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 Chemotherapy decisions for 2nd and 2nd line mCRC therapy
- >50% of CRC is KRAS-mutated
- Standard 2nd line therapy in KRAS mutated patients is chemotherapy (FOLFOX/FOLFIRI) + Bevacizumab
- KRAS mutation is associated with poorer overall survival. Lymph node metastasis, advanced TNM stages and higher Duke stages

Onvansertib (also known as PCM-075 and IMA-201-B37)
- In 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)

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), cotreatment and paired dose. Combination Index ranged between 0.3 and 0.8
- In vivo, the combination of onvansertib with irinotecan significantly reduced tumor growth compared to either drug alone

KRAS mutation is a biomarker for onvansertib sensitivity
- PLK1 was identified to be synthetic lethal for KRAS mutated cells in two CRC cell lines
- KRAS mutated H1357 cells showed higher sensitivity to onvansertib compared with KRAS wild-type cells

Key Eligibility Criteria
- Histologically confirmed metastatic and unresectable CRC
- KRAS mutation in exon 2, 3 or 4 in primary tumor or metastasis, assessed by a CLIA validated test
- Exclusive of prior or concurrent chemotherapy or biologic therapy administered within 4 weeks of the first dose of study drug
- All patients must have received a minimum of 2 previous regimens of chemotherapy and/or targeted therapy

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 this 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 has completed the DLT phase as of September 17th 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

Clinical Data
Characterization of DLTs and adverse events
- Enrollment Status as of September 2nd
- 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 64 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

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
- In the first patient treated, KRAS G12D mutation allelic frequency went from 12.4% to 2.7% in 7 days (44-fold decrease)

Tumor Biomarker Drives Therapy Decisions for 2nd and 2nd Line mCRC Therapy
- >50% of CRC is KRAS-mutated
- KRAS mutation is a biomarker for onvansertib sensitivity

Onvansertib, a highly selective PLK1 inhibitor, has shown promising pre-clinical data to fill the niche for this population.

- Enrolled the first patient treated, KRAS G12D mutation allelic frequency went from 12.4% to 2.7% in 7 days (44-fold decrease)