Abstract #CT161

A Phase 2 Study of Onvansertib (PCM-075) in Combination with Abiraterone and Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer

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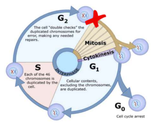
Background

Polo-like Kinase 1 (PLK1):

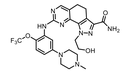
- Serine/threonine kinase, master regulator of mitotic progression
- Inhibition of PLK1 causes mitotic arrest in prometaphase and subsequent cell death
- Over-expressed in numerous cancer types, including mCRPC, and associated with poor prognosis



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

- First-in-class, 3rd-generation, oral and highly-selective PLK1 inhibitor
- Short half life of ~24-hours
- Induces G2/M arrest and apoptosis in cancer cells
- Safe and well tolerated (Phase 1 safety trial in patients with solid tumors)[1] with recommended Phase 2 dose established
- Current clinical trials: Acute Myeloid Leukemia (AML) – NCT03303339; metastatic Castration-Resistant Prostate Cancer (mCRPC) – NCT03414034 and metastatic Colorectal Cancer (mCRC) – NCT03829410

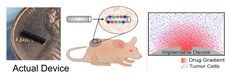
PLK Member	PCM-075 IC50 (nM)1
PLK1	2
PLK2	> 10,000
PLK3	> 10,000



Chemical Formula: $C_{29}H_{32}F_3N_9O_3$
Molecular Weight: 532.53
tPSA: 131.38
CLogP: 2.29445

Synergy with Abiraterone + PLK Inhibitor:

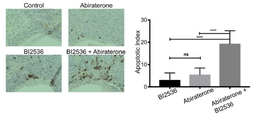
- Synergy with abiraterone (Abi) identified in a novel in-vivo castration-resistant prostate cancer (CRPC) assay



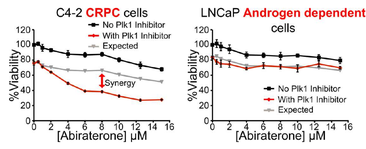
Actual Device

A novel *in vivo* assay to define personalized multi-drug combination therapy for advanced prostate cancer
S. Balk, G. Bubley, A. Patnaik, X. Yuan, O. Jonas, M. Yaffe

C4-2 CRPC Xenografts



- AR and PLK1 regulate each other; mechanism may be AR-independent



Phase 2 Trial (NCT03414034) Design and Objectives

Onvansertib in Combination with Abiraterone and Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Dosing Regimen: Onvansertib – 24 mg/m² Days 1-5 (21-Day Cycle) + Abiraterone daily

Duration: 4 Cycles = 12 Weeks

Primary Endpoint: Disease Control PSA Stabilization or Decline

Primary

- Observe effects of onvansertib in combination with abiraterone and prednisone on disease control rate (PSA decline or stabilization) in patients with mCRPC and early abiraterone resistance

Secondary

- Changes in PSA after addition of onvansertib relative to baseline
- Time to PSA progression and radiographic progression after addition of onvansertib
- Radiographic response after addition of onvansertib
- Disease control rate in per-protocol analysis
- Assess safety/tolerability of combination regimen

Exploratory

- Assess target inhibition of PLK1 in peripheral blood mononuclear cells (PBMC) and circulating tumor cells (CTCs)

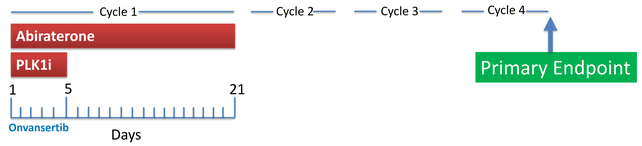
Key Eligibility Criteria

Inclusion:

- mCRPC on first-line abiraterone
  - Abiraterone can have been started in castration-sensitive setting or castration-resistant setting
  - Prior response to abiraterone confirmed
- Early abiraterone resistance
  - Two rising PSAs on abiraterone: one rise of ≥0.3 ng/mL and one confirmatory value not showing decline, separated by 1 week

Exclusion:

- Prior enzalutamide or apalutamide
- Rapidly progressive disease or significant symptoms related to disease progression



Biomarker Strategy

- Evaluate potential biomarkers of response in CTCs and circulating tumor DNA (ctDNA)
  - Genomic alterations – ctDNA
  - Variant androgen receptor splicing (AR-V7) – CTCs

- Several studies have evaluated whether the presence of the constitutively active androgen-receptor splice variant 7 (AR-V7) in tumor cells confers a primary or an acquired resistance to novel ARSi or other therapies, and whether it could be used as a treatment selection tool in clinical practice
- Published data consistently demonstrate that the benefit of ARSi occurs predominantly in AR-V7-negative CRPC patients while most AR-V7-positive CRPC patients do not respond well or durably to abiraterone
- Trovagene is working with Epic Sciences and Johns Hopkin to evaluate CTCs, and Guardant to evaluate ctDNA, from patients in the Phase 2 trial of onvansertib + abiraterone to assess the AR-V7 status
- To date, 2 of 6 patients who have completed 4 cycles (12 weeks) of treatment are confirmed **AR-V7+** and have shown a PSA response when onvansertib is added to abiraterone, and also had the lowest increase in CTC count from C1D1 to C5D1

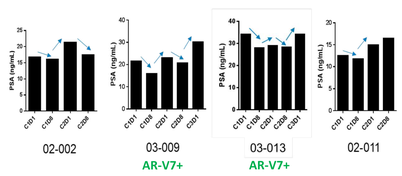
Patient	CTC Count (C1D1)	CTC Count (C5D1)	CTC Fold Change	AR-V7 (C1D1)	AR-V7 (C5D1)	CT-DNA Deleterious Mutation (Gene)	CT-DNA Deleterious Mutation (Change)	CT-DNA Somatic CNV (Gene)	CT-DNA Somatic CNV (Copy Number)
02-003	4.4	78.6	17.9	Negative	Positive	TP53	p.C275Y_c.824G>A	None	None
03-004	0.4	1.2	3.0	Negative	Negative	AR	p.T878A_c.2632A>G	AR	1.72
02-007	2.5	17.3	6.9	Negative	Negative	EGFR IDH1	p.A822T_c.2464G>A p.R132C_c.394C>T	None	None
03-009	3.7	5.4	1.5	Positive	Negative	BRAF STK11 TP53	p.G469A_c.1406G>C p.R333C_c.997C>T c.376-2A>C (splice_acceptor)	AR KRAS	8.27 5.92
03-013	2.2	3.0	1.4	Positive	Positive	NF1 MYC	p.I1605V_c.4813A>G p.S245Y_c.734C>A	CDK6	2.32
01-014	87.1	Not Avail.	N/A	Negative	Not Avail.	Not Tested	Not Tested	Not Tested	Not Tested

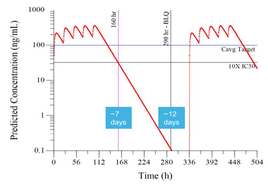
Future Direction

- Plan to open a second arm using a dose-intensified schedule: onvansertib days 1-5 of a 14-day cycle (each arm will be analyzed independently for safety and efficacy)
  - ***Rationale:*** Transient PSA declines are seen in some patients; the goal is to maximize exposure to drug without causing drug accumulation

Dosing Regimen Arm A: Onvansertib – 24 mg/m² Days 1-5 (21-Day Cycle) + Abiraterone daily → 4 Cycles = 12 Weeks → Disease Control PSA Stabilization or Decline

Dosing Regimen Arm B: Onvansertib – 24 mg/m² Days 1-5 (14-Day Cycle) + Abiraterone daily → 6 Cycles = 12 Weeks → Disease Control PSA Stabilization or Decline



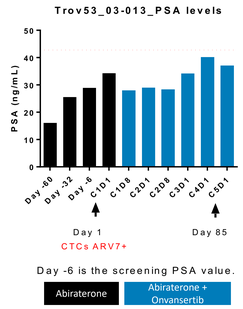


Preliminary Efficacy

Enrollment Status	Number of Patients
Number of patients treated	15
No DLTs (safety lead-in)	0
Number of patients currently on treatment	6

- 6 patients have completed 4 cycles (3 months) of treatment with onvansertib + abiraterone
- 2 of 6 patients had observed declines in PSA levels after dosing with onvansertib
- To date, 1 patient has achieved the efficacy endpoint (03-013) of disease stabilization based on PSA levels (primary endpoint)

- C1D1 = Cycle 1, Day 1
- PSA value at C1D1 prior to onvansertib dosing
- Each Cycle = 21 days with oral dosing of onvansertib days 1-5 + 16 days off treatment
- Abiraterone is dosed daily
- Efficacy endpoint assessed at 12 weeks (after 4 cycles)



Efficacy endpoint
25% of baseline PSA (C1D1)

CT scan at end of 12 weeks (efficacy endpoint) indicates ~30% tumor shrinkage (unconfirmed Partial Response to be assessed in a subsequent scan)

Efficacy evaluation at Day 85

- PSA doubled, increasing >100%, in the 60 days (Day -60 to C1D1) prior to starting combination therapy (16.05ng/ml to 34.23 ng/ml) and increased only 8.4% while on study (84 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

- All SAEs reported as possibly related to study drug are listed in the table below
- Neutropenia 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

SAEs Reported						
	Patient	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Anemia				1		1
Leukopenia					1*	1
Neutropenia					1*	1
Syncope				1		1
Thrombocytopenia					1*	1

*Protocol subsequently amended to allow for treatment with standard-of-care growth factor to manage on-target, reversible neutropenia and thrombocytopenia

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 a 30% decrease in tumor size by RECIST criteria (unconfirmed Partial Response to be confirmed with subsequent CT scan in May 2019)
- PSA trajectory in the patient achieving the primary efficacy endpoint changed from 100% increase (16.05ng/ml to 34.23 ng/ml) in the 60 days prior to study to 8.4% increase during 84 days on study, indicating alteration of the natural history of early abiraterone resistance
- Both patients that 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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REFERENCES:
[1] Weiss et al., Invest New Drugs, 2017