ProSTAR: A phase 1b/2 study of CPI-1205, a small molecule inhibitor of EZH2, combined with enzalutamide (E) or abiraterone/prednisone (A/P) in patients with metastatic castration-resistant prostate cancer (mCRPC)

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**Background**

- **Enhancement of zeste homolog 2 (EZH2) is the catalytic subunit of the PRC2 complex and overexpression is associated with poor outcomes in prostate cancer.**
- **CPI-1205 is a potent, selective, and cofactor-competitive EZH2 inhibitor.**

**Objectives**

- Determine preliminary signs of efficacy with each combination in patients with mCRPC 1
- CPI-1205 monotherapy achieved objective responses and substantial target engagement at well tolerated doses

**Methods**

PHASE 1B STUDY OBJECTIVES

- **Primary Objective:** Determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of CPI-1205 + E or CPI-1205 + A/P in patients with mCRPC.
- **Secondary Objectives:**
  - Evaluate safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD).
  - Evaluate preliminary signs of efficacy with each combination.
- **Exploratory Objectives:**
  - Evaluate the plasma pharmacodynamics effects and PK/PD relationship of CPI-1205.
  - Evaluate and identify potential novel predictive biomarkers utilizing genomics, proteomics, and protein expression technologies.

**Results**

- CPI-1205 exposure sufficient in TID dosing to achieve target plasma concentrations and substantial target engagement.
- CPI-1205 is generally well tolerated.

**Conclusions**

- Significant number of patients had maintenance of prior progressions at baseline (53% E/58% A/P) and at the RP2D (57% E/65% A/P).
- PSA >80% response in 9/13 ARV7+ patients (69% E/55% A/P).
- Median H3K27me3 MFI was increased (n=1, 6.3%, transient and reversible). There were 2 patients who received CPI-1205 discontinued treatment.
- Patients treated with or without C.
- These observations support the clinical evaluation of CPI-1205 with standard doses of E or A/P in combination in this study.

**References**