Abstract #3695

A Phase 1b/2 Study of Onvansertib (PCM-075) in Combination with FOLFIRI and Bevacizumab for Second Line Treatment of Metastatic Colorectal Cancer in Patients with a KRAS Mutation

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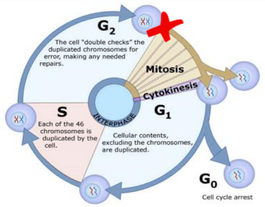
Background

Metastatic Colorectal Cancer (mCRC)

- Tumor biomarkers drive therapy decisions for 1st and 2nd line mCRC therapy
- ~50% of mCRC is KRAS-mutated[1]
- Standard 2nd line therapy in KRAS mutated patients is chemotherapy (FOLFOX/FOLFIRI) + Bevacizumab[1]
- Second-line therapies have only a ~5% response rate in mCRC[1]



Polo-like Kinase 1 (PLK1):

- Serine/threonine kinase, master regulator of mitotic progression
- PLK1 inhibition causes mitotic arrest in prometaphase and subsequent cell death
- PLK1 is upregulated in CRC tissues in comparison with normal colorectal tissues[2]
- Its overexpression is associated with poorer overall survival, lymph node metastasis, advanced TNM stages and higher Dukes stages[2]

Onvansertib (also known as PCM-075 and NMS-1286937):

- First-in-class, 3rd-generation, oral and highly-selective PLK1 inhibitor
- Induces G2/M arrest and apoptosis in cancer cells
- Short half life of ~24-hours
- Safe and well tolerated (Phase 1 safety trial in patients with solid tumors) with recommended Phase 2 dose established[3]

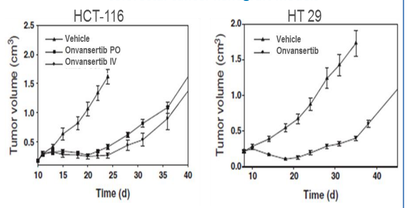
PLK Member	Onvansertib IC_{50} (μM)
PLK1	0.002
PLK2	> 10
PLK3	> 10

Onvansertib in CRC Pre-Clinical Models:

Onvansertib inhibits tumor cell proliferation and tumor growth as a single agent

- Onvansertib showed strong proliferation inhibition in CRC cell lines[4]. IC_{50} values < 1uM in 23/24 cell lines tested, median IC_{50} = 136 nM
- In 3 independent CRC xenograft models (HT-29, HCT-116, Colo-205), onvansertib induced tumor growth inhibition[4]. Maximal tumor regression was of ~84% compared to vehicle

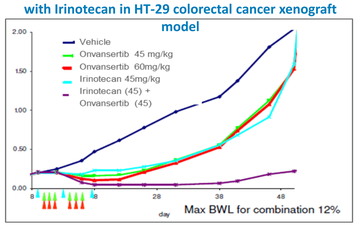
Tumor growth of Onvansertib- and vehicle-treated colorectal cancer xenograft models



Onvansertib synergizes with chemotherapy agents, including irinotecan

- Onvansertib showed synergistic anti-proliferative effects in the HCT-116 cell line with the active metabolite of Irinotecan (SN-38), cisplatin and paclitaxel. Combination index ranged between 0.5 and 0.8
- In vivo, the combination of onvansertib with irinotecan significantly reduced tumor growth compared to either drug alone[4]

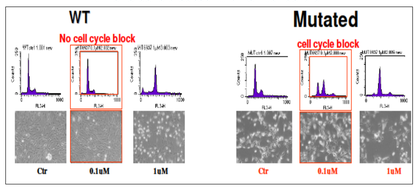
Anti-tumor activity of Onvansertib in combination with Irinotecan in HT-29 colorectal cancer xenograft model



KRAS mutation is a biomarker for onvansertib sensitivity

- PLK1 was identified to be synthetic lethal for KRAS mutated cells in two CRC cell lines[5]
- KRAS mutated NIH3T3 cells showed higher sensitivity to onvansertib compared with KRAS wild-type cells

Cell cycle analysis in KRAS wild type (WT) and mutated NIH3T3 cells treated with Onvansertib

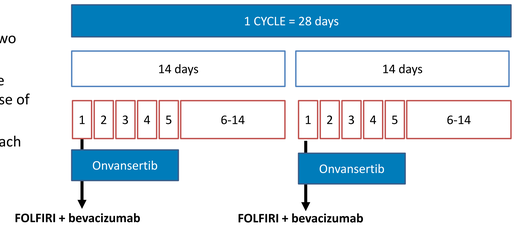


Phase 1b/2 Trial Design and Objectives (NCT03829410)

Study Design:

Dosing schedule: 1 cycle is constituted of two 14-day courses of treatment (28-day cycle)

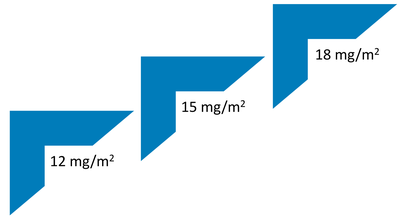
- Onvansertib administered orally, once daily on days 1-5 of each 14-day course of treatment
- FOLFIRI + bevacizumab, on day 1 of each 14-day course of treatment



Dosing escalation in Phase 1b (3+3) design with expansion cohort at RP2D for Phase 2

- Onvansertib dose increase (12, 15, 18mg/m²) in successive cohorts of 3 patients
- Dose limiting toxicities (DLTs) evaluated during the 1st cycle (28 days)

Onvansertib Dose Escalation



Study Objectives:

- **Phase 1b:** Assess the RP2D in combination with FOLFIRI and bevacizumab
- **Phase 2:** Assess preliminary efficacy of the combination FOLFIRI, bevacizumab and onvansertib at the RP2D

Primary Efficacy Endpoint:

- **Phase 1b:** Characterization of DLTs and adverse events
- **Phase 2:** Objective response rate (ORR) in patients who receive at least 1 cycle (2 courses) of treatment

Secondary Efficacy Endpoint (1b/2):

- Progression-free survival (PFS) defined from date of first drug administration to progression or death, whichever occurs first
- Reduction in KRAS allelic burden assessed by liquid biopsies

Exploratory Endpoints (1b/2):

- Use of circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) to evaluate relevant biomarkers correlated with patient response
- Use of archival tumor tissue (if available) to evaluate genomic and transcriptomic profiles associated with patient response

Key Eligibility Criteria

Inclusion:

- Histologically confirmed metastatic and unresectable CRC
- KRAS mutation in exon 2, 3 or 4 in primary tumor or metastasis, assessed by a CLIA-certified lab
- Has failed treatment or is intolerant of fluoropyrimidine and oxaliplatin with or without bevacizumab
- All patients must have received a minimum of 6 weeks of the first-line regimen that included oxaliplatin and a fluoropyrimidine with or without bevacizumab in the same cycle (treatment failure is defined as radiologic progression during or < 6 months after the last dose of first-line therapy)

Exclusion:

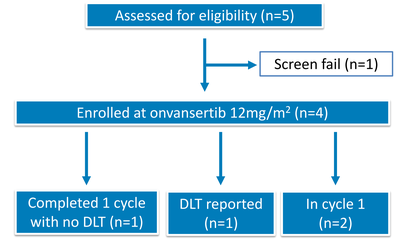
- Concomitant KRAS and BRAF-V600 mutations or MSI-H/dMMR (Microsatellite Instability High/Deficient Mismatch Repair)
- Anti-cancer chemotherapy or biologic therapy administered within 4 weeks prior to the first dose of study drug (the exception is a single dose of radiation up to 8 Gray with palliative intent for pain control up to 14 days before randomization)
- More than one prior chemotherapy regimen administered in the metastatic setting
- Major surgery within 6 weeks prior to randomization
- Untreated brain metastasis

Trial Status and Preliminary Safety

Enrollment Status as of September 1st

Enrollment at the first dose level of onvansertib 12mg/m²

- 1 patient completed the 1st cycle (two courses of 14-day treatment) with no DLT and is currently in cycle 2
- 1 patient had a G4 neutropenic fever, considered a DLT. DLT was likely related to FOLFIRI bolus infusion, and not onvansertib. Patient went off study.
- Cohort was subsequently expanded from 3 to 6 patients
- 2 additional patients are currently in cycle 1 and under evaluation for DLT



Adverse Events Reported as of September 1st

- Grade 2 constipation (n=1)
- Grade 3 abdominal pain (n=1)

Biomarker Strategy

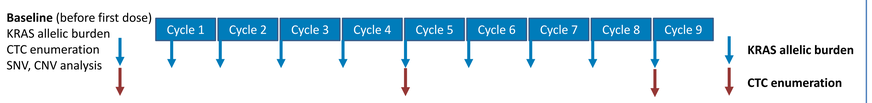
Tumor Characterization :

- Identification of mutations and CNV in ctDNA using Guardant technology

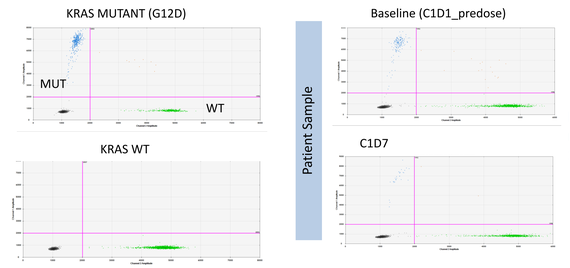
Response Biomarker:

- CTC enumeration (Epic technology)
- Track changes in KRAS allelic burden on liquid biopsy

Schedule of Assessments: Each cycle is constituted of **two** 14-day courses of treatment (28-day cycle)



Assessment of KRAS Allelic Burden by Digital Droplet PCR (ddPCR)



In the first patient treated, KRAS G12D mutation allelic frequency went from 12.4% to 2.7% in 7 days (4.6-fold decrease)

Conclusions and Perspective

- Second-line therapies in KRAS mutated mCRC is limited and associated with poor prognosis. Onvansertib has promising pre-clinical data to fill the niche for this population.
- The objective of this trial is to assess the safety and efficacy of onvansertib (oral and highly-selective PLK1 inhibitor) in combination with FOLFIRI + bevacizumab in mCRC patients whose tumors harbor a KRAS mutation
- The trial has been successfully initiated, 4 patients have been treated and 1 has completed the DLT phase as of September 1st 2019
- One DLT was reported in the first cohort and was likely related to the chemotherapy backbone; consideration will be given to eliminating the 5-FU bolus to decrease toxicity

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REFERENCES
[1] King et al; Amer J Hem/Onc., 2016
[2] Ran et al.; Gene 2019
[3] Weiss et al., Invest New Drugs, 2017
[4] Valsasina et al., Mol Cancer Ther., 2012
[5] Luo et al., Cell, 2009