Official Title: A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial Testing Ipatasertib Plus Abiraterone Plus Prednisone/Prednisolone, Relative to Placebo Plus Abiraterone Plus Prednisone/Prednisolone In Adult Male Patients With Asymptomatic or Mildly Symptomatic, Previously Untreated, Metastatic Castrate-Resistant Prostate Cancer

NCT Number: NCT03072238

Document Date: SAP Version 2: 23-Dec-2020

STATISTICAL ANALYSIS PLAN

TITLE: **A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER TRIAL TESTING IPATASERTIB PLUS ABIRATERONE PLUS PREDNISONE/PREDNISOLONE, RELATIVE TO PLACEBO PLUS ABIRATERONE PLUS PREDNISONE/PREDNISOLONE IN ADULT MALE PATIENTS WITH ASYMPTOMATIC OR MILDLY SYMPTOMATIC, PREVIOUSLY UNTREATED, METASTATIC CASTRATE-RESISTANT PROSTATE CANCER**

PROTOCOL NUMBER: CO39303

STUDY DRUG: Ipatasertib (RO5532961)

VERSION NUMBER: 2

IND NUMBER: 111051

EUDRACT NUMBER: 2016-004429-17

SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted], Ph.D.

DATE FINAL: Version 1: 16 March 2020

DATE AMENDED: Version 2: See electronic date stamp below.

STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
23-Dec-2020 01:46:05	Company Signatory	[redacted]

CONFIDENTIAL

STATISTICAL ANALYSIS PLAN AMENDMENT, VERSION 2
RATIONALE

The Statistical Analysis Plan (SAP) Version 1 for Protocol CO39303 (yielding Version 2, i.e., this document) has been amended to include an additional second overall survival (OS) interim analysis to provide more stable assessments on the key secondary endpoint OS as well as other secondary endpoints with longer patient follow-up following the primary progression-free survival (PFS) analysis, which is also the first OS interim analysis. Fewer OS events were observed at the time of primary analysis than originally projected (observed 140 OS events in 27% patients vs projected 196 OS events in 36% patients, in patients with PTEN loss tumors by IHC; and observed 267 OS events in 24% patients vs projected 363 OS events in 33% patients, in the ITT population). Changes to the SAP along with the rationale are summarized in the following sections:

In Section 2.4.2 (interim and final analysis timing for OS), an additional OS interim analysis has been added for Study CO39303. The overall type 1 error of OS analyses is controlled at 4% because only one of the co-primary endpoints, radiographic progression-free survival (rPFS) in patients with phosphatase and tensin homolog (PTEN) loss tumors by immunohistochemistry (IHC), was met. A total of three analyses of OS in patients with PTEN loss tumors by IHC are to be performed according to the new analysis plan, including two interim analyses and one final analysis. The first OS interim analysis was already performed at the time of rPFS primary analysis. The second OS interim analysis has been added to the original interim analysis plan. The target number of OS events for the final OS analysis remains unchanged per the original SAP Version 1, the type I error for the final OS analysis will be adjusted based on the Lan-DeMets implementation of the O'Brien-Fleming alpha spending function.

In Section 4.4.4.2, the weighted log-rank test has been added as a sensitivity analysis for OS due to the potential risk of non-proportional hazards due to delayed treatment effect.

Additional minor changes have been made to improve clarity and consistency.

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1. BACKGROUND

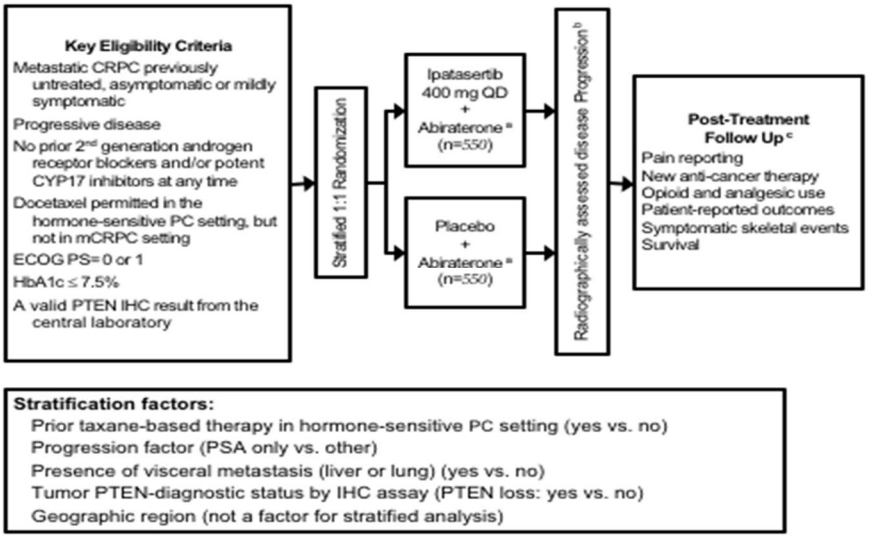
This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for the Study CO39303 (IPATential150). The analyses described in this SAP will supersede those specified in Protocol CO39303.

2. STUDY DESIGN

This is a Phase III, multicenter, international, randomized, double-blind, placebo-controlled study. This study is designed to evaluate the efficacy, safety, and pharmacokinetics of ipatasertib plus abiraterone and prednisone/prednisolone (Ipat+Abi) compared with placebo plus abiraterone and prednisone/prednisolone (Pbo+Abi). The target patient population is asymptomatic or mildly symptomatic patients previously untreated for metastatic castration-resistant prostate cancer (mCRPC). The analysis will be based on the intent-to-treat (ITT) and phosphatase and tensin homolog (PTEN) loss populations, the latter defined using the Ventana PTEN immunohistochemistry (IHC) assay. Patients must have a valid PTEN IHC result from tumor to be enrolled.

The study will enroll approximately 1100 patients at approximately 200 centers worldwide in about 20 months. The study schema is shown in Figure 1.

Figure 1 Study Schema



BID=twice daily; CRPC=castration-resistant prostate cancer; ECOG=Eastern Collaborative Oncology Group; FFPE=formalin-fixed, paraffin-embedded; HbA_{1c}=glycosylated hemoglobin; IHC=immunohistochemistry; mCRPC=metastatic castration -resistant prostate cancer; PCWG3=Prostate Cancer Working Group 3; PS=performance status; PSA=prostate-specific antigen; QD=once daily; RECIST v1.1= Response Evaluation Criteria in Solid Tumors, Version 1.1.

[a] Abiraterone (1000 mg QD)+prednisone/prednisolone (5 mg BID).

[b] In the absence of radiographic disease progression, patients may continue single-agent treatment.

[c] If applicable, patients will return to clinic for tumor assessments (disease follow-up visit) until confirmed radiographic progression.

Approximately 1100 patients will be enrolled to enable the primary analysis for the global study results. After approximately 1100 patients have been randomized into the study, the global enrollment will be closed.

Patients who meet the eligibility criteria will be randomized in a 1:1 ratio to one of the following two treatment arms (each consisting of 28-day cycles of oral administration):

- Arm 1: ipatasertib (400 mg once daily [QD]) plus abiraterone (1000 mg QD) and prednisone/prednisolone (5 mg twice daily [BID])
- Arm 2: placebo (matched to ipatasertib appearance) plus abiraterone (1000 mg QD) and prednisone/prednisolone (5 mg BID)

A randomization scheme will be used across all study sites through a centralized interactive voice- or Web-based response system (IxRS). In this study, randomization of patients will be stratified on the basis of the following factors:

- Prior taxane-based therapy in the hormone-sensitive setting (yes vs. no)
- Progression factor (prostate-specific antigen [PSA] only vs. other)
- Presence of visceral metastasis (liver or lung; yes vs. no)
- Tumor PTEN loss status by IHC assay (yes vs. no)
- Geographic region (not a factor for stratified analysis)

Prior to enrollment, but after signing the Informed Consent Form, patients will have the PTEN loss status of their tumor assessed by the central laboratory using a validated IHC assay with defined criteria for PTEN loss. Patients whose tumor samples have no valid PTEN IHC test result will not be permitted to enroll in the study.

Study assessments (efficacy, safety, patient-reported outcomes, and pharmacokinetic [PK] measurements) and timing of those assessments during each 28-day cycle are presented in Appendix 2.

Radiographic tumor assessments, including computed tomography (CT) or magnetic resonance imaging (MRI), and bone scans will be evaluated locally by the investigators. Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) will be used to assess CT or MRI scans of lesions in soft tissues. Bone lesions will be assessed by bone scan only, using the Prostate Cancer Working Group 3 (PCWG3) criteria to assess disease progression. All scans will be prospectively collected and centrally archived.

Timely and complete disease assessments by imaging methods in this study are imperative. Each tumor assessment will be performed as scheduled according to the calendar, regardless of any study treatment doses omitted, to prevent the introduction of bias into the assessment of efficacy. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point.

In addition, an independent review committee (IRC) will provide an assessment of radiographically assessed disease progression as an exploratory endpoint to support the findings of the investigator assessed outcomes. The data will be collected from all patients. IRC and IRF (independent review facility) are used interchangeably. IRC will be used hereafter.

Patients will receive study treatment until radiographically assessed disease progression (as assessed by the investigator per RECIST v1.1 and/or PCWG3 criteria as applicable), intolerable toxicity, elective discontinuation of the study treatment, elective withdrawal from the study, initiation of new anti-cancer therapy, study completion or termination by F. Hoffmann‑La Roche Ltd (the Sponsor), or physician decision, whichever occurs first. For patients where disease progression is assessed only on the basis of bone scan findings, a confirmatory scan MUST be performed per PCWG3 criteria to establish disease progression. Patients who discontinue one of the study treatments (i.e., ipatasertib/placebo or abiraterone) in the absence of radiographically assessed disease progression may continue the study and receive the remaining single-agent treatment (i.e., abiraterone if ipatasertib/placebo is discontinued or ipatasertib/placebo if abiraterone is discontinued) at the discretion of the investigator.

Patients who discontinued from study treatment will return for a study treatment completion visit within 30 days after the last dose of study treatment.

A crossover between treatment arms is not allowed.

Following radiographically assessed disease progression (as assessed by the investigator per RECIST v1.1 and/or PCWG3 criteria as applicable) and study treatment discontinuation, patients will continue post-treatment follow-up for selected assessments supporting secondary and exploratory efficacy endpoints, until death, loss to follow-up, withdrawal of consent from study, or study termination by the Sponsor.

Sites should record for all patients who are in follow-up survival information including symptomatic skeletal events (SSEs), initiation of subsequent anti-cancer therapy (including the date of the first dose of agent, the date of the last dose of agent, patient's best response, and date of disease progression), date of second radiographically assessed disease progression and any post-progression therapy for prostate cancer (PC) as well as any serious adverse events considered by the investigator to be related to the study treatment (abiraterone and/or ipatasertib/placebo), and anti-diabetic medications for hyperglycemia related to study treatment and opioid consumption for cancer-related pain.

Patients who discontinue from study treatment for reasons other than radiographically assessed disease progression will be asked to return to the clinic for disease follow-up visits approximately every three months to complete tumor assessments until

radiographically assessed disease progression (per RECIST v1.1 and/or PCWG3 as applicable) or withdrawal from the study.

All patients who discontinue from study treatment because of radiographically assessed disease progression or any other reasons will be asked to report, via electronic provisioned device completed at home or at the clinic, pain medications (including dose and type of opioids used), pain severity (7-day recall), and other patient-reported outcome (PRO) measures approximately every 28 days until initiation of any post-progression therapy for PC or up to 1 year, whichever occurs first.

After initiation of the next-line of therapy or 1-year post study treatment discontinuation, whichever occurs first, patients will be asked to report pain severity, analgesic use (yes vs. no), EuroQol 5 Dimensions, 5 Levels (EQ-5D-5L); and three scales from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ‑C30) every 3 months completed at home or at the clinic or via telephone calls.

An independent Data Coordinating Center (iDCC) will prepare all summaries and analyses for the independent Data Monitoring Committee's (iDMC's) review. The safety summaries will include, but will not be limited to, demographic data, adverse events, serious adverse events, and relevant laboratory data (see iDMC charter for details).

Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. Following the data review, the iDMC will provide a recommendation to the Sponsor whether to continue the study, amend the protocol, or stop the study. The final decision will rest with the Sponsor.

Any outcomes of the iDMC's reviews on the safety and benefit-risk balance that affect study conduct will be communicated in a timely manner to the investigators for notification of Institutional Review Boards and Ethics Committees (IRBs/ECs).

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 OUTCOME MEASURES

This study will evaluate the efficacy, safety, and pharmacokinetics of (Ipat+Abi), compared with Pbo+Abi in asymptomatic or mildly symptomatic patients previously untreated for mCRPC. Specific objectives and corresponding endpoints for the study are outlined below (see Table 1).

Table 1 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoint(s)
Co-Primary Efficacy Objectives	
• To evaluate the efficacy in patients with PTEN-loss tumors by IHC • To evaluate the efficacy in the ITT population	• Investigator-assessed rPFS, per PCWG3 criteria
Secondary Efficacy Objectives [a]	
• To evaluate the clinical benefit in the ITT population, and in patients with PTEN-loss tumors by IHC	Key secondary endpoints with type 1 error control: • Overall survival Additional Secondary Endpoints: • Time to pain progression • Time to initiation of cytotoxic chemotherapy for prostate cancer • Time to function deterioration per EORTC QLQ-C30 PF and RF • Time to PSA progression, per the PCWG3 criteria • Time to first opioid use • Time to symptomatic skeletal event • Objective response rate, per RECIST v1.1 and PCWG3 criteria in patients with measurable disease • PSA response rate
• To evaluate the efficacy in patients with PTEN-loss tumors by NGS	• Investigator-assessed rPFS per PCWG3 criteria
Exploratory Efficacy Objectives	
• To evaluate the clinical benefit in the ITT population, and in patients with PTEN-loss tumors by IHC and by NGS	• IRC-assessed radiographic progression • PFS after next line of treatment • Time to deterioration in health-related quality of life, per EORTC QLQ-C30 GHS • Time to deterioration in urinary symptoms per EORTC QLQ-PR25 urinary scale • Time to deterioration in fatigue per EORTC QLQ-C30 fatigue scale • Clinical PFS

Table 1 Objectives and Corresponding Endpoints (cont.)

Safety Objective	
• To evaluate the safety in the ITT population, and in patients with PTEN-loss tumors by IHC	• Incidence, nature, and severity of adverse events, with severity determined through use of NCI CTCAE v4.0
Pharmacokinetic Objective	
• To characterize ipatasertib and abiraterone pharmacokinetics • To characterize ipatasertib exposure, abiraterone exposure in relation to efficacy and safety	• Plasma concentration of ipatasertib and abiraterone at specified timepoints for analysis using population PK methodology • Relationship between plasma concentration or PK parameters of ipatasertib and abiraterone, via safety and efficacy endpoints
Exploratory Biomarker Objectives	
• To evaluate possible predictive and prognostic biomarkers in the tissue and plasma • To identify possible mechanisms of resistance to the study treatments through the comparative analysis of potential biomarkers in the blood	• Explore possible relationships between the tissue- and blood-based biomarkers and patient clinical features (e.g., baseline features) and outcome (e.g., duration of rPFS) [b]
Other Exploratory Objectives	
• To collect patients' perspectives regarding key symptomatic adverse events	• Proportion analyses and change from baseline on selected items from PRO-CTCAE capturing patients' rating of the severity, frequency, interference, and/or occurrence of decreased appetite, nausea, vomiting, diarrhea, constipation, fatigue, and rash
• To collect utilities for pharmacoeconomic modeling	• Utilities derived from scores on EQ-5D-5L

EQ-5D-5L = EuroQol 5 Dimensions, 5 Levels; EORTC = European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30 = EORTC Core Quality of Life Questionnaire; GHS = global health status; IHC = immunohistochemistry; IRC = Independent Review Committee; ITT = intent to treat; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; NGS = next-generation sequencing; PCWG3 = Prostate Cancer Working Group 3; PF = 5-item physical function scale from the EORTC QLQ-C30; PFS = progression-free survival; PK = pharmacokinetic; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PSA = prostate-specific antigen; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RF = 2-item role function scale from the EORTC QLQ-C30; rPFS = radiographic progression-free survival.

[a] Refer to Section 6 for the protocol-specified definition of clinical benefit endpoints.

[b] Refer to Appendix 2 for the protocol-specific definition of the biomarker analysis.

2.3 DETERMINATION OF SAMPLE SIZE

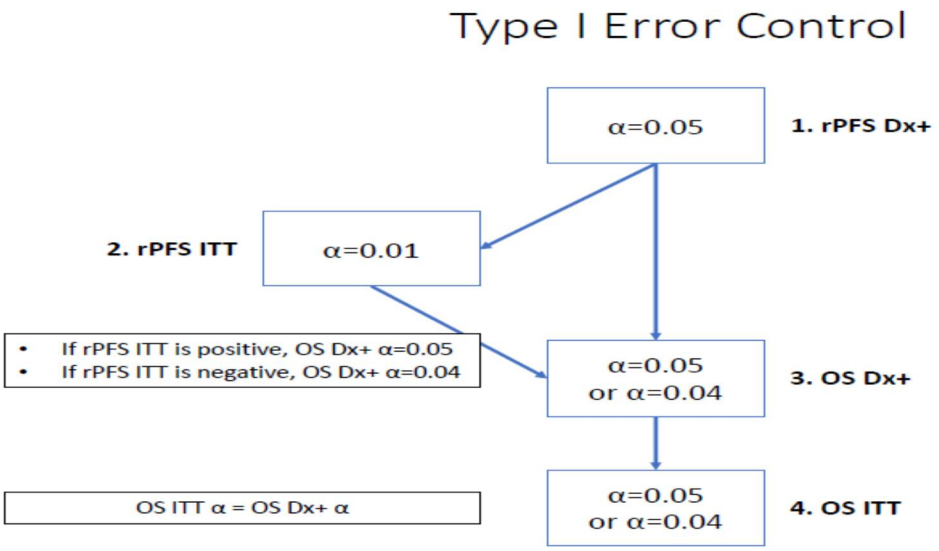
Approximately 1100 patients in total will be randomized into this study in about 20 months. Assuming 50% prevalence of IHC PTEN loss tumors in all patients, it's estimated that approximately 550 patients will have PTEN loss tumors.

The overall type I error (a) for this study is 0.05 (two-sided). Type I error will be controlled for the following efficacy endpoints:

- Co-primary efficacy endpoints: Investigator-assessed radiographic progression-free survival (rPFS) per PCWG3 criteria in the ITT population and in patients with PTEN loss tumors by IHC
- Key secondary endpoints: overall survival (OS) in the ITT population and in patients with PTEN loss tumors by IHC

Type I error will be controlled by comparing these endpoints between treatment arms according to the following testing procedure (Figure 2).

Figure 2 Type I Error Control



Dx+=diagnostic positive; ITT= intention-to-treat; rPFS=radiographic progression-free survival; OS=overall survival.

Testing of rPFS

Both rPFS in the ITT population and in patients with PTEN loss tumors by IHC will be tested at the time of the primary analysis of rPFS in order as follows:

1. Firstly, test the null hypothesis of no difference in rPFS between the two arms in patients with PTEN loss tumors by IHC using the stratified log-rank test with significance level α of 0.05.
2. If the null hypothesis of test 1 described above is rejected, α of 0.05 will then be passed along and allocated between rPFS in the ITT population (0.01) and OS in patients with PTEN loss tumors by IHC (0.04). That is, rPFS in the ITT population will be tested using the stratified log-rank test with significance level α of 0.01.

Testing of OS in patients with PTEN loss tumors by IHC

1. OS in patients with PTEN loss tumors by IHC will be tested only if the test of rPFS in patients with PTEN loss tumors by IHC (i.e., test 1 described above) is positive with α of 0.05. If the test of rPFS in the ITT population (i.e., test 2 described above) is also positive with α of 0.01, then the OS in patients with PTEN loss tumors by IHC will be tested with α of 0.05; otherwise the OS in patients with PTEN loss tumors by IHC will be tested with α of 0.04. When the test of rPFS in patients with PTEN loss tumors by IHC (i.e., test 1 described above) is passed, at the time of the primary analysis of rPFS, an interim analysis of OS in patients with PTEN loss tumors by IHC will be performed. The interim analysis boundary for statistical significance will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming alpha spending function according to the type I error α allocated to this endpoint (see Figure 2).

Testing of OS in the ITT population

1. OS in the ITT population will be tested only if the test of OS in patients with PTEN loss tumors by IHC (i.e., test 3 described above) is positive, and it will be tested with the same type I error α that is used for the test of OS in patients with PTEN loss tumors by IHC. At the time of the primary analysis of rPFS, if the interim analysis of OS in patients with PTEN loss tumors by IHC test is positive, an interim analysis of OS in the ITT population will be performed. At the time of final OS analysis in patients with PTEN loss tumors by IHC, if the test of OS in patients with PTEN loss tumors by IHC is positive, an interim analysis of OS in the ITT population will be performed. The interim analysis boundary for statistical significance will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming alpha spending function according to the type I error α allocated to this endpoint, which should be the same type I error α that is used for the test of OS in patients with PTEN loss tumors by IHC.

The sample size of this study is based on the number of events required to demonstrate efficacy with regard to both rPFS and OS for the comparison of treatment arms in ITT and PTEN loss population by IHC.

The estimates of the number of events required to demonstrate efficacy with regard to rPFS in the comparison of treatment arms are based on the following assumptions:

- In the PTEN loss population
  - A two-sided significance level of 0.05
  - A power of 98.4% to detect a hazard ratio (HR) of 0.61, corresponding to an improvement in median rPFS from 14 months to 23 months
  - No interim analysis for rPFS
  - A dropout rate of 10% per 12 months
- In the ITT population
  - A two-sided significance level of 0.01

- A power of 94.6% to detect an HR of 0.70, corresponding to an improvement in median rPFS from 16.5 months to 23.6 months
- No interim analysis for rPFS
- A dropout rate of 10% per 12 months

The estimates of the number of events required with regard to OS in the comparison of treatment arms are based on the following assumptions:

- In the PTEN loss population:
  - A two-sided significance level of 0.04
  - A power of 63% to detect a HR of 0.76, corresponding to an improvement in median OS from 29 months to 38 months
  - First OS interim analysis performed at approximately 27% event-patient ratio (EPR), a second OS interim analysis to be performed at approximately 44% EPR and OS final analysis to be performed at approximately 63%EPR.
  - A dropout rate of 5% per 24 months
- In the ITT population:
  - A two-sided significance level of 0.04.
  - A power of 60% to detect an HR of 0.83, corresponding to an improvement in median OS from 35 months to 42 months
  - First OS interim analysis was not performed due to the testing hierarchy with 27% EPR. A second OS interim analysis to be performed at approximately 41% EPR, a third OS interim analysis to be performed at approximately 59% EPR and OS final analysis to be performed at approximately 60% EPR.
  - A dropout rate of 5% per 24 months

With these assumptions, approximately 1100 patients in total will be randomized into this study, with approximately 550 patients with PTEN loss tumors by IHC.

2.4 ANALYSIS TIMING

2.4.1 Primary Analysis Timing for rPFS

The primary analysis of rPFS will occur when approximately 275 rPFS events in patients with PTEN loss tumors and approximately 550 rPFS events in the ITT population have been observed, whichever occurs later. The primary analysis is expected to occur approximately 34 months after the first patient is randomized.

In the PTEN loss population, 275 events will allow for 98.4% power to detect an improvement in median rPFS from 14 months in the placebo arm to approximately 23 months in the ipatasertib arm (HR=0.61) at the 5% level of significance (two-sided). These numbers of events correspond to a minimum detectable difference (MDD) in HR of approximately 0.79.

In the ITT population, 550 events will allow for 94.5% power to detect an improvement in median rPFS from 16.5 months in the placebo arm to approximately 23.6 months in the ipatasertib arm (HR=0.70) at the 1% level of significance (two-sided). These numbers of events correspond to an MDD in HR of approximately 0.80 (see Table 2).

Table 2 Primary Analysis for Radiographic Progression-Free Survival

		PTEN Loss			ITT		
Type of Analysis	**Analysis Timing (Months since FPI)**	**No. of Events (Event Ratio %)**	**MDD in Hazard Ratio**	**Power %**	**No. of Events (Event Ratio %)**	**MDD in Hazard Ratio**	**Power %**
rPFS Primary Analysis	34	275 (50)	0.79	98.4	550 (50)	0.80	94.5

FPI=first patient in; ITT=intention-to-treat; MDD=minimum detectable difference; rPFS=radiographic progression-free survival.

2.4.2 Interim and Final Analysis for OS

Following the type I error control diagram shown in Figure 2, since rPFS in patients with PTEN loss tumors by IHC passed the test with a significance level α of 0.05 and rPFS in the ITT population did not pass the test with α of 0.01 at the time of primary analysis of rPFS, the α allocated to OS analysis is 0.04. OS in the patients with PTEN loss tumors by IHC will be tested firstly with α of 0.04, followed by testing OS in the ITT population.

A total of four analyses of OS are planned:

- The first interim analysis of OS was performed at the time of primary analysis of rPFS.
- The second interim analysis of OS will take place when approximately 229 OS events in the patients with PTEN loss tumors by IHC occur, or when the minimum follow-up time (from the last patient enrollment date of 17 January 2019) is approximately 32 months, whichever occurs later.
- The third analysis of OS is the final analysis of OS in the patients with PTEN loss tumors by IHC and it is also the third interim analysis of OS in the ITT population. It is scheduled when there are approximately 327 OS events in patients with PTEN loss tumors by IHC occur. This target number of OS event is unchanged per the original SAP, Version 1.

– The fourth analysis of OS is the final analysis of OS in the ITT population. It is scheduled when there are approximately 660 OS events in the ITT population occur. This target number of OS event is unchanged per the original SAP, Version 1.

The projected analysis timing and the corresponding numbers of OS events for OS interim and final analyses in patients with PTEN loss tumors by IHC and in the ITT population are shown in Table 3. When the timing of the third and fourth analyses are very close, these two analyses could be combined and the alpha-spending will be adjusted using O'Brien-Fleming alpha-spending method.

Table 3 Timing of Overall Survival Analyses

		PTEN Loss		ITT	
Analysis	Time from FPI (months)	Information Fraction (%)	No. of Events (EPR %)	Information Fraction (%)	No. of Events (EPR %)
OS 1st IA	33	43	140 (27)	40	267 (24)
OS 2nd IA	50	70	229 (44)	69	450 (41)
OS 3rd IA/ FA	78	100	327 (63)	98	646 (59)
OS FA	81	-	-	100	660 (60)

FA=final analysis; FPI=first patient in; ITT=intent-to-treat; OS=overall survival; EPR=Event-Patient-Ratio.

The efficacy stopping boundaries for OS interim and final analyses will be calculated using the Lan-DeMets approximation to the O'Brien-Fleming boundary in the patients with PTEN loss tumors by IHC and in the ITT population, respectively. The details of each OS analysis testing are described below, and the efficacy stopping boundaries are shown in Table 4. Crossing the p-value boundaries will be used to claim statistical significance. The projected HR or p-value boundaries in Table 4 are based on the observed (i.e., first OS interim analysis) or projected numbers of OS events listed in Table 3, and the actual boundaries for HR or p-values will be calculated at the time of analysis based on the actual number of OS events observed in patients with PTEN loss tumors by IHC and in the ITT population, respectively.

Table 4 Efficacy Stopping Boundaries and Power for Overall Survival Analyses

<table>
<tr><td>Analysis</td><td>PTEN loss</td><td colspan="4">ITT</td></tr>
<tr><td>OS 1st IA</td><td>α spent=0.0008
HR ≤0.567
p-value ≤0.0008
power=4%</td><td colspan="4">OS 1st IA in PTEN loss is negative
α of 0.0008 cannot be passed along*</td></tr>
<tr><td>OS 2nd IA</td><td>α spent=0.0106
HR ≤0.713
p-value ≤0.0106
power=30%</td><td rowspan="3">OS 2nd IA in PTEN loss is positive, OS in ITT will be tested with αof 0.0392.</td><td>α spent=0.0094
HR ≤0.783
p-value ≤0.0094
power=25%</td><td colspan="2">OS 2nd IA in PTEN loss is negative
α of 0.0106 cannot be passed along*</td></tr>
<tr><td>OS 3rd IA/ FA</td><td>α spent=0.0286
HR ≤0.793
p-value ≤0.0359
power=63%</td><td>α spent=0.0272
HR ≤0.846
p-value ≤0.0337
power=58%</td><td rowspan="2">OS FA in PTEN loss is positive, OS in ITT will be tested with αof 0.0286.</td><td>α spent=0.0266
HR ≤0.840
p-value ≤0.0266
power=54%</td></tr>
<tr><td>OS FA</td><td>-</td><td>α spent=0.0026
HR ≤0.844
p-value ≤0.0293
power=60%</td><td>α spent=0.0020
HR ≤0.837
p-value ≤0.0224
power=56%</td></tr>
</table>

Based on number of events given in Table 3, power for patients with PTEN loss tumors by IHC is computed to detect an improvement in median OS from 29 months in the placebo arm to approximately 38 months in the ipatasertib arm (HR=0.76), and power for the ITT population is computed to detect an improvement in median OS from 35 months in the placebo arm to approximately 42 months in the ipatasertib arm (HR=0.83).

FA=final analysis; IA=interim analysis; HR=hazard ratio; OS=overall survival.

* Not formally tested due to testing hierarchy

FA in ITT population will not be formally tested if all tests are negative in patients with PTEN loss tumors by IHC.

At the first interim analysis of OS (i.e., the primary analysis of rPFS), following the rPFS analyses, OS in patients with PTEN loss tumors by IHC was tested with significance level α of 0.04. A total of 140 (27% of 521 patients) OS events was observed in patients with PTEN loss tumors by IHC. This corresponds to 43% (140/327) information fraction of the final analysis of OS in patients with PTEN loss tumors by IHC, and the O'Brien-Fleming p-value boundary was 0.0008. The first interim analysis for OS in patients with PTEN loss tumors by IHC did not pass the test. Therefore, α of 0.0008 cannot be passed along to the first interim analysis for OS in the ITT population due to the testing hierarchy.

At the second interim analysis of OS, the OS in patients with PTEN loss tumors by IHC will be formally tested firstly. Given that α of 0.0008 was spent at the first interim analysis of OS, the remaining α of 0.0392 will be allocated to the second interim and final analyses of OS in patients with PTEN loss tumors by IHC. With 229 OS events which correspond to 70% (229/327) information fraction, the O'Brien-Fleming p-value boundary is 0.0106. That is, statistical significance will be declared if $p \leq 0.0106$ for the OS in patients with PTEN loss tumors by IHC. The actual interim analysis boundary for statistical significance will be determined based on the actual OS events observed using the Lan-DeMets implementation of the O'Brien-Fleming alpha spending function.

- If the test of the second interim OS analysis in patients with PTEN loss tumors by IHC is positive, then OS in the ITT population will be formally tested with the remaining α of 0.0392 allocated to the second interim, the third interim and the final analyses based on the number of OS events observed using O'Brien-Fleming alpha-spending method. For example, based on the projected numbers of OS events listed in Table 3, the α spent, HR and p-value boundary for each analysis are presented in Table 4. The third interim analysis and final analysis for the OS in the ITT population could be combined and the alpha-spending will be adjusted using O'Brien-Fleming alpha-spending method.
- If the test of the second interim OS analysis in patients with PTEN loss tumors by IHC is negative, α of 0.0106 cannot be passed along to the OS in the ITT population. The second interim OS analysis in the ITT population will not be formally tested due to the testing hierarchy, and only the remaining α of 0.0286 (=0.04-0.008-0.106) will be used for the third interim analysis and final analysis for OS in the ITT population.

The final analysis of OS in patients with PTEN loss tumors by IHC is also the third interim analysis of OS in the ITT population.

- When both the first and second interim analyses of OS in patients with PTEN loss tumors by IHC are negative, the remaining α will be used for the final analysis of OS patients with PTEN loss tumors by IHC. In the example shown in Table 4, α of 0.0286, p-value boundary of 0.0359 will be used.
- When the second interim analysis of OS in patients with PTEN loss tumors by IHC is positive and second interim analysis in the ITT population is negative, the final analysis of OS in patients with PTEN loss tumors by IHC becomes descriptive update and OS in the ITT populations will be formally tested with the remaining α of 0.0298 (=0.04-0.008-0.0094) will be allocated to the third interim and final analyses of OS in the ITT populations as shown in Table 4. The third interim analysis and final analysis for the OS in the ITT population could be combined and the alpha-spending will be adjusted using O'Brien-Fleming alpha spending method.
- When both the second interim analysis of OS in patients with PTEN loss tumors by IHC and the second interim analysis of OS in the ITT population are positive, the final analysis of OS in patients with PTEN loss tumors by IHC and the third and final analyses of OS in the ITT populations will become descriptive updates.

The final OS analysis in the ITT population will be formally tested with the remaining α. As shown in Table 4, the value of α depends on the testing results of the previous OS analyses in patients with PTEN loss tumors by IHC and in the ITT population. The actual α will be recalculated based on the actual numbers of OS events observed.

3. STUDY CONDUCT

3.1 RANDOMIZATION ISSUES

Patients will be allocated to one of two treatment arms through use of a permuted block randomization algorithm with predefined stratification variables, prior taxane-based therapy in the hormone-sensitive setting (yes vs. no), progression factor (PSA only vs. other), presence of visceral metastasis (liver or lung; yes vs. no), and tumor PTEN loss status by IHC assay (yes vs. no). The stratification factor of geographic region will not be a factor used for the stratified analysis. A placebo for ipatasertib will be used in the control arm. Patients, investigators, and the Sponsor will be blinded to treatment assignment.

3.2 INDEPENDENT REVIEW COMMITTEE

An independent Review Committee (IRC) will be set up to provide an assessment of radiographic progression as an exploratory endpoint to support the findings of the investigator-assessed outcomes. The data will be collected from all patients. Refer to the IRC charter and IRC audit plan for further detail.

3.3 DATA MONITORING COMMITTEE

An iDMC will evaluate safety during the study on a regular basis. All summaries and analyses by treatment arm for the iDMC review are prepared by an external iDCC. Members of the iDMC are external to the Sponsor and follow a separate iDMC Charter that outlines their roles and responsibilities, as well as a detailed monitoring plan. Refer to the iDMC charter for further detail.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

4.1.1 ITT Population

The ITT population is defined as all randomized patients, whether or not the patient received the assigned treatment. The ITT patients will be analyzed according to the treatment assigned at randomization by the IxRS.

4.1.2 Safety-Evaluable Population

The safety-evaluable population is defined as patients who received any amount of the study treatment. Patients will be analyzed according to the treatment arm associated with the actual regimen received. Patients who were randomized to the study but who did not receive any study drug will not be included in the safety-evaluable population.

4.1.3 Pharmacokinetic-Evaluable Population

Pharmacokinetic (PK) analyses will be based on PK observations from all patients who received ipatasertib treatment with evaluable PK samples.

4.2 ANALYSIS OF STUDY CONDUCT

Enrollment, treatment discontinuation, treatment discontinuation reasons, major protocol deviations including major deviations of inclusion/exclusion criteria, and reasons for discontinuation from the study will be summarized by treatment arm for the ITT population.

4.2.1 PRO Completion Rates

Completion rates for PRO measures in the ITT population and PTEN loss population will be calculated as the number of patients who completed the assessment divided by the number of patients expected to complete the assessment at each time point for each treatment arm. Reasons for missing assessments, if available, will be summarized using frequencies and percentages. Completion rates will be reported for the following PRO measures: 7-day recall pain severity item (post-screening), the QLQ-C30 and key scales (role functioning [RF], physical functioning [PF], global health status [GHS]), and the EORTC Quality of Life Questionnaire Prostrate Cancer Module [QLQ-PR25] urinary scale.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (including age, race, ethnicity, etc), and baseline disease characteristics such as presence of visceral metastasis (liver or lung; yes vs. no), progression factor (PSA only vs. other), prior taxane-based therapy in the hormone-sensitive setting (yes vs. no), tumor PTEN loss status by IHC assay (yes vs. no), progression criteria at enrollment (prostate-specific antigen only, radiographic only, prostate-specific antigen and radiographic), alkaline phosphatase and hemoglobin will be summarized by treatment arm. Descriptive statistics (mean, median, SD, and range) will be presented for continuous variables, and frequencies and percentages will be presented for categorical variables.

Baseline values are the last available data obtained prior to the patient receiving the first dose of any study treatments on Cycle 1, Day 1 visits unless otherwise noted.

4.4 EFFICACY ANALYSIS

The co-primary efficacy objective for this study is to evaluate the efficacy of Ipat+Abi compared with Pbo+Abi on the basis of rPFS in patients in the ITT population and in patients with PTEN loss tumors determined by IHC assay.

Efficacy analyses will include all patients who were included in the randomization, i.e. ITT population, except for the objective response rate (ORR) analysis. ORR analysis

will include all patients with measurable disease at baseline only. For efficacy, patients will be analyzed according to the treatment arm to which they were randomized.

The stratification factors will be those used for randomization and will be obtained from the IxRS except for the factor "region". Due to the potential risk of over-stratification (Akazawa et al. 1997), if at least one stratum (i.e., a combination of stratification factor levels across all stratification factors) has fewer than 10 rPFS events across treatment arms, the stratification factor which contains the level with the smallest number of patients will be removed from the stratified analyses. The removal of the stratification factors will continue until there is no stratum with fewer than 10 rPFS events. The final set of stratification factors used in stratified analyses will be applied to all endpoints where stratified analyses are planned.

4.4.1 Primary Efficacy Endpoint

The primary endpoint of rPFS is defined as the time from randomization to the first documented disease progression, as assessed by the investigator with use of the PCWG3 criteria (soft tissue by CT or MRI scans according to RECIST v1.1, and bone metastasis by bone scan according to the PCWG3 criteria) or death from any cause, whichever occurs first.

Data for patients without the occurrence of disease progression or death as of the clinical data cutoff date will be censored at the time of the last tumor assessment (or at the time of randomization plus 1 day if no tumor assessment was performed after the baseline visit).

Firstly, the primary efficacy analysis of rPFS in patients with PTEN loss tumors by IHC assay will be performed by the two-sided log-rank test (α= 0.05) using the following factors in stratified analyses to compare rPFS between the two treatment arms:

- Presence of visceral metastasis (liver or lung; yes vs. no)
- Progression factor (PSA only vs. other)
- Prior taxane-based therapy in the hormone-sensitive setting (yes vs. no)

As pre-specified in the protocol, all randomization stratification factors will be used in the stratified analysis except for the factor "region". Values for the stratification factors will be recorded in the IxRS at the time of randomization and will be used in the primary stratified analysis.

A Cox proportional-hazards model stratified using the three factors above will be used to estimate the HR and 95% CI. The results from the unstratified log-rank test will also be provided.

The Kaplan-Meier approach will be used to estimate median rPFS for each treatment arm, and the Kaplan-Meier curve will be constructed to provide a visual description of the difference between the treatment arms.

When the primary efficacy analysis of rPFS in patients with PTEN loss tumors by IHC assay is positive, (i.e., a p-value < 0.05), similar methods will then be used for the primary efficacy analysis of rPFS in the ITT population. The two-sided log-rank test ($\alpha = 0.01$) stratified by the following factors will be used to compare rPFS between the two treatment arms:

- Presence of visceral metastasis (liver or lung; yes vs. no)
- Progression factor (PSA only vs. other)
- Prior taxane-based therapy in the hormone-sensitive setting (yes vs. no)
- Tumor PTEN status by IHC assay (loss vs. non-loss)

4.4.2 Secondary Efficacy Endpoints

The secondary efficacy objectives for this study are to evaluate the OS and additional measures of clinical benefit in the ITT population, and in patients with PTEN loss tumors by IHC and also to evaluate the efficacy in patients with PTEN loss tumors by next-generation sequencing (NGS).

All of the following secondary efficacy endpoints will be analyzed in the ITT population and in patients with PTEN loss tumors determined by IHC assay, unless stated otherwise.

4.4.2.1 Overall Survival

OS is defined as the time from randomization to death due to any cause. Data for patients who are not reported as having died at the time of analysis will be censored at the date when they were last known to be alive. Data for patients who do not have post−baseline information will be censored at the randomization date plus 1 day.

The OS analyses will be performed by stratified two-sided log-rank tests with the significance levels 0.04 or 0.05 depending on the results of co-primary efficacy analyses in the ITT population and patients with PTEN loss tumors by IHC. The key OS analyses will be performed by stratified two-sided log-rank tests with the significance levels as described in Section 2.3. The analyses will be conducted according to an analysis hierarchy and α-spending algorithm to control for the type I error rate (see Figure 2) and to account for interim analyses (see Section 2.4.2).

The same analysis methods as described in Section 4.4.1 will also be performed for OS analyses.

4.4.2.2 Time to Pain Progression

Cancer-related pain progression refers to pain onset for those patients asymptomatic at baseline (i.e., patients with a score of 0 or 1 on pain severity at its worst on the 10-point numeric rating scale [NRS]) or pain worsening for those patients who are mildly symptomatic at baseline (score of 2 or 3).

Time to pain progression will be defined as the time from randomization to the first occurrence of a confirmed clinically meaningful cancer-related pain progression event as defined below.

Pain progression is defined as a ≥ 2-point absolute increase from baseline, defined as Cycle 1 Day 1, or screening if missing. Pain progression at a given timepoint will be considered clinically meaningful if followed by any of the following:

- A subsequent pain severity assessment within 1 cycle + 2-week window (28 days + 14 days) showing that the score on pain severity at its worst is maintained or increased.
- Initiation or increase in opiate analgesic as measured in the analgesic quantification algorithm (AQA) within 1 cycle + 2-week window (28 days + 14 days) following the initial pain event.
- Initiation of palliative therapy within 1 cycle + 2-week window (28 days + 14 days) following the initial pain event.
- An increase in prednisone/prednisolone usage for the intent of treating cancer pain within 1 cycle + 2-week window (28 days + 14 days) following the initial pain event; or a prescription for any other glucocorticosteroid for the intent of treating cancer pain within 1 cycle + 2-week window (28 days + 14 days) following the initial pain event.
- In the absence of further pain assessments and initiation of analgesic or palliative therapy, documentation of death attributable to cancer progression (not death of other causes, including adverse events) within a 3-month interval following the initial pain event for these patients who might be lost at follow-up.

Note that an initiation of opioid analgesic use for cancer-related pain will be defined by a documentation of an opioid prescription for cancer-related pain followed by patient's record of opioid intake or availability of an Analgesic Quantification Algorithm (AQA) daily score. For patients reporting use of opioid for cancer-related pain at baseline, the confirmatory event of opioid escalation will be defined as an increase in AQA daily score of one point or more.

All patients who underwent randomization will be included in the time to pain progression analysis.

The analysis for this secondary endpoint will include any pain progression event collected until initiation of the next line of therapy or up to one year following treatment discontinuation, whichever occurs first. Note that data collected post initiation of next

line of therapy will not be used for the analysis of the secondary endpoint but will be used to inform understanding of the disease burden post-progression in exploratory analyses.

Patients without occurrence of pain progression at the time of analysis will be censored at the last available pain severity assessment.

Patients whose death is not preceded by an increase in pain of $\geq$2 points will be censored at the latest date of the last pain severity assessment.

In addition, patients with pain severity score $>$3 at screening or at baseline, or patients who has missing baseline pain data will be censored at the randomization date plus 1 day.

The same analysis methods as described in Section 4.4.1 for the primary endpoint rPFS will be used for this time to pain progression endpoint.

4.4.2.3 Time to Initiation of Cytotoxic Chemotherapy

Time to initiation of cytotoxic chemotherapy is defined as the time from randomization to initiation of cytotoxic chemotherapy for PC. Cytotoxic chemotherapy was defined as the use of any of the following antineoplastic agents for PC: docetaxel, cabazitaxel, mitoxantrone, estramustine, cisplatin, carboplatin, cyclophosphamide, doxorubicin, mitomycin, irinotecan, 5-fluorouracil, gemcitabine, or etoposide. Data for patients who do not receive cytotoxic chemotherapy will be censored at the last known date of no cytotoxic chemotherapy administered.

The same analysis methods as described in Section 4.4.1 for the primary endpoint rPFS will be used for this time to initiation of cytotoxic chemotherapy endpoint.

4.4.2.4 Time to Function Deterioration

Time to confirmed function deterioration is defined as the time from the date of randomization to the date of 10-point or more decrease on either the EORTC QLQ-C30 PF or RF scale scores (range, 0-100) held for two consecutive assessments, or a 10-point or more score decrease followed by death (any cause) within 28 days, whichever occurs first.

Patients who do not have a confirmed function deterioration event as defined above will be censored at the last assessment date. Patients without a baseline or post-baseline PRO assessment will be censored at randomization.

The same analysis methods as described in Section 4.4.1 for the primary endpoint rPFS will be used for this time to function deterioration endpoint.

4.4.2.5 Time to Prostate-Specific Antigen Progression

PSA progression is defined as a PSA increase that is ≥ 25% and ≥ 2 ng/mL above the baseline or nadir, which is confirmed by a second value ≥ 3 weeks later (per the PCWG3 criteria).

Time to PSA progression is defined as the time from the date of randomization to the first occurrence of PSA progression. Data for patients without the occurrence of PSA progression as of the clinical data cutoff date will be censored at the time of the last PSA assessment (or at the time of randomization plus 1 day if no PSA assessment was performed after the baseline visit). The analysis methods will be the same as for the primary efficacy endpoint (see Section 4.4.1).

4.4.2.6 Time to First Opioid Use

Time to first opioid use is defined as the documentation of the first opioid prescription for cancer-related pain followed by the patient's record of opioid intake or availability of an Analgesic Quantification Algorithm (AQA) daily score. Patients reporting use of opioid for cancer-related pain at baseline will be excluded from the analysis.

The same analysis methods as described in Section 4.4.1 for the primary endpoint rPFS will be used for this time to first opioid use endpoint.

4.4.2.7 Time to Symptomatic Skeletal Events

An SSE is defined using one of the following: (1) use of external-beam radiotherapy to relieve skeletal symptoms (including initiation of radium-223 to treat symptoms of bone metastases); (2) occurrence of a new symptomatic pathological bone fracture (vertebral or non-vertebral), (3) clinically apparent occurrence of spinal cord compression, or (4) a tumor-related orthopedic surgical intervention. Descriptive statistics of the number and percentage of patients with SSE will be summarized by treatment group.

Time to SSE is defined as the time from randomization to the first occurrence of an SSE. Censoring rules will be applied as follows:

- Observations from patients who do not have post-baseline information will be censored at the date of randomization plus 1 day.
- Patients for whom an SSE has not been observed will be censored at the last time known to be alive and without an SSE.
- Observations from patients who died before having an event will be censored on the date of death.
- Observations from patients who discontinued study without experiencing an SSE will be censored on the date of study discontinuation.

The same analysis methods as described in Section 4.4.1 for the primary endpoint rPFS will be used for this time to first SSE endpoint.

4.4.2.8 Objective Response Rate

An objective response is defined as a complete response (CR) or partial response (PR) on two consecutive occasions ≥4 weeks apart, as determined by the investigator using RECIST v1.1 and PCWG3 criteria, in patients with measurable disease at baseline. Patients without a post-baseline tumor assessment will be considered non-responders. Patients who have concurrent or prior bone progression by PCWG3 will not be considered to have had a response.

ORR is defined as the proportion of patients who have an objective response in patients with measurable disease at baseline. An estimate of ORR will be calculated for each treatment arm, and its 95% CI will be calculated using the Clopper-Pearson method. ORR will be compared between treatment arms using the stratified Cochran-Mantel-Haenszel test. The stratification factors will be the same as those described for the analysis of the primary endpoint (see Section 4.4.1). The difference in ORR between treatment arms will be calculated, and its 95% CI will be calculated using the normal approximation to the binomial distribution.

4.4.2.9 Duration of Response

A duration of response (DOR) is defined for patients with an objective response as the time from the first documented objective response to documented disease progression as determined by the investigator using RECIST v1.1 and PCWG3 criteria, or death from any cause, whichever occurs first. Data for patients who are alive and who have not experienced disease progression at the time of analysis will be censored at the date of the last tumor assessment. If no tumor assessments were performed after the date of the first occurrence of the objective response (CR or PR), DOR will be censored at the date of the first occurrence of the objective response. Because the determination of DOR is based on a non-randomized subset of patients, formal hypothesis testing will not be performed. DOR will be estimated using the Kaplan-Meier methodology. Comparisons between treatment arms will be made using the stratified and unstratified log-rank test for descriptive purposes only.

4.4.2.10 Prostate-Specific Antigen Response Rate

PSA response rate is defined as the proportion of patients achieving a PSA decline ≥50% from baseline. Patients without a post-baseline PSA assessment will be considered non-responders. The analysis population for PSA response rate will be all randomized patients. The analysis methods will be the same as for the ORR endpoint (see Section 4.4.2.8).

4.4.2.11 Investigator-Assessed rPFS in Patients with PTEN Loss Tumors by NGS

Investigator-assessed rPFS per PCWG3 criteria will be analyzed in patients with PTEN loss tumors by NGS. The same analysis methods as described in Section 4.4.1 for the primary endpoint rPFS will be used.

4.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints will be analyzed in the ITT population and in patients with PTEN loss tumors determined by IHC assay, unless stated otherwise. P-values will be reported for descriptive purposes. The exploratory efficacy endpoints include IRC-assessed radiographic progression, PFS on next-line therapy (PFS2), descriptive summaries for pain progression, descriptive PRO score summaries, time to deterioration in health-related quality of life, time to deterioration in urinary symptoms, time to deterioration in fatigue.

4.4.3.1 IRC-assessed Radiographic Progression

rPFS as assessed by the IRC (IRC-Assessed rPFS) is defined as the time from randomization to the first documented disease progression as determined by the IRC using PCWG3 criteria (soft tissue by CT or MRI scans according to RECIST v1.1, and bone metastasis by bone scan according to the PCWG3 criteria) or death from any cause, whichever occurs first. Refer to the IRC charter and IRC audit plan for further detail.

The same analysis methods as described in Section 4.4.1 for the primary endpoint rPFS will be used.

4.4.3.2 Progression-Free Survival 2 (PFS2)

PFS2 is defined as the time from randomization to first disease progression, as assessed by the investigator on next-line treatment, or death from any cause, whichever occurs first. Specifically, next-line therapy is defined as the treatment received after the first disease progression. Patients who do not experience disease progression on next-line therapy or death will be censored at the last time known to be alive without objective disease progression on next-line therapy. Observations from patients who do not have post-baseline information will be censored at the date of randomization plus 1 day.

The same analysis methods as described in Section 4.4.1 for the primary endpoint rPFS will be used for the PFS2 endpoint. This analysis will be performed as data allows.

4.4.3.3 Descriptive Summaries for Pain Progression

The following descriptive summaries for the time to confirmed cancer-related pain progression endpoint (see Section 4.4.2.2) will be performed by treatment arm.

The number and percentage of patients and each of the confirmatory events for the time to pain progression endpoint will be summarized by treatment arm.

Pain severity scores will be summarized as frequencies and percentages at each time point by treatment arm, where a patient's pain severity score is classified as either no/mild pain (scores of 0-4), moderate pain (scores of 5-6), or severe pain (scores of 7-10).

A table and/or stacked bar chart will be used to summarize the number and proportion of patients who reported meaningful pain increase, pain decrease, or stable pain at each time point by treatment arm. Specifically, patients who reported a ≥ 2-point absolute increase above baseline in pain severity score will be classified as "pain increase," patients who reported a ≥ 2-point decrease from baseline in pain severity score will be classified as "pain decrease," and patients who reported less than a 2-point change from baseline in pain severity score will be classified as "stable pain".

Mean pain severity scores will be cross-tabulated with cancer-related opioid use by treatment arm and time point.

4.4.3.4 Descriptive PRO Score Summaries

Descriptive analyses will include summary statistics (mean, SD, median, interquartile range [IQR], minimum, maximum) of PRO scores and score changes from baseline at each assessment time point by treatment arm. For graphs of mean scores and/or score changes from baseline, two-sided 95% CIs will be presented. Descriptive summaries will be reported for the 7-day recall pain severity item (post-screening), each QLQ-C30 scale, and the QLQ-PR25 urinary scale.

4.4.3.5 Time to Deterioration in health-related quality of life

Confirmed deterioration in GHS is defined as a 10-point or more decrease on the EORTC QLQ-C30 GHS scale score (range, 0-100) held for two consecutive assessments, or a 10-point or more score decrease followed by death (any cause) within 28 days.

The same analysis methods as described in Section 4.4.1 for the primary endpoint rPFS will be used for this time to deterioration in GHS endpoint.

4.4.3.6 Time to Deterioration in Urinary Symptoms

Confirmed deterioration in urinary symptoms is defined as a 10-point or more increase on the EORTC QLQ-PR25 urinary scale score (range, 0-100) held for two consecutive assessments, or a 10-point or more score increase followed by death (any cause) within 28 days.

The same analysis methods as described in Section 4.4.1 for the primary endpoint rPFS will be used for this time to deterioration in urinary symptoms endpoint

4.4.3.7 Time to Deterioration in Fatigue

Confirmed deterioration in fatigue is defined as a 10-point or more increase on the EORTC QLQ-C30 fatigue scale score (range, 0-100) held for two consecutive assessments, or a 10-point or more score increase followed by death (any cause) within 28 days.

The same analysis methods as described in Section 4.4.1 for the primary endpoint rPFS will be used for this time to deterioration in fatigue endpoint.

4.4.3.8 Time to Initiation of Subsequent Anticancer Therapy

Time to initiation of subsequent anticancer therapy is defined as the time from randomization to initiation of subsequent anticancer therapy post-study treatment for PC. Data for patients who do not receive anticancer therapy will be censored at the last known date of no anticancer therapy administered. The same analysis methods as described in Section 4.4.1 for the primary endpoint rPFS will be used for this time to initiation of first anticancer therapy endpoint.

4.4.3.9 Clinical PFS

Clinical PFS is defined as time from randomization to the earliest occurrence of one of the following:

- First documented disease progression (as described in Section 4.4.1)
- Patient-reported pain progression (as described in Section 4.4.2.2)
- Symptomatic skeletal event (as described in Section 4.4.2.7)
- Initiation of subsequent anticancer therapy (as described in Section 4.4.3.8)

4.4.4 Sensitivity Analyses

4.4.4.1 Radiographic Progression-Free Survival

Sensitivity analyses will be performed to evaluate the robustness of the primary analysis results. The following sensitivity analyses of rPFS will be performed in the ITT population and in patients with PTEN loss tumors by IHC.

rPFS censoring for missing visits

An analysis of rPFS censoring for missing visits will be performed. Data for patients with an rPFS event who missed two or more consecutive scheduled assessment immediately prior to the rPFS event will be censored at the last tumor assessment prior to the missed visits. Due to the change in assessment schedule for both soft tissue and bone scans (assessments at the end of Cycles 2, 4, 6, and every 3 cycles thereafter), a cutoff of 5 month (20 weeks) will be used to assess whether a patient missed two or more consecutive scheduled assessment immediately prior to the rPFS event.

The same analysis methods as described in Section 4.4.1 for the primary endpoint rPFS will be used for rPFS censoring for missing visits analysis.

rPFS censoring for non-protocol therapy

Non-protocol therapy (NPT) is defined as any anti-cancer therapy other than study treatment. The impact of NPT on the primary endpoint of investigator-assessed rPFS by RECIST v1.1 will be evaluated. A sensitivity analysis will be performed in which data for patients who received NPT prior to the rPFS event will be censored at the last tumor assessment date before the patient received NPT.

The same analysis methods as described in Section 4.4.1 for the primary endpoint rPFS will be used for rPFS censoring for non-protocol therapy analysis.

4.4.4.2 Delayed Treatment Effect

The weighted log-rank analysis (Fleming and Harrington 1991) that weighs more on late events (Fine 2007) will be conducted to assess a potential delayed treatment effect for OS.

Statistical methodologies analogous to those used in the analysis of OS as specified in Section 4.4.2.1 will be used for these sensitivity analyses. The sensitivity analysis is based on the stratified analyses.

4.4.4.3 Time to Pain Progression

The impact of alternative event definitions and the analysis population will be examined as follows, including but not limited to:

- Time to confirmed cancer-related pain progression will be evaluated as the time from randomization date to the date of a patient's 2-point or more score increase on the pain severity item held for two consecutive assessments, or a 2-point or more score increase followed by death (any cause) within 1 cycle + 2-week window (28 days + 14 days).
- Radiographic disease progression (within 1 cycle + 2-week window of the patient's 2-point or more score increase) will be considered as a confirmatory pain progression event criterion.
- Time to confirmed cancer-related pain progression analysis will also be performed in the PRO-evaluable analysis population, defined as patients with a non-missing baseline assessment and at least one post-baseline assessment.
- Instead of censoring patients with pain severity score > 3 at screening or at baseline as specified in section 4.4.2.2, time to confirmed pain progression analyses will be performed to
    - Exclude patients with pain severity score > 3 at screening or at baseline, or patients with missing baseline pain data from the analysis population
    - Include patients with pain severity score > 3 at screening or at baseline, and their post-baseline pain data in pain progression definition. Patients who have missing baseline pain data will be censored at the randomization date plus 1 day.

The same analysis methods as described in Section 4.4.1 for the primary endpoint rPFS will be used for this time to pain progression endpoint.

4.4.5 Subgroup Analyses

The consistency of the rPFS and OS results will be examined in subgroups defined by demographic and baseline characteristics and stratification factors. Summaries of rPFS and OS, including the unstratified HR estimated from a Cox proportional hazards model

and Kaplan-Meier estimates of median PFS and OS, will be produced by treatment arm for each of the defined subgroups, and displayed in a forest plot in the ITT population and in patients with PTEN loss tumors by IHC.

The subgroups to be considered include but are not limited to the following:

- Age (<65, ≥65 and <75, ≥75 years) at randomization
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Unknown)
- Lactate dehydrogenase (LDH) (≤upper limit of normal [ULN], >ULN)
- Eastern Cooperative Oncology Group (ECOG) performance status (0, 1, 2)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Prior taxane-based therapy in hormone-sensitive setting (yes, no)
- Progression factor (PSA only, Other)
- Presence of visceral metastasis (liver or lung) (yes, no)
- Tumor PTEN-diagnostic status by IHC assay (PTEN loss, PTEN intact) for ITT population only
- Geographic Region (EU, Asia-Pacific, North America, Rest of World)

4.5 SAFETY ANALYSES

Safety analyses will be conducted in all patients who were randomized and received any amount of ipatasertib, placebo, or abiraterone (the safety-evaluable population).

Patients will be analyzed accordingly to the treatment arm associated with the actual regimen received. Specifically, a patient will be included in the Ipat+Abi arm in the safety analyses if this patient has received any amount of ipatasertib, regardless of the initial treatment assignment at randomization.

Sponsor-selected adverse events (AEs) will be presented in more detail including AE severity and AE seriousness. Additionally, time to first AE onset and duration to AE resolution will also be presented for rash, diarrhea, and hyperglycemia. The Sponsor proposes to define the medical concepts representing the selected AEs by using Medical Dictionary for Regulatory Activities (MedDRA) SMQs, AEGTs, and manually selected groups of preferred terms (PTs).

Safety endpoints will include incidence, severity, and seriousness of adverse events, deaths, and clinically significant laboratory measurements. All safety endpoints will be analyzed in the safety-evaluable population by all patient population and PTEN loss population by IHC, unless stated otherwise.

4.5.1 Exposure of Study Medication

Study treatment exposure, including but not limited to treatment duration, number of doses, total cumulative dose, dose intensity with respect to total dose, and dose intensity with respect to total number of doses will be summarized with descriptive statistics. The number of missed doses will also be displayed. Reasons for discontinuation from the study treatment will be summarized.

4.5.2 Adverse Events

Verbatim description of AEs will be mapped to the latest effective MedDRA thesaurus terms and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI CTCAE v4.0). Adverse events will be summarized by mapped term, appropriate thesaurus level and NCI CTCAE Grade.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported, e.g. serious adverse events related to invasive procedures such as biopsies.

After initiation of study drug, all AEs, regardless of relationship to study drug, will be reported until 28 days after the last dose of study. After this period, investigators should report any serious adverse events (SAEs) and adverse events of special interest (AESI) that are believed to be related to prior treatment with study drug.

Summary tables of the following will be provided, including, but not limited to:

- SAEs
- AEs leading to study treatment discontinuation
- AEs leading to dose reduction or interruption
- Treatment-related AEs
- Severe adverse events (Grade 3 or higher)
- AEs leading to death
- AEs by highest NCI CTCAE Grade
- Selected Adverse Events of Interest (including sponsor-defined AESI)

A summary table of common AEs, i.e., those occurring in at least 10% of patients, will be provided.

Multiple occurrences of the same event will be counted once at the maximum severity. All listings of AEs will include all AEs with onset on or after the first study drug treatment up to the data cutoff date.

All deaths and causes of death will be summarized.

4.5.3 Laboratory Data

Laboratory data will be classified according to NCI CTCAE v 4.0 and will be summarized descriptively over time including change from baseline. Highest NCI CTCAE Grade post-baseline will also be reported and shift tables from baseline to worst value during the study post-baseline will be presented. Summary statistics (number of patients, mean, 95% CI, median, and range) of absolute values and mean changes from baseline will be calculated for HbA1c at each assessment time point for each arm within each cohort.

A Hy's law analysis will be provided. The potential Hy's law quadrant is defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increases above 3-fold the ULN with concomitant total bilirubin increases above 2-fold the ULN.

4.5.4 Vital Signs and ECOG Performance Status

Vital signs will be summarized descriptively over time including change from baseline. ECOG performance status will also be summarized over time.

4.5.5 Electrocardiograms

The baseline ECG of the patients will be summarized and results of study drug discontinuation visits will be listed.

4.6 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Ipatasertib and its metabolite (G-037720) levels will be measured on Days 1 and 15 of Cycle 1, Day 1 of Cycle 3, and Day 1 of Cycle 6. Ipatasertib and its metabolite plasma concentration versus time data, together with information on dosing and patient characteristics, will be pooled and analyzed using a population PK (PopPK) analysis approach, as appropriate. Non-linear mixed-effect modeling will be used for the estimation of PopPK parameters for ipatasertib. Covariates such as patient demographics (e.g., age, body size), may be tested for significance on PK parameters of interest.

The PK data may be combined with the safety, efficacy, and biomarker data for exposure-response modeling as an exploratory objective. PK and PK/pharmacodynamic analyses may be reported in separate stand-alone reports. Additional analyses may be explored as warranted by the data.

Abiraterone levels will be measured on Day 15 of Cycle 1 and Day 1 of Cycle 3. Abiraterone trough plasma concentrations will be compared between arms (ipatasertib vs. placebo).

4.7 Exploratory Biomarker Analyses

Exploratory biomarker analyses (in tumor tissues and plasma, whole blood, or serum) will be performed in an effort to understand the association of these markers with study

drug response, including efficacy and/or adverse events. The results will be presented in a separate report.

Whole genome sequencing (WGS) data will be analyzed in the context of this study and explored in aggregate with data from other studies to increase researchers' understanding of disease pathobiology and guide the development of new therapeutic approaches.

4.8 OTHER EXPLORATORY ANALYSES

4.8.1 Patient-Reported Symptomatic Adverse Events

Compliance rates in the safety-evaluable population will be summarized as the number of patients who completed the questionnaire (11 PRO-CTCAE items and the global assessment of treatment side effect bother item) divided by the number of patients expected to complete the questionnaire at each time point for each treatment arm.

Descriptive analysis of the overall side effect bother item will be performed by treatment arm at each visit in the safety-evaluable population. Data will be summarized descriptively for on-study treatment visits in addition to a patient's closest assessment in the 28 days prior to treatment discontinuation due to AEs. Distribution of responses and change from baseline will be summarized by treatment arm as frequencies and percentages, where patients are considered either improved, no change, or worsened, at each time point. Stacked bar charts or lollipop charts may be used to illustrate the distribution of responses and the change in response (either improved, no change, or worsened) at each time point by treatment arm.

Descriptive item-level analyses of the 11 PRO-CTCAE items may be performed by treatment arm at each visit in the safety population. The distribution of responses for each item attribute ("frequency", "severity", "interference", "presence") may be summarized as frequencies and percentages at each visit and by treatment arm. Change from baseline for each item may be summarized by treatment arm as frequencies and percentages, where patients are considered either improved [by 1, 2, 3, or 4], no change, or worsened [by 1, 2, 3, or 4], at each time point. For each item, the cumulative incidence of patients reporting scores of 3 or 4 may also be presented graphically by treatment arm during the study.

4.8.2 Health Utilities

EQ-5D-5L health utilities will be used to inform pharmacoeconomic modeling. These results will be presented separately from the CSR.

4.9 MISSING DATA

In safety analyses, all deaths are included, from all sources, regardless of completeness of death date; patients who died with only a partial death date available will be included.

In efficacy analyses, a death is considered an event if and only if a complete death date is available; patients who died with only a partial death date available will be censored.

4.10 INTERIM ANALYSES

4.10.1 Planned Interim Safety Analyses

The iDMC will evaluate safety data (including SAEs, deaths, and AESI) during the study on a periodic basis, approximately every 3 months for the first year and approximately every 6 months thereafter, until the time of the rPFS primary analysis, according to the policies and procedures detailed in an iDMC charter. The Sponsor will be blinded until the rPFS primary analysis. No interim efficacy analyses are planned for the primary endpoint of rPFS.

An iDCC will prepare all summaries and analyses for the iDMC's review. The safety summaries will include demographic data, AEs, SAEs, and relevant laboratory data.

Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. Following the data review, the iDMC will provide a recommendation to the Sponsor whether to continue the study, amend the protocol, or stop the study. The final decision will rest with the Sponsor.

Any outcomes of the iDMC's reviews on the safety and benefit-risk balance that affect study conduct will be communicated in a timely manner to the investigators for notification of IRBs/ECs and competent authorities as required.

4.10.2 Planned Interim Efficacy Analyses

No interim efficacy analyses are planned for the primary endpoint of rPFS.

As described in Section 2.3 if the test of rPFS in patients with PTEN loss tumors by IHC is positive, then OS in patients with PTEN loss tumors by IHC will be further tested. An interim analysis will be performed at the time of rPFS primary analysis, which is approximately 34 months after the first patient in, and the final analysis will be performed approximately 24 months after the rPFS primary analysis.

As described in Section 2.3 if the test of OS in patients with PTEN loss tumors by IHC is positive, then OS in the ITT population will be further tested. Interim analyses will be performed at the time of rPFS primary analysis which is approximately 34 months after the first patient in, and at the time of the final analysis of OS in patients with PTEN loss tumors by IHC which is approximately 24 months after the rPFS primary analysis; and the final analysis will be performed approximately 9 months after the final analysis of OS in patients with PTEN loss tumors by IHC.

4.10.3 Optional Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one interim efficacy analysis for futility. Below are the

specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

If an interim analysis is conducted, the Sponsor will remain blinded. The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC charter.

The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis will be documented in the SAP, and the SAP will be submitted to relevant health authorities at least 2 months before the conduct of the interim analysis. The iDMC charter will be updated to document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., stop the study for futility), and the iDMC charter will also be made available to relevant health authorities.

If there is a potential for the study to be stopped for futility as a result of the interim analysis, the threshold for declaring futility will be included in the SAP. Additional criteria for recommending that the study be stopped for futility may be added to the iDMC charter. An interim analysis that might lead to stopping the study for futility will not occur before at least 67% of the information in both the ITT population and patients with PTEN loss tumors has been accumulated.

After the primary analysis for PFS, additional OS interim analyses may be conducted to provide additional OS data, per the recommendation from health authorities. If conducted, the Lan-DeMets-spending function with an O'Brien-Fleming boundary will be used to control the overall type I error for OS accounting for the additional OS interim analyses.

5. References

Akazawa K, Nakamura T, Palesch Y. Power of logrank test and Cox regression model in clinical trials with heterogeneous samples. Stat Med. 1997 16:583-97.

Fine GD. Consequences of delayed treatment effects on analysis of time-to-event endpoints. Ther Innov Regul Sci 2007;41:535−9.

Fleming TR and Harrington DP. Counting processes and survival analysis. New York: John Wiley & Sons, 1991.

Appendix 1
Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER TRIAL TESTING IPATASERTIB PLUS ABIRATERONE PLUS PREDNISONE/PREDNISOLONE, RELATIVE TO PLACEBO PLUS ABIRATERONE PLUS PREDNISONE/PREDNISOLONE IN ADULT MALE PATIENTS WITH ASYMPTOMATIC OR MILDLY SYMPTOMATIC, PREVIOUSLY UNTREATED, METASTATIC CASTRATE-RESISTANT PROSTATE CANCER**
PROTOCOL NUMBER:	CO39303
VERSION NUMBER:	7 (VHP)
EUDRACT NUMBER:	2016-004429-17
NCT NUMBER:	NCT03072238
IND NUMBER:	130663
TEST PRODUCT:	Ipatasertib (RO5532961)
PHASE:	III
INDICATION:	Metastatic Castrate-Resistant Prostate Cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of ipatasertib plus abiraterone and prednisone/prednisolone compared with placebo plus abiraterone and prednisone/prednisolone in patients with metastatic castrate-resistant prostate cancer (mCRPC). Specific objectives and corresponding endpoints for the study are outlined below.

Objectives	Corresponding Endpoint(s)
Co-Primary Efficacy Objectives	
• To evaluate the efficacy in the ITT population • To evaluate the efficacy in patients with PTEN-loss tumors by IHC	• Investigator-assessed rPFS, per PCWG3 criteria
Secondary Efficacy Objectives [a]	
• To evaluate the clinical benefit in the ITT population, and in patients with PTEN-loss tumors by IHC	Key secondary endpoints with type 1 error control: • Overall survival

Objectives	Corresponding Endpoint(s)
Secondary Efficacy Objectives (cont.) [a]	
	Additional Secondary Endpoints: • Time to pain progression • Time to initiation of cytotoxic chemotherapy for prostate cancer • Time to function deterioration per EORTC QLQ-C30 PF and RF • Time to PSA progression, per the PCWG3 criteria • Time to first opioid use • Time to symptomatic skeletal events • ORR, per RECIST v1.1 and PCWG3 criteria in patients with measurable disease • PSA response rate
• To evaluate the efficacy in patients with *PTEN*-loss tumors by NGS	• Investigator-assessed rPFS per PCWG3 criteria
Exploratory Efficacy Objectives	
• To evaluate the clinical benefit in the ITT population, and in patients with PTEN-loss tumors by IHC and by NGS	• IRF-assessed radiographic progression • PFS after next line of treatment • Time to deterioration in health-related quality of life, per EORTC QLQ-C30 GHS • Time to deterioration in urinary symptoms per EORTC QLQ-PR25 urinary scale • Time to deterioration in fatigue per EORTC QLQ-C30 fatigue scale • Clinical PFS
Safety Objective	
• To evaluate the safety in the ITT population and in patients with PTEN-loss tumors by IHC	• Incidence, nature, and severity of adverse events, with severity determined through use of NCI CTCAE v4.0
Pharmacokinetic Objective	
• To characterize ipatasertib and abiraterone pharmacokinetics • To characterize ipatasertib exposure, abiraterone exposure in relation to efficacy and safety	• Plasma concentration of ipatasertib and abiraterone at specified timepoints for analysis using population PK methodology • Relationship between plasma concentration or PK parameters of ipatasertib and abiraterone, via safety and efficacy endpoints
Exploratory Biomarker Objectives [b]	
• To evaluate possible predictive and prognostic biomarkers in the tissue and plasma • To identify possible mechanisms of resistance to study treatments through the comparative analysis of potential biomarkers in the blood	• Explore possible relationships between the tissue- and blood-based biomarkers and patient clinical features (e.g., baseline features) and outcome (e.g., duration of rPFS) [b]

Objectives	Corresponding Endpoint(s)
Other Exploratory Objectives	
• To collect patients' perspectives regarding key symptomatic adverse events	• Proportion analyses and change from baseline on selected items from PRO-CTCAE capturing patients' rating of the severity, frequency, interference, and/or occurrence of decreased appetite, nausea, vomiting, diarrhea, constipation, fatigue, and rash
• To collect utilities for pharmacoeconomic modeling	• Utilities derived from scores on EQ-5D-5L

EQ-5D-5L = EuroQol 5 Dimensions, 5 Levels; EORTC = European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30 = EORTC Quality of Life Questionnaire Core 30; GHS = global health status; IHC = immunohistochemistry; IRF = independent review facility; ITT = intent to treat; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; NGS = next-generation sequencing; ORR = objective response rate; PCWG3 = Prostate Cancer Working Group 3; PF = physical functioning; PFS = progression-free survival; PK = pharmacokinetic; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PSA = prostate-specific antigen; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RF = role functioning (2-item scale from the EORTC QLQ-C30); rPFS = radiographic progression-free survival.

[a] Refer to Section 6 for the protocol-specified definition of clinical benefit endpoints.

[b] Refer to Appendix 2 for the protocol-specific definition of the biomarker analysis.

Study Design

Description of Study

This is a Phase III, multicenter, international, randomized, double-blind, placebo-controlled study. The target patient population is asymptomatic or mildly symptomatic patients previously untreated for mCRPC. Patients must have documented metastatic disease by presence of bone lesions on bone scan and/or soft tissue lesions on computed tomography (CT)/magnetic resonance imaging (MRI). Analysis will be based on the intent-to-treat (ITT) and PTEN-loss populations, the latter defined using the Ventana PTEN immunohistochemistry (IHC) assay. Patients must also have a valid PTEN IHC result from tumor to be enrolled.

All eligible patients will receive abiraterone 1000 mg administered orally once daily (QD), prednisone/prednisolone 5 mg orally BID, and either ipatasertib at a dose of 400 mg (experimental arm) or placebo administered orally QD (control arm). Study treatment will continue until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination.

Tumor measurement for disease evaluation will be performed with bone scans and CT/MRI, and response will be evaluated per Prostate Cancer Working Group 3 (PCWG3) guidelines. For patients who have evidence of progression by bone scan alone, a confirmatory scan must be performed. For patients with soft tissue progression, a confirmatory scan is not needed. Patients with progression by PSA alone without evidence of radiographically assessed disease progression should continue on study treatment until evidence of radiographically assessed disease progression. Images for tumor assessments will be collected for independent data review to enable blinded, independent central review as needed. Cross over will not be allowed.

Number of Patients

The study will enroll approximately 1100 patients at approximately 200 centers worldwide in about 20 months.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

General Inclusion Criteria

- Signed Informed Consent Form(s)
- Ages ≥ 18 years
- Eastern Collaborative Oncology Group performance status of 0 or 1 at screening
- Adequate hematologic and organ function within 28 days before the first study treatment, defined using the following (hematologic parameters must be assessed ≥ 14 days after a prior transfusion, if any):

  Neutrophils: ANC ≥ 1500 cells/μL (1.5×10^9/L)

  Hemoglobin ≥ 10 g/dL

  Platelet count $\geq 100{,}000$ cells/μL

  Total bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN) with the following exception:

  - Patients with known Gilbert disease who have serum bilirubin $\leq 3 \times$ ULN may be enrolled.

  AST and ALT $\leq 1.5 \times$ ULN, with the exception that patients with liver metastasis may have AST and/or ALT $\leq 2.5 \times$ ULN and total bilirubin $\leq 1.5 \times$ ULN

  Serum creatinine $< 1.5 \times$ ULN and creatinine clearance ≥ 50 mL/min based on Cockroft–Gault glomerular filtration rate estimation:

  $$\frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})}$$

  Serum albumin ≥ 3.5 g/dL

  Serum potassium ≥ 3.5 mmol/L

  Fasting glucose ≤ 150 mg/dL (8.3 mmol/L) and hemoglobin $A_{1c} \leq 7.5\%$ (58 mmol/mol)
- Ability to comply with the study protocol, in the investigator's judgment
- Willingness and ability of patients to use the electronic device to report selected study outcomes (e.g. symptom severity). Caregivers and site staff can assist with patient diary input but patient must be able to independently comprehend and answer the questionnaires.
- Life expectancy of at least 6 months
- Agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom along with another effective contraceptive method during the treatment period and for at least 28 days after the last dose of study treatment to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- For enrollment into the China extension cohort, residence in the People's Republic of China

Disease-Specific Inclusion Criteria

- Histologically confirmed prostate adenocarcinoma without neuroendocrine differentiation or small-cell features
- Consent to provide a formalin-fixed, paraffin-embedded (FFPE) tissue block (preferred) or a minimum of 15 (20 preferred) freshly cut unstained tumor slides from the most recently collected, available tumor tissue accompanied by an associated pathology report (with tumor content information, Gleason score, and disease staging) for PTEN IHC and next-generation sequencing (NGS) testing and for other protocol-mandated secondary and exploratory assessments. If only 12–14 slides are available, the patient may still be eligible for the study, after discussion with and approval by the Medical Monitor. Cytologic or fine-needle aspiration samples are not acceptable. Tumor tissue from bone metastases is not acceptable.
- A valid PTEN IHC result (central laboratory tested with results directly sent to interactive voice-or Web-based response technology [IxRS]), patients with an "invalid" or "failed" PTEN IHC result are not permitted to enroll
- Metastatic disease documented prior to randomization by clear evidence of bone lesions on bone scan and/or measurable soft tissue disease by CT and/or MRI (at least one target lesion) according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

  Patients whose spread of disease is limited only to regional pelvic lymph nodes are not eligible.
- Asymptomatic or mildly symptomatic form of prostate cancer

  A score of 0 or 1 on the pain at its worst (24-hour recall) 10-point Numeric Rating Scale will be considered asymptomatic, and a score of 2 or 3 will be considered mildly symptomatic.
- Progressive disease before initiating study treatment, defined using at least one of the following criteria:

  Two rising PSA levels measured ≥ 1 week apart, with second result ≥ 1 ng/mL according to PCWG3 criteria

  - Patients who have received an anti-androgen therapy must have PSA progression after withdrawal (≥ 4 weeks since last flutamide or ≥ 6 weeks since last treatment of bicalutamide or nilutamide).

  Radiographic evidence of disease progression in soft tissue according to RECIST v1.1 and/or bone scan according to PCWG3 criteria
- Ongoing androgen deprivation with gonadotropin-releasing hormone (GnRH) analog or bilateral orchiectomy, with serum testosterone ≤ 50 ng/dL (≤ 1.7 nmol/L) within 28 days before randomization

  Patients on GnRH analog must have therapy initiated at least 4 weeks before Cycle 1, Day 1 and treatment must be continued throughout the study.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

General Exclusion Criteria

- Inability or unwillingness to swallow whole pills
- History of malabsorption syndrome or other condition that would interfere with enteral absorption
- Clinically significant history of liver disease consistent with Child-Pugh Class B or C, including cirrhosis, current alcohol abuse, or current known active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV)

Active infection is defined as requiring treatment with antiviral therapy or presence of positive test results for hepatitis B (hepatitis B surface antigen [HBsAg] and/or total hepatitis B core antibody [anti-HBc]) or HCV antibody. Unless required by local regulations, patients are not required to have HIV, HBV, or HCV assessments at screening if these assessments have not been previously performed.

Patients who are positive for anti-HBc are eligible only if test results are also negative for HBsAg and polymerase chain reaction is negative for HBV DNA.

Patients who are positive for HCV serology are eligible only if testing for HCV RNA is negative.

- Need of more than 10 mg/day of prednisone or an equivalent dose of other anti-inflammatory corticosteroids as a current systemic corticosteroid therapy to treat a chronic disease (e.g., rheumatic disorder)

  Concurrent use of inhaled corticosteroids is allowed.
- Active infection requiring intravenous antibiotics within 14 days before Cycle 1, Day 1
- Immunocompromised status because of current known active infection with HIV or because of the use of immunosuppressive therapies for other conditions
- Major surgical procedure or significant traumatic injury within 28 days prior to Cycle 1, Day 1, or anticipation of the need for major surgery during study treatment
- History of ventricular dysrhythmias or risk factors for ventricular dysrhythmias, such as structural heart disease (e.g., severe left ventricular systolic dysfunction, left ventricular hypertrophy), untreated coronary heart disease (symptomatic or with ischemia demonstrated by diagnostic testing), myocardial infarction or atrial thrombotic events within the past 6 months, severe or unstable angina, New York Heart Association Class III and IV heart disease or depressed left ventricular ejection fraction (LVEF; previously documented LVEF < 50% without documentation of recovery), clinically significant electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia), or family history of sudden unexplained death or long QT syndrome
- History of another malignancy within 5 years prior to randomization, except for either adequately treated non-melanomatous carcinoma of the skin, adequately treated melanoma in situ, adequately treated non-muscle-invasive urothelial carcinoma of the bladder (Tis, Ta and low grade T1 tumors), or other malignancies where the patient has undergone potentially curative therapy with no evidence of disease and are deemed by the treating physician to have a recurrence rate of <5% at 5 years.
- Any other diseases; cardiovascular, pulmonary, or metabolic dysfunction; physical examination finding; or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patients at high risk from treatment complications

Disease-Specific Exclusion Criteria

- Pathologic findings consistent with small-cell or neuroendocrine carcinoma of the prostate
- Use of opioid medication for cancer-related pain, including codeine and dextropropoxyphene, currently or any time within 4 weeks of Cycle 1, Day 1
- Any therapy including chemotherapy (e.g. docetaxel) or biological therapy (e.g., vaccine, immunotherapy) for the treatment of castration-resistant prostate cancer. Previous treatment with flutamide, steroidal anti-androgens, androgens, estrogens, bicalutamide, nilutamide, or 5-α reductase inhibitor is permitted.

  In the setting of hormone-sensitive prostate cancer, chemotherapy (e.g., docetaxel) is permitted provided that it is initiated within 6 months from the time of first castration (i.e., concurrent initiation of chemotherapy and ADT for HSPC). Patient should not have progressed during or within 3 months after the completion of chemotherapy-based treatment (i.e., rapid progression on chemotherapy for HSPC).

- Prior treatment with abiraterone or other known potent CYP17 inhibitors (e.g., ketoconazole, orteronel) or investigational agents that block androgen synthesis. Previous treatment with itraconazole and fluconazole is permitted.
- Prior treatment with enzalutamide or other potent androgen-receptor blockers, approved or experimental (e.g., ARN-509, ODM-201, or galeterone)
- Prior treatment with flutamide (Eulexin®), steroidal anti-androgens (e.g., cyproterone acetate, chlormadinone acetate), androgens, or estrogens treatment within 4 weeks of Cycle 1, Day 1
- Prior treatment with bicalutamide (Casodex®) or nilutamide (Nilandron®) within 6 weeks of Cycle 1, Day 1
- Prior treatment with 5-α reductase inhibitors within 4 weeks of Cycle 1, Day 1
- Prior treatment with systemic radiopharmaceuticals (e.g., radium-223 and strontium-89). Radiopharmaceuticals for the purpose of imaging are permitted. Focal palliative radiation to treat cancer-related pain is permitted provided that the last treatment with radiation is at least 14 days prior to Cycle 1, Day 1.
- Prior treatment with approved or experimental therapeutic agents with known inhibition of the PI3K pathway, including PI3K inhibitors, AKT inhibitors, and mTOR inhibitors
- Administration of an investigational therapeutic agent within 28 days of Cycle 1, Day 1
- Known untreated or active CNS metastases (progressing or requiring anticonvulsant medications or corticosteroids for symptomatic control); a CT or MRI scan of the brain will be performed at screening if required by the local health authority.
- Patients with a history of treated CNS metastases are eligible, provided they meet all of the following criteria:

  An evaluable or measurable disease according to the inclusion criteria outside the CNS

  Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

  No history of intracranial hemorrhage or spinal cord hemorrhage

  Minimum of 2 weeks between completion of radiotherapy and Cycle 1, Day 1, and recovery from significant (Grade $\geq$ 3) acute toxicity, with no ongoing requirement for $\geq$ 10 mg/day of prednisone or an equivalent dose of another corticosteroid
- Any chronic therapy or use of food supplements that are strong CYP3A4/5 inducers or inhibitors or sensitive substrates of CYP3A or CYP2D6 with a narrow therapeutic window

Abiraterone-Specific Exclusion Criteria

- Uncontrolled hypertension (systolic blood pressure $\geq$ 160 mmHg or diastolic blood pressure $\geq$ 95 mmHg)

  Patients with a history of hypertension are eligible, provided blood pressure is controlled by anti-hypertensive treatment prior to or within the 28 days of screening period.
- History of pituitary or adrenal dysfunction
- Any ongoing cardiac arrhythmias (including atrial fibrillation) that require medical therapy

Ipatasertib-Specific Exclusion Criteria

- Type 1 or Type 2 diabetes mellitus requiring insulin at study entry

  Patients who are on a stable dose of oral diabetes medication $\geq$ 4 weeks prior to initiation of study treatment may be eligible for enrollment.
- History of inflammatory bowel disease (e.g., Crohn disease and ulcerative colitis), active bowel inflammation (e.g., diverticulitis)

End of Study

The end of this study is defined as the date when the last patient, last visit occurs (i.e., the date at which the last data point required for statistical analysis or safety follow-up is received).

Length of Study

The total length of the study, from randomization of the first patient to the end of the study, is expected to be approximately 7 years.

Investigational Medicinal Products

Test Product (Investigational Drug)

Ipatasertib drug product will be supplied by the Sponsor as 100-mg and 200-mg tablets packaged in bottles. Ipatasertib tablets are given once daily beginning on Cycle 1, Day 1 until disease progression or intolerable toxicity.

For information on the formulation, packaging, and handling of abiraterone acetate, see the local prescribing information.

Comparator

The placebo drug product will be supplied by the Sponsor as a tablet formulation and will be matched in size, color, and shape to ipatasertib tablets to maintain the study blind. Placebo tablets are given once daily beginning on Cycle 1, Day 1 until disease progression or intolerable toxicity.

Non-Investigational Medicinal Product

For information on the formulation, packaging, and handling of prednisone/prednisolone, see the local prescribing information.

Statistical Methods

Primary Analysis

This study has two co-primary endpoints: rPFS in the ITT population and rPFS in patients with PTEN-loss tumors by IHC. At the time of primary analysis of rPFS, rPFS in patients with PTEN-loss tumors by IHC will be firstly tested with α of 5%. If the test is positive, then rPFS in the ITT population will be tested with α of 1%.

The primary analysis of rPFS will occur when approximately 275 rPFS events in patients with PTEN-loss tumors and approximately 550 rPFS events in the ITT population have been observed, whichever occurs later. The primary analysis is expected to occur approximately 34 months after the first patient is randomized.

In the PTEN-loss population, 275 events will allow for 98.4% power to detect an improvement in median rPFS from 14 months in the placebo arm to approximately 23 months in the ipatasertib arm (HR = 0.61) at the 5% level of significance (two-sided). The largest hazard ratio deemed to be statistically significant will be approximately 0.79 (with median rPFS improvement from 14 months in the placebo arm to approximately 17.7 months in the ipatasertib arm).

In the ITT population, 550 events will allow for 94.5% power to detect an improvement in median rPFS from 16.5 months in the placebo arm to approximately 23.6 months in the ipatasertib arm (HR =0.70) at the 1% level of significance (two-sided). The largest hazard ratio deemed to be statistically significant will be approximately 0.80 (with median rPFS improvement from 16.5 months in the placebo arm to approximately 20.6 months in the ipatasertib arm.

Determination of Sample Size

Approximately 1100 patients in total will be randomized into this study in about 20 months. Assuming 50% prevalence of IHC PTEN-loss tumors in all patients, it's estimated that approximately 550 patients will have PTEN loss tumors.

Interim Analysis

An iDMC will evaluate safety data (including, but not limited to, serious adverse events, death, and adverse events of special interest) during the study on a periodic basis, approximately every 3 months for the first year and approximately every 6 months thereafter, until the time of the rPFS primary analysis, according to the policies and procedures detailed in an iDMC charter. The Sponsor will be blinded until the rPFS primary analysis.

No interim efficacy analyses are planned for the primary endpoint of rPFS.

A total of four analyses of OS are planned:

- The first interim analysis of OS was performed at the time of primary analysis of rPFS.
- The second interim analysis of OS will take place when approximately 229 OS events in the patients with PTEN loss tumors by IHC occur, or when the minimum follow-up time (from the last patient enrollment date of 17 January 2019) is approximately 32 months, whichever occurs later.
- The third analysis of OS is the final analysis of OS in the patients with PTEN loss tumors by IHC and it is also the third interim analysis of OS in the ITT population. It is scheduled when there are approximately 327 OS events in patients with PTEN loss tumors by IHC occur. This target number of OS event is unchanged per the original Protocol Version 6, section 6.1.3.
- The fourth analysis of OS is the final analysis of OS in the ITT population. It is scheduled when there are approximately 660 OS events in the ITT population occur. This target number of OS event is unchanged per the original Protocol Version 6, section 6.1.3.

The projected analysis timing and the corresponding numbers of OS events for OS interim and final analyses in patients with PTEN loss tumors by IHC and in the ITT population are presented in the Section 6.8.2 of the Protocol Version 7. When the timing of the third and fourth analyses are very close, these two analyses could be combined and the alpha-spending will be adjusted using O'Brien-Fleming alpha-spending method.

Appendix 2
Schedule of Assessments

Assessment/Procedure (Window)	Screening [a]	Cycle 1				Cycle 2		Cycle 3		Cycles ≥ 4	Study Treatment Discontinuation [b]	Disease Follow-Up [c]	Post-Treatment Follow-Up [d]
	Days –28 to –1	Day 1	Day 4 (±1)	Day 8 (±2)	Day 15 [e] (±2)	Day 1	Day 15 [e]	Day 1	Day 15 [e]	Day 1	Within 30 days of the Last Study Treatment	Every 3 (±1) Months	Every 3 (±1) Months
Informed consent(s)	x [f]												
Demographic data (age, sex, and self-reported race/ethnicity)	x												
Medical history and baseline conditions [g]	x												
Archival FFPE tumor tissue	x [h]												
PTEN IHC results	x												
Patient randomization number assignment (IxRS)	x												
Concomitant medications [i]	x	x		x	x	x	x	x	x	x	x	x [j]	
Adverse events [k]	x	x	x	x	x	x	x	x	x	x	x	x	x
Complete physical examination [l]	x [a]										x		
Limited physical examination [m]				x	x	x	x	x	x	x			
ECOG performance status	x [a]	x				x		x		x	x	x	x
Vital signs [n]	x	x	x	x	x	x	x	x	x	x	x		
Weight and height (height at screening only)	x	x				x		x		x	x		
Electrocardiogram [o]	x [o]	As clinically indicated									x [o]		
Historic values for PSA velocity	x [p]												
PSA [p]	x [p, q]	x [r]				x [r]		x [r]		x [r]	x		

Appendix 2
Schedule of Assessments (cont.)

Assessment/Procedure (Window)	Screening [a]	Cycle 1				Cycle 2		Cycle 3		Cycles ≥ 4	Study Treatment Discontinuation [b]	Disease Follow-Up [c]	Post-Treatment Follow-Up [d]
	Days –28 to –1	Day 1	Day 4 (±1)	Day 8 (±2)	Day 1	Day 1	Day 15 [e]	Day 1	Day 15 [e]	Day 1	Within 30 days of the Last Study Treatment	Every 3 (±1) Months	Every 3 (±1) Months
Serum testosterone [s]	x										x		
Hematology [t]	x	x [r]		x [r]	x [r]	x [r]	x [r]	x [r]	x [r]	x [r]	x		
Fasting blood glucose [u]	x	x	x	x	x	x	x	x	x	x	x		
Home glucose monitoring [v]		Post-meal blood glucose measurement and recording in daily glucose log (while receiving ipatasertib/placebo treatment)											
Chemistry panel [w]	x	x [r]		x [r]	x [r]	x [r]	x [r]	x [r]	x [r]	x [r]	x		
Urinalysis [x]	x	As clinically indicated									x		
Coagulation: aPTT, PT, and INR	x	As clinically indicated									x		
Amylase and lipase	x					x				Day 1 of Cycles 4, 6, 9, 12, and every 3 cycles thereafter	x		
Fasting lipid profile	x					x					x		
Hemoglobin A_{1c}	x					x							
Tumor assessment of soft tissue per RECIST v1.1 [y]	x [a]					End of Cycles 2, 4, 6, and every 3 cycles thereafter [aa]					x	x	
Tumor assessment: bone scan [z]	x [a]										x	x	
Pain severity at its worst NRS (24h recall) [bb]	x												

Appendix 2
Schedule of Assessments (cont.)

Assessment/Procedure (Window)	Screening [a]	Cycle 1				Cycle 2		Cycle 3		Cycles ≥ 4	Study Treatment Discontinuation [b]	Disease Follow-Up [c]	Post-Treatment Follow-Up [d]
	Days –28 to –1	Day 1	Day 4 (±1)	Day 8 (±2)	Day 15 [e] (±2)	Day 1	Day 15 [e]	Day 1	Day 15 [e]	Day 1	Within 30 days of the Last Study Treatment	Every 3 (±1) Months	Every 3 (±1) Months
Pain severity at its worst NRS (7-day recall) [bb]		x				x		x		x	x	x	x
EORTC QLQ-C30, Urinary Scale from EORTC PR-25 [bb]		x				x		x		x	x	x	x
EQ-5D-5L [bb]		x				x		x		x	x	x	x
PRO-CTCAE (selected items) [bb]		x		x	x	x	x	x	x	x			
Medication log [cc]		Record per medication consumption									x	x	
Study treatment administration [dd]		Daily administration of ipatasertib/placebo, abiraterone plus prednisone/prednisolone											
Symptomatic skeletal events [ee]		Record any symptomatic skeletal events									x	x	x
Drug accountability						x		x		x	x		
Plasma PK sample [ff]		See Appendix 3											
Blood sample for NGS control [gg]		See Appendix 3											
Blood sample for pharmacogenomics [gg]		See Appendix 3											
Plasma sample for somatic tumor mutations [gg]		See Appendix 3											
Plasma sample for exploratory biomarkers [gg]		See Appendix 3											

Appendix 2
Schedule of Assessments (cont.)

Assessment/Procedure (Window)	Screening [a]	Cycle 1				Cycle 2		Cycle 3		Cycles ≥ 4	Study Treatment Discontinuation [b]	Disease Follow-Up [c]	Post-Treatment Follow-Up [d]
	Days –28 to –1	Day 1	Day 4 (±1)	Day 8 (±2)	Day 15 [e] (±2)	Day 1	Day 15 [e]	Day 1	Day 15 [e]	Day 1	Within 30 days of the Last Study Treatment	Every 3 (±1) Months	Every 3 (±1) Months
Blood sample for RBR (for DNA extraction; optional) [hh]		See Appendix 3											
Subsequent line of prostate cancer therapy and outcome [ii]												x	x
Survival follow-up												x	x

CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC = European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30 = EORTC Quality of Life Questionnaire Core 30; EORTC QLQ-PR25 = EORTC Quality of Life Questionnaire Prostrate Cancer Module; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels; FFPE = formalin-fixed, paraffin-embedded; IHC = immunohistochemistry; IxRS = interactive voice- or Web-based response system; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; NGS = next-generation sequencing; NRS = Numeric Rating Scale; PK = pharmacokinetic; PCWG3 = Prostate Cancer Working Group 3; PRO = patient-reported outcome; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology for Adverse Events; PSA = prostate-specific antigen; RBR = Research Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Notes: All visits should occur within ±3 days of the scheduled visit, unless otherwise specified. On treatment visit days, all assessments should be performed prior to dosing, unless otherwise specified. Patients should receive their first dose of study treatment no later than 7 days after randomization. Unplanned visits not specified by the protocol or unscheduled assessments (possibly including PK sample collection) may be performed as clinically indicated at discretion of the investigator; the associated data should be recorded on the relevant eCRF in support of an adverse event diagnosis or tumor assessments.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Cycle 1, Day 1 may be used; such tests do not need to be repeated for screening. Bone scans within 42 days prior to Cycle 1, Day 1 may be used. If eligibility assessments were not completed within 28 days from the original date of the screening visit, the patient will need to be rescreened for eligibility (see Section 4.5.1 of the protocol for details).

Appendix 2
Schedule of Assessments (cont.)

[b] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit within 30 (±3) days after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit, provided that all tests required at the treatment discontinuation visit are performed. Tumor assessments at the treatment discontinuation visit may be omitted if the most recent prior assessment was performed less than 28 days ago or the patient has already had confirmation of radiographic disease progression.

[c] After treatment discontinuation, patients who discontinue study treatment in the absence of radiographically assessed disease progression will return to the clinic for tumor assessment follow-up visits approximately every 3 months from the last tumor assessment (CT or MRI scan and bone scans) until radiographically assessed disease progression. Refer to Section 4.5.5 of the protocol and PCWG3 guidelines. Following initiation of a new anti-cancer therapy for prostate cancer, information on disease progression from patient's medical records may be used to complete disease follow-up via telephone calls and/or clinic visits.

[d] After treatment discontinuation and radiographically assessed disease progression, unless the patient requests to be withdrawn from survival follow-up, the required information will be collected via telephone calls and/or clinic visits, or patients' medical records, approximately every 3 months until death, loss to follow-up, or study termination by the Sponsor.

[e] Day 15 clinical visit and assessments up to Cycle 3 only. During subsequent cycles, site personnel may contact the patient by telephone to assess the occurrence of adverse events as described in footnote "k". The rationale for the telephone call is to allow proactive medical management of adverse events and to minimize delayed reporting by patient, owing to the monthly clinic visit schedule.

[f] Informed consent, including optional consent, must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment.

[g] Medical history includes clinically significant diseases within the previous 5 years, surgeries, complete cancer history (including prior cancer therapies and procedures), complete cardiovascular history, reproductive status, smoking history, use of alcohol, and drugs of abuse (see Section 4.5.2 of the protocol).

[h] A tumor tissue block or a minimum of 15 (20 preferred) freshly cut, unstained slides from patients will be collected at screening. If only 12–14 slides are available, the patient may still be eligible for the study, after discussion with and approval by the Medical Monitor. A valid PTEN IHC test result (from the central laboratory) must be available prior to initiation of study treatment on Cycle 1, Day 1. If archival tissue is insufficient, a fresh tumor biopsy meeting the minimum requirement may be used.

[i] Includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening (or 28 days prior to initiation of study treatment on Cycle 1, Day 1, whichever occurs first) until 28 days after the last dose of study treatment.

[j] Opioid consumption for cancer-related pain and anti-diabetic medications for hyperglycemia related to study treatment should be recorded in the eCRF from Cycle 1, Day 1 to initiation of the next line of prostate cancer therapy.

Appendix 2
Schedule of Assessments (cont.)

[k] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the last dose of study treatment. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study treatment. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed by the investigator as stable and no further changes are expected, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered by the investigator to be related to study treatment or trial-related procedures until a final outcome can be reported.

[l] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At study discontinuation visit, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[m] Perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[n] Vital signs include respiratory rate, pulse (heart) rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Oxygen saturation per pulse oximetry (optional). Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[o] ECG recordings will be obtained as part of the screening assessment as clinically indicated during study treatment, and at the end of treatment visit. ECGs will be reviewed by the investigator to determine patient eligibility at screening. Baseline evaluation of LVEF by MUGA or ECHO should be considered for patients with cardiac risk factors and/or history of coronary artery disease.

[p] If the progression disease will be based on PSA at screening, at least two PSA samples (obtained at least 1 week apart) will be assessed locally at screening for confirmation of eligibility (if no data are available prior to screening).

[q] Regardless of PSA used for confirmation of progression disease at screening, historic values of PSA will be collected as available for calculation of PSA velocity per PCWG3 criteria (at least three PSA values with each values $\geq$ 0.2 ng/dL, including the most recent value during androgen-derivation therapy, and the interval between first and last PSA value to be $\geq$ 8 weeks but $\leq$ 12 months). A central laboratory sample should also be submitted at screening and at all other timepoints. If medically indicated, additional PSA samples may be collected and tested locally. An increase in PSA, without evidence of radiographic progression or unequivocal clinical progression, should not be used as a criterion to start a new systemic anti-cancer therapy during the study.

[r] May be performed $\leq$ 96 hours prior to dosing for each clinic visit during study treatment, screening assessments performed $\leq$ 96 hours prior to dosing on Cycle 1, Day 1 do not have to be repeated on Cycle 1, Day 1. PSA may be performed $\leq$ 96 hours prior to dosing at each Day 1 visit.

[s] Serum testosterone samples will be assessed locally and centrally at screening for determination of eligibility and at study treatment discontinuation to confirm testosterone remains at castration level.

Appendix 2
Schedule of Assessments (cont.)

[t] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, bands [optional] eosinophils, basophils, monocytes, lymphocytes, and other cells).

[u] For all clinic visits during study treatment, the glucose level of the patient must be performed $\leq$ 96 hours prior to dosing, except for Cycle 1, Day 4, which must be done ≤ 24 hours prior to the visit, and must be reviewed prior to further ipatasertib/placebo administration and prior to discharge from the clinic. Blood glucose may be obtained by a glucometer (fingerstick). For fasting blood glucose, patients should fast $\geq$ 8 hours prior to testing.

[v] Patients enrolled will be supplied with a blood glucose meter and a blood glucose log to record blood glucose at least once daily. Self-monitoring should be performed at least once daily by the patient after "a bigger meal" throughout the study treatment period (i.e., until discontinuation of ipatasertib/placebo).

[w] Chemistry panel includes sodium, potassium, chloride, magnesium, bicarbonate, BUN (or urea), creatinine, total protein, albumin, phosphorus, calcium, uric acid, and liver function test panel (total and direct bilirubin, alkaline phosphatase, ALT, AST, and LDH). The occurrence of Grade $\geq$ 3 abnormalities should be monitored at a minimum of every 2 weeks.

[x] Includes dipstick (pH, specific gravity, glucose, protein, ketones, blood).

[y] Tumor assessments should include the chest, abdomen, and pelvis (and other body regions if clinically indicated) at screening and at subsequent tumor assessments, even if there are no detectable lesions at baseline. CT scans are the preferred imaging modality for tumor assessments. MRI scans may be substituted for CT scans and the same imaging method used at screening must be used throughout the study. Soft tissue responses will be assessed locally by the investigator (and/or radiologists) according to RECIST v1.1 for patient management. All films should be submitted for central archive to enable radiologic review if determined by the Sponsor to be necessary for the primary endpoint analysis.

[z] A technetium bone scan will be performed at screening (within 42 days before Cycle 1, Day 1) to evaluate for the presence of bone metastases. In cases of ambiguous findings on bone scan, an X-ray or CT/MRI confirmatory scan should performed at baseline, to ensure that ambiguous findings on bone scan are related to cancer and not healing bone. For adequate assessment of bone lesions, it is expected that the radiologist will adjust the window leveling accordingly (refer to the Imaging Charter). In case of isotope shortage, the Sponsor or Medical Monitor should be contacted if the scan cannot be performed within 1 week from the allowable window. All films should be submitted for central archive, to enable radiologic review if determined necessary for primary endpoint analysis by the Sponsor.

[aa] Tumor assessments should be performed $\pm$ 7 days of the scheduled cycles.

Appendix 2
Schedule of Assessments (cont.)

[bb] The pain severity at its worst (24-hour recall) NRS at screening will be completed on paper. The PRO questionnaires, namely, the EORTC QLQ-C30 scales, urinary scale from QLQ-PR25, pain severity (7-day recall) NRS, and EQ-5D-5L, should be completed by patients using a provisioned electronic device or back-up paper forms as needed. It is imperative that each questionnaire aforementioned is completed at Cycle 1, Day 1 to have a baseline, then on Day 1 of each cycle, at the end-of-treatment visit, and at unscheduled visits as clinically indicated. In addition, these questionnaires will be completed approximately every 28 days from treatment discontinuation (for any reason) to initiation of subsequent line of therapy. Selected scales from the abbreviated EORTC QLQ-C30 (physical functioning [PF], role functioning [RF], global health status [GHS]), pain NRS, and EQ-5D-5L will also be completed after initiation of subsequent line of therapy or 1 year after treatment discontinuation, whichever occurs first, then every 3 months until death. The PRO-CTCAE will be completed by patients at Cycle 1 Days 1, 8, and 15, then from Cycle 2 to Cycle 6 on Days 1 and 15, and then on Day 1 of each subsequent cycle and as clinically indicated while on study treatment. All PRO questionnaires are required to be completed prior to any study assessment(s) that could bias patient's responses.

[cc] Consumption of analgesics (including opioids) will be documented by the patients or their caregivers, using the provisioned devices or back-up paper forms.

[dd] If dosing of study treatment is withheld for any reason, study day count should continue and the omitted dose will not be made up and will be reported on the eCRF as "not administered" for that day.

[ee] Symptomatic skeletal events in this study are defined using one of the following: (1) use of external-beam radiotherapy to relieve skeletal symptoms (including initiation of radium-223 to treat symptoms of bone metastases); (2) occurrence of a new symptomatic pathological bone fracture (vertebral or non-vertebral), (3) clinically apparent occurrence of spinal cord compression, or (4) a tumor-related orthopedic surgical intervention.

[ff] See Appendix 3 for PK sample collection.

[gg] Samples will be collected only at sites with local regulatory authority approval. See Appendix 2 of the protocol for further details.

[hh] The optional RBR blood sample (for DNA extraction) requires an additional informed consent and can be collected at any time during the course of the study. See Appendix 3 for further details.

[ii] Subsequent line of prostate cancer therapy is defined as initiation of cytotoxic chemotherapy, radium-223 (Xofigo®), alternate potent anti-androgen (e.g., enzalutamide), other approved or investigational agent used for the treatment of prostate cancer. Required information includes date of first dose of agent, date of last dose of agent, patient's best response, and date of disease progression.

Appendix 3
Schedule of Pharmacokinetic Samples and Exploratory Biomarker Samples

Study Visit	Timepoint(s)	Sample Type
Cycle 1, Day 1	Prior to ipatasertib/placebo and abiraterone	Blood for NGS control
		Plasma (somatic tumor mutations)
		Plasma (exploratory biomarkers)
		Pharmacogenetic blood sample
		Optional blood for RBR (for DNA extraction) [a]
	1–3 hours post–ipatasertib/placebo and abiraterone administration	PK plasma sample for ipatasertib/placebo
Cycle 1, Day 15 (± 3 days)	Prior to ipatasertib/placebo and abiraterone	PK plasma sample for ipatasertib/placebo and abiraterone
	1–3 hours post–ipatasertib/placebo and abiraterone administration	PK plasma sample for ipatasertib/placebo
Cycle 3, Day 1	Prior to ipatasertib/placebo and abiraterone	Plasma (somatic tumor mutations)
		Plasma (exploratory biomarkers)
		PK plasma sample for ipatasertib/placebo and abiraterone
	1–3 hours post–ipatasertib/placebo and abiraterone administration	PK plasma sample for ipatasertib/placebo
Cycle 6, Day 1	Prior to ipatasertib/placebo and abiraterone administration	PK plasma sample for ipatasertib/placebo
Cycle 12, Day 1	At visit	Plasma (somatic tumor mutations)
		Plasma (exploratory biomarkers)
SDDV	At visit	Plasma (somatic tumor mutations)
		Plasma (exploratory biomarkers)

NGS = next-generation sequencing; PK = pharmacokinetic; RBR = Research Biosample Repository; SDDV = study drug discontinuation visit.

Notes: After Cycle 1, Day 1, all study visits and assessments during the treatment period should be performed within ± 3 days of the scheduled date. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays. PK samples will be collected in both arms.

If ipatasertib/placebo (either alone or with abiraterone) has been on temporary hold for ≥ 2 days prior to PK assessment timepoint, then PK sampling for both ipatasertib/placebo and abiraterone may be rescheduled to another day within that cycle after ipatasertib/placebo has been administered for at least 3 consecutive days prior to the visit day. If only abiraterone is held for any number of days prior to PK sampling time point, continue sampling of ipatasertib/placebo as per schedule; do not collect abiraterone PK sample and resume abiraterone sampling at the next scheduled timepoint. If ipatasertib/placebo is permanently discontinued, PK sampling for ipatasertib/placebo and abiraterone can be discontinued.

[a] Requires additional informed consent and can be collected at any time during the course of the study.