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)

Abstract CT094

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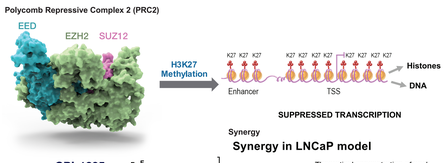
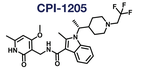
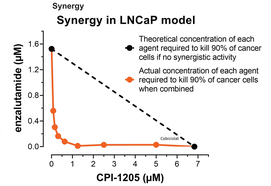
BACKGROUND

- Enhancer of zeste homolog 2 (EZH2) is the catalytic subunit of the PRC2 complex and methylates histone H3 on lysine 27, resulting in suppression of gene expression.
- EZH2 mutations and increased expression are often observed in cancer, leading to repression of genes associated with apoptosis and differentiation.[1,2]
- Overexpression of EZH2 in metastatic castration-resistant prostate cancer (mCRPC)[3] and decreased expression of target genes are correlated with disease stage and poor prognosis.[4]
- Many mCRPC tumors remain dependent on androgen receptor signaling (ARS), but eventually develop resistance to ARS inhibitors, such as E and A/P.
- Preclinical ARS-dependent prostate cancer cell models are sensitive to EZH2 inhibition.[5-8]
- Combining EZH2 inhibitors with ARS inhibitors results in synergistic cell growth inhibition.[5-8]
- CPI-1205 is a potent, selective, and cofactor-competitive EZH2 inhibitor.[9]
- CPI-1205 monotherapy achieved objective responses and substantial target engagement at well tolerated doses in a phase 1 clinical trial in patients with non-Hodgkin's lymphoma.[10]
- These observations support the clinical evaluation of CPI-1205 with standard doses of E or A/P in mCRPC. Data presented here are based on the phase 1b portion of the study with data cut of 6 Feb 2019.



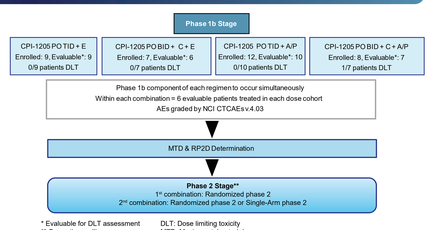




STUDY DESIGN

In this multicenter phase 1b/2 study, patients with mCRPC previously treated with Enzalutamide (E) or Abiraterone (A/P) are enrolled in different cohorts exploring two regimens of oral CPI-1205 on a continuous 28-day cycle: 1) 800 mg TID or 2) 400 mg BID with cobicistat (C), a CYP3A4 inhibitor, combined with the standard dose of E (160 mg QD) or standard dose of A/P (1000 mg QD/5 mg BID). C is used to increase systemic exposure of CYP3A substrates. Pre-treatment with C successfully increased the exposure of CPI-1205 in another study, which led to the interest to explore the addition of C to the treatment combination in this study.

An expansion cohort in heavily pretreated patients will be initiated with the dose regimen that was deemed safe by the study safety committee. After consideration of safety, PK, and PD, the RP2D will be established, and phase 2 will be initiated. One or both of the combinations, CPI-1205 with E and with A/P, might proceed to phase 2. If both combinations are chosen for phase 2, one combination might proceed to a randomized phase 2, and the second combination might proceed to another randomized phase 2 or a single-arm phase 2. NCT03480646.



* Evaluable for DLT assessment
** Currently enrolling

DLT: Dose limiting toxicity
MTD: Maximum tolerated dose

PHASE 1B STUDY OBJECTIVES

Primary Objective:

- Determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of CPI-1205 + E and CPI-1205 + A/P in patients with mCRPC

Secondary Objectives:

- Characterize the safety, tolerability, pharmacokinetic (PK) profile
- Determine preliminary signs of efficacy with each combination
  - Prostate specific antigen (PSA) 50% response, circulating tumor cell (CTC) 30% response, or objective response per Prostate Cancer Working Group 3 (PCWG3)

Exploratory Objectives:

- Evaluate the pharmacodynamic effects and PK/PD relationship of CPI-1205
- Evaluate and identify potential novel predictive biomarkers utilizing genomics, transcriptomics, and protein expression technologies

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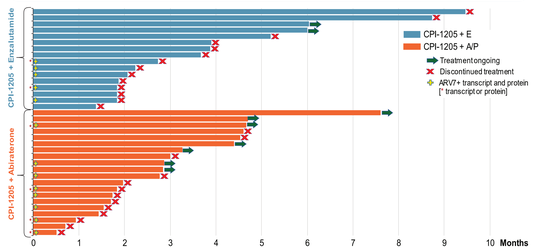
PHASE 1B RESULTS

BASELINE CHARACTERISTICS

Demographics	Enzalutamide (N=16)	Abiraterone (N=20)	Overall (N=36)
Age (Years)			
n	16	20	36
Median	71.5	73.5	72.5
Min-Max	55-90	63-86	55-90
ECOG PS [n, (%)]			
0	9 (56.3%)	10 (50.0%)	19 (52.8%)
1	7 (43.8%)	10 (50.0%)	17 (47.2%)
PSA (ng/mL)			
n	16	19	35
Mean	86.5	385.81	248.98
Median	26.3	30.8	30.5
Min-Max	2.7-350.9	5.9-4205.5	2.7-4205.5
CTC Count Unfavorable [n, (%)]	8 (50.0%)	12 (60.0%)	20 (55.6%)
ARV7+ [n, (%)]	5 (31.3%)	8 (40.0%)	13 (36.1%)
Prior Chemotherapy [n, (%)]	5 (31.3%)	8 (40.0%)	13 (36.1%)
Taxane-based for mCRPC [n, (%)]	2 (12.5%)	5 (25%)	7 (19%)
Target Lesion [n, (%)]	5 (31.3%)	8 (40.0%)	13 (36.1%)
LDH (U/L)			
n	16	20	36
Mean (Min-Max)	324.2 (140-846)	333.4 (131-758)	329.3 (131-846)
Baseline abnormal [n, (%)]	7 (43.8%)	11 (55.0%)	18 (50.0%)
HGB (g/L)			
n	16	20	36
Mean	119.7	115.1	117.1
Min-Max	96-149	68-144	68-149

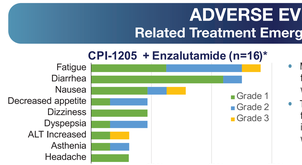
*ARV7 (Androgen Receptor Splice Variant 7); protein and/or transcript levels are tested.

TREATMENT DURATION



9/36 patients are still ongoing • 2 patients on treatment with CPI-1205 + E • 7 patients on treatment with CPI-1205 + A

ADVERSE EVENTS
Related Treatment Emergent AEs (≥10%)



- Most commonly reported study-drug-related TEAEs are fatigue (56.3%), diarrhea (50.1%), and nausea (31.4%), which were manageable with supportive care.
- The only Grade 3 study-drug-related TEAEs include fatigue (n=1, 6.3%), nausea (n=1, 6.3%), and ALT increased (n=1, 6.3%, transient and reversable). There were no Grade 4 events reported.
- Most commonly reported study-drug-related TEAEs are diarrhea (30%), nausea (25%), and fatigue (20%), which were manageable with supportive care.
- ≥ Grade 3 study-drug-related TEAEs include fatigue (Gr3, n=1, 5%) and increased ALT (Gr4, n=1, 5%); transient and reversible). This ALT elevation was the only DLT reported in the trial: a reversible increase in transaminases, which is a known AE associated with A.

*Patients treated with or without C.
One Grade 4 ALT elevation was reported.
Study-drug-related TEAEs: Reported as related to CPI-1205.

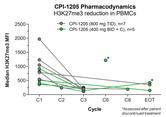
CPI-1205 PK AND PD DATA

Mean Steady State Pharmacokinetic Parameters of CPI-1205*				
Combination	E		A/P	
Treatment Regimen	800 mg TID CPI-1205	400 mg BID CPI-1205 + C	800 mg TID CPI-1205	400 mg BID CPI-1205 + C
No. of patients	n=9	n=7	n=11	n=6
C_{max} (ng/mL)	30 (23)	112 (224)	50 (101)	328 (240)
C_{min} (ng/mL)	531 (48)	878 (76)	671 (43)	3,068 (56)
AUC_{ss} (ng/mL)	4,516 (36)	9,352 (111)	6,250 (80)	35,962 (62)
CL/F (L/h)	531 (36)	86 (111)	384 (80)	22 (62)

Mean Steady State Pharmacokinetic Parameters of E or A/P*				
Combination	E		A/P	
Treatment Regimen	800 mg TID CPI-1205	400 mg BID CPI-1205 + C	800 mg TID CPI-1205	400 mg BID CPI-1205 + C
No. of patients	n=9	n=8	n=11	n=4
C_{max} (ng/mL)	6,387 (26)	8,245 (35)	4.2 (62)	5.1 (57)
C_{min} (ng/mL)	6,328 (18)	10,137 (24)	78 (62)	93 (120)
AUC_{ss} (ng/mL)	160,773 (21)	207,612 (31)	499 (61)	632 (105)

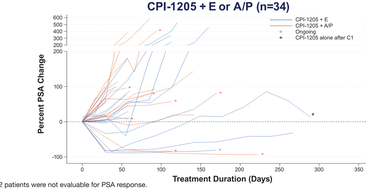
* All values are reported as the geometric mean (geometric %CV).

- PK parameters assessed with steady-state drug exposure levels presented.



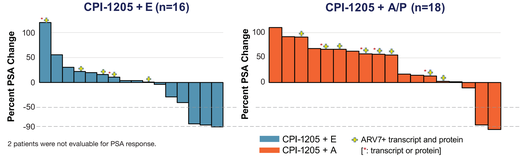
- PD response assessed in peripheral blood cells by detecting H3K27me3 level.
- CPI-1205 exposure sufficient in TID dosing regimen to elicit substantial PD response, with similar results observed when combined with either E or A.

PSA: PERCENT CHANGE FROM BASELINE



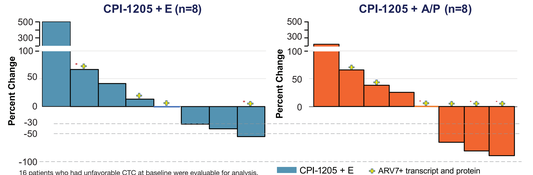
2 patients were not evaluable for PSA response.

PSA: BEST PERCENT CHANGE FROM BASELINE



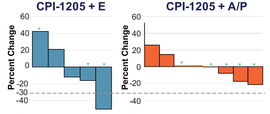
2 patients were not evaluable for PSA response.

CTC: BEST PERCENT CHANGE FROM BASELINE



16 patients who had unfavorable CTC at baseline were evaluable for analysis.

RECIST 1.1 TARGET LESION PERCENT CHANGE (n=13)



- 6/13 (46%) experienced reduction in tumor burden.
- Among 13 patients with measurable disease. 9 (69%) patients had PR/SD as best response per RECIST 1.1.
- 7/13 (54%) patients had DCR ≥ 3 months.

	PR	SD (any duration)	DCR (any duration)	DCR (≥ 3 months)
CPI-1205 + E	1/5 (20%)	2/5 (40%)	3/5 (60%)	3/5 (60%)
CPI-1205 + A/P	0/8 (0%)	6/8 (75%)	6/8 (75%)	4/8 (50%)

DCR: Disease Control Rate includes patients with best response of SD or PR.
PR: Partial Response; SD: Stable Disease.

* By central review.

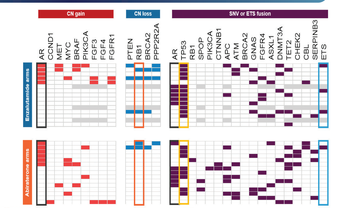
PSA ≥80 AND RECIST 1.1 RESPONSE BY ARV7 STATUS

	ARV7 Positive (n=13)				ARV7 Negative (n=23)			
	PSA ≥80 Response	RECIST 1.1 Response**			PSA ≥ 80 Response	RECIST 1.1 Response**		
		CR	PR	SD		CR	PR	SD
CPI -1205 + E	0/5	0	0/2	1/2 (50%)	3/11 (27%)	0	1/3 (34%)	1/3 (34%)
CPI -1205 + A/P*	0/8	0	0/0	0/0	2/10 (20%)	0	0/8	6/8 (75%)

*2 patients with ARV7 negative status are not evaluable for PSA.
**11 ARV7 negative and 2 ARV7 positive patients had measurable disease at baseline.

SUMMARY OF ctDNA MUTATION ANALYSIS

- Genomic aberrations were detected from cell free DNA (cfDNA). Germline variants and suspected clonal hematopoiesis associated variants were not filtered from presented dataset. Genes with previously published frequency[11] of >5% or detected in ≥2 samples in current study are presented.
- Current study shows variation in frequency of aberrations identified compared to published reports, including under-representation of *AR* amplification and *ETS* fusions, and over-representation of *AR* mutations, *TP53* mutations, and *RB1* copy number loss (poor prognostic indicators).
- 19% (5/27) patients had inactivating alterations in 2, or all 3, of the PTEN, RB1, or TP53 genes (commonly observed of aggressive and/or neuroendocrine disease).
- Additional analyses of tumor biopsies ongoing.



Frequencies calculated from mCRPC cohort with prior E or A treatment.[11]
Grayed out boxes indicate gene was not included in genomics panel

CONCLUSIONS

- A significant number of patients had multiple indicators of poor prognosis at baseline (56% unfavorable CTC enumeration, 50% high LDH, and 36% ARV7 expression).
- The combination of CPI-1205 800 mg TID or 400 mg BID with C administered with E or A/P were generally well tolerated.
- Co-administration with C did not completely reverse the reduction of CPI-1205 exposure in patients who received CPI-1205 in combination with E.
- The CPI-1205 TID dosing regimen was sufficient to elicit a substantial PD response with similar results observed when combined with either E or A/P.
- CPI-1205 800 mg TID in combination with standard doses of E or A/P was selected as the RP2D.
- Several patients in both arms demonstrated PSA responses, RECIST responses, and/or CTC reductions in this advanced mCRPC second-line setting.
- Based on these encouraging results, we are conducting a phase 2 single-arm trial with CPI-1205 given in combination with A/P and a randomized trial of CPI-1205 given in combination with E in second-line mCRPC. An expansion cohort in heavily pre-treated patients has also been initiated.

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