Phase 1b/2 Study of the Polo-like kinase 1 (PLK1) Inhibitor, Onvansertib, in Combination with FOLFIRI and Bevacizumab for Second Line Treatment of KRAS-Mutated Metastatic Colorectal Cancer

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Background

Effective second-line treatment is needed in KRAS-mutated metastatic colorectal cancer (mCRC)

• Second-line treatments (chemotherapy ± targeted agents) have a poor prognosis: 5-13% response rates, median progression-free survival (PFS) 2-6 months, median overall survival (OS) 6-9 months

• KRAS is mutated in 40-50% of CRC patients and, to-date, RAS-therapies have failed with the majority of KRAS mutations considered to be undruggable:
  - Anti-farnesyl inhibitors and inhibitors of downstream effectors of RAS show no, or limited, efficacy
  - Covalent inhibitors of KRAS G12C (representing 8% of KRAS mutations in CRC) have shown limited activity in CRC

• Alternative strategies to inhibit KRAS include targeting synthetic lethal partners of mutant KRAS (i.e. proteins that are essential in KRAS-mutant but not wild-type cells)

• Onvansertib, an oral and highly-specific PLK1 inhibitor, is a promising therapeutic option for KRAS-mutated CRC:
  - PLK1, a key regulator of mitosis, is overexpressed in CRC and associated with poor clinical parameters1

• A genome-wide RNAi screen identified PLK1 inhibition to be synthetic lethal with mutant KRAS in CRC1,2

• KRAS mutated cells were hypersensitive to inhibition of PLK1

Anti-Tumor Activity of Onvansertib in Combination with Irinotecan and 5-FU in the HCT-116 KRAS-mutant CRC Xenograft Model

Phase 1b/2 Trial Design and Objectives (NCT03829410)

Onvansertib in combination with FOLFIRI and bevacizumab in second line KRAS-mutated mCRC

Study Design

• Phase 1b: onvansertib dose escalation (12, 15, 18 mg/m2) in successive cohorts of 3 patients and dose limiting toxicities (DLTs) evaluated during the 1st cycle (28 days)

• Phase 2: expansion cohort at the MTD or RP2D

Efficacy endpoints:

• Primary: objective response rate (ORR) in patients who receive at least 1 cycle of treatment

• Secondary: progression-free survival (PFS) and reduction in KRAS allele burden assessed by liquid biopsy

Phase 1b Enrollment and Baseline Characteristics

As of August 20, 2020

| Variable | n (%)
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<td>Number of patients (n)</td>
<td>19</td>
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<td>Number of cycles treated (N)</td>
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Tumors treated: 12 KRAS mutant, 14 KRAS wild-type

Most Common Treatment-Emergent Adverse Events

• Safety
  - 2 patients had DLTs that were both attributed to the 5-FU bolus: GI-neutropenia (above dose level 12 mg/m2) and GI neoplasms (above dose level 18 mg/m2)

  - 12 mg/m2 and 15 mg/m2 dose levels were cleared for safety; 4 patients have been treated at 18 mg/m2 dose level and 2 more will be enrolled

  - Grade 3/4 adverse events (AEs) reported in 32 patients were neutropenia, anemia, and abdombinal pain (n=2); resolved within 2.5 weeks

  - No major or unexpected toxicities were attributed to onvansertib

  - 4 (40%) of the 11 evaluable patients achieved a partial response (PR), including 4 confirmed PRRs and 1 patient proceeded to curative surgery

  - 4 (36%) patients had durable responses of >5.5 months (range 5.5 to 12 months)

  - Only 3 patients progressed in <6 months while on treatment

Preliminary Efficacy

Preliminary efficacy demonstrated onvansertib + FOLFIRI and bevacizumab in the first 11 evaluable patients

• 5 (45%) patients achieved partial response (PR)

• 4 patients had confirmed PR; 1 patient went to curative surgery; 1 patient who confirmed PR did not proceed to treatment

• 3/4 patients with measurable responses of >5.5 months (range 5.5 to 12 months)

• 4 patients remain on treatment; and median PFS has not yet been reached

KRAS Biomarker Analyses

KRAS variants: evaluation included KRAS (all) and the 3 most common in CRC

• 7 different variants were detected by targeted next-generation sequencing in circulating tumor DNA (ctDNA) isolated from patient plasma at baseline

• Clinical responses were observed across different KRAS variants, including the 3 most common (G12D, G12V, G13D) representing 69% of KRAS variants in CRC

• Phase 2 trial will further assess the safety and efficacy of onvansertib at the RP2D in combination with FOLFIRI + bevacizumab, as well as the value of KRAS liquid biopsy to predict treatment response

KRAS Biomarker

• Clinical responses were observed across different KRAS variants, including the 3 most common in CRC

• Patients achieving a PR showed the greatest decreases in plasma KRAS mutant allele burdens after one cycle of therapy

Conclusions

Onvansertib induces potent anti-tumor activity as single agent and showed synergy in combination with irinotecan and 5-FU in the HCT-116 KRAS mutant xenograft model

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Study Sponsored by Cardinal Oncology, Inc.