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: Protocol Version 8: 15-Nov-2022

PROTOCOL

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:	8
TEST *COMPOUND*:	Ipatasertib (RO5532961)
STUDY PHASE:	*III*
***REGULATORY AGENCY IDENTIFIER NUMBERS*:**	*IND Number:* 130663 *EudraCT Number: 2016-004429-17* *EU Trial Number: To be determined* *NCT Number: NCT03072238*
SPONSOR*'S NAME AND LEGAL REGISTERED ADDRESS:*	F. Hoffmann-La Roche Ltd *Grenzacherstrasse 124* *4070 Basel, Switzerland*
APPROVAL:	See electronic signature and date stamp on the final page of this document.

VHP Protocol		Associated Global Protocol	
Version	**Date Final**	**Version**	**Date Final**
8	See electronic date stamp on the final page of this document.	—	—
7 (VHP)	24 December 2020	7	23 December 2020
6 (VHP)	30 April 2019	6	13 February 2019
5 (VHP)	14 August 2018	5	19 October2018
		4	1 June 2018
		3	7 March 2018
		2	9 November 2017
		1	21 December 2016

PROTOCOL AMENDMENT, VERSION 8: RATIONALE

The intent of this amendment is to simplify the protocol assessments after the final overall survival (OS) analysis, which is the last efficacy analysis planned for the study. The primary goals of the amendment have been to reduce the number of study visits and limit assessments in support of efficacy analyses after the final OS analysis.

With the Clinical Trials Regulation (CTR) entering into application on 31 January 2022 and the retirement of the Voluntary Harmonization Procedure (VHP) in European countries, the Sponsor has decided to consolidate the former CO39303 VHP and CO39303 non-VHP protocol versions into one protocol with this protocol amendment. The countries which have been following the VHP protocol are Austria, Belgium, Denmark, Hungary, Ireland, Italy, Norway, Poland, Portugal, Spain, and the United Kingdom. All other countries have been following the non-VHP protocol.
The VHP protocol is different from the non-VHP protocol in its requirement for daily glucose self-monitoring at home. Mandatory self-monitoring of glucose was implemented with Protocol Version 5 VHP dated 14 August 2018 in response to a health authority requirement issued via VHP to implement minimum once daily post-prandial home glucose monitoring for the entire duration of study treatment to monitor the risk of hyperglycemia.

In addition, safety requirements for hyperglycemia Grade 1 are different between the two protocol versions. Home glucose monitoring is already performed daily for patients from VHP countries whereas, for patients from non-VHP countries, home glucose monitoring should only be considered. For hyperglycemia Grade 2 and above, home glucose monitoring is mandatory for all patients. The differences between the two protocol versions are highlighted in Sections 4.5.7 and 5.1.1.2 as well as in Appendix 1. Of note, the differential requirements regarding glucose monitoring were already described in previous VHP and non-VHP protocol versions, and there were no changes introduced related to this aspect as part of this amendment. Therefore, the countries should continue with country-specific requirements for home glucose monitoring without introducing any changes.

Changes to the protocol, along with a rationale for each change, are summarized below:

- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (front matter and Section 5.4.1). Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites.
- The synopsis has been simplified to align with CTR, TransCelerate, and the Clinical electronic Structured Harmonised Protocol (CeSHarP) M11s.
- Updates to indicate that after the final OS analysis, study visits will be performed every 3 months instead of monthly for patients who are still on ipatasertib treatment. Only safety data will be collected at study visits. Tumor assessments will continue to be performed as per local practice and at the investigator's discretion, but these

data will not be collected. Patients who have already discontinued from study treatment and patients who are in the placebo arm and are receiving abiraterone only will no longer be followed after the final OS analysis, and no data will be collected from these patients (Sections 3.1, 4.5.6, and Appendix 1).

- Updates to indicate that, after the final OS analysis, the following assessments are no longer required were made (Sections 3.1, 4.5.6, 4.5.7, 4.5.10, 4.5.11, Appendix 1, and Appendix 2):
  - All patient-reported outcome (PRO) assessments
  - Consumption of analgesics information (including opioids)
  - Eastern Cooperative Oncology Group (ECOG) Performance Status
  - Symptomatic skeletal event
  - Optional blood for RBR (for DNA extraction)
  - Plasma samples for somatic tumor mutations and exploratory biomarkers analysis
  - Subsequent line of prostate cancer therapy and outcome
  - Disease Follow up and Post-Treatment Follow up visits for patients who have discontinued from study treatment
  - Study visits for patients who are in the placebo arm and are still receiving abiraterone after the final OS analysis
  - Serum testosterone and PSA samples for the central laboratory should no longer be collected since no additional analysis will be performed after this analysis
- A section describing duration of participation has been added to align with CTR requirements (Section 3.2.1)
- The responsibilities of the investigator and the role of the Medical Monitor in determining patient eligibility and during study conduct have been clarified (Sections 4.1.1, 4.3.2.1, 4.4.2, 4.5.7, Appendix 1).
- Clarified that after the final OS analysis, investigators and patients will be unblinded about the treatment that the patient has been receiving in the study because efficacy analysis will be completed and blinding will no longer be required (Section 4.2)
- Clarified that after the patients' unblinding, the patients who are on placebo and abiraterone will continue receiving abiraterone only. These patients will no longer be required to attend study visits. The only patients that will continue to be followed via regular 3-mothly study visits are those that are receiving ipatasertib (Section 4.3.1.1)
- Update to indicate that after the patients' unblinding, home glucose monitoring will be performed in countries with mandatory self-monitoring of glucose only for patients who are receiving ipatasertib (Section 4.5.7, Appendix 1)

- Clarified that the post-trial access to ipatasertib may be provided through the extension study or post-trial access program for patients who are still receiving ipatasertib after the final OS analysis (Section 4.3.5).
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 4.5.12).
- Update to reflect guidelines provided to VHP and non-VHP countries regarding home-glucose monitoring in case of hyperglycemia (Section 5.1.1.2).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Section 8.4).
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Section 9.6).
- A comprehensive list of investigational medicinal products and auxiliary medicinal products (non-investigational medicinal product) has been added to align with CTR requirements (Section 4.3 and Appendix 14).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in *italics*. This amendment represents cumulative changes to the original protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

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:	8
TEST COMPOUND:	*Ipatasertib (RO5532961)*
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

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**
REGULATORY AGENCY IDENTIFIER NUMBERS:	*IND Number: 130663* *EudraCT Number: 2016-004429-17* *EU Trial Number: To be determined* *NCT Number: NCT03072238*

Study Rationale

The purpose of this study is to assess 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).

Objectives and Endpoints

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 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

Objectives	Corresponding Endpoint(s)
Secondary Efficacy Objectives (cont.) [a]	
• To evaluate the efficacy in patients with *PTEN*-loss tumors by NGS	• Investigator-assessed rPFS per PCWG3 criteria
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 and 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

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.

OVERALL* Design *and Study population

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.

Several key aspects of the study design and study population are summarized below.

Phase:	*Phase III*	***Population Type:***	*Adult Patients*
Control Method:	*Placebo-controlled*	***Population Diagnosis or Condition:***	*Asymptomatic or mildly symptomatic patients previously untreated for mCRPC*
Interventional Model:	*Double-blind*	***Population Age:***	*≥18 years*
Test Compound(s):	*Ipatasertib (RO5532961); Abiraterone acetate*	***Site Distribution:***	*Multi-site and Multi-region*
Active Comparator:	*Not Applicable*	***Study Intervention Assignment Method:***	*Randomization*
Number of Arms:	*2*	***Number of Participants to Be Enrolled:***	*1100*

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. *The dose of ipatasertib/placebo can be reduced up to two times for management of drug-related toxicities. There will be no dose reductions for abiraterone for conditions other than hepatotoxicity.*

Recommended dose modifications for hepatotoxicity are outlined in Section 5.1.1.6.

Duration of Participation

The total duration of study participation for each individual, from randomization of the first patient to the end of the study, is expected to be approximately 7 years

Committees

List any committees that will be reviewing data during the study.

Independent Committees: *Independent Data Monitoring Committee*

Other Committees: *Not applicable*

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADT	androgen deprivation therapy
anti-HBc	hepatitis B core antibody
AQA	Analgesic Quantification Algorithm
AR	androgen receptor
BID	twice daily
CN	copy number
CRPC	castration-resistant prostate cancer
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
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
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FISH	fluorescence in situ hybridization
FMI	Foundation Medicine, Inc.
GHS	global health status
GnRH	gonadotropin-releasing hormone
HBV	hepatitis B virus
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug (Application)

Abbreviation	Definition
IRB	Institutional Review Board
IRF	independent review facility
ISH	in situ hybridization
ITT	intent to treat
IV	intravenous
IxRS	interactive voice-or Web-based response technology
LOH1	loss of heterozygosity with copy number = 1
LPLV	last patient, last visit
LVEF	left ventricle ejection fraction
mCRPC	metastatic castrate-resistant prostate cancer
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NRS	Numeric Rating Scale
OS	overall survival
PCWG3	Prostate Cancer Working Group 3
PF	physical function
PFS	progression-free survival
PFS2	secondary progression-free survival
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetic
PopPK	population pharmacokinetics
PRO	patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
PSA	prostate-specific antigen
PTEN	phosphatase and tensin homolog
QD	once daily
QLQ-C30	Quality of Life Questionnaire Core 30
QLQ-PR25	Quality of Life Questionnaire Prostate Cancer Module
QoL	quality of life
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RF	role functioning
rPFS	radiographic progression-free survival

Abbreviation	Definition
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SNV	single nucleotide variant
SSE	symptomatic skeletal event
ULN	upper limit of normal
VAS	visual analog scale
VHP	*Voluntary Harmonization Procedure*
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON METASTATIC CASTRATE-RESISTANT PROSTATE CANCER

Prostate cancer is the most commonly diagnosed cancer in men and the second leading cause of death in men in the Western world (Ferlay et al. 2015). Although most men are diagnosed with localized disease, progression to metastatic disease to the bones and visceral organs leads to significant morbidity and mortality (Logothetis et al. 2012; Basch et al. 2014). In the United States, prostate cancer is the most common non-skin cancer diagnosed, with over 180,890 new cases and 26,120 deaths (American Cancer Society 2016). Likewise, in Europe, prostate cancer leads male cancer diagnoses with approximately 417,000 new cases and 92,000 deaths (Ferlay et al. 2013).

Treatment of localized prostate cancer often incorporates multimodality therapy and can be associated with significant functional sequelae. Multimodality treatment includes surgery and/or radiation with or without androgen deprivation therapy (ADT). For men with metastatic disease, primary treatment for prostate cancer is ADT; however, most patients will progress despite reduction in testosterone levels to castrate levels ($<$50 ng/dL) either through surgical or medical castration. Despite the current availability of life-extending therapies for metastatic castration-resistant prostate cancer (mCRPC), the majority of men will die of their disease as the median life expectancy in this population is less than 3 years (Ryan et al. 2013; Beer et al. 2014).

The phosphoinositide 3-kinase (PI3K)-AKT pathway is one of the most frequently activated pathways in prostate cancer, with genomic alterations occurring in approximately 50% of cases with genetic loss of phosphatase and tensin homolog *(PTEN)* as the most common cause (Robinson et al. 2015). Deregulation of this pathway results in activation of downstream targets (e.g., PRAS40, mammalian target of rapamycin [mTOR], GSK3b, FOXO, etc.) involved in survival, proliferation, cell-cycle progression, growth, migration, and angiogenesis (Yuan and Cantley 2008). Prostate-specific deletion of *PTEN* in mouse models mimics features of human prostate cancer, and AKT1 deletion in a conditional *PTEN* knockout model significantly reduces prostate cancers (Chen et al. 2006; Guertin et al. 2009; Nardella et al. 2009). Additionally, *PTEN* deletion promotes androgen independence in cell lines and mouse models of prostate cancer (Gao et al. 2006; Jiao et al. 2007). Activation of the PI3K-AKT pathway is physiologically relevant as it compensates for androgen receptor (AR) downregulation and provides a means for receptor blockade escape; in a similarly reciprocal manner, blockade of the PI3K-AKT pathway leads to increased stability and activity of the androgen receptor, demonstrating the cooperative action of both pathways to enable prostate cancer progression (Carver et al. 2011; Mulholland et al. 2011).

Clinical studies have consistently demonstrated that low PTEN expression and PTEN loss (further described as PTEN loss) is associated with worse prognosis

(Yoshimoto et al. 2007; Reid et al. 2010; Antonarakis et al. 2012; Chaux et al. 2012; Zafarana et al. 2012; Cuzick et al. 2013; Barnett et al. 2014; Ferraldeschi et al. 2015; Kim et al. 2015), regardless of whether patients are newly diagnosed, receiving treatment for localized disease, or have late-line advanced metastatic castration–resistant disease. Collectively, these results suggest that activation of the PI3K-AKT pathway is an important driver for prostate cancer and that the pathway is a relevant target for treatment.

1.2 BACKGROUND ON IPATASERTIB

Ipatasertib is a potent, highly selective, small-molecule inhibitor of all three isoforms of the serine/threonine kinase AKT and showed potent activity in nonclinical models, including prostate cancer, and in models both in vitro and in vivo with PTEN loss. In nonclinical prostate cancer models unselected for PTEN loss, the combination of ipatasertib with hormonal therapy (abiraterone acetate [hereafter referred to as abiraterone] or enzalutamide) resulted in more substantial tumor growth inhibition versus either agent alone. In the Phase Ib/II study GO27983 in the post-docetaxel setting, ipatasertib (400-mg dose) when added to abiraterone and prednisone/prednisolone showed improved radiographic progression-free survival (rPFS) benefit compared with abiraterone and prednisone/prednisolone in the all-comer population and, in particular, in patients with PTEN-loss tumors (see Section 1.3).

Refer to the Ipatasertib Investigator's Brochure for details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

The activity of anti-hormonal therapies in the metastatic castration-resistant setting has resulted in improved survival for patients with prostate cancer. Abiraterone acetate (Zytiga®), a pro-drug for abiraterone, is an androgen biosynthesis inhibitor that blocks the enzyme CYP17, which is expressed in testicular, adrenal, and prostatic tumor tissues. The efficacy and safety of abiraterone were initially demonstrated in patients with mCRPC who had received prior docetaxel and were assessed in a Phase III, randomized, placebo-controlled, multicenter, clinical trial (de Bono et al. 2011). A total of 1195 patients were randomized 2:1 to receive either abiraterone orally at a dose of 1000 mg once daily (QD) in combination with prednisone/prednisolone orally at a dose of 5 mg twice daily (BID; n = 797) or placebo QD plus prednisone/prednisolone at the same dose of 5 mg BID (n = 398). This Phase III study demonstrated that abiraterone is well tolerated and prolongs overall survival (OS) relative to placebo in patients with mCRPC previously treated with taxanes. These results indicate that AR signaling continues to play a critical role in the setting of castration-resistant disease. Additional clinical benefit for abiraterone was demonstrated in the pre-docetaxel setting (Ryan et al. 2013). Although treatment with abiraterone can significantly delay progression of disease and improve OS, there is nearly universal development of

therapeutic resistance and disease progression. Refer to the Zytiga® prescribing information (Zytiga PI) for additional details.

Recent nonclinical data suggest that reciprocal crosstalk between the AR and PI3K/AKT pathways occurs in *PTEN*-loss mCRPC. Specifically, activation of the PI3K/AKT pathway is associated with repressed androgen signaling, and inhibition of the PI3K/AKT pathway restores AR signaling in *PTEN*-deficient prostate cells. Proposed mechanisms to account for these observations include PI3K/AKT inhibition resulting in feedback activation of AR via upregulation of human epidermal growth factor receptor kinases and inhibition of AR, relieving feedback inhibition of AKT by the phosphatase PH domain and leucine-rich repeat-protein phosphatase (Carver et al. 2011). This reciprocal cooperativity between PI3K/AKT and AR pathways suggests inhibition of only one pathway would lead to suboptimal clinical efficacy. Therefore, combined inhibition of the AR and PI3K/AKT pathways may result in measurable decline of tumor cell viability and more durable clinical benefit. Given the strong implication of PI3K/AKT activity in prostate cancer cell survival and therapeutic resistance, ipatasertib could be particularly effective given in combination with abiraterone in PTEN-loss mCRPC dependent on the PI3K/AKT pathway for growth and survival.

A Phase Ib/II clinical trial (Study GO27983; NCT01485861) was conducted to evaluate ipatasertib in combination with abiraterone and prednisone/prednisolone in patients with mCRPC (de Bono et al. 2016a, 2018). The Phase Ib portion of the study was open label, using dose escalation to determine the recommended Phase II dose of ipatasertib. In the Phase II portion of the trial, patients with mCRPC previously treated with docetaxel-based therapy were randomized to three arms (in a 1:1:1 ratio) in a double-blind fashion: ipatasertib 400 mg, ipatasertib 200 mg, or placebo. Each arm was in combination with abiraterone (1000 mg) and prednisone/prednisolone (5 mg twice daily [BID]). Patients were stratified according to previous enzalutamide treatment (yes or no), number of chemotherapeutic regimens (1 or >1), and progression (prostate-specific antigen [PSA] only or other). The co-primary efficacy endpoints were rPFS in the intent-to-treat (ITT) population (i.e., with unselected tumors), as well as in patients with PTEN-loss tumors. Secondary endpoints included safety, OS, time to PSA progression, and PSA response rate.

The primary efficacy endpoint, as measured by rPFS at both dose levels over abiraterone and prednisone/prednisolone, indicated a larger improvement at 400 mg versus placebo (stratified hazard ratio [HR] $=0.75$; 90% CI: 0.56 to 1.04; $p=0.17$) relative to ipatasertib 200 mg versus placebo (stratified HR $=0.94$; 90% CI: 0.69 to 1.28; $p=0.75$). A trend for improved OS was observed in the ipatasertib 400-mg arm versus the placebo arm (median, 18.9 vs. 15.6 months, respectively; stratified HR $=0.72$; $p=0.22$), which was overall improved as assessed by HRs compared with the ipatasertib 200-mg vs. placebo arm (median, 21.5 vs. 15.6 months, respectively; stratified HR $=0.96$; $p=0.87$). Additionally, time to PSA progression was prolonged in the ipatasertib 400-mg plus abiraterone and prednisone arm compared with the placebo

plus abiraterone and prednisone arm (median, 5.6 vs. 3.7 months, respectively; stratified HR = 0.70; p = 0.07) and relative to the ipatasertib 200-mg plus abiraterone and prednisone arm (median, 3.8 vs. 3.7 months, respectively; stratified HR = 0.95; p = 0.79). Overall, both ipatasertib treatment arms had numerically favorable results over the placebo, with the ipatasertib 400-mg arm trending for improved OS.

Ipatasertib dose levels of 400 mg and 200 mg QD in combination with abiraterone and prednisone were generally well tolerated; the adverse events were manageable and reversible in patients with mCRPC. Major adverse events attributable to ipatasertib include diarrhea, nausea, asthenia, vomiting, rash, and hyperglycemia. The most common adverse events (≥ 10%) associated with abiraterone are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection, and confusion. Although data for the combination of ipatasertib and abiraterone indicate reasonable patient tolerability, there is some overlap in adverse event types. Adverse events of special interest, in addition to overall safety, will be monitored as outlined in this protocol.

In addition, as a component of the co-primary analysis, rPFS in patients with PTEN loss was assessed. PTEN expression was analyzed by immunohistochemistry (IHC) via the Institute of Cancer Research assay (de Bono et al. 2016b). PTEN status was IHC evaluable in 165 cases, with PTEN loss reported in 71 cases (43%). PTEN loss was associated with a worse rPFS outcome in the placebo arm, but ipatasertib improved rPFS compared with placebo at both the 200-mg and 400-mg doses, with a greater treatment effect at 400 mg and in PTEN-loss cancers (de Bono et al. 2016b). Exploratory PTEN-loss assays included a Ventana IHC assay, and genomic loss of *PTEN* was further explored by fluorescence in situ hybridization (FISH) and next-generation sequencing (NGS). There was high concordance for *PTEN* loss between FISH, NGS, and IHC. This clinical data strongly support PTEN loss as being a predictive response biomarker for mCRPC for agents targeting the PI3K-AKT pathway.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of ipatasertib plus abiraterone plus prednisone or prednisolone (hereafter referred to as “abiraterone”), compared with placebo plus abiraterone 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 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 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	• 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

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 and 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; 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; 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] See Section 6 for the protocol-specified definition of clinical benefit endpoints.

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

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, multicenter, international, randomized, double-blind, placebo-controlled study. This study is designed to evaluate the efficacy, safety, and

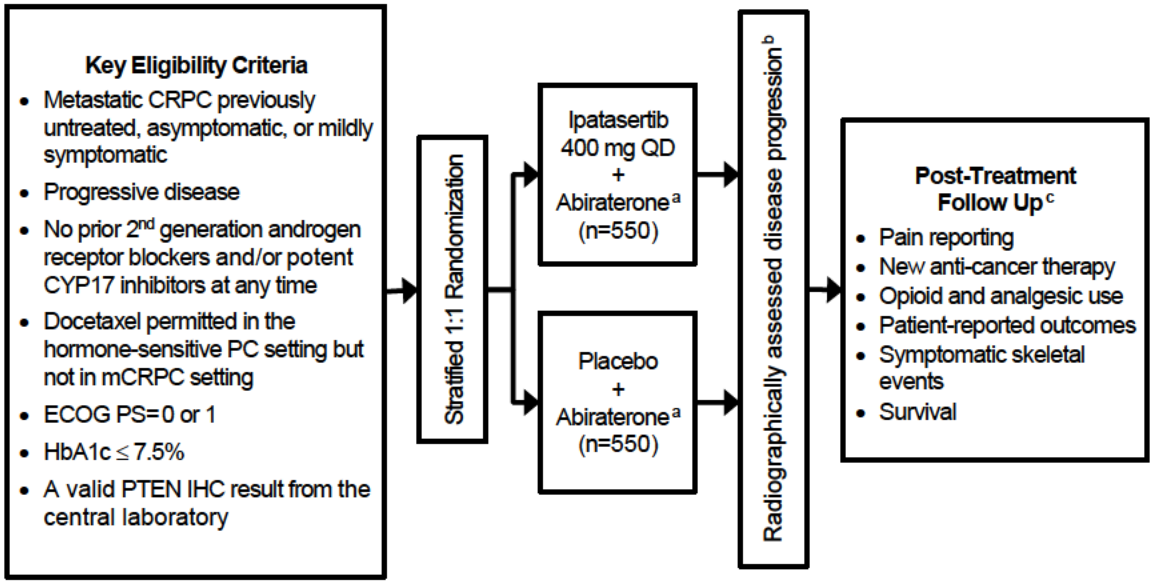
pharmacokinetics of ipatasertib plus abiraterone compared with placebo plus abiraterone. The target patient population is asymptomatic or mildly symptomatic patients previously untreated for mCRPC. Patients must have documented metastatic disease by presence of bone lesions on bone scan and/or soft tissue lesions on computed tomography (CT)/magnetic resonance imaging (MRI). Analysis will be based on the ITT and PTEN-loss populations, the latter defined using the Ventana PTEN 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 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 per schedule in Appendix 1, 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.

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



Stratification factors:

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

BID = twice daily; CRPC = castration-resistant prostate cancer; ECOG = Eastern Collaborative Oncology Group; HbA1c = glycosylated hemoglobin; IHC = immunohistochemistry; mCRPC = metastatic castrate-resistant prostate cancer; PC = prostate cancer; PCWG3 = Prostate Cancer Working Group 3; PS = performance status; PSA = prostate-specific antigen; PTEN = phosphatase and tensin homolog; QD = once daily.

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

[b] In the absence of radiographically assessed disease progression per RECIST v1.1 and/or per PCWG3 criteria, patients may continue single-agent treatment in the event other study treatments are stopped due to toxicity or other reason. If radiographic progression of disease is suspected based ONLY on new lesion(s) by bone scan, study treatment should continue until a subsequent bone scan confirms the presence of the new lesion(s) and progression, per PCWG3 criteria.

[c] If applicable, patients will return to clinic for tumor assessments (disease follow-up visit) until confirmed radiographic progression of disease by RECIST v1.1 and/or PCWG3 criteria. *These assessments will not be performed after the final OS analysis.*

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. If necessary, additional Chinese patients may be recruited into the China extension cohort until a total of approximately 200 Chinese patients are enrolled in the combination of the global (main study) cohort

and the China extension cohort. The Chinese patients enrolled in the China extension cohort will undergo the same schedule of assessments and will receive study treatment as in the global (main study) cohort.

The China subgroup may include all Chinese patients enrolled in the global (main study) cohort and the China extension cohort. The China subgroup analysis will be performed as described in the Statistical Analysis Plan (SAP) and summarized in a separate clinical study report. The Chinese patients enrolled in the global (main study) will be analyzed together with all other patients enrolled in the main study and reported in the main study clinical study report.

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

- Arm 1: abiraterone (1000 mg QD) plus prednisone/prednisolone (5 mg BID) plus ipatasertib (400 mg QD)
- Arm 2: abiraterone (1000 mg QD) plus prednisone/prednisolone (5 mg BID) plus placebo (matched to ipatasertib appearance)

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 (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 invalid 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 1.

Radiographic tumor assessments, including CT or 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 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 timepoint.

In addition, an independent review facility (IRF) may provide an assessment of radiographically assessed disease progression as an exploratory endpoint to support the findings of the investigator assessed outcomes. Details are included in the SAP. The data will be collected from all patients.

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

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 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, as well as any serious adverse events considered by the investigator to be related to study treatment (abiraterone and/or ipatasertib/placebo).

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 3 months to complete tumor assessments until radiographically assessed disease progression (per RECIST v1.1 and/or PCWG3 criteria as applicable) or withdrawal from study.

All patients who discontinue from study treatment because of radiographically assessed disease progression or any other reasons will be asked to report 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 prostate cancer or up to 1 year, whichever occurs first.

After initiation of post-progression therapy or after 1 year, 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.

After the final OS analysis, only patients who are still receiving ipatasertib will be required to attend study visits. Adverse events and drug accountability will be collected at 3 monthly study visits until the patient's discontinuation from study treatment. Tumor assessments will no longer be required at the study visits but will be conducted as per local practice and at the Investigator discretion. Tumor assessment data will no longer be collected after the final OS analysis (please see Appendix 1). For all patients who have discontinued study treatment, only reportable serious adverse events will be collected after the final OS analysis.

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).

3.2 END OF STUDY AND LENGTH 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; see Section 4.6).

In addition, the Sponsor may decide to terminate the study at any time. The Sponsor may evaluate whether to continue providing ipatasertib in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

3.2.1 *Duration of Participation*

The total *duration* of study *participation for each individual,* from randomization of the first patient to the end of the study, is expected to be approximately 7 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Dose Rationale for the Combination

In the aforementioned Phase Ib/II study, ipatasertib was administered at doses of 200 mg and 400 mg QD, continuously in 28-day treatment cycles. Abiraterone was administered at a dose of 1000 mg QD alongside prednisone at a dose of 5 mg BID, continuously in 28-day treatment cycles. The combination was well tolerated. Based upon the spectrum and frequency of adverse events attributable to the ipatasertib and abiraterone/prednisone combination, in addition to the trend of favorable efficacy, the recommended dose was determined to be 400 mg ipatasertib given continuously in 28-day treatment cycles, in combination with the standard dose for abiraterone.

Complete information for ipatasertib is found in the Investigator's Brochure, as the single reference safety document. The single reference safety document for abiraterone is the most recent version of the Summary of Product Characteristics (SmPC).

3.3.2 Rationale for Patient Population

The Phase II study (GO27983) evaluated ipatasertib in combination with abiraterone and prednisone in the post-docetaxel mCRPC setting. This study will give the same combination in an mCRPC patient population that has not received docetaxel treatment in this setting (i.e., patients may have received docetaxel or other therapies in the hormone-sensitive setting). Specifically, this study will investigate the efficacy and safety of ipatasertib as an add-on therapy to abiraterone and prednisone (standard of care) in previously untreated asymptomatic or mildly symptomatic patients with mCRPC. Although there are currently no data with this combination in previously untreated patients with mCRPC, the expectation is that the mechanism of action for ipatasertib is relevant in the pre- and post-docetaxel settings because PI3K-AKT pathway alterations are frequent in prostate cancer and are not limited to specific disease stage(s) as

discussed above. For patients with untreated mCRPC, options for therapy include either hormonal-based therapies or cytotoxic chemotherapy. Current recommendations support the use of cytotoxic therapy for symptomatic disease, and therefore the defined study population will include only those patients with asymptomatic or mildly symptomatic disease at enrollment. As described in Section 1.3, there was a greater rPFS improvement with the addition of ipatasertib to abiraterone in patients with PTEN-loss cancers versus those without evidence of PTEN loss using both protein-based and DNA-based assays. As such, Study CO39303 was designed to test for a significant improvement of rPFS in patients with PTEN-loss tumors as a co-primary endpoint alongside testing rPFS in the all-comer population (see Section 6.4.1).

3.3.3 Rationale for Control Group

Abiraterone is indicated in combination with prednisone for the treatment of patients with mCRPC. Abiraterone has demonstrated activity in both pre- and post-docetaxel mCRPC settings. Thus, the treatment benefit seen with ipatasertib in combination with abiraterone and prednisone in the post-docetaxel setting is likely to be observed in the pre-docetaxel setting (Section 1.3).

During this study, abiraterone administration will be as described in the most recent version of the local prescribing information.

3.3.4 Rationale for Double-Blind Design

This is a double-blind study. The use of abiraterone plus placebo control is to allow for discrimination between patient outcomes (changes in symptoms, signs, and other morbidity) caused by ipatasertib plus abiraterone and outcomes caused by natural progression of disease and patient expectations (via PROs).

3.3.5 Rationale for China Extension Cohort

In order to characterize the efficacy and safety profile of ipatasertib in addition to abiraterone to potentially support a regulatory submission in China, a China extension cohort will be included in the study. This study will initially enroll approximately 1100 patients across all sites in a global enrollment phase. If at least 1 patient is enrolled in China during the global enrollment phase, additional patients in China will be enrolled into a subsequent China extension phase, as needed, to enroll a total of approximately 200 patients in the China subpopulation. Thus, the China subpopulation will include patients enrolled at sites in China during both the global enrollment phase and the China extension phase, if it is necessary.

3.3.6 Rationale for Pharmacokinetic Sampling and Schedule

A sparse sampling strategy will be applied in this study (see Appendix 2 for schedule). The sampling schedule is designed to enable characterization of ipatasertib PK following first dose and at steady-state using population PK (popPK) methodology. Individual

PK parameters estimated from the sparse sampling scheme will be used for exploratory exposure–response analyses.

3.3.7 Rationale for Patient-Reported Outcomes Assessments

In this study, examining and measuring the patient's experience of symptoms and their interference with daily life will be accomplished using patient-completed rating scales. Symptomatic bone metastases are associated with high pain severity, which interferes with patients' ability to function.

Because these concepts cannot be observed, they are therefore best documented through standardized PROs. PRO assessments provide the means to validly and reliably quantify subjective information, which can only by ascertained by the study patients in response to specific questions from validated instruments.

Instruments implemented in the study—namely, a pain severity Numeric Rating Scale (NRS), the EORTC QLQ-C30, and the urinary scale from the Prostate Cancer Module (EORTC QLQ-PR-25), the EQ-5D-5L in its entirety (including the visual analog scale [VAS]) and selected items from the National Cancer Institute (NCI)-developed Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) item bank—have been selected on the basis of their content validity and performance and to minimize patients' completion burden.

A patient-completed log will be used to document the consumption of analgesic medications (including opioid) to treat pain related to prostate cancer. The term "opioid" in the context of this study encompasses both natural and synthetic substances that act on the main opioid receptors.

Changes in symptom severity and interference with daily life will be documented at specified time points throughout the study. Data will be collected via a patient provisioned electronic device, including reminding alerts in order to maximize compliance. Back-up paper forms will be available if needed in order to capture patient data. It is critical to rigorously collect the PRO data as they support secondary endpoints.

PRO data collected after initiation of post-progression therapy until death will be used as a unique opportunity to quantify patients' post-treatment experience in terms of humanistic outcomes.

In addition, the EQ-5D-5L will be completed to inform pharmacoeconomic models.

3.3.8 Tissue and Blood-Based Biomarker Assessments

A key objective of the study biomarker analysis is to investigate candidate biomarkers assessed in tumor tissue and blood, obtained prior to treatment, for their potential

predictive value in identifying patients who may benefit from treatment with abiraterone and prednisone in combination with ipatasertib.

3.3.8.1 PTEN Expression Analysis by IHC

Analysis of the co-primary endpoint of rPFS in patients with tumor PTEN loss in Study GO27983 demonstrated that these patients derived greater rPFS benefit relative to those without PTEN loss using multiple protein- and DNA-based methods.
The Ventana PTEN IHC assay is a validated assay that will be performed at a central laboratory and will be used to prospectively describe the PTEN status of baseline tumor sample, as described in the laboratory manual.

3.3.8.2 RNA and DNA Sequencing Analysis

NGS techniques such as targeted exome sequencing and whole genome sequencing (WGS) may offer a unique opportunity to identify biomarkers of response and/or de novo mechanisms of resistance to the study treatments. In addition to the mutational activation of proteins detected by IHC techniques, NGS methodologies can detect changes in RNA and DNA that can also activate the PI3K and AR pathways. Therefore, the NGS analysis of DNA and RNA from the patient specimens (e.g., tumor tissue and/or plasma-derived nucleic acids) allows further in-depth molecular characterization of the patient samples to help develop an integrative genomic landscape of patients with castrate-resistant prostate cancer (CRPC).

3.3.8.3 Plasma Sample for Somatic Tumor Mutation Analysis

There is increasing evidence that circulating-tumor DNA obtained from blood specimens of cancer patients is representative of the DNA and mutational status of tumor cells (Diehl et al. 2008; Maheswaran et al. 2008). Assays are available that can detect the major AR mutations and copy number (CN; and other cancer-related genes) in plasma, and results from these analyses may be correlated with the mutation result in tumor specimens (Romanel et al. 2015). The use of circulating tumor DNA to monitor response to treatment is an area of great interest. It could allow for an early, non-invasive, and quantifiable method for use in the clinical setting to identify candidates for specific therapies and monitoring of disease mutation status over time (Higgins et al. 2012). In addition, sensitive methods for the purification and quantitation of RNA expression levels and specific RNA variants (e.g., AR-V7) have enabled the analysis of RNA extracted from cancer cell vesicles released in blood (Del Re et al. 2016) and enables the opportunity to explore RNA-based methodologies to identify possible predictive or prognostic biomarkers in CRPC.

3.3.8.4 Blood Sample for the Detection of Plasma Protein Biomarkers

Emerging evidence indicates that increases in levels of systemic cytokines and chemokines, such as receptor tyrosine kinase growth factors, can attenuate responses to drugs, particularly, targeted agents (Wilson et al. 2012). Assays that assess the expression of soluble, systemic cytokines and chemokines from the plasma of patients may be performed using ELISA-based mass spectrometry or appropriate methodologies.

3.3.8.5 Blood Sample for Next-Generation Sequencing

NGS technologies generate a large quantity of sequencing data. Tumor DNA can contain both reported and unreported chromosomal alterations because of the tumorigenesis process. To help control for sequencing calls in previously unreported genomic alterations, a blood sample for NGS control will be taken during predose to determine whether an observed alteration identified in the tumor tissue is somatic throughout the evaluation of the DNA isolated in peripheral blood.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 1100 patients with mCRPC are expected to be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

4.1.1.1 General Inclusion Criteria

- Signed Informed Consent Form(s)
- Ages ≥ 18 years
- Eastern Collaborative Oncology Group (ECOG) performance status of 0 or 1 at screening (see Appendix 3)
- 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

4.1.1.2 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 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 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 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 NRS 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 (see Appendix 4):

    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.

4.1.2 Exclusion Criteria

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

4.1.2.1 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 IV 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

4.1.2.2 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:

    Evaluable or measurable disease according to the inclusion criteria outside the CNS is present.

    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

4.1.2.3 Abiraterone-Specific Exclusion Criteria

- Uncontrolled hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥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

4.1.2.4 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 ≥4 weeks prior to initiation of study treatment may be eligible for enrollment. Patients must meet the laboratory eligibility criteria for fasting blood glucose and hemoglobin A1c as outlined in Section 4.1.1.
- History of inflammatory bowel disease (e.g., Crohn disease and ulcerative colitis), active bowel inflammation (e.g., diverticulitis)

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

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 prostate cancer setting (yes vs. no), progression disease factor (PSA 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 arm assignment *until the final OS analysis, at which time unblinding will be done by the Sponsor, and patients and investigators will be informed about the treatment the patient has been receiving*.

If unblinding is necessary *before the final OS analysis* for patient management related to adverse events during study treatment (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment arm assignment), the investigator will be able to break the treatment arm code by contacting the IxRS; approval from the Sponsor is not required in such circumstances. Treatment arm codes should not be broken except in emergency situations. If the investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. In the event of unblinding prior to study completion, the investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding on account of a serious adverse event).

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment arm code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug.

4.3 STUDY TREATMENT

The investigational medicinal products (IMPs) for this study, ipatasertib, placebo, and abiraterone acetate, will be given to patients orally daily. Prednisone/prednisolone is a non-investigational medicinal product (non-IMP) in the study. *Appendix 14 identifies all investigational medicinal products, auxiliary medicinal products, and non-investigational medicinal products for this study.*

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Ipatasertib and Placebo

Ipatasertib drug product will be supplied by the Sponsor as 100-mg and 200-mg tablets packaged in bottles. For information on the formulation and handling of ipatasertib, see the Ipatasertib Investigator's Brochure.

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. For information on the formulation and handling of placebo, see the Ipatasertib Investigator's Brochure. *After the final OS analysis and the patients' unblinding, the patients who are on placebo will no longer be provided with placebo.*

A sufficient amount of ipatasertib/placebo should be provided to the patient to last until the next visit or, at the investigator's discretion, to last for up to one treatment cycle. Patients will be instructed to bring their study drug and medication diary with them to each study visit.

4.3.1.2 Abiraterone Acetate

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

Note: Abiraterone must be taken on an empty stomach. Abiraterone should be taken at least two hours after eating, and no food should be eaten for at least one hour after taking the tablets. These should be swallowed whole with water.

Note: Women who are or may be pregnant should not handle abiraterone without protection (e.g., gloves).

4.3.1.3 Prednisone/Prednisolone

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

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Ipatasertib, Placebo, and Abiraterone Acetate

Treatment should be initiated no later than 7 days after randomization. Ipatasertib/placebo tablets are given once daily beginning on Cycle 1, Day 1 until the patient experiences disease progression, intolerable toxicity, elective withdrawal from 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. Ipatasertib/placebo may be dosed with or without food. If a dose is missed or omitted (not taken within 8 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose the following day. Missed, omitted, or vomited doses will not be made up.

For all clinic visits, the glucose level of the patient must be reviewed prior to further ipatasertib/placebo administration and prior to discharge from the clinic.

On Days 1 and 15 of Cycle 1 and on all other clinic visit days that require a predose blood draw for PK sampling (see Appendix 2) and/or laboratory assessments, patients will be instructed to take their morning oral dose of study drug in the clinic after completion of the pretreatment assessments outlined in Appendix 1. For all other days of Cycle 1 and other cycles, the daily dose of study drug should be taken approximately the same time each day at home.

Patients may temporarily suspend study treatment for up to 28 consecutive days if they experience a toxicity that is considered related to study treatment and requires a dose hold. Patients who miss >28 consecutive days of scheduled treatment with ipatasertib/placebo or >28 consecutive days of abiraterone because of study treatment–related adverse events will discontinue the respective study treatment, except for patients with a favorable benefit–risk assessment who may be allowed to re-initiate treatment *at the investigator's discretion following consultation with the* Medical Monitor. Treatment interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed *at the investigator's discretion following consultation* with *the* Medical Monitor. 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 remaining single-agent treatment (i.e., abiraterone if ipatasertib/placebo is discontinued or ipatasertib/placebo if abiraterone is discontinued) until radiographically assessed disease progression. Patients whose treatment with ipatasertib/placebo is transiently held or discontinued for adverse effects should continue abiraterone, and vice versa. The prednisone/prednisolone dose may be reduced or discontinued for safety in either treatment arm. Equivalent doses of dexamethasone (e.g., 0.5 mg BID) may be substituted for prednisone/prednisolone.

An increase in PSA, without evidence of radiographically assessed disease progression, should not be used as a criterion to discontinue study treatment and to start a new systemic anti-neoplastic therapy during the study.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1. Complete information for ipatasertib is found in the Investigator's Brochure as the single reference safety document. The single reference safety document for abiraterone is the most recent version of the SmPC.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

4.3.3 Dosage Modifications

Every effort should be made to administer study treatment on the planned dose and schedule. However, in the event of significant treatment-related toxicity, administration of study drugs (ipatasertib/placebo or abiraterone or prednisone/prednisolone) may need to be adjusted as described below and in further detail in Section 5.1. Depending on the nature of the toxicity observed, dosing adjustment(s) may be required for just one or both study drugs in the combination. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify investigators at the first occurrence of any adverse sign or symptom.

Dose modifications may occur in three ways:

- Dosing interruption
- Dosing reduction(s)
- Permanent discontinuation

Patients discontinuing ipatasertib/placebo treatment because of treatment-related toxicity may continue on the active treatment phase of the study receiving abiraterone monotherapy as per the investigator's discretion. Patients discontinuing abiraterone treatment because of treatment-related toxicity may continue in the active treatment phase of the study receiving ipatasertib/placebo monotherapy as per the investigator's discretion.

4.3.3.1 Ipatasertib/Placebo

The ipatasertib/placebo dose reduction instructions provided in Table 2 are intended to serve as recommended guidelines to allow ongoing treatment for patients without signs or symptoms of disease progression while monitoring patient safety. Guidelines for implementing dosage modifications and treatment interruption or discontinuation for patients who experience specific adverse events are provided in Section 5.1.1.

Table 2 Dose Reductions for Ipatasertib/Placebo

Dose Level	Ipatasertib 400 mg/Placebo
Starting Dose Level	400 mg
First Dose Reduction	300 mg
Second Dose Reduction	200 mg
Indication for further dose reduction	Discontinue treatment

No more than two dose reductions are allowed, and dose re-escalation is not permitted.

4.3.3.2 Abiraterone

There will be no dose reductions for abiraterone for conditions other than hepatotoxicity. Recommended dose modifications for hepatotoxicity are outlined in Section 5.1. Refer to the local prescribing information for other guidance.

4.3.3.3 Prednisone/Prednisolone

The dose of prednisone/prednisolone may be decreased to 5 mg daily for adverse effects or taken as 10 mg once daily, at the discretion of the investigator. In the event discontinuation of prednisone/prednisolone is necessary for the management of study treatment–related adverse events, it may be replaced by equivalent doses of dexamethasone. Patients may continue other study treatments despite discontinuation of prednisone/prednisolone. For patients who were taking chronic prednisone $\leq$ 10 mg/day (or equivalent) prior to start of study treatment, the total daily dose of prednisone with study treatment will be 10 mg/day (or less, if decreased by investigator).

Any overdose or incorrect administration of prednisone/prednisolone will not be collected as an adverse event unless accompanied with concurrent symptoms.

4.3.4 Investigational Medicinal Product Accountability

All IMPs required for completion of this study, ipatasertib/placebo and abiraterone, will be provided by the Sponsor where required by local health authority regulations. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist or mobile nurse]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have

been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Accountability Log.

Refer to the Ipatasertib Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.5 Post-Trial Access to Ipatasertib

The Sponsor will offer post-trial access to the study drug ipatasertib free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being.
- There are no appropriate alternative treatments available to the patient.
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient).
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for mCRPC.
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for mCRPC.

- Provision of study drug is not permitted under the laws and regulations of the patient's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

Participants who are still receiving ipatasertib after the final OS analysis may be eligible to receive ipatasertib via a post-trial access program or as part of an extension study.

4.4 CONCOMITANT THERAPY, PROHIBITED THERAPY, AND EXCLUDED DRUGS

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, homeopathic remedies, nutritional supplements) used by a patient from 7 days before the screening visit (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. In addition, anti-diabetic medications for hyperglycemia related to study treatment and opioid consumption for cancer-related pain should be recorded in the eCRF from Cycle 1, Day 1 to initiation of the next line of prostate cancer therapy. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients who are taking GnRH agonists or antagonists should continue their use during the study treatment. For patients who did not undergo orchiectomy, concurrent treatment with GnRH analog is mandatory during the study treatment and must be recorded on the concomitant medication eCRF.

Concurrent use or initiation of bisphosphonates, or other approved bone-targeting agents, and standard-of-care steroid and pain management are allowed and should not result in discontinuation of study treatment. All such medications should be recorded on the Concomitant Medications eCRF until initiation of a subsequent line of therapy and identified for their use as pain relief.

Because the hyperglycemia observed with ipatasertib treatment is consistently associated with endogenous elevations in insulin, insulin-based therapy to manage any hyperglycemia should be used with caution because severe hypoglycemic episodes could potentially occur. Therefore, initial treatment should be considered with metformin (preferred), sulfonylureas, and other hypoglycemic treatments.

Focal palliative radiotherapy (e.g., external-beam radiotherapy to address single sites of disease) for preexisting bone metastasis or other oncology-related issues may be considered; however, patients should be evaluated for evidence of radiographically

assessed progression, clinically apparent SSE, and unequivocal clinical progression prior to initiation of palliative radiation.

Patients who require radiation or surgery as part of medical treatment in the absence of radiographically assessed disease progression must exercise caution, and all study treatment should be temporarily held for at least 7 days before and after the procedure (at least 14 days after radiation is recommended). After the temporary treatment hold is complete, study treatment may be re-initiated when the patient has sufficiently recovered.

Diarrhea is observed with ipatasertib and abiraterone, and patients will be asked to be cognizant of the onset, duration, severity, and frequency of symptoms. Treatments such as loperamide (racecadotril as used in Europe), a loperamide/simethicone combination, or bismuth subsalicylate are options for treatment. Additional details are provided in Section 5.1.1.1.

4.4.2 Prohibited Therapy

Use of the following therapies and food supplements is prohibited during study treatment:

- Cytotoxic chemotherapy, systemic radiopharmaceuticals (e.g., radium-223, strontium-89, excluding imaging agents), alternate anti-hormone therapies (e.g., enzalutamide), or other investigational agents for the treatment of prostate cancer are not allowed.
  - Initiation of any of these treatments requires discontinuation of study treatment.
- Quinidine or other anti-arrhythmic agents with a narrow therapy window.
- Systemic corticosteroid use ($\geq$20 mg of prednisone or prednisolone or an equivalent dose of other anti-inflammatory corticosteroids) for $>$7 days or use of other immunosuppressant agents
- Chronic use of a strong CYP3A4/5 inhibitor or inducer, or sensitive CYP3A and CYP2D6 substrates with a narrow therapeutic window that are deemed not permissible *by the investigator in consultation with the* Medical Monitor after enrollment (refer to the guidance below). Patients are permitted to take moderate inhibitors of CYP3A4 with caution.
- Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.
  - Formulations containing St. John's Wort are prohibited due to CYP3A4 induction.

4.4.2.1 Protocol-Specific Guidance on CYP450–Drug Interactions

- Strong CYP3A4/5 inhibitors, such as but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir,

telithromycin, troleandomycin, voriconazole, and/or grapefruit juice or grapefruit supplements

  - Itraconazole, a strong CYP3A4 inhibitor, increases ipatasertib AUC and C_{max} by approximately 5-fold and 2-fold, respectively (DDI Study GP30057). Given that ipatasertib is a substrate of CYP3A4/5, other strong inhibitors of CYP3A4/5 may also result in an increase in ipatasertib exposure.

- Strong CYP3A4/5 inducers, such a, but not limited to rifampin, carbamazepine, rifapentine, phenytoin, phenobarbital, and/or St. John's wort or hyperforin
  - In vitro data suggest that abiraterone and ipatasertib are partially metabolized by CYP3A4, and the presence of strong CYP3A4 inducers in vivo have shown to reduce their exposure by approximately 50%.
- CYP3A4/5 substrates with a narrow therapeutic index
  - In vitro data suggest that ipatasertib is a time-dependent inhibitor of CYP3A4/5, and in vivo data of ipatasertib have been shown to moderately increase CYP3A4 substrate midazolam exposure by approximately 2.2-fold.
- CYP2D6 substrates with a narrow therapeutic index
  - In vitro data suggest that abiraterone is a strong inhibitor of CYP2D6, and in vivo data of abiraterone have been shown to moderately increase CYP2D6 substrates exposure by approximately 2.8 to 2.9-fold.

Patients who require short-term use of a strong CYP3A4/5 inhibitor or use of sensitive CYP3A substrates with a narrow therapeutic window for medical treatment (i.e., an alternative treatment cannot be used) must exercise caution and ipatasertib/placebo should be temporarily held until at least 7 days after the last dose of these drugs. Patients should be closely monitored. Patients who require short-term use of moderate CYP3A4 inhibitors may continue study treatment with caution.

Use of CYP3A4 inhibitors or inducers concomitantly with abiraterone should be according to the local prescribing information. Avoid co-administration of abiraterone with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate (refer to abiraterone prescribing information).

Refer to the following information for further guidance on CYP450–drug interactions and a list of common substrates, inhibitors, and inducers:

- Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (U.S. Food and Drug Administration [FDA]): http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

4.5 STUDY ASSESSMENTS

Please see Appendix 1 for the schedule of activities to be performed during the study.

All activities must be performed and documented for each patient. Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose when administered in the clinic; dosing will occur only if the clinical assessment is acceptable.

4.5.1 Informed Consent Forms and Screening Log

Voluntary, written, dated, and signed informed consent for participation in the study must be obtained before performing any study-related procedures. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

If eligibility assessments for PTEN tumor testing and/or CT/MRI are not completed within 28 days prior to planned date of Cycle 1, Day 1, bone scans are not completed within 42 days prior to planned date of Cycle 1, Day 1, or if appropriate wash-out for medications/procedures per exclusion criteria have not been fulfilled during screening window prior to the planned date of Cycle 1, Day 1, the patient will need to be rescreened for eligibility. Rescreening refers to repeating the entire screening process except for assessments that are still within the 28-day window. In the case of rescreening, and if required by local regulation, HBV, HCV, HIV testing from the initial screening may be acceptable for screening assessment if performed < 60 days from Cycle 1, Day 1. Patients will be allowed to be rescreened only once. Blood samples may be redrawn because of sample handling problems, breakage, or sample integrity, without the patient being considered a rescreen.

4.5.2 Medical History and Demographic Data

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. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, homeopathic remedies, nutritional supplements) used by the patient from 7 days before screening (or 28 days before initiation of study treatment on Day 1 of Cycle 1, whichever occurs first) will be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination should be performed at screening and at study treatment discontinuation visit and should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory,

gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse (heart) rate systolic and diastolic blood pressures while the patient is in a seated position, and oral, axilla, or tympanic temperature. Oxygen saturation will be assessed by pulse oximetry at rest (optional). Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits (or as clinically indicated), record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 ECOG Performance Status

Performance status will be measured using the ECOG Performance Status scale (see Appendix 3) and recorded on the eCRF.

4.5.6 Tumor and Response Evaluations

On the basis of the recommendations of the PCWG3 guidelines (Scher et al. 2016), tumor assessments will be performed at screening, every 8 weeks (approximately every two cycles) following randomization for 24 weeks (i.e., Cycles 2, 4, and 6), and every 12 weeks thereafter (i.e., Cycles 9 and every three cycles after) regardless of dose delays. Any measurable and non-measurable disease should be documented at screening and re-assessed at each subsequent tumor evaluation. Baseline tumor assessments should be performed by CT/MRI within $\leq$28 days and by bone scan within 42 days of Cycle 1, Day 1. Subsequent tumor assessments during the study should be performed $\pm$7 days of the scheduled tumor assessment date. A tumor assessment must be done at the treatment completion visit as well, unless the most recent assessment was completed $\leq$28 days before the treatment completion visit or radiographically assessed disease progression has already been confirmed.

Patients who discontinue study treatment for reasons other than confirmed radiographically assessed disease progression (e.g., toxicity) should continue to undergo scheduled tumor assessments per the protocol schedule until death, the patients experiences confirmed radiographically assessed disease progression per PCWG3 guidelines, the patient withdraws consent, or the study is closed, whichever occurs first. Tumor assessments should continue regardless of whether the patient starts a new anti-cancer therapy in the absence of confirmed radiographically assessed disease progression unless the patient withdraws consent.

After the final OS analysis, tumor assessments will no longer be required at study visits for patients who are still on ipatasertib treatment, but they should be performed as per local practice and at the investigator's discretion in order to monitor for possible tumor progression and whether the patient is in need for a new cancer therapy. These tumor assessment data will not be collected. Patients who are in the placebo arm and are receiving abiraterone only will no longer be required to attend study visits after the final OS analysis. These patients will be followed up by investigators as per local practice.

Response assessments will be performed by the investigator, on the basis of CT or MRI scans, according to RECIST v1.1 (see Appendix 5) for soft tissue disease and on the basis of bone scan according PCWG3 criteria (see Appendix 6) for the bone lesions.

The same imaging method and serum marker tests used at screening must be used throughout the study. A documented standard-of-care tumor assessment performed within 28 days before Cycle 1, Day 1 may be used for the screening assessment, provided it meets the following requirements:

- CT scans are the preferred imaging modality for soft tissue tumor assessments. Tumor assessments should include a diagnostic quality, contrast-enhanced CT scan of the chest, abdomen, and pelvis at baseline. CT scans of other body region(s) should be included if clinically indicated. To be suitable for RECIST v1.1 assessments, CT scans should have a maximum thickness of 5 mm and no gaps. Subsequent tumor assessments should include CT scans of the chest, abdomen, and pelvis (and other known body region[s] if applicable). In addition to the scheduled on-protocol CT scans, CT scans may be performed at the investigator's discretion at any time if progressive disease is suspected.
- In patients for whom a CT scan is contraindicated because of an allergy to CT IV contrast, a CT of the chest without contrast and MRI of the abdomen and pelvis with contrast are recommended.
- MRI scans may be performed in lieu of CT scans.
- In case MRI measurements are performed, the following conditions should be met:
  - At screening, tumor assessments should include a diagnostic quality, contrast-enhanced MRI scan of the chest, abdomen, and pelvis.
  - MRI scans of other body region(s) should be included if clinically indicated.
  - To be suitable for RECIST v1.1 assessments, MRI scans should ideally have a maximum thickness of 5 mm and minimal gaps. Subsequent tumor assessments should include MRI scans of the chest, abdomen, and pelvis (and other known body region[s] if applicable).
  - In addition to the scheduled on-protocol MRI scans, MRI scans may be repeated at the investigator's discretion at any time if progressive disease is suspected.

- Bone lesions should be assessed by bone scans and evaluated by PCWG3 criteria. During study treatment, the bone scan may be performed with ±1 week for flexibility in the event of isotope shortage; the Medical Monitor should be contacted if the scan cannot be performed within allowed time window. For adequate assessment of bone lesions, it is expected that the radiologist will adjust window leveling accordingly. If progressive disease is suspected only on the basis of new lesions detected by bone scan, a confirmatory bone scan MUST be performed at least 6 weeks after the initial scan which showed disease progression. Bone scans done prior to Week 12 of study treatment may show a false positive due to "flare" phenomenon and should not be considered a confirmatory scan for disease progression (see Appendix 7 for guidance).
- PSA samples collected will be tested at a central laboratory obtained on Day 1 of each cycle starting with Cycle 1. If medically indicated, additional PSA samples maybe collected and tested locally. Patients with rising PSA levels only (i.e., in the absence of radiographic or clinical disease progression) should remain on study treatment per PCWG3 criteria and recommendations.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Laboratory samples should be drawn according to the schedule of activities (see Appendix 1 and Appendix 2). Screening local laboratory assessments obtained ≤96 hours before Cycle 1, Day 1 do not have to be repeated for Cycle 1, Day 1.

- Hematology: complete blood count, including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils [bands, segmented–optional], eosinophils, basophils, lymphocytes, monocytes, and other cells), and platelet count
- Coagulation (aPTT, PT, and INR)
- Fasting blood glucose (may be obtained by a glucometer [fingerstick])
- Chemistry panel: BUN or urea, creatinine, sodium, potassium, chloride, magnesium, phosphorus, bicarbonate, uric acid, calcium, total protein, albumin, total and direct bilirubin, alkaline phosphatase, AST, ALT, and LDH
- For investigational sites in countries where bicarbonate may not be collected as part of the standard chemistry panel, bicarbonate will not be measured.
- Fasting lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, amylase, and lipase) performed following ≥8-hour fast
- Glycosylated hemoglobin (HbA_{1c})
- Urinalysis: specific gravity, pH, glucose, protein, ketones, and blood
- PSA (local laboratory assessment at screening, a central laboratory sample should also be submitted at screening *and at every cycle visit). After the final OS analysis, PSA central laboratory samples should no longer be collected.*
- Serum testosterone (local and central laboratory sample should also be assessed at screening and study treatment discontinuation visit). *After the final OS analysis, serum testosterone central laboratory samples should no longer be collected.*

- *In countries where home self-monitoring of glucose is mandatory*[1]*, self*-monitoring of glucose levels will be performed at least once daily by all patients after a "bigger meal" throughout the study treatment period (i.e., until discontinuation of ipatasertib/placebo). *After the final OS analysis and patients' unblinding, home glucose monitoring will be performed only for patents who are receiving ipatasertib.*

Instruction manuals and supply kits will be provided for central laboratory assessments. The following assessments will be performed at Genentech, at a central laboratory, or at a specialty laboratory:

- Blood samples for PK analyses (see Appendix 2): plasma samples to measure ipatasertib and abiraterone
- Blood sample for DNA extraction to enable analysis via WGS and NGS
- Pharmacogenomic sample (if approved by local regulatory authorities)
- PSA samples collected at screening and subsequently on Day 1 of every cycle to be tested at a central laboratory
- In the event that multiple tissue blocks are available for a given patient (i.e., primary tumor and metastatic site), the most recently collected tumor sample that fulfills the criteria listed below should be submitted.
- Evaluation of the patient's archival tumor sample for PTEN status must occur prior to enrollment.
  - Archival or newly collected (fresh) tumor samples for central laboratory assessment of PTEN loss: All patients must consent to protocol-mandated exploratory assessments at baseline. Tumor tissue should be of good quality on the basis of total and evaluable tumor content. Evaluation of the patient's tumor sample for adequate tumor tissue content and determination of PTEN status by a central laboratory must occur before the initiation of study treatment. A tumor block or a minimum of 15 (20 preferred) unstained slides from a FFPE tissue sample will be required for enrollment eligibility purposes. If only 12–14 slides are available, the Medical Monitor should be consulted.
  - An associated pathology report should also be sent with the sample. If slides are provided, the 15–20 slides should originate from the same tumor block. If only 12–14 slides are available, the Medical Monitor should be consulted. Alternatively, the patient may agree to the collection of a fresh tumor sample if feasible. A detailed description of tissue quality requirements and procedures for collection, handling, and shipping of the samples will be provided in a separate laboratory manual. Tumor tissue from bone metastases is not acceptable.

[1] *Countries with mandatory self-monitoring of glucose are Austria, Belgium, Denmark, Hungary, Ireland, Italy, Norway, Poland, Portugal, Spain, and the United Kingdom.*

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.12), biologic samples will be destroyed when the final Clinical Study Report (CSR) has been completed, with the following exceptions:

- Plasma samples collected for PK analysis will be destroyed no later than 5 years after the final CSR has been completed.
- Blood samples collected for WGS will be stored until they are no longer needed or until they are exhausted.

When a patient withdraws from the study, samples collected before the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

4.5.8 Assay Methods for Biomarker Samples

If multiple tumor samples that were surgically obtained at different times are submitted to satisfy this enrollment criterion, the assay result (i.e., tumor PTEN IHC status) will be on the basis of a valid result from the most recently collected tumor sample that meets the protocol tumor tissue eligibility criteria.

4.5.8.1 Ventana PTEN IHC

The PTEN IHC assay will be performed by a central investigational testing site.

PTEN loss is defined as a minimum of 50% of the specimen's tumor area with no detectable PTEN staining in a patient's FFPE prostate cancer sample. A designation of PTEN IHC status (e.g., PTEN loss, PTEN intact, or invalid/failed) will be assigned to a sample. Patients with an "invalid" or "failed" PTEN IHC result will not be eligible for enrollment.

4.5.8.2 Foundation Medicine Next-Generation Sequencing

On samples with sufficient tumor tissue, NGS will be performed using the Foundation Medicine, Inc. solid tumor platform (FMI NGS).

The FMI NGS platform detects somatic genomic alterations within hundreds of cancer-related genes in tumor tissue samples. These somatic alterations include base substitutions, insertions, deletions, CN alterations, and rearrangements (Frampton et al. 2013; Sun et al. 2014).

If research reports of the FMI NGS assay are available, the investigator may obtain the report on request upon documented radiographic progression (per PCWG3 criteria) with discontinuation from the study treatment phase, or following end of the study, whichever occurs earlier, unless required by law. If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The FMI NGS assay has not been cleared or approved by health authorities. The NGS reports are generated for research purposes and are not provided for the purpose of guiding future treatment decisions. Results may not be available for samples that do not meet testing criteria.

The proposed definition of the *PTEN* loss NGS classifier by the FMI NGS assay is a composite group consisting of genetic abnormalities predicted to lead to a loss of *PTEN* function as described below.

- Homozygous deletion (CN of 0)
- Single nucleotide variants (SNVs) that are predicted to contain a deleterious mutation, described below, with a concomitant loss of the non-mutant *PTEN* allele defined by loss of heterozygosity with $CN = 1$ (LOH1) or loss of heterozygosity with $CN > 1$ (LOHx)
- LOH1 without concomitant SNVs that is predicted to be a deleterious mutation
- Known dominant negative SNV (e.g., C124S, G129E, R130X; Papa et al. 2014); details to be provided in the SAP

It is anticipated that approximately 40% of patients with mCRPC would be classified as part of a *PTEN*-loss sample using this definition.

Additional exploratory analyses may be performed to assess for associations between somatic alterations identified by NGS and clinical study measures and may provide information on response or resistance to therapy.

4.5.8.3 Circulating-Tumor DNA and RNA Analysis

Circulating-tumor DNA and RNA may be extracted from plasma samples collected from patients and used for the detection of oncogenic mutations, copy number changes, DNA methylation, and/or RNA expression using appropriate technologies.
The prevalence of the mutations measured at baseline and after treatment may provide information on response or resistance to therapy.

4.5.8.4 Messenger RNA Expression Profiling

In cases where there is sufficient archival tissue to isolate RNA, gene expression may be performed using gene expression assays conducted using appropriate technologies. Analysis may include the entire transcriptome or a limited panel of genes that are important for prostate cancer biology, immune oncology, and signaling related to the AR and PI3K pathways.

4.5.8.5 Copy Number Analysis

The level of CN alterations in cancer-related genes may be determined using DNA-based technologies, either cytogenetically, using chromosomal in situ hybridization (ISH), NGS platforms, reverse transcription PCR, or equivalent technologies. For cytogenetic assays, detection may be either fluorescence-based (FISH assay) or chromogenic-based (chromogenic ISH). Data on increased CN of PI3K pathways–activating genes may provide information on response or resistance to therapy.

4.5.8.6 Plasma Biomarker Analyses

Assays that assess the expression of soluble, systemic cytokines, and chemokines from the plasma of patients will be completed using appropriate methodologies, such as ELISA-based, mass spectrometry–based, or equivalent technologies.

4.5.8.7 Plasma Pharmacokinetic Assay

Plasma samples will be evaluated for ipatasertib, its metabolite (G-037720) and for abiraterone through use of a validated liquid chromatography tandem mass spectrometry assay. Samples may be used for exploratory evaluation of ipatasertib related metabolites and additional PK and pharmacodynamic assessments or assay development.

4.5.8.8 Pharmacogenetic Polymorphism Assay

For the pharmacogenetic analysis, gene mutations will be assayed using multiplex PCR, allele-specific PCR, direct sequencing, or other acceptable methods.

4.5.9 Electrocardiograms and Multigated Acquisition Scan/Echocardiogram

An ECG will be obtained at screening and as clinically indicated during study treatment and at the end of treatment visit. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

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 clinically significant cardiac disease (including anatomic abnormality, coronary artery disease, congestive heart failure, or previously documented LVEF $<$50%.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.10 PROs

To more fully characterize the clinical profile of ipatasertib, patients will rate their symptoms and their functioning impacts through use of the following instruments: the EORTC QLQ-C30 and selected items from the Quality of Life Questionnaire Prostate Cancer Module (QLQ-PR25), pain severity NRS, selected items from the PRO-CTCAE, and the EQ-5D-5L. In addition, patients will record their analgesic medication consumption in a log from Cycle 1, Day 1 to initiation of the next line of prostate cancer therapy.

Patients will complete these assessments as follows:

- Pain severity at its worst (24-hour recall) NRS will be captured at screening to be used for inclusion.
- A medication analgesic log will be completed, starting on Cycle 1, Day 1 until initiation of subsequent line of therapy or 1-year post-treatment discontinuation, whichever occurs first.
- Selected items from the PRO-CTCAE will be completed by at Cycle 1 on Days 1, 8, and 15; from Cycle 2 to Cycle 6 on Days 1 and 15; and on Day 1 of each subsequent cycle and as clinically indicated while on study treatment.
- The pain severity at its worst (7-day recall) NRS, the EORTC QLQ-C30, the 8-item urinary scale from the QLQ-PR25, and the EQ-5D-5L (including VAS) will be completed on Cycle 1, Day 1 and every cycle thereafter until the end of treatment visit (included) and 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 EORTC QLQ-C30 (physical functioning [PF], role functioning [RF], global health status [GHS]), the pain severity at its worst (7-day recall) NRS, and the EQ-5D-5L in its entirety will be completed by patients every 3 months after initiation of subsequent line of therapy or 1 year after treatment discontinuation, whichever occurs first, until death. Patients will be asked (i.e., not part of the electronic device) to report any recent (7-day) analgesic uses (response: yes or no).

The pain severity at its worst (24-hour recall) NRS completed at screening at the site will be administered on paper and documented on the appropriate eCRF.

It is imperative that each PRO questionnaire and NRS be completed on Cycle 1, Day 1 until initiation of subsequent line of therapy, disregarding treatment discontinuation. All PRO questionnaires and NRS that are completed at the clinic are required to be completed prior to any study assessment(s) that could bias patient responses.

The questionnaires and NRS will be translated in the country language(s) and as feasible in the local language.

Patients will use an electronic device to capture all PRO data. Instructions to use the device and to complete the PRO questionnaires and medication log will be provided by site staff once the patient is randomized and before initiation of study treatment. If needed, back-up paper forms will be available to ensure collection of PRO data from each patient. The data will be transmitted to a centralized database maintained by the vendor and will be available for access by appropriate study personnel at the site.

After the final OS analysis, PROs data and analgesics medication consumption information will no longer be collected (see Appendix 1).

4.5.10.1 EORTC QLQ-C30 and Urinary Scale from QLQ-P25

The EORTC QLQ-C30 (see Appendix 8) consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), GHS/quality of life (QoL), and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week (van Andel et al. 2008). In addition, an 8-item urinary scale from the EORTC prostate module (EORTC QLQ-PR25; see Appendix 9) will be added to capture symptom-specific to prostate cancer (Dąbrowska-Bender et al. 2015).

All items other than those forming the GHS scale are rated on a 4-point categorical scale. A high score (4) for a functional scale represents a high or healthy level of functioning, a high score (7) for the GHS/QoL represents a high QoL, but a high score for a symptom scale or item represents a high level of symptomatology or problems.

To understand patients' symptom experience post-treatment and the course of their health-related QoL, the PF, RF, and GHS scales will be completed as part of the follow-up visits. These scales were selected for their content validity in documenting patients' functioning in daily activities and QoL.

4.5.10.2 Pain Assessments

Cancer-related pain will be assessed using a patient report of pain severity at its worst and rated on a 10-point NRS, with 10 indicating a worst outcome. This assessment is a commonly used assessment across diseases and treatments. Patients will complete the pain severity assessment (24-hour recall) at screening; this recall period was selected to account for the fact that patients will have had no training to appropriately recall their pain experience over a longer time period. Following randomization, patients will complete the pain severity assessment (7-day recall) at each visit. Recognizing that a monthly assessment using a short assessment window (past 24 hours) would provide only limited information of patients' experience with signs of clinical deterioration, the assessment window was broadened to 7 days.

Thresholds to inform a clinical deterioration on the pain severity NRS were documented in patients with breast cancer and bone metastases and will be applied to this study (Mathias et al. 2011; Cleeland et al. 2013; see Appendix 10).

4.5.10.3 Medication Log

A country-specific patient-reported medication log will be used to document analgesic use for cancer-related pain, particularly opioid intake (e.g., name of molecule, form, number of pills/patch) from Cycle 1, Day 1 to initiation of the next line of prostate cancer therapy. The patient medication log should be used when completing the concomitant medications eCRF pages for the consumption of analgesics for cancer-related pain.

4.5.10.4 PRO-CTCAE

The PRO-CTCAE is an item bank reflecting 78 symptomatic adverse events rated according to their severity, interference with daily function, frequency, and/or occurrence. The item bank was designed and validated as a repository of stand-alone items.

Symptoms selected for this study include those symptoms occurring in $\geq 15\%$ of patients for any treatment (ipatasertib and/or abiraterone) and/or those with a Grade ≥ 3 event, with incidence of $> 5\%$ in the treatments of any treatment (ipatasertib and/or abiraterone), and/or those with a Grade ≥ 3 with incidence of $\geq 5\%$ in the treatments of any study arm.

Only adverse events relevant for patient reporting, as being subjective, with or without observable components (e.g., vomiting and nausea, respectively) or primarily observable with subjective components (e.g., rash), were selected (Basch et al. 2014).
Adverse events of which assessments relied on laboratory testing (e.g., anemia) that were presented as being primarily asymptomatic or with non-specific signs and symptoms (e.g., hyperglycemia) were disregarded. Adverse events that did not have an identifiable symptom equivalent in the PRO-CTCAE were also excluded. Lastly, considering patients' completion burden, symptoms with substantial coverage across PRO measures (e.g., pain) were also excluded from the pool. Based on the above criteria, eight symptomatic adverse events were selected from the PRO-CTCAE item bank, namely decreased appetite, nausea, vomiting, constipation, diarrhea, rash, and fatigue, representing a total of 11 items. The free-text item from the PRO-CTCAE item bank was not included.

An additional item providing an overall assessment of symptom tolerability was added to the 11 select PRO-CTAE items (see Appendix 12).

Based on the data available to date regarding the tolerability of ipatasertib in combination with abiraterone, the targeted symptomatic adverse events should have occurred by Cycle 6. Therefore, patients will be asked to complete the 11-item PRO-CTCAE $+1$ tolerability item on Days 1, 8, and 15 of Cycle 1, on Days 1 and 15 of

each cycle until Cycle 6, and then on Day 1 of each cycle and as clinically indicated while on study treatment.

4.5.10.5 EQ-5D-5L

The EQ-5D-5L is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQoL Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a VAS that measures health state. Published weighting systems allow for the creation of a single composite score of the patient's health status. The EQ-5D-5L will be used in this study to inform pharmacoeconomic evaluations (see Appendix 13).

4.5.11 Survival Follow-Up

Survival follow-up information will be collected via telephone calls, patient's medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, or study termination by Sponsor. All patients will be followed for survival information unless the patient requests to be withdrawn from study; this request must be documented in the source file and signed by the investigator. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. *After the final OS analysis, survival follow-up information will no longer be collected.*

4.5.12 Optional Samples for Research Biosample Repository

4.5.12.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biologic samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.12) will not be applicable at that site.

4.5.12.3 Sample Collection

Leftover patient samples (e.g., blood and/or residual tumor tissue samples) collected for this study will be stored in the RBR and used for research purposes, including but not limited to research on biomarkers related to ipatasertib or prostate cancer.

The above samples may be sent to one or more laboratories for DNA extraction to enable analysis of germline mutations, somatic mutations via WGS, NGS, or other genomic analysis methods.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.12.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number. Patient medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses, data derived from RBR specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.12.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.12.6 Withdrawal from the Research Biosample Respository

Patients who give consent to provide RBR specimens have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the trial site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from Study CO39303 does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from Study CO39303.

4.5.12.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include but are not limited to the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

Patients discontinuing study treatment for any reason other than radiographically assessed disease progression should continue to undergo tumor response evaluations until confirmed radiographic evidence of progressive disease regardless of initiation of another anti-cancer therapy. Additionally, because the secondary endpoint of pain progression may occur after radiographic progression, collection of pain endpoints will continue to be collected on a periodic basis, until initiation of another anti-cancer therapy or up to 1 year, whichever occurs first. See Section 5.1 for adverse events and discontinuation details.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include but are not limited to the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include but are not limited to the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Ipatasertib is not approved, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with ipatasertib in completed and ongoing studies.

The anticipated important safety risks for ipatasertib and abiraterone are outlined below. Refer to the Ipatasertib Investigator's Brochure for a complete summary of safety information. Refer to the abiraterone and prednisone/prednisolone local prescribing information for a summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events, as well as expedited reporting of protocol-defined adverse events of special interest regardless of seriousness. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below to investigators. Educational materials will be provided to patients outlining these safety guidelines.

This study will use an iDMC. The iDMC will be responsible for ongoing monitoring of the safety of patients in the study according to the iDMC Charter. During the study, the

iDMC will evaluate safety data on a periodic basis, approximately every 3 months for the first year and approximately every 6 months thereafter, until the time of the primary analysis. The iDMC will make recommendation as to whether or not the trial should continue based on ongoing reviews of safety data. The Sponsor will designate an iDCC to prepare data for iDMC review. Only if action or consultation with health authorities is required will other than designated Sponsor staff be involved. Clinical sites will be restricted from access to study results until the conclusion of the study.

5.1.1 Management of Selected Identified and Potential Risks of Ipatasertib and Abiraterone

Guidelines for managing selected adverse events are provided in this section to improve safety and tolerability; however, patients may be treated per institutional practices as appropriate. If any observed toxicity is attributable to only one drug as assessed by the investigator, the dose of the other drug may not require modification. Reasons for dose modifications (interruptions or reduction) or delays, the supportive measure taken, and the outcome will be recorded in the eCRF.

5.1.1.1 Diarrhea

For diarrhea occurring after Cycle 2 that persists for more than 5 days, despite treatment with an anti-diarrheal agent, a stool culture for infectious workup (i.e., *Clostridium difficile*, enteric bacteria, CMV) will be obtained, and diarrhea should be treated with the appropriate antibiotic.

Table 3 Diarrhea Management Guidelines

Severity of Diarrhea	Management Guideline
Grade 1	Continue study drugs at the current dose level. Manage with loperamide 4 mg initially, and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea free interval. Dietary modifications such as avoiding any lactose-containing foods. Hydration with 8–10 glasses of clear liquid such as broth and low-calorie electrolyte-enhanced drinks per day.
Grade 2	Manage with loperamide as early as possible 4 mg initially, and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea free interval. Dietary modifications such as avoiding any lactose-containing foods. Hydration with 8–10 glasses of clear liquid, such as broth and low-calorie electrolyte-enhanced drinks, per day. For non-infectious diarrhea lasting more than 48 hours despite optimal loperamide treatment, manage with second-line anti-diarrheal agents, including, but not limited to Lomotil®, codeine, or octreotide, or as per institutional guidelines. Interrupt ipatasertib/placebo until diarrhea improves to Grade ≤ 1. Ipatasertib can be resumed at the same dose or one dose lower per investigator evaluation upon improvement to Grade ≤ 1. Reduce ipatasertib/placebo by one additional dose level (see Table 2) for recurrent Grade 2 diarrhea.
Grade 3	Rule out infectious etiology. Treatment per Grade 2 management guidelines and supportive care. Interrupt ipatasertib/placebo until diarrhea improves to Grade ≤ 1. Ipatasertib/placebo should be reduced by one dose level (see Table 2) when treatment is restarted. For recurrent Grade 3 diarrhea, reduce ipatasertib/placebo dose by one additional dose level (see Table 2), or permanently discontinue ipatasertib/placebo per investigator discretion.
Grade 4	Management as per Grade 3 guidelines. Permanently discontinue ipatasertib/placebo.

5.1.1.2 Fasting Hyperglycemia

Fasting is defined as abstaining from food and drink (with the exception of water) for at least 8 hours.

Dose modification guidelines for fasting hyperglycemia attributable to study treatment are outlined below (see Table 4) and are intended to provide guidance for fasting glucose measurements assessed in the clinic. Decisions regarding study treatment should be made on fasting levels drawn in the clinic whenever possible.

Home glucose measurements may be used to trigger contact between patient and the investigative site team and may lead to an unscheduled clinic visit to assess fasting

glucose. Guidance for when to call the investigator/site staff (or designated endocrinologist, if applicable) should be provided to patients for hypoglycemia (e.g., glucose value under 70 mg/dL [3.9 mmol/L]) and hyperglycemia (e.g., glucose value over 300 mg/dL [16.7 mmol/L]). Alternative thresholds may be selected as clinically indicated per investigator discretion or institutional guidance and noted in the source documents. For any patients performing home glucose monitoring, a blood glucose log should be reviewed at each clinic visit (and source data retained); entry of results into the patient's eCRF will be limited to values, which result in intervention.

In the event of ipatasertib/placebo interruption, anti-diabetic medications may need to be held or reduced (per investigator judgement) and glucose should be monitored closely to minimize the risk of hypoglycemia.

Ipatasertib/placebo should be discontinued for recurrent Grade 4 fasting hyperglycemia or a single event of hyperglycemia Grade ≥3 associated with metabolic acidosis Grade ≥3.

Table 4 Fasting Hyperglycemia Management Guidelines

Severity of Fasting Hyperglycemia	Management Guideline
Grade 1: fasting glucose value >ULN to 160 mg/dL (8.9 mmol/L)	Monitor fasting glucose per protocol. *Continue* home glucose monitoring daily *for patients from countries with mandatory self-monitoring of glucose.* [a] *For all other patients, consider home glucose monitoring*.
Grade 2: fasting glucose value >160 to 250 mg/dL (>8.9 to 13.9 mmol/L)	Interruption of ipatasertib/placebo until fasting hyperglycemia resolves to Grade ≤ 1. Continue home glucose monitoring *for patients from countries with mandatory self-monitoring of glucose.* [a] *For all other patients, initiate home glucose monitoring.* Start oral anti-diabetic medications (e.g., metformin). If patient is already on an oral anti-diabetic medication, the dose of ipatasertib/placebo should be reduced by one dose level (refer to Table 2). If the patient previously has not been receiving any oral anti-diabetic medication, ipatasertib/placebo may be resumed at the previous dose level with initiation of oral anti-diabetic medication.

Table 4 Fasting Hyperglycemia Management Guidelines (cont.)

Grade 3: fasting glucose value >250 to 500 mg/dL (>13.9 to 27.8 mmol/L)	Interrupt ipatasertib/placebo until resolution to Grade ≤1. Continue home glucose monitoring *for patients from countries with mandatory self-monitoring of glucose [a]. For all other patients, initiate home glucose monitoring or continue with it if already started.* Treat hyperglycemia as medically appropriate. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). If the patient is already on an oral anti-diabetic mediation, ipatasertib/placebo should be reduced by one dose level when treatment is restarted. If previously, the patient has not been receiving any oral anti-diabetic medication, ipatasertib/placebo may be resumed at the previous dose level with initiation of oral anti-diabetic medication. If Grade ≥3 fasting hyperglycemia recurs, the dose of ipatasertib/placebo should be reduced by one dose level when treatment is restarted.
Grade 4: fasting glucose value >500 mg/dL (>27.8 mmol/L)	Interrupt ipatasertib/placebo until resolution to Grade ≤1. Treat hyperglycemia as medically appropriate. Continue home glucose monitoring *for patients from countries with mandatory self-monitoring of glucose [a]. For all other patients, initiate home glucose monitoring or continue with it if already started.* Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). Assess for volume depletion and appropriate intravenous or oral hydration. Reduced ipatasertib/placebo by one dose level when treatment is restarted. If Grade 4 hyperglycemia recurs, permanently discontinue ipatasertib/placebo.

ULN = upper limit of normal; *VHP = Voluntary Harmonization Procedure.*

Note: For all grades, the patient should receive education on a diabetic diet.

[a] *The countries with mandatory self-monitoring of glucose are Austria, Belgium, Denmark, Hungary, Ireland, Italy, Norway, Poland, Portugal, Spain, and the United Kingdom. Mandatory self-monitoring of glucose was implemented with Protocol Version 5 (VHP) dated 14 August 2018 in response to a health authority requirement issued via VHP to implement minimum once daily post-prandial home glucose monitoring for the entire duration of study treatment to monitor the risk of hyperglycemia.*

5.1.1.3 Nausea and/or Vomiting

Dose reductions for nausea and/or vomiting should occur only if the symptoms persist despite a minimum of two treatments with adequate (combination) anti-emetic treatment(s), including ondansetron (or equivalent anti-emetic; see Table 5).

For persistent nausea and/or vomiting attributable to ipatasertib/placebo, dosage-modification guidelines are outlined in Table 5 .

Table 5 Nausea and Vomiting Management Guidelines

Severity of Nausea and Vomiting	Management Guideline
Grade 1	Provide maximum supportive care as needed.
Grade 2	Provide maximum supportive care as needed. Provide ondansetron (or equivalent anti-emetic medication) as needed.
Grade ≥3	Interrupt ipatasertib/placebo until nausea or vomiting resolves to Grade ≤2. Provide maximum supportive care as needed. Provide ondansetron (or equivalent anti-emetic) as needed. If Grade ≥3 nausea or vomiting recurs, ipatasertib/placebo should be reduced by one dose level (refer to Table 2) when treatment is restarted.

5.1.1.4 Rash

Ipatasertib/placebo should be permanently discontinued for rash associated with Stevens-Johnson syndrome, toxic epidermal necrolysis, or other suspected severe hypersensitivity or allergic reaction. Dosage modification and symptom management guidelines for skin toxicity, including erythema multiforme, attributable to ipatasertib/placebo are shown below (see Table 6).

Table 6 Rash Management Guidelines

Severity of Rash	Management Guideline
Grade 1	Continue study drugs. Consider topical corticosteroids.
Grade 2	Interrupt ipatasertib/placebo treatment until resolution to Grade ≤1 or the toxicity is no longer clinically significant. Treat rash with topical corticosteroids. Consider treatment of rash with oral corticosteroids. Follow above guidance and reduce ipatasertib/placebo by one dose level for recurrent Grade 2 rash.

Table 6 Rash Management Guidelines (cont.)

Severity of Rash	Management Guideline
Grade 3	Interrupt ipatasertib/placebo treatment until resolution to Grade ≤1 or the toxicity is no longer clinically significant. Treat rash with topical and systemic corticosteroids. Consider dermatological consultation. If the skin toxicity resolves to Grade ≤1 or is no longer clinically significant within 28 days, following completion of the steroid taper, ipatasertib/placebo may be resumed at one dose level below the previous dose (refer to Table 2). If recovery of the skin toxicity to Grade ≤1 does not occur or skin toxicity remains clinically significant continuously for 4 weeks, or Grade 3 rash recurs, permanently discontinue ipatasertib/placebo.
Grade 4	Administration of systemic steroids (oral or intravenous) is recommended. Consider dermatological consultation and skin biopsy. Ipatasertib should be permanently discontinued.

5.1.1.5 Pneumonitis

Pneumonitis is not known to be causally related to any of the study drugs; however, it has been observed with other drugs treating pathways similar to ipatasertib. Every effort should be made to determine the etiology of dyspnea and changes in pulmonary function (see Table 7).

Table 7 Pneumonitis Management Guidelines

Severity of Pneumonitis	Management Guideline
Grade 1	Continue study drugs. Perform CT scan and pulmonary function tests. Repeat CT scan every 8 weeks until a return to baseline.
Grade 2	Prescribe corticosteroids if there are clinical symptoms and infectious etiology is ruled out. Interrupt ipatasertib/placebo treatment as long as corticosteroids are being given. Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. If pneumonitis resolves to Grade ≤ 1 after completion of the steroid taper, ipatasertib/placebo may be resumed at either the previous dose or one dose level below the previous dose (see Table 2) per investigator assessment. For recurrent Grade 2 pneumonitis, ipatasertib/placebo must be resumed at one dose level below the previous dose. Discontinue ipatasertib/placebo if recovery to Grade ≤ 1 is not evident within 28 days.

Table 7 Pneumonitis Management Guidelines (cont.)

Severity of Pneumonitis	Management Guideline
Grade 3	If infectious etiology is ruled out, prescribe corticosteroids as clinically indicated. Interrupt ipatasertib/placebo treatment as long as corticosteroids are being given. Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended. If pneumonitis resolves to Grade ≤ 1, following completion of the steroid taper, continue ipatasertib/placebo at one dose level below the previous dose (see Table 2). Discontinue ipatasertib/placebo if recovery to Grade ≤ 1 is not evident within 28 days. For recurrent non-infectious Grade 3 pneumonitis events, ipatasertib/placebo should be permanently discontinued.
Grade 4	If infectious etiology is ruled out, prescribe corticosteroids as clinically indicated. Permanently discontinue ipatasertib/placebo. Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended.

CT = computed tomography; PFT = pulmonary function test.

5.1.1.6 Hepatotoxicity

Permanently discontinue abiraterone and ipatasertib/placebo for any patients who develop a concurrent elevation of ALT and/or AST greater than $3 \times$ ULN and total bilirubin greater than $2 \times$ ULN and/or clinical jaundice in the absence of biliary obstruction or other causes responsible for the concurrent elevation, including patients having abnormal liver function tests that meet Hy's law criteria (see Section 5.3.5.6). Dosage modification and symptom management guidelines for hepatotoxicity, attributable to study treatment are shown below (see Table 8).

Table 8 Hepatotoxicity Management Guidelines

Severity of LFT Elevation	Management Guideline
Grade 1 AST or ALT > baseline $- 3 \times$ ULN or T bilirubin > baseline $- 1.5 \times$ ULN	Continue study drugs.
Grade 2 AST or ALT > 3–5 $\times$ ULN or T bilirubin > 1.5–3.0 $\times$ ULN	Continue study drugs. The frequency of liver function test monitoring should be increased as clinically indicated if the investigator judges that the laboratory abnormalities are potentially related to study medication.

LFT = liver function test; ULN = upper limit of normal.

Table 8 Hepatotoxicity Management Guidelines (cont.)

Severity of LFT Elevation	Management Guideline
Grade 3 AST or ALT > 5–20 × ULN or T bilirubin > 3–10 × ULN	Immediately interrupt abiraterone and ipatasertib/placebo. On return of LFTs to baseline or to AST and ALT ≤ 2.5 × ULN and total bilirubin ≤ 1.5 × ULN levels, restart ipatasertib/placebo at previous dose level (see Table 2) and restart abiraterone at reduced dose of 750 mg QD. Following treatment resumption, monitor serum transaminases and bilirubin at a minimum every 2 weeks for 3 months and monthly thereafter. If another Grade 3 event occurs, interrupt abiraterone and ipatasertib/placebo. On return of LFTs to baseline or AST and ALT ≤ 2.5 × ULN and total bilirubin ≤ 1.5 × ULN levels, restart ipatasertib/placebo, reducing the dose by one level and abiraterone at a reduced dose of 500 mg QD. Further Grade 3 occurrences must result in permanent discontinuation of abiraterone and ipatasertib/placebo.
Grade 4 AST or ALT > 20 × ULN or T bilirubin > 10 × ULN	Permanently discontinue abiraterone and ipatasertib/placebo.

LFT = liver function test; QD = once daily; ULN = upper limit of normal.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9

- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
  - This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE v4.0; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event;

see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.6).
- Suspected transmission of an infectious agent by the study drug, as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting—transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Grade ≥3 diarrhea
- Grade ≥3 hyperglycemia
- Grade ≥3 rash
- Grade ≥2 pneumonitis
- Grade ≥2 colitis/enterocolitis

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact.
All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but before initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28 days after the last dose of study drug or initiation of subsequent lines of anti-cancer therapy, whichever occurs first.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 9 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 9 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 10):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

Table 10 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

For adverse events, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated LDH" as opposed to "abnormal LDH"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

Deaths that are attributed by the investigator solely to progression of mCRPC should be recorded on the Death Attributed to Progressive Disease eCRF. During the study adverse event reporting period (as defined in Section 5.3.1) all other deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). Instructions for reporting deaths that occur after the adverse event reporting period are provided in Section 5.6. An independent monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the

cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study.
When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of mCRPC

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1 and PCWG3 criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Hospitalization is an outcome, and should not be reported as an adverse event.
Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
  - The patient has not experienced an adverse event.
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours.

5.3.5.11 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. No attempt will be made to reconcile the findings from reports of treatment-related symptoms by the clinicians (NCI CTCAE) and from the patients (NCI PRO-CTCAE) given the different ways in which these two data sources are collected.

Although sites are not expected to review the PRO data, it is possible that an investigator could become aware of PRO data that may be indicative of an adverse event. Under these circumstances, the investigator will determine whether the criteria for an adverse event have been met, and, if so, will report the event on the Adverse Event eCRF.

5.3.5.12 Cases of Accidental Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse
Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug
  - In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse
  - In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the

event; see Section 5.4.2). For ipatasertib, placebo, and abiraterone, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with ipatasertib, placebo, and abiraterone, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.

- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, *access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately.*

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur before Study Drug Initiation

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. The Serious *Clinical Trial Adverse Event/Special Situations Form* provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the *Clinical Trial Adverse Event/Special Situations Form* provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur >28 days after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 28 days after the last dose of study drug. The investigator should report the pregnancy on the Clinical Trial Pregnancy Reporting Form in paper format and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number

or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.2 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 28 days [see Section 5.3.1] after the last dose of study drug), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

After the end of the adverse event-reporting period, if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment, the event should be reported through use of the Adverse Event eCRF.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Ipatasertib Investigator's Brochure
- SmPC for abiraterone

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

All analyses discussed in this section will be restricted to the patients enrolled in the global enrollment phase only (i.e., excluding the China extension cohort), unless otherwise noted.

6.1 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.

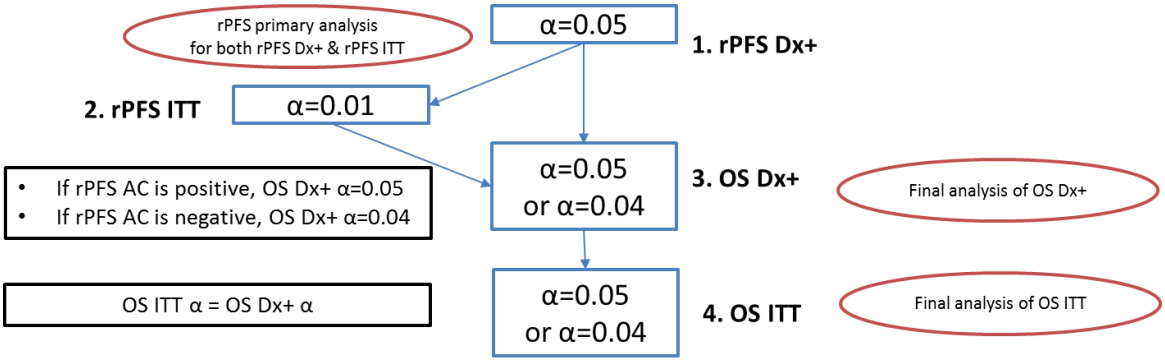
6.1.1 Type I Error Control

The overall type I error (α) 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 rPFS (per PCWG3 criteria, see Section 6.4.1) in the ITT population and in patients with PTEN-loss tumors by IHC
- Key secondary endpoints: 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 = diagnosis; ITT = intent to treat; OS = overall survival; rPFS = radiographic progression-free 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:

- 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.
- 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

- 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

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.

6.1.2 Co-Primary Endpoint: Progression-Free Survival

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.

6.1.3 Key Secondary Endpoint: Overall Survival

The "final" analysis of OS in patients with PTEN-loss tumors by IHC is scheduled to be around 24 months after the rPFS primary analysis when there are approximately

327 OS events in patients with PTEN-loss tumors by IHC (with an assumption of 5% loss to follow-up for OS per two years). It's estimated that, for the interim analysis of OS in patients with PTEN-loss tumors at the time of the rPFS primary analysis, there are approximately 196 OS events in patients with PTEN-loss tumors (i.e., with information fraction of approximately 60%).

- If the test of rPFS in the ITT population is 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. With alpha spending to the IA (at the rPFS primary analysis), at the final analysis of OS in patients with PTEN-loss tumors, the largest hazard ratio deemed to be statistically significant will be approximately 0.803 (with median OS improvement from 29 months in the placebo arm to approximately 36.1 months in the ipatasertib arm).
- If the test of rPFS in the ITT population is negative with α of 0.01, then the OS in patients with PTEN-loss tumors by IHC will be tested with α of 0.04. With alpha spending to the IA (at the rPFS primary analysis), at the final analysis of OS in patients with PTEN-loss tumors, the largest hazard ratio deemed to be statistically significant will be approximately 0.795 (with median OS improvement from 29 months in the placebo arm to approximately 36.5 months in the ipatasertib arm).

The "final" analysis of OS in the ITT population is scheduled to be around 9 months after the "final" analysis of OS in patients with PTEN-loss tumors by IHC and when there are approximately 660 OS events in the ITT population (with an assumption of 5% loss to follow-up for OS per two years). It's estimated that, for the interim analysis of OS in the ITT population, the information fractions are approximately 50% and 90%at the time of the rPFS primary analysis and the "final" analysis of OS in patients with PTEN-loss tumors by IHC respectively.

- If the OS in patients with PTEN-loss tumors by IHC is tested with α of 0.05, then the OS in the ITT population will be tested with α of 0.05 as well. With alpha spending to the IAs, at the final analysis of OS in the ITT population, the largest hazard ratio deemed to be statistically significant will be approximately 0.852 (with median OS improvement from 35 months in the placebo arm to approximately 41.1 months in the ipatasertib arm).
- If the OS in patients with PTEN-loss tumors by IHC is tested with α of 0.04, then the OS in the ITT population will be tested with α of 0.04 as well. With alpha spending to the IAs, at the final analysis of OS in the ITT population, the largest hazard ratio deemed to be statistically significant will be approximately 0.846 (with median OS improvement from 35 months in the placebo arm to approximately 41.4 months in the ipatasertib arm).

6.1.4 China Extension Cohort

After approximately 1100 patients have been randomized into the global main study and if China has not reached approximately 200 patients, ex-China enrollment (i.e., global enrollment) will be closed and additional Chinese patients may be recruited into the China extension cohort to enroll a total of approximately 200 Chinese patients

(i.e., the China subgroup) in the combination of the global (main study) cohort and the China extension cohort.

Among the approximately 200 Chinese patients in the ITT population, 100 rPFS events will allow to demonstrate approximately 83% probability of maintaining ≥50% of rPFS risk reduction from the global cohort. It is estimated that there will be approximately 53 rPFS events among the Chinese patients with PTEN-loss tumors that can demonstrate approximately 84% probability of maintaining ≥50% of rPFS risk reduction from the global cohort.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, study treatment administration, and discontinuations from the study will be summarized by treatment arm. The incidence of treatment discontinuation for reasons other than disease progression will be tabulated by treatment arm. Major protocol violations, including violations of inclusion/exclusion criteria, will be summarized by treatment arm.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, and race), 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) and tumor PTEN-loss status by IHC assay (yes vs. no) will be summarized by treatment arm. Continuous variables will be summarized with use of means, SDs, medians, and ranges. Categorical variables will be summarized by counts and proportions.

6.4 EFFICACY ANALYSES

The primary objective for this study is to evaluate the efficacy of ipatasertib plus abiraterone compared with placebo plus abiraterone 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, 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.

6.4.1 Primary Efficacy Endpoint

The primary endpoint of rPFS is defined as the time from date of randomization to the first occurrence of 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 ($\alpha = 0.05$) 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)

A Cox proportional-hazards model stratified using the four 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)

6.4.2 Key Secondary Efficacy Endpoints

6.4.2.1 Overall Survival

OS will be measured from randomization to the time of 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 analysis populations for OS are: patients in the ITT population and patients with PTEN-loss tumors as determined by IHC. The key OS analyses will be performed by stratified two-sided log-rank tests with the significance levels as described in Section 6.1. Additional similar analyses as those specified for the primary endpoint

(see Section 6.4.1) will also be performed for OS analyses, including unstratified log-rank test, Cox proportional-hazards model, Kaplan-Meier approach, etc.

OS will be analyzed at the time of rPFS primary analysis and the event-driven time points as described in Section 6.1.

6.4.2.2 Time to Pain Progression

Pain severity 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 NRS) or pain worsening for those patients who are mildly symptomatic at baseline (score of 2 or 3). Pain severity progression is defined as a $\geq$2-point absolute increase from baseline.

Pain severity progression at a given timepoint will be considered clinically meaningful if followed by any of the following:

- A subsequent pain severity assessment within approximately 28 days showing that the score on pain severity at its worst is stable or increased
- Initiation of opioid analgesic medication as measured by the Analgesic Quantification Algorithm (AQA) score within approximately 28 days following the initial pain event. AQA scores range from 0 to 7, in which a score of 0 is no analgesic use and a score of 7 is strong opioid use (Chung et al. 2014). The QA score will be calculated based on the consumption of opioids documented in the eCRF. Equianalgesic potency conversions and AQA are displayed in Appendix 11.
- Initiation of palliative radiotherapy within approximately 28 days following the initial pain event
- Any increase in glucocorticosteroids usage for the intent of treating cancer pain within approximately 28 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 be defined as an increase from a score 0 or 1 at the time of the initial pain event to a score of $\geq$2 on the AQA reported on at least 7 consecutive days in the 28-day period until the pain assessment.

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.

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 ≥ 2 points will be censored at the latest date of the last pain severity assessment.

In addition, patients who do not report baseline data will be censored at the randomization date plus 1 day.

The same analysis methods as described in Section 6.4.1 for the primary endpoint rPFS will be used for this time to pain progression endpoint.

6.4.2.3 Time to Initiation of Cytotoxic Chemotherapy

Time to initiation of cytotoxic chemotherapy is defined as the time interval from the date of randomization to the date of initiation of cytotoxic chemotherapy for prostate cancer. Cytotoxic chemotherapy was defined as the use of any of the following antineoplastic agents for prostate cancer: 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 6.4.1 for the primary endpoint rPFS will be used for this time to initiation of cytotoxic chemotherapy endpoint.

6.4.2.4 Time to Function Deterioration

Time to function deterioration is defined as the time interval from the date of randomization to the date of a decrease of 10-point or more on either the 0–100 PF or the RF scores from the EORTC QLQ-C30.

The analysis methods will be the same as for the primary endpoint (see Section 6.4.1).

6.4.2.5 Time to Prostate-Specific Antigen Progression

PSA progression is defined as a PSA increase that is $\geq 25\%$ 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. The analysis methods will be the same as for the primary efficacy endpoint (see Section 6.4.1).

6.4.2.6 Time to First Opioid Use

Time to first opioid use is defined as the time interval from the date of randomization to the date of an initiation of opioid analgesic use for cancer-related pain, and consumption reported on at least 7 consecutive days.

The analysis methods will be the same as for the primary efficacy endpoint (see Section 6.4.1).

6.4.2.7 Time to Symptomatic Skeletal Events

Time to first SSE is defined as the time interval from the date of randomization to the date of an SSE. The analysis methods will be the same as for the primary efficacy endpoint (see Section 6.4.1).

6.4.2.8 Objective Response Rate

An objective response is defined as a CR or PR on two consecutive occasions $\geq$4 weeks apart, according to RECIST v1.1 and PCWG3 criteria, in patients with measurable disease at baseline. Patients without a postbaseline tumor assessment will be considered non-responders.

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 Blyth-Still-Casella 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 6.4.1). 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.

6.4.2.9 Prostate-Specific Antigen Response Rate

PSA response rate is defined as the proportion of patients achieving a PSA decline $\geq$50% from baseline. Patients without a postbaseline 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 6.4.2.1).

6.4.2.10 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 analysis methods will be the same as for the primary efficacy endpoint (see Section 6.4.1).

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints will be evaluated in patients in the ITT population and in patients with PTEN-loss tumors by IHC. P-values will be reported for descriptive purposes. The exploratory efficacy endpoints include IRF-assessed radiographic progression, PFS after next line of treatment (secondary PFS; PFS2), time to deterioration in health-related QoL, 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, and PRO-CTCAE. Analyses will be performed as data allows as described in the SAP.

6.5 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 ipatasertib plus abiraterone arm in the safety analyses if this patient receives any amount of ipatasertib, regardless of the initial treatment assignment at randomization.

Safety endpoints will include incidence, severity, and seriousness of adverse events, deaths, and clinically significant laboratory measurement.

Adverse events will be summarized by mapped Medical Dictionary for Regulatory Activities preferred terms. All adverse events occurring during or after the first dose of study treatment until the end of the adverse event reporting window will be summarized by treatment arm. In addition, serious adverse events, adverse events of special interest, and adverse events leading to study drug discontinuation will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity.

Deaths will be summarized by treatment arm.

Laboratory data with values outside the normal ranges will be identified. In addition, selected laboratory data will be summarized by treatment arm and grade.

Drug exposure will be summarized to include duration of treatment, cumulative dose, and dose intensity by treatment arm.

6.6 PHARMACOKINETIC 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 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, sex, 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).

6.7 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. Results will be presented in a separate report.

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.

6.8 INTERIM ANALYSES

6.8.1 Planned Interim Safety Analyses

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 (see Section 6.4.1), according to the policies and procedures detailed in an iDMC charter. The Sponsor will be blinded until the rPFS primary analysis.

An iDCC will prepare all summaries and analyses for the iDMC's review. The safety summaries will include demographic data, adverse events, serious adverse events, 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 IRB/ECs and competent authorities as required.

6.8.2 Planned Interim Efficacy Analyses

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 approximately 327 OS events in patients with PTEN-loss tumors by IHC occur. This target number of OS events 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 approximately 660 OS events in the ITT population occur. This target number of OS events 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 shown in Table 11. 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 11 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)

EPR = Event–Patient-Ratio; FA = final analysis; FPI = first patient in; ITT = intent-to-treat; OS = overall survival; *PTEN = phosphatase and tensin homolog*.

6.8.3 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.

6.9 CHINA SUBGROUP ANALYSES

The primary efficacy objective of the China subgroup analysis is to evaluate whether the efficacy, as measured by rPFS, of ipatasertib plus abiraterone compared with placebo plus abiraterone in the Chinese patients with mCRPC is consistent with the efficacy observed in the global cohort. Consistency is defined as maintaining $\geq$50% of risk reduction from the global cohort. Therefore, the China subgroup is not powered to demonstrate the statistical significance of efficacy and no formal hypothesis testing will be performed. The results of the China subgroup analyses will be summarized in a separate CSR. The statistical details for such analyses in the China subgroup will be documented in the SAP.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected through the use of an electronic device provided by a vendor. If back-up paper forms are used by the patient, the data will be entered by the sites through an electronic portal. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). The electronic data are available for view access only via secure access to a vendor-hosted, password-protected Web portal. Only identified and trained users may view the data, and their actions become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

At screening, patients will complete one pain severity item (24-hour recall) by paper in the clinic. Upon randomization, patients will use an electronic device to capture PRO data. Back-up paper forms will be available if needed in order to capture patient data. The data from the electronic device will be transmitted to a centralized database maintained by the electronic device vendor.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all data in a machine-readable format.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include but are not limited to hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve

as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMPs, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor.
Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) *or Clinical Trials Regulation (536/2014)* and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form) will be provided to each site.
If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the

Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Given the complexity and exploratory nature of the analyses, data derived from exploratory biomarker specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV occurs or the date at which the last data point required for statistical analysis has been observed [see Section 6.4]).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. The Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This study will be sponsored and managed by F. Hoffmann-La Roche Ltd. Approximately 200 centers worldwide will participate in the study and approximately 1100 patients will be enrolled. After approximately 1100 patients have been randomized into the study, ex-China enrollment (i.e., global enrollment) will be closed and additional Chinese patients will be recruited into the China extension cohort to enroll a total of approximately 200 Chinese patients (i.e., the China subgroup) if that number of Chinese patient is not reached within the global enrollment.

Randomization will occur through use of an IxRS. Central facilities will be used for study assessments throughout the study (e.g., specified laboratory tests and PK analyses). Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will be convened to evaluate safety data during the study according to policies and procedures detailed in the iDMC charter.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/or other *summaries of clinical study results may be available in health authority databases for public access, as required by local regulation,*

and will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following Web site:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective CSR. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

American Cancer Society. Cancer facts & figures 2016. Atlanta: American Cancer Society; 2016.

Antonarakis ES, Keizman D, Zhang Z, et al. An immunohistochemical signature comprising PTEN, MYC, and Ki67 predicts progression in prostate cancer patients receiving adjuvant docetaxel after prostatectomy. Cancer 2012;118:6063–71. doi:10.1002/cncr.27689. Epub 6 June 2012.

Barnett CM, Heinrich MC, Lim J. Genetic profiling to determine risk of relapse free survival in high-risk localized prostate cancer. Clin Cancer Res 2014;20:1306–12. doi:10.1158/1078-0432.CCR-13-1775. Epub 18 December 2013.

Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). J Natl Cancer Inst 2014;106:1–11. doi:10.1093/jnci/dju244.

Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014;371:424–33. doi:10.1056/NEJMoa1405095. Epub 2014 June 1.

Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53–72.

Carver BS, Chapinski C, Wongvipat J, et al. Reciprocal feedback regulation of PI3K and androgen receptor signaling in PTEN-deficient prostate cancer. Cancer Cell 2011;19:575–86. doi:10.1016/j.ccr.2011.04.008.

Chaux A, Peskoe SB, Gonzalez-Roibon N, et al. Loss of PTEN expression is associated with increased risk of recurrence after prostatectomy for clinically localized prostate cancer. Mod Pathol 2012;25:1543–9. doi:10.1038/modpathol.2012.104. Epub 8 June 2012.

Chen ML, Xu PZ, Peng XD, et al. The deficiency of Akt1 is sufficient to suppress tumor development in Pten (+/1) mice. Genes Dev 2006;20:1569–74.

Chung KC, Barlev A, Braun AH, et al. Assessing analgesic use in patients with advanced cancer: development of a new scale—the Analgesic Quantification Algorithm. Pain Med 2014;15:225–32. doi:10.1111/pme.12299. Epub 8 January 2014.

Cleeland CS, Body J-J, Stopeck A, et al. Pain outcomes in patients with advanced breast cancer and bone metastases: results from a randomized, double-blind study of denosumab and zoledronic acid. Cancer 2013;119:832–8. doi:10.1002/cncr.27789. Epub 5 September 2012.

Cuzick J, Yang ZH, Fisher G, et al. Prognostic value of PTEN loss in men with conservatively managed localised prostate cancer. Br J Cancer 2013;108:2582–9. doi:10.1038/bjc.2013.248. Epub 21 May 2013.

Dabrowska-Bender M, Sloniewski R, Religioni U, et al. Analysis of quality of life subjective perception by patients treated for prostate cancer with the EORTC QLQ-C30 questionnaire and QLQ-PR25 module. J Cancer Educ 2015; doi:10.1007/s13187-015-0954-5. [Epub ahead of print]

de Bono JS, de Giorgi U, Massard C, et al. Randomized phase II study of Akt blockade with ipatasertib (GDC-0068) and abiraterone (abi) vs abi alone in patients with metastatic castration-resistant prostate cancer (mCRPC) after docetaxel chemotherapy (A. MARTIN study) [abstract]. J Clin Oncol 2016a;34(suppl;abstr 5017).

de Bono JS, de Giorgi U, Massard C, et al. PTEN loss as a predictive biomarker for the Akt inhibitor ipatasertib combined with abiraterone acetate in patients with metastatic castration-resistant prostate cancer (mCRPC) [abstract]. Ann Oncol 2016b;27(suppl 6):718O.

de Bono JS, de Giorgi U, Rodrigues DN, et al. Randomzied phase II study of Akt blockade with or without ipatasertib in abiraterone-treated patients with metastatic prostate cancer with and without PTEN loss. Clin Cancer Res 2018;doi:10.1158/1078-0432.

de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995–2005. doi:10.1056/NEJMoa1014618.

Del Re M, Biasco E, Crucitta S, et al. The detection of androgen receptor splice variant 7 in plasma-derived exosomal RNA strong predicts resistance to hormonal therapy in metastatic prostate cancer patients. Eur Urol 2016;pii:S0302-2838(16)30479-1. doi:10.1016/j.eururo.2016.08.012. [Epub ahead of print]

Diehl F, Schmidt K, Choti MA, et al. Circulating mutant DNA to assess tumor dynamics. Nat Med 2008;14:985–90. doi:10.1038/nm.1789. Epub 31 July 2007.

EuroQoL Group. EuroQoL–a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.

Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015:136;E359–86. doi:10.1002/ijc.29210. Epub 9 October 2014.

Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Euro J Cancer 2013;49:1374–1403. doi:10.1016/j.ejca.2012.12.027. Epub 26 February 2013.

Ferraldeschi R, Nava Rodrigues D, Riisnaes R, et al. PTEN protein loss and clinical outcome from castration-resistant prostate cancer treated with abiraterone acetate. Eur Urol 2015;67:795–802. doi:10.1016/j.eururo.2014.10.027. Epub 4 November 2014.

Frampton GM, Fichtenholtz A, Otto GA, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. Nat Biotechnol 2013;31:1023–31. doi:10.1038/nbt.2696. Epub 20 October 2013.

Gao H, Ouyang X, Banach-Petrosky WA, et al. Emergence of androgen independence at early stages of prostate cancer progression in Nkx3.1 Pten mice. Cancer Res 2006;66:7929–33.

Guertin DA, Stevens DM, Saitoh M et al. mTOR complex 2 is required for the development of prostate cancer induced by Pten loss in mice. Cancer Cell 2009;15:148–59. doi:10.1016/j.ccr.2008.12.017.

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of the EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36. doi:10.1007/s11136-011-9903-x. Epub 9 April 2011.

Higgins MJ, Jelovac D, Barnathan E, et al. Detection of tumor PIK3CA status in metastatic breast cancer using peripheral blood. ClinCanRes 2012;18:3462–9. doi:10.1158/1078-0432.CCR-11-2696. Epub 15 March 2012.

Jannsen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;22:1717–27. doi:10.1007/s11136-012-0322-4. Epub 25 November 2012.

Jiao J, Wang S, Qiao R, et al. Murine cell lines derived from Pten null prostate cancer show the critical role of PTEN in hormone refractory prostate cancer development. Cancer Res 2007;67:6083–91.

Kim SH, Kim SH, Joung JY, et al. Overexpression of ERG and wild-type PTEN are associated with favorable clinical prognosis and low biochemical recurrence in prostate cancer. PLoS One 2015;10:e0122498. doi:10.1371/journal.pone.0122498. eCollection 2015.

Logothetis CJ, Basch E, Molina A, et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from COU-AA-301 randomised trial. Lancet Oncol 2012;13:1210–7. doi:10.1016/S1470-2045(12)70473-4. Epub 9 November 2012.

Maheswaran S, Sequist LV, Nagrath S, et al. Detection of mutations in EGFR in circulating lung-cancer cells. New Engl J Med 2008;359:366–77. doi:10.1056/NEJMoa0800668. Epub 2 July 2008.

Mathias SD, Crosby RD, Qian Y, et al. Estimating minimally important differences for the worst pain rating of the Brief Pain Inventory-Short Form. J Support Oncol 2011;9:72–8.

Mulholland DJ, Tran LM, Li Y, et al. Cell autonomous role of PTEN in regulating castration-resistant prostate cancer growth. Cancer Cell 2011;19:792–804. doi:10.1016/j.ccr.2011.05.006. Epub 27 May 2011.

Nardella C, Carracedo A, Alimonti A, et al. Differential requirement of mTOR in postmitotic tissues and tumorigenesis. Sci Signal 2009;2:ra2. doi:10.1126/scisignal.2000189.

Papa A, Wan L, Bonora M, et al. Cancer-associated PTEN mutants act in a dominant-negative manner to supress PTEN protein function. Cell 2014;157:595–610. doi:10.1016/j.cell.2014.03.027.

Reid AHM, Attard G, Ambroisine L, et al. Molecular characterisation of ERG, ETV1 and PTEN gene loci identifies patients at low and high risk of death from prostate cancer. Br J Cancer 2010;102:678–84. doi:10.1038/sj.bjc.6605554. Epub 26 January 2010.

Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015;161:1215–28. doi:10.1016/j.cell.2015.05.001.

Romanel A, Tandefelt DG, Conteduca V, et al. Plasma AR and abiraterone-resistant prostate cancer. Sci Transl Med 2015;7:312re10. doi:10.1126/scitranslmed.aac9511.

Ryan CJ, Smith MR, de Bono JS, et al. Randomized Phase 3 trial of abiraterone acetate in men with metastatic castration-resistant prostate cancer and no prior chemotherapy. N Engl J Med 2013;368:138–48. doi:10.1056/NEJMoa1209096.

Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Onc 2016:34:1402–18. doi:10.1200/JCO.2015.64.2702. Epub 22 February 2016.

Sun J, Frampton G, Wang K, et al. A computational method for somatic vs. germ-line variant status determination from targeted next-generation sequencing of clinical cancer specimens without a matched normal control. [abstract]. Cancer Res 2014;74(19 Suppl): abstr 1893. doi:10.1158/1538-7445.AM2014-1893.

van Andel G, Bottomley A, Fossa SD, et al. An international field study of the EORTC QLQ-PR25: A questionnaire for assessing the health-related quality of life of patients with prostate cancer. Eur J Cancer 2008;44:2418–24. doi:10.1016/j.ejca.2008.07.030. Epub 5 September 2008.

Wilson TR, Fridlyand J, Yan Y, et al. Widespread potential growth-factor-driven resistance to anticancer kinase inhibitors. Nature 2012;487:505–9. doi:10.1038/nature11249.

Yoshimoto M, Cunha IW, Coudry RA, et al. FISH analysis of 107 prostate cancers shows that PTEN genomic deletion is associated with poor clinical outcome. Br J Cancer 2007;97:678–85. doi:10.1038/sj.bjc.6603924. Epub 14 August 2007.

Yuan TL, Cantley LC. PI3K pathway alterations in cancer: variations on a theme. Oncogene 2008;27:5497–510. doi:10.1038/onc.2008.245.

Zafarana G, Ishkanian AS, Malloff CA, et al. Copy number alterations of c-MYC and PTEN are prognostic factors for relapse after prostate cancer radiotherapy. Cancer 2012;118:4053–62. doi:10.1002/cncr.26729. Epub 26 January 2012.

ZYTIGA® (abiraterone acetate) tablets U.S. Prescribing Information, Janssen Biotech, Inc.

ZYTIGA® (abiraterone acetate) tablets, Summary of Product Characteristics, European Medicines Agency. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002321/human_med_001499.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124.

Appendix 1
Schedule of Activities

Assessment/Procedure (Window)	Screening [a]	Cycle 1				Cycle 2		Cycle 3		Cycles ≥ 4	Study Treatment Discontinuation [b]	Disease Follow-Up [c; jj]	Post-Treatment Follow-Up [d; jj]
	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 [jj]	x [jj]	x	x

Appendix 1
Schedule of Activities (cont.)

Assessment/Procedure (Window)	Screening [a]	Cycle 1				Cycle 2		Cycle 3		Cycles ≥ 4	Study Treatment Discontinuation [b]	Disease Follow-Up [c; jj]	Post-Treatment Follow-Up [d; jj]
	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
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, jj]	x *jj*		
Serum testosterone [s]	x										x *jj*		
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					x		
Fasting lipid profile	x					x					x		

Appendix 1
Schedule of Activities (cont.)

Assessment/Procedure (Window)	Screening [a]	Cycle 1				Cycle 2		Cycle 3		Cycles ≥ 4	Study Treatment Discontinuation [b]	Disease Follow-Up [c; jj]	Post-Treatment Follow-Up [d; jj]
	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
Hemoglobin A_{1c}	x					x				Day 1 of Cycles 4, 6, 9, 12, and every 3 cycles thereafter			
Tumor assessment of soft tissue per RECIST v1.1 [y]	x [a]					End of Cycles 2, 4, 6, and every 3 cycles thereafter [aa, jj]					x *jj*	x	
Tumor assessment: bone scan [z]	x [a]										x *jj*	x	
Pain severity at its worst NRS (24h recall) [bb]	x												
Pain severity at its worst NRS (7–day recall) [bb]		x				x		x		x *jj*	x *jj*	x	x
EORTC QLQ-C30, Urinary Scale from EORTC PR-25 [bb]		x				x		x		x *jj*	x *jj*	x	x
EQ-5D-5L [bb]		x				x		x		x *jj*	x *jj*	x	x
PRO-CTCAE (selected items) [bb]		x		x	x	x	x	x	x	x *jj*			
Medication log [cc]		Record per medication consumption *jj*									x *jj*	x	
Study treatment administration [dd]		Daily administration of ipatasertib/placebo, abiraterone plus prednisone/prednisolone											

Appendix 1
Schedule of Activities (cont.)

Assessment/Procedure (Window)	Screening [a]	Cycle 1				Cycle 2		Cycle 3		Cycles ≥ 4	Study Treatment Discontinuation [b]	Disease Follow-Up [c; jj]	Post-Treatment Follow-Up [d; jj]
	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
Symptomatic skeletal events [ee]		Record any symptomatic [jj] skeletal events									x [jj]	x	x
Drug accountability						x		x		x	x		
Plasma PK sample [ff]		See Appendix 2											
Blood sample for NGS control [gg]		See Appendix 2											
Blood sample for pharmacogenomics [gg]		See Appendix 2											
Plasma sample for somatic tumor mutations [gg]		See Appendix 2											
Plasma sample for exploratory biomarkers [gg]		See Appendix 2											
Blood sample for RBR (for DNA extraction; optional) [hh]		See Appendix 2											
Subsequent line of prostate cancer therapy and outcome [ii]												x	x
Survival follow-up												x	x

Appendix 1
Schedule of Activities (cont.)

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. *After the final OS analysis, for the patients who are still on ipatasertib, the study visits will occur every 3 months (± 7 days) instead of monthly. The patients who are receiving abiraterone only will no longer be required to attend study visits.*

[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 for details).

[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. See Section 4.5.5 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. *These data will not be collected after the final OS analysis.*

[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. *These data will not be collected after the final OS analysis.*

[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.

Appendix 1
Schedule of Activities (cont.)

[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).

[h] A tumor tissue block or a minimum of 10–15 (15 slides 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.

[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 ≥0.2 ng/dL, including the most recent value during androgen-derivation therapy, and the interval between first and last PSA value to be ≥8 weeks but ≤12 months). A central laboratory sample should also be submitted at screening and at all other timepoints. *PSA central laboratory samples will no longer be collected after the final OS analysis.* 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 ≤96 hours prior to dosing for each clinic visit during study treatment; screening assessments performed ≤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 ≤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. *Serum testosterone central laboratory samples will no longer be collected after the final OS analysis.*

[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 ≤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 ≥8 hours prior to testing.

[v] *Countries with mandatory self-monitoring of glucose are Austria, Belgium, Denmark, Hungary, Ireland, Italy, Norway, Poland, Portugal, Spain, and the United Kingdom. Patients enrolled in these countries* 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). *After the final OS analysis and patients' unblinding, this test should only be performed for patients who are receiving ipatasertib.*

[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 ≥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 *be* 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 ±7 days of the scheduled cycles. *After the final OS analysis, tumor assessments will no longer be required at study visits, but they will be performed as per local practice and at the investigator's discretion. Data will not be collected from tumor assessments performed after the final OS analysis.*

[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. *PRO data will not be collected after the final OS analysis.*

[cc] Consumption of analgesics (including opioids) will be documented by the patients or their caregivers, using the provisioned devices or back-up paper forms. *These data will not be collected after the final OS analysis.*

[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. *These data will not be collected after the final OS analysis.*

Appendix 1
Schedule of Activities (cont.)

[ff] See Appendix 2 for PK sample collection. *All samples in Appendix 2 are no longer required after the final OS analysis.*

[gg] Samples will be collected only at sites with local regulatory authority approval. See Appendix 2 for further details. *All samples in Appendix 2 are no longer required after the final OS analysis.*

[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 2 for further details. All samples in Appendix 2 are no longer required after the final OS analysis.*

[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. *These data will not be collected after the final OS analysis.*

[jj] *Until the final OS analysis.*

Appendix 2
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

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. *All samples in Appendix 2 are no longer required after the final OS analysis.*

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

Appendix 2
Schedule of Pharmacokinetic Samples and Exploratory Biomarker Samples (cont.)

Study Visit	Timepoint(s)	Sample Type
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.

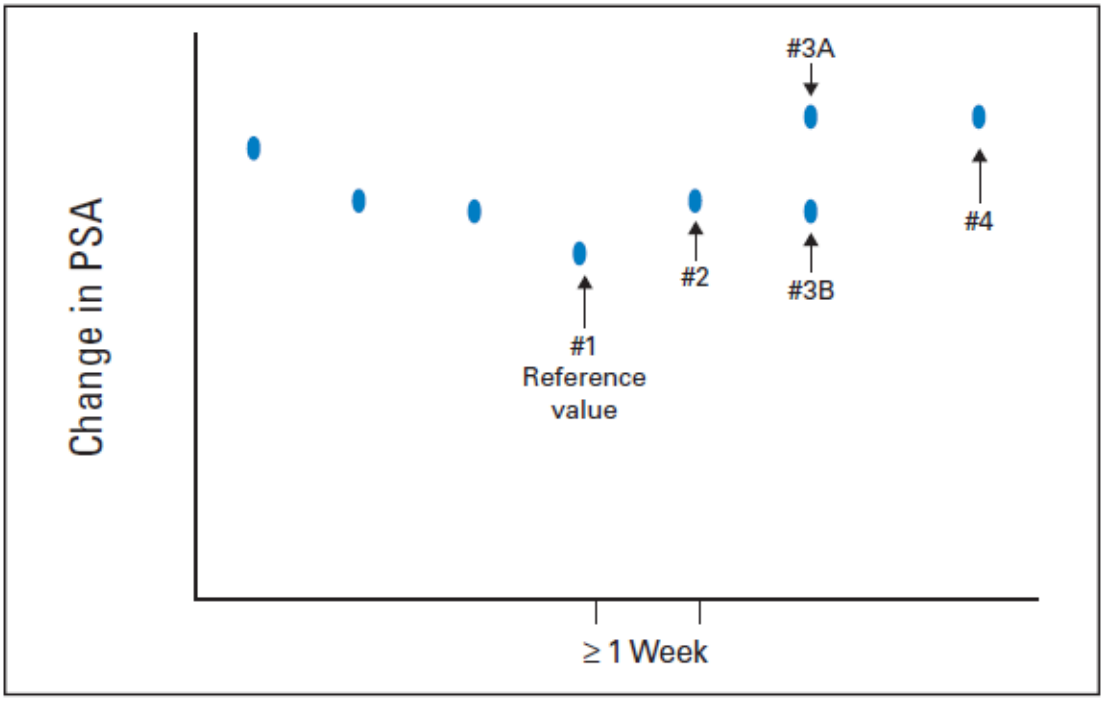
All samples in Appendix 2 are no longer required after the final OS analysis.

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

Appendix 3
Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix 4
PSA Progression Eligibility Criteria



PSA = prostate-specific antigen.

Eligibility based on prostate-specific antigen (PSA) changes. The reference value (#1) is the last PSA measured before increases are documented, with subsequent values obtained a minimum of 1 week apart. If the PSA at time point 3 (value #3A) is greater than that at point 2, then eligibility has been met. If the PSA is not greater than point 2 (value #3B), but value #4 is, the patient is eligible assuming that other criteria are met, if values 3A or #4 are 1 ng/mL or higher.

REFERENCES

Bubley GJ, Carducci M, Dahut W, et al: Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: Recommendations from the PSA Working Group. J Clin Oncol 1999;17:3461–7. [Erratum: J Clin Oncol 2000;18:2644, J Clin Oncol 2007;25:1154].

Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 2008;26:1128–59.

Appendix 5
Response Evaluation Criteria in Solid Tumors: Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1 [2] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[3]

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

MEASURABLE TUMOR LESIONS

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

NON-MEASURABLE TUMOR LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal

---

[2] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.

[3] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Appendix 5
Response Evaluation Criteria in Solid Tumors:
Excerpt from Original Publication (cont.)
Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward.</u> Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in the assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

Appendix 5
Response Evaluation Criteria in Solid Tumors: Excerpt from Original Publication (cont.)
TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but additionally, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added

into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

RESPONSE CRITERIA

Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- **Complete response (CR)**: disappearance of all target lesions

  Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

- **Partial response (PR)**: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- **Progressive disease (PD)**: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.

- **Stable disease (SD)**: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero

even if CR criteria are met since a normal lymph node is defined as having a short axis < 10 mm.

Target Lesions That Become Too Small to Measure. While in the study, all lesions (nodal and non-nodal) that are recorded at baseline should be recorded as actual measurements at each subsequent evaluation, even when very small (e.g., 2 mm).

However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on the CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and below measurable limit (BML) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked.)

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and, in that case, BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

- **CR**: disappearance of all non-target lesions and (if applicable) normalization of tumor marker level)

  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).
- **Non-CR/Non-PD**: persistence of one or more non-target lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- **PD**: unequivocal progression of existing non-target lesions

  The appearance of one or more new lesions is also considered progression.

Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the

presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III studies when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare progressive disease (PD) for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some “new” bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient’s baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a “new” cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify whether it represents truly new disease. If repeat scans

confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

EVALUATION OF RESPONSE

Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1 Timepoint Response: Patients with Target Lesions (With or Without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2 Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some studies; thus, assigning "stable disease" when no lesions can be measured is not advised.

Appendix 5
Response Evaluation Criteria in Solid Tumors:
Excerpt from Original Publication (cont.)
Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be “unable to assess” since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be “unable to assess” except where there is clear progression. Overall response would be “unable to assess” if either the target response or the non-target response is “unable to assess,” except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

Appendix 5
Response Evaluation Criteria in Solid Tumors:
Excerpt from Original Publication (cont.)
Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 1, Table 2, and

Appendix 5
Response Evaluation Criteria in Solid Tumors:
Excerpt from Original Publication (cont.)
Table 3.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 6
Criteria for Radiographic Progression per Prostate Cancer Working Group 3

Date Progression Detected (Visit) [a]	Criteria for Progression	Criteria for Confirmation of Progression (Requirement and Timing)	Criteria for Documentation of Disease Progression on Confirmatory Scan
Week 8	Bone lesions: Two or more new lesions compared to **baseline** bone scan by PCWG3.	Timing: at least 6 weeks after progression identified or at Week 16 visit. [c]	Two or more new bone lesions on bone scan (compared to Week 8 scan).
	Soft tissue lesions: Progressive disease on CT or MRI scan by RECIST v1.1 [b]	No confirmatory scan required for soft tissue disease progression.	NA
Week 16 or later	Bone lesions: Two or more new lesions on bone scan compared **to Week 8** bone scan.	Timing: at least 6 weeks after progression identified; required for bone lesions observed on bone scan [c]	Persistent [d] or increased number of bone lesions on bone scan compared to prior scan.
	Soft tissue lesions: Progressive disease on CT or MRI scan by RECIST v1.1. [b]	No confirmatory scan required for soft tissue disease progression.	NA

CT = computed tomography; MRI = magnetic resonance imaging; NA = not applicable; PCWG3 = Prostate Cancer Working Group 3, RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Note: Adapted from Scher et al. 2016.

[a] In a situation where the bone scan at Week 8 is missed, the first post-treatment bone scan should be treated as the "Week 8" bone scan. Progression detected by bone scan at an unscheduled visit will require a confirmatory scan at least 6 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan.

[b] For RECIST v1.1, see Appendix 5. Up to five lesions (with a maximum of 2 lesions per organ) will be recorded as target lesions (e.g., lung, liver, adrenal, nodal).

[c] Confirmation must occur at the next available scan regardless of whether the patient will continue study treatment.

[d] For confirmation, at least two of the lesions first identified as new must be present at the next available scan.

Appendix 7
Bone Scan Tumor Assessment Tool

Bone Scan Tool for Assessing Radiographic Progression (for use after the week 8 scan)
1.Are there new lesions compared to the WEEK 8 SCAN? ❑ YES (If YES, proceed to question 2.) ❑ NO (If NO, the patient does not have disease progression by bone scan.)
2.Is this the FIRST SCAN after the WEEK 8 SCAN to show an *additional* 2 or more new lesions compared to the WEEK 8 SCAN? ❑ YES (Progressive disease is CONFIRMED by rapid progression "2+2" rule) ❑ NO (If NO, proceed to question 3.)
3. Is this the SECOND SCAN after the WEEK 16 SCAN to show 2 or more new lesions compared to the WEEK 8 scan? ❑ YES (Progressive disease is CONFIRMED by the "+2 confirmed" rule) ❑ NO (if NO, the patient does not have confirmed disease progression by bone scan)

"Yes" to question 2 OR question 3, confirms PROGRESSIVE DISEASE by bone scan. Please report this PD confirmation on the appropriated eCRF page .

Appendix 8
European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30: EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 9
European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire: Urinary Scale from EORTC QLQ-PR25

EORTC QLQ-PR25

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week	Not at all	A little	Quite a bit	Very much
1. Have you had to urinate frequently during the day?	1	2	3	4
2. Have you had to urinate frequently at night?	1	2	3	4
3. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
4. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
5. Have you had difficulty going out of the house because you needed to be close to a toilet?	1	2	3	4
6. Have you had any unintentional release (leakage) of urine?	1	2	3	4
7. Did you have pain when you urinated?	1	2	3	4
8. Have your daily activities been limited by your urinary problems?	1	2	3	4

Appendix 10
Pain Severity Assessments

Pain Severity Assessment (Screening)*

Please rate your pain by circling the one number that best describes your pain at its **worst** in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Pain Severity Assessment (Cycle 1, Day 1 and following Assessments)*

Please rate your pain by tapping the one number that best describes your pain at its **worst** in the last week.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

Note: Questions from Brief Pain Inventory and Brief Pain Inventory-Short Form per author permission.

Appendix 11
Analgesic Quantification Algorithm Score Categories and Equianalgesic Potency Conversions

Analgesic Quantification Algorithm Score Categories

Score	Description
0	No analgesic
1	Non-opioid analgesics
2	Weak opioids (i.e., codeine and tramadol)
3	Strong opioids ≤ 75 mg OME/day
4	Strong opioids > 75–150 mg OME/day
5	Strong opioids > 150–300 mg OME/day
6	Strong opioids > 300–600 mg OME/day
7	Strong opioids > 600 mg OME/day

OME = oral morphine equivalent.

Equianalgesic Potency Conversions

	Equianalgesic Dose (mg)				
Name	IV	SC	IM	PO	OME
Morphine	10	10	10	30	30
Fentanyl [a]	0.1	0.1	0.1	2.4	30
Hydromorphone	1	1	1	5	20
Methadone	10	10	10	20	30
Oxycodone	—	—	—	20	30
Hydrocodone	—	—	—	40	40
Codeine	120	120	120	200	30
Tramadol	100	100	100	100	30
Buprenorphine	0.3	0.3	0.3	0.2	30
Butorphanol	—	—	2	—	30
Nalbuphine	10	10	10	—	30
Pentazocine	60	60	60	60	20

IM = intramuscular; OME = oral morphine equivalent; PO = oral; SC = subcutaneous.

[a] Fentanyl, 0.1 mg transdermal has an OME of 30 mg.

Source: Chung et al. 2014.

Appendix 12
Treatment-Related Symptoms

NCI PRO-CTCAE™ ITEMS
(selected from Item Library Version 1.0)

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days.

In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
○ None	○ Mild	○ Moderate	○Severe	○ Very severe

In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

In the last 7 days, how OFTEN did you have NAUSEA?				
○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

In the last 7 days, how OFTEN did you have VOMITING?				
○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

In the last 7 days, did you have any RASH?	
○ Yes	○ No

Appendix 12
Treatment-Related Symptoms (cont.)

In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

---

In the last 7 days, how BOTHERED were you by the side effect(s) of your treatment?				
○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

Appendix 13
EuroQol 5-Dimension, 5 Levels Questionnaire: EQ-5D-5L

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑

Appendix 13
EuroQol 5-Dimension, 5 Levels Questionnaire: EQ-5D-5L (cont.)

I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

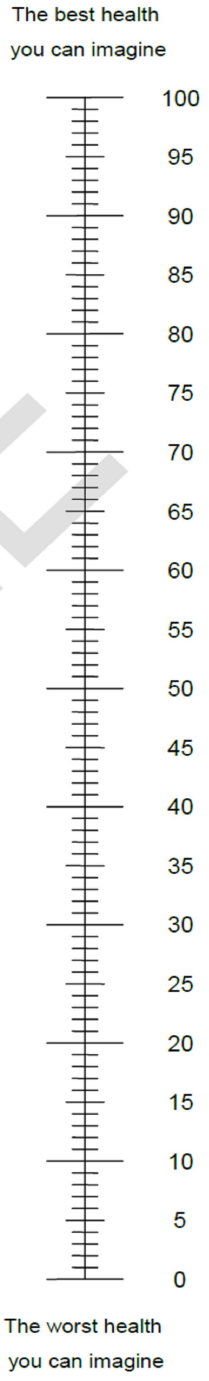
ANXIETY / DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

Appendix 13
EuroQol 5-Dimension, 5 Levels Questionnaire: EQ-5D-5L (cont.)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

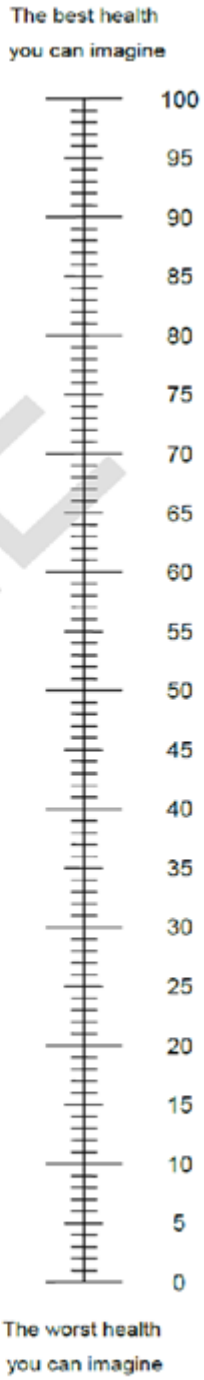
YOUR HEALTH TODAY = ☐



Appendix 13
EuroQol 5-Dimension, 5 Levels Questionnaire: EQ-5D-5L (cont.)

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 14 Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table A1-1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	*IMP/AxMP Designation*	*Marketing Authorization Status in EEA*	*Used within Marketing Authorization*
Ipatasertib (RO5532961)	*IMP (test product)*	*Unauthorized*	*Not applicable*
Abiraterone	*IMP (test product)* [a]	*Authorized*	*No*[a]
RO5532961 placebo	*IMP (placebo)*	*Unauthorized*	*Not applicable*
Prednisone	*AxMP (background therapy)*	*Authorized*	*Yes*
Prednisolone	*AxMP (background therapy)*	*Authorized*	*Yes*

AxMP =auxiliary medicinal product; EEA =European Economic Area; IMP =investigational medicinal product; mCRPC =metastatic castrate-resistant prostate cancer.

[a] *Abiraterone is approved for the treatment of mCRPC but not in combination with ipatasertib.*

Table A1-2 Investigational and Non-Investigational Medicinal Product Designations for European Economic Area and United Kingdom

Product Name	*IMP/NIMP Designation*	*Marketing Authorization Status in EEA and UK*	*Used within Marketing Authorization*
Ipatasertib (RO5532961)	*IMP (test product)*	*Unauthorized*	*Not applicable*
Abiraterone	*IMP (test product)* [a]	*Authorized*	*No* [a]
RO5532961 placebo	*IMP (placebo)*	*Unauthorized*	*Not applicable*
Prednisone	*NIMP (background therapy)*	*Authorized*	*Yes*
Prednisolone	*NIMP (background therapy)*	*Authorized*	*Yes*

EEA =European Economic Area; IMP =investigational medicinal product; mCRPC =metastatic castrate-resistant prostate cancer; NIMP =non-investigational medicinal product.

[a] *Abiraterone is approved for the treatment of mCRPC but not in combination with ipatasertib.*

Signature Page for Prot CO39303 Ipatasertib v8 - Published
System identifier: RIM-CLIN-458114

Approval Task	[redacted] Company Signatory 15-Nov-2022 14:32:13 GMT+0000