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

Abstract #1044

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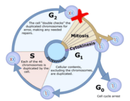
Background

Polo-like Kinase 1 (PLK1)

- Serine/threonine kinase, master regulator of mitotic progression
- PLK1 is over-expressed in dividing cancer cells
- Inhibition of PLK1 causes mitotic arrest and subsequent cell death



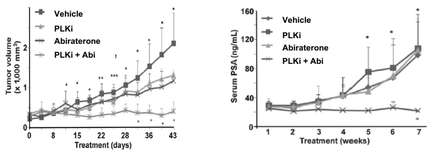
Onvansertib (also known as PCM-075 and NMS-1286937)

Active Clinical Trials:

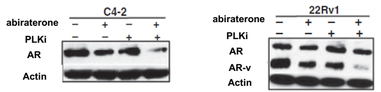
- Acute Myeloid Leukemia (AML) NCT03303339
- metastatic Castration-Resistant Prostate Cancer (mCRPC) NCT03414034
- metastatic Colorectal Cancer (mCRC) NCT03829410

PLK Inhibitor Synergizes with Abiraterone (Abi) in Preclinical Models

- Combination of PLKi and abiraterone blocks tumor growth and PSA increase in a CRPC xenograft model[1]



- AR-V7+ detection in CTCs is associated with abiraterone resistance[2]
- AR-V7+ has a shorter progression-free survival and overall survival in mCRPC intent-to- treat with abiraterone[3]
- Combination of abiraterone and PLK inhibitor (PLKi) reduces AR and AR-V7 protein expressions in CRPC cell lines[1]



Phase 2 Trial (NCT03414034) Design and Objectives

	Dosing Regimen	Duration	Efficacy Endpoint
Amr A Onvansertib Days 1-5 3-week dosing schedule	Onvansertib – 24 mg/m² 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/m² 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
- Radiographic response following the addition of onvansertib
- Time to PSA and radiographic progression following the addition of onvansertib

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

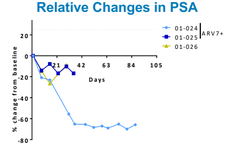
Number of patients (N)	Arm A	Arm B
Subjects Treated	21	3
Subjects Completing 12-weeks of Treatment	11	1
Subjects Currently on Treatment	7	3
AR-V7+ Subjects (Epic or JHU)	3	2

Preliminary Efficacy and Safety

Efficacy:

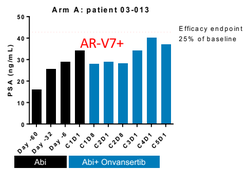
- Efficacy endpoint of disease stabilization, based on PSA levels, achieved in 2 subjects: 1 patient in Arm A (03-013) and 1 patient in Arm B (01-024)
- Initial disease stabilization or reduction, based on PSA levels, achieved in 3 Arm B subjects: 14-day dosing schedule (50% greater onvansertib drug exposure vs 21-day dosing schedule in Arm A)

Arm B: 14-Day Dosing Schedule Relative Changes in PSA

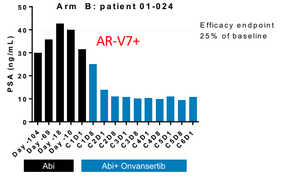


Efficacy and AR-V7 Status

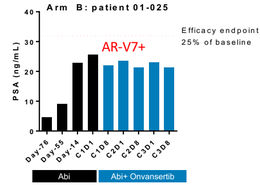
- Initial PSA stabilization or decrease was observed in all AR-V7+ subjects (n=4) treated to-date who completed 12-weeks of treatment or are currently on treatment
- The patients who reached the primary efficacy endpoint of disease stabilization were AR-V7+



- PSA increased >100% in the 60 days prior to addition of onvansertib
- PSA increased only 8.4% during the treatment period (84days), achieving efficacy endpoint of PSA stabilization
- Subject achieved Partial Response based on RECIST criteria



- Subject received palliative radiation 2 weeks prior to trial
- PSA level was greatly reduced (92%) after the initial 2-week treatment course and remained stable over 12 week efficacy evaluation period
- Subject achieved efficacy endpoint and remains on study



- PSA increased >500% in the 76 days prior to trial enrollment
- PSA decreased 35% in the first 35 days on study (C3D8)
- Subject remains on study

Safety

- Reported SAEs were all hematological (anemia, neutropenia, thrombocytopenia and WBC decrease), 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

AE reported in >10% patients (N=24)					
	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Anemia	5	2	1*		8
Constipation	3				3
Fatigue	5				5
Hypophosphatemia	3				3
Neutropenia	3		1	2*	6
Thrombocytopenia	4		1	1*	6
Urinary frequency nocturia	3				3
WBC decrease	1		2	1*	4

*were considered SAEs

Conclusions and Perspective

- Preliminary efficacy with PSA stabilization or reduction was observed in the initial 3 subjects enrolled in Arm B (2-week dosing schedule and 50% greater drug exposure to onvansertib over the treatment course), suggesting that a shorter dosing schedule may maximize response to treatment.
- All AR-V7+ subjects showed initial PSA reduction or stabilization (n=4); 2 met the primary efficacy endpoint at 12 weeks and 1 is starting week 7 of treatment.
- The combination of onvansertib and abiraterone for AR-V7+ subjects may offer a new treatment option for patients who are resistant to AR-Signaling Inhibitor (ARSi) therapies and whose prognosis is poor.

References:

[1]Zhang et al., Cancer Res 74(22) 6635-47, 2014
[2]Antonarakis et al., N EngJ Med, 371: 1028-38, 2014
[3]Amstrong et al., J Clin Oncol, 37: 1120-1129, 2019

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