Protocol Number: TROV-053

Official Title: A Phase 2 Study of Onvansertib (PCM-075) in Combination with Abiraterone and Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer

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CARDIFF ONCOLOGY

STATISTICAL ANALYSIS PLAN

Protocol Title: A PHASE 2 STUDY OF ONVANSERTIB (PCM-075) IN COMBINATION WITH ABIRATERONE AND PREDNISONE IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Protocol Number: TROV-053

Phase: Phase 2

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SAP Date: 18MAY2023

Status: FINAL v1.0

SUMMITANALYTICAL	**AD ST-07** **Statistical Analysis Plan Approval Form**

Sponsor: Cardiff Oncology, Inc.
Protocol: TROV-053
Protocol Title: A PHASE 2 STUDY OF ONVANSERTIB (PCM-075) IN COMBINATION WITH ABIRATERONE AND PREDNISONE IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

SAP Version: FINAL v1.0
SAP Date: 18MAY2023

The statistical analysis plan has been reviewed and approved.

Sponsor:
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Cardiff Oncology, Inc.

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Signature Date

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[redacted] 19-May-2023

Signature Date

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2. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Only abbreviations and terms relevant to the SAP are repeated herein. The reader is referred to the protocol for the complete and comprehensive list of abbreviations and definitions of terms for the study.

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse Event
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical study report
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
MedDRA	Medical Dictionary for Regulatory Activities
mCRPC	Metastatic Castration-Resistant Prostate Cancer
mL	Milliliter
PBMCs	Peripheral blood mononuclear cells
PFS	Progression-free survival
PK	Pharmacokinetic
PLK1	Polo-Like Kinase 1
PSA	Prostate-specific antigen
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System Organ Class
TNM	Tumor, lymph nodes, metastasis
WHO-DD	World Health Organization – Drug Dictionary

3. INTRODUCTION

3.1. Preface

This document presents a statistical analysis plan (SAP) for Cardiff Oncology's Protocol TROV-053 (*A Phase 2 Study of Onvansertib (PCM-075) in Combination with Abiraterone and Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer*).

Reference materials for this statistical plan include the protocol (Version 1.8 Dated: 13Nov2020) and Case Report Forms (dated: 3JUN2020).

The SAP described hereafter is an *a priori* plan. The SAP will be finalized and approved prior to database lock. Statistical programming may occur as study data accumulate in order to have analysis programs ready at the time the study finishes.

For the reasons stated here the conduct of the study in the field is considered to be independent of any study outcome that might materialize upon enactment of the currently proposed statistical plan.

3.2. Purpose of Analyses

The purposes of the planned analyses described in this SAP are to assess the efficacy and safety profiles of onvansertib (PCM-075) in combination with abiraterone acetate (abiraterone) and prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) with early progressive disease (PSA rise but minimally symptomatic or asymptomatic) and currently receiving androgen deprivation therapy plus abiraterone and prednisone. Results from the analyses completed will be included in the final clinical study report (CSR) for TROV-053, and may also be utilized for regulatory submissions, manuscripts, or other clinical development activities.

Post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study data. These analyses will be clearly identified, where appropriate, in the final CSR. Additional analyses not prospectively identified in this SAP may also be completed for publications, or regulatory or funding inquiries. These analyses, if performed, may not be reported in the CSR, but will be fully documented in the document containing the additional analyses.

3.3. Summary of Statistical Analysis Changes to the Protocol

Exploratory endpoints are not included in this SAP.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Study Objectives

4.1.1. Primary Objective

- To observe the effects of onvansertib (study drug) in combination with abiraterone and prednisone on disease control as assessed by prostate-specific antigen (PSA) decline or stabilization in patients with mCRPC currently receiving abiraterone and prednisone.

4.1.2. Secondary Objectives

Efficacy:
To observe the effects of onvansertib (study drug) in combination with abiraterone and prednisone in patients with mCRPC on the following:

1) Change in PSA relative to baseline.
2) Time to PSA progression.
3) Time to radiographic progression based on the Prostate Cancer Working Group 3 (PCWG3) guidelines.
4) Radiographic response (per Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria) in patients with measurable disease.
5) Disease control as assessed by prostate-specific antigen (PSA) decline or stabilization in patients currently receiving abiraterone and prednisone who are adherent to study treatment.

Safety:
To assess the safety of onvansertib (study drug) in combination with abiraterone and prednisone in patients with mCRPC.

4.2. Study Endpoints

4.2.1. Primary Efficacy Endpoint

Proportion of patients achieving disease control after 12 weeks of study treatment, as defined by lack of PSA progression (per PCWG3 criteria)

4.2.2. Secondary Endpoints

Efficacy

- Change in PSA at 12 weeks, as a percentage of baseline
- Maximal change in PSA, as a percentage of baseline
- Best PSA response, as an absolute change relative to baseline
- Time to PSA progression (per PCWG3 criteria)

- Time to radiographic progression (per PCWG3)
- Radiographic response (RECIST 1.1) in patients with measurable disease
- Proportion of patients who are adherent to study treatment (per-protocol analysis) achieving disease control after 12 weeks of study treatment, as defined by lack of PSA progression (per PCWG3 criteria)

Safety

- Safety, as per Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
- Number of reported DLTs when combining onvansertib (study drug) with abiraterone

5. STUDY METHODS

5.1. General Study Design and Plan

As background for the statistical methods presented below, this section provides an overview of the study design and plan of study execution. The protocol is the definitive reference for all matters discussed in what follows.

This is a multicenter, open-label, Phase 2 study of the safety and efficacy of onvansertib (study drug) in combination with the standard dose of abiraterone and prednisone in patients with mCRPC. Patients who enter the study will have early progressive disease (PSA rise but minimally symptomatic or asymptomatic) currently receiving androgen-deprivation therapy plus abiraterone and prednisone.

This study will consist of a Screening Period, a Treatment Period conducted in 21-day treatment cycles (Arm A terminated after Protocol v1.5), 14-day cycles (Arm B), and 21-day cycles (Arm C added after Protocol v1.5), and End-of-Study (EOS) Visit.

This study initially had two arms, Arm A conducted in a 21-day treatment cycle and Arm B conducted in a 14-day treatment cycle. The Principal Investigator and Sponsor have made the decision to discontinue Arm A and to add Arm C to this study. The study continues with two arms, each with a different dosing schedule. Arm B is a 14-day treatment cycle, with study drug (onvansertib at 24 mg/m2 QD) administered on Days 1-5 of each cycle. Arm C is a 21-day treatment cycle, with study drug (onvansertib at 12 mg/m2 QD) administered on Days 1-14 of each cycle.

Any patients enrolled and continuing on treatment in Arm A can transition to Arm B (with a re-consent) at the start of their next cycle and at the discretion of the Investigator.

In Arm A, prostate-specific antigen (PSA) levels are collected at baseline, on Day 1 of the first 5 cycles, and on Day 8 and Day 15 during cycles 1 through 4. PSA levels are also collected every 3 months after cycle 5 and at end-of-trial (EOT). Radiographic imaging will be obtained after every 4 cycles.

In Arm B, PSA levels are collected at baseline and on Days 1 and 8 of the first 6 cycles. PSA levels are also collected on Day 1 of each cycle after Cycle 6 and at EOT. Radiographic imaging will be obtained after every 6 cycles.

In Arm C, PSA levels are collected at baseline and on Days 1, 8 and 15 of the first 4 cycles. PSA levels are also collected on Day 1 of each cycle after Cycle 4 and at EOT. Radiographic imaging will be obtained every 4 cycles.

End-of-Study evaluations are required within 28 days of the last dose of onvansertib. Follow-up information will be collected via voice or written contact approximately every 6 weeks until disease progression from patients with stable disease or better at the end of treatment assessments.

The schedule for assessments when Arm A is still enrolling is presented in Table 1; the schedule of assessments when Arm A is no longer enrolling, but Arm C added is presented in Table 2.

Table 1 Schedule of Assessments (Arm A)

Event	Screening ≤ 28 days prior to enrollment	On Treatment			End of Study[m]
		Day 1	Day 8 (may be conducted at local lab except during cycle 1)	Day 15 (may be conducted at a local lab)	
Informed consent	X				
Confirmation of all eligibility criteria	X				
Medical history[a]	X				X
Prior systemic and radiation therapy[b]	X				
Physical examination[c]	X	X			X
ECOG performance status	X	X			X
Concomitant medication review	X	X			X
Adverse Event review	X	X			X
Triplicate 12-lead ECG (performed sequentially - no mandated time frame)	X		X (cycle 1 only)		
Clinical chemistry[d]	X	X			
Hematology, including CBC with differential, and platelet count[d]	X	X	X	X	
Blood samples for pharmacodynamic assessment[e]		X (pre- & post-drug administration cycle 1 only)			
Prostate-specific antigen[f]	X	X	X	X	X
Blood samples for circulating tumor DNA (ctDNA)[g]		X			X
Blood samples for circulating tumor cells (CTCs)[h]		X			

Blood samples for ARV7 test[i]		X (cycle 1 only)			
Radionuclide bone scan and CT of abdomen/pelvis with contrast[j]	X	X			
PCM-075 administration[k]		Days 1-5			
Abiraterone and prednisone administration[l]		Days 1-21			

Abbreviations: AE=adverse event; CBC=complete blood count; ECOG=Eastern Cooperative Oncology Group (performance score); EOS=end-of-study.

[a] Medical history: including relevant medical history collection, as well as Gleason score and TNM stage at diagnosis

[b] Collect radiation site, administered dose per fraction and treatment duration.

[c] Physical examination includes height (at screening only), weight, vital signs, and general physical examination

[d] Blood chemistry panel includes sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, blood urea nitrogen, creatinine, glucose, albumin, alkaline phosphatase, total bilirubin, AST, ALT. Testosterone will be drawn during screening to confirm castration but does not need to be repeated after screening. CBC at Day 8 (Arm A and B) and 15 (Arm A) will be collected only for the first 12 weeks. CBC and chemistry testing may occur up to 48 hours prior to days 1, 8 and 15. All visits have a +/- 3-day window.

[e] Blood samples for pharmacodynamic and diagnostic biomarker analysis will be obtained pre-dose and 1.5-hour post dose (all ±10 minutes) after administration of PCM-075 on Day 1 of Cycle 1. These blood samples will be collected in one 10-mL CellSave tube at each draw (and sent to Trovagene overnight at ambient temperature).

[f] Prostate-specific antigen must have been performed on 2 occasions at least one week apart to document progression of disease prior to or during the screening window. In Arm A, prostate-specific antigen (PSA) levels will be collected at baseline, on Day 1 of the first 5 cycles, and on Day 8 and Day 15 during cycles 1-4. In Arm B, prostate-specific antigen (PSA) levels will be collected at baseline, on Day 1 of first 7 cycles, and Day 8 of cycles 1-6. PSA levels will also be collected every 3 months after cycle 5 (Arm A) and cycle 7 (Arm B) and at end-of-trial (EOT).

[g] Blood for ctDNA assessment to be collected on Day 1 (pre-dose) of each cycle, and at EOS. At each timepoint, blood will be collected in three 10-mL Streck tubes (for overnight delivery to Trovagene). ctDNA samples may be collected any time before dosing. PCM-075 does not need to be taken in clinic on these days.

[h] In Arm A, blood for CTC assessment to be collected on Day 1 (pre-dose) of Cycles 1, 3 and 5. In Arm B, blood for CTC assessment to be collected on Day 1 (pre-dose) of Cycles 1, 4 and 7. At each timepoint, blood will be collected in one 10-mL Streck tube (for delivery overnight to Epic Sciences).

[i] Blood samples for AR-V7 assessment to be collected on Day 1 (pre-dose) of Cycle 1 only. The blood samples will be collected in three 8.5 mL BD Vacutainer ACD Solution A tubes for overnight delivery to Johns Hopkins Genomics (MDL).

[j] In Arm A, radiographic imaging will be obtained after every 4th cycle until EOS. In Arm B, radiographic imaging will be obtained after every 6th cycle until EOS. Radiographic imaging includes CT abdominal/pelvis with contrast (or MRI if contraindication to intravenous contrast) and bone scan. Radiographic imaging may occur up to 7 days prior to day 1.

[k] Patients will take PCM-075 on Days 1 through 5 (Arm A and Arm B) of each cycle. PCM-075 will be dosed in the clinic on day 1 of cycles 1 and 2 but otherwise will be taken at home.

[l] Patients will take abiraterone and prednisone continuously throughout the study. Abiraterone should be brought from home on day 1 of cycles 1 and 2 and not taken until PCM-075 is administered (after pre-dosing bloods have been drawn). Otherwise, all medications will be taken at home.

[m] End of study assessments should be conducted within 28-days after the last dose of PCM-075.

Table 2 Schedule of Events (Arm B and Arm C)

Event	Screening ≤ 28 days prior to enrollment	On Treatment (Arm B: 14-Day Cycles and Arm C: 21-day Cycles)			End of Study[m]
		Day 1 (± 3 days, except Cycle 1)	Day 8 (± 3 days) (may be conducted at local lab except during Cycle 1)	Day 15 (± 3 days) (Arm C only and may be conducted at local lab except during Cycle 1)	
Informed consent	X				
Confirmation of all eligibility criteria	X				
Medical history[a]	X				X
Prior systemic and radiation therapy[b]	X				
Physical examination[c]	X	X			X
ECOG performance status	X	X			X
Concomitant medication review	X	X			X
AE review		X			X
Triplicate 12-lead ECG (performed sequentially - no mandated time frame)	X		X (Cycle 1 only)		
Clinical chemistry[d]	X	X			

Event	Screening ≤ 28 days prior to enrollment	On Treatment (Arm B: 14-Day Cycles and Arm C: 21-day Cycles)			End of Study[m]
		Day 1 (± 3 days, except Cycle 1)	Day 8 (± 3 days) (may be conducted at local lab except during Cycle 1)	Day 15 (± 3 days) (Arm C only and may be conducted at local lab except during Cycle 1)	
Hematology, including CBC with differential, and platelet count[d]	X	X	X	X	
Prostate-specific antigen[e]	X	X	X	X	X
Blood samples for ctDNA[f]	X	X (Cycles 2 to 7 for Arm B, Cycles 2 to 5 for Arm C)			X
Blood samples for CTCs[g]		X (Cycle 1 only)			
Blood samples for AR-V7 test[h]		X (Cycle 1 only)			
Blood samples for CTC enumeration[i]		X (Cycle 1 and Cycle 7 for Arm B; Cycle 1 and Cycle 5 for Arm C)			X[i]
Radionuclide bone scan and CT of abdomen/pelvis with contrast[j]	X	X[j]			
Onvansertib administration[k]		Days 1-5 (Arm B) and Days 1-14 (Arm C)			
Abiraterone and prednisone administration[l]		Days 1-14 (Arm B) and Days 1-21 (Arm C)			

AE=adverse event; CBC=complete blood count; CT=computed tomography; CTC=circulating tumor cell; ctDNA=circulating tumor DNA; ECOG=Eastern Cooperative Oncology Group (performance score); EDTA=Ethylenediaminetetraacetic acid; EOS=end-of-study; MRI=magnetic resonance imaging
Note: all study visits have a ± 3 day window except Cycle 1 Day 1.

[a] Medical history: including relevant medical history collection, as well as Gleason score and TNM stage at diagnosis.
[b] Collect radiation site, administered dose per fraction and treatment duration.
[c] Physical examination includes height (at screening only), weight, vital signs, and general physical examination.
[d] Blood chemistry panel includes sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, blood urea nitrogen, creatinine, glucose, albumin, alkaline phosphatase, total bilirubin, AST, ALT. Testosterone will be drawn during screening to confirm castration but does not need to be repeated after screening. CBC at Day 8 (Arms B and C) and Day 15 (Arm C) will be collected only for the first 12 weeks. CBC and chemistry testing may occur up to 48 hours prior to the Days 1, 8, and 15 visits.
[e] Prostate-specific antigen (PSA) must have been performed on 2 occasions at least one week apart to document progression of disease prior to or during the screening window. PSA levels will be collected at baseline, on Days 1 and 8 of first 6 cycles for Arm B and on Days 1, 8, and 15 of the first 4 cycles for Arm C. PSA levels will also be collected on Day 1 of each cycle after Cycle 6 (Arm B) or after Cycle 4 (Arm C) and at end-of-study (EOS).
[f] Blood for ctDNA assessment to be collected during screening, and on Day 1 (predose) of Cycles 2 to 7 (Arm B) or Cycles 2 to 5 (Arm C), and at EOS. At each time point, blood will be collected in three 10-mL Streck tubes (for overnight delivery to Cardiff Oncology). ctDNA samples may be collected any time before dosing. Onvansertib does not need to be taken in clinic on these days.
[g] Blood for CTC assessment to be collected on Day 1 (predose) of Cycle 1 only. Blood will be collected in one 10-mL Streck tube (for delivery overnight to Epic Sciences) and in two 10-mL EDTA tubes (for same day delivery to David Miyamoto laboratory).
[h] Blood samples for AR-V7 assessments to be collected on Day 1 (predose) of Cycle 1 only. The blood samples will be collected in three 8.5 mL BD Vacutainer ACD Solution A tubes for overnight delivery to Johns Hopkins Genomics (MDL). If the samples arrive more than 24 hours after collection to MDL, the samples will be collected again during the next visit.
[i] Blood samples for CTC enumeration using the CellSearch assay to be collected on Day 1 (predose) of Cycle 1 (both arms), Day 1 of Cycle 7 (Arm B), and Day 1 of Cycle 5 (Arm C). For patients discontinuing before Cycle 7 (Arm B) and Cycle 5 (Arm C), samples will be collected at EOS. The blood samples will be collected in two 10-mL CellSave tubes for overnight delivery to Michigan Medicine Laboratories.
[j] Radiographic imaging will be obtained at screening and on Day 1 after every 6th cycle for Arm B (eg, Day 1 of Cycle 7, Day 1 of Cycle 13, Day 1 of Cycle 19) and after every 4th cycle for Arm C (eg, Day 1 of Cycle 5, Day 1 of Cycle 9, Day 1 of Cycle 13) until EOS. Radiographic imaging includes CT abdominal/pelvis with contrast (or MRI if contraindication to intravenous contrast) and bone scan. Radiographic imaging may occur up to 7 days prior to Day 1.
[k] Patients will take onvansertib on Days 1 through 5 of each cycle in Arm B and on Days 1 through 14 of each cycle in Arm C. Onvansertib will be dosed in the clinic on Day 1 of Cycle 1 but otherwise will be taken at home.
[l] Patients will take abiraterone and prednisone continuously throughout the study. **Abiraterone should be brought from home on Day 1 of Cycle 1 and not taken until onvansertib is administered (after predosing blood samples have been drawn).** Otherwise, all medications will be taken at home.
[m] End of study assessments should be conducted within 28 days after the last dose of onvansertib.

5.2. Randomization and Blinding

There is no randomization or blinding in this study.

6. SAMPLE SIZE

This is a 3 arm study that consists of determining the disease control rate of onvansertib (study drug) in combination with abiraterone and prednisone in patients with mCRPC. A 30% disease-control rate will be considered clinically relevant for further evaluation.

The trial will begin with a safety lead-in phase. Safety data for the initial 3 patients in each arm will be reviewed by the Investigators and the Sponsor for evaluation of DLTs. If no DLTs or other unacceptable safety events have occurred in the first 3 patients during the safety lead-in phase, dosing of subsequent patients may begin, and an additional 29 patients in each arm will be enrolled at the same dose level. If 1 DLT is observed in the first 3 patients enrolled, an additional 3 patients may be enrolled if deemed safe. If no further DLTs occur in these 3 additional patients, dosing may begin for subsequent patients. An additional 27 patients will be treated in each arm at the same dose level. Two dose reductions are allowed for the study in each arm. If 2 DLTs occur in the first 3 patients, or if an additional DLT occurs among the 3 additional patients enrolled, the dose of onvansertib (study drug) will be reduced by 25% (Arm B – 18 mg/m2; Arm C – 9 mg/m2) and dosing of an additional 3 lead-in patients will begin in identical fashion as described above. If 2 or more DLTs occur in up to 6 patients at a 12mg/m2 (Arm B), or 6 mg/m2 (Arm C) all enrollment in that arm of the study will be discontinued (details can be found in Section 8.1.2). If 2 or more DLTs occur in up to 6 patients in both arms, all enrollment in the study will be discontinued.

The original study design prior to Protocol v1.8 included 2 study arms rather than the current 3 study arms. Accordingly, the original sample size calculation was based on only 2 study arms, as described below.

A maximum of 90 patients (45 in each arm) will be enrolled to ensure 32 evaluable patients in each arm at the recommended dose level will be included in the efficacy analysis.

The probability of seeing 0 DLTs in the first 3 patients is 73% if the true, but unknown, rate of DLTs is 0.1. The probability of calling the dose level safe is 91% if the true but unknown rate of DLT is 0.1.

Based on Simon's two-stage optimal design, 32 patients are required in each arm to detect a 30% disease-control rate, assuming that the null hypothesis is 10% with 90% power and 8% type I error. The study arm will terminate early if 0 or 1 out of the first 13 patients achieve disease control at 12 weeks. Assuming the study continues to full enrollment, if 6 or more out of a total of 32 patients achieve disease control at 12 weeks, the experimental treatment will be considered potentially effective. The probability of stopping at the first stage is 0.62. At any time during the study, the principal investigator and sponsor can decide to move forward with the treatment arm that is assessed to be most effective and safe; however, no direct statistical comparison will be performed between treatment arms.

7. GENERAL CONSIDERATIONS

7.1. Analysis Populations

There will be four (4) analysis populations defined for this study.

7.1.1. Efficacy Population

The Efficacy Population includes all patients who receive at least one dose of study drug at the final recommended dose according to their arm assignments. Replaced patients are not included (note that at the time of SAP finalization, no patients had been replaced). The Efficacy Population will be used for the primary efficacy analysis.

Should patients transition from the treatment arm in which they were initially enrolled to one of the other treatment arms, efficacy analysis will be based on the original treatment arm assignment.

7.1.2. 100% Per-Protocol Population (100% PP)

100% PP Population will consist of patients who have been administered 100% of the originally assigned study drugs in at least one full cycle, and without major protocol deviations. Replaced patients are not included. This population will be used to conduct all secondary efficacy analyses.

Should a patient transition from the treatment arm in which they were initially enrolled to one of the other treatment arms, efficacy analysis will be based on the original treatment arm assignment.

7.1.3. 90% Per-Protocol Population (90% PP)

90% PP Population will consist of patients who have taken 90% or more of the originally assigned study drugs in at least one full cycle, and without major protocol deviations. Replaced patients are not included. This population will be used to conduct all secondary efficacy analyses.

Should a patient transition from the treatment arm in which they were initially enrolled to one of the other treatment arms, efficacy analysis will be based on the original treatment arm assignment.

7.1.4. Safety Population

Includes all patients who receive any dose of study drug. Replaced patients will be included if dosed. This population will be used to conduct all safety analyses. Patients in Arm A who have transitioned to other dosage levels and those who have not transitioned will be presented separately.

7.2. Covariates and Subgroups

7.2.1. Planned Covariates

There is no covariate variable in this study.

7.2.2. Subgroup

There are no subgroup analyses in this study.

7.3. Management of Analysis Data

7.3.1. Handling of Unscheduled Assessments

For safety labs, ECG and vital signs, unscheduled tests within the visit windows as noted in the column names of Table 1 and Table 2 will be included at the nearest regularly scheduled test. If there is a scheduled test and one or more unscheduled tests assigned to the same time point, the most conservative test (i.e., a test with low or high results) will be used. This applies to continuous change from baseline analyses. Visits that are not within visit windows will not be included in table summaries.

Note unscheduled PSA results will be handled differently depending on specific efficacy analyses and sometimes may be included. Details see Section 9.2.

7.3.2. Handling of Assessment from Discontinuation Visit

If a patient has terminated prior to week 12 visit and has not achieved disease control, he will be considered as not having achieved disease control at week 12 (conservatively) for the primary efficacy endpoint.

For safety measures, early termination visits will be handled like other scheduled visits if it occurs on a scheduled visit, otherwise as an unscheduled visit will be handled as described in Section 7.3.1.

7.3.3. Replacement Patients

Patients who are discontinued prior to completing the first treatment cycle for any reason other than toxicity, or who have not received at least 80% of the intended doses, may be replaced.

Replaced patients will be included/excluded from study populations according to the definitions provided in Section 7.1.

7.3.4. Missing Data

In general, there will be no imputations made to accommodate missing data points. All data recorded on the case report form (CRF) and laboratory transfers will be included in data listings that will accompany the clinical study report.

7.3.4.1. Handling of Missing Date Values

Partial or Missing Dates

The following conventions will be used to impute missing portions of dates for adverse events, concomitant medications and date of diagnosis, if warranted. Note that the imputed values outlined here may not always provide the most conservative date. In those circumstances, the imputed value may be replaced by a date that will lead to a more conservative analysis.

1. Start Dates
    a. If the year is unknown, then the date will not be imputed and will be assigned a missing value.
    b. If the month is unknown, then:
        i. If the year matches the first dose date year, then impute the month and day of the first dose date
        ii. Otherwise, assign 'January.'
    c. If the day is unknown, then:
        i. If the month and year match the first dose date month and year, then impute the day of the first dose date.
        ii. Otherwise, assign the first day of the month.
2. Stop Dates
    a. If the year is unknown, then the date will not be imputed and will be assigned a missing value
    b. If the month is unknown, then assign 'December.
    c. If the day is unknown, then assign the last day of the month.

7.3.5. Pooling of Study Centers

The data from multiple study centers will be pooled for data analyses.

7.3.6. Coding Conventions for Events and Medications

All adverse events, and medical history will be mapped to the Medical Dictionary for Regulatory Activities (MedDRA Version 24.0) system for reporting (preferred term and body system).

Prior and Concomitant medications will be coded using WHO-DD (Drug Dictionary) Version C3 Format- Mar 1, 2021.

7.3.7. Analysis Software

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher) for

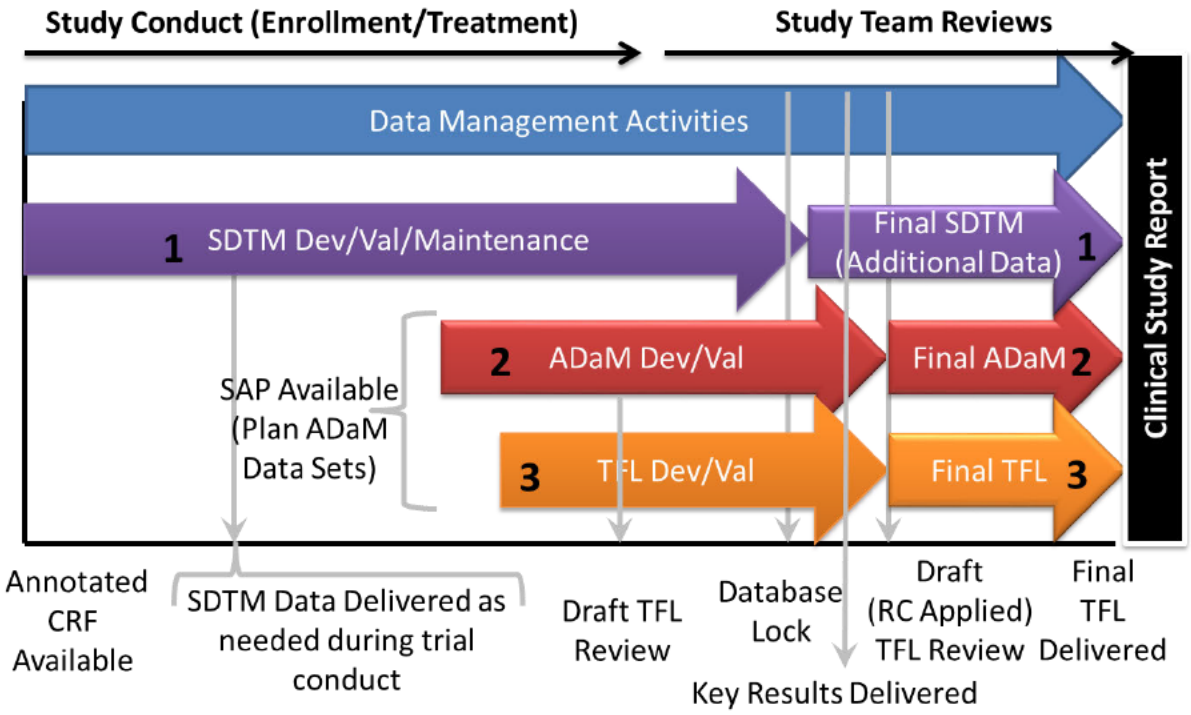
Windows. If the use of other software is warranted, the final clinical study report will detail what software was used and for what purposes.

7.3.8. Study Data

All study data will be formulated into regulatory compliant data sets to provide transparency, traceability, and integrity of trial analysis results from the collection source. Observed study data will be mapped to the CDISC Study Data Tabulation Model (SDTM) and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model (ADaM) architecture. All planned analyses will be performed using the ADaM data sets developed for this study.

The methods for programming the CDISC SDTM and ADaM data sets are described in Figure 1.

Figure 1 SDTM, ADaM, and TFL Development and Validation



Where:

1. Development, Validation, and Maintenance of SDTM Domains.
2. Development and Validation of Analysis Data Sets (ADaM), with input source the appropriate SDTM domains.
3. Development and Validation of Tables, Figures, and Listings (TFL), with input data source the analysis specific ADaM data sets.

7.4. Planned Study Analyses

7.4.1. Statistical Summaries: Descriptive and Inferential

Descriptive summaries of variables will be provided. For continuous variables, the number of non-missing values (n) and the median, mean, standard deviation, minimum, and maximum will be tabulated. For categorical variables, the counts and proportions of each value will be tabulated. Expansion of descriptive table categories may occur if such elaborations are thought to be useful. For primary analysis, disease control rate (total numbers of patients with stable disease or better divided by total number of patients with at least one dose of PCM-075) will be summarized as percentage with 90% CI. For time to event variables, point estimates (25th, 50th, and 75th percentiles) along with 90% confidence intervals (CIs) will be tabulated. Maximum PSA decline will also be summarized using waterfall plot graphically. For time to event variables, point estimates (25th, 50th, and 75th percentiles) along with 95% confidence intervals (CIs) will be tabulated. Survival estimates will also be shown graphically.

For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. The standard deviation / standard error will be displayed to two levels of precision greater than the data collected.

Change from baseline will be calculated as the post-baseline measurement minus the baseline value.

All collected data will be presented in listings. Data not pertinent to analysis according to this plan will not appear in any tables or figures but will be included in the data listings.

7.5. Multiple Testing Procedures

No adjustments for multiplicity will be performed in this study.

8. SUMMARY OF STUDY DATA

8.1. Patient Disposition

A summary of the analysis sets includes the number and percentage of patients for the following categories: patients screened, patients enrolled, patients in the Safety Population, Efficacy Population, 100% and 90% PP Populations. All percentages will be based on the number of patients enrolled, by treatment arm and total.

Discontinuation information will also be summarized in this table, including the patients who discontinued from the study with reasons for withdrawal. All percentages will be based on the number of patients enrolled.

A by-patient data listing of study completion information including the reason for premature study withdrawal, if applicable, will be presented.

Arm A patients who do not transition to Arm B and those who do will be summarized in the same Arm A column combined, but they will be labeled differently in listings.

8.2. Inclusion/Exclusion Criteria

A listing of all enrolled patient's inclusion and exclusion criteria will be presented.

8.3. Protocol Deviations

The study monitor will record any protocol deviations identified, including, but not limited to, patients that were enrolled even though they did not meet all eligibility criteria, patients who took concomitant medications specifically prohibited by the protocol, and patients who received the wrong study drug or incorrect dose. The Investigator and research staff will collaborate with the study monitor to identify the reason for each protocol deviation.

The major protocol deviations will be identified and finalized prior to database lock. All protocol deviations will be presented in a data listing. A summary table will be generated based on the classification of protocol deviations.

Arm A patients who do not transition to Arm B and those who do will be summarized and listed separately.

8.4. Demographics and Baseline Characteristics

Patient demographic data and baseline characteristics will be listed and summarized descriptively by treatment arm and total, for the Safety Population. Individual patient demographics and baseline characteristics will be provided in listings.

Variables of interest include age (continuous), sex, ethnicity, race, baseline BSA, baseline ECOG performance (0 or 1), baseline PSA level (continuous), time since diagnosis (months) and baseline total Gleason Score. BSA is calculated as

$$BSA\ (m^2) = \sqrt{height\ (cm) \times weight\ (kg)/3600}$$

Arm A patients who do not transition to Arm B and those who do will be summarized together in one Arm A column.

8.5. Medical History

Medical history will be coded using the MedDRA Version 24.0.

Medical history will be summarized (frequency and percentage) by System Organ Class (SOC), and Preferred Term (PT). A patient is counted only once within each SOC or PT.

Arm A patients who do not transition to Arm B and those who do will be summarized together in one Arm A column.

Patient medical history data will be presented in a listing.

8.6. Prostate Cancer History

The following variables will be summarized by treatment cohort and total for the Safety Population.

Time since initial diagnosis (months) as defined by date of Cycle 1 Day 1 – date of initial diagnosis + 1 in months.

- Initial tumor, node and metastasis (TNM) stage separately.
- Primary, secondary and total Gleason Score.

Arm A patients who do not transition to Arm B and those who do will be summarized together in one Arm A column.

Patient prostate cancer history data will be presented in a listing.

8.7. Prior Systemic Therapies and Radiotherapies

Systemic therapies and radiotherapies will not be coded and will only be listed.

8.8. Prior and Concurrent Medications

The number and percentages of all concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 4 and PT. The total number of concomitant

medications and the number and percentages of patients with at least 1 concomitant medication will be summarized. All summaries will be performed using the Safety Population.

The number and percentages of all prior medications will be summarized similarly to concomitant medications in a separate table.

Arm A patients who do not transition to Arm B and those who do will be summarized together in one Arm A column.

A concomitant medication is defined as any medication taken on or after the day of first dose of onvansertib or biraterone. Prior medications are defined as any medication that starts and ends prior to the day of first dose of onvansertib or biraterone. If it is unclear whether a medication is concomitant, then it will be summarized as concomitant.

8.9. Extent of Exposure to Study Medication

The following variables will be summarized descriptively for onvansertib, abiraterone and prednisone using the Safety Population:

- Number of cycles with at least one dose administered (for onvansertib only)
- Total dose in mg exposed

Arm A patients who transfer to Arm B will be summarized with Arm B.

A data listing will also be presented for extent of exposure.

9. EFFICACY ANALYSES

Unless otherwise specified, efficacy analyses will be done using the Efficacy Population.

9.1. Primary Efficacy Analysis

The primary efficacy endpoint is disease control rate, as defined by lack of PSA progression (per PCWG3 criteria). Disease control rate is the proportion of patients achieving disease control at or before week 12 from the initiation of treatment on Cycle 1 Day 1. If a patient achieved disease control prior to week 12, but relapsed at or before week 12, disease control is still considered achieved. Disease status unknown or Not Evaluable are counted as disease not under control. Arm A patients who transferred to Arm B and those who did not transfer are summarized in separate columns.

The number and percentage of patients who exhibit disease control in the Efficacy Population will be presented. The corresponding 90% Wilson Confidence Interval (CI) will be computed.

The same analysis will be run using the 100% and 90% PP Populations as a sensitivity analysis.

9.2. Secondary Efficacy Analyses

The following measures will be summarized using the PP Populations. Arm A patients who transferred to Arm B and those who do not will be summarized separately.

9.2.1. Change in PSA at Week 12

Absolute and percent change from baseline in PSA at Week 12 will be summarized. If a patient does not have a week 12 (+/- 3 days) PSA measure, then they are not included in this analysis.

9.2.2. Maximal Decline in PSA

Maximal percentage decline and maximal absolute decline in PSA from baseline at any time after the start of treatment on Cycle 1 Day 1 until subject discontinues from study, will be summarized using a waterfall plot. All unscheduled and scheduled PSA results are included. Arm A patients who transferred to Arm B and those who do not will be summarized separately.

9.2.3. Time to PSA Progression or Death

Time to PSA progression or death in weeks is defined as time from Cycle 1 Day 1 (initiation of treatment) until initiation of any PSA progression based on the PSA laboratory report.

If a subject discontinues from study without confirmed PSA progression or death, then they are censored at the last PSA laboratory date.

Kaplan-Meier method will be used, and 25th and 75th percentiles together with median time to event with its 95% confidence interval will be presented. Arm A patients who transferred to Arm B and those who do not will be summarized separately.

9.2.4. Time to Radiographic Progression or Death

Time to radiographic progression or death in weeks is defined as time from Cycle 1 Day 1 (initiation of treatment) until initiation of any radiographic progression, captured via the Radiographic Progression Assessment CRF.

If a patient discontinues from study prior to any confirmed radiographic progression or death, then they are censored at the last valid assessment date. The time to event analysis will be conducted similarly as time to PSA progression. Arm A patients who transferred to Arm B and those who do not will be summarized separately.

9.2.5. Radiographic Response Rate

Radiographic response (RECIST 1.1) rate is the proportion of patients who have best overall response of stable disease, partial or complete response within 12 weeks (Week 12 visit + 3 days), in patients with measurable disease (satisfies inclusion criterion #7) at screening. The number and percentage of patients that exhibit radiographic response will be presented. Arm A patients who transferred to Arm B and those who do not will be summarized separately.

10. SAFETY ANALYSES

All safety analyses will be conducted using the Safety population for all study populations. All AEs and abnormal laboratory results will be graded according to the NCI-CTCAE (v4.03).

10.1. Adverse Events

All adverse events (AEs) collected will be considered treatment-emergent as AEs are only collected once a patient starts receiving IP.

The number and percentage of patients with any adverse events (AEs) will be displayed by system organ class and preferred term (MedDRA Version 24.0). Within each system organ class and each preferred term, patients will be counted only once if they had more than one event reported during the treatment period.

Arm A patients who transitioned to Arm B will be summarized separately from those who do not.

AEs will also be summarized by greatest reported severity for each event preferred term. Counts indicate patients reporting one or more AEs that map to the severity grade classification for each preferred term. At each level of summarization (system organ class or event preferred term) patients are only counted once, and only the worst severity case of repeated instances of the same AE will be used in tabulations. AEs will also be summarized by strongest investigator assessment of relationship to study drug in a similar manner.

The following tables will be presented for AEs.

- Overall summary of AEs consisting of total number of patients reported any AE, DLTs, Serious AEs, related AEs, AEs leading to discontinuation, toxicity $\geq$ grade 3 and AEs leading to death.
- AE incidents by SOC and PT.
- DLT incidents by SOC and PT.
- AE incidents by relationship to onvansertib by SOC and PT.
- AE incidents by relationship to abiraterone by SOC and PT.
- AE incidents by severity by SOC and PT.
- AE incidents leading to discontinuation of onvansertib by SOC and PT.
- SAEs incidents by SOC and PT.

- SAEs incidents by relationship to onvansertib by SOC and PT.
- SAEs incidents by relationship to abiraterone by SOC and PT.
- Non-serious AEs above reporting threshold of 5% of the patients in any arm or overall.

A conservative approach will be taken to assess the relationship of an AE to study drug; if the relationship of an event is missing, it will be considered treatment-related. Missing severity will be coded as severe.

All AEs will be listed individually by patient. SAEs will be provided in a separate listing.

10.2. Clinical Laboratory Evaluations

Clinical Laboratory results will be summarized descriptively by time point for the observed value as well as for the change from baseline value. In addition, laboratory shift tables will be presented for all lab parameters where low/normal/high or abnormal/normal status can be ascertained (percentages will be based on the number of patients who have laboratory results at each visit). Each cycle will be summarized separately. Arm A patients who transferred to Arm B and those who do not will be summarized separately.

10.3. Vital Signs

Vital sign results will be summarized descriptively by time point for the observed value as well as for the change from baseline value. All vital sign data by patient will be presented in a listing.

10.4. Physical Examinations

Physical examination results will be summarized using the number and percentage of patients with abnormalities in each body system examined. Arm A patients who transferred to Arm B and those who do not will be summarized separately.

10.5. ECGs

ECG parameters in triplicates are taken at baseline and on Day 8 for Cycle 1 only. The parameters will be summarized descriptively for the observed value as well as for the change from baseline. For triplicate measures, averages will be taken for each patient-timepoint and then summarized. Each triplicate will be presented separately in a listing. Arm A patients who transferred to Arm B and those who do not will be summarized separately.

10.6. ECOG performance status

ECOG performance status (0-5) will be summarized by cycle. Arm A patients who transferred to Arm B and those who do not will be summarized separately.

All ECOG data will be presented in listings.