Phase 1b study of ompenaclid (RGX-202-01), a first-in-class oral inhibitor of the creatine transporter SLC6A8, in combination with FOLFIRI and bevacizumab in RAS-mutated second-line advanced/metastatic colorectal cancer – updated results

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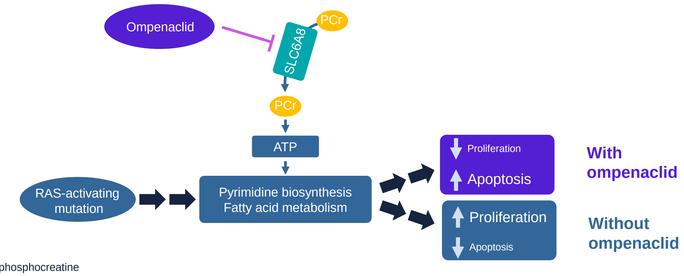
Introduction

- RAS-mutated (RAS-mut) tumors are present in up to 45% of patients with metastatic colorectal cancer (mCRC).[1]
- mCRC cell survival is aided by the upregulation of creatine kinase B and the creatine transporter SLC6A8.[2]
- Ompenaclid (RGX-202-01) is an oral SLC6A8 inhibitor that reduces intracellular phosphocreatine (PCr) and adenosine triphosphate (ATP) pools, inducing tumor cell apoptosis (Figure 1).[3]
- In animal models, ompenaclid plus 5-fluorouracil (5-FU) exhibited synergistic anti-tumor efficacy.[3]
- In patients with RAS-mut mCRC, ompenaclid monotherapy exhibited anti-tumor activity, a favorable safety profile and no dose-limiting toxicities.[4]
- Clinical data indicate that ompenaclid ≥ 2400 mg twice daily (BID) provides robust and maximal pharmacodynamic effects.[4,5]
- Ompenaclid has activity in RAS-mut mCRC regardless of the specific mutation.[5]
- In RAS-mut mCRC, 2nd-line FOLFIRI/bevacizumab (BEV) has an overall response rate (ORR) of ~15%, median progression-free survival (mPFS) of ~5–6 months and median overall survival (mOS) of ~11–18 months.[6]
- The aims of this Phase 1b study are to evaluate efficacy and safety of standard of care (SOC) (FOLFIRI/BEV) plus ompenaclid as 2nd-line therapy in patients with RAS-mut mCRC.

Figure 1. Ompenaclid mechanism of action



PCr = phosphocreatine

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.[7] Unlike RAS-mut targeting agents, ompenaclid's mechanism of action interferes with multiple downstream biosynthetic pathways.

Methods

Key eligibility criteria

- RAS-mut advanced/mCRC; wild type (WT) patients were also initially enrolled.
- Measurable disease by Response Evaluation Criteria in Solid Tumour (RECIST) version 1.1, Eastern Cooperative Oncology Group (ECOG) ≤ 1.
- Demonstrated progression with an oxaliplatin-based regimen.
- Only 1 prior line of therapy for advanced/mCRC with the following exception:
  - Patients were eligible if they had recurrence within 12 months of completion of an oxaliplatin-based adjuvant therapy and no treatment for advanced/mCRC.
- Adequate organ function.

Table 1. Baseline characteristics

RAS status		RAS-mut (n=46)	WT (n=9)
Median age, years (range)		58 (31–82)	63 (32–85)
Race, n (%)	White	36 (78)	6 (67)
	African American	8 (17)	1 (11)
	Asian	1 (2)	0
	Not reported / other	1 (2)	2 (22)
Sex, n (%)	Male	27 (59)	6 (67)
	Female	19 (41)	3 (33)
ECOG, n (%)	0	23 (50)	4 (44)
	1	23 (50)	5 (56)
≥ 2 metastatic organ sites, n (%)		38 (83)	9 (100)
Prior therapies, n (%)	Oxaliplatin + 5-FU	46 (100)	9 (100)
	Bevacizumab	30 (65)	8 (89)

Study treatment

- All patients received ompenaclid (2400 or 3000 mg BID) in combination with FOLFIRI/BEV:
  - BEV intravenous (IV) 5 mg/kg, followed by irinotecan 180 mg/m^2 IV concurrently with folinic acid 400 mg/m^2 IV, followed by 5-FU 2400 mg/m^2 IV over 46 hours on Days 1 and 15 of each 28-day cycle.

References:
1. Jones et al. *Br J Cancer* 116, 923-929 (2017). **2.** Loo et al. *Cell* 160, 393-406 (2015). **3.** Kurth et al. *Sci Adv* 7 (2021). **4.** Bendell et al. J *Clin Oncol* 38(15) 2020 Suppl 3504. **5.** Hendifar et al. J *Clin Oncol* 40(16) 2022 Suppl 3579. **6.** Fakih et al. *Oncologist* 27(8), 663-674 (2022). **7.** Mukhopadhyay et al. *Nat Cancer* 2(3) 2021.

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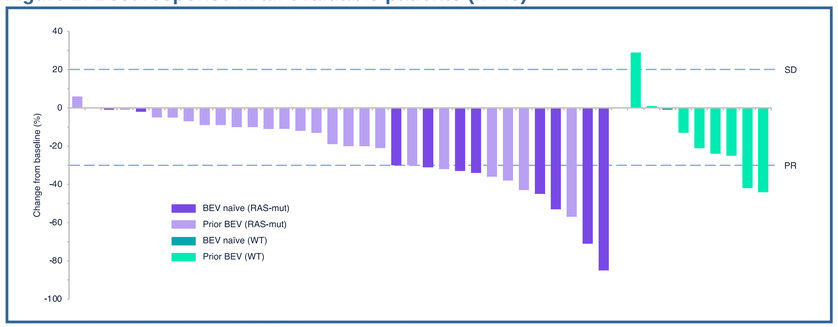
Results

Efficacy

Figure 2. Best response in all evaluable patients (n=43)

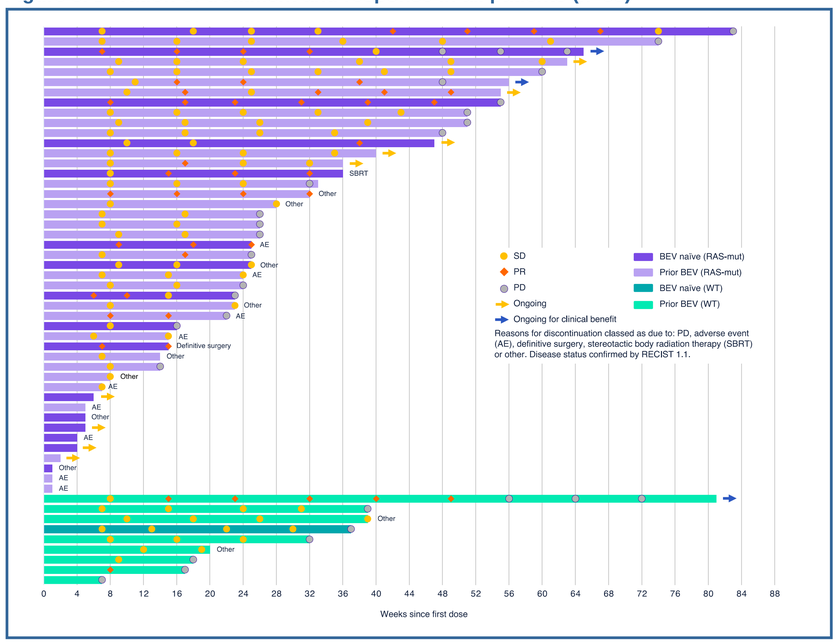


Percentage change from baseline of tumors in evaluable patients. Data cut-off 4 Jun 2024; open database.

Summary of efficacy

- Patients with RAS-mut mCRC experienced durable clinical benefit with an ORR of 41%, duration of response of 9.4 months and mPFS of 11.0 months.
- Clinical benefit (PRs and durable SDs) was observed in patients with diverse *KRAS* and *NRAS* mutations.
- Patients with WT mCRC had an ORR of 22%, duration of response of 5.7 months and mPFS of 8.7 months.
- BEV-naïve patients with RAS-mut mCRC experienced a higher response rate of 57% (8 of 14 patients).
- ORR and mPFS observed to date in patients with RAS-mut tumors clearly exceed that expected with SOC FOLFIRI/BEV alone in 2nd-line mCRC.
- Median time to response in RAS-mut tumors was 2.9 months. Tumor regressions generally deepened over time in patients with RAS-mut tumors.
- First radiographic evidence of PR appearing as late as 40 weeks after initiation of study therapy.

Figure 3. Duration of treatment and response in all patients (n=55)



Data cut-off 4 Jun 2024; open database.

Table 2. Best response

- Preferential activity in RAS-mut vs WT is consistent with preclinical and Phase 1 data.

RAS status (evaluable patients)	RAS-mut (n=34)	WT (n=9)
PR, n (%)	14 (41)	2 (22)
SD, n (%)	20 (59)	6 (67)
PD, n (%)	0 (0)	1 (11)

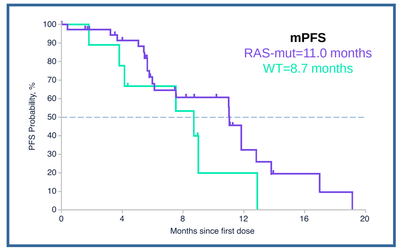
Patients were evaluable for RECIST 1.1 response if they completed at least one treatment cycle and had at least one follow-up scan for RECIST assessment.

55 enrolled patients: 46 RAS-mut mCRC (34 evaluable and 12 not evaluable [6 dropped out without a scan, 4 ongoing and yet to be scanned, 2 treated with insufficient dose]) and 9 WT mCRC (all evaluable).

- The response rate in the RAS-mut ITT patient population was 30%.

Figure 4. PFS in RAS-mut vs WT mCRC

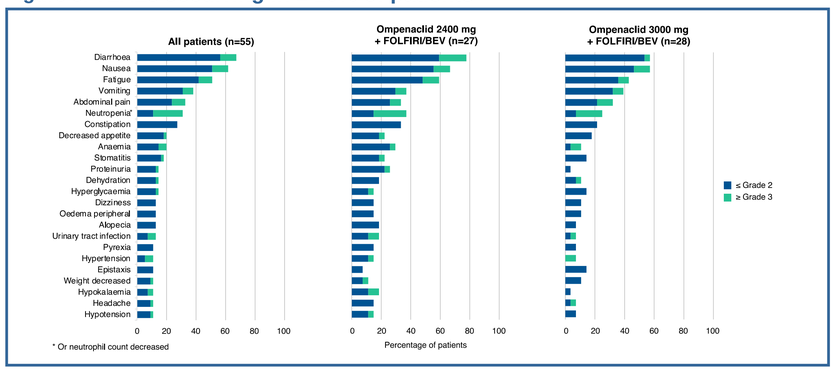
- Ompenaclid + SOC increased mPFS and mOS in RAS-mut vs WT mCRC.



PFS analysis included all patients enrolled (n=55). PFS data are not yet final as of the cut-off date 4 Jun 2024 due to continuing patient follow-up and the limited number of PD events.

Safety

Figure 5. TEAEs occurring in ≥ 10% of patients



* Or neutrophil count decreased

Data cut-off 4 Jun 2024.

- The most common Grade ≤ 2 TEAEs were diarrhea (56%) and nausea (51%).
- The most frequent Grade ≥ 3 TEAEs were neutropenia (20%), diarrhea (11%) and nausea (11%).
- The only Grade 5 TEAE was 1 patient with an intestinal perforation, deemed related to BEV.
- At the evaluated dose levels, ompenaclid added to FOLFIRI/BEV was well tolerated.

Conclusion

- Ompenaclid plus FOLFIRI/BEV provided promising efficacy
- Treatment with ompenaclid resulted in clinical benefit, with durable ORR and PFS exceeding that of 2nd-line SOC in RAS-mut mCRC.
- The overall safety profile is similar to SOC and other anti-angiogenic combinations in 2nd-line patients with mCRC.
- Ompenaclid has activity in RAS-mut mCRC regardless of the specific mutation.[5]
- Preferential activity in patients with RAS-mut mCRC is consistent with preclinical and Phase 1 data.
- Ompenaclid represents a novel approach to target pan-RAS-mut mCRC, a population with high unmet medical need.
- An ongoing randomized Phase 2 blinded placebo-controlled trial will further explore the safety and efficacy of the combination of ompenaclid with FOLFIRI/BEV in 2nd-line RAS-mut mCRC.

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A. Hendifar has no conflict of interest to declare.
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