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# A Phase 2, Randomized, Open-label Study of Onvansertib in Combination with Standard-of-Care (SoC) Versus SoC Alone for First-line Treatment of RAS-mutated Metastatic Colorectal Cancer.

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## Background

- Colorectal cancer is the second most common cause of cancer death in the US[1].
- 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[2].
- 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 PLK1 inhibitor.
- Potent activity in CRC preclinical models as single agent and in combination with irinotecan[3,4,5].
- The combination of onvansertib + Bev resulted in synergistic antitumor activity in KRAS-mutant CRC patient-derived xenograft models (Poster#2031).
- 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-naïve) 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.

## Study Design

- This is a multicenter, randomized, open-label study to –
  - Assess the efficacy and safety of onvansertib (20 mg and 30 mg) in combination with FOLFIRI and bevacizumab or FOLFOX and bevacizumab versus FOLFIRI and bevacizumab or FOLFOX and bevacizumab alone.
  - Select the optimal dose of onvansertib for use in a future Phase III registrational study.

### ENROLLMENT CRITERIA

1st line mCRC

KRAS+/NRAS+

Unresectable

No prior bev, FOLFIRI or FOLFOX treatment

**R**
N=90
1:1:1

- Onv 20mg + FOLFIRI/Bev or FOLFOX/Bev (n=30)
- Onv 30mg + FOLFIRI/Bev or FOLFOX/bev (n=30)
- SoC: FOLFIRI/Bev or FOLFOX/Bev (n=30)

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.
- WOCP 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 glucuronidation of bilirubin; known Gilbert's syndrome.
- Use of strong CYP3A4 or CYP2C19 inhibitors or strong CYP3A4 inducers.
- QTc >470

## Study Endpoints

**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.
- PK and PD exposure response-evaluation.

## Study Status

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

References:

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