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


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 hypoxic conditions.3-5
• Ompenaclid (RGX-202-01) is a first-in-class oral SLC6A8 inhibitor that reduces intracellular PCr and adenosine triphosphate (ATP) levels, leading to tumor cell apoptosis (Fig. 1).6
• Targeting the metabolic dependencies of RAS-mut mCRC tumors invades the therapeutic approach, regardless of a specific RAS pathway mutation.7
• 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).8
• In patients with RAS-mut mCRC, ompenaclid monotherapy demonstrated anti-tumor activity with a favorable safety profile without dose-limiting toxicities (DLTs).9
• Clinical data suggest robust and maximal pharmacodynamic improvements are achieved with ompenaclid ≥ 2400 mg twice-daily (BID).10

Fig 1. Ompenaclid mechanism of action

By inhibiting 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 manipulates action interferences with multiple downstream biochemical pathways.11

Methods

Key eligibility criteria

• Advanced (ad) or metastatic RAS-mut CRC, wild-type (WT) patients were also initially enrolled.
• Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, Eastern Cooperative Oncology Group (ECOG) ≤ 1.
• Demonstrated progression with an osilaplatin-based regimen.
• Only 1 prior line of therapy for admCRC with the following exceptions: patients who had if they had recurrence within 12 months of completion of an osilaplatin-based adjacent therapy and no treatment for admCRC.

Fig 2. Treatment cohorts

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>RAS status (%)</th>
<th>WT (n=22)</th>
<th>RAS- mut (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race, %</td>
<td>White</td>
<td>77 (10)</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>Median 64</td>
<td>66 (10)</td>
</tr>
<tr>
<td>Sex, %</td>
<td>Male</td>
<td>55 (10)</td>
</tr>
<tr>
<td>ECOG</td>
<td>0</td>
<td>92 (10)</td>
</tr>
<tr>
<td>ECOG</td>
<td>1</td>
<td>8 (10)</td>
</tr>
<tr>
<td>2 Pretreatment organ sites, %</td>
<td>9 (10)</td>
<td>26 (30)</td>
</tr>
<tr>
<td>Prior chemotherapy, %</td>
<td>0</td>
<td>86 (10)</td>
</tr>
<tr>
<td>BEV naïve</td>
<td>0</td>
<td>95 (10)</td>
</tr>
</tbody>
</table>

Table 2. Best response in RAS-mut vs WT

<table>
<thead>
<tr>
<th>RAS status (%)</th>
<th>WT (n=22)</th>
<th>RAS- mut (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS, mos</td>
<td>4.0 (10)</td>
<td>1.5 (10)</td>
</tr>
<tr>
<td>mOS, mos</td>
<td>15.9 (10)</td>
<td>9.7 (10)</td>
</tr>
</tbody>
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Table 3. Summary of efficacy

• Patients with RAS-mut mCRC experienced durable clinical benefit with an ORR of 37% and mPFS of 10.3 months.
• Clinical benefit (PRs and durable SDs) was observed in patients with diverse KRAS and NRAS mutations.
• Patients with BEV naïve 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.

Fig 3. TEAEs occurring in ≥ 10% of patients

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

Summary of efficacy

- 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 data.12-14

PKPD

- Systemic exposure was comparable with both doses with up to a 4× increase in urine creatine, suggesting robust target inhibition.15

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-mut 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- 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 Phase 2 blinded randomized placebo-controlled trial will further explore the safety and efficacy of the combination of ompenaclid with FOLFIRI/BEV in both RAS-mutant mCRC and will include a subgroup analysis based on usage of BEV in the 1st line setting.