### Background

**Polio-like Kinase 3 (PLK3):**
- Serine/threonine kinase, master regulator of mitotic progression
- Inhibition of PLK3 causes mitotic arrest in prometaphase and subsequent cell death
- Over-expressed in numerous cancer types, including mCRPC and associated with poor prognosis

**Onvansertib**
- Also known as PCM-075 and NARS-1256577
- Oral, highly selective PLK inhibitor
- Short half-life (~24 hours)
- Induces G2/M arrest and apoptosis in cancer cells
- Early and well tolerated (Phase 1 safety trial in patients with solid tumors)

### Synergy with Abiraterone + PLK Inhibitor:
- Synergy with abiraterone (AIB) identified in a novel in-vitro castration-resistant prostate cancer (CRPC) assay

**Abiraterone + Onvansertib:**
- Drug combination therapy for advanced prostate cancer
- In vivo experiments: Inhibits PLK3 in drug-resistant PCa (also known as PCM-075 or PCM3, class 3 PLK inhibitors)
- Replicates known effect of abiraterone and PLK inhibitor on disease control

### Primary
- Observes effects of onvansertib in combination with abiraterone and prednisone on disease control
- Plan to open a second arm using a dose of onvansertib
- Evaluate potential biomarkers of response in CTCs and circulating tumor DNA (ctDNA)
- Study aims to maximize exposure to drug without causing drug-related toxicities

### Exploratory
- Access target inhibition of PLK3 in peripheral blood mononuclear cells (PBMC) and circulating tumor cells (CTCs)

### Future Direction
- Plan to open a second arm using a dose-intensified schedule: onvansertib daily for 15 of a 14-day cycle (each arm will be analyzed independently for safety and efficacy)
- Relostrin: Transient PSA declines are seen in some patients; the goal is to maximize exposure to drug without causing drug-related toxicities

### Key Efficacy Criteria
- **Onvansertib**
  - Early PSA responses
  - PSA trajectory in the patient achieving the primary efficacy endpoint changed from 100% increase (16.05ng/ml to 150.91ng/ml) to 0% increase
- **Onvansertib + Abiraterone**
  - PSA trajectory in patients with at least 4 cycles of treatment

### Preliminary Efficacy
- **Patients:** 8 patients have completed 3 cycles of treatment with onvansertib + abiraterone
- **Efficacy:** 6 patients had observed declines in PSA levels after dosing with onvansertib
- **Efficacy endpoint assessed at 12 weeks after 4 cycles**
- **CTC and ctDNA analysis:**
  - PSA doubling, increasing >100% in the 60 days (Day 10 to Day 22) prior to starting combination therapy (16.05ng/ml to 34.23 ng/ml) and increased only 4% while on study (88 days), demonstrating disease stabilization and achieving primary efficacy endpoint
- **Tumor assessed at C1D1:**
  - As a variant known as AR-V7, considered an aggressive tumor that is resistant to anti-androgen therapy

### Safety
- **SAEs** reported as possibly related to study drug are listed in the table below
- Neuropathy and thrombocytopenia are expected, on-target, reversible side effects associated with the mechanism of action of onvansertib
- **No unexpected, off-target toxicities have been reported in patients treated to date**

### Conclusions and Perspective
- **Early PSA response was observed with the addition of onvansertib to daily abiraterone in 2 of 6 patients, with 1 patient achieving the efficacy endpoint of disease control and 10% decrease in tumor size by RECIST criteria**
- **PSA trajectory in the patient achieving the primary efficacy endpoint changed from 100% increase (16.05ng/ml to 34.23 ng/ml) in the 40 days prior to study by 6.4% increase during 88 days on study, indicating attenuation of the natural history of early PSA progression**
- **Both patients who showed an early response (at C1D8) with decreases in PSA levels, also tested positive for AR-V7**
- **Further exploration of the combination of onvansertib and abiraterone is warranted in AR-V7-positive patients, who have resistance to AR-targeting therapies and poor prognosis**
- **PSA data suggest that reducing cycle time from 3 weeks to 2 weeks may maximize response to treatment; a second arm is being added with a shortened dosing schedule (patients will be alternately assigned to each arm)**

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