Official Title: ProSTAR: A Phase 1b/2 Study of CPI-1205, a Small Molecule Inhibitor of EZH2, Combined with Enzalutamide or Abiraterone/Prednisone in Patients with Metastatic Castration Resistant Prostate Cancer

NCT Number: NCT03480646

Document Date: Statistical Analysis Plan (Phase 1b)_Version 3.0: 30 October 2020
Statistical Analysis Plan (Phase 2)_Version 2.0: 13 April 2021

16.1.9 Documentation of Statistical Methods

Statistical Analysis Plan (Phase 1), Version 3.0	30 Oct 2020
Statistical Analysis Plan (Phase 2), Version 2.0	13 Apr 2021

STATISTICAL ANALYSIS PLAN

Protocol No: 1205-201

ProSTAR: A Phase 1b/2 Study of CPI-1205, a Small Molecule Inhibitor of EZH2, Combined with Enzalutamide or Abiraterone/Prednisone in Patients with Metastatic Castration Resistant Prostate Cancer

Analysis Plan for Phase 1b cohorts with escalation and expansion doses

Version: Final 3.0

Date: 30/Oct/2020

[redacted]

REVISION HISTORY

Version	Version Date	Author	Summary of Changes Made
Draft 1.0	29-Nov-2018	[redacted]	New Document
Draft 2.0	21-Jan-2019	[redacted]	Updated per comments
Draft 3.0	27-Mar-2019	[redacted]	Updated per comments
Final 1.0	24-Apr-2019	[redacted]	Final
Final 1.1	23-Aug-2019	[redacted]	Final Draft
Final 2.0	19-Sep-2019	[redacted]	Final
Final 3.0	30-Oct-2020	[redacted]	Updated per comments to new Final version

[redacted]

SIGNATURE PAGE - CONSTELLATION PHARMACEUTICALS

Declaration

The undersigned has/have reviewed and agree to the statistical analyses and procedures of this clinical study, as presented in this document.

[redacted], MD MPH
Digitally signed by [redacted], MD MPH
Date: 2020.12.22 05:42:58 -05'00'

[redacted] **Date (DD Mmm YY)**

[redacted]

[redacted]
Digitally signed by [redacted]
Date: 2020.12.18 17:26:32 -05'00'

[redacted] **Date (DD Mmm YY)**

Senior Clinical Trial Manager

[redacted]
Digitally signed by [redacted]
Date: 2020.12.18 17:05:37 -05'00'

[redacted] **Date (DD Mmm YY)**

[redacted]

[redacted]

SIGNATURE PAGE - [redacted]

Declaration

The undersigned agree to the statistical analyses and procedures of this clinical study.

If this document has been signed electronically, signature(s) and date(s) are present at the end of the document:

Document prepared and approved by:

[redacted]	**Date (DD Mmm YY)**
[redacted] **Biostatistician**	

[redacted]

TABLE OF CONTENTS

[redacted]

[redacted]

LIST OF TABLES

[redacted]

LIST OF FIGURES

ABBREVIATION AND ACRONYM LIST

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AR	Androgen receptor
AR-V	Androgen receptor splice variant
AST	Aspartate aminotransferase
ATC	Anatomical-therapeutic-chemical
AUC	Area under the concentration-time curve
BID	Two times a day
BMI	Body mass index
BP	blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence interval
C_{max}	Maximum observed concentration
C_{min}	Minimum observed concentration in the dosing interval
CPK	Serum lipids and creatine phosphokinase
CR	Complete response
CRR	Central radiology review
CSP	Clinical study protocol
CSR	clinical study report
CTC	Circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
CTCCR	CTC conversion rate
CTCRR	CTC 30% response rate
C_{trough}	Minimum (trough) concentration
D	Day
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone

[redacted]

Abbreviation / Acronym	Definition / Expansion
DLT	Dose-limiting toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report forms
FL	Follicular lymphoma
FSH	Follicle-stimulating hormone
GCB-DLBCL	Germinal center B-cell–like diffuse large B cell lymphoma
[redacted]	[redacted]
[redacted]	[redacted]
HDL	High density lipoprotein
HPEC	Heavily pretreated expansion cohort
INR	International normalized ratio
IP	Investigational product
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LH	Luteinizing hormone
mCRPC	Metastatic castration resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI	National cancer institute
ORR	Objective response rate
OS	Overall survival
PCWG3	Prostate cancer clinical trials working group 3
PD	Pharmacodynamic
PFS	Progression free survival
PK	Pharmacokinetic
PO	Orally; by mouth
[redacted]	[redacted]
PPR	Pain progression
PR	Partial Response
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

Abbreviation / Acronym	Definition / Expansion
PSA	Prostate specific antigen
PSA50	PSA 50% response rate
PT	Prothrombin time
[redacted]	[redacted]
QTcF	QT interval corrected by the Fridericia correction formula
Rac	Accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
rPFS	Radiographic progression free survival
rPFS2	Radiographic progression free survival, Second Definition
SAE	Serious adverse event
SAP	Statistical analysis plan
SHBG	Sex hormone-binding globulin
SOC	System organ class
SRE	Skeletal-related event
SSC	Study safety committee
SSE	Symptomatic skeletal even
TEAE	Treatment-emergent adverse event
TID	Three times a day
TLFs	Tables, Listings and Figures
T_{max}	Time to maximum concentration
TSH	Thyroid stimulating hormone
TTNST	Time to initiation of new systemic treatment for prostate cancer
TTOA	Time to opioid analgesics
TTPPR	Time to pain progression
TTPSAP	Time to PSA progression
TTSRE	Time to first SRE
TTSSE	Time to First SSE
TTUCP	Time to unequivocal clinical progression
UCP	Unequivocal clinical progression
WBC	White blood cell
WHODDE	World Health Organization Drug Dictionary drug

[redacted]

1. INTRODUCTION

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data. It describes the main variables and populations, anticipated data transformations and manipulations methods. And it also describes other details of the analyses not provided in the Clinical Study Protocol (CSP) of all data (source documents /electronic case report forms [eCRFs]) and captured electronically in RAVE.

The analyses described are based on the final clinical study protocol Amendment 3, Version 4.0, dated 26 July 2018 for "ProSTAR: A Phase 1b/2 Study of CPI-1205, a Small Molecule Inhibitor of EZH2, Combined with Enzalutamide or Abiraterone/Prednisone in Patients with Metastatic Castration Resistant Prostate Cancer" and eCRF Version 5.0, dated 28 September 2018. This Statistical Analysis Plan will include description of analyses for cohorts in **Phase 1b**. Pharmacokinetic (PK) and pharmacodynamic (PD) analyses will be described in a separate SAP.

The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made. Any deviations from the SAP after database lock, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in an SAP Addendum and documented in the clinical study report (CSR).

2. STUDY OBJECTIVES

2.1 Phase 1b (Dose Escalation) Primary Objectives and Endpoints

- **The primary objective at the Phase 1b (Dose Escalation)** is to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of CPI-1205 + enzalutamide and CPI-1205 + abiraterone/prednisone in patients with metastatic castration resistant prostate cancer (mCRPC). The MTD will be determined for CPI-1205 orally (PO) two times a day (BID) with cobicistat for each combination. The Study Safety Committee (SSC) may also select to determine the MTD for CPI-1205 PO three times a day (TID), however, only one of the CPI-1205 dosing schedules (i.e., either TID or BID with cobicistat) will be selected as the RP2D for each combination.

[redacted]

- **The primary endpoint at the Phase 1b (Dose Escalation)** is that the MTD will be determined based on the rate of dose-limiting toxicities (DLTs). The RP2D will be selected based on PK and the overall tolerability of the combination, but will not exceed the MTD.

2.2 Phase 1b (Dose Escalation) Secondary Objectives and Endpoints

The secondary objectives and endpoints at the Phase 1b (Dose Escalation) include the following,

- To characterize the safety and tolerability profile of CPI-1205 (with or without cobicistat) + enzalutamide and CPI-1205 (with or without cobicistat) + abiraterone/prednisone.
  - The secondary endpoints for AEs will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03).
  - Laboratory evaluations, vital signs, physical examinations, and electrocardiograms (ECGs) will also be evaluated.
- To characterize the pharmacokinetic profiles of CPI-1205, cobicistat, enzalutamide and abiraterone, and evaluate any PK interactions when CPI-1205 (with or without cobicistat) is given in combination with either enzalutamide or abiraterone.
  - The secondary endpoints for PK parameters include: area under the concentration versus time curves (AUC)last, maximum concentration (Cmax), time to maximum concentration (Tmax), minimum (trough) concentration (Ctrough; defined as the level at 24 hours post dose or the level pre-dose), peak-to-trough ratio and accumulation ratio (for both Cmax and AUClast).
- To evaluate preliminary signs of efficacy of CPI-1205 (with or without cobicistat) + enzalutamide and CPI-1205 (with or without cobicistat) + abiraterone/prednisone.
  - Prostate specific antigen (PSA) 50% response rate (PSA50) is defined as the proportion of patients with a ≥50% reduction in PSA from baseline.
  - Time to PSA progression is defined as the time from D1 of treatment to the date of PSA progression.
  - Radiographic progression free survival (rPFS), defined per Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria as time from D1 of treatment to the date when the first site of disease is found to progress (using a manifestation-specific definition of progression), or death, whichever occurs first. The proportion of patients who remain radiographic progression free at 3 months will also be assessed.

[redacted]

- For patients with measurable soft tissue disease, ORR per PCWG3 is defined as the proportion of patients with a CR or PR. Duration of Response (DOR) is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that radiographic progression is documented per PCWG3.
- In patients with measurable disease in non-parenchymal soft tissue, ORR (excluding parenchymal lesions) is defined as the proportion of patients with a CR or PR per PCWG3 in soft tissue excluding the parenchyma (i.e., liver and lung), DOR (excluding parenchymal lesions) is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that radiographic progression is documented per PCWG3 in soft tissue excluding the parenchyma.
- Time to first skeletal-related event (SRE) is defined as the time from D1 of treatment to the date of first SRE and the time to first symptomatic skeletal event (SSE) is defined as the time from D1 of treatment to the date of first SSE.
- Time to unequivocal clinical progression (UCP) is defined as the time from D1 of treatment to the date of unequivocal clinical progression.
- Time to initiation of new systemic treatment for prostate cancer (TTNST) is defined as the time from D1 of treatment to the date any new systemic treatment for prostate cancer is initiated.

[redacted]

- Time to pain progression (PPR) is defined as the time from D1 of treatment to the date of pain progression. For patients who enter the trial not on opioid analgesics, time to opioid analgesics (TTOA) is defined as the time from D1 of treatment to the date of first opioid usage.
- In patients who enter the trial with unfavorable circulating tumor cells (CTCs) (five or more cells per 7.5mL of Blood), conversion to favorable status is defined as four or fewer cells per 7.5 mL of Blood and the CTC conversion rate (CTCCR) is the proportion of patients who convert to favorable status.
- In patients who enter the trial with unfavorable CTCs (five or more cells per 7.5mL of blood), the CTC 30% response rate (CTCRR) is defined as the proportion of patients who have a ≥30% reduction in CTCs from baseline.

[redacted]

[redacted]

2.3 Phase 1b HPEC Primary Objectives and Endpoints

- The primary objective in the Phase 1b HPEC is to estimate ORR as determined by central radiology review (CRR) of CPI-1205 (with or without cobicistat) + enzalutamide OR abiraterone/prednisone in the HPEC.

  The endpoint is ORR per PCWG3.

2.4 Phase 1b HPEC Secondary Objectives and Endpoints

The secondary objectives and endpoint at the Phase 1b (HPEC) include the following.

- To characterize the safety and tolerability profile of CPI-1205 (with or without cobicistat) + enzalutamide OR abiraterone/prednisone in the heavily pretreated population.
- To estimate ORR as determined at the site by the investigator.
- To estimate ORR (excluding parenchymal lesions) as determined by CRR.
- To estimate PSA50.
- To estimate time to PSA progression (TTPSAP).
- To estimate rPFS as determined by CRR and at the site by the investigator.
- To estimate Overall Survival (OS).
- To estimate duration of response (DOR) as determined by CRR and at the site by the investigator and DOR (excluding parenchymal lesions) as determined by CRR.
- To estimate time to first SRE (TTSRE) and the time to first SSE (TTSSE).
- To estimate time to unequivocal clinical progression (TTUCP).
- To estimate time to initiation of new systemic treatment for prostate cancer (TTNST).
- [redacted].
- To estimate the time to pain progression (TTPPR) and the time to opioid analgesics (TTOA).

[redacted]

- To estimate the CTC 30% response rate and CTC conversion rate in patients with unfavorable CTCs.

[redacted]

- To further characterize PK profiles of CPI-1205, cobicistat (if applicable), enzalutamide or abiraterone, and further evaluate any PK interactions when CPI-1205 (with or without cobicistat) is given in combination with either enzalutamide or abiraterone.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

3. STUDY DESIGN

3.1 Overall Study Design

This is a phase 1b/2, multi-center, open-label study of CPI-1205 alone and with cobicistat in patients with mCRPC in combination with either enzalutamide or abiraterone/prednisone.

During phase 1b dose escalation and prior to Amendment 2, patients were enrolled into phase 1b Dose Level 1A (CPI-1205 PO TID + enzalutamide or abiraterone/prednisone). As of Amendment 2, new patients will be enrolled into cohorts including 1) dose escalating CPI-1205 PO BID + fixed dose cobicistat PO BID + enzalutamide and 2) dose escalating CPI-1205 PO BID + fixed dose cobicistat PO BID + abiraterone/prednisone. Based on emerging data, the SSC may elect to add additional patients to cohort 1A and/or to cohort (-)1A, and to determine an MTD for CPI-1205 PO TID. Cohorts of CPI-1205 PO BID may also be explored.

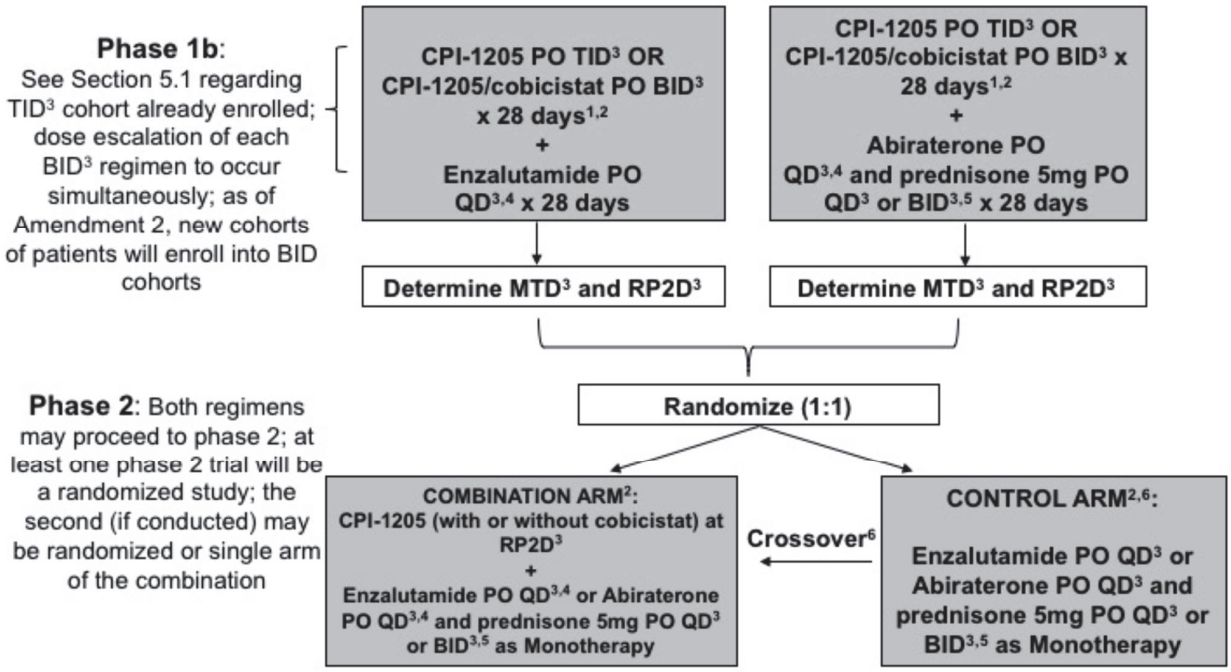
As of Amendment 3, phase 1b expansion cohort(s) have been added in the heavily pretreated population (HPEC). A HPEC may begin enrollment if [redacted] treated with a specific regimen (i.e., CPI-1205 with or without cobicistat, in combination with enzalutamide or abiraterone) at a given dose level during phase 1b dose escalation experience a DLT. The SSC will recommend which regimen(s) and dose to evaluate in the HPEC based on safety, PK, efficacy, etc. A Simon's 2-stage design will be used for any HPEC that opens. After enrollment of [redacted] patients (stage 1), the SSC will recommend whether to continue to stage 2 at the current dose and schedule based on efficacy, or whether a change in CPI-1205 schedule (e.g., from TID without cobicistat to BID with cobicistat) is warranted based on safety, PK, efficacy, etc.

Following determination of the MTD in each of the CPI-1205 BID + cobicistat combinations (and possibly in the CPI-1205 TID combination) and after evaluation of the BID cohorts without cobicistat (if applicable) during phase 1b dose escalation, only one of the CPI-1205 dosing schedules will be selected as the RP2D for each combination (i.e., with enzalutamide and with abiraterone/prednisone). One or both of the combinations may proceed to phase 2 after consideration of PK and PD results, data from the HPEC and safety data. Analysis for Phase 2 cohorts will be described in a separate SAP.

CPI-1205 will be given PO TID or BID (as of the CSP Amendment 2); cobicistat dosing will begin with one dose the evening prior to day 1 of CPI-1205 (i.e., the evening of day 0), and then continue PO BID starting on day 1 of CPI-1205, enzalutamide and abiraterone will be given PO once daily, and prednisone will be given PO BID (or with frequency of prednisone at the discretion of the investigator). Rules regarding administration of each agent with or without food is outlined in Section 6.1 in the CSP. In addition, classes of concomitant drugs that are prohibited or to be used with caution are outlined in Section 6.3 in the CSP.

[redacted]

Figure 1 Study Design Schematic



[1]See Sections 5.4.1 and 5.4.2 for doses to be administered within each cohort
[2]Repeat 4 week cycles until radiographic disease progression, clinical progression or SRE AND planned initiation of other systemic treatment for prostate cancer
[3]BID=twice daily; TID=three times daily; QD=once daily; MTD=maximum tolerated dose; RP2D=recommended phase 2 dose
[4]In combination arms, dose of enzalutamide and/or abiraterone may be increased after Cycle 2 based on PK and only after consultation with the Medical Monitor. **NOTE:** If abiraterone increased it may be given PO BID. See Sections 6.2.3 and 6.2.5.
[5]Frequency of prednisone at the discretion of the investigator
[6]At the time of radiographic or clinical progression or SRE, control arm patients may be eligible to cross over to combination arm if they meet eligibility as outlined in Section 5.5.1.

3.2 Schedule of Assessments

The Schedule of Events is presented in Table 7-1 in the CSP for phase 1b dose escalation and in Table 7-2 in the CSP for the phase 1b HPEC.

The Screening period includes the 28 days before the first day of treatment. Screening assessments should be performed within 28 days prior to the first day of Cycle 1 unless otherwise noted in footnotes of the Schedules of assessments in the CSP.

There is no window for visits during Cycles 1 and 2; however, clinical laboratory parameters (see Section 7.1.4.3) may be drawn within 48 hours prior to day of visit. Starting in Cycle 3, a window of ± 3 days

[redacted]

will be applied to all clinic visits. When applicable, specific windows for assessments (e.g., 6 hours [±1 hr]) are provided in the footnotes of tables with schedules of assessments.

4. STUDY POPULATION

The patients enrolled in this study will be adults (aged ≥ 18 years) with a histologically confirmed diagnosis of metastatic adenocarcinoma of the prostate that has progressed in the setting of medical or surgical castration (i.e., mCRPC). During phase 1b dose escalation, prior treatment for mCRPC must have included at least one line with a second generation androgen inhibitor (prior chemotherapy is also allowed). For the phase 1b HPEC, prior treatment must have included and patient must have progressed on chemotherapy in the mCRPC setting, and patients must have been treated with and progressed on two lines of therapy with a second generation androgen inhibitor, one from each class (i.e., a CYP17 inhibitor [e.g., abiraterone, orteronel] AND an AR inhibitor [e.g., enzalutamide, apalutamide]). The last second generation androgen inhibitor treatment received must not be from the same class as that incorporated in the applicable HPEC; i.e., if the HPEC incorporates enzalutamide, the last second generation androgen inhibitor therapy cannot be enzalutamide, apalutamide, etc. Patients must also have at least one measurable lymph node.

Detailed lists of inclusion and exclusion criteria are shown in Sections 3.2 - 3.5 in the CSP.

5. DETERMINATION OF SAMPLE SIZE

The number of patients in phase 1b dose escalation will depend on safety but could range from approximately [redacted] per combination (including patients from the CPI-1205 TID and CPI-1205 BID with cobicistat cohorts). Approximately 30 evaluable patients will be enrolled in any Simon's 2-stage design for any phase 1b HPEC that opens.

During phase 1b dose escalation, dose escalation will proceed following the rules outlined in Section 5.4.3 in the CSP. It is estimated that a range of approximately [redacted] per combination (including patients from the CPI-1205 TID and CPI-1205 BID with cobicistat cohorts) will be enrolled in order to determine the MTD and RP2D. As of Amendment 3, phase 1b expansion cohort(s) have been added in the heavily pretreated population. A HPEC may begin enrollment if [redacted] patients treated with a specific regimen (i.e., CPI-1205 with or without cobicistat, in combination with enzalutamide or abiraterone) at a given dose level during phase 1b dose escalation experience a DLT.

[redacted]

6. RANDOMIZATION

There will be no randomization in phase 1b (dose escalation or HPEC). The variability in the dose of CPI-1205 with which patients will be treated during phase 1b dose escalation and the small size of this study preclude the use of any meaningful stratification in phase 1b (all cohorts).

7. STATISTICAL ANALYSIS CONVENTIONS

7.1 Analysis Variables

7.1.1 Demographic and Background Variables

The assessment of demographic and baseline variables should be performed in 28 days before the first dose. The following demographic and baseline variables will be descriptively evaluated:

- Age, sex, ethnicity and race
- Height (cm) and weight (kg) at baseline
- Prior medication (cancer therapy, radiation therapy)
- CTC unfavorable (>=5) count
- ECOG score

7.1.2 Medical History

During the Screening period, the patient will have a complete medical history taken including:

- All previous lines of therapy for the treatment of prostate cancer in the order they were administered.
- Details on prior radiation therapy
- Type of progression on entry
- Document any previous [redacted] results [redacted]

All medical history will be coded using the version 22.1 of the Medical Dictionary for Regulatory Activities (MedDRA).

[redacted]

7.1.3 Study Treatment

CPI-1205 will be supplied as [redacted] tablets to be administered orally. During phase 1b dose escalation, CPI-1205 will be given PO TID without cobicistat, or, as of Amendment 2, CPI-1205 will be given PO BID combined with fixed dose cobicistat PO BID. CPI-1205 PO BID without cobicistat may also be explored. CPI-1205 (with or without cobicistat) will be combined with either enzalutamide or abiraterone/prednisone. In the phase 1b HPEC(s), CPI-1205 may be given with or without cobicistat in combination with enzalutamide or abiraterone with the specific regimen(s) and dose chosen based on data from the phase 1b dose escalating cohorts.

7.1.4 Safety Variables

The following safety assessments will be performed:

- DLTs
- AEs
- Serious AEs (SAEs)
- Clinical laboratory evaluations
- Vital signs
- ECG
- Echocardiogram
- Physical examination
- ECOG Performance Status
- Concomitant medications

7.1.4.1 Dose-limiting toxicity

Dose-limiting toxicity is defined as an adverse event or abnormal laboratory value that meets any of the criteria listed below in Table 1 and where a relationship to the investigational agent (CPI-1205 alone or when given with cobicistat) cannot be ruled out. Toxicities will be graded according to the NCI CTCAE v4.03. See Section 6.3.5 in the CSP for management of and supportive care for any treatment related toxicities (including DLT). For the purpose of making dose escalation decisions all DLTs occurring during the first cycle of treatment with CPI-1205 (with or without cobicistat) must be included.

[redacted]

During phase 1b dose escalation, patients are evaluable for DLT if, in Cycle 1, the patient receives ≥ 75% of the planned doses of CPI-1205 (and, if applicable, cobicistat) and either abiraterone or enzalutamide (depending on the combination), is observed for ≥ 28 days following the first dose, and is considered by the SSC to have sufficient safety data available to conclude that a DLT did not occur. Patients who do not meet these minimum treatment and safety evaluation requirements and who do not experience DLT will be replaced with new patients if the minimum evaluable patients per dose level has not been satisfied. If a patient misses >25% of doses in Cycle 1 for reasons not related to toxicity, the patient can be replaced. If a patient misses >25% of doses in Cycle 1 for reasons related to toxicity, this will be considered a DLT, and the patient cannot be replaced. Patients will be analyzed by the dose level to which they were originally assigned, including those who receive subsequent treatment at a lower dose level.

Table 1 Definitions of Dose-Limiting Toxicities

Toxicity	Any of the following:
Hematology	Grade 4 neutropenia (ANC< 0.5 x 109/L) lasting >7 days
	Febrile neutropenia of any (ANC < 1.0 x 109/Land single oral temperature >38.3°C or ≥ 38°C for >1 hour)
	Grade 4 thrombocytopenia (platelets < 25 x 109/L) of any duration
	Grade 3 thrombocytopenia (platelets between 25-49 x 109/L) with bleeding or any requirement for platelet transfusion
Hepatic	≥ Grade 3 total bilirubin (except Gilbert's disease)
	≥ Grade 3 ALT/AST lasting >7 days in patients who enroll with ≤ Grade 1 ALT/AST
	≥ Grade 3 ALT/AST lasting >7 days in patients who enroll with Grade 2 ALT/AST
	ALT/AST > 3 x ULN (i.e., ≥ Grade 2) with bilirubin > 2 x ULN without another explanation (e.g., cholestasis) in patients who enroll with ≤ Grade 1 ALT/AST

[redacted]

Toxicity	Any of the following:
	Doubling of ALT/AST with bilirubin > 2 x ULN without another explanation (e.g., cholestasis) in patients who enroll with Grade 2 ALT/AST
Metabolic	≥ Grade 3 electrolyte disturbance of >72 hours (supplementation allowed)
Gastrointestinal	≥ Grade 3 vomiting or Grade 3 nausea of >72 hours duration in spite of optimal anti-emetic supportive care
	≥ Grade 3 diarrhea of >72 hours duration in spite of optimal antidiarrheal supportive care
Other	Grade 3 fatigue lasting >72 hours
	Other CPI-1205-related non-hematologic toxicities ≥ Grade 2 that, in the opinion of the investigator, require dose reduction or discontinuation of treatment with CPI-1205
	<75% of total doses within Cycle 1 (i.e., < 63 doses) are taken for reasons related to CPI-1205 toxicity
	Other toxicities may be considered a DLT as determined by the Investigator in conjunction with the SSC

7.1.4.2 Adverse Events

AEs, TEAEs, SAEs and SUSAR:

Adverse events will be recorded from the time of informed consent until 30 days after administration of the last dose of study drug. All AEs and SAEs that occur during the reporting period will continue to be followed until the event resolves, the investigator assesses the event as stable, the event is determined to be irreversible, or the patient is lost to follow-up.

A treatment-emergent AE (TEAE) is defined as any AE that occurs after administration of the first dose of study treatment and through 30 days after the last dose of study medication, any event that is considered drug related regardless of the start date of the event, or any event that is present at baseline but worsens in severity after baseline or is subsequently considered drug-related by the investigator.

[redacted]

An SAE is any AE occurring at any dose and regardless of causality that:

- Results in **death**.
- Is **life-threatening**. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form).
- Requires in patient **hospitalization or prolongation of existing hospitalization**.
- Results in **persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a **congenital anomaly/birth defect**
- Is an **important medical event**. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in the definitions for SAEs.

A SUSAR is an event that meets the criteria for an SAE, that is at least possibly related to study drug (study treatment administration is one of several biologically plausible causes of the AE) and is unexpected (if the specificity or severity of it is not consistent with the applicable product information).

AE Grade and Relationship

For AEs and SAEs, intensity and the relationship of the event to study drug administration will be assessed and recorded. Intensity of each AE, including any laboratory abnormality, will be determined by using the NCI CTCAE, Version 4.03. In those cases where the NCI CTCAE criteria do not apply, intensity will be defined according to the following criteria:

[redacted]

Table 2 Severity Assessment Terminology for Reporting Adverse Events (CTCAE v 4.03)

Event Intensity	Description	Grade
Mild	Awareness of sign or symptom but easily tolerated	1
Moderate	Discomfort enough to cause interference with normal daily activities	2
Severe	Inability to perform normal daily activities	3
Life-threatening or disabling*	Immediate risk of death from the reaction as it occurred	4
Death	Leading to death	5

The causal relationship of AEs/SAEs to the investigational product (IP) will be determined by the Investigator according to best medical judgement as follow: related (possibly, probably, or definite) or not-related (not-related or unlikely).

7.1.4.3 Clinical Laboratory Evaluations

If hematology, clinical chemistry, lipids, serum lipids and creatine phosphokinase (CPK) labs were performed within 3 days of the first day Cycle 1, they do not need to be repeated on the first day Cycle 1. During any subsequent visit in Cycle 1 and for any Cycle 2 visit, blood for these evaluations may be drawn within 48 hours prior to day of visit.

COAGULATION PARAMETERS

Prothrombin time (PT)/International normalized ratio (INR) and activated partial thromboplastin time (aPTT) will be determined during Screening for all patients. Subsequent measurement of the PT/INR and aPTT will be performed on the first day of Cycle 2 and thereafter only as clinically indicated.

HEMATOLOGY

A complete blood count (CBC) with differential will be obtained during Screening, on D1, D8, D15 and D22 of Cycle 1, on D1 and D15 of Cycles 2 and 3, on D1 of Cycles 4+, at the End of Treatment Visit, and at the Safety Follow-up Visit during phase 1b dose escalation. During phase 1b HPEC CBC, a

[redacted]

complete blood count (CBC) with differential will be collected during Screening, on D1 and D15 of Cycle 1, on D1 of Cycles 2+, at the End of Treatment Visit, and at the Safety Follow-up Visit.

The CBC with differential consists of the following: hemoglobin, total white blood cell (WBC) count, differential WBC count, and platelet count.

CLINICAL CHEMISTRY

A clinical chemistry panel will be obtained during Screening, on D1, D8,D15 and D22 of Cycle 1, on D1 and D15 of Cycles 2 and 3, on D1 of Cycles 4+, at the End of Treatment Visit, and at the Safety Follow-up Visit during phase 1b dose escalation. During phase 1b HPEC, collections will occur during Screening, on D1 and D15 of Cycle 1, on D1of Cycles 2+, at the End of Treatment Visit, and at the Safety Follow-up Visit.

The clinical chemistry panel consists of the following: sodium, potassium, carbon dioxide, chloride, blood urea nitrogen (BUN), serum creatinine, total bilirubin, alkaline phosphatase, albumin, AST, ALT, lactate dehydrogenase (LDH), uric acid, calcium, magnesium, phosphate, serum glucose.

SERUM LIPIDS AND CREATINE PHOSPHOKINASE (CPK)

Serum lipids and CPK will be obtained during Screening, on D1 of each cycle, at the End of Treatment Visit and at the Safety Follow-up Visit for all patients.

Serum lipids will include total cholesterol, cholesterol low density lipoprotein (LDL), cholesterol high density lipoprotein (HDL) and triglycerides.

THYROID FUNCTION TESTS

Thyroid function tests include thyroid stimulating hormone (TSH) and T4 to be obtained at Screening, on C3D1, and every other subsequent cycle (i.e., C5D1, C7D1, etc.) during phase 1b (all cohorts).

OTHER ENDOCRINOLOGY

Other endocrinology labs will be obtained at Screening and on C2D1 and C4D1 for all patients.

Endocrinology labs include: sex hormone-binding globulin (SHBG), androstenedione, ehydroepiandrosterone (DHEA), DHEA sulfate, dihydrotestosterone (DHT), estradiol, folliclestimulating hormone (FSH), luteinizing hormone (LH), prolactin and total testosterone.

[redacted]

7.1.4.4 Vital Signs

Vital signs (BP, heart rate, and oral temperature) will be taken during Screening and on D1 of each cycle of treatment.

On C1D1, vital signs will be taken prior to dosing and will be repeated 3 h (± 30 min) after dosing for any cohort/study arm that includes CPI-1205; for any control arm that includes only abiraterone/prednisone or enzalutamide, vital signs will be obtained pre-dose only.

7.1.4.5 Electrocardiograms

A 12-lead ECG will be obtained as part of the Screening evaluation. On C1D1, an ECG will be performed prior to dosing and will be repeated 3 h (±30 min) after dosing for any cohort/study arm that includes CPI-1205; for any control arm that includes only abiraterone/prednisone or enzalutamide, ECGs will be obtained pre-dose only. Subsequent ECGs will only be performed during treatment if clinically indicated. ECGs will also be performed at the Safety Follow-Up Visit.

7.1.4.6 Physical Examination

An assessment of signs and symptoms and a complete physical examination will be conducted during Screening and at the Safety Follow-up Visit. The Screening physical examination will record the patient's height and weight, the Safety Follow-up Visit physical examination will record weight only.

An assessment of signs and symptoms and an abbreviated physical examination (directed toward the identification of signs of treatment-related toxicity and disease progression or regression) including the patient's weight will be performed D1 of each cycle and at the End of Treatment Visit.

A physical exam and signs and symptoms assessment do not need to be repeated on C1D1 if the Screening evaluations are conducted ≤ 3 days prior to C1D1. In this case, the Screening evaluations will be considered baseline.

7.1.4.7 ECOG Performance Status

ECOG performance status (see Grade 0 to 5 in Appendix 1 in the CSP) will be assessed during Screening, on the first day of each cycle, at the End of Treatment Visit, and at the Safety Follow-up Visit.

ECOG performance status must be documented by 2 independent evaluators.

[redacted]

7.1.4.8 Concomitant Medication

All concomitant medications and supportive therapies will be recorded from Screening through the Safety Follow-up Visit. Concomitant medications and therapies that are prohibited or to be used with caution are described in Section 6.3 in the CSP.

7.1.5 Efficacy Variables

Efficacy results will be reported separately for phase 1b dose escalation and phase 1b HPEC.

7.1.5.1 PSA Evaluation

For the purpose of PSA evaluation, baseline PSA will be the PSA measured pre-dose on C1D1 (or the PSA measured during Screening if PSA was collected ≤ 7 days prior to C1D1).

7.1.5.2 PSA Progression (for Study Entry)

Phase 1b Dose Escalation:

If progressive disease at study entry is based on PSA, PSA increase must be ≥25% and an absolute increase of ≥2 ng/mL in < 6 months from end of last therapy prior to enrollment;

Phase 1b HPEC:

If progressive disease at study entry is based on PSA, PSA must be ≥ 2 ng/mL (or PSA ≥ 1 ng/mL if PSA progression is the only manifestation of progressive disease) and rising PSA must be documented by at least 2 consecutive measurements a minimum of 1-week apart.

7.1.5.3 PSA 50% Response

To be evaluable for PSA 50% response, baseline PSA must be ≥ 2 ng/mL (unless PSA progression is the only manifestation of progressive disease, in which case baseline PSA must be ≥ 1 ng/mL).

PSA response is defined according to the Prostate-Specific Antigen Working Group criteria [1].

PSA 50% response (PSA50) is defined as a ≥50% reduction in PSA from baseline. The reduction must be confirmed by a second PSA value 4 or more weeks later. PSA50 rate is the proportion of patients with a PSA 50% response.

[redacted]

7.1.5.4 PSA Progression (on Treatment)

PSA progression during study treatment is defined according to PCWG3. The PCWG3 criteria [2] are based on modifications of the RECIST 1.1 criteria [3]. See Section 10.3 in the CSP for details on RECIST 1.1.

Early rises (before 12 weeks) in PSA should be ignored.

For patients with PSA decline from baseline, the PSA progression date is defined as the date that a 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir is documented, which is confirmed by a second value obtained 3 or more weeks later.

For patients without a PSA decline from baseline, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the baseline is documented beyond 12 weeks.

Time to PSA progression (TTPSAP) is defined as the time from D1 of treatment to the date of PSA progression, or death, whichever occurs first.

7.1.5.5 PCWG3 Criteria (Radiographic Evaluation)

Objective Response Rate with measurable soft tissue disease (ORR) is defined as the proportion of patients with a complete response (CR) or partial response (PR) per PCWG3 and as determined by Investigator or by CRR.

Objective Response Rate (excluding parenchymal lesions) (ORR sensitivity) is defined as the proportion of patients with a CR or PR per PCWG3 in soft tissue excluding the parenchyma (i.e., liver and lung). This rate could be defined only for patients with measurable disease in non-parenchymal soft tissue.

Radiographic progression free survival (rPFS) is defined per PCWG3 as time from D1 of treatment to the date when the first site of disease is found to progress (using a manifestation-specific definition of progression), or death, whichever occurs first. The proportion of patients who remain radiographic progression free at 3 months will also be assessed. Table 4 describes the censoring rules for rPFS.

Table 3 Radiographic Progression Free Survival

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	NA	Remove from rPFS analysis

[redacted]

Situation	Date of Progression or Censoring	Outcome
Not Evaluable (NE) baseline tumor assessment (but the actual assessment was done) and patient did not die	If post-baseline tumor assessment is evaluable, the date of the post-baseline tumor assessment which is evaluable Or If no evaluable tumor at any post-baseline (or no post-baseline tumor assessment), the date of censoring is the earliest of (1) date of last study visit; or (2) date of study discontinuation.	Progressed if there is any evaluable tumor at post-baseline Or Censored if NE at all post-baselines
No on study tumor assessments, but with evaluable baseline tumor assessment and patient did not die	The earliest of (1) the date of last study visit; or (2) the date of study discontinuation.	Censored
Subsequent anti-cancer therapy started without death or radiographical progression per PCWG3 reported prior or on the same day	The date of initiation of the subsequent anti-cancer therapy	Censored
Documented radiographical progression per PCWG3 and no new anti-cancer started before	Date of the first documented radiographical progression per PCWG3	Progressed
No radiographical progression and no death, and no new anti-cancer therapy started	The earliest of (1) the date of last study visit; or (2) the date of study discontinuation.	Censored
Death without radiographical progression per PCWG3 and no new anti-cancer started before	Date of death	Progressed

Radiographic progression free survival, Second Definition (rPFS2) is defined similarly to rPFS with several changes in censoring rules, shown in Table 5.

Table 4 Radiographic Progression Free Survival, Second Definition

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	NA	Remove from rPFS analysis

[redacted]

Situation	Date of Progression or Censoring	Outcome
Not Evaluable (NE) baseline tumor assessment (but the actual assessment was done) and patient did not die	If post-baseline tumor assessment is evaluable, the date of the post-baseline tumor assessment which is evaluable Or If no evaluable tumor at any post-baseline (or no post-baseline tumor assessment), the date of censoring is date of First Dose	Censored
No on study tumor assessments, but with evaluable baseline tumor assessment and patient did not die	Date of First Dose	Censored
Subsequent anti-cancer therapy started without death or radiographical progression per PCWG3 reported prior or on the same day	Date of last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy	Censored
Documented radiographical progression per PCWG3 and no new anti-cancer started before	Date of the first documented radiographical progression per PCWG3	Progressed
No radiographical progression and no death, and no new anti-cancer therapy started	Date of last evaluable tumor assessment	Censored
Death without radiographical progression per PCWG3 and no new anti-cancer started before	Date of death	Progressed

Duration of Response (DOR) is defined as time from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that radiographic progression is documented per PCWG3. For patients who had response and did not have documented radio progression during the study duration or death or started subsequent anti-cancer therapy without a prior reported radio progression, the end of the response will be the date of censoring (rules follow Table 3).

Sensetivity DOR (excluding parenchymal lesions) is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that radiographic progression is documented per PCWG3 in soft tissue excluding the parenchyma. For patients who had response and did

not have documented radio progression during the study duration or death or started subsequent anti-cancer therapy without a prior reported radio progression, the end of the response will be the date of censoring (rules follow Table 3).

Overall Survival (OS) is defined as the time from D1 of treatment to the date of death at any time during the trial. Table 6 below describes how data will be handled for the analysis of OS.

Table 5 Overall Survival

Situation	Date of OS Event or Censoring	Outcome
Death	Date of Death	Event
Alive at follow-up	Study completion date, including follow-up	Censored

7.1.5.6 Enumeration of CTCs

Blood will be collected for the enumeration of CTCs following recommendations from PCWG3.

Favorable or unfavorable status will be determined.

- Unfavorable is defined as five or more cells per 7.5 mL of blood.
- Favorable is defined as four or fewer cells per 7.5 mL of blood.

CTC 30% response (CTCRR) is defined as ≥ 30% reduction in CTCs from baseline in patients with unfavorable CTC status. Any CTC 30% response must be confirmed by an additional CTC enumeration at least 4 weeks later.

CTC conversion (i.e., conversion from unfavorable to favorable) (CTCCR) is another way to measure response via CTCs. Any conversion from unfavorable to favorable CTC status must be confirmed by an additional CTC enumeration at least 4 weeks later.

7.1.5.7 Unequivocal Clinical Progression

Unequivocal clinical progression (UCP) includes development of any of the following clinically

significant disease-specific events:

- Spinal cord or nerve root compression
- Pathologic fracture

- Metastatic disease in an anatomy for which no baseline scan (e.g., spine, base of skull) is available for comparison to allow documentation of interval change on serial imaging studies.
- Progressive disease in an anatomy for which there is a baseline imaging assessment, but serial imaging has not been performed (e.g., prostate bed).
- A clinical indication for radiation therapy.
- At least 2 of the following clinical signs/symptoms in comparison to baseline:
  - An increase in ECOG performance status of > 1 grade.
  - ≥ 10% weight loss, not attributable to intentional weight loss.
  - New urinary outflow obstruction attributable to cancer.
  - Progressive anemia, defined as either:
    - a decrease in hemoglobin of ≥ 2 g/dL and to a level below the lower limit of normal in the central lab reference range, **or**
    - a requirement for therapy with a hematopoietic growth factor (e.g., Procrit®) or transfusion with packed red blood cells for anemia.

Time to unequivocal clinical progression (TTUCP) is defined as the time from the first day of treatment to the date of unequivocal clinical progression, or the earliest of the following for those who did not have the documentation for unequivocal clinical progression (1) the date of death; (2) the date of last study visit; or (3) the date of study discontinuation.

7.1.5.8 Skeletal Events (SREs and SSEs)

SREs are defined as: asymptomatic nonclinical fractures as evaluated via serial imaging, clinical pathologic fractures, spinal cord compression, and surgery or radiation therapy to bone.

Time to first SRE (TTSRE) is defined as the time from D1 of treatment to the date of first SRE, or the earliest of the following for those who did not have the SRE (1) the date of death; (2) the date of last study visit; or (3) the date of study discontinuation.

SSEs are defined as: symptomatic fracture, radiation or surgery to bone, or spinal cord compression.

[redacted]

Time to first SSE (TTSSE) is defined as the time from day one of treatment to the date of first SSE, or the earliest of the following for those who did not have the SSE (1) the date of death; (2) the date of last study visit; or (3) the date of study discontinuation.

7.1.5.9 Pain/Analgesic Usage

[redacted]

Pain Progression:
Pain progression will be evaluated in all patients.

For patients with no baseline pain, pain progression (PPR) is defined as the development of pain. For patients with baseline pain, progression is defined as a ≥2-point increase in pain on the NRS on 2 consecutive evaluations 4 weeks apart, without any decrease in analgesic usage score.

Time to pain progression (TTPPR) is defined as the time from D1 of treatment to the date of pain progression, or the earliest of the following for those who did not have the pain progression (1) the date of death; (2) the date of last study visit; or (3) the date of study discontinuation.

Opioid Usage:
Opioid usage is defined as a 2 or 3 on the WHO analgesic ladder.

For patients who enter the trial not on opioid analgesics time to opioid analgesics (TTOA) is defined as the time from D1 of treatment to the date of first opioid usage, or the earliest of the following for those who did not have the opioid usage (1) the date of death; (2) the date of last study visit; or (3) the date of study discontinuation.

[redacted]

7.1.5.10 Other variables

Time to initiation of new systemic treatment for prostate cancer (TTNST) is defined as the time from D1 of treatment to the date any new systemic treatment for prostate cancer is initiated, or the earliest of the following for those who did not have the new systemic treatment for prostate cancer: (1) the date of death; (2) the date of last study visit; or (3) the date of study discontinuation.

Progression Free Survival (PFS) is defined as time from D1 of treatment to the date of the first documented progression or death whichever occurs first. Radiographical progression, PSA progression and unequivocal clinical progression are considered as progression above. The censoring scheme of PFS will be the same as the primary censoring scheme for rPFS (rules follow Table 3).

[redacted]

7.2 Analysis Populations

Full Analysis set (FAS) is defined as all patients who received at least one dose of the study drug.

[redacted]

FAS Analysis set will be used for time-to-event analyses for the phase 1.

Safety analysis set is defined as all patients who receive any amount of study drug.

DLT analysis set is defined for phase 1b to include any patient who receives ≥ 75% of the planned doses of CPI-1205 (and, if applicable, cobicistat) and either abiraterone or enzalutamide (depending on the combination), is observed for ≥ 28 days following the first dose and is considered by the SSC to have sufficient safety data available to conclude that a DLT did not occur. If a patient misses >25% of doses in Cycle 1 for reasons related to toxicity, he or she will be included in the DLT analysis set.

Efficacy analysis set (EAS): A patient from a phase 1b dose escalation and HPEC is evaluable for the primary endpoint of objective response if:

- In Cycle 1, the patient receives ≥ 75% of the planned doses of CPI-1205 (and, if applicable, cobicistat) and either abiraterone or enzalutamide (depending on the regimen);
- Has at least one baseline and post-baseline corresponding efficacy assessment.

The first requirement above is not necessary for a non-primary analysis.

7.3 Statistical Analysis Methods

The statistical methods employed in this protocol will be primarily descriptive and graphical in nature. Continuous variables will be summarized using descriptive statistics [n, mean, standard deviation, median, minimum, and maximum]. Categorical variables will be summarized showing the number and percentage (n, %) of patients within each classification. Safety and efficacy will be assessed in the appropriate treated populations. These data will be descriptively summarized by each dose level in Phase 1b and overall as appropriate.

Time-to-event endpoints (e.g., time to PSA progression, time to first SRE/SSE) will be estimated using the Kaplan-Meier (KM) method. Descriptive statistics for analyses of such endpoints will include number of subjects with events, number of subjects censored, estimated 25% quartile, estimated median, estimated 75% quartile, and their corresponding 95% CIs. Kaplan-Meier plots will be plotted for each time to event variables.

[redacted]

7.3.1 Listings and Descriptive Statistics

Data for all enrolled subjects who receive at least 1 dose of study drug will be presented in data listings. A subject who is enrolled but does not receive study drug will be included in those listings for which there is data but will be excluded from all data summaries. Data summaries will only include those subjects that receive study drug.

Unless otherwise stated, the last non-missing observed measurement prior to the first dose of study drug(s) will be considered the baseline measurement.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings:

- Present original observed values in listings. For any derived values from the observed values add one more decimal digit. For any sub-derived values (derived from derived values) add two more decimal digits. Do not use more than four digits after the point if number of significant digits of observed value is greater than three.
- Estimates and confidence intervals will be presented to two decimal places.
- P-values will be presented to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001," if a p-value is greater than 0.999 it will be reported as ">0.9999."

Listings should be presented by cohort, dosing group unless otherwise stated.

7.3.2 Statistical Significance Level

No formal statistical hypothesis is planned. Two-sided 95% confidence intervals may be used to describe the precision of the point estimates where appropriate.

7.3.3 Software

The tables, listings, figures and any non-descriptive statistical analysis will be produced using SASSoftware (Version 9.3 or higher). The REPORT procedure (SAS PROC Report) will be used to produce all tables and listings; SAS/GRAPH will be used to produce all figures. All figures will be displayed in black and white. The PROC LIFETEST will be used to produce all curves of Kaplan and Meier for time to event variables.

[redacted]

All tables, listings, and graphs will be presented in landscape orientation using Courier New 8pt font and will be incorporated into a MS Word document as a (RTF) rich text file (margins: top 1.5'', left, right, and bottom 1'').

7.3.4 Missing Data

There will be no imputation of missing data.

7.3.5 Interim Analysis

A Simon's 2-stage design will be used to evaluate ORR in any HPEC that opens. After enrollment of [redacted] patients (stage 1), the SSC will recommend whether to continue to stage 2 at the current dose and schedule based on efficacy (i.e., if at least 1 response is seen), or whether a change in CPI-1205 schedule is warranted based on safety, PK, efficacy, etc. If the schedule is changed, a new Simon's 2-stage design will be followed with [redacted] patients enrolled in stage 1. If there are no responses within these [redacted] patients, Constellation may temporarily hold the study enrollment until the totality of the cohort's data is evaluated and the decision can be made about further study conduct.

No other formal interim analysis is planned. Data will be evaluated on a continuous basis.

7.3.6 Protocol Deviations

Deviations from the protocol will be assessed as 'minor' or 'major'. CSR reportable ("major") protocol deviations (PDs) are defined in accordance with ICH E3 as important PDs related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment resulting in the potential to jeopardize the safety or rights of the trial subjects or the scientific value of the trial.

All major PDs will be classified into the following categories, but not all deviations listed below will necessarily be declared a major PD:

- Disallowed Medications
- Inclusion/Exclusion criteria
- Informed Consent
- Investigational Product (IP) Admin/Study Treat
- Procedures/Tests

[redacted]

- Visit Schedule
- Withdrawal Criteria

Number and percentage of subjects with a major protocol deviation will be summarized by the category of deviation and dose group. The listing of protocol deviations by dose group and subject will be provided.

All protocol deviations will be discussed between [redacted] and also the Sponsor during the clean file meeting before database lock in order to determine whether these may warrant exclusion of a subject from the statistical analyses.

7.3.7 Demographic Data

Demographic data will be summarized by dose group based on the Safety Analysis Set. Descriptive statistics will be presented for continuous variables including age, height, weight, and body mass index (BMI) at baseline. The frequency and percentage of patients will be tabulated for categorical variables including sex, race, ethnicity, age group (18-44 years, 45-64 years, ≥65 years), disease category, prior therapy, patient cancer therapy status, ECOG status and CTC at baseline.

Age presented in the table is the age per EDC at the Day of Informed Consent. Age will be calculated as the number of complete years between a patient's birth year and the date of informed consent.

A by-patient listing of demographic information will be provided.

7.3.8 Cancer History and Previous Treatment

The frequency and percentage of disease diagnosis, history and status will be summarized by dose group in the Safety Analysis Set. Type of progression on entry, previous therapy for myelofibrosis, previous radiotherapy, previous systemic anti-cancer therapy [redacted] will be listed by dose group and subject.

7.3.9 Medical and Surgical History

By-patient listings of significant medical history data prior to dosing will be provided based on the Safety Analysis Set. Only those body systems where a condition or abnormality has been reported will be listed.

[redacted]

The summary will be sorted by decreasing frequency of SOC then decreasing frequency of preferred term within an SOC coded using MedDRA, version 22.1 or higher version.

7.3.10 Concomitant Medication

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary drug (WHODDE, Version 201709), and will be presented by Anatomical-Therapeutic-Chemical (ATC) therapeutic classification and PT.

All prescription medications, over-the-counter medications, or alternative therapies taken within 28 days prior to the first dose of study drug through 30 days after the last dose of study drug will be recorded. The frequency and percentage of prior medications and concomitant medications will be tabulated by dose group and by ATC/preferred term based on the Safety Analysis Set.

By-patient listings of prior and concomitant medications will be provided.

7.3.11 Dose Administration

A summary of CPI-1205 exposure will be provided by dose group. Specifically, the number of doses administered will be tabulated, and total treatment duration (days), total cumulative dose (mg) and relative dose intensity for the study will be summarized. The descriptive statistics (n, mean, SD, median, min, and max) of treatment cycles and completed cycles patients will also be summarized.

The number and percent of patients with 100%, ≥ 85%, ≥ 75% and <75% of dose compliance will be summarized. A tabulation of treatment delays, missed doses, interrupted doses, and dose reductions will be provided. The descriptive statistics (n, mean, SD, median, min, and max) of dose compliance will also be summarized.

A by-patient listing of study drug administration will be provided.

Study treatment attributes used in analysis include the following:

- Dose compliance in a cycle = 100 * actual cumulative dose/planned total dose
- Dose compliance overall = = 100 * overall total cumulative dose/overall planned total dose
- Treatment duration (in days) = last dose date - first dose date +1.
- Treatment duration (weeks) = (last dose date - first dose date +1) / 7.

[redacted]

- Planned dose intensity is determined separately for different dose schedules:
  - Planned dose intensity per day (mg/dose) = cumulative planned dose (mg) / planned cumulative treatment duration (days)
- Actual dose intensity is determined separately for different dose schedules:
  - Actual dose intensity per day (mg/dose) = cumulative actual dose (mg) / actual cumulative treatment duration (days)
- Relative dose intensity (%) = 100 * actual dose intensity/planned dose intensity

7.3.12 Pharmacokinetics and Pharmacodynamics Analysis

PK and PD sampling data will be listed. PK and PD analyses and summaries are not included in this SAP.

7.3.13 Efficacy Analysis

The primary and secondary efficacy analyses will be performed based on evaluable patients within each dose group using the Efficacy Analysis Set.

PSA 50% response rate, ORR, ORR (excluding parenchymal lesions), CTC 30% response rate, and CTC conversation rate will be tabulated along with percentages. 95% exact confidence intervals (CIs) will be constructed using the Clopper-Pearson exact method for binomial proportions.

The proportion of subjects who remain radiographic progression free at 3 months with its corresponding 2-sided 95% Clopper-Pearson CIs will be reported using the Clopper Pearson exact method for binomial proportions

Proportion of subjects with pain palliation with its corresponding 2-sided 95% Clopper-Pearson CIs will be reported using the Clopper Pearson exact method for binomial proportions.

Time-to-event endpoints of TTPSAP, rRFS, rPFS2, PFS, OS, DOR, TTSRE, TTSSE, TTUCP, TTNST, TTPPR, and TTOAwill be estimated using Kaplan-Meier methods and summarized. Descriptive statistics for analyses of such endpoints will include the number and percentage of subjects with events, the number and percentage of subjects censored, median, 25^{th}, and 75^{th} percentile estimates and their corresponding 95% CIs, and minimum and maximum duration in months. Kaplan-Meier plots will be plotted for time-to-event endpoints.

[redacted]

All above analyses will be produced per cohorts separately and by each dose schedule as shown in Table 6.

Table 6 Efficacy Analyses

Analysis Variable	Phase 1b (Escalation)	HPEC
ORR	Yes	Yes
ORR (excluding parenchymal lesions)	Yes	Yes
DOR	Yes	Yes
DOR (excluding parenchymal lesions)	Yes	Yes
PSA50, TTPSAP	Yes	Yes
OS		Yes
rPFS, rPFS2, PFS	Yes	Yes
TTSSE, TTSRE	Yes	Yes
TTUCP	Yes	Yes
TTNST	Yes	Yes
[redacted]		
TTPPR	Yes	Yes
TTOA	Yes	Yes
CTCCR	Yes	Yes
CTCRR	Yes	Yes

[redacted]

7.3.14 Safety Analysis

7.3.14.1 Dose Limiting Toxicities

A by-patient listing and a separate TEAE summary table (by toxicity type) for patients with DLTs in their first treatment cycle will be provided for the DLT Analysis Set by dose group for each phase 1b separately.

7.3.14.2 Adverse Events

The verbatim AE terms will be coded using the latest available version of MedDRA (Version 22.1 or higher) and will be classified by SOC and PT.

Unless specified otherwise, adverse event summary counts of AEs will be the number of subjects reporting adverse events and not the number of events reported. If the same AE (SOC or PT) is reported multiple times for the same subject, it will only appear once for that specified treatment and category in the summary tables.

For subjects with multiple adverse events of the same PT and of different severities, the AE with the highest assessment of severity will be used in the summaries presented by severity.

For purposes of the summary tables, AEs will be classified as either being related to study drug or not related. For subjects with multiple adverse events of the same PT and of different relationship, the AE with the strongest assessment of relationship will be used in the summaries presented by relationship.

The following AE Tables and Listings will be provided:

- Listing by Dose Group/Arm and Patient
- Overall Summary of TEAEs. This table will summarize the number and percentage of patients with the following:
  - Any TEAEs
  - Drug-Related TEAEs
  - DLTs
  - Serious TEAEs
  - Drug-related SAEs

- TEAEs of grade 3 or above
- Drug-Related TEAEs of grade 3 or above
- Most Frequently Reported (≥10%) TEAEs
- TEAEs with outcome of Deaths
- TEAEs Leading to Discontinuation of Study Drug

7.3.14.3 Clinical Safety Laboratory Tests

Abnormal laboratory values will be graded by the CTCAE v 4.03 for gradable tests. Descriptive statistics (n, mean, standard deviation, median and range) of the parameters in Hematology, Chemistry, Coagulation, Thyroid function and Endocrinology and the changes from baseline will be presented by dose group.

In the shift table for the parameters in Hematology, Chemistry and Coagulation based on being lower than a lower normal limit (worst low), a value above the upper normal limit will be considered as grade 0. The shift table for high worst is defined similar.

Mean laboratory values over time will be plotted for key laboratory parameters.

7.3.14.4 Vital Signs

Vital signs will be listed by cohort, dose group, subject and visit. Descriptive statistics for the actual values and the changes from baseline of vital signs over time will be tabulated by dose group and by visit.

7.3.14.5 Twelve-Lead Electrocardiogram

ECG data will be listed by cohort, dose group, subject and visit. The average value of multiple measurements at a visit will be used in the summary tables as well as in calculation of change from baseline.

Normal, abnormal, or abnormal clinically significant ECG will be summarized by dose group and visit.

The number and percentage of subjects with maximum post-dose QTcF values of <=450, >450 ms and <=480, >480 ms and <=500, and >500 ms, and maximal change from baseline values of <=30, >30 <=60ms, and >60 ms will be summarized by dose group and visit.

[redacted]

7.3.14.6 Physical Examination

The results of the physical examination will be listed only by cohort, dosing group, subject and visit.

Number and percentage of patients with abnormal results of physical examination will be summarized by dose, visit and body system.

7.3.14.7 Echocardiogram

Echocardiogram results will be listed by cohort and dosing group. They will not be summarized.

7.3.14.8 ECOG

ECOG performance will be summarized by dose group, visit and performance status. ECOG performance will be listed by dose group, subject and visit.

Change in ECOG from baseline will be summarized by dose group, visit and performance status.

[redacted]

[redacted]

8. REFERENCES

[1] G. e. a. Bubley, "Eligibility and response guidelines for phase II clinical Prostate-Specific Antigen Working Group," *Clin Oncol,* vol. 17, no. 11, pp. 3461-7, 1999.

[2] H. e. a. Scher, "Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3," *J Clin Oncol,* vol. 34, no. 12, pp. 1402-18, 2016.

[3] E. e. a. Eisenhauer, "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)," *Eur J Cancer,* vol. 45, no. 2, pp. 228-47, 2009.

[4] "Protocol: A Phase 1b/2 Study of CPI-1205, a Small Molecule Inhibitor of EZH2, Combined with Enzalutamide or Abiraterone/Prednisone in Patients with Metastatic Castration Resistant Prostate. Version 4.0". 26 July 2018.

[redacted]

STATISTICAL ANALYSIS PLAN

Protocol No: 1205-201

ProSTAR: A Phase 1b/2 Study of CPI-1205, a Small Molecule Inhibitor of EZH2, Combined with Enzalutamide or Abiraterone/Prednisone in Patients with Metastatic Castration Resistant Prostate Cancer

Analysis Plan for Phase 2 Cohorts

Version: Final 2.0

Date: 13/APR/2021

[redacted]

REVISION HISTORY

Version	Version Date	Author	Summary of Changes Made
Draft 1.0	29-Nov-2018	[redacted]	New Document
Draft 2.0	21-Jan-2019	[redacted]	Updated per comments
Draft 3.0	29-May-2020	[redacted]	Updated per comments
Final 1.0	30-Oct-2020	[redacted]	Updated per comments
Final 2.0	13-Apr-2020	[redacted]	Update Signature page ([redacted])

[redacted]

SIGNATURE PAGE - CONSTELLATION PHARMACEUTICALS

Declaration

The undersigned has/have reviewed and agree to the statistical analyses and procedures of this clinical study, as presented in this document.

[redacted], MD MPH
Digitally signed by [redacted], MD MPH
Date: 2021.04.14 11:02:11 -04'00'

[redacted]
Date (DD Mmm YY)

[redacted]

[redacted]
Digitally signed by [redacted]
Date: 2021.04.14 11:09:40 -04'00'

[redacted]
Date (DD Mmm YY)

Clinical Trial Manager

[redacted]
Digitally signed by [redacted]
Date: 2021.04.14 08:11:28 -07'00'

[redacted]
Date (DD Mmm YY)

[redacted]

[redacted]

TABLE OF CONTENTS

[redacted]

[redacted]

ABBREVIATION AND ACRONYM LIST

Abbreviation / Acronym	Definition / Expansion
AE	Adverse event
aPTT	Activated partial thromboplastin time
AR	Androgen receptor
AR-V	Androgen receptor splice variant
ATC	Anatomical-therapeutic-chemical
AUC	Area under the concentration-time curve
BID	Two times a day
BMI	Body mass index
BUN	Blood urea nitrogen
CBC	Complete blood count
CIs	Confidence intervals
C_{max}	Maximum concentration
CPK	Creatine phosphokinase
CR	Complete response
CRR	Central radiology review
CSP	Clinical study protocol
CTCAE	Common Terminology Criteria for Adverse Events
CTCCT	CTC conversion
CTCRR	CTC 30% response
C_{trough}	Minimum (trough) concentration
C1D1	Cycle 1 day 1
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone
DOR	Duration of Response
ECG	Electrocardiogram

[redacted]

Abbreviation / Acronym	Definition / Expansion
FSH	Follicle-stimulating hormone
[redacted]	[redacted]
[redacted]	[redacted]
HDL	Cholesterol high density lipoprotein
INR	International normalized ratio
IP	Investigational product
LDH	Lactate dehydrogenase
LDL	Cholesterol low density lipoprotein
LH	Luteinizing hormone
mCRPC	Metastatic castration resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
NCI	National cancer institute
NRS	Numerical rating scale
ORR	Objective response rate
OS	Overall survival
PCWG3	Prostate cancer clinical trials working group 3
PD	Progressive Disease
PK	Pharmacokinetic
PO	Orally; by mouth
[redacted]	[redacted]
PPR	Pain progression
PR	Partial response
[redacted]	[redacted]
[redacted]	[redacted]
PSA	Prostate specific antigen
PSA50	PSA 50% response rate
PT	Prothrombin time
[redacted]	[redacted]

[redacted]

Abbreviation / Acronym	Definition / Expansion
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
rPFS	Radiographic progression free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation or single dose
SE	Standard error of the mean
SHBG	Sex hormone-binding globulin
SOC	System organ class
SRE	Skeletal-related event
SSE	Symptomatic skeletal even
TEAE	Treatment-emergent adverse event
TID	Three times a day
T_{max}	Time to maximum concentration
TSH	Thyroid stimulating hormone
TTNST	Time to initiation of new systemic treatment for prostate cancer
TTOA	Time to opioid analgesics
TTPPR	Time to pain progression
TTPSA	Time to PSA progression
TTSRE	Time to first SRE
TTSSE	Time to First SSE
TTUPR	Time to unequivocal clinical progression
UPR	Unequivocal clinical progression
WHODDE	World Health Organization Drug Dictionary drug

[redacted]

1. INTRODUCTION

The Statistical Analysis Plan (SAP) details the statistical methodology to be used in analyzing study data. It describes the main variables and populations, anticipated data transformations and manipulations methods. And it also describes other details of the analyses not provided in the Clinical Study Protocol (CSP [1]) of all data (source documents /electronic case report forms [eCRFs]) and captured electronically in RAVE.

The analyses described are based on the final clinical study protocol Amendment 3, Version 4.0, dated 26 July 2018 for "ProSTAR: A Phase 1b/2 Study of CPI-1205, a Small Molecule Inhibitor of EZH2, Combined with Enzalutamide or Abiraterone/Prednisone in Patients with Metastatic Castration Resistant Prostate Cancer" and eCRF Version 8.0, dated 28 September 2018. This Statistical Analysis Plan will include description of analyzes for cohorts on **Phase 2 (Randomized and Single Arm)**. Pharmacokinetic (PK) and pharmacodynamic analyses will be described in a separate SAP.

The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. Any deviations from the SAP after database lock, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in the SAP Addendum and documented in the clinical study report (CSR).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Phase 2 (Randomized) Primary Objectives and Endpoints

The primary objective at the Randomized Phase 2 is to evaluate the effect of CPI-1205 (with or without cobicistat) + enzalutamide **OR** abiraterone/prednisone (combination arm) versus(vs) enzalutamide **OR** abiraterone/prednisone alone (control arm) in patients with mCRPC.

The primary endpoints at the Randomized Phase 2 include the following:

– PSA50 is defined as the proportion of patients who have a ≥50% reduction in PSA from baseline, after at least 1 dose of study treatment and prior to or on the end of treatment or C1D1 of cross-over time.

[redacted]

- The composite response rate is defined as the proportion of patients who have either a CTC 30% response or an objective response after at least 1 dose of study treatment and prior to or on the end of treatment or C1D1 of cross-over time.
    - CTC 30% response is defined as a ≥30% reduction in CTCs from baseline in patients who enter the trial with unfavorable CTCs (five or more cells per 7.5mL of blood) prior to or on the end of treatment or C1D1 of cross-over time.
    - Objective response is defined as a confirmed CR or PR per PCWG3 prior to or on the end of treatment or C1D1 of cross-over time in patients who enter the trial with measurable soft tissue disease. Response will be based on CRR.

2.2 Phase 2 (Randomized) Secondary Objectives and Endpoints

The secondary objectives at the Randomized Phase 2 include the following,

- To compare rPFS and rPFS at 3 months between the combination arm and control arm.
- To compare time to PSA progression between the combination arm and control arm.
- To compare ORR and DOR in patients with soft tissue disease between the combination arm and control arm.
- To compare ORR (excluding parenchymal lesions) and DOR (excluding parenchymal lesions) in patients with non-parenchymal soft tissue disease between the combination arm and the control arm.
- To compare the composite response rate (where response is defined as PSA 50% response or objective response) in patients with soft tissue disease between the combination arm and the control arm.
- To compare the composite response rate (where response is defined as PSA 50% response or CTC 30% response) in patients with unfavorable CTCs between the combination arm and the control arm.
- To compare the time to first SRE and the time to first SSE between the combination arm and control arm.
- To compare the time to unequivocal clinical progression between the combination arm and control arm.

[redacted]

- To compare the time to initiation of new systemic treatment for prostate cancer between the combination arm and control arm.

[redacted]

- To compare the time to pain progression and the time to opioid analgesics between the combination arm and the control arm.
- To compare the CTC 30% response rate and CTC conversion rate in patients with unfavorable CTCs between the combination arm and the control arm.
- To compare OS between the combination arm and the control arm.

[redacted]

- To evaluate the safety of CPI-1205 in combination with enzalutamide **OR** abiraterone/prednisone (combination arm).
- In the combination arm(s) only to further characterize the PK profiles of CPI-1205, cobicistat (if applicable), enzalutamide or abiraterone, and further evaluate any PK interactions when CPI-1205 (with or without cobicistat) is given in combination with either enzalutamide or abiraterone.

Note: Radiographic response and progression are defined per the PCWG3 criteria and may be evaluated by CRR and at the site by the investigator. ORR (excluding parenchymal lesions) and DOR (excluding parenchymal lesions) will only be evaluated by CRR. The combination arm referred to in the objectives below may be with or without cobicistat.

The secondary efficacy endpoints at the Randomized Phase 2 are the following:

- Time to PSA progression is defined as the time from D1 of treatment to the date of PSA progression based on lab data prior to on the initiation of new anti-cancer therapy or C1D1 of cross-over time.
- rPFS is defined per PCWG3 by central review data as time from D1 of treatment to the date when the first site of disease is found to progress (using a manifestation-specific definition of progression), or death, whichever occurs first, prior to or on the initiation of new-anti-cancer therapy or C1D1 of cross-over time. radiographic progression-free survival at 3 months will also be estimated.
- For patients with measurable soft tissue disease, ORR is defined as the proportion of patients with a CR or PR per PCWG3. DOR is measured from the time measurement criteria are met for CR or PR

[redacted]

(whichever status is recorded first) until the first date that radiographic progression is documented per PCWG3, prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time.

- In patients with measurable disease in non-parenchymal soft tissue, ORR (excluding parenchymal lesions) is defined as the proportion of patients with a CR or PR per PCWG3 in soft tissue excluding the parenchyma (i.e., liver and lung), prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time. DOR (excluding parenchymal lesions) is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that radiographic progression is documented per PCWG3 in soft tissue excluding the parenchyma, prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time.
- For patients with measurable soft tissue disease, an additional composite response rate is defined as the proportion of patients who have either a PSA 50% response (a ≥50% reduction in PSA from baseline) or an objective response (CR or PR per PCWG3), prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time.
- In patients with unfavorable CTCs, an additional composite response rate is defined as the proportion of patients who have either a PSA 50% response (a ≥50% reduction in PSA from baseline) or a CTC 30% response (≥30% reduction in CTCs from baseline), prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time.
- OS is defined as the time from D1 of treatment to the date of death at any time during the trial.
- Time to first SRE is defined as the time from D1 of treatment to the date of first SRE prior to or on the initiation of new anti-cancer therapy or cross-over time.
- Time to unequivocal clinical progression is defined as the time from D1 of treatment to the date of first unequivocal clinical progression prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time.
- Time to initiation of new systemic treatment for prostate cancer is defined as the time from D1 of treatment to the date any new systemic treatment for prostate cancer is initiated.

[redacted]

- Time to pain progression is defined as the time from D1 of treatment to the date of first pain progression prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time. For patients who enter the trial not on opioid analgesics, time to opioid analgesics is defined as the time

[redacted]

from D1 of treatment to the date of first opioid usage prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time.

- In patients who enter the trial with unfavorable CTCs (five or more cells per 7.5mL of blood), conversion to favorable status is defined as four or fewer cells per 7.5 mL of blood. The CTC conversion rate is the proportion of patients who convert to favorable status prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time.
- In patients who enter the trial with unfavorable CTCs (five or more cells per 7.5mL of blood), the CTC 30% response rate is defined as the proportion of patients who have a ≥30% reduction in CTCs from baseline prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time.

Additional secondary endpoints at the Randomized Phase 2 are the following:

- AEs will be graded according to the NCI CTCAE v4.03. Laboratory evaluations, vital signs, physical examinations, and ECGs will also be evaluated.
- PK parameters will include: AUC_{last}, C_{max}, T_{max}, C_{trough} (defined as the level at 24 hours post dose or the level pre-dose), peak-to-trough ratio and accumulation ratio (for both Cmax and AUC_{last}).

[redacted]

2.3 Phase 2 (Single Arm) Primary Objectives and Endpoints

The primary objective at the single arm phase 2 is to evaluate the effect of the combination selected for the single arm phase 2.

The primary endpoints at the single arm phase 2 are the same to the primary endpoints at the Randomized Phase 2 (see Section 2.1). Because there is no treatment cross-over in the Single Arm Phase 2 trial, assessments between D1 of treatment and prior to or on the initiation of new anti-cancer therapy will be evaluated for each primary efficacy endpoint.

2.4 Phase 2 (Single Arm) Secondary Objectives and Endpoints

If the Single Arm Phase 2 is conducted, the same endpoints will be evaluated as for the Randomized Phase 2 (see Section 2.2), but they will be estimated or evaluated for the single arm rather than compared

[redacted]

as for the Randomized Phase 2. For the time to event analyses except DOR, the origin of event will be Day 1 of treatment in the Single Arm Phase 2 trial.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

3. STUDY DESIGN

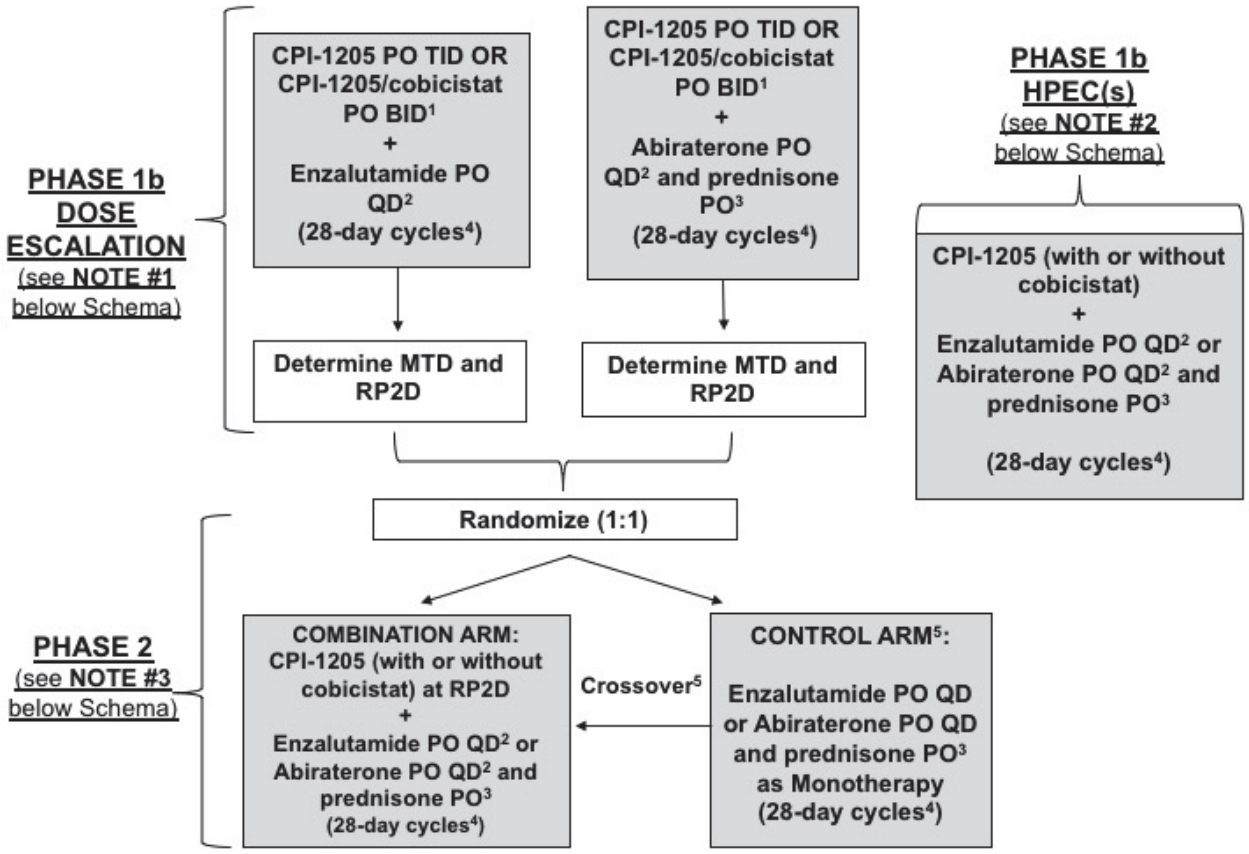
3.1 Overall Study Design

After the determination of the MTD during Phase 1b in each of the CPI-1205 BID + cobicistat combinations (and possibly in the CPI-1205 TID combination) and evaluation of the BID cohorts without cobicistat (if applicable) during phase 1b dose escalation, only one of the CPI-1205 dosing schedules will be selected as the RP2D for each combination (i.e., with enzalutamide and with abiraterone/prednisone).

[redacted]

One or both of the combinations may proceed to phase 2 after consideration of PK and pharmacodynamic results, data from the HPEC(s) and safety data. If only one partner product is chosen for phase 2, the phase 2 study will proceed as an open-label Randomized Phase 2 trial, with patients randomized to either the combination arm (CPI-1205 at the RP2D [with or without cobicistat] in combination with enzalutamide or abiraterone/prednisone) or the control arm (enzalutamide or abiraterone/prednisone as monotherapy). If both partner products are chosen for phase 2, the second phase 2 will be either a second open-label randomized trial, or a single arm phase 2 trial (following a Simon's 2-stage design) of CPI-1205 at the RP2D (with or without cobicistat) in combination with either enzalutamide or abiraterone/prednisone. The design of the second trial will be determined by the Sponsor, and will be based on factors such as preliminary efficacy and PK.

Figure 1 Study Design Schematic



[redacted]

3.2 Schedule of Assessments

The Schedule of Events for phase 2 is presented in Table 7-3 in the CSP. Table 7- 4 in the CSP is the Schedule of Events for patients who cross over to the combination arm from the control arm of Randomized Phase 2 trial.

The Screening period includes the 28 days before the first day of treatment. Screening assessments should be performed within 28 days prior to Cycle 1 Day 1 (C1D1) unless otherwise noted in footnotes of tables with schedules of assessments.

There is no window for visits during Cycles 1 and 2, however, clinical laboratory parameters (see Section 7.1.4.2) may be drawn within 48 hours prior to day of visit. Starting in Cycle 3, a window of ± 3 days will be applied to all clinic visits. When applicable, specific windows for assessments (e.g., 6 hours [±1 hr]) are provided in the footnotes of tables with schedules of assessments.

4. STUDY POPULATION

The patients enrolled in this study will be adults (aged ≥ 18 years) with a histologically confirmed diagnosis of metastatic adenocarcinoma of the prostate that has progressed in the setting of medical or surgical castration (i.e., mCRPC). During phase 2, enrollment will be limited to patients who have received only one line of a second generation androgen inhibitor (from a different class than the agent chosen for the applicable phase 2 study), who progressed after at least 24 weeks of treatment with the second generation androgen inhibitor, and who have not received prior chemotherapy for mCRPC. During phase 2, progressive disease may present as PSA, soft tissue and/or bone disease progression and at least 50% patients must also have measurable soft tissue disease.

Detailed lists of inclusion and exclusion criteria for phase 2 are shown in Sections 3.6 - 3.7 in the CSP.

5. DETERMINATION OF SAMPLE SIZE

[redacted]

[redacted]

Randomized Phase 2:

The primary objective of the randomized phase 2 trial(s) is to evaluate the effect of CPI-1205 (with or without cobicistat) + enzalutamide **OR** abiraterone/prednisone (combination arm) vs enzalutamide **OR** abiraterone/prednisone alone (control arm). [redacted]

Single Arm Phase 2:

A Simon's 2-stage design will be utilized if a single arm phase 2 trial is conducted [redacted]

[redacted]

6. RANDOMIZATION

There will be no randomization in the phase 2 single arm trial (if conducted). The small size of this study preclude the use of any meaningful stratification in the phase 2 single arm trial.

If phase 2 is pursued, at least one randomized phase 2 trial is planned. For the randomized phase 2 study(ies), eligible patients will be randomly assigned in a 1:1 ratio to the combination arm (CPI-1205 [with or without cobicistat] at the RP2D in combination with enzalutamide or abiraterone/prednisone) or the control arm (enzalutamide or abiraterone/prednisone as monotherapy). [redacted]

7. STATISTICAL ANALYSIS CONVENTIONS

7.1 Analysis Variables

7.1.1 Demographic and Background Variables

The assessment of demographic and baseline characteristics should be performed during the 28 days before the first dose. The following demographic and baseline variables will be descriptively evaluated:

- Age, Sex, Ethnicity and Race
- Height (cm) and Weight (kg) at baseline
- Prior medication (cancer therapy, radiation therapy)
- CTC unfavorable (>=5) count
- ECOG score
- Measurable Disease by Target Lesion at Baseline per investigator
- Measurable Disease by Target Lesion at Baseline per central review data

7.1.2 Medical History

During the Screening period, the patient will have a complete medical history taken including:

[redacted]

- All previous lines of therapy for the treatment of prostate cancer in the order they were administered.
- Details on prior radiation therapy
- Type of progression on entry
- Document any previous [redacted] results [redacted]

7.1.3 Study Treatment

All drugs in this trial are to be administered continuously. Although a cycle of treatment during this study is defined as 28 days, there are no scheduled interruptions in treatment. The division of treatment into 28-day cycles is solely for the purpose of guiding the timing of the safety, PK, pharmacodynamic, and efficacy evaluations that are performed during the study.

At the time any patient crosses over from the control arm to the combination arm in a randomized phase 2 study, the first cycle of combination treatment will be considered Cycle 1.

CPI-1205 will be dosed TID or BID with cobicistat. Cohorts of CPI-1205 BID without cobicistat may also be evaluated. The CPI-1205 dose will not be adjusted for body weight or body surface area; all patients treated in the same cohort/at the same dose level will receive the same total milligram dose of CPI-1205 per day.

During Screening, patients will be provided with oral **cobicistat** to be started the evening prior to Cycle 1 day 1 (C1D1) of CPI-1205 (i.e., day 0), with one dose to be taken the evening of day 0 with food. Cobicistat will then be given BID starting on day 1 of CPI-1205, continuing throughout CPI-1205 dosing. Once CPI-1205 BID dosing begins, patients should be instructed to take each dose of cobicistat at least 1 hour after each CPI-1205 dose, with food.

Patients should be instructed to take their once daily 160mg dose of **enzalutamide** by ingesting four 40mg capsules orally at approximately the same time every day (in the morning) immediately after the first CPI-1205 dose (if applicable). All 4 capsules should be consumed over as short a time as possible (e.g., all capsules within 5 minutes).

Patients should be instructed to take their once daily 1000mg dose of **abiraterone** by ingesting four 250mg tablets orally at approximately the same time every day (in the morning) immediately after the

[redacted]

first CPI-1205 dose (if applicable). Patients will be instructed to take 5mg **prednisone**, BID (or with frequency of the prednisone at the discretion of the investigator).

7.1.4 Safety Variables

The following safety assessments will be performed:

- AEs
- SAEs
- Clinical laboratory evaluations
- Vital signs
- ECG
- Physical examination
- ECOG
- Concomitant medications

[redacted]

7.1.4.1 Adverse Events

AEs, TEAEs, SAEs and SUSAR:

Adverse events will be recorded from the time of informed consent until 30 days after administration of the last dose of CPI-1205 or partner drug for patients on the control arm of any randomized phase 2 study who do not participate in the crossover. All AEs and SAEs that occur during the reporting period will continue to be followed until the event resolves, the investigator assesses the event as stable, the event is determined to be irreversible, or the patient is lost to follow-up.

Treatment-emergent AEs are defined as any AEs that occurs after administration of the first dose of study treatment and through 30 days after the last dose of study medication, any event that is considered drug related regardless of the start date of the event, or any event that is present at baseline but worsens in severity after baseline or is subsequently considered drug-related by the investigator.

An SAE is any AE occurring at any dose and regardless of causality that:

[redacted]

- Results in **death**.
- Is **life-threatening**. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form).
- Requires in patient **hospitalization or prolongation of existing hospitalization**.
- Results in **persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a **congenital anomaly/birth defect**
- Is an **important medical event**. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in the definitions for SAEs.

A SUSAR is an event that meets the criteria for an SAE, that is at least possibly related to study drug (study treatment administration is one of several biologically plausible causes of the AE) and is unexpected (if the specificity or severity of it is not consistent with the applicable product information).

AE Grade and Relationship

For AEs and SAEs, intensity and the relationship of the event to study drug administration will be assessed and recorded. Intensity of each AE, including any laboratory abnormality, will be determined by using the National Cancer Institute (NCI) CTCAE, Version 4.03. In those cases where the NCI CTCAE criteria do not apply, intensity will be defined according to the following criteria:

[redacted]

Table 1 Severity Assessment Terminology for Reporting Adverse Events (CTCAE v 4.03)

Event Intensity	Description	Grade
Mild	Awareness of sign or symptom but easily tolerated	1
Moderate	Discomfort enough to cause interference with normal daily activities	2
Severe	Inability to perform normal daily activities	3
Life-threatening	Immediate risk of death from the reaction as it occurred	4
Death		5

The causal relationship of AEs/SAEs to study treatment will be determined by the Investigator according to best medical judgement as follows: related (possibly, probably, or definitely) or not-related (unrelated or unlikely).

7.1.4.2 Clinical Laboratory Evaluations

If hematology, clinical chemistry, lipids and CPK labs were performed within 3 days of C1D1, they do not need to be repeated on C1D1. During any subsequent visit in Cycle 1 and for any Cycle 2 visit, blood for these evaluations may be drawn within 48 hours prior to day of visit.

COAGULATION PARAMETERS

Prothrombin time (PT)/International normalized ratio (INR) and activated partial thromboplastin time (aPTT) will be determined during Screening for all patients. Subsequent measurement of the PT/INR and aPTT will be performed on D1 of Cycle 2 and thereafter only as clinically indicated.

HEMATOLOGY

A complete blood count (CBC) with differential will be obtained during Screening, on D1 and D15 of Cycle 1, on D1 of Cycles 2+, at the End of Treatment Visit, and at the Safety Follow-up Visit during phase 2, and on D1 and D15 of Cycle 1, on D1 of Cycles 2+, at the End of Treatment Visit, and at the Safety Follow-up Visit after crossover.

[redacted]

The CBC with differential consists of the following: hemoglobin, total WBC count, differential WBC count, and platelet count.

CLINICAL CHEMISTRY

A clinical chemistry panel will be obtained during Screening, on D1 and D15 of Cycle 1, on D1 of Cycles 2+, at the End of Treatment Visit, and at the Safety Follow-up Visit during phase 2 and during on D1 and D15 of Cycle 1, on D1 of Cycles 2+, at the End of Treatment Visit, and at the Safety Follow-up Visit after crossover.

The clinical chemistry panel consists of the following: sodium, potassium, carbon dioxide, chloride, blood urea nitrogen (BUN), serum creatinine, total bilirubin, alkaline phosphatase, albumin, AST, ALT, lactate dehydrogenase (LDH), uric acid, calcium, magnesium, phosphate, serum glucose.

SERUM LIPIDS AND CREATINE PHOSPHOKINASE (CPK)

Serum lipids and CPK will be obtained during Screening, on D1 of each cycle, at the End of Treatment Visit and at the Safety Follow-up Visit in all patients.

Serum lipids will include total cholesterol, cholesterol low density lipoprotein (LDL), cholesterol high density lipoprotein (HDL) and triglycerides.

THYROID FUNCTION TESTS

Thyroid function tests include thyroid stimulating hormone (TSH) and T4 will be obtained at Screening, on C3D1, and every other subsequent cycle (i.e., C5D1, C7D1, etc.) during phase 2.

After crossover, thyroid function tests will be obtained on C1D1, C3D1 and every other cycle thereafter (i.e., C5D1, C7D1, etc.).

OTHER ENDOCRINOLOGY

Other endocrinology labs will be obtained at Screening, on C2D1 and on C4D1 in all patients. Endocrinology labs include: sex hormone-binding globulin (SHBG), androstenedione, ehydroepiandrosterone (DHEA), DHEA sulfate, dihydrotestosterone (DHT), estradiol, folliclestimulating hormone (FSH), luteinizing hormone (LH), prolactin and total testosterone.

[redacted]

7.1.4.3 Vital Signs

Vital signs (BP, heart rate, and oral temperature) will be taken during Screening and on D1 of each cycle of treatment.

On C1D1, vital signs will be taken prior to dosing, and will be repeated 3 h (± 30 min) after dosing for any cohort/study arm that includes CPI-1205; for any control arm that includes only abiraterone/prednisone or enzalutamide, obtain pre-dose only.

7.1.4.4 Electrocardiograms

A 12-lead ECG will be obtained as part of the Screening evaluation. On C1D1, an ECG will be performed prior to dosing, and will be repeated 3 h (±30 min) after dosing for any cohort/study arm that includes CPI-1205; for any control arm that includes only abiraterone/prednisone or enzalutamide, obtain pre-dose only. Subsequent ECGs will only be performed during treatment if clinically indicated. ECG will also be performed at the Safety Follow-Up Visit.

7.1.4.5 Physical Examination

An assessment of signs and symptoms and a complete physical examination will be conducted during Screening and at the Safety Follow-up Visit. The Screening physical examination will record the patient's height and weight, the Safety Follow-up Visit physical examination will record weight only.

An assessment of signs and symptoms and an abbreviated physical examination (directed toward the identification of signs of treatment-related toxicity and disease progression or regression) including the patient's weight, will be performed D1 of each cycle and at the End of Treatment Visit.

A physical exam and signs and symptoms assessment do not need to be repeated on C1D1 if the Screening evaluations are conducted ≤ 3 days prior to C1D1. In this case, the Screening evaluations will be considered baseline.

7.1.4.6 ECOG Performance Status

ECOG performance status (see Grade 0 to 5 in Appendix 1 in the CSP) will be assessed during Screening, on the D1 of each cycle, at the End of Treatment Visit, and at the Safety Follow-up Visit.

ECOG performance status must be documented by 2 independent evaluators.

[redacted]

7.1.4.7 Concomitant Medication

All concomitant medications and supportive therapies will be recorded from Screening through the Safety Follow-up Visit. Concomitant medications and therapies that are prohibited or to be used with caution are described in Section 6.3, Appendix 4 and Appendix 5 in the CSP.

[redacted]

[redacted]

7.1.5 Efficacy Variables

7.1.3.1PSA Evaluation

For the purpose of PSA evaluation, baseline PSA will be the PSA measured pre-dose on C1D1 (or the PSA measured during Screening if PSA was collected ≤ 7 days prior to C1D1).

7.1.3.1.1 PSA Progression (for Study Entry)

At Phase 2, if progressive disease at study entry is based on PSA, PSA must be ≥ 2 ng/mL (or PSA ≥ 1 ng/mL if PSA progression is the only manifestation of progressive disease) and rising PSA must be documented by at least 2 consecutive measurements a minimum of 1-week apart.

7.1.3.1.2 PSA 50% Response

To be evaluable for PSA 50% response, baseline PSA must be ≥ 2 ng/mL (unless PSA progression is the only manifestation of progressive disease, in which case baseline PSA must be ≥ 1 ng/mL).

PSA response is defined according to the Prostate-Specific Antigen Working Group criteria [1].

PSA 50% response (PSA50) is defined as a ≥50% reduction in PSA from baseline. The reduction must be confirmed by a second PSA value 4 or more weeks later. PSA50 is the proportion of patients with a PSA 50% response.

7.3.1.1.3 PSA Progression on Treatment

PSA progression during study treatment is defined according to PCWG3.

Early rises (before 12 weeks) in PSA should be ignored.

For patients with PSA decline from baseline, PSA progression is defined as a 25% or greater increase and an absolute increase of 2 ng/mL or more from the nadir is documented, which is confirmed by a second value obtained 3 or more weeks later.

For patients without a PSA decline from baseline, PSA progression is defined as a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the baseline is documented beyond 12 weeks.

Time to PSA progression (TTPSA) is defined as the time from D1 of treatment to the date of PSA progression confirmed prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time.

[redacted]

7.1.3.2PCWG3 Criteria (Radiographic Evaluation)

The PCWG3 criteria [2] are based on modifications of the RECIST 1.1 criteria [3]. See Section 10.3 in the CSP for details on RECIST 1.1.

Objective Response Rate (ORR) for patients with measurable soft tissue disease is defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) per PCWG3 prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time.

ORR (excluding parenchymal lesions) for patients with measurable disease in non-parenchymal soft tissue is defined as the proportion of patients with a confirmed CR or PR per PCWG3 in soft tissue excluding the parenchyma (i.e., liver and lung) prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time.

For patients with measurable soft tissue disease, an additional composite response rate is defined as the proportion of patients who have either a PSA 50% response (a ≥50% reduction in PSA from baseline) or an objective response (CR or PR per PCWG3) prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time.

Radiographic progression free survival (rPFS) is defined per PCWG3 as time from D1 of treatment to the date when the first site of disease is found to progress (using a manifestation-specific definition of progression), or death, whichever occurs first prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time. The proportion of patients who remain radiographic progression free at 3 months will also be estimated.

Duration of Response (DOR) is defined as time from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that radiographic progression is documented per PCWG3 or death prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time.

DOR will be calculated for responders only.

DOR (excluding parenchymal lesions) is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that radiographic progression is documented per PCWG3 in soft tissue excluding the parenchyma prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time. DOR will be calculated for responders only.

[redacted]

Overall Survival (OS) is defined as the time from D1 of treatment to the date of death at any time during the trial.

7.1.3.3 Enumeration of CTCs

Blood will be collected for the enumeration of CTCs following recommendations from PCWG3.

Favorable or unfavorable status will be determined.

- Unfavorable is defined as five or more cells per 7.5 mL of blood.
- Favorable is defined as four or fewer cells per 7.5 mL of blood.

CTC 30% response (CTCRR) is defined as ≥ 30% reduction in CTCs from baseline in patients with unfavorable CTC status. Any CTC 30% response must be confirmed by an additional CTC enumeration at least 4 weeks later.

CTC conversion (i.e., conversion from unfavorable to favorable) (CTCCR) is another way to measure response via CTCs. Any conversion from unfavorable to favorable CTC status must be confirmed by an additional CTC enumeration at least 4 weeks later.

Composite response (first definition) is defined as CTC 30% response or objective response (CR or PR) per PCWG3 criterion in patients who enter the trial with measurable soft tissue disease. Objective response will be based on CRR.

In patients with unfavorable CTCs, composite response rate (second definition) is defined as the proportion of patients who have either a PSA 50% response (a ≥50% reduction in PSA from baseline) or a CTC 30% response (≥30% reduction in CTCs from baseline).

7.1.3.4 Unequivocal Clinical Progression

Unequivocal clinical progression (UPR) includes development of any of the following clinically

significant disease-specific events:

- Spinal cord or nerve root compression
- Pathologic fracture

[redacted]

- Metastatic disease in an anatomy for which no baseline scan (e.g., spine, base of skull) is available for comparison to allow documentation of interval change on serial imaging studies.
- Progressive disease in an anatomy for which there is a baseline imaging assessment but serial imaging has not been performed (e.g., prostate bed)
- A clinical indication for radiation therapy
- At least 2 of the following clinical signs/symptoms in comparison to baseline:
  - An increase in ECOG performance status of > 1 grade
  - ≥ 10% weight loss, not attributable to intentional weight loss
  - New urinary outflow obstruction attributable to cancer. Urinary retention may be due to disease progression, treatment induced prostatitis, or stricture from scar tissue after surgery, so subjects should be carefully evaluated.
  - Progressive anemia, defined as either:
    - a decrease in hemoglobin of ≥ 2 g/dL and to a level below the lower limit of normal in the central lab reference range, **or**
    - a requirement for therapy with a hematopoietic growth factor (e.g., Procrit®) or transfusion with packed red blood cells for anemia

Time to unequivocal clinical progression (TTUPR) is defined as the time from D1 of treatment to the date of first unequivocal clinical progression prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time, if applicable.

7.1.3.5Skeletal Events (SREs)

SREs are defined as: asymptomatic nonclinical fractures as evaluated via serial imaging, clinical pathologic fractures, spinal cord compression, and surgery or radiation therapy to bone.

Time to first SRE (TTSRE) is defined as the time from D1of treatment to the date of first SRE prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time, if applicable.

[redacted]

7.1.3.6 Pain/Analgesic Usage

[redacted]

Pain Progression:

Pain progression will be evaluated in all patients.

For patients with no baseline pain, pain progression (PPR) is defined as the development of pain. For patients with baseline pain, progression is defined as a ≥2-point increase in pain on the NRS on 2 consecutive evaluations 4 weeks apart, without any decrease in analgesic usage score.

Time to pain progression (TTPPR) is defined as the time from D1 of treatment to the date of first pain progression prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time, if applicable.

Opioid Usage:

Opioid usage is defined as a 2 or 3 on the WHO analgesic ladder.

Time to opioid analgesics (TTOA) is defined as the time from D1 of treatment to the date of first opioid usage prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time, if applicable.

7.1.3.7 Other variables

Time to initiation of new systemic treatment for prostate cancer (TTNST) is defined as the time from D1 of treatment to the date any new systemic treatment for prostate cancer is initiated prior to cross-over, if applicable.

7.2 Analysis Populations

Full analysis set (FAS) is defined as all patients who received at least one dose of the study drug.

[redacted]

FAS will be used for time-to-event endpoints for the Randomized Phase 2 and Single Arm phase 2.

Safety analysis set (SAF) is defined as all patients who receive at least one dose of study drug.

Efficacy analysis set (EAS) for the Randomized Phase 2 and Single Arm Phase 2 is defined as all randomized patients with at least 1 dose of study treatment and with at least one efficacy assessment. EAS will be used for the efficacy summaries except time-to-events endpoints.

If the single arm phase 2 trial is conducted, a patient evaluable for the primary endpoints will be included in the **efficacy analysis set (EAS)** if:

- In Cycle 1, the patient receives ≥ 75% of the planned doses of CPI-1205 (and, if applicable, cobicistat) and either abiraterone or enzalutamide (depending on the combination selected for phase 2)
- He has at least one post-baseline PSA measurement (if evaluable for PSA 50% response)
- He has at least one post-baseline CTC assessment (for patients with ≥ 5 CTCs)
- He has at least one post-baseline imaging assessment (for patients with measurable disease)

The **pharmacodynamic and pharmacokinetic analysis sets** are not included in this SAP.

7.3 Statistical Analysis Methods

7.3.1 General Presentation Consideration

Continuous variables will be summarized using descriptive statistics [n, mean, standard deviation, median, minimum, and maximum]. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical variables will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Percentages will be presented to one decimal place.

[redacted]

Percentages will not be presented for zero counts. Percentages will be calculated using n as the denominator. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only.

Time-to-event endpoints (e.g., time to PSA progression, time to first SRE) will be estimated using the Kaplan-Meier (KM) method and Cox-regression method. Descriptive statistics for analyses of such endpoints will include the number and percentage of subjects with events, the number and percentage of subjects censored, estimated 25% quartile, estimated median, estimated 75% quartile, and their corresponding 95% CIs, and minimum and maximum duration in months. Kaplan-Meier curves will be plotted for each survival analysis. The log-rank test using the Chi-square test will be used to compare the combination arm with the control arm in the Randomized Phase 2 trial. The Cox-regression with the treatment as the only fixed factor will be used to estimate hazard ratio and its 95% CIs of instantaneous risks between two arms in the Randomized Phase 2 trial. 95% CIs will be obtained by inverting the score test.

Confidence intervals (CIs) will be presented to one more decimal place than the raw data.

P-values if reported will be presented to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001", if a p-value is greater than 0.999 it will be reported as ">0.9999".

Graphs may also be presented where appropriate.

Unscheduled visits will not be included in by-visit summaries, but will be considered in baseline derivations and in analyses such as maximum grade shift from baseline.

7.3.2 Listings and Descriptive Statistics

Data for all enrolled patients who receive at least 1 dose of study drug will be presented in data listings. A patient who is enrolled but does not receive study drug will be included in those listings for which there is data but will be excluded from all data summaries. Data summaries will only include those patients that receive study drug.

Unless otherwise stated, the last non-missing observed measurement prior to the first dose of study drug(s) will be considered the baseline measurement.

Listings should be created by Cohort, Dosing Group unless other way is stated.

[redacted]

7.3.3 Statistical Significance Level

No formal statistical hypothesis is planned. Two-sided 95% confidence intervals may be used to describe the precision of the point estimates where appropriate.

7.3.4 Standard Dictionaries for Coding

The following dictionaries will be used to code medical verbatim terms for the clinical data below.

Types of Data	Coding Tools and Latest Version
Adverse events	Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1
Prior and concomitant medications	World Health Organization Drug Dictionary
Prior systemic therapies	MedDRA Version 22.1
Prior anticancer therapies	MedDRA Version 22.1
Medical history	MedDRA Version 22.1

7.3.5 Software

The tables, listings, figures and any non-descriptive statistical analysis will be produced using SAS Software (Version 9.3 or higher). The REPORT procedure (SAS PROC Report) will be used to produce all tables and listings; SAS/GRAPH will be used to produce all figures. All figures will be produced in black and white. The PROC LIFETEST will be used to produce all curves of Kaplan and Meier for time to event variables and compute log-rank tests. The PROC PHREG will be used to conduct the Cox-regression to estimate hazard ratio and its 95% CIs by inverting score test.

All tables, listings, and graphs will be produced to landscape orientation using Courier New 8pt font and will be incorporated into a MS Word document as a (RTF) rich text file (margins: top 1.5'', left, right, and bottom 1'').

7.3.6 Missing Data

In general, missing data will not be imputed unless otherwise specified. For the derivation of treatment emergent adverse events or concomitant medications, however, the missing or partial date will be temporarily imputed for programming purposes.

[redacted]

7.3.7 Interim Analysis

No formal interim analysis is planned. Data will be evaluated on a continuous basis.

7.3.8 Patient Treatment Disposition, Eligibility and Protocol Deviations

Treatment Disposition of patients will be summarized for all enrolled subjects in the Phase 2 trial. The number and percentage of patients will be provided for those who are on treatment, those who discontinue treatment but are still in follow-up, and those who discontinue from the treatment. Further, patients who discontinue treatment will be summarized by the primary reason for discontinuation.

The date and time the informed consent was signed and patients with informed consent and re-consent data will be listed by treatment group and patient.

Patients who did not meet the eligibility criteria will be listed.

Deviations from the protocol will be assessed as 'minor' or 'major'. CSR reportable ("major") protocol deviations (PDs) are defined in accordance with ICH E3 as important PDs related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment resulting in the potential to jeopardize the safety or rights of the trial subjects or the scientific value of the trial.

All major PDs will be classified into the following categories, but not all deviations listed below will necessarily be declared a major PD:

- Disallowed Medications
- Inclusion/Exclusion criteria
- Informed Consent
- Investigational Product (IP) Admin/Study Treat
- Procedures/Tests
- Visit Schedule
- Withdrawal Criteria

[redacted]

Number and percentage of subjects with a major protocol deviation will be summarized by the category of deviation and treatment group. The listing of protocol deviations by treatment group and subject will be provided.

7.3.9 Demographic Data

Demographic variables and other baseline characteristics will be summarized by treatment group based on Phase 2 safety analysis set. Descriptive statistics will be presented for continuous variables including age, height, weight, and body mass index (BMI) at baseline. The frequency and percentage of patients will be tabulated for categorical variables including sex, race, ethnicity, age group (18-44 years, 45-64 years, ≥65 years), disease category, prior therapy, and patient cancer therapy, ECOG status and CTC at baseline.

Age presented in the table is the age per EDC at the Day of Informed Consent. Age will be calculated as the number of complete years between a patient's birth year and the date of informed consent.

A by-patient listing of demographic information will also be provided.

7.3.10 Cancer/Disease History and Previous Cancer and/or Radiation Treatment

The frequency and percentage of disease type will be tabulated by treatment group in the safety analysis set. Disease of initial diagnosis, details of tumor histology/cytology, stage at study entry diagnosis, primary tumor, regional lymph nodes, distant metastases, location of metastases and type of progression at study entry will be listed by treatment group and subject.

The frequency and percentage of prior cancer therapy type will be tabulated by treatment group in the safety analysis set. Prior cancer therapy (either immunotherapy, hormonal therapy, chemotherapy, systemic therapy, other type of therapy) including type, therapy agent, line of therapy, treatment setting, number of cycles, best response, type of progression and reason for discontinuation will be listed by treatment group and subject.

The frequency and percentage of prior radiotherapy type will be tabulated by treatment group in the safety analysis set. Prior radiation therapy including type of radiation therapy, site of radiotherapy, start and end dates, total dose gray and response to it will be listed by treatment group and subject.

[redacted]

7.3.11 Medical and Surgical History

By-patient listings of significant medical history data prior to dosing will be provided based on phase 2 safety analysis set. Only those body systems where a condition or abnormality has been reported will be listed. They will be coded using MedDRA, version 22.1 or later and summarized by system organ class (SOC) and preferred term. The summary based on the Phase 2 safety analysis set will be sorted by the decreasing frequency of SOC then by the decreasing frequency of preferred term within an SOC.

7.3.12 Concomitant Medication

Prior and concomitant medications from screening through the end of the study will be coded using the World Health Organization Drug Dictionary drug (WHODDE, Version 201709), and will be presented by Anatomical-Therapeutic-Chemical (ATC) therapeutic classification and preferred term.

Prior medications are defined as medications taken prior to C1D1, which include both those ended prior to C1D1 and ongoing at C1D1. Concomitant medications include those who were on going at C1D1 and started on and after C1D1 and prior to the initiation of new anti-cancer therapy and C1D1 of cross-over time, if necessary. The frequency and percentage of prior medications and concomitant medications will be tabulated by treatment group and by ATC/preferred term in the safety analysis set.

By-patient listings of prior and concomitant medications will also be provided by treatment group and subject.

7.3.13 Dose Administration and Exposure

A summary of CPI-1205 exposure will be provided based on the Phase 2 Safety Analysis Population. Specifically, the number of doses administered, total treatment duration (days), total cumulative dose (mg) and relative dose intensity for the study will be summarized. A tabulation of modifications will be provided.

Extent of exposure will include the following variables:

Treatment Duration (days): (date of last dose – date of first dose + 1)
Treatment Duration (weeks): (date of last dose – date of first dose + 1) divided by 7.

Number of treatment cycles started: Number of cycles initiated will be derived from the CRF data as the number of cycle X day 1 visits attended. Number of treatment cycles completed: Number of cycles completed will be determined from the number of cycles initiated minus the number of cycles where there was any dose not taken

[redacted]

Cumulative dose is defined as the total dose taken by the patient throughout the treatment period.

Total planned dose is defined as the dose that should have been taken during the treatment period based on initial dose, which is initial planned dose × treatment duration (days).

Dose intensity = cumulative dose (mg) / total planned dose × 100.

A by-patient listing of study drug administration will be provided. And patients with treatment delays, missing doses, and dose holding will also be listed.

7.3.14 Efficacy Analysis

The primary and secondary efficacy analyses will be performed using the Phase 2 efficacy analysis set, and will be based on evaluable patients within each treatment group.

For the analysis of the composite response rates, and PSA50, ORR, and CTC 30% response rate in phase 2, if the trial is randomized between 2 treatment arms, treatment difference in these proportions will be calculated along with a 2-sided exact 95% CIs and the estimated rates for each treatment will be reported with a 2-sided 95% Clopper-Pearson CIs using the Clopper Pearson exact method for binomial proportions. If the single arm phase 2 trial is conducted, the 2-sided 95% confidence interval using exact method based on binomial distribution will be presented for the estimated rates.

All time to event endpoints (e.g., time to PSA progression, time to first SRE, time to unequivocal clinical progression, time to initiation of new systemic treatment, time to pain progression, and the time to opioid analgesics) will be estimated using both the Kaplan-Meier method and Cox-regression method with the treatment as the only fixed factor. Descriptive statistics for analyses of such endpoints will include the number and percentage of subjects with events, the number of subjects censored, estimated 25% quartile, estimated median, estimated 75% quartile, and their corresponding 95% CIs, and minimum and maximum duration in months.

In the randomized Phase 2 trial, for all time-to-event analyses except for OS,DOR, rPFS and PFS, all events after D1 of treatment and prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time (if necessary) will be counted and subjects without an event will be censored at the initiation of new anti-cancer therapy, C1D1 of cross-over time, the date of last study visit, the date of study discontinuation, or the date of death, whichever is the earliest. For OS, death during the trial after D1 of treatment will be counted and subjects remained alive in the trial will be censored at the date of the last

[redacted]

visit or the date of study discontinuation. In the Randomized Phase 2 trial, time-to-event analyses will be conducted in the full analysis set.

In the single-arm Phase 2 trial, for all time-to-event analyses except for OS, DOR, rPFS and PFS ,all events after D1 of treatment and prior to or on the initiation of new anti-cancer therapy will be counted and subjects without an event will be censored at the initiation of new anti-cancer therapy, the date of last study visit, the date of study discontinuation, or the date of death, whichever is the earliest. For OS, death during the trial after Day 1 will be counted and subjects remained alive in the trial will be censored at the date of last visit or the date of study discontinuation. In the Single Arm Phase 2 trial, time-to-event analyses will be conducted in the full analysis set.

Times of events for each endpoint between the combination arm and control arm in the Randomized Phase 2 trial will be compared statistically using the log-rank method using the chi-square test and the Cox-regression with the treatment group as the only fixed factor. P-value from log-rank test using SAS PROC LIFETEST procedure and the hazard ratio estimate with its 95% CIs by inverting the score test from the Cox-regression using SAS PROC PHREG procedure will be estimated.

7.3.14.1 Primary Efficacy Variables

Primary efficacy variables at the randomized phase 2 include the following,

- **PSA50** will be calculated as the proportion of patients who have a ≥50% reduction in PSA from baseline, after at least 1 dose of study treatment and prior to or on the end of treatment or C1D1 of cross-over time. A 2-sided 95% Clopper-Pearson CIs will also be reported using the Clopper Pearson exact method for binomial proportions.
- **Composite response rate** will be calculated as the proportion of patients who have either a CTC 30% response or an objective response after at least 1 dose of study treatment and prior to or on the end of treatment or C1D1 of cross over time. A 2-sided 95% Clopper-Pearson CIs will also be reported using the Clopper Pearson exact method for binomial proportions.

7.3.14.2 Secondary Efficacy Variables

Secondary efficacy variables at the Randomized Phase 2 include the following,

- **rPFS**

[redacted]

rPFS is defined as time from Day 1 of treatment to the first event of radiographic progression per PCWG3 by central radiology review or death, whichever is the earlier, prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time (if applicable). Otherwise, subjects will be censored at the earliest of the following dates: (1) the date of last study visit; or (2) the date of study discontinuation, (3) C1D1 of cross-over time.

To compare rPFS between the combination arm and control arm in the Randomized Phase 2 trial, the log-rank method using the chi-square test will be performed and KM curve will be plotted. For such a comparison, the hazard ratio and its corresponding 2-sided 95% CIs will also be estimated based on the Cox-regression with the treatment as the only fixed factor in the model. KM curve will be plotted to demonstrate the probability of remaining event free over time in the Single Arm Phase 2 trial.

The proportion with its corresponding 2-sided 95% CIs for patients who remain radiographic progression free at 3 months will also be calculated using the Kaplan-Meier method .

- **Time to PSA progression**

  Time to PSA progression is defined as from D1 of treatment to the date of PSA progression per lab data prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time (if applicable). Otherwise, subjects will be censored at the earliest of the following dates: (1) the date of death; (2) the date of last study visit; (3) the date of study discontinuation, (4) C1D1 of cross-over time To compare time to PSA progression between the combination arm and control arm in the Randomized Phase 2 trial, the log-rank method using the chi-square test will be performed and KM curve will be plotted. For such a comparison the hazard ratio and its corresponding 2-sided 95% CIs will be estimated based on the Cox-regression with the treatment as the only fixed factor in the model.

- In patients with measurable soft tissue disease, **ORR** will be calculated as the proportion of patients with a confirmed CR or PR per PCWG3. ORR with its corresponding 2-sided 95% Clopper-Pearson CIs will be reported using the Clopper Pearson exact method for binomial proportions. To compare ORR between the combination arm and control arm in the Randomized Phase 2 trial, difference in ORR will be calculated along with a 2-sided exact 95% CIs. DOR is defined as the time from the date of first CR or PR (whichever status is recorded first) per PCWG3 to the first date of radiographic progression documented prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time. Otherwise, subjects will be censored at the earliest of the following dates: (1) the date of

[redacted]

last study visit; or (2) the date of study discontinuation, (3) C1D1 of cross-over time. **DOR** will be estimated using the KM method. To compare DOR between the combination arm and control arm in the Randomized Phase 2 trial, the log-rank method using the chi-square test will be performed and KM curve will be plotted. For such a comparison the hazard ratio and its corresponding 2-sided 95% CIs will also be estimated based on the Cox-regression with the treatment as the only fixed factor in the model.

- In patients with measurable disease in non-parenchymal soft tissue, **ORR (excluding parenchymal lesions)** will be calculated as the proportion of patients with a confirmed CR or PR per PCWG3 in soft tissue excluding the parenchyma. ORR (excluding parenchymal lesions) with its corresponding 2-sided 95% Clopper-Pearson CIs will be reported using the Clopper Pearson exact method for binomial proportions. To compare ORR (excluding parenchymal lesions) between the combination arm and control arm in the Randomized Phase 2 trial, difference in above proportions will be calculated along with a 2-sided Exact 95% CIs. **DOR (excluding parenchymal lesions)** will be estimated using the KM method. To compare DOR (excluding parenchymal lesions) between the combination arm and control arm in the Randomized Phase 2 trial, the log-rank method using the chi-square test will be performed and KM curve will be plotted. For such a comparison the hazard ratio and its corresponding 2-sided 95% CIs will also be estimated based on the Cox regression with the treatment as the only fixed factor in the model.
- In patients with measurable soft tissue disease, **composite response rate** will be calculated as the proportion of patients who have either a PSA 50% response (a ≥50% reduction in PSA from baseline) or an objective response (CR or PR per PCWG3). To compare above composite response rate between the combination arm and control arm in the Randomized Phase 2 trial, the difference in proportions will be calculated along with a 2-sided 95% Clopper-Pearson CIs.
- In patients with unfavorable CTCs, **composite response rate** will be calculated as the proportion of patients who have either a PSA 50% response (a ≥50% reduction in PSA from baseline) or a CTC 30% response (≥30% reduction in CTCs from baseline). To compare above composite response rate between the combination arm and control arm in the Randomized Phase 2 trial, the difference in proportions will be calculated along with a 2-sided 95% Clopper-Pearson CIs.
- **Time to first SRE** will be assessed using KM methods the time from D1 of treatment to the date of first SRE prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time, or the

[redacted]

earliest of the following dates: (1) the date of death; (2) the date of last study visit; (3) the date of study discontinuation; (4) C1D1 of cross-over time.

To compare Time to first SRE between the combination arm and control arm in the Randomized Phase 2 trial, the log-rank method using the Chi-square test will be performed and KM curve will be plotted. For such a comparison the hazard ratio and its corresponding 2-sided 95% CIs will also be estimated based on the Cox-regression with the treatment as the only fixed factor in the model.

- **Time to unequivocal clinical progression** will be assessed using KM methods as the time from D1 of treatment to the date of unequivocal clinical progression prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time, or the earliest of the following dates: (1) the date of death; (2) the date of last study visit; (3) the date of study discontinuation; (4) C1D1 of cross-over time. To compare the time to unequivocal clinical progression between the combination arm and control arm in the Randomized Phase 2 trial, the log-rank method using the Chi-square test will be performed and KM curve will be plotted. For such a comparison the hazard ratio and its corresponding 2-sided 95% CIs will also be estimated based on the Cox regression with the treatment as the only fixed factor in the model.
- **Time to initiation of new systemic treatment for prostate cancer** will be assessed using KM methods as the time from D1 of treatment to the date any new systemic treatment for prostate cancer is initiated prior to C1D1 of cross-over time, or the earliest of the following dates: (1) the date of death; (2) the date of last study visit; (3) the date of study discontinuation; (4) C1D1 of cross-over time,. To compare time to initiation of new systemic treatment for prostate cancer between the combination arm and control arm in the Randomized Phase 2 trial, the log-rank method using the Chi-square test will be performed and KM curve will be plotted. For such a comparison the hazard ratio and its corresponding 2-sided 95% CIs will also be estimated by the Cox-regression with the treatment as the only fixed factor in the model.

[redacted]

[redacted]

- **Time to pain progression** will be assessed using KM methods as the time from D1 of treatment to the date of pain progression prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time, or the earliest of the following dates: (1) the date of death; (2) the date of last study visit; (3) the date of study discontinuation; (4) C1D1 of cross-over time. **Time to opioid analgesics** will be assessed using KM methods as the time from D1 of treatment to the date of first opioid usage prior to or on the initiation of new anti-cancer therapy or C1D1 of cross-over time, or the earliest of the following dates:(1) the date of death; (2) the date of last study visit; (3) the date of study discontinuation; (4) C1D1 of cross-over time. To compare time to pain progression and time to opioid analgesics between the combination arm and control arm in the Randomized Phase 2 trial, the log-rank method using the Chi-square test will be performed and KM curve will be plotted. For such a comparison, the hazard ratio and its corresponding 2-sided 95% CIs will also be estimated by the Cox regression with the treatment as the only fixed factor in the model.
- In patients with unfavorable CTCs (five or more cells per 7.5mL of blood), **CTC conversion rate** will be calculated as the proportion of patients who convert to favorable status (four or fewer cells per 7.5mL of blood). To compare CTC conversion rate between the combination arm and control arm, the difference in proportions will be calculated along with a 2-sided Exact 95% CIs.
- In patients with unfavorable CTCs (five or more cells per 7.5mL of blood), **CTC 30% response rate** will be calculated as the proportion of patients who have a ≥30% reduction in CTCs from baseline. To compare CTC 30% response rate between the combination arm and control arm, the difference in proportions will be calculated along with a 2-sided Exact 95% CIs.
- **OS** will be assessed using KM methods as the time from D1 of treatment to the date of death during the trial. To compare OS between the combination arm and control arm in the Randomized Phase 2 trial, the log-rank method using the Chi-square test will be performed and KM curve will be plotted. For such a comparison the hazard ratio and its corresponding 2-sided 95% CIs will also be estimated by the Cox-regression with the treatment as the only fixed factor in the model.

[redacted]

7.3.15 Safety Analysis

7.3.15.1 Adverse Events

The verbatim AE terms will be coded using the latest available version of Medical Dictionary Regulatory Activities (MedDRA, Version 22.1 or later) and will be classified by system organ class (SOC) and preferred term.

Unless specified otherwise, counts of AEs will be the number of patients reporting adverse events and not the number of events reported. If the same AE (SOC or preferred term) is reported multiple times for the same patient, it will only appear once for that specified treatment and category in the summary tables.

For patients with multiple adverse events of the same preferred term and of different severities, the AE with the highest assessment of severity will be used in the summaries presented by severity.

For purposes of the summary tables, AEs will be classified as either being related to study drug or not related. For patients with multiple adverse events of the same preferred term and of different relationship, the AE with the strongest assessment of relationship will be used in the summaries presented by relationship.

Treatment-emergent AEs are defined as any AEs that occurs after administration of the first dose of study treatment and through 30 days after the last dose of study medication, any event that is considered drug related regardless of the start date of the event, or any event that is present at baseline but worsens in severity after baseline or is subsequently considered drug-related by the investigator.

TEAEs will be presented as frequencies and percentages by treatment group including the following categories:

- Any TEAEs
- Drug-related TEAEs
- TEAEs with CTCAE Grade 3 or above
- Drug-related TEAEs with CTCAE Grade 3 or above
- Most Frequently Report (≥10%) TEAEs
- SAEs

[redacted]

- Drug-related SAEs
- TEAEs Leading to Death
- TEAEs Leading to Discontinuation of Study Drug CPI-1205
- TEAEs Leading to Dose Reduction of Study Drug CPI-1205
- TEAEs Leading to Dose Interruption of Study Drug CPI-1205

All AEs including those occurred after C1D1 of cross-over time and initiation of anti-cancer therapy will be listed by treatment group, subject and visit.

7.3.15.2 Clinical Safety Laboratory Tests

Abnormal laboratory values will be graded by the CTCAE v 4.03 for gradable tests. Descriptive statistics (n, mean, standard deviation, median and range) of the parameters in Hematology, Chemistry, Coagulation, Thyroid function and Endocrinology and the changes from baseline will be presented by treatment group prior to C1D1 of cross-over time. For randomized Phase 2, such descriptive summary will also be presented by treatment group after C1D1 of cross-over time. Baseline of cross-over will be C1D1 – CR or last assessment prior to cross-over if C1D1 – CR is not available.

In the shift table for the parameters in Hematology, Chemistry and Coagulation based on being lower than a lower normal limit (worst low), a value above the upper normal limit will be considered as grade 0. The shift table for high worst is defined similar. For randomized Phase 2, such one shift table will also be presented by treatment group after C1D1 of cross-over time. Baseline of cross-over will be C1D1 – CR or last assessment prior to cross-over if C1D1 – CR is not available.

Mean laboratory values over time will be plotted for key laboratory parameters.

The data of clinical laboratory tests including those after C1D1 of cross-over time will be listed by treatment group, subject and visit.

7.3.15.3 Vital Signs

Descriptive statistics for the actual values and the changes from baseline of vital signs over time will be tabulated by treatment group and visit, prior to or on the initiation of new anti-cancer therapy or C1D1

[redacted]

of cross over time. For randomized Phase 2, such descriptive summary of the actual values and the changes from baseline of vital signs will also be presented by treatment group after C1D1 of cross-over time. Baseline of cross-over will be C1D1 – CR or last assessment prior to cross-over if C1D1 – CR is not available.

The data of vital signs including those after C1D1 of cross-over time will be listed by treatment group, subject and visit.

7.3.15.4 Twelve-Lead Electrocardiogram

Baseline is defined as the mean of the last three non-missing triplicate assessments before dosing. The average value of multiple measurements at a visit prior to C1D1 of cross-over time will be used in the summary tables as well as in calculation of change from baseline.

Normal, abnormal, or abnormal clinically significant ECGs will be summarized by treatment group and visit.

Number and percentage of subjects with maximum post-dose QTcF values of <=450, >450 ms and <=480, >480 ms and <=500, and >500 ms, and maximal change from baseline values of <=30, >30 <=60ms, and >60 ms will be summarized by treatment group.

The data of ECG including those after C1D1 of cross over will be listed by treatment group, subject and visit.

7.3.15.5 Physical Examination

Number and percentage of patients with abnormal results will be summarized by treatment group, visit and body system. The data for physical examination will be listed by treatment group, subject and visit.

7.3.15.6 ECOG

ECOG performance will be summarized by treatment group, visit and performance status. ECOG performance will be listed by treatment group, subject and visit.

Change in ECOG from baseline over time prior to C1D1 of cross-over time will be summarized by treatment group, visit and performance status.

[redacted]

The data of ECOG including those after C1D1 of cross over will be listed by treatment group, subject and visit.

[redacted]

[redacted]

8. REFERENCES

[1] G. e. a. Bubley, "Eligibility and response guidelines for phase II clinical Prostate-Specific Antigen Working Group," Clin Oncol, vol. 17, no. 11, pp. 3461-7, 1999.

[2] H. e. a. Scher, "Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3," J Clin Oncol, vol. 34, no. 12, pp. 1402-18, 2016.

[3] E. e. a. Eisenhauer, "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)," Eur J Cancer, vol. 45, no. 2, pp. 228-47, 2009.

[4] "Protocol: A Phase 1b/2 Study of CPI-1205, a Small Molecule Inhibitor of EZH2, Combined with Enzalutamide or Abiraterone/Prednisone in Patients with Metastatic Castration Resistant Prostate. Version 4.0". 26 July 2018.

[5] Brookmeyer R. and Crowley J. A Confidence Interval for the Median Survival Time. Biometrics 1982; 38:29-41.

[6] Kalbfleisch JD, Prentice RL: The Statistical Analysis of Failure Time Data. New York, John Wiley & Sons, 1980.