Abstract: TP5266
Poster: P10

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

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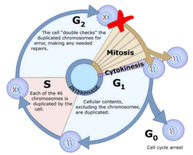
Background



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, 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]

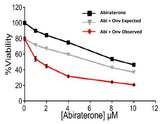
PLK Member	Onvansertib IC_{50} (μM)
PLK1	0.002
PLK2	> 10
PLK3	> 10

Clinical Trial Rationale

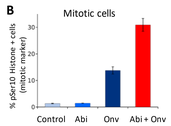
PLK Inhibitor synergizes with abiraterone in preclinical models

- 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]

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



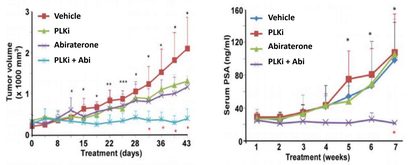
Onvansertib + Abiraterone Significantly Increase Mitotic Arrest



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]

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



Phase 2 Trial Design and Objectives (NCT03414034)

Study Design:

		Dosing Regimen	Duration	Efficacy Endpoint
Ongoing	Arm 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
Ongoing	Arm B Onvansertib Days 1-5 2-week dosing schedule	Onvansertib – 18 mg/m² Days 1-5 + Abiraterone daily	6 Cycles = 12 Weeks	Disease Control PSA Stabilization or Decline
Planned	Arm C Onvansertib Days 1-14 3-week dosing schedule	Onvansertib – 12 mg/m² Days 1-14 + Abiraterone daily	4 Cycles = 12 Weeks	Disease Control PSA Stabilization or Decline

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

Inclusion Criteria:

- Receiving first-line abiraterone treatment with prior evidence of response
- 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 Criteria:

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

Enrollment Status and Safety Assessment

Enrollment status as of January 31st 2020

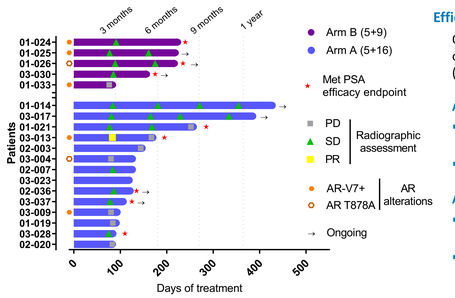
Number of patients (N)	Arm A	Arm B
Subjects Treated	30	8
Subjects Completing 12-weeks of Treatment	14	5
Subjects Currently on Treatment	4	4
AR-V7+ Subjects (Epic or JHU)	4	3

Safety assessment as of January 31st 2020

- Safety lead-in was completed in Arm A at 24 mg/m² and is ongoing in Arm B at 18 mg/m²
- Most frequent G3/G4 AEs were expected, on-target, reversible hematological (anemia, neutropenia, thrombocytopenia and leukopenia), associated with the mechanism of action of onvansertib
- Hematological AEs were reversible and effectively managed by dose delay, dose reduction and/or growth factor support
- Grade 3 hypophosphatemia was reported in 3 patients, next cycle treatment was delayed for 2 patients to allow recovery

	AE reported in ≥10% patients (N=38)				
	Grade 1	Grade 2	Grade 3	Grade 4	All grades
Anemia	7	4	1		12
Fatigue	10	2			12
Neutropenia	1	1	8	2	12
Thrombocytopenia	10	1		1	12
Leukopenia	2	2	3	1	8
Back pain	2	3			5
Hypokalemia	3	1	1		5
Hypophosphatemia	1	1	3		5

Efficacy in Abiraterone-Resistant Patients



Efficacy observed in 63% (n=12/19) of patients remaining on treatment at 12 weeks across arms

Overall, 63% (12 of 19) 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=5): Onvansertib Days 1-5 in a 2-week dosing schedule

- 80% (4 of 5) patients had SD at 12 weeks, with 3 patients achieving the efficacy endpoint (PSA stabilization) and 3 patients remain on treatment
- 60% (3 of 5) patients have or had progression-free survival of >7 months

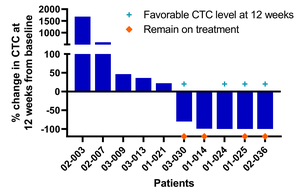
Arm A (n=14): Onvansertib Days 1-5 in a 3-week dosing schedule

- 57% (8 of 14) patients had SD or PR at 12 weeks, with 5 patients achieving the efficacy endpoint (PSA stabilization) and 4 patients remain on treatment
- 21% (3 of 14) patients have or had progression-free survival; 2 patients remain on treatment for >1 year

Onvansertib-induced CTC decrease is associated with progression-free survival

- CTC count, reported as favorable or unfavorable (<5 versus ≥5 CTC/7.5mL of blood, respectively) is a prognostic factor for survival in CRPC and the conversion from unfavorable to favorable is associated with improved survival[7]
- At baseline, 25 (78%) patients had unfavorable CTC count with median of 19 CTC/7.5mL
- 10 of the unfavorable patients were re-analyzed after 12 weeks of treatment
  - 5 (50%) patients had a ≥80% CTC decrease, including 2 AR-V7+ patients (01-024 and 01-025)
  - 4 (40%) patients converted from unfavorable to favorable CTC level (<5 CTC/7.5mL)
  - 3 (30%) patients had no detectable CTC
  - Median time on treatment for patients with decrease CTC (n=5) is 7 months to-date, with 4 patients remaining on treatment
  - Conversely, median time on treatment for patients with increase CTC (n=5) was 5 months, and none of these patients remain on treatment

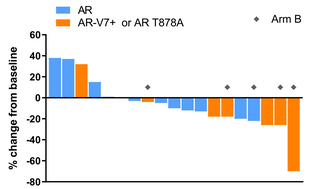
% Change in CTC at 12-weeks vs baseline in patients with unfavorable CTC level at baseline



Efficacy observed in patients with abiraterone-resistant AR alterations

- AR mechanisms of resistance to abiraterone include the expression of the constitutively active AR splice variant AR-V7 and the AR gain-of function point mutation T878A[6]
- Among the 19 patients who completed the 12-week treatment (Arm A + B):
  - 5 patients were AR-V7+ at baseline
  - 2 patients had AR T878A mutations at baseline
- Onvansertib showed efficacy in patients with AR alterations (N=7):
  - 6 (86%) patients had a decrease in PSA levels with the addition of onvansertib
  - 4 (57%) patients had SD or PR at 12 weeks with 3 (43%) patients achieving the primary efficacy endpoint
  - 3 patients have or had progression-free survival of >7 months, 2 patients remain on treatment

Best PSA response in AR-V7+ and AR T878A patients



Conclusions

- Overall, across both arms (A and B), a 63% (12 of 19) response (SD + PR) was observed in patients evaluable for efficacy (completed 12 weeks of treatment); 6 patients have been on treatment for ≥7 months
- Onvansertib induced profound CTC decrease in patients with unfavorable CTC count (>80% decrease in 5 of 10 patients tested); CTC decrease was associated with prolonged response to treatment and progression-free survival
- 6 of 7 patients with AR alterations (AR-V7+ or AR T878A) had an immediate decrease in PSA following onvansertib treatment; efficacy (SD+PR) was achieved in 57% (4 of 7) patients
- In both arms (A and B) onvansertib in combination with abiraterone was safe and well-tolerated
- A more continuous dosing schedule (Arm C – onvansertib 12 mg/m² on days 1-14 of a 21-day cycle) is planned, and currently under IRB review, to evaluate safety and efficacy evaluation
- Adding onvansertib to abiraterone in mCRPC patients resistant to abiraterone (rising PSA) validates pre-clinical studies and shows promise as a new therapeutic option

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