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

#2969

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Background

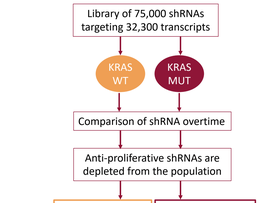
Effective second-line treatment is needed in KRAS-mutated metastatic colorectal cancer (mCRC)

- Second-line treatments (chemotherapy ± targeted agents) have a poor prognosis:
  - ORR – 5%, PFS – 5.7 months, OS – 11.2 months[1]
- KRAS is mutated in 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)

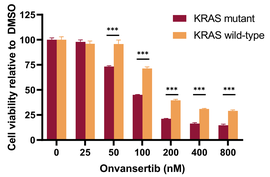
Onvansertib, an oral and highly-selective PLK1 inhibitor, is a promising therapeutic option for KRAS-mutated CRC:

- PLK1, a key regulator of mitosis, is overexpressed in CRC and associated with poor clinical parameters[2]
- A genome-wide RNAi screen identified PLK1 inhibition to be synthetic lethal with mutant KRAS in CRC cells[3]:
  - KRAS mutant cells were hypersensitive to inhibition of PLK1
  - Similarly, onvansertib induced more profound mitotic arrest and cell death in mutant KRAS cells than wild-type (WT) cells

Genome-Wide RNAi Screen[3]



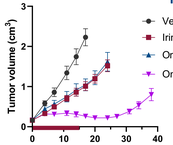
Cell Viability in Onvansertib-Treated KRAS Mutant and WT Isogenic CRC Cells



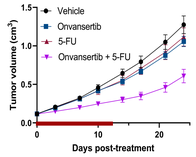
DLD-1 cells treated for 72h with DMSO or onvansertib. Cell viability was measured with CellTiterGlo. Two-way ANOVA, p<0.0001

- Onvansertib induced 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

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



TGI on Day 17	
Onvansertib	55%
Irinotecan	53%
Onv+Irin	88%



TGI on Day 21	
Onvansertib	16%
5-FU	13%
Onv+5FU	56%

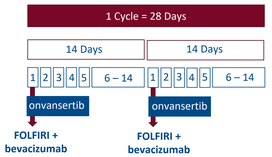
Treatment

Data are represented as mean tumor volume ± SEM TGI= tumor growth inhibition

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

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

Treatment Schedule



Study Design

- Phase 1b: onvansertib dose escalation (12, 15, 18mg/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 allelic burden assessed by liquid biopsies

Key Eligibility criteria

- Metastatic and unresectable CRC
- KRAS mutation in primary tumor or metastasis
- Has failed treatment or is intolerant to oxaliplatin-based chemotherapy
- Progression <6 months of first-line or maintenance therapy
- Negative for BRAF V600E mutation and MSI-H/dMMR

Phase 1b Enrollment and Baseline Characteristics

As of August 20, 2020

Number of patients (N)	Cohort 1 Onvansertib 12 mg/m²	Cohort 2 Onvansertib 15 mg/m²	Cohort 3 Onvansertib 18 mg/m²
Treated	6	3	4
Completing 1st cycle	6	3	3
Currently on Treatment	2	0	3

Total patients N=13	Median [range] or n (%)
Age, years	62 [37-77]
Sex	
Male	8 (62%)
Female	5 (38%)
ECOG	
0	5 (38%)
1	8 (62%)
Primary tumor site	
Colon	6 (46%)
Rectum	5 (38%)
Other	2 (15%)
Liver metastasis	
None	5 (38%)
Liver and other	6 (46%)
Liver only	2 (15%)
Number of metastatic organs	
1	4 (31%)
≥2	9 (69%)
Prior Bevacizumab treatment	
Yes	9 (69%)
No	4 (31%)

Safety

Most Common Treatment-Emergent Adverse Events

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Fatigue	3	6	1		10
Diarrhea	6	2			8
Nausea	6	2			8
Neutropenia	1	2	4	1	8
Alopecia	6	1			7
Abdominal or stomach pain	2	3	2		7
Mucositis	2	2			4
Thrombocytopenia	2	2			4
ALT increase	2			1	3
Anemia	2	1			3
Bloating	3				3
Nosebleed	3				3
Vomiting	1	2			3
WBC decrease		3			3

- 2 patients had DLTs that were both attributed to the 5-FU bolus: G4 neutropenic fever (dose level 12 mg/m²) and G4 neutropenia (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 ≥2 patients were neutropenia (n=5) and abdominal pain (n=2)); all resolved within 2.5 weeks
- No major or unexpected toxicities were attributed to onvansertib

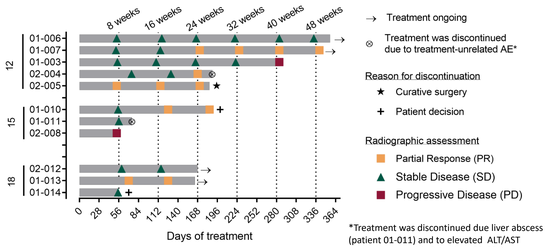
n=number of patients (total N=13)
WBC=white blood cells; ALT= alanine aminotransferase

Preliminary Efficacy

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

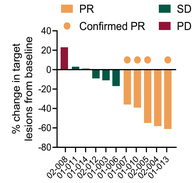
- 5 (45%) patients achieved partial response (PR)
  - 4 patients had a confirmed PR; 1 patient went to curative surgery
  - 1 patient with non-confirmed PR went off study after PR due to treatment-unrelated AE
- 8 (73%) patients had durable responses of >5.5 months (range 5.5 to 12 months); 4 patients remain on treatment; and median PFS has not yet been reached
- Only 1 patient progressed in <6 months while on treatment

Treatment Response and Duration



*Treatment was discontinued due liver abscess (patient 01-011) and to elevated ALT/AST related to hepatitis B (patient 02-004). Patients were censored at time of last dose.

Best Radiographic Response



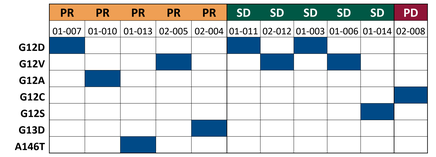
Baseline Characteristics of Patients Achieving a Partial Response (n=5)

	Median or n (%)		n (%)
Age, years	71 [37-76]	**Liver metastasis**	
Sex		None	1 (20%)
Male	2 (40%)	Liver and other	2 (40%)
Female	3 (60%)	Liver only	2 (40%)
ECOG		**Metastatic organs**	
0	1 (20%)	1	3 (60%)
1	4 (80%)	≥2	2 (40%)
Primary tumor		**Prior Bevacizumab**	
Colon	4 (80%)	Yes	4 (80%)
Rectum	1 (20%)	No	1 (20%)

KRAS Biomarker Analyses

KRAS variants in patients evaluable for efficacy (N=11)

- 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[4]

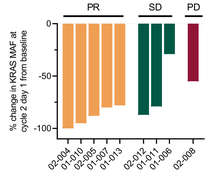


Serial monitoring of KRAS mutant in plasma

- Decreases in plasma KRAS mutation level has been demonstrated to be an early marker for therapeutic response[5]
- KRAS mutant allelic frequency (MAF) was measured by digital droplet PCR (ddPCR) at baseline and at the end of the Cycle 1
- 9 of the 11 patients had a KRAS variant detected by ddPCR at baseline

- All patients showed a decrease in KRAS MAF after the 1st cycle of treatment
- The greatest changes in KRAS MAF were observed in patients achieving a PR (ranging from -78% to -100%)
- The patient with PD had only a -55% decrease in KRAS MAF

% KRAS MAF Changes After Cycle 1



Conclusions

Safety

- The combination of onvansertib and FOLFIRI/Bev is well-tolerated
- The first two dose levels (onvansertib 12 mg/m² and 15 mg/m²) were cleared for safety; the 3rd dose escalation level (18 mg/m²) is enrolling

Efficacy

- 5 (45%) of the 11 evaluable patients achieved a partial response (PR), including 4 confirmed PRs and 1 patient proceeded to curative surgery
- 8 (73%) patients had durable responses of >5.5 months (range 5.5 to 12 months); 4 patients remain on treatment

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 mutant KRAS after one cycle of therapy

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

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