Abstract #TPS219

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

DJ Einstein MD[1]; AD Choudhury MD PhD[2]; P Saylor MD[3]; JC Patterson PhD[4]; PJP Croucher PhD[5]; M Ridinger PhD[5]; M Erlander PhD[5]; MB Yaffe MD PhD[4]; G Bubley MD[1]

[1]Beth Israel Deaconess Medical Center, Boston, MA; [2]Dana-Farber Cancer Institute, Boston, MA; [3]Massachusetts General Hospital, Boston, MA; [4]Massachusetts Institute of Technology, Cambridge, MA; [5]Cardiff Oncology, San Diego, CA

Clinical Trial Background and Rationale

Metastatic CRPC

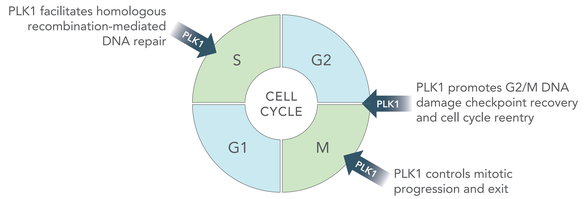
- Metastatic CRPC is a leading cause of cancer death worldwide.
- Abiraterone (abi) + prednisone is a standard-of care in either castration-sensitive or castration-resistant disease and increases survival.
- Unfortunately, over time (~9-15 months) CRPC develops resistance to anti-androgen therapy and new therapeutic approaches are necessary for these patients.

PLK1 – A Promising Target for Prostate Cancer

- Serine/threonine kinase, master regulator of the cell cycle progression:[1]
  - Controls mitotic entry and progression.
  - Is involved in the DNA damage response through the regulation of homologous recombination-mediated DNA repair and the promotion of the G2/M DNA damage checkpoint recovery.
- Is overexpressed in prostate cancer and linked to higher tumor grades.[2]

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.

FIGURE 1. PLK1 FUNCTIONS THROUGH THE CELL CYCLE

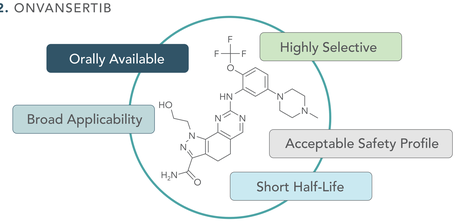


Onvansertib

- Is a highly specific and orally available PLK1 inhibitor with a 24-hour half-life.
- Has demonstrated safety in advanced/metastatic solid tumors.[1]

1. Weiss et al., *Invest New Drugs*, 2018.

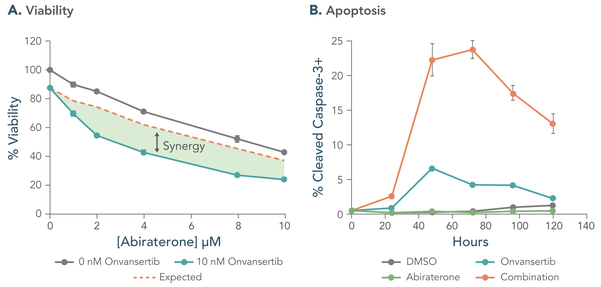
FIGURE 2. ONVANSERTIB



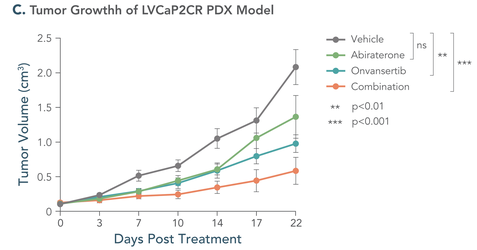
Onvansertib in Combination with Abi in CRPC Preclinical Models

- Onvansertib sensitized CRPC cells to abiraterone and the combination resulted in synergistic apoptotic cancer cell death (Figures 3A and 3B).
- Onvansertib induced significant tumor growth inhibition in combination with abiraterone in a LVCaP2CR AR-v7 positive abiraterone-resistant patient derived xenograft (PDX) model (Figure 3C).

FIGURE 3. ONVANSERTIB ANTI-TUMOR ACTIVITY IN CRPC PRECLINICAL MODELS



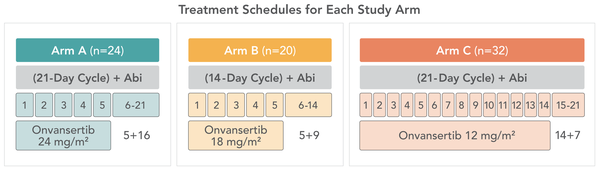
- C4-2 cells were treated with onvansertib +/- abiraterone.
- Viability was measured 72h post-treatment using the CellTiterGlo assay. Synergy was calculated with the Bliss model.
- Apoptosis was assessed by measuring the % of cleaved-caspase 3 cells by flow cytometry.



- Castrated male mice were inoculated with the LVCaP2CR PDX model and treated with vehicle, onvansertib, abiraterone or the combination for 3 weeks (n=8/group).
- One-way ANOVA and Dunnett's test were used for statistical analyses on Day 22.

Trial Design

FIGURE 4. TREATMENT SCHEDULE



Study Sites and Principal Investigators

- **Beth Israel Deaconess Medical Center, Boston:** Dr. David Einstein
- **Dana Farber Cancer Center, Boston:** Dr. Atish Choudhury
- **Massachusetts General Hospital, Boston:** Dr. Philip Saylor

Eligibility Criteria

Key Inclusion Criteria

- Histologically confirmed prostate adenocarcinoma without significant small-cell/ neuroendocrine or other variant histologies. Must have either undergone surgical castration or continue on GnRH agonist/antagonist on the appropriate schedule throughout the study period.
- Castration confirmed by testosterone <50 ng/dL.
- Currently on treatment with abi/prednisone for castration-sensitive prostate cancer (CSPC) or CRPC. Patients who have received abiraterone for CSPC must have had a response to hormonal therapy, as defined by any decline in prostate specific antigen (PSA), radiographic response, and/or clinical benefit after starting hormonal therapy. Patients who have received abi for CRPC must have responded to abi, defined by any decline in PSA, radiographic response, and/or clinical benefit after starting abi.
- Initial signs of abi resistance defined as 2 rising PSAs; one rise of ≥0.3 ng/mL separated by one week.

Key Exclusion Criteria

- Prior treatment with enzalutamide or apalutamide or experimental therapies directed against androgen receptor.
- Rapidly progressing disease or significant symptoms related to disease progression.
- Systemic corticosteroids except as part of on label treatment prostate cancer regimens.

Endpoints

Efficacy Endpoints

- **Primary:** Disease control evaluated as PSA decline or stabilization (PSA rise <25% over baseline) after 12 weeks of treatment
- **Secondary:** Radiographic response per RECIST v1.1 and PCWG3 criteria, time to PSA progression, and time to radiographic response.

Safety Endpoints

- Safety, as per CTCAE version 4.03.
- Number of reported DLTs for patients on onvansertib with abiraterone combination.

Correlative Analyses

Objectives

- Analyses of circulating tumor DNA (ctDNA), circulating tumor cells (CTCs) and archival tumor tissue to identify potential genomic and transcriptomic biomarkers of response.
- Assess treatment response in patients with AR-driven mechanisms of resistance to abiraterone, such as the expression of the constitutively active AR splice variant AR-V7, AR gain-of function point mutations and AR amplification.[1]
- Assess treatment response in patients with favorable and unfavorable CTC counts at baseline (<5 versus ≥5 CTC / 7.5 mL of blood, respectively)[2] and the changes in CTC counts after 12 weeks of treatment.

1. Watson et al., *Nat Rev Cancer*, 15(12):701-711, 2015; **2.** Pantel et al., *Clin Chem*, 65(1):87-99, 2019.

Method

1. Blood collection at baseline for:

ctDNA Analysis:
- Targeting sequencing (Guardant OMNI®; 500-gene panel)

CTC Analyses:
- Enumeration (CellSearch®, Epic Sciences) ⟶ Repeated at 12-week
- AR-V7 status (John Hopkins, Epic Sciences)
- Single cell CNV analysis (Epic Sciences)
- Gene expression analysis (Dr. Miyamoto, MGH)

2. Request of archival tumor tissue for gene expression analysis (Veracyte).

Statistical Considerations

- With 32 patients in each arm, there will be 90% power to detect a change in disease-control rate at 12 weeks from 10% (null) to 30% (alternative). Based on a Simon's two-stage optimal design, the study will terminate early if <2 of the first 13 patients in each arm achieve disease control.
- Assuming the study continues to full enrollment, if 6 or more out of a total of 32 patients in one or both arms achieve disease control at 12 weeks, the experimental treatment will be considered potentially effective at the corresponding dose schedule. The probability of stopping at the first stage is 0.62.

Enrollment

TABLE 1. ENROLLMENT AS OF 25-JAN-2022

Number of Patients (N)	Arm A (5+16)	Arm B (5+9)	Arm C (14+7)
Treated	24	20	24
Completing 12-Weeks	14	15	15
Currently on Treatment	0	3	11

Study Contact: David Einstein, MD, deinstei@bidmc.harvard.edu

Presented at: ASCO GU 2022, Trials in Progress Poster Session A: Prostate Cancer