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

NCT Number: NCT03414034

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1 CLINICAL STUDY PROTOCOL

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
Study Phase:	2
Product Name:	Onvansertib (PCM-075)
IND Number:	105112
Sponsor:	Cardiff Oncology, Inc. 11055 Flintkote Avenue San Diego, CA 92121 Phone: [redacted] Email: [redacted]
Issue Date:	13 Nov 2020
Version Number:	1.8
Prior Version:	v1.7 dated 24 Nov 2019

This study will be performed in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments), and local legal and regulatory requirements.

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

PROTOCOL APPROVAL SIGNATURES
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11/16/2020
Date

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Title

11/16/2020
Date

INVESTIGATOR SIGNATURE PAGE

Protocol No: TROV-053
Protocol Version: 1.8
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I have read the attached protocol and hereby agree that it contains all the necessary details for performing the Product Study.

I will provide copies of the protocol to the Investigational Review Board and all members of the Study team responsible to me who participate in the Study. I will discuss this material with them to ensure that all participating personnel at the Study site are fully informed regarding the investigational device and the conduct of the protocol.

Once the Investigational Review Board approves the protocol, I will not modify this protocol without obtaining the prior approval of both the Sponsor and the Investigational Review Board. I will submit the protocol modifications and/or any informed consent modifications to the Sponsor and the Investigational Review Board, as applicable, and approval will be obtained before any modifications are implemented.

Investigator's Signature	Date
Investigator's Printed Name	
Study Site Name	
Address	
City, State, Zip Code, Country	

3 SYNOPSIS

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
IND Number:	105112
Number of Study Sites:	This study will be conducted at 3 sites
Phase:	2
Principal Investigator	[redacted]
Objectives:	Primary • To observe the effects of onvansertib in combination with abiraterone acetate (abiraterone) and prednisone on disease control as assessed by prostate-specific antigen (PSA) decline or stabilization in patients with metastatic castration-resistant prostate cancer (mCRPC) currently receiving abiraterone and prednisone Secondary Efficacy • To observe the effects of onvansertib in combination with abiraterone and prednisone on change in PSA relative to baseline in patients with mCRPC • To observe the effects of onvansertib in combination with abiraterone and prednisone on time to PSA progression in patients with mCRPC • To observe the effects of onvansertib in combination with abiraterone and prednisone on time to radiographic progression, based on the Prostate Cancer Working Group 3 (PCWG3) guidelines • To observe the effects of onvansertib in combination with abiraterone and prednisone on radiographic response (per Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria) in patients with mCRPC and measurable disease • To observe the effects of onvansertib in combination with abiraterone acetate (abiraterone) and prednisone on disease control as assessed by PSA decline or stabilization in patients with mCRPC currently receiving abiraterone and prednisone who adhere to study treatment Safety • To assess the safety of onvansertib in combination with abiraterone and prednisone in patients with mCRPC

	Exploratory • To assess target inhibition of Polo-like kinase 1 (PLK1) in peripheral blood mononuclear cells (PBMCs) and CTCs • Use of circulating tumor cells and circulating tumor deoxyribonucleic acid (ctDNA) to evaluate relevant biomarkers correlated with patient response • Use of archival tumor tissue (if available) to evaluate genomic profiles (DNA/ribonucleic acid [RNA]) associated with patient response
Study Design:	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) while currently receiving androgen-deprivation therapy plus abiraterone and prednisone. For eligibility, progressive disease must have been demonstrated by two rising PSA values separated by at least 1 week, one showing a rise of at least 0.3 ng/mL and one confirmatory value not showing a decline, while on abiraterone therapy. This study will consist of a Screening Period, a Treatment Period conducted in 14-day cycles (Arm B), and 21-day cycles (Arm C), and End-of-Study (EOS) Visit. This study previously 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 will continue with two arms, each with a different dosing schedule. Arm B is a 14-day treatment cycle, with study drug (onvansertib) administered on Days 1-5 of each cycle. Arm C is a 21-day treatment cycle, with study drug (onvansertib) 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. At any time during the trial, the Principal Investigator and Sponsor can make the decision to discontinue one of the arms. <u>Screening Period</u> Within 28 days prior to enrollment, screening assessments will be performed, as presented in the Schedule of Events. Key assessments at screening include medical history (including relevant medical history collection, as well as Gleason score and tumor-node-metastasis [TNM] stage at diagnosis), prior and concomitant medications, baseline PSA, and baseline radiographic scans (computed tomography [CT] abdominal/pelvis with contrast - or magnetic

	resonance imaging [MRI] if contraindication to intravenous [IV] contrast - and bone scan). Treatment Period In Arm B, the Treatment Period will begin with a safety lead-in of 3 patients. On Day 1 of each cycle, onvansertib (study drug) will be administered orally (PO) once daily (QD) at a dose of 24 mg/m^2 for 5 days (Day 1 through Day 5) in a 14-day cycle. In Arm C, the Treatment Period will begin with a safety lead-in of 3 patients. On Day 1 of each cycle, onvansertib (study drug) will be administered orally PO QD at a dose of 12 mg/m^2 for 14 days (Day 1 through Day 14) in a 21-day cycle. Beginning on Day 1 and continuing uninterrupted throughout each cycle, patients will also receive abiraterone and prednisone. Dosing of onvansertib (study drug) can be administered at the same time the patient is administered their dose of abiraterone. Dosing of prednisone should be as directed with food at a different time after the pharmacodynamic (PD) samples are obtained. Dose-limiting toxicities (DLTs) are defined as a Grade ≥ 3 hematologic AE or non-hematologic AE of Grade ≥3 that is considered related to the study drug. In the event of a DLT, onvansertib should be held until a hematologic DLT resolves to Grade 2 or less, or a nonhematologic DLT resolves to Grade 1 or less. If the DLT is judged to be unrelated to abiraterone and prednisone by the treating Investigator, abiraterone and prednisone may be continued. If a hematologic DLT does not resolve to Grade 2 or less or a nonhematologic DLT does not resolve to Grade 1 or less within 2 weeks, the patient will be discontinued from study treatment. The safety lead-in period in Arm B is the first two 14-day cycles, and in Arm C is the first 21-day cycle, plus an additional 2 weeks to resolve to Grade 2 or less. If the DLT resolves, the dose of onvansertib will be reduced by 25% (18 mg/m^2 - Arm B; 9 mg/m^2 - Arm C) in subsequent cycles. If a DLT occurs at the 25% reduced dose and resolves within 2 weeks, then the patient can proceed at a 50% reduced dose (Arm B - 12 mg/m^2, Arm C – 6 mg/m^2). If subsequent DLTs occur at the 50% reduced dose that do not resolve within 2 weeks, then the patient should be discontinued from the study. If a patient experiences excessive toxicity at 50% of the original starting dose, that patient should be discontinued from study treatment. At the end of Cycle 2 (Arm B) and Cycle 1 (Arm C), safety data for the initial 3 patients will be reviewed by the Investigators and the Sponsor for evaluation of DLTs or other safety events determined by the Investigators and Sponsor to be unacceptable. If no DLTs or other unacceptable safety events have occurred in the first 3 patients, dosing of subsequent patients may begin. If 1 DLT is observed in the first 3 patients enrolled, an additional 3 patients may be enrolled if deemed safe by the Sponsor and Study Investigators. If no further DLTs occur in these 3 additional patients, dosing may begin for subsequent patients. 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 will be reduced by 25% (Arm B -18 mg/m^2; Arm C – 9 mg/m^2) and dosing of an additional 3 lead-in patients will begin in identical fashion as described above. A second dose reduction to 50% of the original dose (12 mg/m^2 - Arm B; 6 mg/m^2 - Arm C) and enrollment of 3-6 additional patients will be allowed if necessary. If 2 or more DLTs occur in up to 6 patients in one of the arms at a 50% reduced dose, all enrollment in that arm of the study will be discontinued. If 2 or more DLTs occur in up to 6 patients in both arms, at a 50% reduced dose, all enrollment in the study will be discontinued. Dose adjustments for abiraterone and prednisone are allowed and will be based on dose modification guidelines provided in the relevant package insert. Patients will continue treatment in the study (Cycle 1, Cycle 2, Cycle 3, etc.) until symptomatic or radiographic disease progression or death, unacceptable toxicity, withdrawal of consent, or discontinuation based on Investigator discretion. In Arm B, PSA levels will be collected at baseline andon Days 1 and 8 of the first 6 cycles. PSA levels will also be collected on Day 1 of each cycle after Cycle 6 and at EOS. Radiographic imaging will be obtained after every 6 cycles. In Arm C, PSA levels will be collected at baseline and on Days 1, 8, and 15 of the first 4 cycles. PSA levels will also be collected on Day 1 of each cycle after Cycle 4 and at the EOS. Radiographic imaging will be obtained after every 4 cycles. Patients who have progressive disease per PCWG3 criteria will be removed from the study. Patients who have progressive disease only by PSA rise and/or new lesions on imaging and without progressive symptoms may continue on study at the discretion of the Investigator if they are believed to be clinically benefitting. (Per PCWG3 criteria, new bone lesions would need to be confirmed on subsequent imaging in order to qualify as disease progression). Patients whose PSA value has decreased or remained stable from Baseline will remain in the study until radiographic or symptomatic progression. <u>End-of-Study</u> End-of-Study evaluations are required within 28 days of administration of the last dose of onvansertib. <u>Follow-Up</u> 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.
Sample Size:	Up to 90 patients

Endpoints:	Primary • Proportion of patients achieving disease control after 12 weeks of study treatment, as defined by lack of PSA progression (per PCWG3 criteria) Secondary *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 criteria) • 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 the National Cancer Institute (NCI) - Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 [Appendix 19.1]. • Number of reported DLTs when combining onvansertib (study drug) with abiraterone *Exploratory* • To assess target inhibition of PLK1 in PBMCs and CTCs • Use of circulating tumor cells and ctDNA to evaluate relevant biomarkers correlated with patient response • Use of archival tumor tissue (if available) to evaluate genomic profiles (DNA/RNA) associated with patient response
Indication:	Metastatic Castration-Resistant Prostate Cancer
Diagnosis and Main Eligibility Criteria:	Patients who meet all of the following inclusion criteria and none of the exclusion criteria will be eligible to be enrolled in the study. Inclusion Criteria: 1. Ability to understand and the willingness to sign a written informed consent document. 2. Males ≥ 18 years of age on the day of consenting to the study. 3. Ability to swallow the study drug as a whole tablet.

	4. Histologically confirmed prostate adenocarcinoma without significant small-cell/neuroendocrine or other variant histologies. Patients must have either undergone surgical castration or continue on gonadotropin-releasing hormone (GnRH) agonist/antagonist on the appropriate schedule throughout the study period. 5. Castration confirmed by testosterone <50 ng/dL. 6. Asymptomatic or minimally symptomatic disease. 7. Metastatic disease by bone scan or nodal or visceral lesions on CT or MRI at any time (past or present). 8. Patient currently receiving abiraterone and prednisone for metastatic prostate cancer. 9. Patient has been on abiraterone for castration-sensitive prostate cancer (CSPC) or CRPC. Patients who have received abiraterone for CSPC must have had a response to hormonal therapy, as defined by any decline in PSA, radiographic response, and/or clinical benefit after starting hormonal therapy. Patients who have received abiraterone for CRPC must have responded to abiraterone, defined by any decline in PSA, radiographic response, and/or clinical benefit after starting abiraterone. 10. Two rising PSA values separated by at least 1 week, one showing a rise of at least 0.3 ng/mL and one confirmatory value not showing a decline, while on abiraterone therapy. 11. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1. 12. Patient has adequate bone marrow and organ function as shown by: 1. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L 2. Platelets ≥ 100 x 10^9/L 3. Hemoglobin (Hgb) ≥ 9.0 g/dL 4. Serum creatinine ≤ 2 x the upper limit of normal (ULN) 5. Total serum bilirubin ≤ 1.5 x ULN (in patients with known Gilbert Syndrome, a total bilirubin ≤ 3.0 x ULN, with direct bilirubin ≤ 1.5 x ULN) 6. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x ULN (or ≤ 5.0 x ULN if hepatic metastases are present)

	13. The effects of onvansertib (study drug) on the developing human fetus are unknown. For this reason and because chemotherapeutic agents are known to be teratogenic, men must agree to use adequate contraception. Specifically, they must agree to use a condom (even men with vasectomies) and another effective method of birth control if he is having sex with a woman of childbearing potential or agree to use a condom if he is having sex with a woman who is pregnant while on study drug and for 3 months following the last dose of study drug. They must also agree not to donate sperm during the study and for 3 months after receiving the last dose of study drug. 14. Patients with prior malignancies at low risk of recurrence (in the opinion of the Investigator) or patients with concurrent malignancies that are not likely to require treatment for the duration of the study are not excluded. Exclusion Criteria: Patients eligible for this study must not meet any of the following criteria: 1. Inability to comply with study procedures. 2. Any condition that in the opinion of the Investigator, would preclude participation in this study. 3. Major surgery within 28 days prior to starting study drug or has not recovered from major side effects of the surgery. 4. Rapidly progressive symptoms of mCRPC 5. Acute neurological dysfunction as a result of bone metastasis. 6. Previously treated with enzalutamide or experimental therapies directed against androgen receptor (ie, apalutamide). 7. Use of any chemotherapy, investigational agents, immunotherapy, or hormonal therapy (other than abiraterone), other than GnRH agonists within 28 days of the start of treatment on protocol. Use of bone targeted agents including bisphosphonates and RANK ligand inhibitors is allowed if on stable dose; Xgeva or Zometa cannot be started within 28 days of initiating study therapy. 8. Systemic corticosteroids except as part of on label treatment prostate cancer regimens. Note: Topical applications (eg, rash), inhaled sprays (eg, obstructive airways diseases), eye drops or local injections (eg, intra-articular) are allowed.

	9. Treatment with any of the drugs listed in Section 8.4.5 at the time of study treatment initiation. 10. Has received wide field radiotherapy (including therapeutic radioisotopes such as radium 223) ≤ 28 days or limited field radiation for palliation ≤ 14 days prior to starting study drug or has not recovered from side effects of such therapy. 11. New York Heart Association (NYHA) Class III or IV heart disease, active ischemia or any other uncontrolled cardiac condition, or hypertensive or metabolic condition 12. Myocardial infarction in the previous 12 weeks (from the start of treatment) 13. QT interval with Fridericia's correction [QTcF] >470 milliseconds. The QTcF should be calculated as the arithmetic mean of the QTcF on triplicate ECGs. In the case of potentially correctible causes of QT prolongation (e.g., medications, hypokalemia), the triplicate ECG may be repeated once during screening and that result may be used to determine eligibility. 14. Planned concomitant use of medications known to prolong the QT/QTc interval 15. Presence of risk factors for torsade de pointes, including family history of Long QT Syndrome or uncorrected hypokalemia
Drug, Dose, and Mode of Administration:	**Arm B: Onvansertib:** 24 mg/m^2 oral (PO) daily (QD) on Days 1-5 every 14 days (1 cycle) - [onvansertib can be administered at the same time as dosing of abiraterone] **Arm C: Onvansertib:** 12 mg/m^2 PO QD on Days 1-14 every 21 days (1 cycle) - [onvansertib can be administered at the same time as dosing of abiraterone] **Abiraterone acetate:** 1000 mg PO QD; four 250 mg tablets or two 500 mg film-coated tablets (unless previously dose-reduced for toxicity, in which case prior dose should be continued) **Prednisone:** 5 mg PO QD (unless previously started at 5 mg twice daily [BID] or increased for abiraterone toxicity, in which case prior dose should be continued)
Efficacy Evaluation:	All patients evaluable for efficacy will be assessed for response to treatment using the recommendations of the PCWG3.[1] In Arm B, PSA levels will be collected at baseline and on Days 1 and 8 of the first 6 cycles. PSA levels will also be collected on Day 1 of each cycle after

	Cycle 6 and at EOS. Radiographic imaging will be obtained after every 6 cycles. In Arm C, PSA levels will be collected at baseline and on Days 1, 8 and 15 of the first 4 cycles. PSA levels will also be collected on Day 1 of each cycle after Cycle 4 and at EOS. Radiographic imaging will be obtained after every 4 cycles. Efficacy Endpoints: • Proportion of patients achieving disease control after 12 weeks of study treatment, as defined by lack of PSA progression (per PCWG3 criteria) • 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 criteria) • Radiographic response (RECIST 1.1) in patients with measurable disease
Safety Evaluation:	Toxicity will be graded using the NCI-CTCAE version 4.03 [Appendix 19.1] 1. Safety analyses will be conducted on all patients who have received at least one dose of study drug, and will include the frequency of all AEs and laboratory abnormalities as well as the frequency of dose interruptions, dose reductions, and treatment discontinuations. All AEs must be attributed to study drugs unless there is a reasonably acceptable alternate cause for the AEs. 2. Additional safety assessments will include physical examination; medical history (including Gleason score and TNM stage at diagnosis); ECOG performance status; weight; vital signs measurements; and clinical laboratory testing.
Pharmacodynamic and Diagnostic Biomarker Evaluation:	Blood samples for pharmacodynamics analysis and genomic profiling will be collected at pre-defined time points pre- and post-administration of onvansertib (study drug) + abiraterone/prednisone.
Statistical Methods:	**Safety Analysis** Safety assessment data for all patients who receive at least one dose of study drug will be listed and summarized and will include data from AEs and concomitant medication queries, physical examination findings, ECOG performance status, weight and vital signs measurements, and clinical laboratory testing values. Descriptive statistics will be generated as appropriate (eg, mean, median, range, and standard deviation for continuous data; and frequency for categorical data).

	Efficacy Analysis Data from all patients who receive at least one dose of onvansertib (study drug) at the final recommended dose level in combination therapy will be included in the treated patient population efficacy analysis. Patients completing at least one 14-day treatment cycle (Arm B) or at least one 21-day treatment cycle (Arm C) will be included in the per protocol 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 (ie, patients who cross-over are not analyzed for efficacy based on the new treatment arm); however, changes in the temporal PSA trajectory after crossing over will be assessed in the treatment arm to which the subject is currently assigned. Descriptive statistics will be generated as appropriate (ie, mean, median, range, and standard deviation). Median survival statistics will be estimated using the Kaplan-Meier method. **Pharmacodynamic Analysis** PBMCs, circulating tumor cells and ctDNA isolated from blood samples will be used to assess inhibition of PLK1 activity by onvansertib (study drug) and to evaluate relevant biomarkers correlated with patient response. Archival tumor tissue (if available) will be used to evaluate genomic profiles (DNA/RNA) associated with patient response.
Sample Size Rationale	This is a two arm study that consists of determining the disease control rate of onvansertib (study drug) in combination with abiraterone 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/m^2; Arm C – 9 mg/m^2) 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/m^2 (Arm B), or 6 mg/m^2 (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.

	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.

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Androgen receptor
AR-V7	Androgen receptor splice variant 7
AST	Aspartate aminotransferase
AUC	Area under the curve
BID	Twice daily
Cavg	Average concentration
CBC	Complete blood count
Cmax	Maximum concentration
CFR	Code of Federal Regulations
CRF	Case Report Form
CSPC	Castration-sensitive Prostate Cancer
CRPC	Castration-resistant Prostate Cancer
CT	Computed tomography
CTC	Circulating tumor cell
ctDNA	Circulating tumor DNA
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOS	End-of-study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GnRH	Gonadotropin-releasing hormone

Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational new drug
IRB	Institutional Review Board
IV	intravenous
M	Mitotic phase
mCRPC	Metastatic castration-resistant prostate cancer
mCSPC	Metastatic castration-sensitive prostate cancer
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NYHA	New York Heart Association
PBMCs	peripheral blood mononuclear cells
PCa	Prostate cancer
PCWG3	Prostate Cancer Working Group 3
PD	pharmacodynamic
PLK1	Polo-Like Kinase 1
PSA	prostate-specific antigen
PO	Orally
QD	Daily
QTcF	QT interval with Fridericia's correction
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	Ribonucleic acid
SAE	Serious Adverse Event
TNM	Tumor, lymph nodes, metastasis
ULN	Upper Limit of Normal

5 ADMINISTRATIVE STRUCTURE

Investigator:	[redacted]
Contract Research Organization:	PRA Health Sciences
Medical Monitor:	[redacted]

6 INTRODUCTION

6.1 Background

6.1.1 Metastatic Castration-Resistant Prostate Cancer

Prostate cancer (PCa) is the second most frequently diagnosed cancer and fifth most common cause of cancer death among men, causing an estimated 300,000 deaths worldwide in 2012.[2] Although most men with metastatic prostate cancer initially respond to the historical standard-of-care, androgen-deprivation therapy, resistance inevitably develops after months to years, which is then known as metastatic castration-resistant prostate cancer (mCRPC). Resistance may be mediated by reactivation of androgen-receptor signaling through persistent adrenal androgen production, up-regulation of intratumoral testosterone production, modification of the biologic characteristics of androgen receptors, and steroidogenic parallel pathways.[3] Despite the availability of multiple hormonal and non-hormonal agents, survival after the diagnosis of mCRPC remains limited. In addition, targeted approaches based on biomarkers have only recently emerged in this setting.[4]

Abiraterone acetate is the prodrug of abiraterone. It targets cytochrome P-450c17, a critical enzyme in androgen biosynthesis. The active D4A metabolite inhibits multiple steroidogenic enzymes and antagonizes the androgen receptor.[5] Large randomized trials have demonstrated an overall survival benefit with abiraterone for mCRPC before[6; 7] or after[8] docetaxel therapy. It may also be effective in the neoadjuvant setting for localized PCa,[9] although Phase 3 trials are ongoing. Finally, two recent studies demonstrated a survival advantage of early use of abiraterone in metastatic castration-sensitive prostate cancer (mCSPC),[9; 10] as opposed to its use at the time of castration-resistance as second-line therapy. Therefore, the standard of care has recently changed to include first-line use of abiraterone in combination with androgen-deprivation therapy.

Although abiraterone is clearly effective in both mCSPC and mCRPC, patients will still inevitably develop resistance. In addition, the efficacy of subsequent hormonal manipulations after abiraterone is often limited.[11] Thus, abiraterone-resistant PCa is still a major clinical challenge. As abiraterone is increasingly used in first-line setting, a growing population of patients will eventually experience secondary disease progression that is resistant to further hormonal manipulation.[10] At this point, only docetaxel, cabazitaxel, and radium-223 have demonstrated survival benefits in trials, [12; 13; 14; 15] but only on the order of months versus comparator therapies; median overall survival in all trials was limited to less than two years. Benefits may be even more limited in the modern patient population that has had access to abiraterone and enzalutamide. Clearly, new and better therapeutic options for PCa are urgently needed.

6.1.2 Polo-like Kinase 1

Polo-like kinase 1 (PLK1) is the most well characterized member of the 5 members of the family of serine/threonine protein kinases and strongly promotes the progression of cells through mitosis. PLK1 performs several important functions throughout mitotic (M) phase of the cell cycle, including the regulation of centrosome maturation and spindle assembly, the

removal of cohesins from chromosome arms, the inactivation of anaphase-promoting complex/cyclosome inhibitors, and the regulation of mitotic exit and cytokinesis.[16] During the various stages of mitosis PLK1 localizes to the centrosomes, kinetochores, and central spindle.

PLK1 is ubiquitously expressed in normal proliferating tissues and is over-expressed in a wide variety of human tumors (including lung, colon, prostate, ovary, breast, head and neck squamous cell carcinoma,[18; 19; 20; 21; 22; 23]) and hematologic malignancies.[24; 25; 26] In addition, several studies have shown that this over-expression correlates with poor prognosis. For example, in head and neck squamous cell carcinoma, the 5-year survival rate of patients with medium vs high expression levels falls from 43% to 12% in patients with tumors over-expressing PLK1.[23]

In addition, PLK1 is not expressed in differentiated postmitotic cells such as neurons, where instead, expression of PLK2 and PLK3 are detected.[27] Therefore, PLK1 selective inhibitors could have an advantage in comparison with classical antimitotic agents like taxanes or vinca alkaloids, which cause major side effects such as neuropathy, as PLK1 selective inhibitors do not act on tubulins that are present in non-proliferating tissues (such as neurons).[28] These properties make PLK1 a very attractive new target for cancer therapy.[29]

6.1.3 Onvansertib (Also Known as PCM-075 and NMS-1286937)

Onvansertib (also known as PCM-075 and NMS-1286937) is the first PLK1 specific adenosine triphosphate competitive inhibitor administered by oral route to enter clinical trials with proven antitumor activity in different preclinical models.[10; 11; 12; 13; 14] The compound shows high potency in proliferation assays having low nanomolar activity on a large number of cell lines, both from solid as well as hematologic tumors. Onvansertib potently causes a mitotic cell-cycle arrest followed by apoptosis in cancer cell lines and inhibits xenograft tumor growth with a clear PLK1-related mechanism of action at well tolerated doses in mice after oral administration. Onvansertib has favorable pharmacologic parameters and good oral bioavailability in rodent and nonrodent species, as well as proven antitumor activity in different nonclinical models using a variety of dosing regimens, which may potentially provide a high degree of flexibility in dosing schedules, warranting investigation in clinical settings.

The major metabolic pathways found in the different animal species were N-oxidation of the N-methyl-piperazine ring to give N-oxide M2 and hydroxylation on an aliphatic carbon atom of the methylene bridge of the pyrazoloquinazoline moiety to give metabolite M1. Qualitatively, no marked differences in the metabolism of onvansertib were observed between species and, quantitatively, some differences were observed cross-species.

The potential inhibitory capacity of onvansertib towards the major human cytochrome P450 (CYP) isoforms responsible for hepatic drug metabolism in man (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) was investigated using human liver microsomes (Table 6-1). Onvansertib was able to inhibit the metabolic activities of CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 isoforms to different extents, with IC_{50} values ranging from 20 μM to 66 μM. No significant inhibitory effects against CYP1A2 were found. Considering

that the concentrations relevant to achieve significant anti-tumoral activity of the compound in mice were in the order of 1 µM, the likelihood that onvansertib would show clinically relevant metabolic drug-drug interactions is considered low.

Table 6-1 Summary of Mean Inhibitor Potency of Onvansertib for Human Liver P450s

P450 Enzyme	Enzyme Reaction	IC_{50} (µM)[a]
CYP1A2	Tacrine 1-hydroxylation	> 100
CYP2C8	Paclitaxel 6-hydroxylation	20.2 ± 1.6
CYP2C9	Diclofenac 4-hydroxylation	20.4 ± 3.2
CYP2C19	Mephenytoin 4-hydroxylation	36.9 ± 15.7
CYP2D6	Bufuralol 1-hydroxylation	26.8 ± 5.4
CYP3A4	Testosterone 6β-hydroxylation	52.7 ± 9.8
CYP3A4	Midazolam 1'-hydroxylation	66.2 ± 4.0

Source: Report No. 0204-2007-R
Abbreviations: IC_{50}=inhibitory drug concentration that produces 50% of the maximal effect; SEM=standard error of mean.
[a] Data are mean±SEM.

Onvansertib has been evaluated pre-clinically in combination with more than 10 different chemotherapeutics, including cisplatin, cytarabine, doxorubicin, gemcitabine and paclitaxel, as well as targeted therapies such as abiraterone, HDAC inhibitors, FLT3 inhibitors, and bortezomib. These therapeutics are used clinically for treatment of many hematologic and solid cancers, including acute myeloid leukemia, non-Hodgkin's lymphoma, metastatic castration-resistant prostate cancer, adrenocortical carcinoma, triple negative breast cancer, small cell lung cancer, and ovarian cancer.

To date, a single Phase 1 safety study with onvansertib has been conducted in adult patients with advanced/metastatic solid tumors at a single study site in the US.[17] The primary objective was to determine first cycle dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) of onvansertib administered orally for 5 consecutive days every 3 weeks (ie, 21-day treatment cycle). Secondary objectives were to define the safety profile of onvansertib, determine the pharmacokinetics (PK) of onvansertib in plasma (at the MTD), and document any antitumor activity.

A total of 21 patients were enrolled, and 19 patients were treated. No DLTs occurred at the first 3 dose levels (6, 12, and 24 mg/m^2/day). At the subsequent dose level (48 mg/m^2/day), 2 of 3 patients developed DLTs. An intermediate level of 36 mg/m^2/day was therefore investigated. Four patients were treated and two DLTs were observed. After further cohort expansion, the MTD was determined to be 24 mg/m^2/day.

The best observed treatment response was disease stabilization, which occurred in 5 of the 16 evaluable patients. One patient among the 16 evaluable patients had prostate cancer and had disease progression. The study identified thrombocytopenia and neutropenia as the primary toxicities, which is consistent with the expected mechanism of action of onvansertib and results from preclinical studies. These hematologic toxicities were reversible, with recovery usually occurring within 3 weeks.

Onvansertib (study drug) is a gelatin capsule and must be swallowed whole by the patient. Further details regarding the nonclinical and clinical studies of onvansertib are provided in the onvansertib Investigator's Brochure (IB). In addition, the current abiraterone and prednisone package inserts provide a description of the AEs that can be expected with their administration (Appendix 19.3).

6.2 Study and Dose Rationale

There is an urgent unmet medical need of patients who have mCRPC. PLK1 is one of the most upregulated pathways in prostate cancer following castration.[30] Loss of phosphatase and tensin homolog deleted on chromosome 10 (PTEN) tumor suppressor is a majority driver of advanced prostate cancer but results in mitotic stress. Inactivation of PTEN is correlated with overexpression of PLK1, which is critical for PTEN-depleted cells to adapt to mitotic stress.[31] The mechanism may be a result of the regulatory effect of nuclear PTEN on the E3 ubiquitin ligase anaphase-promoting complex/cyclosome APC-Cdh1, which ubiquitinates and degrades PLK1.[32] PLK1 confers tumorigenic competence of PTEN-depleted prostate cancer cells in a mouse xenograft model, and inhibition by a PLK1 tyrosine kinase inhibitor or siRNA preferentially suppresses tumor growth of PTEN-depleted cells.[31] Preclinical evidence from both in-vitro and in-vivo studies indicate that PLK1 inhibition may enhance the efficacy of abiraterone in PCa.[33; 34] Multiple mechanisms for the observed synergy of PLK1 inhibition plus abiraterone have been proposed. Liu and colleagues have observed that oxidative stress activated the PI3K-AKT-mTOR pathway and androgen receptor (AR) signaling in a PLK1-dependent manner in prostate cancer cells. In addition, Plk1 inhibition down-regulated SREBP-dependent expression of enzymes involved in androgen biosynthesis. Finally, PLK1 inhibition enhanced cellular responses to abiraterone and overcame abiraterone resistance in cultured PCa cells and patient-derived tumor xenografts.[33; 34] Although these effects were primarily believed to be mediated by AR signaling, members of Michael Yaffe's laboratory have observed synergy with the combination of abiraterone plus PLK1 inhibition in non-AR expressing tumor cell lines across multiple tumor types (e.g., ovarian, triple negative breast cancer, head and neck) and have also demonstrated these synergistic effects in-vivo (e.g., ovarian cancer xenografts). They found that cancer cell lines having the capability of demonstrating synergy had consistently different transcriptional pathways activated a priori. One of these pathways is the elevated expression of genes involved in retinoic acid metabolism (Yaffe, unpublished data). This pathway and other candidate pathways are considered hypothesis generating and will be correlated with efficacy endpoints within this trial.

Based on the body of data with therapies targeting PLK, there appears to be potential clinical benefit for patients with mCRPC. The aim of this study is to explore treatment with onvansertib in combination with standard of care abiraterone and prednisone in patients with mCRPC.

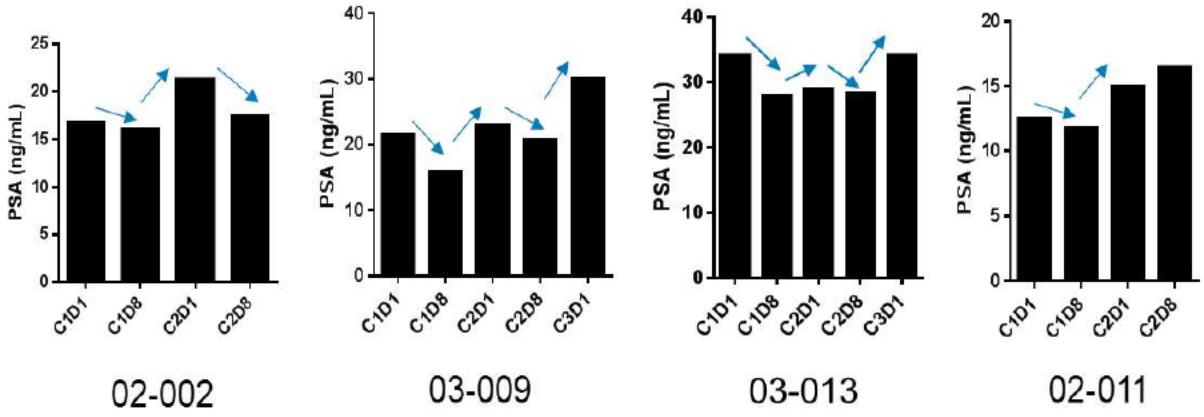
Dosing Schedule Rationale

The onvansertib starting dose will be 24 mg/m^2 based on results from the prior Phase 1 trial (Study PLKA-937-001) with the dosing schedule based on a 14-day cycle: Days 1-5 onvansertib followed by 9 days off. The FDA has granted approval of a protocol having a 14-

day dosing schedule [onvansertib administered on Days 1-5, with 9 days off] in a Phase 1b/2 trial with the combination of onvansertib and FOLFIRI + bevacizumab (with known overlapping toxicities) in metastatic Colorectal Cancer (mCRC).

The rationale for Arm B, a shortened dosing schedule, is based on observed temporal changes in PSA values from patients previously enrolled in Arm A, a 21-day dosing schedule. As of protocol version 1.5 (dated 24 Jan 2019), 8 patients had received >1 cycle , and in 4 of these patients, changes in PSA appeared to be correlated with the dosing schedule. As shown in Figure 1, after onvansertib dosing on Days 1-5, PSA values go down at Day 8 relative to baseline but then increase between Day 8 and the start of the next cycle. In particular, for patients 02-002, 03-009 and 03-013, this pattern is observed for both Cycles 1 and 2. This may indicate that in a 21-day cycle, the 16 days off enables the tumor to recover and continue to grow (as per observed increased PSA levels).

Figure 1 PSA Values of 4 Patients Enrolled in a 21-day Dosing Schedule.



Based on preliminary data from Arm B, more consistent disease control was observed with the more intensive schedule. Therefore, Arm A was closed and patients remaining on Arm A were offered the option to transition to the Arm B schedule.

To date, the most common adverse event associated with onvansertib is neutropenia, and neutropenia was increased with the more intense dosing schedule (Arm B versus Arm A). Onvansertib-induced neutropenia was efficiently managed by dose delay, dose reduction, and growth factor support and did not lead to treatment discontinuation in Arm B, supporting that onvansertib-associated hematological toxicities are manageable and reversible.

To examine this further, pharmacokinetics data from the Phase 1 trial were used to simulate onvansertib drug exposure over a 21-day period within the different dosing schedules (Table 6-). For evaluating drug exposure, maximum concentration (C_{max}), area under the curve 0-504 hours (AUC_{0-504}) and the average concentration (Cavg; AUC_{0-504}/504 days) were calculated. C_{avg} was assessed given that this parameter has been shown to be predictive for neutropenia (35). The effective drug level threshold was set at 10X the IC_{50} (32.5 ng/ml) to account for effects of plasma protein binding. Onvansertib drug exposure and average concentration in

patients treated at 24 mg/m^2 or 18 mg/m^2 in the 5+9 schedule (Arm B) are higher than in patients treated at 24 mg/m^2 in the 5+16 schedule (Arm A). These increases in drug exposure and average concentration were associated with a higher response to treatment and manageable toxicities, supporting the idea that intensifying the dosing regimen increased treatment efficacy without compromising patient's safety.

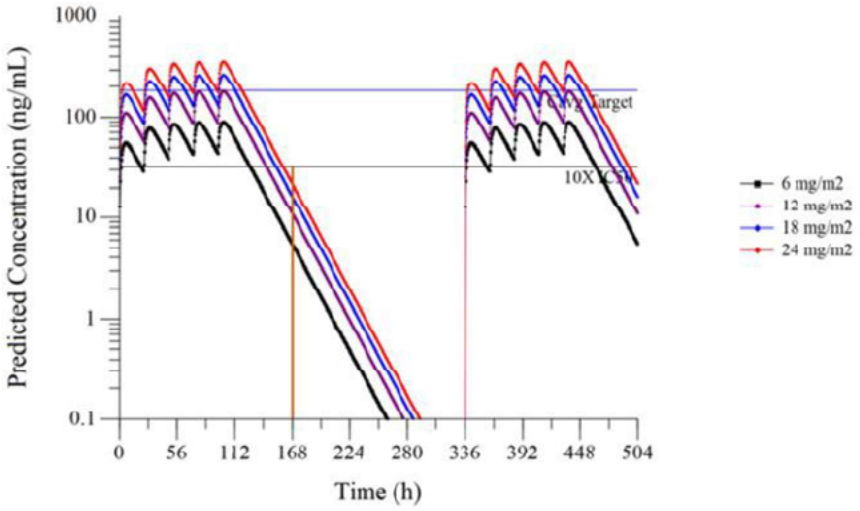
A new arm (Arm C) is proposed, in which patients will be treated for 14 days with onvansertib in 21-day cycles (14+7). In comparison to Arm B (5+9 at 24 mg/m^2), Arm C schedule has a lower C_{max}, AUC_{0-504}, and C_{avg} with a 2-fold increase in time above 10X IC_{50} (Table 6-2). Specifically, based on these simulations, Arm C patients will be exposed to lower onvansertib concentrations over a 21-day period (AUC, C_{avg}) than Arm B patients (Table 6-1), suggesting that the 14+7 dosing schedule will not result in an increase in onvansertib-related toxicities. In addition, in Arm B onvansertib concentration is above the 10X IC_{50} only for the first ~7 days (168 hrs) of the 14-day cycle (Figure 2). The time above 10X IC_{50} in Arm C is significantly increased (334 hrs vs 159 hrs) (Table 6-2) and may therefore result in a more profound and durable response in patients.

Table 6-2 Pharmacokinetic Profiles of the Different Dosing Regimens

	Dosing Schedule	Dose (mg/m^2)	C_{max} (ng/mL)	C_{avg} (ng/mL)	AUC_{0-504} (ng*hr/mL)	Time Above 10X IC_{50} (32.5 ng/mL)
Arm A	5 + 16	24	357	66.1	33300	159 h
Arm B	5 + 9	24	357	99.1	66000	159 h
	5 + 9	18	268	74.4	49500	152 h
Arm C	14 + 7	12	179	85.9	43300	334 h
	14 + 7	9	134	64.3	32400	327 h

C_{avg} is calculated as AUC_{0-504}/504

Figure 2 Onvansertib Predicted Concentrations for a 5+9 Dosing Schedule (Arm B)



Finally, G3/G4 neutropenia was reported in Arm B patients treated for 5 days at 24 mg/m^2 and upon dose reduction to 18mg/m^2 no further neutropenia were reported in those patients.

6.3 Risks and Benefits for Patients

In a Phase 1 clinical study, onvansertib demonstrated a safety profile that was manageable, with transient AEs that were related to the drug's mechanism of action.

The current safety clinical profile of onvansertib in treated patients indicates that hematological toxicity (thrombocytopenia and neutropenia) is the most relevant toxicity of treatment. Recovery from hematologic toxicity was prompt in all reported patient cases, occurring in 1 to 2 weeks from the onset, even without colony-stimulating factor support. Therefore, the toxicity of onvansertib appears to be manageable with conventional treatments. No other relevant toxicities were observed during the study.

7 STUDY OBJECTIVES

7.1 Primary Objectives

- 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

7.2 Secondary Objectives

Efficacy:

- To observe the effects of onvansertib (study drug) in combination with abiraterone and prednisone on change in PSA relative to baseline in patients with mCRPC
- To observe the effects of onvansertib (study drug) in combination with abiraterone and prednisone on time to PSA progression in patients with mCRPC
- To observe the effects of onvansertib (study drug) in combination with abiraterone and prednisone on time to radiographic progression based on the Prostate Cancer Working Group 3 (PCWG3) guidelines
- To observe the effects of onvansertib (study drug) in combination with abiraterone and prednisone on radiographic response (per Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 criteria) in patients with mCRPC and measurable disease
- 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 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

7.3 Exploratory Objectives

- To assess target inhibition of PLK1 based on PBMCs and circulating tumor cells (CTCs)
- Use of CTCs and circulating tumor DNA (ctDNA) to evaluate relevant biomarkers correlated with patient response
- Use of archival tumor tissue (if available) to evaluate genomic profiles (DNA/RNA) associated with patient response

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan

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. For eligibility, progressive disease must have been demonstrated by two rising PSA values separated by at least 1 week, one showing a rise of at least 0.3 ng/mL and one confirmatory value not showing a decline, while on abiraterone therapy. Cycle 1 Day 1 PSA does not impact the eligibility to enroll/start treatment.

This study will consist of a Screening Period, a Treatment Period conducted in 14-day cycles (Arm B), and 21-day cycles (Arm C), and End-of-Study (EOS) Visit.

Onvansertib (study drug) is supplied by the Sponsor through the Drug Depot, Almac, while abiraterone and prednisone are supplied commercially.

This study previously 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 will continue with two arms, each with a different dosing schedule. Arm B is a 14-day treatment cycle, with study drug (onvansertib) administered on Days 1-5 of each cycle. Arm C is a 21-day treatment cycle, with study drug (onvansertib) 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.

At any time during the study the Principal Investigator and Sponsor can make the decision to discontinue one of the arms.

8.1.1 Screening Period

Within 28 days prior to enrollment, screening assessments will be performed, as presented in the Schedule of Events. Key assessments at screening include medical history (including Gleason score and tumor, lymph nodes and metastasis [TNM] stage at diagnosis), prior and concomitant medications, baseline PSA, and baseline radiographic scans (computed tomography [CT] abdominal/pelvis with contrast - or magnetic resonance imaging [MRI] if contraindication to intravenous (IV) contrast - and bone scan).

For eligibility, progressive disease must have been demonstrated by two rising PSA values separated by at least 1 week, one showing a rise of at least 0.3 ng/mL and one confirmatory value not showing a decline, while on abiraterone therapy. Cycle 1 Day 1 PSA does not impact the eligibility to enroll/start treatment.

8.1.2 Treatment Period

In Arm B, the Treatment Period will begin with a safety lead-in of 3 patients. On Day 1 of each cycle, onvansertib will be administered orally (PO) once daily (QD) at a dose of 24 mg/m^2 for five days (Day 1 through Day 5) out of a 14-day cycle.

In Arm C, the Treatment Period will begin with a safety lead-in of 3 patients. On Day 1 of each cycle, onvansertib (study drug) will be administered PO QD at a dose of 12 mg/m^2 for 14 days (Day 1 through Day 14) in a 21-day cycle.

The safety lead-in period is the first two 14-day cycles (Arm B) and the first 21-day cycle (Arm C), plus an additional 2 weeks for any hematologic DLTs to resolve to Grade 2 or less or any nonhematologic DLT to resolve to Grade 1 or less. At the end of the 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 (see Table 8-1 in Section 8.1.2.1 and bulleted list below) or other safety events determined by the Investigators and Sponsor to be unacceptable.

- If 1 DLT is observed in the first 3 patients enrolled in Arm B or Arm C, an additional 3 patients may be enrolled in the respective arm, if deemed safe by the Sponsor and Study Investigators. If no further DLTs occur in these 3 additional patients, dosing may begin for subsequent patients. To reach the required sample size of 32 patients in each arm, an additional 27 patients would be enrolled at the original dose level in each arm (the patient experiencing the DLT would be excluded from efficacy analysis even if continuing on trial since the dose would be reduced).
- If 2 DLTs occur in the first 3 patients in Arm B or Arm C, or if an additional DLT occurs among the 3 additional patients enrolled, the dose of onvansertib will be reduced by 25% (18 mg/m^2 – Arm B and 9 mg/m^2 – Arm C) and dosing of an additional 3 lead-in patients will begin in identical fashion as described above.
    - If no DLTs are observed in the 3 patients treated at 18 mg/m^2 - Arm B and 9 mg/m^2 - Arm C, then 29 more patients will be enrolled and treated at 18 mg/m^2 and 9 mg/m^2, respectively.
- A second dose reduction to 50% of the original dose (12 mg/m^2 - Arm B and 6 mg/m^2 - Arm C) and enrollment of 3-6 additional patients will be allowed if necessary.
    - If no DLTs are observed in the 3 patients treated at 12 mg/m^2 – Arm B or 6 mg/m^2 – Arm C), then 29 more patients will be enrolled and treated at 12 mg/m^2 and 6 mg/m^2, respectively.
    - If 1 DLT occurs in the 3 patients treated at 12 mg/m^2 – Arm B or 6 mg/m^2 – Arm C, then 3 additional patients will be enrolled and treated at 12 mg/m^2 or 6 mg/m^2, respectively. If no further DLTs are observed after these 6 patients are treated at 12 mg/m^2 – Arm B or 6 mg/m^2 – Arm C, then 27 more patients will be enrolled and treated at 12 mg/m^2 and 6 mg/m^2, respectively.
    - If 2 or more DLTs occur in up to 6 patients at 12 mg/m^2 – Arm B or 6 mg/m^2 – Arm C, all enrollment in the respective study arm will be discontinued.

If no DLTs or other unacceptable safety events have occurred in the safety lead-in cohort(s), dosing of subsequent patients (expansion phase) may begin; 29 additional patients in each arm would be enrolled at the same dose level.

If a patient forgets to take their dose of study drug on any day during Day 1-5 of the cycle (Arm B) or Day 1-14 of the cycle (Arm C), they will have the opportunity to take the scheduled dose within 4-6 hours of the original scheduled time on that same day. If a patient misses a dose of study drug on any day during Day 1-5 of the cycle (Arm B) or Day 1-14 (Arm C), they will not be able to make-up the missed dose on the next day or move the Day 1-5 (Arm B) or Day 1-14 (Arm C) dosing schedule out to additional consecutive days (eg Day 6 or Day 15). If onvansertib is vomited, participants should not retake drug but should take it instead at the next scheduled time.

Beginning on Day 1 and continuing uninterrupted throughout each cycle, patients will also receive abiraterone and prednisone. Dosing of onvansertib can be administered at the same time the patient is administered their dose of abiraterone.

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

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

Patients who have progressive disease per PCWG3 criteria will be removed from the study. Patients who have progressive disease only by PSA rise and/or new lesions on imaging and without progressive symptoms may continue on study at the discretion of the Investigator if they are believed to be clinically benefitting (per PCWG3 criteria, new bone lesions would need to be confirmed on subsequent imaging in order to qualify as disease progression). Patients whose PSA value has decreased or remained stable from Baseline will remain in the study until radiographic or symptomatic progression.

Patients do not need to re-meet eligibility on Cycle 1 Day 1.

8.1.2.1 Dose Modifications and Management of DLTs

Guidance for dose modifications for onvansertib and management of onvansertib DLTs can be found in Table 8-1.

Table 8-1 Dose Modification and Management of Dose-limiting Toxicities

Hematologic Toxicities	
CTCAE Grade	**Dose Modifications**
Grade ≤ 2	No dose adjustment is required
Grade ≥ 3	Withold treatment and initiation of next cycle until recovery to Grade ≤2 Resume at next lower dose
Nonhematologic AE Assessed as Related to the Study Drug	
CTCAE Grade	**Dose Modifications**
Grade ≤ 2	No dose adjustement is required
Grade ≥ 3	Withhold treatment until symptoms resolve to Grade ≤1 Resume at next lower dose

Note: Arm C participants will have two on-treatment CBCs, Day 1 and Day 8. The same dose modifications apply at both timepoints. If a patient experiences grade ≥ 3 hematologic toxicity as assessed by the Day 8 CBC, then no further onvansertib should be taken during that cycle. Resumption of onvansertib with the next cycle would be based on the next cycle's Day 1 CBC, and would resume at the next lower dose level.
AE = adverse event; CBC = complete blood count; CTCAE = Common Terminology Criteria for Adverse Events

A DLT is defined as a Grade ≥ 3 hematologic AE or a Grade ≥3 nonhematologic AE that is considered related to the study drug(s). In the event of a DLT, onvansertib should be held until a hematologic DLT resolves to Grade 2 or less, or a nonhematologic DLT resolves to Grade 1 or less. If the DLT is judged to be unrelated to abiraterone and prednisone by the treating Investigator, abiraterone and prednisone may be continued. If a hematologic DLT does not resolve to Grade 2 or less or a nonhematologic DLT does not resolve to Grade 1 or less within 2 weeks, the patient will be discontinued from study treatment. If the DLT resolves, the dose of onvansertib will be reduced by 25% (18 mg/m^2 – Arm B and 9 mg/m^2 – Arm C) in subsequent cycles. An additional reduction in dose to 50% of the original starting dose (12 mg/m^2 – Arm B and 6 mg/m^2 – Arm C) may also be made based on Investigator judgment for toxicity in later cycles. If a patient experiences excessive toxicity at 50% of the original starting dose, that patient should be discontinued from study treatment. Dose modifications for Grade ≥ 3 hematologic and Grade ≥3 IP-related nonhematologic DLTs are presented in Table 8-1.

Dose adjustments for abiraterone and prednisone are allowed and will be based on dose modification guidelines provided in the relevant package insert. Patients will continue treatment in the study (Cycle 1, Cycle 2, Cycle 3, etc) until symptomatic or radiographic disease progression or death, unacceptable toxicity, withdrawal of consent, or discontinuation based on Investigator discretion.

8.1.3 End-of-Study

End-of-Study evaluations are required within 28 days of the last dose of onvansertib.

8.1.4 Study Endpoints

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)

Secondary efficacy endpoints:

- 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)

Secondary safety endpoints:

- Safety, as per CTCAE version 4.03 [Appendix 19.1]
- Number of reported DLTs when combining onvansertib with abiraterone

Exploratory endpoints:

- Inhibition of the PLK1 target in PBMC and CTCs
- Biomarkers correlated with patient response in both CTCs and ctDNA
- Genomic profiles (DNA/RNA) from archival tumor tissue (if available) and possible association with patient response

8.2 Study Duration

The Screening Period will be up to 28 days prior to enrollment. Patients will continue treatment in the study (Cycle 1, Cycle 2, Cycle 3, etc) until symptomatic or radiographic disease progression or death, unacceptable toxicity, withdrawal of consent, or discontinuation based on Investigator discretion.

8.3 Eligibility Criteria

Patients who meet all of the following inclusion criteria and none of the exclusion criteria will be eligible to be enrolled in the study.

8.3.1 Inclusion Criteria

1. Ability to understand and the willingness to sign a written informed consent document.

2. Males ≥ 18 years of age on the day of consenting to the study.
3. Ability to swallow the study drug as a whole tablet.
4. Histologically confirmed prostate adenocarcinoma without significant small-cell/neuroendocrine or other variant histologies. Patients must have either undergone surgical castration or continue on gonadotropin-releasing hormone (GnRH) agonist/antagonist on the appropriate schedule throughout the study period.
5. Castration confirmed by testosterone <50 ng/dL.
6. Asymptomatic or minimally symptomatic disease.
7. Metastatic disease by bone scan or nodal or visceral lesions on CT or MRI at any time (past or present).
8. Patient currently receiving abiraterone and prednisone for metastatic prostate cancer.
9. The eligible patient will be currently on treatment with abiraterone/prednisone for castration-sensitive prostate cancer (CSPC) or castration-resistant prostate cancer (CRPC). Patients who have received abiraterone for CSPC must have had a response to hormonal therapy, as defined by any decline in PSA, radiographic response, and/or clinical benefit after starting hormonal therapy. Patients who have received abiraterone for CRPC must have responded to abiraterone, defined by any decline in PSA, radiographic response, and/or clinical benefit after starting abiraterone.
10. Two rising PSA values separated by at least 1 week, one showing a rise of at least 0.3 ng/mL and one confirmatory value not showing a decline, while on abiraterone therapy. Cycle 1 Day 1 PSA does not impact the eligibility to enroll/start treatment.
11. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1.
12. Patient has adequate bone marrow and organ function as shown by:
    1. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    2. Platelets ≥ 100 x 10^9/L
    3. Hemoglobin (Hgb) ≥ 9.0 g/dL
    4. Serum creatinine ≤ 2 x the upper limit of normal (ULN)
    5. Total serum bilirubin ≤ 1.5 x ULN (in patients with known Gilbert Syndrome, a total bilirubin ≤ 3.0 x ULN, with direct bilirubin ≤ 1.5 x ULN)
    6. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x ULN (or ≤ 5.0 x ULN if hepatic metastases are present)
13. The effects of onvansertib (study drug) on the developing human fetus are unknown. For this reason and because chemotherapeutic agents are known to be teratogenic, men must agree to use adequate contraception. Specifically, they must

agree to use a condom (even men with vasectomies) and another effective method of birth control if he is having sex with a woman of childbearing potential or agree to use a condom if he is having sex with a woman who is pregnant while on study drug and for 3 months following the last dose of study drug. They must also agree not to donate sperm during the study and for 3 months after receiving the last dose of study drug.

14. Patients with prior malignancies at low risk of recurrence (in the opinion of the Investigator) or patients with concurrent malignancies that are not likely to require treatment for the duration of the study are not excluded.

8.3.2 Exclusion Criteria

Patients must not meet any of the following exclusion criteria:

1. Inability to comply with study procedures.
2. Any condition that in the opinion of the Investigator, would preclude participation in this study.
3. Major surgery within 28 days prior to starting study drug or has not recovered from major side effects of the surgery.
4. Rapidly progressive symptoms of mCRPC.
5. Acute neurological dysfunction as a result of bone metastasis.
6. Previously treated with enzalutamide or experimental therapies directed against androgen receptor (ie, apalutamide).
7. Use of any chemotherapy, investigational agents, immunotherapy, or hormonal therapy (other than abiraterone), other than GnRH agonists within 28 days of the start of treatment on protocol. Use of bone targeted agents including bisphosphonates and RANK ligand inhibitors is allowed if on stable dose; Xgeva or Zometa cannot be started within 28 days of initiating study therapy.
8. Systemic corticosteroids except as part of on label treatment prostate cancer regimens. Note: Topical applications (eg, rash), inhaled sprays (eg, obstructive airways diseases), eye drops or local injections (eg, intra-articular) are allowed.
9. Treatment with any of the drugs listed in Section 8.4.5. at the time of study treatment initiation.
10. Has received wide field radiotherapy (including therapeutic radioisotopes such as radium 223) ≤ 28 days or limited field radiation for palliation ≤ 14 days prior to starting study drug or has not recovered from side effects of such therapy.
11. New York Heart Association (NYHA) Class III or IV heart disease, active ischemia or any other uncontrolled cardiac condition, or hypertensive or metabolic condition.
12. Myocardial infarction in the previous 12 weeks (from the start of treatment).

13. QT interval with Fridericia's correction [QTcF] [16] >470 milliseconds. The QTcF should be calculated as the arithmetic mean of the QTcF on triplicate ECGs. In the case of potentially correctible causes of QT prolongation, (e.g., medications, hypokalemia), the triplicate ECG may be repeated once during screening and that result may be used to determine eligibility.
14. Planned concomitant use of medications known to prolong the QT/QTc interval.
15. Presence of risk factors for torsade de pointes, including family history of Long QT Syndrome or uncorrected hypokalemia.

8.3.3 Removal of Patients from Therapy or Assessment

Patients will be discontinued from further study drug administration in the event of any of the following:

- Intolerable toxicity as determined by the Investigator
- Progression of disease requiring an alternate therapy, in the opinion of Investigator
- Entry into another therapeutic clinical study or start of additional anticancer therapy
- Significant deviation from the protocol or eligibility criteria, in the opinion of the Medical Monitor or Investigator
- Noncompliance with study procedures
- Patient withdrawal of consent and decision to discontinue participation
- Termination of the study by the Sponsor
- Any other reason that, in the opinion of the Investigator, would justify removal of the patient from the study

In the event that a patient is withdrawn from the study every effort will be made by the Investigator to document and report the reasons for withdrawal as thoroughly as possible. The reason(s) for withdrawal must be clearly reported on the appropriate page of the patient's electronic case report form (eCRF). An eCRF must be completed for any patient who receives study drug. An end-of-study reason must be recorded for any patient who receives study drug. The requirement for patient replacement is outlined in Section 11.

If a patient is discontinued from the study for any reason, every effort must be made to perform all EOS assessments (Section 9.1). In the event that the patient fails to return for the necessary visit(s), an effort must be made to contact the patient to determine the reason, and this information should be recorded in the appropriate source record and reported as a deviation.

8.4 STUDY DRUG TREATMENT

8.4.1 Description of Study Treatments

8.4.1.1 Onvansertib (Study Drug)

The chemical name of onvansertib (PCM-075H) is 1-(2-hydroxyethyl)-8-{[5-(4-methylpiperazin-1-yl)-2-(trifluoromethoxy) phenyl] amino}- 4,5-dihydro-1H-pyrazolo[4,3-h] quinazoline-3-carboxamide fumarate salt.

Onvansertib will be supplied as 5 mg and 20 mg (as free base) hard gelatin capsules that will be administered PO.

- A size 4 opaque caramel body and Swedish orange cap hard gelatin capsule contains 6.09 mg of onvansertib (PCM-075H) corresponding to 5 mg as free base, lactose monohydrate, pregelatinized starch, and glyceryl behenate. The capsule body shell contains gelatin, black iron oxide, red iron oxide, yellow iron oxide, and titanium dioxide; the capsule cap shell contains gelatin, red iron oxide, and titanium dioxide.
- A size 4 opaque Swedish orange body and cap hard gelatin capsule contains 24.36 mg of PCM-075H corresponding to 20 mg as free base, lactose monohydrate, pregelatinized starch and glyceryl behenate. The capsule shell contains gelatin, red iron oxide, and titanium dioxide.

DuBois formula for BSA calculation is acceptable, as is DFCI policy.

8.4.1.1.1 Storage Conditions

Onvansertib is stable at room temperature for up to 12 months. However, for optimal shelf-life, onvansertib is to be stored under refrigerated conditions (5°C ± 3°C; 36°F to 46°F) in the original packaging prior to usage. The research pharmacy may dispense onvansertib in standard pharmacy amber or white vials. It does not need to be transported with ice packs, but once brought to patient's home, it should be stored in a refrigerator, ideally within 24 hours.

Abiraterone and prednisone are standard-of-care and the patient will bring their medication with them and no dispensing instructions will be needed. DFCI can use DFCI SOC dispensing instructions.

8.4.1.1.2 Shelf-life

When onvansertib is stored at 5°C ± 3°C (36°F to 46°F), on the basis of the available stability information, a shelf-life of 48 months is currently assigned to the 5 mg and 20 mg (as free base) hard gelatin capsules.

Concurrent stability studies on the clinical batches are being conducted with 5 mg and 20 mg (as free base) hard gelatin capsules in order to evaluate the chemical, physical, and microbiological parameters. The onvansertib expiry date will be extended accordingly with the stability results. Any unexpected findings will be promptly communicated to Investigators and to the applicable regulatory authorities.

8.4.1.1.3 Dose Levels

The starting onvansertib (study drug) dose is 24 mg/m^2 administered PO on Day 1 through Day 5 every 14 days (1 cycle) – Arm B and 12 mg/m^2 on Day 1 through Day 14 every 21-days (1 cycle) – Arm C. Dosing of onvansertib can be administered at the same time the patient is administered their dose of abiraterone. Dosing of prednisone should be administered as prescribed. Since abiraterone is typically taken while on an empty stomach and therefore first thing in the morning, onvansertib can be dosed then as well but this is not required. There are no food restrictions (can be taken with or without food and no dietary instructions). However, on the first day of each cycle (when onvansertib is taken in clinic with abiraterone), patients will be fasting due to requirements for abiraterone. Dose rounding is to the nearest 5 mg, rounded up for dose calculations ending in 0.5-0.9. (For example, if 24 mg/m^2 dose is calculated at 43.5 mg, the dose would be rounded up to 45 mg, which would be provided as two 20 mg capsules and one five-mg capsule of onvansertib). Screening weight is acceptable for initial dose calculation. Sites may use their institutional standards for dose recalculation. A patient will not be enrolled in the study until they are deemed to have met eligibility criteria and successfully completed all screening evaluations.

8.4.1.1.4 Growth Factor Support (Arm B Only)

If Grade ≥ 3 neutropenia is noted in a patient in Arm B at the Day 8 lab checks during the first two cycles, or if a cycle is delayed due to Grade ≥ 3 neutropenia in a patient in Arm B, Investigators are strongly encouraged to add growth factor support for future cycles. This is especially encouraged if the patient has a history of neutropenia. Growth factor support could include standard doses of pegfilgrastim (6 mg subcutaneous once) given at least 24 hours after the Day 5 dose of onvansertib but no later than Day 8, or filgrastim (5 µg/kg/day subcutaneous daily) started at least 24 hours after the Day 5 dose of onvansertib and continued through nadir until there are two successive rises in ANC. If filgrastim is used, complete blood counts (CBCs) may need to be done twice weekly to monitor counts. The addition of growth factor support would not impact management of AEs or DLTs described above.

Growth factor support is considered non-standard-of-care and therefore billed to study Sponsor.

8.4.1.2 Abiraterone Acetate

The abiraterone acetate dose will be 1000 mg PO daily (QD) (unless previously dose-reduced for toxicity, in which case prior dose should be continued) on Day 1 through Day 21 (1 cycle) and all subsequent cycles. The dose of abiraterone can be modified in accordance with the product package insert (Appendix 19.3). It may not be crushed, chewed, or dissolved.

Storage of abiraterone should also be in accordance with the product package insert.

Abiraterone is to be taken while fasting at least 2 hours before each dose and at least 1 hour after each dose. Missed doses of abiraterone may be taken up to 12 hours after scheduled dosing time. If it is less than 12 hours prior to next scheduled dose, the missed dose will be

skipped and dosing will resume at next scheduled dosing time. If abiraterone is vomited, participants should not retake drug but should take it instead at the next scheduled time.

8.4.1.3 Prednisone

Prednisone dosing is all per the package insert and is standard-of-care. The prednisone dose will be 5 mg PO QD (unless previously started at 5 mg twice daily [BID] or increased for abiraterone toxicity, in which case prior dose should be continued) Day 1 through Day 21 (1 cycle) and all subsequent cycles. The dose of prednisone can be modified in accordance with the abiraterone product package insert (Appendix 19.3). It may be crushed, chewed, or dissolved.

Prednisone is generally taken with food. Missed doses of prednisone may be taken up to 12 hours after scheduled dosing time. If it is less than 12 hours prior to next scheduled dose, the missed dose will be skipped and dosing will resume at next scheduled dosing time. If prednisone is dosed twice daily, then the window for taking a missed dose is 6 hours after the scheduled dosing time. If prednisone is vomited, participants should not retake drug but should take it instead at the next scheduled time.

8.4.1.4 Androgen Suppression Therapy

Patients receiving GnRH agonist/antagonist therapy prior to study entry should remain on their current treatment throughout the study period.

8.4.2 Dosing Schedule

Patients will receive study drugs according to the dosing schedule outlined in Section 9.1.

8.4.3 Study Drug Inventory and Accountability

In accordance with current Good Clinical Practice (GCP), each study site will keep an accounting of all study drug supplies. Details of receipt, storage, administration, and return or destruction will be recorded in the study drug accountability record according to the standard operating procedure of the study site. Copies of the study drug accountability record will be provided to the Sponsor.

Study drug must only be dispensed to patients enrolled in the study and only as directed by this protocol. Administration of study drugs will be accurately recorded in each patient's source documents and case report form.

8.4.4 Treatment Compliance

The study drug will be administered PO as 5 mg and 20 mg hard gelatin capsules. Compliance will be ascertained by Investigational Site staff by individual patient assessment and monitoring per the site standard operating procedures. The Sponsor will provide a diary for patients to track their daily medication intake.

8.4.5 Concomitant Medications and Treatments

Concomitant medications are all medications (or treatments) other than study drugs that are taken or received by the patient at any time during the study starting at the time that the first dose of study drug was administered through the final study visit assessment. Use of all concomitant medications, including any change in therapy, must be recorded and updated in the source documentation and on the case report form.

All inter-current medical conditions will be treated at the discretion of the Investigator according to acceptable community and/or institutional standards of medical care.

The following medications are prohibited during the study:

- Investigational agents
- Other antineoplastic agents
- Radiotherapy
- 5 α reductase inhibitors
- Chemotherapy
- Immunotherapy
- Anti-androgens (eg, bicalutamide, nilutamide, flutamide, cyproterone acetate)
- Systemic ketoconazole (or other azole drugs such as fluconazole or itraconazole)
- Diethylstilbestrol or similar and other preparations such as saw palmetto thought to have endocrine effects on prostate cancer
- Radiopharmaceuticals such as strontium (89Sr) or samarium (153Sm) or similar analogues such as radium-223
- Digoxin, digitoxin, and other digitalis drugs
- Fludrocortisone acetate (Florinef)

9 ASSESSMENTS

9.1 Schedule of Assessments

The Schedule of Assessments is provided in Table 9-1.

Every attempt should be made to have each patient attend each visit as scheduled. Per protocol blood collection time points should be adhered to as closely as possible.

Table 9-1 Schedule of Assessments

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			
Hematology, including CBC with differential, and platelet count[d]	X	X	X	X	
Prostate-specific antigen[e]	X	X	X	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)	
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 [redacted]).

[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.

9.2 Study Visits

The following sections describe the pretreatment, treatment, and post-treatment evaluations in this study.

9.2.1 Screening

The Investigator is responsible for keeping a record of all patients screened for entry into the study and those that are subsequently excluded. The reason(s) for patient exclusion from the study must also be recorded.

Each patient (or patient's legal representative if applicable) must provide written informed consent before any study specific assessments may be performed.

The following screening procedures must be performed within 28 days prior to enrollment:

1. Record ECOG performance status
2. Complete medical history, as well as Gleason score and TNM stage at diagnosis
3. A careful history of all prior systemic and radiation treatments, including radiation site, administered dose per fraction and treatment duration
4. Physical examination, including height (at screening only), weight, vital signs, and general physical examination
5. Blood sample collection for clinical chemistry laboratory testing
6. Blood sample collection for hematology laboratory testing, including CBC panel, including differential and platelet count
7. Blood sample collection for PSA
8. Blood sample for ctDNA analysis
9. Recording of concomitant medication use
10. Radiographic scans, including CT abdominal/pelvis with contrast (or MRI if contraindication to intravenous contrast) and bone scan.
11. Confirmation of all eligibility criteria

9.2.2 Treatment Period

9.2.2.1 Evaluations During Treatment

9.2.2.1.1 Day 1 – Cycle 1

1. Physical examination, including weight and vital signs
2. Blood sample collection for clinical chemistry laboratory testing
3. Blood sample collection for hematology laboratory testing, including CBC panel, including differential and platelet count
4. Blood sample collection for PSA prior to treatment of abiraterone and onvansertib
5. Blood sample collection for CTCs prior to administration of abiraterone and onvansertib
6. Blood sample collection for androgen receptor splice variant 7 (AR-V7) test prior to administration of abiraterone and onvansertib

7. Blood sample collection for CTC enumeration prior to administration of abiraterone and onvansertib
8. Study drug administration (onvansertib can be administered at the same time as the dose of abiraterone):
    a. Onvansertib (Days 1 through 5- Arm B and Days 1 through 14 – Arm C): Day 1 dose to be administered in clinic
    b. Abiraterone (throughout the cycle): Day 1 dose to be administered in clinic (see note in Study Calendar)
    c. Prednisone (throughout the cycle): can be taken as directed at a different time after the PD samples are obtained
9. Adverse event and concomitant medication recording

9.2.2.1.2 Day 8 for the first 12 weeks of treatment

1. Blood sample collection for hematology laboratory testing, including CBC panel, including differential and platelet count
2. Blood sample collection for PSA
3. Patients do not need to bring their doses of abiraterone and onvansertib (Arm C) to the clinic on Day 8 and can take them at home beforehand as they normally would

9.2.2.1.3 Day 15 (Arm C only) for the first 12 weeks of treatment

1. Blood sample collection for hematology laboratory testing, including CBC panel, including differential and platelet count
2. Blood sample collection for PSA
3. Patients do not need to bring their dose of abiraterone to the clinic on Day 15 and can take it at home beforehand as they normally would

9.2.2.1.4 Day 1– Cycle 2 and Beyond

1. Physical examination, including weight and vital signs
2. Blood sample collection for clinical chemistry laboratory testing
3. Blood sample collection for hematology laboratory testing, including CBC panel, including differential and platelet count
4. Blood sample for collection of ctDNA prior to administration of abiraterone and onvansertib, Cycles 2 to 7 for Arm B and Cycles 2 to 5 for Arm C
5. Blood sample collection for CTC enumeration prior to administration of abiraterone and onvansertib, Cycle 7 for Arm B and Cycle 5 for Arm C
6. Blood sample collection for PSA
7. Radiographic scans, including CT abdominal/pelvis with contrast (or MRI if contraindication to intravenous contrast) and bone scan. Radiographic imaging will be obtained up to 7 days before Day 1 after every 6th cycle for Arm B (eg, up to 7 days before Day 1 of Cycle 7, Day 1 of Cycle 13, Day 1 of Cycle 19) and after every 4th cycle for Arm C (eg, up to 7 days before Day 1 of Cycle 5, Day 1 of Cycle 9, Day 1 of Cycle 13) until EOS.
8. Adverse event and concomitant medication recording

9.2.3 End of Study/Follow-Up

Within 28 days after the last dose of onvansertib, the following evaluations will be conducted:

1. Physical examination, including weight and vital signs
2. Adverse event and concomitant medication recording
3. Blood sample for ctDNA
4. Blood sample collection for CTC enumeration if patient has discontinued treatment before Cycle 7 for Arm B and before Cycle 5 for Arm C
5. Blood sample collection for PSA

Any patient with a suspected study drug-related toxicity at the last follow-up visit must be followed until resolution or until the event is considered irreversible. This may require additional clinical assessments and laboratory tests. The follow-up results will be recorded on the appropriate page of the CRF, as well as in the patient's source documentation.

9.3 Efficacy Assessments

All patients treated at the final recommended dose level and evaluable for efficacy will be assessed for response to treatment using the recommendations of the PCWG3 for standardization of response criteria, treatment outcomes, and reporting for therapeutic studies.[1] If any dose of onvansertib is missed in Days 1-5 of a cycle (Arm B) or Days 1-14 of a cycle (Arm C) this will need to be documented. The primary analysis will be performed as intention-to-treat, including all patients who received any doses of onvansertib.

The primary efficacy variable is disease control assessed by PSA and radiographic scans and symptoms evaluated by the Investigator. All radiographic progression events should be reviewed by the overall PI to ensure adherence to PCWG3 criteria; in particular, bone scans must have number of lesions enumerated to confirm progression per PCWG3. PSA levels will be collected at baseline, on Days 1 and 8 of first 6 cycles (Arm B) and on Days 1, 8, and 15 of Cycles 1-4 (Arm C). PSA levels will also be collected on Day 1 of each cycle after Cycle 6 (Arm B) and after Cycle 4 (Arm C) and at end-of-study (EOS).

Efficacy Endpoints:

- Proportion of patients achieving disease control after 12 weeks of study treatment, as defined by lack of PSA progression (per PCWG3 criteria)
- 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 criteria)
- Radiographic response (RECIST 1.1) in patients with measurable disease

9.4 Safety Assessments

Toxicity will be graded using the National Cancer Institute Common Terminology Criteria (NCI-CTCAE version 4.03; Appendix 19.1).

- Safety analysis will be conducted on all patients who have received at least one dose of study drug, and will include the frequency of all AEs and laboratory abnormalities as well as the frequency of dose interruptions, dose reductions, and treatment discontinuation.
- A DLT is defined as a Grade 4 hematologic AE or Grade ≥3 non-hematologic AE that is considered related to the study drug (onvansertib). A DLT would result in a hold of drug until a hematologic DLT resolved to Grade 2 or less, or a nonhematologic DLT resolved to Grade 1 or less. The DLT must resolve within 2 weeks or the patient will be discontinued from study treatment. If the DLT resolves, the dose of onvansertib will be reduced by 25%(18 mg/m^2- Arm B or 9 mg/m^2 – Arm C) in subsequent cycles. If a DLT occurs at the 25%reduced dose and resolves within 2 weeks, then the patient can proceed at a 50% reduced dose (12 mg/m^2 – Arm B or 6 mg/m^2 – Arm C). If subsequent DLTs occur at the 50%reduced dose that do not resolve within 2 weeks, then the patient should be discontinued from the study. If a patient experiences excessive toxicity at 50% of the original starting dose, that patient should be discontinued from study treatment. See Table 8-1 for dose modifications related to hematologic and nonhematologic DLTs.
- Additional safety assessments will include physical examination; medical history (including Gleason score and TNM stage at diagnosis); ECOG performance status; weight; vital signs measurements; and clinical laboratory testing.

Safety assessments will be performed as per the Schedule of Assessments (Section 9.1). Safety assessment may be performed at additional time points during the study at the discretion of the Investigator in the interest of patient safety.

The Investigators will monitor patients for safety and to evaluate efficacy of onvansertib doses to minimize exposure of patients to a non-efficacious dose level.

9.5 Pharmacodynamic and Correlative Biomarker Evaluation

Pharmacodynamic and correlative biomarker evaluation will be obtained as outlined in Table 9-1. Details of the pharmacodynamic and biomarker evaluations will be included in the laboratory manual. Required tubes are listed in the footnotes of the Schedule of Assessments.

10 ADVERSE EVENT REPORTING

10.1 Definitions

10.1.1 Adverse Event

An AE is defined in Title 21 Code of Federal Regulations (CFR) 312.32(a) as follows:

- Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An AE can arise with any use of the drug (eg, off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

10.1.2 Unexpected Adverse Events

An unexpected AE is defined in 21 CFR 312.32(a) as follows:

- An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

10.1.3 Serious Adverse Event

A serious adverse event (SAE) is defined in 21 CFR 312.32(a) as follows:

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- Patient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in patient hospitalization, or the development of drug dependency or drug abuse.

An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

10.1.4 Definition of Dose-limiting Toxicities

DLTs are defined as a Grade 4 hematologic AE or Grade ≥ 3 non-hematologic AE that is considered related to the study drug. A DLT would result in a hold of drug until a hematologic DLT resolved to Grade 2 or less or a nonhematologic DLT resolved to Grade 1 or less. The DLT must resolve within 2 weeks or the patient will be discontinued from the study. The DLT period for patients in the safety lead-in phase is the initial two 14-day cycles (Arm B) or one 21-day cycle (Arm C), plus an additional 2 weeks for a hematologic DLT to resolve to Grade 2 or less, or a nonhematologic DLT to resolve to Grade 1 or less, if warranted. DLTs that occur during this time will result in additional patients accrued to safety lead-in and potentially dose modifications, as per the protocol. If the DLT resolves, the dose of onvansertib will be reduced by 25% (18 mg/m^2 – Arm B or 9 mg/m^2 – Arm C). All AEs must be attributed to study drug unless there is a reasonably acceptable alternate cause for the AEs. DLTs are continually assessed throughout the treatment period and addressed per the protocol (**Error! Reference source not found.**).

10.2 Severity of Adverse Events

Each AE will be graded according to the NCI-CTCAE version 4.03 (Appendix 19.1). In most cases AE terms will be listed in the CTCAE, with grading criteria specific to that term. If the AE is not specifically defined in the CTCAE, it is to be reported using the "Other, specify" term under the appropriate system organ class and graded according to the general CTCAE severity guidelines.

10.3 Relationship of Adverse Events to the Study Drug

The Investigator must attempt to determine if an AE is in some way related to the use of onvansertib. All AEs must be attributed to study drug unless there is a reasonably acceptable alternate cause. This relationship should be described as follows:

- **Unrelated:** The event has no temporal relationship to study drug administration (too early or late or study drug not taken), or there is a reasonable causal relationship between the AE and another drug, concurrent disease or circumstance.
- **Unlikely:** The event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
- **Possibly:** The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug BUT the event could have been produced by an intercurrent medical condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be

unlikely related to the use of the study drug or the event could be the effect of a concomitant medication.

- **Probably:** The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug AND the event cannot have been reasonably explained by an intercurrent medical condition or the event cannot be the effect of a concomitant medication.
- **Definitely:** The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug.

10.4 Monitoring of Adverse Events

AEs will be monitored continuously during the study starting immediately after the first dose of study drug is administered. Patients will be instructed to report all AEs experienced during the study, and patients will be assessed for the occurrence of AEs throughout the study.

All AEs will be followed until resolution or stabilization of the event. This may require additional clinical assessments and laboratory tests.

10.5 Reporting Procedures

10.5.1 Routine Reporting of Adverse Events

AEs, whether or not associated with study drug administration, will be recorded on the AE form of the CRF and will be submitted to the Sponsor at regularly scheduled intervals.

The information to be entered in the CRF will include:

1. Time of onset of any new AE or the worsening of a previously observed AE. In most cases, date of onset will be adequate; however, for days when the patient is in the clinic and receives study drug, the time (based on a 24-hour clock) of onset should also be recorded
2. Specific type of reaction in standard medical terminology
3. Time of resolution of the event (or confirmation ongoing). In most cases, date of resolution will be adequate; however, for events that initiate and resolve on days where the patient is in the clinic and receives study drug, the time (based on a 24-hour clock) of resolution should also be recorded
4. Severity/grade of AE. The severity should be rated according to NCI-CTCAE version 4.03 (Appendix 19.1)
5. An assessment should be made of the relationship of the AE to the study drug according to the definitions outlined in Section 10.3
6. Description of action taken in treating the AE and/or change in study drug administration or dose

Follow-up assessments should be repeated to document return of any abnormalities to normal, or to document other outcome of the AE.

10.5.2 Reporting of Serious Adverse Events, Including Death

Serious adverse events, including death due to any cause, which occur during this study or within 30 days following the last dose of onvansertib, whether or not related to the administration of study drug, must be reported to the Medical Monitor by telephone or email **within 24 hours of learning of the event**.

Serious adverse event forms will be provided by the Sponsor or Sponsor Designated Contract Research Organization. The study site should send the SAE Form to the Medical Monitor as soon as possible so that the tracking procedure can begin immediately upon receipt of the information. Once the Medical Monitor is informed of an SAE with preliminary information obtained, the study site will be instructed to update the SAE Form with additional information, as per the following guidelines.

If all information is not known at the time of the incident, an initial report should still be made. In the event there is a question as to whether the event is serious, the information should be forwarded to the Medical Monitor for review. The Investigator is responsible for following up on completion of the SAE Form. The Investigator will submit substantiating data in hard copy form, such as diagnostic test reports and progress notes, to the Medical Monitor. In the case of fatality, autopsy reports will be furnished to the Medical Monitor as soon as available.

During the initial communication, the Medical Monitor will require the following information about the patient and the reported SAE:

1. Patient identification including patient number, initials, and date of birth
2. Date of first dose of study drugs and details of administration, including study drug names (including labeled strength and manufacturer), lot number, expiration date, and dose
3. Date of last dose of study drugs (ie, prior to onset of SAE) and details of administration, including study drug names (including labeled strength and manufacturer, lot number, expiration date, and dose)
4. Medical diagnosis of the event in standard medical terminology (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event)
5. Date of onset of the AE
6. Date of resolution of the AE (or confirmation ongoing)
7. Severity of the AE (see Section 10.2)
8. Assessment of the attribution of the AE to the study drug (see Section 10.3)
9. Reason AE is considered serious (per definition in Section 10.1.3)
10. Whether the AE is expected (see Section 10.1)
11. Action taken in treating the AE and/or change in study drug administration or dose (including concomitant medications or therapies administered, whether hospitalization or prolongation of hospitalization was required, diagnostic procedures performed, and whether the patient was discontinued from the study)
12. All concomitant medications (including doses, routes, regimens, and indications)
13. Pertinent clinical laboratory testing data

14. Medical history

The Investigator and the Medical Monitor will review each SAE report and evaluate the relationship of the adverse experience to study drugs and to underlying disease. Based on the Investigator's and Medical Monitor's assessment of the adverse experience, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of patients participating in the clinical study. If the discovery of a new adverse experience related to the study drug raises concern over the safety of continued administration of study drug, the Sponsor will take immediate steps to notify the regulatory authorities.

Further action that may be required includes the following:

1. Alteration of existing research by modification of the protocol
2. Discontinuation or suspension of the study
3. Alteration of the informed consent process by modification of the existing consent form and informing current study participants of new findings
4. Modification of previously identified expected adverse experiences to include adverse experiences newly identified as study medication-related

Any SAE that is determined by the Sponsor to be reportable to Food and Drug Administration (FDA) as an Investigational New Drug (IND) Safety Report [as defined in 21 CFR 312.32] will be reported to FDA by the Sponsor within the specified time frame. All IND Safety Reports will also be promptly provided to the Investigator for submission to his or her Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Similarly, any SAE that is determined by the Sponsor to require expedited reporting to other regulatory authorities will be reported to the appropriate authorities by the Sponsor within the specified time frames, and will be provided to the Investigator for submission to his or her IRB/IEC.

10.5.3 Other Events Requiring Immediate Reporting

10.5.3.1 Overdose

An overdose is defined as a patient receiving a dose of investigational product in excess of that specified in the IB, unless otherwise specified in this protocol. Any overdose of a study patient with the investigational product, with or without associated AEs/SAEs, is required to be reported to the Medical Monitor within 24 hours of knowledge of the event. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE.

10.5.3.2 Pregnancy

Should the Investigator become aware of a pregnancy of a female partner of a male participant, the pregnancy should be reported within 24 hours of knowledge of the event. After obtaining the patient's consent (or patient and pregnant partner's consent in the case of a male participant), monitoring of the pregnancy and infant should comply the following procedures:

- If the outcome is an abnormal neonate (infant), as much follow-up information as possible to permit evaluation of the case will be collected, including where possible, medical confirmation, medical investigations and medical record summary details. Follow up should continue for at least one year post birth.
- If the outcome is a normal neonate, follow-up data should continue for one month.

11 PATIENT DISCONTINUATION AND TRIAL DISCONTINUATION

11.1 Patient Discontinuation

A patient may choose to withdraw from this study at any time for any reason without penalty of jeopardizing their health care or loss of benefits to which the patient is otherwise entitled.

Patients will be discontinued from study drug (onvansertib) treatment if one or more of the following events occur:

1. Clinically significant progressive disease
2. Patient refusal to remain on study
3. Non-compliance or inability to comply with protocol requirements by patient
4. Development of unacceptable toxicity (regardless of study drug relationship)
5. Determination by the Investigator that it is no longer safe for the patient to continue therapy.

Patients who have an ongoing AE at the time of discontinuation will continue to be followed until resolution of the event to Grade ≤1 or baseline, or until the event is considered irreversible.

Patients who are discontinued prior to completing the first treatment cycle (21 days) for any reason other than toxicity, or who have not received at least 80% of the intended doses, will be replaced.

11.2 Study Discontinuation

Treatment may be continued longer at the discretion of the treating physician if there is no evidence of disease progression and the patient is not experiencing unacceptable toxicity, and if both the patient and physician agree that further therapy is in the patient's best interest.

If onvansertib is discontinued, the patient may remain on abiraterone/prednisone at the discretion of the Investigator but the patient will be discontinued from the trial.

The Sponsor has the right to terminate this study, and the Investigator/Investigational Site has the right to close the site, at any time, although this should occur only after consultation between involved parties. The Investigator must notify the IRB/IEC in writing of a premature termination of a study or closure of Investigational Site, and must send a copy of the notification to the Sponsor.

At any time during the trial, the Principal Investigator and Sponsor can make the decision to discontinue one of the arms.

Events that may trigger premature termination of a study or closure of an Investigational Site include, but are not limited to, a new toxicity finding, a request to discontinue the study from a regulatory authority, non-compliance with the protocol, slow recruitment, or change in development plans for the study drug.

12 STATISTICAL METHODS

12.1 Determination of Sample Size

This is a study that consists of determining the disease control rate of onvansertib in combination with abiraterone 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, dosing of subsequent patients may begin, and an additional 29 patients in each arm will be enrolled at the same dose level.

A maximum of 90 patients (45 in each arm) will be enrolled to ensure 32 evaluable patients in each arm at the final 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. 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 (ie, patients who cross-over are not analyzed for efficacy based on the new treatment arm); however, changes in the temporal PSA trajectory after crossing over will be assessed in the treatment arm to which the subject is currently assigned.

The study arm will terminate early if 0 or 1 out of the first 13 patients in the respective arm achieve disease control at 12 weeks. Assuming the study continues to full enrollment, if 6 or more out of a total of 32 patients in one or both arms achieve disease control at 12 weeks, the experimental treatment will be considered potentially effective at the corresponding dose schedule. The probability of stopping at the first stage is 0.62.

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.

12.2 Statistical Analysis of Safety Data

Data from all patients who receive at least one dose of study drug (onvansertib) will be included in the safety analysis.

Safety will be assessed primarily based on AEs. The severity of AEs will be graded as mild, moderate, severe, or life-threatening according to NCI-CTCAE version 4.03 (Appendix 19.1). All reported toxicities, regardless of attribution, by toxicity type and maximum grade will be summarized, and sorted by number of patients experiencing the toxicity. The maximum grade

consolidates the reports of a given toxicity for a patient over time by taking the maximum across time.

12.3 Statistical Analysis of Efficacy Data

Patients treated at the final recommended dose will be included in the efficacy analysis. For the primary analysis, disease control rate (total number of patients with stable disease or better divided by total number of patients with at least one dose of onvansertib) will be summarized as percentage with 90% CI. Maximum PSA decline will be summarized using waterfall plot graphically.

The completion of study drug onvansertib will be evaluated, investigated, and summarized descriptively although we do not expect many patients with non-adherence issues.

The secondary analysis will be per-protocol analysis, the study populations are patients who complete 100% of study drug and patients who complete 90% of study drug scheduled during the first four cycles. Disease control rate will be summarized as percentages with 90% CI for each of the 2 cohorts. 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 (ie, patients who cross-over are not analyzed for efficacy based on the new treatment arm); however, changes in the temporal PSA trajectory after crossing over will be assessed in the treatment arm to which the subject is currently assigned.

Time to PSA progression and time to radiological progression will be summarized using Kaplan Meier estimates in patients who received at least one dose of protocol therapy.

Best overall response by RECIST 1.1 will be summarized in patients who received at least one dose of protocol therapy.

13 ACCESS TO SOURCE DOCUMENTS AND RETENTION OF RECORDS

The Investigator will make the source documents for this study available for monitoring by the Sponsor or its representatives, or by regulatory authorities or health authority inspectors.

Patient medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. All reports and communications relating to patients in this study will identify each patient only by their initials and number. Medical information resulting from a patient's participation in this study may be given to the patient's personal physician or to the appropriate medical personnel responsible for the patient's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, the Sponsor (or designee), and the IRB/IEC.

The information developed in this clinical study will be used by the Sponsor in the clinical development of the study drug and therefore may be disclosed by the Sponsor as required for disclosure as a public company to other clinical Investigators, to other pharmaceutical companies, to the FDA and to other government agencies.

Any information, inventions, or discoveries (whether patentable or not), innovations, suggestions, ideas, and reports, made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions, as the Sponsor deems necessary or appropriate to obtain patents in the Sponsor's name covering any of the foregoing.

The Investigator will retain all study documents for at least 2 years after the last approval of a marketing application in an International Council for Harmonisation (ICH) region (ie, US, Europe, or Japan), and until there are no pending or contemplated marketing applications in an ICH region. If no application is filed or if the application is not approved for such indication, the Investigator will retain all study documents for at least 2 years after the Investigation is discontinued and regulatory authorities have been notified.

The Investigator will notify the Sponsor prior to destroying any study records. Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in writing in advance.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements will be made between the Investigator and the Sponsor for storage. If source documents are required for continued care of the patient, appropriate copies for storage off-site will be made.

14 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Data Collection

All data required by the study protocol will be entered onto case report forms and must be verifiable against source documents. Case report forms will be completed for every patient who is enrolled in this study.

Only authorized Investigational Site personnel will enter data on the case report forms. Any corrections to data entered into the case report form will be made in such a way that the original entry is not obscured. The date of the correction and the initials of the person making the correction will be documented.

The case report forms will be kept up-to-date by the Investigator and the research staff at the Investigational Site. The Investigator will be responsible for reviewing all data and case report form entries and will sign and date each patient's case report form, verifying that the information is true and correct.

14.2 Study Monitoring

The study will be monitored to evaluate the progress of the study, to verify the accuracy and completeness of the case report forms, to assure that all protocol requirements, applicable laws and/or regulations, and Investigator's obligations are being fulfilled, and to resolve any inconsistencies in the study records.

The Investigator will allow the study monitor to periodically review, at mutually convenient times during the study and after the study has been completed, all case report forms and office, hospital, and laboratory records supporting the participation of each patient in the study.

The study monitor will compare the case report form data against source documentation in order to verify its accuracy and completeness. The Investigator and research staff will collaborate with the study monitor to resolve any identified data discrepancies in a timely manner.

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 (see Section 8.4.5), 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 study monitor will compare the Investigational Site study drug accountability record against the study drug inventory (unused and used) at the site. The Investigator and research staff will collaborate with the study monitor to resolve any identified discrepancies in a timely manner.

Each issue identified during study monitoring visits will be documented and reported to both the Sponsor and the Investigator.

14.3 Data Management

After the case report forms have been reviewed by the study monitor and all identified discrepancies have been identified, the Investigator signed copy of the case report forms will be forwarded to PRA (the Clinical Research Organization for the study) Data Management. PRA is responsible for data and safety monitoring. Queries generated by Data Management will be sent to the study site for resolution. The Investigator is responsible for the review and approval of all responses.

All case report form data will be entered into a validated database and an electronic audit study of edits maintained. Laboratory data may be imported to the database electronically.

The database will be authorized for lock once no data queries are outstanding, all study data are considered clean, and all defined procedures completed.

14.4 Sponsor Audits

At some point during the study, individuals from the Sponsor's Quality Assurance group or their authorized representative may visit the Investigator's site to conduct an audit of the study. The purpose of this visit will be to determine the Investigator's adherence to the protocol, applicable regulations, and the Sponsor's procedures, in addition to assessing the accuracy of the study data. Prior to initiating this audit, the Investigator will be contacted by the Sponsor to arrange a convenient time for this visit. The Investigator and staff will cooperate with the auditors and allow access to all patient records supporting the case report forms and other study-related documents.

14.5 Inspection by Regulatory Authorities

At some point during the study, a regulatory authority may visit the Investigator to conduct an inspection of the study. The Investigator and staff will cooperate with the inspectors and allow access to all source documents supporting the case report forms and other study-related documents. The Investigator will immediately notify the Sponsor when contacted by any regulatory authority for purposes of conducting an inspection.

15 ETHICS

15.1 Declaration of Helsinki

The study will be conducted in accordance with the Declaration of Helsinki.

15.2 Good Clinical Practice and Regulatory Compliance

This study will be conducted in accordance with the principles of GCP (current ICH guideline) and the requirements of all local regulatory authorities regarding the conduct of clinical studies and the protection of human patients.

15.3 Institutional Review Board/Independent Ethics Committee

The protocol, informed consent form (ICF), IB, and any materials (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) for this study will be reviewed and approved by a duly constituted IRB/IEC.

The Investigator will ensure that all aspects of the IRB/IEC review are conducted in accordance with current institutional, local, and national regulations. A letter documenting the IRB/IEC approval will be provided to the Sponsor prior to initiation of the study.

Amendments to the protocol will be patient to the same requirements as the original protocol. A letter documenting the IRB/IEC approval will be provided to the Sponsor prior to implementation of the changes described in the protocol amendment.

Revisions to the ICF will be reviewed and approved by the IRB/IEC prior to use in the study. The Investigator will inform the IRB/IEC of all reportable AEs. IND Safety Reports provided by the Sponsor to the Investigator will be promptly forwarded to the IRB/IEC by the Investigator. Updates to the IB provided by the Sponsor to the Investigator will be submitted to the IRB/IEC by the Investigator.

The Investigator will submit all periodic reports and updates that the IRB/IEC may require. After completion or termination of the study, the Investigator will submit a final report to the IRB/IEC. The structure and content of the report will meet that described in Structure and Content of Clinical Study Reports E3 (ICH Harmonized Tripartite Guideline, dated November 30, 1995).

15.4 Informed Consent

No study-related procedures, including screening evaluations, will be performed until the patient has given written informed consent.

The ICF will clearly describe the nature, scope, and potential risks and benefits of the study, in a language that the patient understands. The ICF will conform to all the requirements for informed consent according to ICH GCP and US FDA guidelines (21 CFR 50) and any additional elements required by the Investigator's institution or local regulatory authorities. The Investigator will submit the ICF to the IRB/IEC for review, and will provide the Sponsor with a letter documenting the IRB/IEC approval prior to initiation of the study.

The IRB/IEC approved ICF will be given to each prospective participant. The patients will be given adequate time to discuss the study with the Investigator or site staff and to decide whether or not to participate. Each patient who agrees to participate in the study and who signs the ICF will be given a copy of the signed, dated, and witnessed document. The original signed ICF will be retained by the Investigator in the study files.

The Investigator will also obtain authorization from the patient to use and/or disclose Protected Health Information in compliance with Health Insurance Portability and Accountability Act (HIPAA) or equivalent. Written HIPAA authorization may be obtained as part of the informed consent process.

If a protocol amendment substantially alters the study design or increases the potential risk to the patient, or the known risks of the study drug change over the course of the study, the ICF will be revised and submitted to the IRB/IEC for review and approval. The revised ICF must be used to obtain consent from patients currently enrolled in the study if they are affected by the amendment and to obtain consent from new patients prior to enrollment.

15.5 Emergency Departure from Protocol

When an emergency occurs that requires a departure from the protocol for an individual, a departure will be only for that patient. The Investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the Sponsor's Medical Monitor immediately by telephone. Such contacts will be made as soon as possible to permit a decision as to whether or not the patient (for whom the departure from protocol was affected) is to continue in the study. The case report form and source documents will completely describe the departure from the protocol and state the reasons for such departure. In addition, the IRB/IEC will be notified in writing of such departure from protocol.

16 PUBLICATION POLICY

All information and data obtained in the course of the study are the property of the Sponsor and are considered confidential. To avoid disclosures that could jeopardize proprietary rights, the institution and/or the Investigator agree to certain restrictions on publications (eg, abstracts, speeches, posters, manuscripts, and electronic communications), as detailed in the clinical study agreement.

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, HIPAA or equivalent.

17 PROTOCOL AMENDMENTS AND MODIFICATIONS

The Investigator will ensure that the study is conducted in accordance with the procedures and evaluations described in this protocol. The Investigator will not modify the protocol without first receiving Sponsor authorization to do so, except in those cases intended to reduce immediate risk of the patients. The Sponsor is responsible for submitting protocol amendments to the appropriate governing regulatory authorities. The Investigator is responsible for submitting protocol amendments to the appropriate IRB/IEC. Approval by the IRB/IEC will be obtained before protocol modifications are implemented, except in those cases intended to reduce immediate risk to patients.

18 REFERENCES

1. Scher H, Morris M, Stadler W. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations from the Prostate Cancer Clinical Trials Working Group 3. Journal of Clinical Oncology. 2016;24:1402-18.

2. World Health Organization. WHO World Cancer Report. 2014.

3. Yamaoka M, Hara T, Kusaka M. Overcoming persistent dependency on androgen signaling after progression to castration-resistant prostate cancer. Clin Cancer Res. 2010 Sep 1;16(17):4319-24.

4. Mateo J, Carreira S, Sandhu S. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N Engl J Med. 2015 Oct 29;373(18):1697-708.

5. Li Z, Bishop AC, Alyamani M, et al. Conversion of abiraterone to D4A drives anti-tumour activity in prostate cancer. Nature 2015;523:347-51.

6. de Bono J, Logothetis C, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364(21):1995-2005.

7. Fizazi, K, Scher, H, Molina, A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012;13(10):983-92.

8. Ryan C, Molina A, Griffin T. Abiraterone in metastatic prostate cancer. N Engl J Med. 2013;368(15):1458-9.

9. Taplin M, Montgomery B, Logothetis C. Intense androgen-deprivation therapy with abiraterone acetate plus leuprolide acetate in patients with localized high-risk prostate cancer: results of a randomized phase II neoadjuvant study. J Clin Oncol. 2014;32(33):3705-15.

10. Fizazi K, Tran N, Fein L. et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2017;377(4):352-360.

11. de Bono J, Spears M. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med. 2017;377(4):338-351.

12. Chi K, Annala M, Sunderland K. A randomized phase II cross-over study of abiraterone + prednisone (ABI) vs enzalutamide (ENZ) for patients (pts) with metastatic, castration-resistant prostate cancer (mCRPC). Genitourinary (Prostate) Cancer. Abstract 5002. 2017.

13. Tannock I, de Wit R, Berry W, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351(15):1502-12.

14. Petrylak D, Tangen C, Hussain M, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med. 2004;351(15):1513-20.

15. de Bono J, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376(9747):1147-54.

16. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013 Jul 18;369(3):213-23.

17. Weiss GJ, Jameson G, VonHoff DD, Phase I dose escalation study of NMS-1286937, an orally available Polo-like Kinase 1 inhibitor, in patients with advanced or metastatic solid tumors. Invest New Drugs. 2017 Jul 20. 10637-017-0491-7.

18. Wolf G, Elez R, Doermer A, Holtrich U, Ackermann H, Stutte HJ, *et al*. Prognostic significance of polo-like kinase (PLK) expression in non-small cell lung cancer. Oncogene 1997;14(5): 543-9.

19. Weichert W, Kristiansen G, Schmidt M, Gekeler V, Noske A, Niesporek S, *et al*. Polo-like kinase 1 expression is a prognostic factor in human colon cancer. World J Gastroenterol. 2005; 11(36): 5644-50.

20. Weichert W, Schmidt M, Gekeler V, *et al.* Polo-like kinase 1 is overexpressed in prostate cancer and linked to higher tumor grades. Prostate 2004; 60(3): 240-5.

21. Weichert W, Denkert C, Schmidt M, *et al.* Polo-like kinase isoform expression is a prognostic factor in ovarian carcinoma. Br. J. Cancer 2004; 90: 815-821.

22. Weichert W, Kristiansen G, Winzer KJ, *et al.* Polo-like kinase isoforms in breast cancer: expression patterns and prognostic implications. Virchows Arch 2005; 446: 442-450.

23. Knecht R, Elez R, Oechler M, et al. Prognostic Significance of Polo-like Kinase (PLK) Expression in Squamous Cell Carcinomas of the Head and Neck. Cancer Res 1999; 59: 2794-2797.

24. Renner AG, Dos Santos C, Recher C, et al. Polo-like kinase 1 is overexpressed in acute myeloid leukemia and its inhibition preferentially targets the proliferation of leukemic cells. Blood. 2009; 114(3): 659-62.

25. Mito K, Kashima K, Kikuchi H, et al. Expression of Polo-Like Kinase (PLK1) in non-Hodgkin's lymphomas. Leukemia and Lymphoma. 2005; 46(2): 225-31.

26. Ikezoe T, Yang J, Nishioka C, et al. A novel treatment strategy targeting polo-like kinase 1 in hematological malignancies. Leukemia. 2009; 23(9): 1564-76.

27. Kauselmann G, Weiler M, Wulff P, *et al.* The polo-like protein kinases Fnk and Snk associate with a Ca (2+)- and integrin-binding protein and are regulated dynamically with synaptic plasticity. EMBO J. 1999; 18(20): 5528-39.

28. Jackson JR, Patrick DR, Dar MM, Huang PS. Targeted anti-mitotic therapies: can we improve on tubulin agents? Nature Reviews Cancer 2007; 7: 107-117.

29. Strebhardt K, Ullrich A. Targeting polo-like kinase 1 for cancer therapy. Nat Rev Cancer 2006; 6(4):321-30.

30. Li J, Karki A, Hodges KB, Cotargeting Polo-Like Kinase 1 and the Wnt/β-Catenin Signaling Pathway in Castration-Resistant Prostate Cancer. Mol Cell Biol 2015 Dec 35(24):4185-8.

31. Liu XS, Sonf B, Elzey BD, Polo-Like Kinase 1 Facilitates Loss of PTEN-Induced Prostate Cancer Formation. J Biol Chem 2011 Sep 2;1-12.

32. Song MS, Carracedo A, Salmena L, Nuclear PTEN Regulates the APC-CDH1 Tumor-Suppressive Complex in a Phosphatase-Independent Manner. Cell 2011 Jan 21;144:187-199.

33. Zhang Z, Hou X, Shao C, et al. PLK-1 inhibition enhances the efficacy of androgen signaling blockade in castration-resistant prostate cancer. Cancer Res. 2014;74(22):6635-47.

34. Zhang Z, Chen L, Wang H, et al. Inhibition of Plk1 represses androgen signaling pathway in castration-resistant prostate cancer. Cell Cycle. 2015;14(13):2142-8.

35. Patel M, Palani S, Chakravarty A, Yang J, Shyu WC, Mettetal J. Dose Schedule Optimization and the Pharmacokinetic Driver of Neutropenia. PLOS. 2014;9(10):1-12.

19 APPENDICES:

19.1 Appendix 1: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

NCI-CTCAE version 4.03 will be used in this study for AE reporting.

A copy of CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program (CTEP).

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

19.2 Appendix 2: Eastern Cooperative Oncology Group Performance Status

Grade	Eastern Cooperative Oncology Group Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Note: As previously published.

19.3 Appendix 3: Package Insert for Zytiga® (Abiraterone Acetate)

- A copy of the package insert for Zytiga® (abiraterone acetate) can be downloaded from the following link:
  https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202379lbl.pdf