Phase 1b/2 study of ompenaclid, 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

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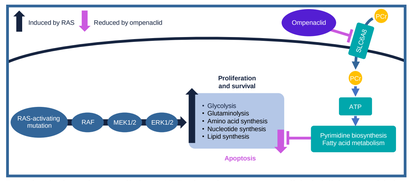
Introduction

- Colorectal cancer (CRC) is the 2nd most common cause of cancer death, causing almost 1 million deaths/year.[1]
- Up to 45% of patients with metastatic CRC (mCRC) have RAS-mutant (RAS-mut) tumors.[2]
- SLC6A8, which imports creatine and phosphocreatine (PCr), is upregulated in mCRC cells to aid survival under hypoxia.
- Ompenaclid (RGX-202-01) is a first-in-class oral SLC6A8 inhibitor that reduces intracellular PCr and adenosine triphosphate (ATP) leading to tumor cell apoptosis (Fig 1).[3]
- Targeting the metabolic dependencies of RAS-mut mCRC broadens the therapeutic approach, regardless of a specific RAS pathway mutation.
- On target resistance to SLC6A8 has not been observed with ompenaclid in preclinical models.
- In animal models, ompenaclid monotherapy demonstrated robust anti-tumor activity and exhibited synergistic efficacy with 5-fluorouracil (5-FU).[4]
- In patients with RAS-mut mCRC, ompenaclid monotherapy demonstrated anti-tumor activity with a favorable safety profile without dose-limiting toxicities (DLTs).[5]
- Clinical data suggest robust and maximal pharmacodynamic effects are achieved with ompenaclid ≥ 2400 mg twice daily (BID).[5,6]

Fig 1. Ompenaclid mechanism 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. Unlike other RAS-mut targeting agents, ompenaclid's mechanism of action interferes with multiple downstream biosynthetic pathways.

- Preliminary efficacy data suggest that ompenaclid has activity in RAS-mut mCRC regardless of the specific mutation.[6]
- FOLFIRI/bevacizumab (BEV) is a standard-of-care (SOC) 2nd line regimen for mCRC, which provides overall response rate (ORR) of ~15%, median progression-free survival (mPFS) of ~5-6 months and median overall survival (mOS) of ~11-18 months.[7]
- The aims of this phase 1b/2 study are to evaluate safety, pharmacodynamics and pharmacokinetics (PK/PD) and efficacy of ompenaclid plus SOC (FOLFIRI/BEV) in 2nd line RAS-mut mCRC.

Methods

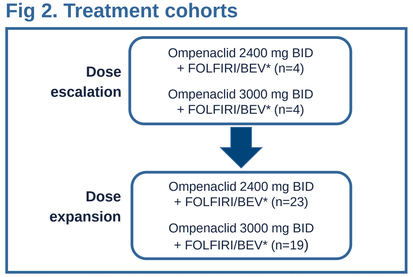
Key eligibility criteria

- Advanced (adv) or metastatic RAS-mut CRC; 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 adv/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 adv/mCRC.

Table 1. Baseline characteristics

RAS status (n)		RAS-mut (n=41)	WT (n=9)
Median age, years (range)		58 (43-82)	63 (32-85)
Race, n (%)	White	32 (78)	6 (67)
	African American	7 (17)	1 (11)
	Asian	1 (2)	0
	Not reported / other	1 (2)	2 (22)
Sex, n (%)	Male	25 (61)	6 (67)
	Female	16 (39)	3 (33)
ECOG, n (%)	0	20 (49)	4 (44)
	1	21 (51)	5 (56)
≥ 2 metastatic organ sites, n (%)		34 (83)	9 (100)
Prior therapies, n (%)	Oxaliplatin + 5-FU	41 (100)	9 (100)
	BEV	28 (68)	8 (89)

Fig 2. Treatment cohorts



*BEV intravenous (IV) 5 mg/kg, followed by irinotecan 180 mg/m² IV concurrently with folinic acid 400 mg/m² IV, followed by 5-FU 2400 mg/m² IV over 46 hours on days 1 and 15 of each 28-day cycle.

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.** Loo *et al. Cell* 160, 393-406 (2015). **4.** Kurth *et al. Sci Adv* 7 (2021). **5.** Bendell *et al. J Clin Oncol* 38(15) 2020 Supple 3504. **6.** Hendifar *et al. J Clin Oncol* 40(16) 2022 Suppl 3579. **7.** Bennouna *et al. Lancet Oncol.*14, 29-37 (2013).

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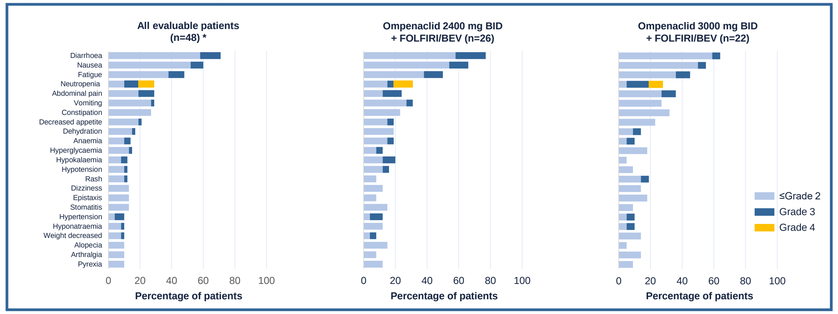
Results

Safety

Fig 3. TEAEs occurring in ≥ 10% of patients

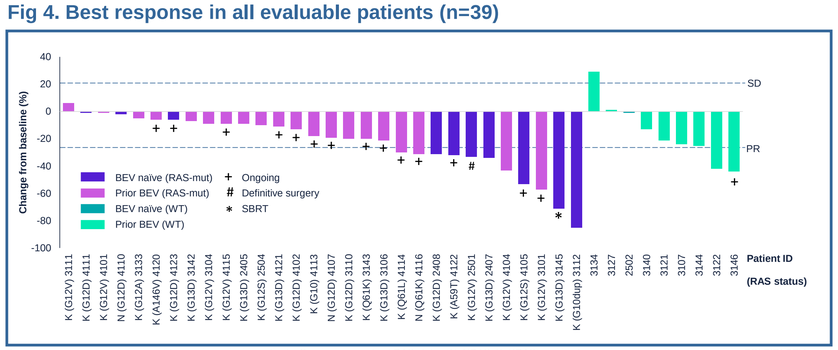


*Includes all patients who have discontinued study treatment and patients with study treatment ongoing who have completed ≥ 1 cycle with AE data entered. Data cut-off 18 Sep 2023.

- In the Dose Escalation Phase, there were no DLTs observed for either the 2400 mg BID or 3000 mg BID dose with the combination.
- The most common Grade ≤ 2 TEAEs were diarrhea (58%) and nausea (52%).
- The most frequent Grade ≥ 3 TEAEs were neutropenia (18%), diarrhea (13%), fatigue (10%) and abdominal pain (10%).
- The only Grade 5 TEAE was 1 patient (2% of total patients) with an intestinal perforation, deemed related to BEV.
- At the evaluated dose levels, ompenaclid added to FOLFIRI/BEV was well tolerated.

Efficacy

Fig 4. Best response in all evaluable patients (n=39)



Percentage change from baseline of tumors in evaluable patients. Graph shows patient RAS status (N=NRAS, K=KRAS) and best overall response after ompenaclid + FOLFIRI/BEV treatment. Data cut-off 18 Sep 2023; open database.

Table 2. Best response

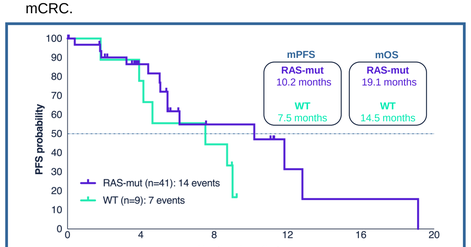
- Preferential activity in RAS-mut vs WT is consistent with preclinical and Phase 1 data.

RAS status (evaluable patients)	RAS-mut (n=30)	WT (n=9)
PR, n (%)	11 (37)	2 (22)
Confirmed PR, n	8*	1*
Unconfirmed PR, n	3**	1†
SD, n (%)	19 (63)	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.
* Response confirmed by a follow-up scan. ** One PR scan and therapy continues with next scans pending. † One PR scan and then therapy discontinued.
Summary: Total enrolled patients: 50 = 41 RAS-mut (30 evaluable, 8 not evaluable for ORR, 3 patients enrolled pending 1st scans) + 9 WT (all evaluable).

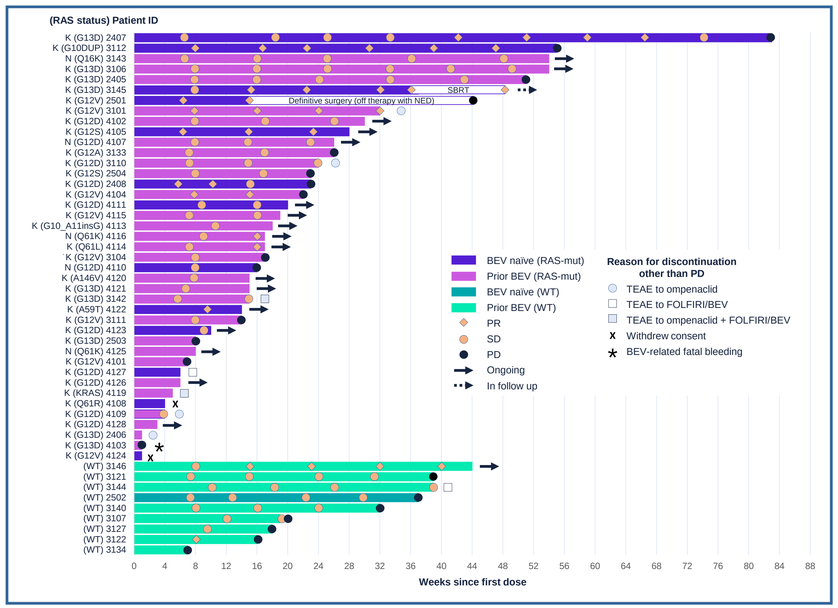
Fig 5. PFS in RAS-mut vs WT mCRC

- Ompenaclid + SOC increased PFS and OS in RAS-mut vs WT mCRC.



PFS analysis included all patients enrolled (n=50). PFS data are not yet final as of the cut-off date 18 Sep 2023 due to continuing patient follow-up and the limited number of PD events.

Fig 6. Duration of treatment and response in all patients (n=50)



Graph shows patient RAS status (N=NRAS, K=KRAS). Data cut-off 18 Sep 2023; open database, data subject to change.

Summary of efficacy

- Patients with RAS-mut mCRC experienced durable clinical benefit with an ORR of 37% and mPFS of 10.2 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% and a mPFS of 7.5 months.
- Patients not previously treated with BEV experienced a higher response rate.
- 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.
- Tumor regressions generally deepened over time in patients with RAS-mut tumors, with first radiographic evidence of PR appearing as late as 40 weeks after initiation of study therapy, consistent with previously presented ompenaclid monotherapy Phase 1 and preclinical efficacy data.[4,5]

PK/PD

- Systemic exposure was comparable with both doses with up to a x48 increase in urine creatine, suggesting robust target inhibition.[6]

Conclusion

- Ompenaclid plus FOLFIRI/BEV provided encouraging efficacy and induced potent inhibition of SLC6A8.
- Treatment with ompenaclid resulted in clinical benefit, with ORR and PFS exceeding that of 2nd line SOC in RAS-mutant mCRC.
- The overall safety profile is similar to SOC and other anti-angiogenic combinations in 2nd line patients with mCRC.
- Preferential activity in patients with RAS-mutant mCRC is consistent with preclinical and Phase 1 data.
- Ompenaclid represents a novel approach to target pan-RAS-mutant mCRC, a population with high unmet medical need.
- An ongoing Phase 2 blinded randomized placebo-controlled trial will further explore the safety and efficacy of the combination of ompenaclid with FOLFIRI/BEV in 2nd line RAS-mutant mCRC and will include a subgroup analysis based on usage of BEV in the 1st line setting.