**Background**

- Colorectal cancer is the second most common cause of cancer death in the US.
- The cancer-specific mortality of colorectal cancer is predominantly due to metastatic disease. Despite significant progress in the treatment of metastatic CRC (mCRC), most patients succumb to the disease.
- RAS-mutant mCRC represents ~50% of mCRC patients and have poorer prognosis than RAS wild-type patients.
- Chemotherapy in combination with bevacizumab (Bev) has been a standard first-line treatment for RAS-mutated mCRC patients for the last 2 decades. The prognosis of these patients remains poor.

**Rationale**

Onvansertib: a promising therapeutic option for RAS-mutant mCRC:
- Oral, highly selective PUK1 inhibitor.
- Potent activity in CRC preclinical models as single agent and in combination with irinotecan.
- The combination of onvansertib + Bev resulted in synergistic antitumor activity in KRAS-mutant CRC patient-derived xenograft models (Poster #2033).
- The combination of oxaliplatin + 5-FU with onvansertib was also efficacious in CRC patient-derived xenograft models (data not shown).

The Phase 1b/2 Study of Onvansertib + FOLFIRI/Bev (NCT03829410):
- Onvansertib + FOLFIRI/Bev demonstrated higher objective response rates (ORR = 29%) relative to historical controls, in the second-line treatment of patients with KRAS-mutated mCRC who had failed a first-line 5-FU/oxaliplatin containing regimen.
- Combination of onvansertib + FOLFIRI/Bev was well-tolerated.
- A subgroup analysis of baseline characteristics identified that patients not exposed to Bev in 1st line (Bev-naive) exhibit superior clinical benefit compared to patients who received Bev in 1st line: Objective response rate (ORR) - 73.3% vs 15.7% and median progression free survival (mPFS) - 14.9 vs 7.8 months, respectively.
- Please see, Poster #2031 for additional details.

**ENROLLMENT CRITERIA**

**1st line mCRC**

<table>
<thead>
<tr>
<th>KRAS+ / NRAS+</th>
<th>Unresectable</th>
<th>No prior bev, FOLFIRI or FOLFOX treatment</th>
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<tbody>
<tr>
<td>Onv 20mg + FOLFIRI/Bev or FOLFOX/Bev (n=30)</td>
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<tr>
<td>Onv 30mg + FOLFIRI/Bev or FOLFOX/bev (n=30)</td>
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<tr>
<td>SoC: FOLFIRI or FOLFOX/Bev (n=30)</td>
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Each arm will have an equal number of FOLFIRI/Bev and FOLFOX/Bev patients.

**Key Inclusion Criteria**

- Histologically confirmed metastatic colorectal cancer.
- Documented KRAS or NRAS mutation.
- No previous systemic therapy in the metastatic setting.
- Participants must be willing to submit archival tissue or undergo fresh biopsy for KRAS/NRAS status.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- WOCPP must use contraception or take measures to avoid pregnancy.
- Imaging computed tomography (CT) or magnetic resonance imaging (MRI) of chest/abdomen/pelvis and other scans as necessary to document all sites of disease performed within 28 days prior to the first dose of onvansertib.
- Measurable disease as defined per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).
- Must have acceptable organ function.

**Key Exclusion Criteria**

- Concomitant KRAS or NRAS and BRAF-V600 mutation or microsatellite instability high/deficient mismatch repair.
- Prior treatment with a VEGF inhibitor, including bevacizumab or biosimilars.
- Previous oxaliplatin treatment within 12 months prior to randomization, when arm open.
- Known dihydropyrimidine dehydrogenase (DPD) deficiency.
- Anticancer chemotherapy or biologic therapy administered within 28 days prior to the first dose of study drug.
- Untreated or symptomatic brain metastasis.
- Gastrointestinal (GI) disorder(s) that would significantly impede the absorption of an oral agent.
- Uncontrolled intercurrent illness.
- Abnormal glucononidation of bilirubin; known Gilbert's syndrome.
- Use of strong CYP3A4 or CYP2C19 inhibitors or strong CYP3A4 inducers.
- QTc > 470

**Study Design**

Primary
- Objective response rate (ORR) as determined according to RECIST v1.1 by an independent central review.

Key Secondary
- Progression-free survival (PFS) per independent central review.
- Duration of response (DoR) per independent central review.

Secondary
- Characterization of adverse events (AEs); effects on vital signs and laboratory parameters; changes from baseline in electrocardiograms (ECGs), weight, and Eastern Cooperative Oncology Group (ECOG) performance status.
- Disease Control Rate (DCR) per independent central review.
- Overall survival (OS).
- ORR, PFS, DCR, DoR, and OS associated with a reduction in ctDNA mutation allele frequency (MAF).
- PK of onvansertib and metabolites in combination with FOLFIRI and bevacizumab or FOLFOX and bevacizumab versus FOLFIRI and bevacizumab alone.
- Select the optimal dose of onvansertib for use in a future Phase III registrational study.

**Study Status**

- Open and enrolling at 35 sites (planned) in the US.

**References:**
5. Ahn et al., Clin Cancer Res 2024.