A Phase 2 Study of the Combination of PLK1 Inhibitor, Onvansertib, with Abiraterone and Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer

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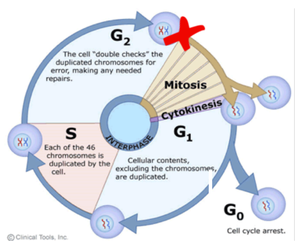
Poster # P042

Background

Polo-like Kinase 1 (PLK1):

- Serine/threonine kinase, master regulator of cell-cycle progression[1]
- Controls G2/Mitosis (G2/M) checkpoint[1]
- Inhibition of PLK1 causes mitotic arrest and subsequent cell death[1]
- PLK1 is overexpressed in prostate cancer and linked to higher tumor grades[2]
- Emerging data demonstrates PLK1 is also a key regulator of cellular functions beyond mitosis that are essential for tumor growth
  - Biosynthesis of DNA
  - DNA Damage Response



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

- First-in-class, third-generation, orally-bioavailable, highly-selective PLK1 inhibitor with a ~24-hour half-life
- Phase I study in solid tumors established the recommended phase 2 dose (RP2D) at 24 mg/m^2[2]

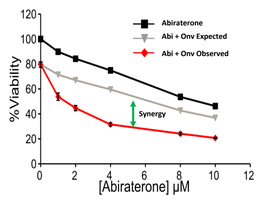
PLK Inhibitor Synergizes with Abiraterone in Preclinical Models

- Onvansertib induces synergistic cell death and mitotic arrest in combination with abiraterone in a castration-resistant prostate cancer (CRPC) model (C4-2)
- Combination of PLKi and abiraterone blocks tumor growth and PSA increase in a CRPC xenograft model[3]

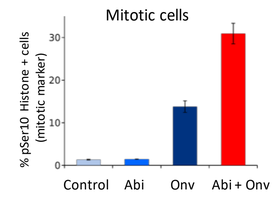
Androgen Receptor Variant 7 (AR-V7)

- AR-V7+ detection in CTCs is associated with abiraterone resistance[4]
- AR-V7+ has a shorter progression-free survival and overall survival in mCRPC intent-to- treat with abiraterone[5]
- Combination of abiraterone and PLK inhibitor (PLKi) reduces AR and AR-V7 protein expressions in CRPC cell lines[3]

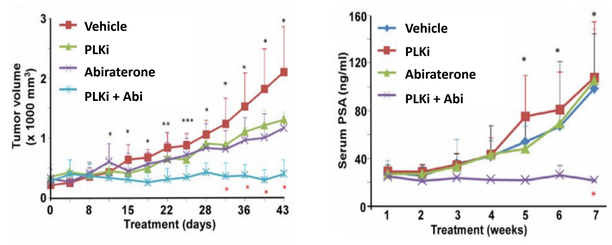
Onvansertib + Abiraterone Demonstrates Synergy in mCRPC model (C4-2)



Onvansertib + Abiraterone Significantly Increase Mitotic Arrest



PLK1 inhibitor and Abiraterone Blocks Tumor Growth and PSA Increase in an AR-V7 Positive CRPC Model (LuCaP35CR)



Phase 2 Trial (NCT03414034) Design and Objectives

	Dosing Regimen	Duration	Efficacy Endpoint
Arm A Onvansertib Days 1-5 3-week dosing schedule	Onvansertib – 24 mg/m^2 Days 1-5 + Abiraterone daily	4 Cycles = 12 Weeks	Disease Control PSA Stabilization or Decline
Arm B Onvansertib Days 1-5 2-week dosing schedule	Onvansertib – 24 mg/m^2 Days 1-5 + Abiraterone daily	6 Cycles = 12 Weeks	Disease Control PSA Stabilization or Decline

Eligibility Criteria

Inclusion:

- First-line abiraterone treatment and response (in castration-sensitive or castration-resistant setting)
- Initial signs of abiraterone resistance defined as 2 rising PSAs; one rise of ≥0.3 ng/mL and one confirmatory value not showing decline, separated by 1 week

Exclusion:

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

Efficacy Endpoints

- Disease control assessed by prostate-specific antigen (PSA) decline or stabilization pre- and post-treatment
- Changes in PSA relative to baseline following the addition of onvansertib to abiraterone
- Radiographic response following the addition of onvansertib to abiraterone
- Time to PSA and radiographic progression following the addition of onvansertib to abiraterone

Correlative Endpoints

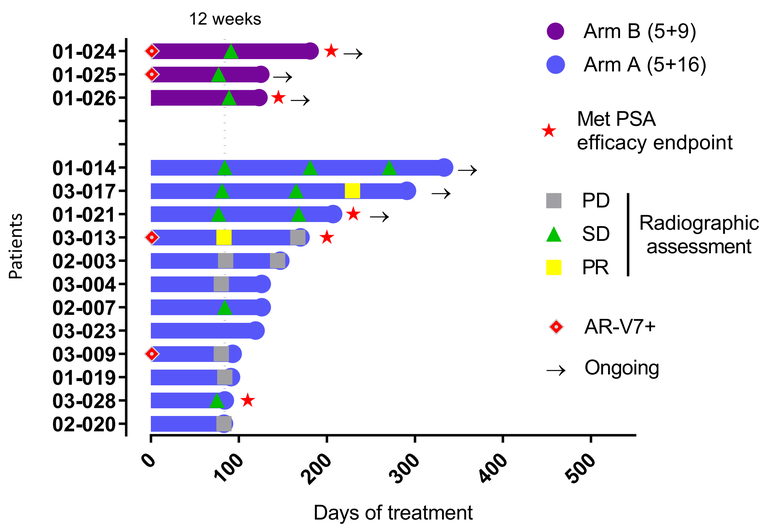
- Analysis of circulating tumor cells (CTC) and circulating tumor DNA (ctDNA) to identify potential biomarkers of response
- Analysis of CTCs to assess AR-V7 status at baseline using the EPIC and Johns Hopkins University (JHU) testing platforms
- Analysis of ctDNA to identify genomic alterations

Enrollment Status (as of October 28th 2019):

Number of patients (N)	Arm A	Arm B
Subjects Treated	24	6
Subjects Completing 12-weeks of Treatment	12	3
Subjects Currently on Treatment	6	5
AR-V7+ Subjects (Epic or JHU)	4	3

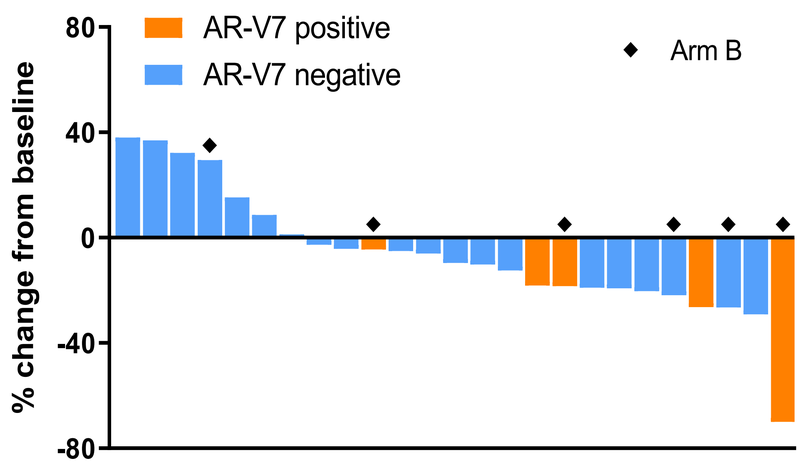
Efficacy in Abiraterone-Resistant Patients

Efficacy Observed in 60% of Patients Across Both Arms (A and B)



- **9 of 15 (60%) of patients achieved partial response (PR) or stable disease (SD) following 12 weeks of treatment with onvansertib + abiraterone. Response to treatment was evaluated based on PSA values (primary endpoint) and radiographic scans.**
  - **Arm B (n=3):**
    - 3 out of 3 patients had stable disease (SD) with 2 of 3 achieving primary efficacy endpoint; all patients remain on treatment (>120 days/>4 months)
    - 14-day dosing schedule (50% greater drug exposure to onvansertib) suggests that a shorter dosing schedule(vs Arm A) maximizes response to treatment
  - **Arm A (n=12):**
    - 6 out of 12 patients had stable disease (SD) or partial response (PR) with 3 of 12 patients achieving the primary efficacy endpoint
    - 3 patients remain on treatment and have been on treatment for >200 days (>7 months)

72% of Patients Showing Decrease in PSA (Best PSA Response)



- **18 out of 25 (72%) of patients had decreases in PSA levels with the addition of onvansertib after 1 cycle of treatment**
- Initial PSA stabilization or decrease was observed in all AR-V7positive patients who completed at least 1 cycle of treatment (n=5)
- Among the AR-V7 positive patients who completed 12-weeks of treatment (n=4)
  - 3 of 4 patients had stable disease (SD) or partial response (PR) with 2 patients achieving the primary efficacy endpoint

Safety

Safety Assessment

- Safety lead-in was completed in Arm A at 24 mg/m^2 and is ongoing in Arm B at 18 mg/m^2
- Most frequent AEs were expected, on-target hematological (anemia, neutropenia, thrombocytopenia and WBC decrease), associated with the mechanism of action of onvansertib
- Hematological AEs were easily and effectively managed by dose delay, dose reduction and/or growth factor support
- No unexpected, off-target toxicities have been reported in patients treated to-date

	AE reported in ≥10% patients (N=30)				
	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Anemia	7	3	1		11
Neutropenia	1	1	6	3	11
Thrombocytopenia	8	1	0	1	10
WBC decrease	2	1	3	1	7
Hypophosphatemia	2	3	1		6
Fatigue	4				4
Alopecia	3				3
Back pain		3			3
Constipation	3				3
Creatine increase	3				3
Hypertension		1	2		3
Hypokalemia	1	1	1		3

Conclusions and Perspective

- **Overall, across both arms (A and B), a 60% response (SD + PR) was observed (n=9/15) in patients evaluable for efficacy (completed 3 months of treatment); 72% of patients (n=18/25) had a decrease in PSA following 1 cycle of treatment; 6 patients remain on treatment for ≥4 months**
- **All 5 AR-V7 positive patients had a decrease in PSA following 1 cycle of treatment with onvansertib; efficacy (SD + PR) observed in 3 out of 4 patients**
- **In both arms (A and B) onvansertib in combination with abiraterone was safe and well-tolerated**
- **An alternative Arm C with a more continuous dosing schedule has been proposed (onvansertib 12 mg/m^2 on days 1-14 of a 21-day cycle) for safety and efficacy evaluation**
- **The addition of onvansertb to treatment in mCRPC patients with resistance to abiraterone (rising PSA) validates prior pre-clinical studies and shows promise as a new therapeutic option**

References:
[1]Zitouni et al., Nat Rev Mol Cell Biol. 2014 Jul;15(7):433-52
[2]Weichert et al., Prostate 2004;60(3):240-5
[3]Zhang et al., Cancer Res 74(22) 6635-47, 2014
[4]Antonarakis et al., N EnglJ Med, 371: 1028-38, 2014
[5]Amstrong et al., J Clin Oncol, 37: 1120-1129, 2019

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