of other biotech companies or university spin-offs.

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