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

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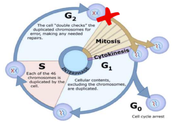
Background



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[1]
- Its overexpression is associated with poorer overall survival, lymph node metastasis, advanced TNM stages and higher Dukes stages[1]

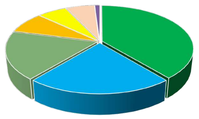
Onvansertib (also known as PCM-075 and NMS-1286937):

- 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[2]

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

Clinical Trial Rationale

Colorectal Cancer



Metastatic Colorectal Cancer (mCRC)

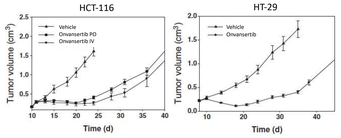
- Tumor biomarkers drive therapy decisions for 1st and 2nd line mCRC therapy
- ~50% of mCRC is KRAS-mutated[3]
- Standard 2nd line therapy in KRAS mutated patients is chemotherapy (FOLFOX/FOLFIRI) + Bevacizumab[3]
- Second-line therapies have only a ~5% response rate in mCRC[4]

Onvansertib in Pre-Clinical Colorectal Cancer Models

As a Single-Agent, Onvansertib Inhibits Tumor Cell Proliferation and Tumor Growth

- Onvansertib showed strong proliferation inhibition in CRC cell lines[5]. 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[6]. Maximal tumor regression was of ~84% compared to vehicle

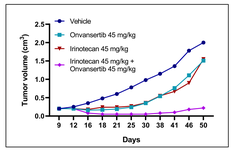
Tumor growth of onvansertib and vehicle-treated CRC xenograft models



Onvansertib is Synergistic in Combination 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[5]

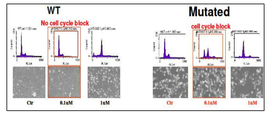
Anti-tumor activity of onvansertib in combination with Irinotecan in HT-29 CRC xenograft model



KRAS Mutation is a Biomarker for Onvansertib Sensitivity

- PLK1 was identified to have synthetic lethality for KRAS mutated cells in two CRC cell lines[6]
- 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

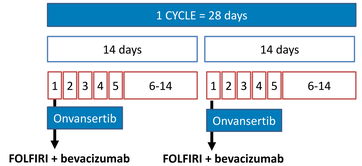


Phase 1b/2 Trial Design and Objectives (NCT03829410)

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 safety 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)

Primary Efficacy Endpoint:

- Objective response rate (ORR) in patients who receive at least 1 cycle (2 courses) of treatment

Secondary Efficacy Endpoint:

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

Exploratory Endpoints:

- Use of circulating tumor cells (CTCs) and ctDNA to evaluate relevant biomarkers correlated with patient response
- Use of archival tumor tissue 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
- Anti-cancer chemotherapy or biologic therapy administered within 4 weeks prior to the first dose of study drug
- More than one prior chemotherapy regimen administered in the metastatic setting
- Untreated brain metastasis

Phase 1b Enrollment Status

Enrollment Status as of January 10th 2020

Number of patients (n)	12 mg/m²	15 mg/m²
Treated	6	2
Completing 1st cycle	6	1
Experiencing a DLT	1	0
Currently on treatment	5	2

Phase 1b Safety Assessment

Safety Assessment as of January 10th 2020

- AEs occurring in more than 1 patient are listed in Table.
- 1 patient had a G4 neutropenic fever (DLT), likely related to the 5-FU bolus infusion
- The only G3/G4 AE reported as possibly related to onvansertib was a G3 neutropenia (n=1), an expected, on-target and reversible toxicity
- Other possibly onvansertib-related G1/G2 AEs were fatigue (n=4) and nausea (n=2)

AEs reported in ≥ 2 patients (n=8)

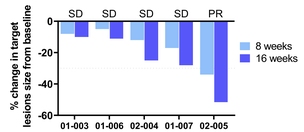
Adverse event	Grade 1-2	Grade 3-4	Total (%)
Fatigue	7		7 (88)
Abdominal pain	2	2	4 (50)
Nausea	4		4 (50)
Stomach pain	3		3 (38)
Alopecia	2		2 (25)
Anemia	2		2 (25)
Back pain	2		2 (25)
Constipation	2		2 (25)
Diarrhea	2		2 (25)
Dry mouth	2		2 (25)
Neutropenia		2	2 (25)

Phase 1b Efficacy Assessment

100% Clinical Benefit by Radiographic Response in Patients Treated at Dose Level 1 (onvansertib 12 mg/m²):

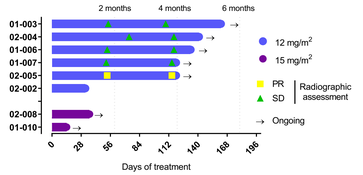
- 100% (5 out of 5) evaluable patients for radiographic assessment had a tumor decrease at 8 weeks and achieved partial response (PR: n=1) or stable disease (SD: n=4); all patients remain on treatment
- Confirmation of tumor decreases and additional tumor regression by radiographic scan was observed at 16 weeks in all patients (5 out of 5); 3 of the 5 patients evaluated at 16 weeks had a >25% tumor decrease; patient 02-005 is proceeding to curative surgery

Radiographic Response - 12 mg/m² Cohort



SD: Stable Disease; PR : Partial Response

Swimmer Plot – All Patients Treated



ctDNA as an Early Marker of Therapeutic Response to Treatment in mCRC

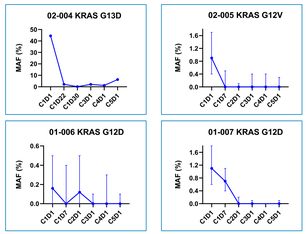
- Circulating tumor DNA (ctDNA) is released by apoptotic tumor cells into the blood stream and can be monitored by liquid biopsy
- Using next-generation sequencing (NGS) and droplet digital PCR (ddPCR), somatic variants can be detected in ctDNA with high sensitivity and specificity; and present the advantage of minimal invasion
- Early changes in ctDNA mutant alleles are predictive of later radiographic response[7]

Patient	KRAS mutation	Patient	KRAS mutation
02-002	p.G12D	01-006	p.G12V
01-003	-	01-007	p.G12D
02-004	p.G13D	02-008	p.G12C
02-005	p.G12V	01-010	p.G12A

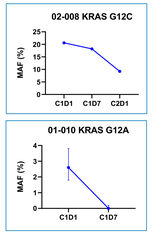
Changes in ctDNA KRAS Mutant Precedes Tumor Shrinkage

- A KRAS mutation was identified in ctDNA in 4 out of 5 patients treated at dose level 1 (onvansertib 12 mg/m²) and in the 2 patients treated to-date at dose level 2 (onvansertib 15 mg/m²)
- Five of the 6 patients with detectable baseline KRAS showed a decrease to undetectable KRAS mutant levels within the 1st cycle of treatment
- Decreases in KRAS mutant in ctDNA was associated with subsequent tumor regression assessed by radiographic scan in patients reaching 8 weeks at dose level 1 (patients at dose level 2 have not yet reached their 8-week radiographic assessment)

KRAS Mutation Allelic Frequencies (MAF) Pre- and Post-Treatment Dose Level 1 (onvansertib 12 mg/m²)



KRAS Mutation Allelic Frequencies (MAF) Pre- and Post-Treatment Dose Level 2 (onvansertib 15 mg/m²)



Conclusions

- In the Phase 1b dose escalation, the 1st dose level (onvansertib 12 mg/m²) was cleared for safety; the 2nd dose level (onvansertib 15 mg/m²) is fully enrolled with no DLTs reported in the two patients treated to-date
- Radiographic scans performed at 8 weeks showed tumor decrease and clinical benefit in 100% (n=5) of evaluable patients treated with onvansertib 12 mg/m² (n=5); 1 patient achieved PR, 4 patients achieved SD
- Radiographic responses were confirmed at 16 weeks with further tumor shrinkage in all patients; 3 patients had a >25% decrease; 1 patient is proceeding to curative surgery
- Five different KRAS mutant variants were detected in 6 patients, which represents >90% of KRAS mutations in CRC; all five KRAS variants decreased within the 1st cycle of treatment (onvansertib dose levels 12 and 15 mg/m²)
- At dose level 1 (onvansertib 12 mg/m²), 4 patients had detectable KRAS mutant ctDNA at baseline; in all 4 patients KRAS was undetectable within the 1st cycle of treatment; this preceded subsequent tumor shrinkage observed with radiographic scans, supporting the predictive value of liquid biopsy
- At dose level 2 (onvansertib 15 mg/m²), the 2 patients treated to-date had detectable KRAS mutant ctDNA at baseline; in 1 patient KRAS was undetectable within the 1st cycle of treatment; radiographic scans will be performed at 8 weeks

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[3] King et al; Amer J Hem/Onc., 2016
[4] Bennouna et al., Lancet Oncol, 2013
[5] Valsasina et al., Mol Cancer Ther, 2012
[6] Luo et al., Cell, 2009
[7] Tie et al., Annals of Oncology, 2015