# A randomized blinded Phase 2 study of ompenaclid vs placebo in combination with FOLFIRI plus bevacizumab in patients with previously treated RAS-mutated advanced/metastatic colorectal cancer

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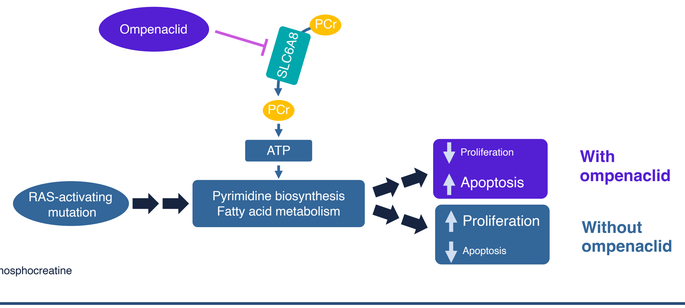
## Background

- Colorectal cancer (CRC) is the 2nd most common cause of cancer death.[1]
- Up to 45% of patients with metastatic CRC (mCRC) have RAS-mutated (RAS-mut) tumors.[2]
- Median progression-free survival for patients with RAS-mut mCRC receiving second-line standard of care treatment is only ~5-6 months and median overall survival is ~11-18 months.[3]
- There is an urgent need to develop novel therapies to improve outcomes for patients with RAS-mut and advanced/mCRC.

## Rationale

- In mCRC, the creatine pathway is activated through upregulation of the creatine transporter SLC6A8 and creatine kinase B (CKB).[4]
- Activation of the creatine pathway fuels cancer cell survival and metastatic progression.[4]
- In animal models of colon cancer, knockdown of SLC6A8 or CKB suppresses metastatic liver colonization.[4]
- Ompenaclid (RGX-202-01) is a first-in-class oral SLC6A8 inhibitor that reduces intracellular creatine and adenosine triphosphate (ATP) leading to tumor cell apoptosis (Fig 1).[5]

### Figure 1. Ompenaclid mode of action



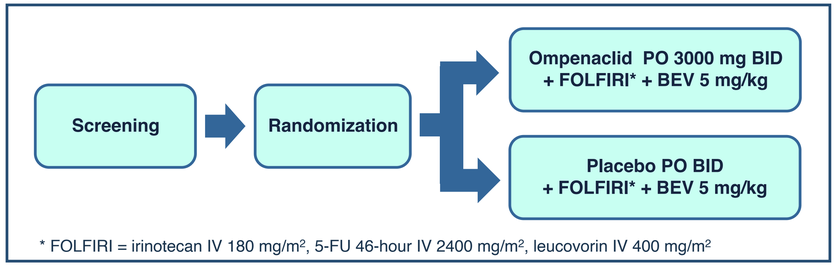

By depleting intracellular ATP levels, ompenaclid inhibits multiple pathways, including pyrimidine synthesis and fatty acid metabolism. These pathways generate critical building blocks upon which RAS-mut tumors depend for growth and survival.[6] Unlike RAS-mut targeting agents, ompenaclid's mechanism of action interferes with multiple downstream biosynthetic pathways.

- Clinical data suggest robust and maximal pharmacodynamic effects are achieved with ompenaclid ≥ 2400 mg twice daily (BID).[7,8]
- In patients with RAS-mut mCRC, ompenaclid monotherapy demonstrated anti-tumor activity with a favorable safety profile and without dose-limiting toxicities.[7]
- In an open-label, single arm study, ompenaclid + leucovorin, 5-fluorouracil (5-FU), irinotecan (FOLFIRI) and bevacizumab (BEV), was shown to have potential clinical benefit and tolerable safety profile in patients with RAS-mut mCRC.[9]
- The aim of this study is to assess the efficacy of ompenaclid in patients with previously treated RAS-mut advanced/mCRC.

## Study design

- A Phase 2, randomized, double-blind, placebo-controlled study.
- Recruitment is near complete with ~70 patients with RAS-mut advanced/mCRC enrolled in Spain, Belgium and France.
- All patients receive irinotecan intravenously (IV) 180 mg/m$^2$, 5-FU 46-hour IV 2400 mg/m$^2$, leucovorin IV 400 mg/m$^2$ and BEV IV 5 mg/kg every 2 weeks.
- Patients are randomized 1:1 to receive oral (PO) placebo or ompenaclid 3000 mg BID (Fig 2).
- Tumor assessments per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 are performed every 8 weeks.
- Safety is assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.
- Treatment continues until progressive disease or other discontinuation criteria are met.
- An independent Data Monitoring Committee is conducting unblinded interim safety and efficacy analyses.
- Following the last dose of ompenaclid, patients are followed for safety at 30 days and for survival approximately every 3 months for up to 2 years.

### Figure 2. Study schema




* FOLFIRI = irinotecan IV 180 mg/m$^2$, 5-FU 46-hour IV 2400 mg/m$^2$, leucovorin IV 400 mg/m$^2$

## Key objectives and endpoints

| Objective | Endpoint |
|---|---|
| **Primary** | |
| • Compare ompenaclid efficacy vs placebo | • Overall response rate per RECIST 1.1 |
| **Secondary** | |
| • Compare additional ompenaclid efficacy parameters vs placebo | • Progression-free survival<br>• Overall survival<br>• Duration of response<br>• Disease control rate |
| • Determine the safety of treatment with ompenaclid | • Adverse events, performance status, physical examinations, clinical laboratory values, vital signs, electrocardiogram |
| • Assess pharmacokinetics of ompenaclid | • Pharmacokinetic parameters |
| • Evaluate exploratory biomarkers that may correlate with efficacy outcomes | • CKB levels identified in baseline tumor samples |

## Key inclusion criteria

- Metastatic or locally advanced and unresectable adenocarcinoma of the colon or rectum.
- RAS-mut tumor confirmed by local laboratory.
- Progression following first-line oxaliplatin-containing regimen for advanced/mCRC.

  *Note*: patients with metastatic recurrence within 12 months of completion of (neo)adjuvant therapy are also eligible.

  *Note*: patients with mismatch repair deficiency/high microsatellite instability must have been treated with pembrolizumab or an approved programmed cell death protein 1 or ligand 1 (PD-1/L1) inhibitor.
- Measurable disease per RECIST v 1.1.
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1.
- Adequate organ function.

## Key exclusion criteria

- Prior therapy within stated timeframes of ompenaclid administration:
  - chemotherapy, external-beam radiation, or systemic anticancer therapy ≤ 14 days;
  - nitrosourea or mitomycin-C within ≤ 42 days;
  - investigational systemic anticancer agent ≤ 28 days or < 5 half-lives.
- Previously received FOLFIRI or other irinotecan-containing treatment regimens.
- Treatment with strong CYP3A4 inhibitors or strong UGT1A1 inhibitors.
- Marked proteinuria (≥ 2 g/24 hours) and/or nephrotic syndrome.

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**FPN: 600TiP**

**References: 1.** WHO/International Agency for Research on Cancer www.iarc.who.int/cancer-type/colorectal-cancer. **2.** Jones et al. *Br J Cancer* 116, 923-929 (2017). **3.** Fakih et al. *Oncologist* 27(8), 663-674 (2022). **4.** Loo et al. *Cell* 160, 393-406 (2015). **5.** Kurth et al. *Sci Adv* 7 (2021). **6.** Mukhopadhyay et al. *Nat Cancer* 2(3) 2021. **7.** Bendell et al. *J Clin Oncol* 38(15) 2020 Suppl 3504. **8.** Hendifar et al. *J Clin Oncol* 40(16) 2022 Suppl 3579. **9.** Hendifar et al. *Ann Onc* 34 (suppl_2) 2023 abstract 646P.

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