Protocol I3Y-MC-JPCM (f)

A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate Plus Prednisone With or Without Abemaciclib in Patients With Metastatic Castration-Resistant Prostate Cancer

NCT03706365

Approval Date: 30-Apr-2024

Protocol I3Y-MC-JPCM(f)
CYCLONE 2: A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate plus Prednisone with or without Abemaciclib in Patients with Metastatic Castration-Resistant Prostate Cancer

abemaciclib (LY2835219)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Numbers:

EudraCT Number: 2016-004276-21
EU CT Number: 2023-506777-36-00

Amendment (f) Electronically Signed and Approved by Lilly on approval date provided below.

Document Number: VV-CLIN-151605

Approved on 30 Apr 2024 GMT

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment e	08-Sep-2023
Amendment d	*30-Aug-2023*
Amendment c	*11-Mar-2021*
Amendment b	*28-Feb-2020*
Amendment a	*10-Oct-2018*
Original Protocol	*10-Jul-2018*

Amendment [f]
This amendment is considered to be nonsubstantial.

Overall rationale for the Amendment f:
The rationale for this amendment is to enable additional flexibility on visits, safety and efficacy assessments, and dispensing during the continued access period.

Section # and Name	Description of Change	Brief Rationale
2. Schedule of Activities (Table JPCM 1 Baseline, Treatment, and Post-Treatment Schedule of Activities)	In Chemistry row, the instructions text is updated to reflect that the Section 7.7.2.3 was changed to Section 7.4.1.2	Correction
2. Schedule of Activities (Table JPCM 2 Continued-Access Schedule of Activities)	Updated the continued-access schedule of activities table	Additional flexibility on visits, safety and efficacy assessments, and dispensing during the continued access period
3.1.5 Rationale for Amendment (e)	Added rationale for amendment (e)	Addition

Table of Contents

Section **Page**

List of Tables

List of Figures

Figure **Page**

List of Appendices

Appendix **Page**

1. Synopsis

Protocol Title:

CYCLONE 2: A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate Plus Prednisone with or without Abemaciclib in Patients with Metastatic Castration-Resistant Prostate Cancer

Regulatory Agency Identifier Number(s):

EudraCT Number: 2016-004276-21
EU CT Number: 2023-506777-36-00

Summary:

Prostate cancer is the second most common cancer and the fifth most leading cause of death among men worldwide, with almost 70% of the cases occurring in more developed regions (SEER 2017).

Metastatic castration-resistant prostate cancer (mCRPC) emerges following androgen-deprivation therapy and is the most lethal phenotype of the disease. CCI [redacted]

This Phase 2/3 study will be conducted in up to 3 parts and is designed to determine the recommended Phase 2 dose and assess the safety and efficacy of abemaciclib in combination with abiraterone acetate plus prednisone for the first-line treatment of patients with mCRPC.

Objectives and Endpoints:

Part 1

Primary objective:

- Determine the recommended Phase 2 dose (RP2D) of abemaciclib in combination with abiraterone acetate and prednisone

Parts 1, 2, and 3

Primary objective:

- Radiographic progression-free survival (rPFS)

Secondary objectives:

- Safety and tolerability of the combination of abemaciclib and abiraterone acetate plus prednisone

Objective response rate and duration of response
Overall survival
(If Part 3 is opened) rPFS by blinded, independent, central review (BICR)
Time to symptomatic progression
Time to prostate-specific antigen (PSA) progression
Time to worst pain progression
Pharmacokinetics (PK) of abemaciclib and abiraterone acetate when administered in combination

Overall Design:

This Phase 2/3, multicenter, multinational, randomized, double-blind, placebo-controlled study is designed to assess the safety and efficacy of abemaciclib when given in combination with abiraterone acetate plus prednisone as first-line therapy for patients with mCRPC.

Patients who meet all of the inclusion criteria and none of the exclusion criteria will be centrally randomized to the abemaciclib or placebo group according to the following stratification factors:

Radiographic progression* at study entry (yes/no)
Measurable disease** (yes/no)
Prior docetaxel for metastatic hormone-sensitive prostate cancer (mHSPC) (yes/no)

* Per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1) for soft tissue and/or per Prostate Cancer Working Group 3 (PCWG3) for bone.

** Per RECIST 1.1.

These stratification factors were chosen because they represent important prognostic factors and/or an imbalance may bias the results.

The study will be conducted in up to 3 parts. Part 1 is a double-blind placebo-controlled safety lead-in portion that will randomize approximately 30 patients in a 2:2:1:1 ratio to explore 2 doses of abemaciclib (150 mg and 200 mg, twice daily or matching placebo) when given in combination with abiraterone acetate 1000 mg once daily plus prednisone 5 mg twice daily. Part 1 is designed to determine the RP2D of abemaciclib.

Part 2 is a double-blind placebo-controlled portion that will randomize approximately 150 patients in a 1:1 ratio between abiraterone acetate 1000 mg once daily plus prednisone 5 mg twice daily and abemaciclib given at the RP2D or matching placebo.

Part 3 may be opened if the prespecified expansion criteria in an adaptive interim analysis are met and will randomize approximately 170 additional patients.

Study Population:

This study will enroll patients with prostate cancer that has spread to other parts of the body and no longer responds to treatments to lower testosterone, a condition referred to as mCRPC.

Eligible participants have progressive disease by PSA and/or imaging during continuous androgen-deprivation therapy (ADT)/post orchiectomy, adequate organ function, and an Eastern

Cooperative Oncology Group performance status of 0 or 1. Prior docetaxel for mHSPC is permitted. Prior treatments with abemaciclib or other CDK4 and 6 inhibitors, abiraterone, or other novel hormonal agents are not allowed. Medical conditions, such as clinically significant heart disease, active or chronic liver disease, and moderate/severe hepatic impairment (Child-Pugh Class B and C), may preclude participation in the study.

Patients who have not undergone bilateral orchiectomy are required to continue background ADT with an luteinizing hormone-releasing hormone agonist/antagonist throughout the study.

The complete list of eligibility criteria is provided in the Section 6 of this protocol.

Number of Patients:
Up to approximately 350 patients with mCRPC will be enrolled.

Planned enrollment for each study part is as follows:

Part 1: approximately 30 patients

Part 2: approximately 150 patients

Part 3: approximately 170 patients

Treatment Arms and Duration:

Patients will have a screening period of up to 28 days prior to randomization. The first dose of study treatment (that is, abiraterone plus prednisone and abemaciclib/placebo) should be initiated no later than 7 days following randomization. Patients will be monitored for safety throughout the study as per the schedule of activities. Study treatment should be continued until radiographic and/or symptomatic progression or until other discontinuation criteria are met (see Section 8). Treatment decisions should not be based on PSA alone; study treatment should be continued in patients who have increasing PSA values in the absence of radiographic or symptomatic progression.

Patients who discontinue the study will not be replaced. Patients will have a safety follow-up visit approximately 30 days after the decision to stop treatment or prior to initiation of a new therapy, whichever occurs first. All patients will be followed for survival.

Dose, administration, and schedule:

Study treatment is defined as blinded study drug (abemaciclib or placebo) and/or abiraterone acetate plus prednisone. Abemaciclib, abiraterone acetate, and prednisone are administered orally on Days 1 through 28 of a 28-day cycle.

Where prednisone is not commercially available, prednisolone may be substituted.

Part 1:

Experimental Arm A1: Abemaciclib 150 mg (3 tablets/capsules) orally twice daily
Experimental Arm A2: Abemaciclib 200 mg (4 tablets/capsules) orally twice daily
Control Arm B1: Placebo (3 tablets/capsules) orally twice daily

- Control Arm B2: Placebo (4 tablets/capsules) orally twice daily
- All arms: Abiraterone acetate 1000 mg orally once daily plus 5 mg prednisone orally twice daily

Approximately CCI [redacted] patient has entered treatment, an internal assessment committee (AC), composed of Lilly members not involved in the day-to-day study conduct, will review safety and available PK data and determine the RP2D of abemaciclib. During the RP2D evaluation period, patients may still enroll in Part 1. Once the RP2D has been selected, patients enrolled in Part 1 will switch to the selected RP2D (abemaciclib or matching placebo) to continue the study. In the situation where blinded study treatment has been dose reduced below the selected RP2D, dose escalation to RP2D will not be implemented and dose-reduced patients will continue study at the same lower dose level. Subsequent patients will then start to enroll in Part 2 and will be randomized to receive abemaciclib at RP2D or matching placebo.

Part 2 and Part 3:

- Experimental Arm A: Abemaciclib at RP2D orally twice daily
- Control Arm B: Placebo (matching number of tablets/capsules) orally twice daily
- Arms A and B: Abiraterone acetate 1000 mg orally once daily plus 5 mg prednisone orally twice daily

An independent data monitoring committee (DMC) composed of members external to Lilly will perform a futility analysis after approximately CCI [redacted] radiographic progression-free survival (rPFS) events and will perform up to 2 adaptive interim analyses, CCI [redacted]. Should the prespecified adaptive expansion criteria be met at either interim analysis, enrollment to Part 3 will open.

Short-term follow-up (post discontinuation): Patients will be followed 30 days after study treatment discontinuation.

Long-term follow-up: After the short-term follow-up visit, ALL patients will enter the long-term follow-up period. Patients will be followed for survival and initiation of subsequent anticancer therapies every 3 months. In addition, patients discontinuing treatment prior to documented radiographic progression will continue to have scheduled disease assessments until documented radiographic progression and will be followed for the development of symptomatic progression. Patients discontinuing treatment due to documented radiographic progression will be followed for the development of symptomatic progression.

Ethical Considerations of Benefit/Risk:
The potential risks of abemaciclib in combination with standard of care abiraterone plus prednisone are justified in consideration of the measures to minimize risks and the anticipated benefit of improved response to therapy, as measured by radiographic progression-free survival in participants with mCRPC. A favorable benefit/risk balance is anticipated for the studied combination.

Data Monitoring Committee: Yes, an independent DMC has been commissioned for this study.

2. Schedule of Activities

Table JPCM.1. Baseline, Treatment, and Post-Treatment Schedule of Activities

	Study Period							
	Baseline (Days Prior to Randomization)		On Treatment Cycle = 28 days (4 weeks)			Post-Treatment Follow-up		Instructions
Activities and Forms to be Completed			**Day 1 of Every Cycle (±3 Days)**	**Day 15 of Cycle 1 and Cycle 2 (±3 Days)**	**Day 15 of Cycle 3 (±3 Days)**	**Short-Term Follow-Up[a] Visit 801 (±3 Days)**	**Long-Term Follow-Up Visit 802-8XX (Every 90±7 Days)**	Procedures and disease assessments (including tumor imaging) should be performed according to the calendar days, regardless of treatment delays.
Baseline Documentation								
Informed Consent	X							Written informed consent must be obtained within 28 days prior to randomization AND prior to conducting any protocol-specific tests/procedures.
Inclusion/Exclusion Evaluation	X							
Medical History Preexisting Conditions	X							Including assessment of preexisting conditions, historical illnesses that resolved, and habits (such as tobacco and alcohol use).
Prior and Concomitant Medication Review	X		X			X		Collect throughout the study; includes information on over-the-counter and prescription analgesics use.
Physical Examination		X	X	X		X		Including height (only at screening), weight, and vital signs (temperature, blood pressure, pulse rate, respiration rate). Perform prior to administering study drug(s).
ECOG Performance Status		X	X			X		Does not need to be repeated on Cycle 1 Day 1 if assessed at baseline ≤3 days prior to treatment initiation.

	Study Period							
	Baseline (Days Prior to Randomization)		On Treatment Cycle = 28 days (4 weeks)			Post-Treatment Follow-up		Instructions
Activities and Forms to be Completed			**Day 1 of Every Cycle (±3 Days)**	**Day 15 of Cycle 1 and Cycle 2 (±3 Days)**	**Day 15 of Cycle 3 (±3 Days)**	**Short-Term Follow-Up[a] Visit 801 (±3 Days)**	**Long-Term Follow-Up Visit 802-8XX (Every 90±7 Days)**	Procedures and disease assessments (including tumor imaging) should be performed according to the calendar days, regardless of treatment delays.
Laboratory Assessments								
Hematology		X	X	X		X		See Appendix 2. Perform ≤3 days prior to administration of study treatment. Does not need to be repeated on Cycle 1 Day 1 if assessed at baseline ≤3 days prior to treatment initiation. Repeat if clinically indicated.
Chemistry		X	X	X	X	X		Includes liver function. See Appendix 2. Perform ≤3 days prior to administration of study treatment. Does not need to be repeated on Cycle 1 Day 1 if assessed at baseline ≤3 days prior to treatment initiation. Repeat if clinically indicated and refer to Section 7.4.1.2 for more frequent hepatic monitoring.
Coagulation		X				X		See Appendix 2. Repeat if clinically indicated.
Urinalysis		X				X		See Appendix 2. Perform ≤3 days prior to administration of study treatment. Does not need to be repeated on Cycle 1 Day 1 if assessed at baseline ≤3 days prior to treatment initiation. Repeat if clinically indicated.
PSA		X	X			X		See Appendix 2. Perform ≤3 days prior to administration of study treatment. Repeat if clinically indicated.
Testosterone		X	X			X		See Appendix 2. Perform ≤3 days prior to administration of study treatment. Repeat if clinically indicated.
Other Clinical Assessments								

	Study Period							
	Baseline (Days Prior to Randomization)		**On Treatment Cycle = 28 days (4 weeks)**			**Post-Treatment Follow-up**		**Instructions**
Activities and Forms to be Completed			**Day 1 of Every Cycle (±3 Days)**	**Day 15 of Cycle 1 and Cycle 2 (±3 Days)**	**Day 15 of Cycle 3 (±3 Days)**	**Short-Term Follow-Up[a] Visit 801 (±3 Days)**	**Long-Term Follow-Up Visit 802-8XX (Every 90±7 Days)**	Procedures and disease assessments (including tumor imaging) should be performed according to the calendar days, regardless of treatment delays.
12-Lead ECG		X	Every 8 weeks for the first 24 weeks, every 12 weeks thereafter (Day 1 of Cycles 3, 5, 7, 10, 13, 16, …)			X		Single ECG performed locally. Hypokalemia should be corrected (and normalization confirmed) prior to ECG collection. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Repeat if clinically indicated.
MUGA Scan or Cardiac ECHO	X							Repeat if clinically indicated.
Adverse Event Assessment			Continuous from time of Informed Consent Form signature until 30 days after last study drug dose.				X	Grading via CTCAE version 5.0 (NCI 2017). After V801, only SAEs that are related to study regimen or protocol procedure will be collected. All drug- or procedure-related AEs and SAEs should be followed until they resolve, are no longer considered to be drug- or procedure-related, become stable or return to baseline, the patient starts a new therapy, the patient dies, or the patient becomes lost to follow-up. Frequency of evaluation is left to the judgment of the investigator.
Study Drug Compliance Assessment			X					
Post-Discontinuation Anti-Cancer Therapies						X	X	

	Study Period							
	Baseline (Days Prior to Randomization)		On Treatment Cycle = 28 days (4 weeks)			Post-Treatment Follow-up		Instructions
Activities and Forms to be Completed			**Day 1 of Every Cycle (±3 Days)**	**Day 15 of Cycle 1 and Cycle 2 (±3 Days)**	**Day 15 of Cycle 3 (±3 Days)**	**Short-Term Follow-Up[a] Visit 801 (±3 Days)**	**Long-Term Follow-Up Visit 802-8XX (Every 90±7 Days)**	Procedures and disease assessments (including tumor imaging) should be performed according to the calendar days, regardless of treatment delays.
Survival Assessment						X	X	Although preferable to collect during a clinic visit, survival information may be collected by contacting the patient or family directly (e.g., via telephone) if no procedures are required. This should be collected at minimum every 90 (±14) days if no other procedures are performed.
Tumor Assessment								
CT or MRI Scan of Chest, Abdomen, and Pelvis	X		Every 8 weeks for the first 24 weeks, every 12 weeks thereafter, independent of treatment delays (e.g. Day 1 of Cycles 3, 5, 7, 10, 13, 16, …), and within 14 days of symptomatic progression if no radiographic progression yet.			X	X	Within 7 days prior to the scheduled calendar day (except in screening period). Unscheduled assessments if signs of disease progression are observed. Radiographic disease assessment per RECIST 1.1 for soft tissue and radionuclide bone scan using PCWG3 criteria for bone, assessed by the investigator/local radiologist. Patients discontinuing treatment prior to documented radiographic progression will continue to have scheduled disease assessments (i.e. per the 'on treatment' period) until documented radiographic progression and will be followed for the development of symptomatic progression. Patients discontinuing treatment due to documented radiographic progression will be followed for the development of symptomatic progression.
Radionuclide Bone Scan	X					X	X	

	Study Period							
	Baseline (Days Prior to Randomization)		**On Treatment Cycle = 28 days (4 weeks)**			**Post-Treatment Follow-up**		**Instructions**
Activities and Forms to be Completed			**Day 1 of Every Cycle (±3 Days)**	**Day 15 of Cycle 1 and Cycle 2 (±3 Days)**	**Day 15 of Cycle 3 (±3 Days)**	**Short-Term Follow-Up[a] Visit 801 (±3 Days)**	**Long-Term Follow-Up Visit 802-8XX (Every 90±7 Days)**	Procedures and disease assessments (including tumor imaging) should be performed according to the calendar days, regardless of treatment delays.
Brain MRI/CT	X							Only required at screening for patients with evidence of neurological changes 14 days prior to receiving study drug to rule out CNS metastases. Unscheduled assessments if signs of CNS disease progression are observed.
Symptomatic progression			X			X	X	Assess: - Symptomatic Skeletal Event, defined as symptomatic fracture, surgery or radiation to bone, or spinal cord compression. - Pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy. - Development of clinically significant symptoms due to locoregional tumor progression requiring surgical intervention or radiation therapy.
Biomarker Assessment								
Blood Sample: Genetics	See Appendix 4.							
Tumor Biopsy								
PK/PD Sampling								
Pharmacodynamics	See Appendix 4.							

	Study Period							
	Baseline (Days Prior to Randomization)		On Treatment Cycle = 28 days (4 weeks)			Post-Treatment Follow-up		Instructions
Activities and Forms to be Completed	**≤28**	**≤14**	**Day 1 of Every Cycle (±3 Days)**	**Day 15 of Cycle 1 and Cycle 2 (±3 Days)**	**Day 15 of Cycle 3 (±3 Days)**	**Short-Term Follow-Up[a] Visit 801 (±3 Days)**	**Long-Term Follow-Up Visit 802-8XX (Every 90±7 Days)**	Procedures and disease assessments (including tumor imaging) should be performed according to the calendar days, regardless of treatment delays.
Pharmacokinetics								
Patient Reported Outcomes								
Worst Pain NRS		X	X			X		The PRO questionnaires must be completed before significant interaction with site personnel and administered in the following order: Worst Pain NRS first, [redacted]
[redacted]		X	X			X		
[redacted]		X	X			X		
Study Treatment								
Abemaciclib/ Placebo			Take prescribed dose BID on Days 1 through 28 of a 28-day cycle.					
Abiraterone Acetate			Take prescribed dose QD on Days 1 through 28 of a 28-day cycle.					
Prednisone			Take prescribed dose BID on Days 1 through 28 of a 28-day cycle.					Where prednisone is not commercially available, prednisolone may be substituted.

Abbreviations: AE = adverse event; BID = twice daily; CNS = central nervous system; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2017); ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group (Oken et al. 1982); CCI [redacted] MUGA = multigated acquisition scan; NRS = numeric rating scale; PCWG3 = Prostate Cancer Working Group 3; PRO = patient-reported outcome; PSA = prostate-specific antigen; QD = once daily; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1 (Eisenhauer et al. 2009); wk = week.

A Short-term follow-up begins when the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days. In all cases, no follow-up procedures will be performed for a patient who withdraws informed consent unless he has explicitly provided permission and consent.

Table JPCM.2. Continued-Access Schedule of Activities

Visit	Study Treatment 501-5XX	Follow-Up[a] 901	Instructions
Procedures			Frequency of visits (in clinic or remote), AE assessments and follow-up, efficacy assessments, and dispensing (for up to 3 cycles) are at the investigator's discretion based on the standard of care and local regulations.
Adverse Events Collection	X	X	Grading via CTCAE, Version 5.0. After V901, only SAEs that are related to study regimen or protocol procedure will be collected. All drug- or procedure-related AEs and SAEs should be followed until they resolve, are no longer considered to be drug- or procedure-related, become stable or return to baseline, the patient starts a new therapy, the patient dies, or the patient becomes lost to follow-up.
Administer Abemaciclib	X		Take prescribed dose BID on Days 1 through 28 of a 28-day cycle.
Administer Abiraterone Acetate	X		Take prescribed dose QD on Days 1 through 28 of a 28-day cycle.
Administer Prednisone	X		Take prescribed dose BID on Days 1 through 28 of a 28-day cycle.

Abbreviations: AE = adverse event; BID = twice daily; CTCAE = Common Terminology Criteria for Adverse Events (NCI 2017); QD = once daily; SAE = serious adverse event.

[a] Continued-access follow-up begins when the patient and the investigator agree that the patient will no longer continue treatment in the continued-access period and lasts approximately 30 days. In all cases, no follow-up procedures will be performed for a patient who withdraws informed consent unless he has explicitly provided permission and consent.

3. Introduction

3.1. Study Rationale

CCI

[redacted]

Study I3Y-MC-JPCM (JPCM) is a Phase 2/3, multicenter, multinational, randomized, double-blind, placebo-controlled study with a lead-in safety evaluation that is designed to determine the safety and efficacy of abemaciclib when combined with abiraterone acetate plus prednisone (hereinafter implies prednisone or prednisolone) for the first-line treatment of patients with metastatic castration-resistant prostate cancer (mCRPC).

Abiraterone acetate was selected over other approved drugs for this study in combination with abemaciclib because:

- abiraterone acetate plus prednisone is commonly used as first-line treatment for mCRPC throughout the world
- abiraterone acetate and abemaciclib have toxicities that are only partially overlapping
- the combination of abiraterone acetate and abemaciclib is not anticipated to result in drug-drug interaction.

3.1.1. Rationale for Amendment a

Protocol Amendment (a) for Study JPCM protocol was amended to allow the use of prednisolone where prednisone is not commercially available, to adjust wording on inadvertently enrolled patients based on regulator's feedback, and to adjust the list for strong and moderate inducers of CYP3A, strong inhibitors of CYP3A, or substrates of CYP2D6s, or transporters with narrow therapeutic range.

In addition, minor editorial changes were made throughout the protocol to improve clarity and practicability of the protocol, secure alignment with the intended study design, and update information available for study drugs.

3.1.2. Rationale for Amendment b

Protocol Amendment (b) for Study JPCM protocol was amended to add a DMC, update the dose modification guidance and the safety language for ILD/pneumonitis, (these updates are in alignment with changes made in the development core safety information of the Investigator's Brochure), implement collection and storage of radiographic images, and update special hepatic data collection guidance to further improve a comprehensive evaluation of patients with treatment emergent abnormal liver tests.

In addition, minor editorial changes have been made throughout the protocol to improve clarity and practicability of the protocol, secure alignment with the intended study design, and update information available for study drugs.

3.1.3. Rationale for Amendment c

Protocol Amendment (c) for Study JPCM protocol was amended to implement an adaptive Phase 2/3 study design by adding Part 3 that will be triggered based on prespecified expansion criteria. If triggered, Part 3 will randomize approximately 170 additional patients. The statistical analysis plan was updated accordingly, including specifying an overall 1-sided type I error rate of 0.025.

Radiographic Progression Free survival is considered to be an appropriate regulatory endpoint in the first line mCRPC setting. Time to prostate-specific antigen (PSA) progression is not considered an appropriately validated surrogate efficacy endpoint and was therefore removed as a co-primary endpoint and changed to a secondary endpoint.

Additionally, rPFS by BICR was added as a secondary endpoint. Time to worst pain progression was added as a secondary endpoint.

CCI [redacted]

Baseline tumor biopsy will be optional in Part 3.

Added and updated safety monitoring guidance on abiraterone acetate related adverse reactions in alignment with prescribing information revised 10/2020. Added and updated safety monitoring guidance on abemaciclib related adverse reactions in alignment with changes made in the development core safety information of the Investigator's Brochure (IB) revised 12/2020.

To ensure appropriate safety monitoring of study participants, maintain data integrity, and minimize disruptions to the conduct of the study, provisions for changes in study conduct during exceptional circumstances (such as pandemics or natural disasters) were added in Appendix 10.

In addition, minor editorial changes have been made throughout the protocol.

3.1.4. Rationale for Amendment d

Protocol Amendment (d) for Study JPCM protocol was amended to comply with the new European Union Clinical Trial Regulation (EU-CTR). Moreover, updated strong and moderate

inducers of CYP3A4, strong inhibitors of CYP3A4, substrates of CYP2D6 with narrow therapeutic range, and transporter substrates with narrow therapeutic range.

In addition, minor editorial changes have been made throughout the protocol.

3.1.5. Rationale for Amendment e

Protocol Amendment (e) for Study JPCM protocol was amended to correct the EudraCT Number.

3.2. Background

3.2.1. Metastatic Castration-Resistant Prostate Cancer

Prostate cancer is a leading cause of mortality and morbidity globally, with more than 1 million cases diagnosed and more than 300,000 deaths annually. Prostate cancer is the second most common diagnosed malignancy, the fifth leading cause of cancer mortality in men, and represents a substantial public health burden. In 2014, there were an estimated 3 million men living with PCa in the United States (SEER 2017).

Advanced or metastatic PCa is an androgen-dependent disease and PCa cells are primarily dependent on AR activity for proliferation and survival. The key element in the control of prostate tumor growth is androgen-deprivation therapy (ADT), which consists of initiating a luteinizing hormone-releasing hormone (LHRH) agonist/antagonist (medical castration) or, less commonly, bilateral orchiectomy (surgical castration) with or without concurrent anti-androgens (Lonergan and Tindall 2011).

Based on the recent findings from the CHAARTED (NCT00309985), STAMPEDE (NCT00268476), and LATITUDE (NCT01715285) trials, all showing significant improvement in overall survival (OS), a combination approach of docetaxel, or abiraterone acetate plus prednisone, with ADT is now also considered a treatment option for men with high-risk forms of metastatic hormone-sensitive prostate cancer (mHSPC; Sweeney et al. 2015; James et al. 2016, 2017; Fizazi et al. 2017).

Although most patients with advanced metastatic disease initially respond to conventional ADT with or without docetaxel or abiraterone acetate, inevitably and despite effective suppression of serum testosterone, disease progresses to mCRPC. The treatment of mCRPC has changed significantly over the last years as a result of the introduction of multiple new systemic therapies that have had a positive impact on treatment outcomes, including OS. Therapies that have been approved for use in mCRPC include novel anti-hormonal agents (abiraterone acetate and enzalutamide), the α-emitting radium isotope radium-223 (bone metastases and no known visceral metastatic disease), the autologous cellular immunotherapy sipuleucel-T (asymptomatic or minimally symptomatic disease), and cytotoxic chemotherapies (mitoxantrone, docetaxel, and cabazitaxel; Sartor and de Bono 2018).

Despite the recent advances in the therapy for mCRPC, median OS remains approximately 18 to 36 months. In addition, the optimal treatment sequencing pathway remains unknown. In practice,

sequencing decisions are made in the light of the distribution, extent, and pace of disease, co-morbidities, patient preferences, and drug availability (Pal et al. 2018). As treating metastatic PCa is becoming increasingly complex, the current focus must be to continue improving outcomes for patients with aggressive disease and explore innovative combinations capable of controlling and delaying tumor progression.

This Phase 2/3, randomized, double-blind, placebo-controlled study will evaluate the clinical benefit of adding abemaciclib to abiraterone acetate plus prednisone in patients with mCRPC.

3.2.2. Abemaciclib

During the cell cycle, the G1 restriction point controls entry into S phase and is essential for maintaining control of cell division (Sherr 1996; Ortega et al. 2002). The CDKs 4 and 6 participate in a complex with D-type cyclins to initiate the transition through the G1 restriction point by phosphorylating and inactivating the retinoblastoma (Rb) tumor-suppressor protein. Alterations in this pathway occur frequently in human cancers and involve (1) loss of CDK inhibitors by mutation or epigenetic silencing, (2) mutation/overexpression of either CDK4 and CDK6 or cyclin D, or (3) inactivation of Rb. These alterations render cells less dependent on mitogenic signaling for proliferation. With the possible exception of those tumors with complete inactivation of Rb, which functions downstream of the CDK4 and CDK6–cyclin D complex, all of these cancers are potentially sensitive to pharmacologic inhibition of CDK4 and CDK6. From a therapeutic standpoint, the goal of inhibiting CDK4 and CDK6 with a small-molecule inhibitor is to prevent cell cycle progression through the G1 restriction point, thus arresting tumor growth.

Abemaciclib is an oral, selective, and potent adenosine triphosphate (ATP)-competitive inhibitor of CDK4 and CDK6. In cancer cells, continuous exposure to abemaciclib inhibited Rb phosphorylation and blocked progression from G1 into S phase of the cell cycle, resulting in senescence and apoptosis. Abemaciclib showed antitumor activity in multiple preclinical pharmacology models and an acceptable toxicity profile in nonclinical species. Abemaciclib has been shown to significantly inhibit tumor growth in multiple murine xenograft models for human cancer.

The clinical activity of abemaciclib has been extensively studied in hormone receptor–positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) metastatic breast cancer (MBC). The demonstration of a robust single-agent activity of abemaciclib was shown in both the JPBA Phase 1b study with a response rate of 33.3% across dose levels and the MONARCH 1 Phase 2 study with a response rate of 19.7% (at 200-mg dose twice daily), in heavily pretreated patients with refractory HR+/HER2− MBC (Patnaik et al. 2016; Dickler et al. 2017). Importantly, the safety profile of abemaciclib allowed for dosing on a continuous schedule.

Two large, randomized, double-blind, placebo-controlled Phase 3 clinical trials have demonstrated the effectiveness of abemaciclib when combined with endocrine therapy (ET) for HR+/HER2− MBC.

In the MONARCH 2 study (NCT02107703), abemaciclib was evaluated in combination with fulvestrant in HR+/HER2− MBC patients receiving prior ET. Abemaciclib plus fulvestrant significantly extended progression-free survival (PFS) versus fulvestrant alone (median, 16.4 vs 9.3 months; hazard ratio, 0.553; 95% confidence interval [CI], 0.449 to 0.681; p<.001). In patients with measurable disease, abemaciclib plus fulvestrant achieved an objective response rate (ORR) of 48.1% (95% CI, 42.6% to 53.6%) compared with 21.3% (95% CI, 15.1% to 27.6%) in the control arm (Sledge et al. 2017).

The MONARCH 3 study (NCT 02246621) evaluated abemaciclib in combination with nonsteroidal aromatase inhibitor (NSAI) letrozole or anastrozole in HR+/HER2− MBC patients who had not received prior systemic therapy for metastatic disease. Median PFS was significantly prolonged in the abemaciclib arm (hazard ratio, 0.54; 95% CI, 0.418 to 0.698; p<.000121; median PFS: 28.2 months in the abemaciclib arm, 14.8 months in the placebo arm). In patients with measurable disease, the confirmed ORR was 55.4% in the abemaciclib arm and 40.2% in the placebo arm (Goetz et al. 2018).

The most common adverse reactions (incidence ≥20%) were diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, alopecia, and thrombocytopenia.

Abemaciclib (VERZENIO) is currently approved by major global regulatory authorities for the treatment of HR+, HER2− advanced or MBC:

- in combination with an aromatase inhibitor for postmenopausal women as initial endocrine-based therapy;
- in combination with fulvestrant for women with disease progression following ET; and as a single agent for adult patients with disease progression following ET and prior chemotherapy in the metastatic setting (approved in the US).

Details on the safety profile of monotherapy abemaciclib as well in combination with other agents is available in the IB.

3.2.3. Abiraterone Acetate

Abiraterone, the active metabolite of abiraterone acetate, irreversibly inhibits cytochrome P450 (CYP)17 (17α-hydroxylase/C17, 20-lyase), an essential enzyme in androgen biosynthesis that is expressed in testicular, adrenal and prostatic tumor tissues. Abiraterone acetate is approved in combination with prednisone for the treatment of patients with high risk mHSPC and mCRPC (abiraterone acetate PI, 2018).

For more information, refer to abiraterone acetate prescribing information.

3.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of abemaciclib is to be found in the IB. Information on AEs expected to be related to abemaciclib may be found in Section 6 (Summary of Data, Guidance for the Investigator, and Developmental Core Safety Information [DCSI]) of

the IB. Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the study may be found in Section 6 (Effects in Humans) of the IB.

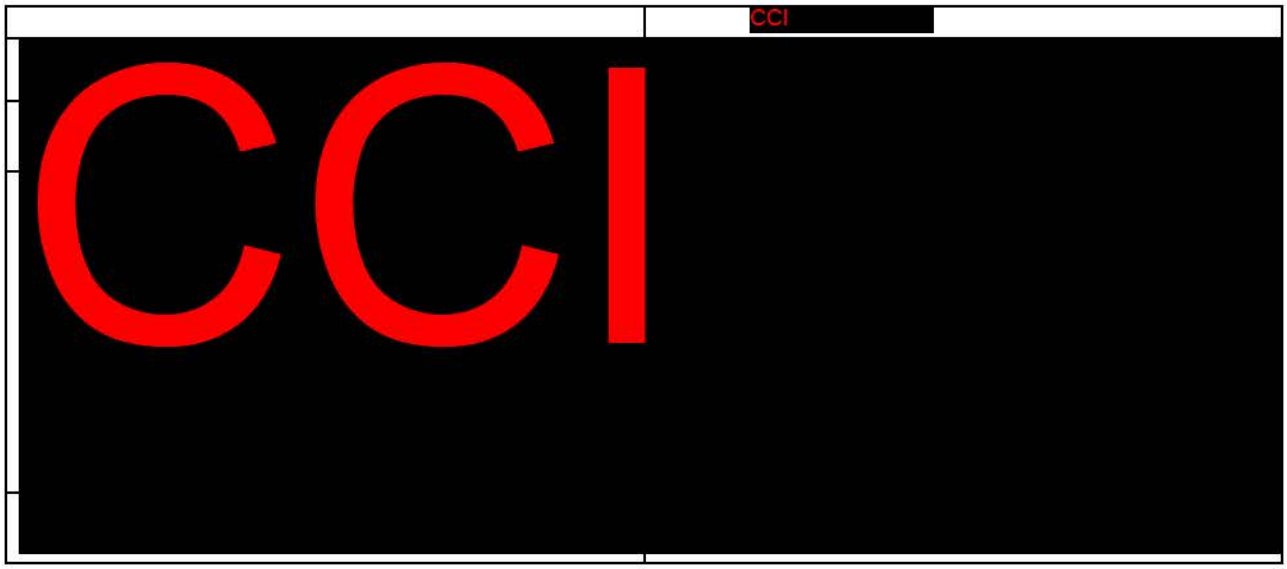
More detailed information about the known and expected benefits and risks of abiraterone acetate or prednisone may be found in the following: Patient Information Leaflet, Package Insert, or Summary of Product Characteristics.

4. Objectives and Endpoints

Table JPCM.3 shows the objectives and endpoints of the study.

Table JPCM.3. Objectives and Endpoints

Objectives Part 1	Endpoints
Primary	
To determine the RP2D of abemaciclib that may be safely administered to patients with mCRPC in combination with abiraterone acetate and prednisone.	Safety (including, but not limited to): TEAEs, SAEs, deaths, and clinical laboratory abnormalities.
Objectives Part 1, 2, and 3: Combined Populations	**Endpoints**
Primary	
To compare the rPFS of patients receiving abiraterone acetate plus prednisone with or without abemaciclib.	rPFS
Secondary	
To characterize further the safety profile of the combination of abemaciclib and abiraterone acetate plus prednisone.	The safety endpoints evaluated will include, but are not limited to, the following: AEs, TEAEs, SAEs, clinical laboratory tests, ECGs, vital signs, and physical examinations.
To compare the efficacy in patients receiving abiraterone acetate plus prednisone with or without abemaciclib.	• ORR and DoR • OS • Time to PSA progression • (If Part 3 is opened) rPFS by blinded, independent, central review (BICR)
Time to symptomatic progression.	Time from randomization to any of the following (whichever occurs earlier): - Symptomatic Skeletal Event: symptomatic fracture, surgery or radiation to bone, or spinal cord compression - Pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy - Development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy.
To characterize the PK of abemaciclib and abiraterone acetate when administered in combination.	Abemaciclib and abiraterone acetate steady-state plasma concentrations.
To assess patient-reported pain.	Time to worst pain progression, using the Worst Pain NRS score and the WHO-AL.
Exploratory	
CCI [redacted]	• CCI [redacted]



Abbreviations: AEs = adverse events; DoR = duration of response; ECG = electrocardiogram; CCI NRS = numerical rating scale; ORR = objective response rate; OS = overall survival; PK = pharmacokinetics; PR = partial response; PSA = prostate-specific antigen; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1 (Eisenhauer et al. 2009); RP2D = recommended Phase 2 Dose; rPFS = radiographic progression free survival; SAE = serious adverse event; TEAE = treatment-emergent adverse event; CCI WHO-AL = World Health Organization – Analgesic Ladder.

5. Study Design

5.1. Overall Design

Study JPCM is a Phase 2/3, multicenter, multinational, randomized, double-blind, placebo-controlled study designed to evaluate the clinical benefit of abiraterone acetate plus prednisone with or without abemaciclib in patients with mCRPC. Planned analyses with detailed descriptions are listed below.

Table JPCM.4. Planned Analyses

Analysis	Timing	Details
RP2D Selection	CCI [redacted]	AC review of safety and PK data only to select RP2D (Section 10.3.5.1).
Futility	Approximately CCI rPFS events	Performed by independent DMC to assess if stopping rule for futility has been met (Section 10.3.5.2).
Adaptive Interim 1	Approximately CCI rPFS events	Performed by independent DMC to assess if criteria for opening enrollment to Part 3 have been met (Section 10.3.5.2).
Adaptive Interim 2	Approximately CCI rPFS events	(If applicable) Performed by independent DMC to assess if criteria for opening enrollment to Part 3 have been met (Section 10.3.5.2).
Primary Analysis of rPFS	Approximately CCI rPFS events if Part 3 not opened Approximately CCI rPFS events is Part 3 is opened for enrollment	Final analysis of primary endpoint (Section 10.3.1.1).
Final Analysis of OS	See SAP	See SAP for details.

Abbreviations: AC = assessment committee; DMC = data monitoring committee; OS = overall survival; PK = pharmacokinetics; RP2D = recommended Phase 2 dose; rPFS = radiographic progression-free survival; SAP = statistical analysis plan.

This study will include a lead-in portion (Part 1) to evaluate safety and tolerability, and to determine the recommended Phase 2 dose (RP2D) of abemaciclib in combination with abiraterone acetate plus prednisone.

Part 1 is a double-blind placebo-controlled safety lead-in period that will randomize approximately 30 patients to explore 2 doses of abemaciclib, 150 mg (Arm A1; 3 tablets/capsules twice daily) and 200 mg (Arm A2; 4 tablets/capsules twice daily), in combination with abiraterone acetate 1000 mg once daily plus prednisone 5 mg twice daily. Both Arms A1 and A2 will be placebo-controlled (Arm B1 and B2; patients will receive 3 or 4 placebo tablets/capsules twice daily and abiraterone acetate 1000 mg once daily plus prednisone 5 mg twice daily). Thus, there will be 4 arms in Part 1 and randomization will be based on a 2:2:1:1 ratio.

Approximately CCI [redacted] patient has entered treatment, an internal assessment committee (AC) will review safety and available pharmacokinetic (PK) data and determine the RP2D. The AC will, at a minimum, be composed of Lilly members not involved in the day-to-day study conduct (the medical director, a Global Patient Safety physician, a PK/pharmacodynamics scientist, and a statistician). In the case of unacceptable and/or unmanageable toxicity of the combination, the AC may decide to discontinue the study upon completion of Part 1. During the evaluation period, patients may still enroll in Part 1. Once RP2D has been selected, patients enrolled in Part 1 will switch to the selected RP2D (or matching placebo) to continue the study. In the situation where blinded study treatment has been dose reduced below the selected RP2D, dose escalation to RP2D will not be implemented and dose-reduced patients will continue study at the same lower dose level. Subsequent patients will then start to enroll in Part 2 and will be randomized to receive abemaciclib at RP2D* or matching placebo.

Part 2 will randomize approximately 150 patients in a 1:1 ratio between 2 arms:

- Arm A (experimental arm): Abiraterone acetate 1000 mg once daily plus prednisone 5 mg twice daily and abemaciclib at RP2D* twice daily
- Arm B (control arm): Abiraterone acetate 1000 mg once daily, prednisone 5 mg twice daily, and placebo (matching number of tablets/capsules twice daily).

* CCI [redacted]

After approximately CCI [redacted] rPFS events, an independent DMC will perform a futility analysis. As described in the DMC Charter, the DMC will consist of at least 3 members external to Lilly, none of whom are involved as study investigators, including at least 1 clinician and 1 statistician. After approximately CCI [redacted] rPFS events, the DMC will perform an interim adaptive analysis. If the prespecified adaptive expansion criteria are met, Part 3 will be opened for enrollment. If the expansion criteria are not met, the DMC will perform another interim adaptive analysis after approximately CCI [redacted] rPFS events. If the prespecified adaptive expansion criteria are met, Part 3 will be opened for enrollment. If opened for enrollment, Part 3 will randomize approximately 170 additional patients in a 1:1 ratio. If the expansion criteria are not met in either interim adaptive analysis, Part 3 will not be opened for enrollment, and scientific evaluation will continue until study completion (Section 7.8).

Abemaciclib, matching placebo, and abiraterone acetate plus prednisone will be administered orally.

Patients (enrolled in Part 1, Part 2, or Part 3) will be centrally randomized to the abemaciclib group(s) and the placebo group(s) according to the following stratification factors:

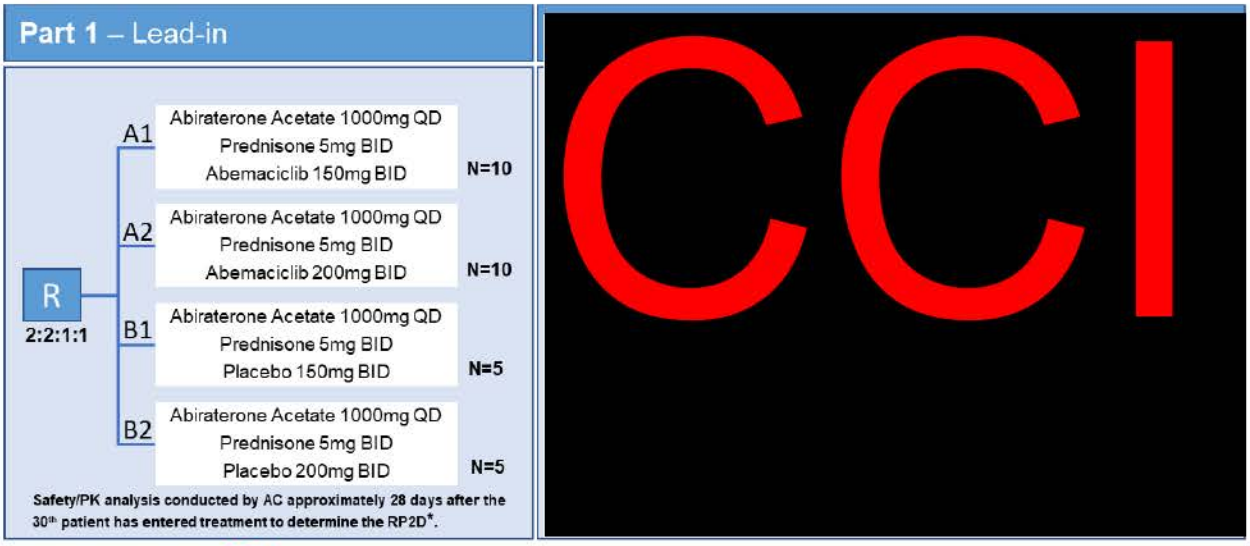
- Radiographic progression* at study entry (yes/no)
- Measurable disease** (yes/no)
- Prior docetaxel for mHSPC (yes/no).

* Per RECIST 1.1 for soft tissue and/or per PCWG3 for bone.

** Per RECIST 1.1.

These stratification factors were chosen because they represent important prognostic factors and/or an imbalance may bias the results. Patients enrolled in Part 1, Part 2, and Part 3 will be combined to form the experimental group (abemaciclib and abiraterone acetate plus prednisone) and control group (placebo and abiraterone acetate plus prednisone); see Section 10.2.

Figure JPCM.1 illustrates the study design.



Note: Part 1: N=30, CCI

Abbreviations: AC = assessment committee; BID = twice daily; mg = milligram; N =number of patients; PK = pharmacokinetic; CCI ; QD = daily; R = Randomization; RP2D = recommended Phase 2 dose.

CCI

Figure JPCM.1. Illustration of study design.

5.2. Number of Patients

Planned enrollment for each study part is as follows:

Part 1: will randomize approximately 30 patients in a 2:2:1:1 ratio

Part 2: will randomize approximately 150 patients in a 1:1 ratio

Part 3: will randomize approximately 170 patients in a 1:1 ratio

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure for the last patient, as shown in the Schedule of Activities, Section 2.

Refer to Figure JPCM.2 for a depiction of study completion, the continued-access period, and end of study.

5.4. Scientific Rationale for Study Design

5.4.1. Study Design and Control Group

Abiraterone acetate 1000 mg once daily in combination with prednisone (or prednisolone) 5 mg twice daily is indicated for the treatment of mCRPC patients, prior to or after docetaxel-based chemotherapy regimen, based on the results of 2 randomized placebo-controlled, multicenter Phase 3 clinical trials: COU-AA-302 and COU-AA-301, respectively (de Bono et al. 2011; Ryan et al. 2013).

In this study, all patients will receive abiraterone acetate 1000 mg once daily plus prednisone (or prednisolone) 5 mg twice daily as per approved posology in this mCRPC population.

The experimental group will receive abemaciclib and the control group will receive matching placebo.

5.4.2. Population

The primary objective is to determine whether abemaciclib in combination with abiraterone acetate plus prednisone improves rPFS. Since optimal sequencing of current mCRPC treatments has not been prospectively/formally established and given that response rates to abiraterone therapy after treatment with enzalutamide (or reverse sequence) are relatively low (15% to 30%; Noonan et al. 2013; Schrader et al. 2014; Smith et al. 2017), the study population will consist of treatment-naïve mCRPC patients. Prior treatment with abiraterone acetate, enzalutamide, apalutamide, darolutamide, radiopharmaceuticals, and sipuleucel-T is not allowed. Prior docetaxel for mHSPC, but not for mCRPC, is permitted.

5.4.3. Radiographic PFS as a Primary Efficacy Endpoint

Metastatic PCa is a heterogeneous disease that progresses through multiple clinical steps with a high prevalence of bone metastases. For mCRPC patients, progression of metastatic bone disease is of paramount clinical importance since it is responsible for the severe morbidity of skeletal-related events such as symptomatic fractures, pain, surgery or palliative radiation to bone, and spinal cord compression. Delaying the emergence or the progression of radiographically detectable distant metastases is a clinically relevant endpoint for the determination of the benefit of the study treatment that is not impacted by posttreatment anticancer therapies. Drug development for PCa has been limited due to the lack of an objective definition for cancer progression and the use of composite time-to-event endpoints that include combinations of radiographic progression, PSA progression, skeletal-related events, development of symptoms, initiation of other anticancer treatment, and death to assess progression-free survival.

Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) designates numerous lesions as nonmeasurable. These include bone metastases without a soft tissue component measuring ≥10 mm (the large majority of bone metastases). Conventional RECIST also lacks provisions to differentiate true progression of bone metastasis from the flare, a paradoxical worsening of the bone scan attributed to bone healing as a result of a favorable antitumor effect.

To ensure consistent and reproducible assessment of rPFS and control for tumor flare, the Prostate Cancer Working Group 2 (PCWG2) definition, later refined by Prostate Cancer Working Group 3 (PCWG3), establishes progression in bone as:

1) the appearance of at least 2 new lesions on the first post-treatment scan, with at least 2 additional lesions on the next scan (2+2 rule), or
2) for radiographic disease progression in bone observed after the first post-treatment scan, at least 2 new lesions (relative to the first post-treatment scan) that are persisting on a confirmatory subsequent scan.

The date of progression is the date of the first post-treatment scan when the first 2 new lesions were documented.

In study COU-AA-302, which randomly assigned chemotherapy-naive patients with mCRPC to receive abiraterone acetate plus prednisone or placebo plus prednisone, rPFS (per RECIST and PCWG2) assessed by independent radiologists and investigators was highly consistent and highly associated with overall survival, providing initial prospective evidence on further developing rPFS as an intermediate endpoint in mCRPC trials. In this study, the consensus guidelines of the RECIST 1.1 for soft tissue and the PCWG3 for bone have been taken into consideration for the determination of rPFS. The rPFS (which also includes death from any cause) will be assessed by the investigator/local radiologist for the primary endpoint, and rPFS by BICR will be evaluated as a secondary endpoint if Part 3 is opened for enrollment.

Overall survival is an important secondary endpoint for this study and is defined as the time from random assignment to the date of death resulting from any cause.

5.5. Justification for Dose

CCI

[redacted]

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet ALL of the following criteria:

[1] Male patients, 18 years of age or older; willing and able to provide written informed consent.

[2] Histologically confirmed adenocarcinoma of the prostate. Well-differentiated neuroendocrine carcinoma, small cell or large cell neuroendocrine carcinoma, sarcomatoid, and carcinoid tumors are excluded.

[3] Metastatic prostate cancer documented by positive bone scan and/or measurable soft tissue metastatic lesions by computed tomography (CT) or magnetic resonance imaging (MRI). If lymph node metastasis is the only evidence of metastasis, it must be ≥1.5 cm in the short axis. Visceral metastasis, including to liver, is allowed.

[4] Serum testosterone level ≤1.73 nmol/L (50 ng/dL) at the screening visit. Patients who have not undergone bilateral orchiectomy are required to continue ADT (LHRH agonists/antagonists) throughout the study.

[5] Progressive disease at study entry demonstrated during continuous ADT/post orchiectomy defined as one or more of the following criteria:

> Sequence of at least 2 rising PSA values at a minimum of 1-week intervals with the last result being at least 1.0 ng/mL if confirmed PSA rise is the only indication of progression. Patients who received an anti-androgen must have PSA progression after withdrawal (≥4 weeks since last flutamide or ≥6 weeks since last bicalutamide or nilutamide).
>
> Radiographic progression per RECIST 1.1 for soft tissue and/or per PCWG3 for bone (i.e., appearance of ≥2 new bone lesions), with or without PSA progression.

[6] Patient must have discontinued all previous treatments for cancer (except ADT and bone loss-prevention treatment), must have recovered from of all acute toxic effects of prior therapy or surgical procedure to Grade ≤1 or baseline (as per Common Terminology Criteria for Adverse Events version 5.0 [CTCAE v 5.0]) prior to randomization, with the exception of alopecia or peripheral neuropathy AND have a washout period from last dose of prior systemic or radiation therapy as follows:

> Patients must discontinue flutamide at least 4 weeks, bicalutamide and nilutamide at least 6 weeks, prior to randomization.
>
> At least 4 weeks must have elapsed from the use of 5-α reductase inhibitors (e.g., dutasteride, finasteride), estrogens, and cyproterone to randomization.

At least 4 weeks must have elapsed from the use of chemotherapy (i.e., docetaxel, for mHSPC) to randomization.

At least 4 weeks must have elapsed from major surgery or radiation therapy prior to randomization.

[7] Mandatory for Part 1 and Part 2; optional for Part 3:

Able and willing to undergo tumor biopsy of at least 1 metastatic site, which should be collected following determination of eligibility and before initiating study treatment.

Biopsy of newly emerged radiographic metastases is desired and preferable to the biopsy of previously existing lesions whenever possible.

Soft-tissue as well as bony metastatic lesions will be considered acceptable. Soft-tissue biopsy is preferred to bone biopsy whenever possible.

Adequate archival metastatic tissue can be used if available in lieu of a new biopsy: if the biopsy was done within 12 weeks prior to randomization and no treatment was initiated from biopsy to study entry.

Optional for Part 1, Part 2, and Part 3:

Biopsy of metastatic tissue at the time of on-study radiographic progression, prior to start of new anti-cancer therapy.

Biopsy of a progressing metastatic lesion is preferred whenever possible.

If patient discontinues study for reasons other than radiographic progression, the biopsy should be considered only if the patient has completed at least 6 cycles of study treatment.

[8] Have adequate organ function, as defined below:

System	**Laboratory Value**
Cardiac	
LVEF	≥50%
Clinical Chemistry	
Serum albumin	≥3 g/dL
Serum potassium	≥3.5 mM
Hematologic	
ANC	1.5×10^9/L
Platelets	100×10^9/L
Hemoglobin	9 g/dL (≥90 g/L) independent of transfusions
Hepatic	
Total bilirubin	1.5×ULN
ALT and AST	2.5×ULN
Renal	
Serum creatinine	1.5×ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ANC = absolute neutrophil count; LVEF = left ventricular ejection fraction; ULN = upper limit of normal.

[9] Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1.

[10] Willing to comply with study procedures. Patients with reproductive potential must agree to use effective contraception and to not donate sperm during the study and for at least 3 months following the last dose of study treatment.

6.2. Exclusion Criteria

Patients will be excluded from the study if they meet **ANY** of the following criteria:

[11] Prior therapy with CYP17 inhibitors (including abiraterone acetate, TAK-700, TOK-001, and ketoconazole).

[12] Prior treatment with abemaciclib or any CDK4 and 6 inhibitors.

[13] Known or suspected contraindications or hypersensitivity to abiraterone acetate, prednisone, or abemaciclib or to any of the excipients.

[14] Prior cytotoxic chemotherapy for metastatic castration resistant prostate cancer (patients treated with docetaxel in the mHSPC are eligible). Prior radiopharmaceuticals for prostate cancer, or prior enzalutamide, apalutamide, darolutamide, or sipuleucel-T. Patients who had prior radiation or surgery to all target lesions.

[15] Are currently enrolled in a clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study. Have participated in any clinical trial for which treatment assignment is still blinded. If patient has participated in a clinical study involving an investigational product, 3 months or 5 half-lives (whichever is shorter) should have passed. If a patient is currently enrolled in a clinical trial involving non-approved use of a device, then agreement with the investigator and the Lilly Clinical Research Physician/Clinical Research Scientist (CRP/CRS) is required to establish eligibility.

[16] Gastrointestinal disorder affecting absorption or inability to swallow large pills.

[17] Have prior malignancies or active concurrent malignancy (with the exception of non-melanomatous skin cancer). Patients with carcinoma in situ of any origin and patients with prior malignancies who are in remission and whose likelihood of recurrence is very low per investigator's judgment are eligible for this study. The Lilly CRP/CRS will approve enrollment of patients with prior malignancies in remission before these patients are enrolled.

[18] The patient has serious preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (e.g., interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea).

[19] The patient has a history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. Atrial fibrillation or other cardiac arrhythmia requiring medical therapy.

[20] Clinically significant heart disease as evidenced by myocardial infarction, arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class II to IV heart failure or cardiac ejection fraction measurement of <50% at baseline.

[21] Patients with clinically active or chronic liver disease, moderate/severe hepatic impairment (Child-Pugh Class B and C), ascites, or bleeding disorders secondary to hepatic dysfunction.

[22] History of adrenal dysfunction.

[23] The patient has active systemic infections (for example, bacterial infection requiring intravenous [IV] antibiotics at time of initiating study treatment, fungal infection, or detectable viral infection requiring systemic therapy) or viral load (such as known human immunodeficiency virus positivity or with known active hepatitis B or C [for example, hepatitis B surface antigen positive]). Screening is not required for enrollment.

[24] Known or suspected central nervous system (CNS) metastatic disease (baseline screening for CNS metastases is not required unless there is presence of signs and/or symptoms of involvement).

[25] Uncontrolled hypertension (systolic blood pressure [BP] ≥160 mmHg or diastolic BP≥95 mmHg). Patients with a history of hypertension are allowed provided BP is controlled by anti-hypertensive treatment.

[26] Life expectancy <6 months.

[27] Patient treated with drugs known to be strong inhibitors or strong or moderate inducers of cytochrome P450 3A4 (CYP3A4) and the treatment cannot be discontinued or switched to a different medication at least 5 half-lives prior to starting study drug.

[28] Have received recent (within 4 weeks prior to randomization) live vaccination. Seasonal flu vaccines that do not contain a live virus are permitted.

[29] Untreated spinal cord compression or evidence of spinal metastases with risk of spinal compression. Structurally unstable bone lesions suggesting impending fracture.

6.3. Lifestyle Restrictions

The following lifestyle restrictions are applicable to all patients on all arms:

While on study, patients should refrain from consuming grapefruit and pomegranate fruits and/or juice, saw palmetto, and other herbal/nonherbal products known to be strong inhibitors of CYP3A, have prostate cancer activity, or affect PSA levels.

Patients must use effective contraception and not donate blood or sperm during the study and for 3 months after the last dose.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened only after discussion with and permission from the Lilly CRP/CRS. Individuals may

be rescreened a maximum of 1 time. The interval between rescreenings should be at least 2 weeks. Each time rescreening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

Repeating of laboratory tests during the 28-day screening period does not constitute rescreening.

7. Treatments

7.1. Treatments Administered

The following treatments will be administered in this study:

Part 1:

- Experimental Arm A1: Abemaciclib 150 mg (3 tablets/capsules) orally twice daily
- Experimental Arm A2: Abemaciclib 200 mg (4 tablets/capsules) orally twice daily
- Control Arm B1: Placebo (3 tablets/capsules) orally twice daily
- Control Arm B2: Placebo (4 tablets/capsules) orally twice daily
- Arms A1, A2, B1, and B2: Abiraterone acetate 1000 mg orally once daily plus 5 mg prednisone orally twice daily.

Part 2 and Part 3:

- Experimental Arm A: Abemaciclib at RP2D* orally twice daily
- Control (Placebo) Arm B: Placebo (matching number of tablets/capsules) orally twice daily
- Arms A and B: Abiraterone acetate 1000 mg orally once daily plus 5 mg prednisone orally twice daily.

CCI [redacted]

Treatment Name [a]	Abemaciclib	Placebo	Abiraterone acetate	Prednisone
Authorized as defined by EU Clinical Trial Regulation	Authorized and not used according to EU authorization	Not authorized	Authorized and not used according to EU authorization	Authorized and used according to EU authorization

[a] Study treatment is defined as any medicinal product(s) or medical device(s) intended to be administered to or used by a study participant according to the study protocol.

Blinded study drug (abemaciclib or placebo) tablets/capsules are 50 mg. Dosing is twice daily. Ideally, doses should be spaced 12 hours apart, with a minimum of 6 hours between doses. Instruct patients to take the doses at approximately the same times every day and to swallow tablets/capsules whole with a glass of water (do not chew, crush, split, dissolve in water, or alter tablets/capsules in any way prior to swallowing). Blinded study drugs may be taken with or without food. If the patient vomits or misses a dose, advice the patient to take the next prescribed dose at the usual time. Instruct patients not to ingest tablets/capsules if broken, cracked, or otherwise not intact. Placebo will be provided as a tablets/capsules formulation and will be matched in size, color, and shape to abemaciclib tablets/capsules to maintain the study blind.

Abiraterone acetate and prednisone should be administered according to the respective prescribing information.

Where prednisone is not commercially available, prednisolone may be substituted.

Patients will continue to receive study treatment until a discontinuation criterion is met (see Section 8). See Section 7.8.1 for information about continued access to study treatment.

Table JPCM.5 shows the treatment regimens.

Table JPCM.5. Treatment Regimens

	Study Drug		Dose	Route	Timing
Part 1 Lead-in	Abemaciclib	Arm A1	150 mg	PO	Twice daily
		Arm A2	200 mg		
	Placebo	Arm B1	3 tablets/capsules	PO	Twice daily
		Arm B2	4 tablets/capsules		
	Abiraterone acetate	Arms A1, A2, B1, and B2	1000 mg	PO	Once daily
	Prednisone	Arms A1, A2, B1, and B2	5 mg	PO	Twice daily
Part 2 and Part 3	Abemaciclib	Arm A	RP2D*	PO	Twice daily
	Placebo	Arm B	RP2D*	PO	Twice daily
	Abiraterone acetate	Arms A and B	1000 mg	PO	Once daily
	Prednisone	Arms A and B	5 mg	PO	Twice daily

Abbreviations: mg = milligram; PO = by mouth; RP2D = recommended Phase 2 dose.

CCI

Investigator Responsibilities

The investigator or his/her designee is responsible for the following:

- following the protocol at all times
- explaining the correct use of the drugs and planned duration of each individual's treatment to the patient/study site personnel/legal representative
- verifying that instructions are followed properly
- maintaining accurate records of study treatment dispensing and collection
- at the end of the study returning all unused medication to Lilly, or its designee, unless Lilly and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law.

7.1.1. Packaging and Labeling

Abemaciclib and matching placebo will be supplied by Lilly or its designee in accordance with current Good Manufacturing Practice. Study treatments and clinical study materials will be labeled as appropriate according to the country's regulatory requirements.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomly assigned to receive abiraterone acetate and prednisone in combination with abemaciclib or placebo.

In Part 1, approximately 30 patients will be randomized in a 2:2:1:1 ratio into Arm A1, Arm A2, Arm B1, or Arm B2. In Part 2, approximately 150 patients will be randomized in a 1:1 ratio into Arm A or Arm B. In Part 3, approximately 170 additional patients will be randomized in a 1:1 ratio into Arm A or Arm B.

Randomization will be stratified by the following factors:

Radiographic progression* at study entry (yes/no)
Measurable disease** (yes/no)
Prior docetaxel for mHSPC (yes/no)

* Per RECIST1.1 for soft tissue and/or per PCWG3 for bone.

** Per RECIST1.1

The interactive Web response system (IWRS) will use randomization stratification factors to assign double-blind study treatment to each patient.

7.2.1. Selection and Timing of Doses

A cycle is defined as an interval of 28 days. Abemaciclib or placebo will be administered orally twice daily at approximately the same times each day on Days 1 through 28 of a 28-day cycle. Ideally, doses should be spaced 12 hours apart, with a minimum of 6 hours between doses. Details on treatment administration for combination therapy are described in the study design; Section 5.1. In the event of a dose suspension due to toxicity immediately prior to the beginning of a cycle, the PK sampling schedule outlined in Appendix 4 may require adjustment and the sponsor should be notified.

A delay or earlier start of a cycle due to holiday, weekend, bad weather, or other unforeseen circumstances will be permitted for a maximum of 7 days and not counted as a protocol deviation. In exceptional cases, such as planned cycle delays (including but not limited to vacation or holidays), additional study treatment may be dispensed after discussion with Lilly CRP/CRS.

A patient may continue to receive study treatment until discontinuation criteria are met (as described in Section 8).

7.3. Blinding

This is a double-blind study.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is completed. Access to unblinded data/documents will be controlled by restricting access to the data/documents in Lilly's data and statistical warehouse. Any changes to this unblinding plan may be described in a protocol amendment, the statistical analysis plan (SAP), and/or a separate unblinding plan document.

Efficacy information will not be shared between sites until the study is completed. Upon study completion (see Section 7.8.1), investigators may unblind patients to study treatment assignment.

Unblinding of the investigator and the patient at the time of documented objective disease progression is permitted to ensure optimal patient management and/or facilitate selection of subsequent treatment. The investigator must consult with the Lilly CRP/CRS prior to unblinding. Unblinding must be performed through the IWRS.

If the investigator or patient becomes unblinded, that patient will be discontinued from study treatment and will undergo post-discontinuation follow-up. Long-term follow up procedures will be followed until death, loss of follow-up, withdrawal of consent, or study completion.

7.3.1. Unblinding at Interim Analyses

See Section 10.3.5 for details on the conduct of interim analyses. The AC will, at a minimum, be composed of Lilly members not involved in the day-to-day study conduct (the medical director, a Global Patient Safety physician, a PK/pharmacodynamics scientist, and a statistician). The AC will conduct only 1 unblinded analysis, of safety and PK data only, to facilitate abemaciclib dose selection prior to Part 2. Thereafter, only the DMC is authorized to evaluate unblinded futility and adaptive interim analyses (see Section 10.3.5). The DMC will be independent and consist of at least 3 members external to Lilly, none of whom are involved as study investigators, including at least 1 clinician and 1 statistician. The DMC will communicate any recommendations based on the interim analyses to the Lilly Senior Management Designee. Further details are included in the DMC Charter. For those analyses assigned to the DMC, only the designated Statistical Analysis Center, which is independent of the sponsor, will perform analyses on unblinded data. Study sites will receive information about interim results only if they need to know for the safety of their patients. Further details are included in the study unblinding plan.

7.3.2. Emergency Unblinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly CRP/CRS prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

Emergency unblinding for AEs must be performed through the IWRS. This option must be used when the patient's acute well-being requires knowledge of the patient's treatment assignment.

All calls resulting in an unblinding event are recorded and reported by the IWRS. If the investigator or patient becomes unblinded, that patient will be discontinued from study treatment and will undergo post-discontinuation follow-up. Long-term follow up procedures will be followed until death, loss of follow-up, or withdrawal of consent, or study completion.

7.3.3. Inadvertent Unblinding

Every effort will be made to blind both the patient and the investigator to the identity of the treatment, but the inadvertent unblinding of a patient may occur. If an investigator, site personnel, or patient is inadvertently unblinded, the unblinding will not be sufficient cause for the patient to be discontinued from study treatment or excluded from study analyses.

In cases in which there are ethical reasons for the patient to remain on the study treatment in the event of unblinding, the investigator must obtain specific approval from a Lilly CRP/CRS for the patient to continue in the study.

7.4. Dose Modification

Dose adjustments (suspensions and reductions) will be made based on the clinical assessment of hematologic and nonhematologic toxicities (defined as an AE possibly related to study treatment per investigator judgment). The CTCAE v 5.0 will be used to assess AEs. Study treatment may be suspended for a maximum of 28 days to allow a patient sufficient time for recovery from study treatment-related toxicity. If a patient does not recover from the toxicity within 28 days from the time of last treatment, the patient should be considered for permanent discontinuation from study treatment. In exceptional circumstances, a delay >28 days is permitted upon agreement between the investigator and the Lilly CRP/CRS.

For more information about abemaciclib/placebo dose modifications for AEs and adverse events of special interest (AESIs), see Section 7.4.1.

Dose reductions for abemaciclib/placebo should be as shown in Table JPCM.6. Abemaciclib/placebo must be reduced sequentially by 1 dose level, unless an exception is granted in consultation with the Lilly CRP/CRS. Mid-cycle dose reductions for abemaciclib/placebo may be implemented by informing patients to reduce the number of 50-mg tablets/capsules taken for each dose (with dose reductions appropriately documented in the electronic case report form [eCRF]). If 1 study treatment (abiraterone acetate or abemaciclib/placebo) has been discontinued or maximally dose reduced due to toxicity and the toxicity has not resolved, patients may continue to receive the other study treatment at the current dose if it is apparent that the toxicity is not related to the other study treatment and the patient continues to receive clinical benefit.

Table JPCM.6. Dose Reductions for Abemaciclib/Placebo

	Blinded Study Drug Dose (Abemaciclib/Placebo)	
Starting dose	150 mg BID	200 mg BID
First dose reduction	100 mg BID	150 mg BID
Second dose reduction	50 mg BID	100 mg BID
Third dose reduction	Discontinue	50 mg BID
Fourth dose reduction		Discontinue

Abbreviation: BID = twice daily; mg = milligrams.

Dose adjustments for abiraterone acetate and prednisone should follow prescribing information. See Section 7.4.1.2. for guidance on dose modification for abnormal liver function test.

For patients requiring a dose reduction of study treatments (abemaciclib/placebo or abiraterone acetate), any re-escalation to a prior dose level is permitted only after consultation with the Lilly CRP/CRS.

7.4.1. Special Treatment Considerations

7.4.1.1. Abemaciclib/Placebo Dose Adjustments and Delays: Hematologic Toxicities, Nonhematologic Toxicities (excluding diarrhea, Interstitial Lung Disease (ILD)/Pneumonitis and ALT/AST increased), Diarrhea, Interstitial Lung Disease/Pneumonitis

Table JPCM.7 is a guidance for management of treatment-emergent, related, and clinically significant AEs of abemaciclib/placebo. An investigator may suspend or reduce doses without 1 of the criteria below being met and would not be considered a protocol deviation.

Table JPCM.7. Toxicity Dose Adjustments and Delays of Abemaciclib/Placebo: Hematologic Toxicities, Nonhematologic Toxicities, Diarrhea, ILD/Pneumonitis

Toxicity Type	CTCAE Grade	Dose Modification
Hematologic Toxicity	Grade 1 or Grade 2	No dose modification is required.
	Grade 3	Suspend dose until toxicity resolves to ≤Grade 2. Dose reduction is not required.

Toxicity Type	CTCAE Grade	Dose Modification
	Recurrent Grade 3, or Grade 4	Suspend dose until toxicity resolves to ≤Grade 2. Resume at next lower dose level.
Hematologic toxicity: If patient requires administration of blood cell growth factors. Additional guidance for use of growth factors is in Section 7.7.2.2	Regardless of severity. (Use of growth factors according to ASCO Guidelines)	Suspend dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2. Resume at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor.
Nonhematologic Toxicity Excluding Diarrhea, Interstitial Lung Disease /Pneumonitis, and ALT/AST increased (see Section 7.4.1.2 for ALT/AST) Additional guidance for monitoring renal function is in Section 9.4.2.3. Additional guidance for venous thromboembolic events is in Section 9.4.2.4.	Grade 1 or Grade 2	No dose modification is required
	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1, or Grade 3 or Grade 4	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose level.
Diarrhea Additional guidance for diarrhea management is in Section 7.7.2.1. See Appendix 9 for CTCAE 5.0 grading.	Grade 1	No dose modification is required.
	Grade 2 that does not resolve within 24 hours to ≤Grade 1	Suspend dose until toxicity resolves to ≤Grade 1. Dose reduction is not required.
	Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures, or Grade 3, or Grade 4, or requires hospitalization	Suspend dose until toxicity resolves to ≤Grade 1. Resume at next lower dose level.
Interstitial Lung Disease/Pneumonitis Additional guidance for Interstitial Lung	Grade 1 or Grade 2	No dose modification is required.
	Grade 2 that persists or recurs despite maximal supportive measures and does not return to baseline or Grade 1 within 7	Suspend dose until toxicity resolves to baseline or Grade ≤1. Resume at next lower dose level.

Toxicity Type	CTCAE Grade	Dose Modification
Disease/Pneumonitis management is in Section 9.4.2.5.	days	
	Grade 3 or Grade 4	Discontinue abemaciclib/placebo.

Abbreviations: ALT = alanine aminotransferase; ASCO = American Society of Clinical Oncology; AST = aspartate aminotransferase.

- Determination of persistent events will be at the discretion of the investigator.
- Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event). As a general guidance, based on the risk/benefit balance assessment per the investigator, for a patient who experiences a new episode of Grade 3 hematological toxicity after more than 8 weeks following the last episode of same Grade 3 hematological toxicity, the investigator may consider resuming the patient on the same drug dose should the patient satisfy the following conditions:
  - The patient showed stable hematological counts (Grade ≤2) during that time frame;
  - In the absence of any infectious sign or risk factor;
  - The patient is benefiting from study treatment.

7.4.1.2. Abemaciclib/Placebo and Abiraterone acetate and Dose Adjustments and Delays - Increased ALT or AST

Measure serum aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and bilirubin levels prior to starting study treatment and every 2 weeks for the first 3 months and monthly thereafter.

Promptly measure ALT, AST, alkaline phosphatase (ALP), total bilirubin (TBL), direct bilirubin (DBL), gamma-glutamyl transferase (GGT), and creatine kinase (CK) if clinical symptoms or signs suggestive of hepatotoxicity develop.

Review concomitant medications that are potentially hepatotoxic if patients develop liver function test abnormalities

CCI [redacted] An investigator may suspend or reduce doses without 1 of the below criteria being met. This would not be considered a protocol deviation.

[a] If at any time, a patient develops a Grade ≥3 elevation of ALT or AST at the reduced dose of 500 mg once daily, permanently discontinue abiraterone.

[b] If recurrent Grade 3 (i.e., within 8 weeks as measured from the restarting date of the study drug) is only observed for AST, the investigator may consult with the Lilly CRP/CRS prior to permanently discontinuing study treatment.

Hepatic monitoring should be initiated for patients who develop liver function test abnormalities. Refer to Section 9.4.2.1 for Hepatic Safety Monitoring.

CCI

Additional safety data should be collected for patients who develop liver function test abnormalities. Refer to Section 9.4.2.2 for Special Hepatic Safety Data Collection.

7.5. Preparation/Handling/Storage/Accountability

Abemaciclib and placebo will be supplied by Lilly and labeled according to country regulation requirements. All study treatment should be stored according to their associated product label and taken as indicated. Patients should store all study treatment in the original package provided and according to the product label (where applicable) and be instructed to keep all medications out of reach from children.

7.6. Treatment Compliance

Patient compliance will be assessed by counting returned tablets/capsules. Study medication administration data will be recorded in the patient's medical record and eCRF. Deviations from the prescribed dosage regimen should be recorded on the eCRF.

Patients who are significantly noncompliant will be discontinued from the study. A patient will be considered significantly noncompliant if he misses more than 7 consecutive days of study medication (full doses) or more than 25% cumulative days of study medication (full doses) during the study. Similarly, a patient will be considered significantly noncompliant if he is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication. Abemaciclib dose suspensions or delays related to toxicity may occur and will not result in a patient being considered noncompliant.

7.7. Concomitant Therapy

Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the eCRF. Concomitant medications and supportive care therapies must also be documented at time of discontinuation and at the 30-day follow up visit.

With the exception of standard LHRH agonists/antagonists, no other anticancer therapy will be permitted while patients are on study treatment (including, but not limited to, hormonal anticancer therapies, CYP17 inhibitors [TAK-700, TOK-001 and ketoconazole], other CDK4 and 6 inhibitors, chemotherapy, radiotherapy, radiopharmaceuticals, and immunotherapy/vaccines).

Drugs or herbal/nonherbal products (e.g., saw palmetto, pomegranate) that have known prostate cancer activity and/or are known to affect PSA levels will be not permitted while the patients are on study treatment. Spironolactone is not permitted. Megestrol acetate as an appetite stimulant is not permitted. Premedication with antiemetics is allowed according to standard practice guidelines.

Patients with bone metastases present on baseline imaging should be appropriately treated with bisphosphonates or RANK-L targeted agents (e.g., denosumab), per respective approved labels. Patients receiving bisphosphonates or RANK-L targeted agents are permitted to switch after initiation of study treatment as long as it is in the absence of disease progression, and due to reasons including, but not limited to, tolerability.

Modulators of CYP3A

Abemaciclib is extensively metabolized through oxidation by CYP3A. In clinical drug interaction studies:

- coadministration of clarithromycin, a strong CYP3A inhibitor, increased exposure (area under the concentration-versus-time curve [AUC]) to abemaciclib by 3.4-fold (Study I3Y-MC-JPBE), and
- coadministration of rifampin, a strong CYP3A inducer, decreased exposure to abemaciclib by 95% (Study I3Y-MC-JPBF).

Strong inhibitors of CYP3A (given via nontopical routes of administration) should be substituted or avoided if possible (Appendix 8). This includes grapefruit or grapefruit juice. In particular, avoid oral administration of the very strong CYP3A inhibitor, ketoconazole.

If coadministration with a strong CYP3A inhibitor is unavoidable, investigators should reduce the dose of abemaciclib/placebo by 50 mg at the start of CYP3A inhibitor treatment. That is, for patients receiving 200 mg twice daily, reduce the dose to 150 mg twice daily. For patients who have already dose reduced to 150 mg or 100 mg twice daily for tolerability, reduce the dose further to 100 mg or 50 mg twice daily, respectively. Alternatively, the investigator may consider suspending abemaciclib/placebo for the duration of the CYP3A inhibitor medication. Dose suspensions ≥28 days must be discussed with Lilly CRP/CRS.

Upon discontinuation of the strong CYP3A inhibitor, abemaciclib/placebo may be resumed at the same dose level or re-escalated to the dose that was used before starting the strong inhibitor after a sufficient washout period (at least 3 half-lives of the strong inhibitor). Re-escalation of the abemaciclib/placebo dose requires review and approval from Lilly CRP/CRS.

Inducers of CYP3A should be substituted or avoided if possible (Appendix 8). Coadministration with a CYP3A inducer ≥28 days must be discussed with Lilly CRP/CRS.

Transporter Substrates

At clinically relevant concentrations, abemaciclib inhibits the transporters P-glycoprotein, breast cancer resistance protein, organic cation transporter 2 (OCT2), multidrug and toxin extrusion protein 1 (MATE1), and MATE2-K. The observed serum creatinine increase in clinical studies with abemaciclib is likely due to inhibition of tubular secretion of creatinine via OCT2, MATE1, and MATE2-K. In vivo interactions of abemaciclib with narrow therapeutic index substrates of these transporters, such as digoxin and dabigatran, may occur.

Abiraterone

Abiraterone is a substrate of CYP3A4, and as such it is recommended to avoid concomitant strong CYP3A4 inducers. Abiraterone is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. For further information regarding the potential for abiraterone and/or prednisone to affect the exposures of other medicinal products, or for the potential for medicinal products to affect the exposures of abiraterone and/or prednisone refer to prescribing information.

7.7.1. Palliative Radiotherapy and/or Surgical Intervention for Prostate Cancer

Palliative radiation or surgical intervention to treat symptoms resulting from metastatic disease are not allowed. Patients with symptomatic disease progression requiring radiation therapy or surgical intervention (no longer clinically benefiting, see section 8.1) will be discontinued from study treatment and have a tumor assessment before receiving radiotherapy or surgery. The reason and date of discontinuation will be collected for all patients.

7.7.2. Supportive Care

Patients should receive full supportive care to maximize quality of life. Patients will receive supportive care as judged by the treating physician. If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult with the Lilly CRP/CRS. Use of any supportive care should be recorded on the eCRF.

7.7.2.1. Supportive Management for Diarrhea

When study treatment is initiated, the patient should receive instructions on the management of diarrhea. In the event of diarrhea (see Appendix 9), supportive measures should be initiated as early as possible. These include:

- At the first sign of loose stools, the patient should initiate anti-diarrheal therapy (e.g., loperamide) and notify the investigator/site for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- If diarrhea does not resolve with antidiarrheal therapy within 24 hours to either baseline or Grade 1, blinded study drug should be suspended until diarrhea is resolved to baseline or Grade 1.
- When blinded study drug recommences dosing should be adjusted as outlined in Section 7.4.1.1.

In severe cases of diarrhea, the measuring of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered.

If diarrhea is severe (requiring IV rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones must be prescribed.

Patients with severe diarrhea or any grade of diarrhea associated with severe nausea or vomiting should be carefully monitored and given IV fluid (IV hydration) and electrolyte replacement.

7.7.2.2. Growth Factors

Growth factors should not be administered to enable a patient to satisfy study inclusion criteria. Granulocyte colony-stimulating factor (G-CSF) or similar agents are not permitted as primary prophylaxis.

The use of G-CSF is permitted at the discretion of the investigator based on American Society of Clinical Oncology (ASCO; Smith et al. 2015) and European Society for Medical Oncology (Crawford et al. 2009) guidelines. If the administration of growth factors is clinically indicated, dosing of abemaciclib/placebo must be suspended and must not be recommenced within 48 hours of the last dose of growth factors being administered. The dose of abemaciclib/placebo must be reduced by 1 dose level following the administration of growth factors.

7.7.2.3. Transfusions

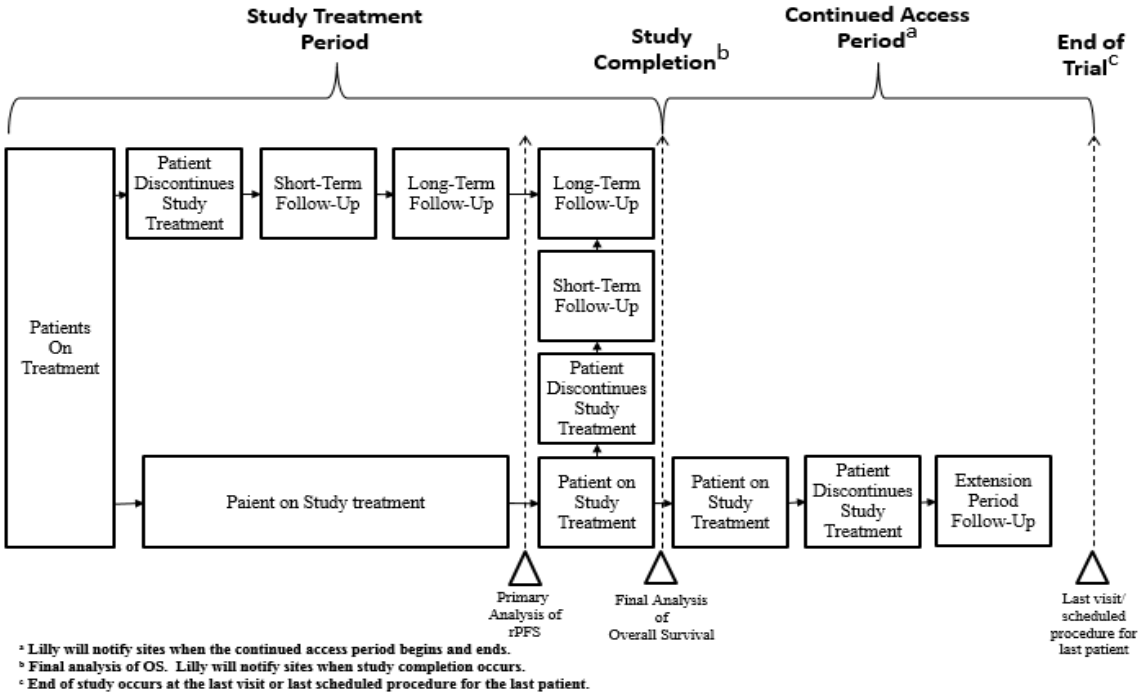
Transfusion therapy is permitted during the study if clinically indicated at any time during the study, but should not be administered to enable a patient to satisfy study inclusion criteria.

Erythropoiesis-stimulating agents (ESAs; including erythropoietin and darbepoetin) may be used in accordance with the ASCO/ASH guidelines (Rizzo et al. 2010).

7.8. Treatment after the End of the Study

Study completion will occur after the final primary analysis of the last study part has been conducted. Investigators will continue to follow the schedule of activities provided in Section 2 until notified by Lilly that study completion has occurred.

Refer to Figure JPCM.2 for a depiction of these concepts for the study: study completion, the continued access period, and end of study.



Abbreviations: OS= overall survival; rPFS= radiographic progression free survival.

Figure JPCM.2. Continued access diagram.

7.8.1. Treatment after Study Completion

Study completion will occur following the final analysis of OS, as determined by Lilly (i.e., the scientific evaluation will be complete). Investigators will continue to follow the Schedule of Activities (Section 2) for all patients until notified by Lilly that study completion has occurred.

Refer to Section 7.3 for unblinding that occurs after study completion.

7.8.1.1. Continued Access

Patients who are still on study treatment at the time of study completion may continue to receive study treatment if they are experiencing clinical benefit and no undue risks. Placebo will no longer be administered and crossover will not be permitted.

The continued access period will apply to this study only if at least 1 patient is still on study treatment when study completion occurs. Lilly will notify investigators when the continued access period begins.

Patients are not required to sign a new ICF before treatment is provided during the continued access period; the initial ICF for this study includes continued access under this protocol.

The patient's continued access to study treatment will end when a criterion for discontinuation is met (Section 8). Continued access follow-up will begin when the patient and the investigator agree to discontinue study treatment and lasts approximately 30 days. Follow-up procedures will be performed as shown in the Continued Access Schedule of Activities (Section 2).

Patients who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply.

Patients who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

In all cases, no follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

Study treatment should be continued as long as the patient consents and complies with study procedures and requirements, is tolerating the study treatment, and until radiographic and/or symptomatic progression.

If the patient had radiographic progression, but no symptomatic progression, and alternate treatment is not initiated, the patient may continue on study treatment at the Investigator's discretion.

Patients with PSA-only progression should continue study treatment until disease progression (radiographic and/or symptomatic progression) where patient safety is not compromised.

Symptomatic progression is defined as:

- Symptomatic skeletal event (SSE), defined as symptomatic fracture, surgery, or radiation to bone or spinal cord compression
- Pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy
- Development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy.

The reason and date of discontinuation will be collected for all patients.

When study treatment is discontinued due to symptomatic progression, the investigator should obtain imaging studies within 14 days to assess for radiographic progression, including a confirmatory bone scan, as appropriate.

All patients discontinuing study treatment will have procedures performed as shown in the Schedule of Activities (Section 2) and enter the short- and long-term follow-up periods and will be followed for the initiation of subsequent anti-cancer therapies every 3 months until death, loss of follow-up, or withdrawal of consent, whichever comes first. In addition, patients discontinuing treatment prior to documented radiographic progression will continue to have scheduled disease assessments until documented radiographic progression and will be followed for the development of symptomatic progression. Patients discontinuing treatment due to documented radiographic progression will be followed for the development of symptomatic progression.

Patients will be discontinued from study treatment in the following circumstances:

- the patient is enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
- the patient is significantly noncompliant with study procedures and/or treatment
- disease progression, radiographic or clinical, as discussed above

unacceptable toxicity

the patient has had maximum dose reductions allowed per protocol (Table JPCM.6) and experiences an AE that would cause an additional dose reduction

the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from study treatment will occur prior to introduction of the new agent

the investigator decides that the patient should be discontinued from study treatment

the patient requests to be discontinued from study treatment

the patient's designee (legal representative) requests that the patient be discontinued from study treatment.

Patients who are discontinued from all study treatment will have follow-up procedures performed as shown in the Schedule of Activities (Section 2).

8.1.1. Discontinuation of Inadvertently Enrolled Patients

The criteria for enrollment must be followed explicitly. If the investigator or site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the Lilly CRP/CRS and the investigator to determine if the patient may continue in the study, with or without study drug. Inadvertently enrolled patients may continue in the study and on study drug when the Lilly CRP/CRS agrees with the investigator that it is medically appropriate for that patient to do so. The patient may not continue in the study with or without study drug if the Lilly CRP/CRS does not agree with the investigator's determination that it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly CRP/CRS to allow the inadvertently enrolled patient to continue in the study with or without study drug. Patients who are discontinued from the study will have follow-up procedures performed as shown in the Schedule of Activities (Section 2).

8.2. Discontinuation from the Study

Patients will be discontinued from the study in the following circumstances:

participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)

the investigator decides that the patient should be discontinued from the study

the patient requests to be discontinued from the study

the patient's designee (legal representative) requests that the patient be discontinued from the study.

Patients who are discontinued from the study will have follow-up procedures performed as shown in the Schedule of Activities (Section 2).

8.3. Lost to Follow-Up

A patient will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Study site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or who the site is otherwise unable to follow-up.

Study site personnel, or an independent third party, will attempt to collect the survival status for all randomized patients who are lost to follow-up, including randomized patients who do not receive study treatment, within legal and ethical boundaries. Public sources may be searched for survival status information. If the patient's survival status is determined, the survival status will be documented and the patient will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect survival status information.

9. Study Assessments and Procedures

Section 2 provides the Schedule of Activities for this study.

Appendix 2 provides a list of the laboratory tests that will be performed for this study.

Appendix 4 provides the schedule for collection of samples in this study.

Unless otherwise stated in the following subsections, all samples collected for specified laboratory tests will be destroyed within 60 days after receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

Baseline and on-study tumor assessments will be performed for each patient as per the Schedule of Activities (Section 2). During study, unscheduled tumor assessment and appropriate imaging should be considered if there are signs or symptoms suggestive of disease progression. All applicable imaging will be done locally. All CT/MRI and bone scans will be collected and stored centrally. The method of assessment used at baseline must be used consistently for serial tumor assessment throughout the study.

See Section 9.1.2 for definitions of the efficacy endpoints.

9.1.1. Appropriateness of Assessments

The measures used to assess safety and efficacy in this study are consistent with those used in most conventional oncology studies.

9.1.2. Definitions of Efficacy Measures

Primary Objective

Radiographic Progression Free Survival

The consensus guidelines of RECIST 1.1 and PCWG3 have been taken into consideration for the determination of radiographic disease progression.

For all patients, imaging studies (radionuclide bone scan and CT or MRI scan of the chest, abdomen, and pelvis) will be performed locally at baseline and repeated every 8 weeks for the first 24 weeks and every 12 weeks thereafter, independent of treatment delay. Imaging may be performed within 7 days prior to the scheduled calendar day (e.g. Day 1 of every second cycle beginning with Cycle 3 and continuing through Cycle 7 (inclusive), and Day 1 of every third cycle after Cycle 7), and within 14 days of symptomatic progression if no radiographic progression yet per the Schedule of Activities.

rPFS will be assessed by sequential imaging studies and is defined as the time from the date of randomization to the earliest date of investigator-determined radiographic disease progression by objective radiographic disease assessment per RECIST 1.1 for soft tissue AND/OR radionuclide bone scan using PCWG3 criteria for bone or death from any cause, whichever occurs first.

The documentation required for the determination of radiographic disease progression in bone is listed in Table JPCM.9.

Disease Progression on Bone Scan as per PCWG3

Progression of disease by bone per PCWG3 is defined as the appearance of at least 2 new lesions on the first post-treatment scan (Week 9), with at least 2 additional lesions on the next scan (Week 17; 2+2 rule), OR for radiographic disease progression in bone observed after the first post-treatment scan (Week 17 or later), at least 2 new lesions relative to the first post-treatment scan (Week 9) that are persisting on a confirmatory subsequent scan (at least 6 weeks later or at the next scheduled assessment).

The date of progression is the date of the first scan when the first 2 (or more) new lesions are documented.

Changes in intensity of uptake alone do not constitute either progression or regression.

Table JPCM.9. Bone Progression per PCWG3

Date Progression Detected	Criteria for Progression	Criteria for Confirmation or Progression (Requirement and Timing)	Criteria for Documentation of Disease Progression on Subsequent Scan
Week 9 (C3D1) (or earlier unscheduled visit)	Two or more new lesions compared to baseline bone scan.	Requires confirmation at least 6 weeks after progression identified or at the Week-17 assessment	Confirmatory scan: Two or more new bone lesions compared to Week-9 scan
Week 17 or later	Two or more new lesions on bone scan compared to Week 9 bone scan.	Requires confirmation at least 6 weeks after progression identified or at the next scheduled assessment.	Confirmatory scan: Two or more persisting (i.e., also present on the prior scan) new lesions relative to Week 9 scan

Source: Scher et al. (2016).

Objective Radiographic Disease Assessment per RECIST 1.1 for Soft Tissue

See Appendix 7. Radiographic disease progression in soft tissue does not require a confirmatory scan.

Secondary Objectives

Radiographic Progression-Free Survival by Blinded, Independent Central Review (BICR)

In addition to the primary endpoint of rPFS by investigator-determined radiographic disease progression or death, rPFS by BICR will be assessed if Part 3 is opened for enrollment.

Time to PSA Progression

Time to PSA progression is defined as the time from the date of randomization to the date of first observation of PSA progression. The PSA progression is defined as a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir (or baseline value if baseline is the smallest on study), which is confirmed by a second value obtained 3 or more weeks later. Any postbaseline PSA measurements within 12 weeks since baseline will be ignored in determining PSA progression.

Duration of Response is defined as the time from first documented evidence of soft tissue complete response (CR) or partial response (PR) until earliest date of disease progression by objective radiographic disease assessment per RECIST 1.1 for soft tissue AND/OR radionuclide bone scan using PCWG3 criteria for bone as assessed by the investigator/local radiologist, or death from any cause, whichever occurs first.

Objective Response Rate is defined as the proportion of participants who have a soft tissue best overall response of CR or PR per RECIST 1.1 as assessed by the investigator/local radiologist. Only patients with measurable soft tissue disease at baseline (defined as having at least 1 target lesion on CT or MRI scans) will be included in the analysis.

Overall Survival is defined as the time from the date of randomization to date of death due to any cause.

Time to Symptomatic Progression is defined as the time from randomization to any of the following (whichever occurs earlier):

- Symptomatic Skeletal Event (SSE, defined as symptomatic fracture, surgery, or radiation to bone, or spinal cord compression
- Pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy
- Development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy.

Exploratory Objectives

CCI [redacted]

9.2. Adverse Events

Lilly standards for reporting AEs are to be followed regardless if country regulatory requirements are less stringent. A clinical study AE is any untoward medical event associated with the use of a drug in humans, irrespective if the AE is considered related to study treatment. Additional events meeting the AE definition are medication error, misuse, or abuse of IMP, including subsequent signs, symptoms, or clinical sequelae.

The investigator will use CTCAE, v 5.0 (NCI 2017) to assign AE terms and severity grades.

Investigators are responsible for:

monitoring the safety of patients in this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient

the appropriate medical care of patients during the study

documenting their review of each laboratory safety report

following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to study treatment or the study, or that caused the patient to discontinue study treatment before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via CRF/electronic data entry/designated data transmission methods the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, study site personnel will record via CRF/electronic data entry/designated data transmission methods any change in the preexisting conditions and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to study treatment via CRF/electronic data entry/designated data transmission methods.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment or a study procedure, taking into account the disease, concomitant treatments, or pathologies. A "reasonable possibility" means that there is a cause and effect relationship between the study treatment and/or study procedure and the AE.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

Study site personnel must report any dose modifications or treatment discontinuations that result from AEs to Lilly or its designee via CRF/electronic data entry/designated data transmission methods, clarifying, if possible, the circumstances leading to the dose modification or discontinuation of treatment.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

death

initial or prolonged inpatient hospitalization

a life-threatening experience (that is, immediate risk of dying)

persistent or significant disability/incapacity

congenital anomaly/birth defect

important medical events that may not be immediately life-threatening or result in death or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above.

Although all AEs after signing the ICF are recorded by the site in the CRF/electronic data entry/designated data transmission methods, SAE reporting to Lilly begins after the patient has signed the ICF and has received study treatment. However, if an SAE occurs after signing the ICF, but prior to receiving study treatment, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

Study site personnel must notify Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a Lilly-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an AE but should be reported. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study (the patient summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Planned hospitalizations or procedures for preexisting conditions that were recorded in the patient's medical history at the time of enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study treatment or other protocol-required procedure) should not be considered SAEs.

Serious adverse events, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study treatment.

SAE regulatory reporting

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor has processes for safety reports for identification, recording, and expedited reporting of suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review board (IRB)/independent ethics committee (IEC), and investigators.

9.2.2. Suspected Unexpected Serious Adverse Reactions

SUSARs are serious events that are not listed in the IB and that the investigator identifies as related to study treatment or study procedure. United States 21 CFR 312.32 and Regulation (EU) No 536/2014 and the associated detailed guidance's or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidance's.

9.2.3. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, to monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

Refer to the specific IB Section 7.3.9 and/or Product Label for the applicable targeted agent(s) with marketed approval.

9.4. Safety

9.4.1. Safety Measures

For each patient, ECGs, vital signs, laboratory tests, or other tests should be collected as shown in the Schedule of Activities (Section 2).

Results from any clinical laboratory test analyzed by a central laboratory (refer to Appendix 2) will be provided to investigative sites by Lilly or its designee.

Refer to Section 9.1.2 for details on the recording of AEs.

9.4.2. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the data monitoring committee (DMC; an advisory group for this study formed to protect the integrity of data; refer to Section 10.3.5) can conduct additional analyses of the safety data.

Refer to Section 7.4.1.2 for Guidance for Abnormal Liver Function Test.

Refer to Section 9.4.2.2 for details regarding hepatic safety data collection in the event of particular circumstances.

9.4.2.1. Hepatic Safety Monitoring

Liver testing (Appendix 5), including ALT, AST, ALP, TBL, DBL, GGT, and creatine kinase (CK), should be repeated within 2 to 4 days to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

If a participant with baseline results of ...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥5x ULN or ALT or AST ≥3x ULN concurrent with TBL ≥2x ULN
ALT or AST ≥1.5x ULN	ALT or AST ≥3x baseline or ALT or AST ≥2x baseline concurrent with TBL ≥2x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

If the abnormality persists or worsens, clinical and laboratory monitoring (Appendix 5) and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), and history of concomitant medications (including over-the-counter, herbal and dietary supplements, history of alcohol drinking, and other substance abuse). In addition, the evaluation should include a blood test for prothrombin time-international normalized ratio; serological tests for viral hepatitis A, B, C, E, and autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Based on the participant's history and initial evaluation results, further testing should be considered, in consultation with the Lilly designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol (Appendix 5). Based on the circumstances and the

investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, and/or a liver biopsy.

For patients who experienced hepatotoxicity and resumed treatment, AST, ALT, and bilirubin should be monitored every week for the first month, every 2 weeks for the following 2 months, and monthly thereafter.

9.4.2.2. Special Hepatic Safety Data Collection

Additional safety data should be collected via the eCRF if 1 or more of the following conditions occur:

In participants enrolled with baseline ALT or AST <1.5 ULN

Elevation of serum ALT or AST to ≥5x ULN on 2 or more consecutive blood tests
The combination of elevated ALT or AST ≥3x ULN and elevated TBL ≥2x ULN

1 1 1 1 1 1 1 1 nls 1

Elevated ALT or AST ≥3x baseline on 2 or more consecutive tests
The combination of elevated ALT or AST ≥2x baseline and elevated TBL ≥2x ULN

In all study participants

Discontinuation from study treatment due to a hepatic event or abnormality of liver tests
Occurrence of a hepatic event considered to be a SAE

9.4.2.3. Guidance for Monitoring Renal Function

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting glomerular function (as measured by iohexol clearance). In clinical studies, increases in serum creatinine occurred within the first month of abemaciclib dosing , remained elevated but stable through the treatment period, were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function, such as blood urea nitrogen, cystatin C, or calculated glomerular filtration rate (GFR) based on cystatin C. Dose adjustments (omission, reduction, or discontinuation) should not solely be based on interpretation of serum creatinine values because these may not reflect renal function. Other measures of renal function such as cystatin C GFR should be used as an alternative to either creatinine or creatinine calculations of GFR. A serum cystatin C is collected with the central chemistry laboratory sample. If deterioration of renal function is suspected per the investigator's clinical assessment, dose alteration should follow the protocol guidance for nonhematological toxicities (Table JPCM.7) if considered related to blinded study drug.

9.4.2.4. Guidance for Venous Thromboembolic Events

In breast cancer, venous thromboembolic event (VTE) has been identified as an adverse drug reaction for abemaciclib in combination with ET. In the randomized Phase 3 studies in breast cancer participants who received abemaciclib in combination with ET, a greater number of

participants experienced VTEs in the abemaciclib plus ET arms than in the placebo plus ET arm or ET alone arm. The majority of participants who experienced VTEs were treated with anticoagulants.

In studies with single-agent abemaciclib use in the metastatic breast cancer population or other tumor types, including nonsmall cell lung cancer, no increased rates of VTEs were observed as compared to the incidence of VTEs for these particular patient populations who were treated with other anticancer agents. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known.

Monitor participants for signs and symptoms of deep vein thrombosis and pulmonary embolism and treat as medically appropriate.

Dose modifications and management of abemaciclib/placebo should follow the protocol guidance for nonhematological toxicities in Section 7.4.1.1, Table JPCM.7.

9.4.2.5. Guidance for Interstitial Lung Disease/Pneumonitis

Interstitial lung disease/pneumonitis has been identified as an adverse drug reaction for abemaciclib. The majority of events observed in clinical trials were Grade 1 or Grade 2 with serious cases and fatal events reported. Additional information is available in the IB.

Ask your participants to report any new or worsening pulmonary symptoms such as dyspnea, cough, and fever and investigate and treat as per your local clinical practice (including corticosteroids as appropriate). If ILD/pneumonitis is suspected, investigations may include imaging, such as high-resolution CT, bronchoalveolar lavage, and biopsy as clinically indicated.

Refer to Section 7.4.1.1, Table JPCM.7 for guidance on dose adjustments of abemaciclib/placebo for participants with ILD/pneumonitis (see Appendix 9 for ILD/pneumonitis CTCAE grades). Discontinue abemaciclib in cases of severe (Grade 3 or Grade 4) ILD/pneumonitis.

9.4.2.6. Guidance for Hypertension, Hypokalemia, Fluid Retention, and Cardiovascular Adverse Reactions Due to Mineralocorticoid Excess

Abiraterone acetate may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition.

Monitor patients for hypertension, hypokalemia, and symptoms of fluid retention at least once a month. Patients with low potassium while on study or a history of hypokalemia from a pre-existing or concurrent medical condition should be considered for more frequent laboratory electrolyte evaluation per investigator's discretion. Control hypertension and correct hypokalemia before and during treatment.

Closely monitor patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia, or fluid retention such as those with heart failure, recent myocardial infarction, cardiovascular disease, or ventricular arrhythmia. QT prolongation and Torsades de Pointes have been observed in patients who develop hypokalemia while taking abiraterone. The safety of abiraterone acetate in patients with left ventricular ejection fraction <50% has not been established.

Refer to abiraterone acetate prescribing information.

9.4.2.7. Guidance for Adrenocortical Insufficiency

Adrenocortical insufficiency was reported in patients receiving abiraterone acetate in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress.

Monitor patients for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with abiraterone acetate. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

Refer to abiraterone acetate prescribing information.

9.4.2.8. Guidance for Hypoglycemia

Severe hypoglycemia has been reported when abiraterone acetate was administered to patients with preexisting diabetes receiving medications containing thiazolidinediones (including pioglitazone) or repaglinide. Monitor blood glucose in patients with diabetes during and after discontinuation of treatment with abiraterone acetate. Assess if antidiabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

Refer to abiraterone acetate prescribing information.

9.5. Pharmacokinetics

Blood samples for PK analysis will be collected as shown in Appendix 4.

Plasma samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor. Concentrations of abemaciclib and its metabolites LSN3106726, LSN2839567, abiraterone, and prednisone will be determined using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following last subject visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses (such as quantification of circulating metabolites and/or protein binding work).

A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon by the investigator and Lilly.

Drug concentration information that could unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.6. Pharmacodynamics

See Sections 9.5 and 9.8.

9.7. Pharmacogenomics

9.7.1. Whole Blood Sample for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in Appendix 4, where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to study treatment and to investigate genetic variants thought to play a role in mCRPC. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel. Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing technologies include whole genome and exome sequencing, genome-wide association studies, multiplex assays, and candidate gene studies. Regardless of the technology utilized, data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, lipids, and other cellular elements.

This study will analyze biomarkers relevant to abemaciclib or abiraterone acetate, mechanism of action of abemaciclib or abiraterone acetate, the variable response to study drug(s), immune function, and pathways associated with cancer. These samples may also be used to develop related research methods or to validate diagnostic tools or assays.

Samples for biomarker research will be collected as specified in Appendix 4, where local regulations allow.

It is possible that biomarker data for patients in the study have already been generated from samples that were collected and analyzed prior to enrolling in this study. This may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Sections 9.7.1, 9.8.1, and 9.8.2.

9.8.1. Tissue Samples for Biomarker Research

Tissue samples for biomarker research will be collected for the purposes described in Section 9.8. The following samples for biomarker research will be collected according to the sampling schedule in Appendix 4, where local regulations allow.

Collection of the following tumor tissue sample(s) is required for Part 1 and Part 2 and optional for Part 3:

Tumor biopsy of at least 1 metastatic site, which should be collected following determination of eligibility and before initiating study treatment.

Biopsy of newly emerged radiographic metastases is desired and preferable to the biopsy of previously existing lesions whenever possible.

Soft-tissue as well as bony metastatic lesions will be considered acceptable. Soft-tissue biopsy is preferred to bone biopsy whenever possible.

Adequate archival metastatic tissue can be used in lieu of a new biopsy if the biopsy was done within 12 weeks prior to randomization AND no treatment was initiated from biopsy to study entry.

Collection of the following tumor tissue sample(s) is optional for all patients participating in this study:

Biopsy of metastatic lesion at the time of disease progression (the progressing metastatic lesion preferred). If a patient discontinues study for a reason other than radiographic progression, the second optional biopsy should be considered only if the patient has completed at least 6 cycles of study treatment.

At the time of tissue collection, every effort should be made to ensure that adequate tumor sample (not a normal adjacent tissue sample or a tumor margin sample) is provided.

The pathology report accompanying archival tissue may also be requested. The pathology report must be coded with the patient number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology report prior to submission.

Tumor tissue samples collected as part of this study will not be returned.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits. This retention period enables the use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later.

Technologies are expected to improve during the 15-year storage period and, therefore, cannot be specifically named. Existing approaches, including mutation profiling, copy number variability analysis, gene expression assays, multiplex assays, and/or immunohistochemistry may be performed on these tissue samples to assess potential associations between these biomarkers and clinical outcomes.

9.8.2. Other Samples for Biomarker Research

The following samples for biomarker research will be collected according to the sampling schedule in Appendix 4, where local regulations allow:

- whole blood for circulating tumor cell collection
- Plasma.

A maximum of 4 samples may be drawn, collected, or removed at additional study time points, if warranted and agreed upon by the investigator and Lilly.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later.

Technologies are expected to improve during the 15-year storage period and, therefore, cannot be specifically named. Existing approaches, including mutation profiling, copy number variability analysis, gene expression assays, multiplex assays, and/or immunohistochemistry may be performed on these tissue samples to assess potential associations between these biomarkers and clinical outcomes.

9.9. Health Economics

9.9.1. Patient-Reported Outcomes

Patient-reported outcome (PRO) measures will be administered manually, by paper and pencil methods, to assess prostate cancer related pain and health-related quality of life (HRQoL). The following 3 PRO questionnaires will be included in this study: the Worst Pain Numeric Rating Scale (NRS), CCI [redacted] Questionnaires should be administered in the language the participant is fluent or literate; according to the Schedule of Activities (Section 2), first the Worst Pain NRS, second CCI [redacted]

Endpoints and analyses using the below PRO measures will be described in the SAP.

Worst Pain NRS

The single-item Worst Pain NRS derived from the validated 15-item Brief Pain Inventory Short Form (BPI-SF) (Cleeland and Ryan 1994) and is scored according to the BPI-SF User Guide (Cleeland 2009). This Worst Pain NRS item measures worst pain over the last 24 hours on a 0 to 10-point NRS, where 0 is 'no pain' and 10 is 'pain as bad as you can imagine'.

CCI [redacted]

9.9.2. Health Care Resource Utilization

Investigators will be asked to report the use of **all** concomitant medications (in particular, analgesics, bisphosphonates, and RANK-L targeted agents), blood product transfusions, radiation therapy, surgery, and hospitalization days.

Data on analgesic medication use will be recorded on the Concomitant Medication eCRF. The use of pain medications from the previous visit should be reviewed with the patient at each subsequent visit. Information on new or stopped analgesics should be recorded. This information should be collected during the study and at the 30-day follow-up visit. Analgesic use will be classified into categories according to the World Health Organization - Analgesic Ladder (WHO-AL; Chung 2014; WHO 2018). The steps of the ladder are: 1) no analgesia, 2) nonopioids (e.g., salicylates and other nonsteroidal anti-inflammatory drugs [NSAIDs]), 3) weak opioids (e.g., codeine), and 4) strong opioids (e.g., morphine, oxycodone, hydromorphone, or methadone).

10. Statistical Considerations

10.1. Sample Size Determination

Patients enrolled in Part 1, Part 2, and Part 3 (if applicable) will be combined to form the experimental group (approximately CCI patients from Parts 1 and 2 in abemaciclib plus abiraterone acetate and prednisone, with an additional CCI patients from Part 3 if opened) and control group (approximately CCI patients from Parts 1 and 2 in placebo plus abiraterone acetate and prednisone, with an additional CCI patients from Part 3 if opened).

Radiographic progression-free survival is the primary endpoint for the study. The overall Type I error is controlled at a one-sided alpha level of 0.025 for the study. Group-sequential design and an extension of Chen's 2-in-1 adaptive design (Chen 2018) will be used to accommodate the event-driven plan for the futility, interims, and final rPFS analyses (see Section 10.3.1.1 for details). If Part 3 is opened, the final rPFS analysis will be performed after approximately CCI PFS events have occurred (i.e., an approximately CCI censoring rate). If Part 3 is not opened, the final rPFS analysis will be performed after approximately CCI rPFS events have occurred (i.e., an approximately CCI censoring rate). CCI

[redacted]

urther details on the marginal and conditional operating characteristics of this design can be found in the SAP, both for the assumed hazard ratio of CCI and other possible effect sizes. CCI

[redacted]

10.2. Populations for Analyses

The following populations will be defined for this study:

Intention-to-treat (ITT) population: will include all randomized patients. The ITT analysis of efficacy data will consider allocation of patients to treatment groups as randomized and not by actual treatment received. This population will be used for all baseline, efficacy (except for soft tissue tumor response related endpoints such as best overall response), and health economics analyses.

Measurable disease population: will include all randomized patients who have measurable disease in soft tissue at baseline according to modified RECIST v1.1. This population will be used for efficacy analyses based on soft tissue tumor response related endpoints such as best overall response.

Safety population: will include all randomized patients who received at least one dose of any study drug, regardless of their eligibility for the study. The safety evaluation will be performed

based on the first dose of study treatment a patient actually received, regardless of the arm to which he was randomized. The safety population will be used for all dosing/exposure, safety, and resource utilization analyses.

Pharmacokinetic population: will include all randomized patients who received at least 1 dose of any study drug and have evaluable PK samples and sufficient dosing information.

Biomarker population: will include the subset of patients from the ITT population from whom a valid assay result has been obtained.

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Lilly or its designee.

Unless otherwise stated, all tests of treatment effects will be conducted at a 1-sided alpha level of .025, and all CIs will be given at a 2-sided 95% level.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Handling of missing, unused, and spurious data are addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate.

10.3.1. Efficacy Analyses

10.3.1.1. Radiographic Progression Free Survival

The primary endpoint of this study is rPFS. The rPFS time is measured from the date of randomization to the earliest date of investigator-determined radiographic disease progression (by objective radiographic disease assessment per RECIST v1.1 for soft tissue AND/OR radionuclide bone scan using PCWG3 criteria for bone) or death from any cause, whichever occurs first. Patients who have neither progressed nor died will be censored at the day of their last radiographic tumor assessment (if available) or date of randomization if no post-initiation (i.e., post-baseline) radiographic assessment is available. The detailed censoring rules are described in the SAP.

There is 1 planned futility analysis, up to 2 planned adaptive interim analyses, and 1 final analysis for rPFS in this study. CCI [redacted].

CCI

The study will only be positive based on the final analysis of rPFS, the primary endpoint. If positive, testing of secondary endpoints will proceed as described in the SAP.

The futility and adaptive interim rPFS analyses will be performed by the DMC. The requirements for unblinding the sponsor at the interim analysis are found in Section 10.3.5.

The primary analysis of rPFS to test the superiority of experimental group to control group in improving rPFS time will be performed on the ITT population at an experiment-wise one-sided alpha level of 0.025 and will use the log-rank test stratified by the randomization factors of:

- Radiographic progression at study entry (yes/no)
- Measurable disease (yes/no)
- Prior docetaxel for mHSPC (yes/no).

These stratification factors were chosen because they represent important prognostic factors and/or an imbalance may bias the results. The corresponding hazard ratio (HR) between treatment groups will be estimated using a stratified Cox regression model (Cox 1972), stratified by the randomization strata. In addition, the Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the rPFS curves as well as rPFS rates at 3, 6, 9, and 12 months for each treatment group.

If Part 3 is opened for enrollment, then at the time of the primary analysis of rPFS, rPFS by BICR will also be assessed using the same methods. Further details on the comparison of rPFS by investigator-determined radiographic progression and rPFS by BICR can be found in the SAP.

10.3.1.2. Overall Survival

Overall survival is defined as the time from randomization until death from any cause. If the patient is alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the patient is known to be alive. Overall survival is an important secondary endpoint for this study. Further details concerning OS analyses can be found in the SAP.

10.3.1.3. Time to Prostate-Specific Antigen Progression

Time to PSA progression is a secondary endpoint of this study. The PSA progression is defined as a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir (or baseline value if baseline is the smallest on study), which is confirmed by a second value obtained 3 or more weeks later. Any post-baseline PSA measurements within 12 weeks since baseline will be ignored in determining PSA progression. Time to PSA progression is measured from the date of randomization to the date of first observation of PSA progression. Patients who have not had PSA progression will be censored at the day of their last PSA assessment (if available) or date of

randomization if no post-initiation (i.e., post-baseline) PSA assessment is available. The detailed censoring rules are described in the SAP.

The time to PSA progression analysis to test the superiority of the experimental group to the control group in improving time to PSA progression will be performed on the ITT population and will use the log-rank test stratified by the randomization factors.

The corresponding hazard ratio between treatment groups will be estimated using a stratified Cox regression model (Cox 1972), stratified by the randomization strata. In addition, the Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the time to PSA progression survival curves as well as rates at 3, 6, 9, and 12 months for each treatment group. These rates will be compared based on a normal approximation for the difference between the rates.

10.3.1.4. Objective Response Rate and Duration of Response

Other secondary efficacy endpoints related to soft tissue tumor response will be defined as shown in Table JPCM.10.

Table JPCM.10. Soft Tissue Tumor Response Related Endpoints

Endpoint	Definition
ORR	The proportion of patients with a soft tissue BOR of CR or PR according to RECIST v1.1, per investigator assessment
DoR	The time from the date of first evidence of a soft tissue CR or PR to the earliest date of investigator-determined radiographic disease progression (by objective radiographic disease assessment per RECIST 1.1 for soft tissue AND/OR radionuclide bone scan using PCWG3 criteria for bone) or death from any cause, whichever is earlier

Abbreviations: BOR = best overall response; CR = complete response; DoR = duration of response; ORR = objective response rate; PCWG3 = Prostate Cancer Working Group 3; PR = partial response; RECIST v 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1.

The ORR of each treatment group will be calculated using the measurable disease population. All rates will be compared between the experimental and control groups based on a normal approximation for the difference between the rates.

The DoR time is defined only for responders (patients with a best overall response of CR or PR) in the measurable disease population. A Kaplan-Meier analysis of DoR will be performed to estimate the DoR curve for each treatment group. Further details can be found in the SAP.

10.3.1.5. Time to Symptomatic Progression

Time to symptomatic progression is defined as the time from randomization to any of the following (whichever occurs earlier):

Symptomatic Skeletal Event (SSE), defined as symptomatic fracture, surgery or radiation to bone, or spinal cord compression
Pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy
Development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy.

For patients not known to have had symptomatic progression at the time of data analysis, data will be censored on the last date at which no symptomatic progression is indicated. Details concerning time to symptomatic progression analyses can be found in the SAP.

10.3.1.6. Other Exploratory Endpoints

CCI [redacted]

10.3.2. Safety Analyses

All patients who receive at least 1 dose of any study drug will be evaluated for safety and toxicity.

The Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 (or higher) will be used to map reported AEs to MedDRA terms. The MedDRA Lower Level Term will be used in the treatment-emergent computation. Treatment-emergent adverse events (TEAEs) will be summarized by System Organ Class (SOC) and by decreasing frequency of Preferred Term (PT) within SOC. Preferred terms identified by Medical as clinically identical or synonymous will be grouped together under a single consolidated PT. For example, 'Neutropenia' and 'Neutrophil count decreased' will be reported as 'Neutropenia.' All listings and summaries will use the PT resulting from this process. The National Cancer Institute (NCI) CTCAE v 5.0 will serve as the reference document for grading the severity of all AEs and other symptoms.

Safety analyses will include summaries of the following:

- TEAEs, including severity and possible relationship to any study drug and/or study treatment
- treatment-emergent SAEs, including possible relationship to study drug and/or study treatment
- AEs leading to dose adjustments of each study treatment
- discontinuations from study treatment due to AEs or death
- treatment-emergent abnormal changes in laboratory values
- treatment-emergent abnormal changes in vital signs.

10.3.3. Other Analyses

10.3.3.1. Patient Disposition

A detailed description of patient disposition will be provided, including a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated, as well as number and percentage of patients completing the study, as defined in the SAP, or discontinuing (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

10.3.3.2. Patient Characteristics

Patient characteristics at baseline will be summarized by treatment group:

Patient demographics
Baseline disease characteristics
Pre-existing conditions
Historical illnesses
Prior anticancer therapy.

Other patient characteristics will be summarized as deemed appropriate.

10.3.3.3. Treatment Compliance

Treatment compliance will be summarized for all treated patients by treatment group.

Compliance information for blinded study drug will be collected through tablets/capsules counts at each cycle/visit. The estimate of percent compliance will be given by:

$$\text{Percent Compliance} = \frac{\text{Actual cumulative dose taken}}{\text{Expected cumulative dose to be taken}} \text{ x } 100$$

The actual cumulative dose taken will be determined based on counting the number of tablets/capsules units returned at each visit and subtracting that number from the number of tablets/capsules dispensed. The expected cumulative dose to be taken will be determined based on the assigned dose and taking into account any dose reductions or omissions.

Compliance information for abiraterone acetate and prednisone will be collected through patient dosing diaries and/or patient recall on the number of doses actually taken in the previous cycle. Otherwise, the estimate of percent compliance will be done using the same formula/calculation for blinded study drug percent compliance.

10.3.3.4. Extent of Exposure

The number of cycles received, dose omissions, dose reductions, and dose intensity will be summarized for all treated patients by treatment group.

10.3.3.5. Concomitant Therapy

A summary of prior and concomitant medications by treatment group will be reported.

10.3.3.6. Post-Study-Treatment-Discontinuation Therapy

The numbers and percentages of patients receiving post-study-treatment-discontinuation anticancer therapies will be provided by type of therapy (surgery, radiotherapy, or systemic therapy) and by drug class and/or name, overall and by line of therapy.

10.3.3.7. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic analyses will be conducted on all patients who have received at least 1 dose of any study drug and have evaluable PK samples and sufficient dosing information. Measures will be taken to support the timely availability of the results of PK analyses. These measures will include periodic transfers for review of data relevant to PK analyses including dosing and

bioanalytical results. No efficacy data will be included in the early-snapshot PK datasets. Finally, this early PK analysis will be conducted by a separate team of PK analysts, independent of the core study team.

The observed concentrations of abemaciclib will be summarized by time and dose. The observed concentrations of prednisone and abiraterone will be summarized by time.

Mean population PK parameters for abemaciclib (and metabolites, if warranted) in plasma (e.g., clearance, exposure, volume of distribution) and inter-individual PK variability may be analyzed using a population PK approach with nonlinear mixed-effect modeling (NONMEM) software. The effect of the combination treatment prednisone and abiraterone acetate on abemaciclib may also be evaluated using a population PK approach.

Pharmacodynamic samples will be collected as specified in the Study Schedule and PK and PD Sampling Schedule (Appendix 4). Refer to these attachments (including footnotes) for important information about these samples and their collection.

Furthermore, if warranted, PD data (such as neutrophil counts in blood or PSA) collected in this study may also be analyzed by means of NONMEM and connected to the population PK model in a PK/PD model.

10.3.3.8. Biomarker Analyses

Sections 9.8.1 and 9.8.2 describe the biomarker samples that will be collected during the course of the study and will be used to carry out biomarker specific exploratory analyses. In addition to characterizing the biomarker data distribution by treatment arm and overall, these analyses may include the assessment of prognostic or predictive relationships between the biomarker(s) being investigated and the clinical efficacy endpoints of the study.

10.3.3.9. Health Outcome/Quality-of-Life Analyses

All health outcome, quality of life, and heath utilization analyses will be described in the SAP.

10.3.4. Subgroup Analyses

A prespecified list of subgroups will be identified in the SAP. The treatment effect within each subgroup will be summarized. Other subgroup analyses not specified in the SAP may be performed as deemed appropriate. These subgroups will be based on important characteristics, for example, prognostic significance.

10.3.5. Interim Analyses

There are planned interim analyses for safety, 1 planned interim analysis for futility, and up to 2 planned adaptive interim analyses. The first safety interim analysis described below will be reviewed by an AC made up of Lilly members not involved in the day to day study conduct to identify the RP2D using only safety and PK data. All other interim analyses will be reviewed by an independent DMC made up of external members, none of whom are involved as study investigators. Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document. Further details may also be found in the DMC Charter.

10.3.5.1. Safety Interim Analyses

The first safety interim analysis is planned at [redacted]. The AC members will review safety and available PK data at the interim analysis to determine the dose of abemaciclib (RP2D) in combination with abiraterone acetate plus prednisone for Part 2. In the case of unacceptable and/or unmanageable toxicity of the combination, the AC may recommend termination of the study upon completion of Part 1. This analysis will only use PK and safety data, and will be the only unblinded analysis the AC will review. After dose selection, only the DMC will be authorized to review unblinded data.

Additionally, the DMC will review safety as described in the DMC charter, no less than approximately every 6 months. At each applicable interim analysis, the DMC may recommend the trial continue without modifications, continue with specific modifications, or be stopped for safety concerns. There will be no prespecified rules for stopping the trial due to safety concerns. The DMC members will review unblinded safety data at each applicable interim analysis. If a significant safety signal is identified, the DMC may recommend a protocol amendment, termination of enrollment, and/or termination of study treatment. The recommendations of the DMC will be communicated to the Lilly Senior Management Designee and, if necessary, an Internal Review Committee.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the treatment group level, members of the DMC can conduct additional analyses of the safety data. Additionally, unblinding of a limited number of Lilly representatives external to the study team may be required for evaluation of selected SAEs for determination of regulatory reporting.

10.3.5.2. Futility/Adaptive Interim Analyses

The interim analysis for futility is planned after approximately [redacted] rPFS events have been observed. Futility for the interim analysis will be determined in terms of rPFS. The DMC should recommend stopping the trial for futility if the observed hazard ratio is [redacted]. The DMC will consider all evidence, including safety and other efficacy parameters, in making this decision.

The planned adaptive interim analyses are based on rPFS, and will occur at approximately [redacted] rPFS and, if necessary, at [redacted] rPFS events. The adaptive interim analyses will be conducted to determine whether Part 3 of the study should be opened for enrollment. The expansion decision criteria will be based on the conditional probability that the final rPFS analysis, given Part 3 will be opened for enrollment, will be positive. Further details on the decision rule, the model used for the decision criteria, and simulation results illustrating their operating characteristics can be found in the SAP. Should Part 3 be opened for enrollment after the first adaptive interim analysis at [redacted] rPFS events, a second adaptive interim analysis will not be performed.

The sponsor has no intent to stop the study based on the adaptive interim analyses and all patients will continue follow-up for all study objectives until study close. In addition, patients will remain blinded for the duration of the study unless the criteria in Section 7.3 are met.

Only the DMC is authorized to evaluate unblinded adaptive interim and futility analyses. Study sites will receive information about interim results only if they need to know for the safety of their patients.

11. References

Chung KC, Barlev A, Braun AH, Qian Y, Zagari M. Assessing analgesic use in patients with advanced cancer: development of a new scale—the analgesic quantification algorithm. *Pain Med.* 2014;15(2):225-232.

Cleeland CS. The Brief Pain Inventory user guide. 2009;1-63.

Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singap.* 1994;23(2):129-138.

Cox DR. Regression models and life-tables. J Royal Stat Soc Ser B. 1972;74(2):187-220.

Crawford J, Armitage J, Balducci L, Bennett C, Blayney DW, Cataland SR, Dale DC, Demetri GD, Erba HP, Foran J, Freifeld AG, Goemann M, Heaney ML, Htoy S, Hudock S, Kloth DD, Kuter DJ, Lyman GH, Michaud LB, Miyata SC, Tallman MS, Vadhan-Raj S, Westervelt P, Wong MK; National Comprehensive Cancer Network. Myeloid growth factors. *J Natl Compr Cancer Netw*. 2009;7(1):64-83.

de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, Chi KN, Jones RJ, Goodman OB Jr, Saad F, Staffurth JN, Mainwaring P, Harland S, Flaig TW, Hutson TE, Cheng T, Patterson H, Hainsworth JD, Ryan CJ, Sternberg CN, Ellard SL, Fléchon A, Saleh M, Scholz M, Efstathiou E, Zivi A, Bianchini D, Loriot Y, Chieffo N, Kheoh T, Haqq CM, Scher HI; COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med.* 2011;364(21):1995-2005.

Dickler MN, Tolaney SM, Rugo HS, Cortés J, Diéras V, Patt D, Wildiers H, Hudis CA, O'Shaughnessy J, Zamora E, Yardley DA, Frenzel M, Koustenis A, Baselga J. MONARCH 1, A Phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2− metastatic breast cancer. *Clin Cancer Res.* 2017;23(17):5218-5224.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.

CCI [redacted]

Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, Özgüroğlu M, Ye D, Feyerabend S, Protheroe A, De Porre P, Kheoh T, Park YC, Todd MB, Chi KN; LATITUDE Investigators. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2017;377(4):352-360.

Goetz MP, Martin M, Di Leo A, Im SA, Awada A, Forrester T, Frenzel M, Cox J, Barriga S, Toi M, Iwata H, Johnston S. MONARCH 3: abemaciclib as initial therapy for patients with HR+, HER2- advanced breast cancer – results from the preplanned final PFS analysis [abstract]. AACR Annual Meeting 2018. 14-18 April 2018; Chicago IL. Philadelphia (PA) AACR; 2018. Abstract nr CT040.

James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, Ritchie AW, Parker CC, Russell JM, Attard G, de Bono J, Cross W, Jones RJ, Thalmann G, Amos C, Matheson D, Millman R, Alzouebi M, Beesley S, Birtle AJ, Brock S, Cathomas R, Chakraborti P, Chowdhury S, Cook A, Elliott T, Gale J, Gibbs S, Graham JD, Hetherington J, Hughes R, Laing R, McKinna F, McLaren DB, O'Sullivan JM, Parikh O, Peedell C, Protheroe A, Robinson AJ, Srihari N, Srinivasan R, Staffurth J, Sundar S, Tolan S, Tsang D, Wagstaff J, Parmar MK; STAMPEDE investigators. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet* 2016;387:1163-1177.

James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, Ritchie AWS, Amos CL, Gilson C, Jones RJ, Matheson D, Millman R, Attard G, Chowdhury S, Cross WR, Gillessen S, Parker CC, Russell JM, Berthold DR, Brawley C, Adab F, Aung S, Birtle AJ, Bowen J, Brock S, Chakraborti P, Ferguson C, Gale J, Gray E, Hingorani M, Hoskin PJ, Lester JF, Malik ZI, McKinna F, McPhail N, Money-Kyrle J, O'Sullivan J, Parikh O, Protheroe A, Robinson A, Srihari NN, Thomas C, Wagstaff J, Wylie J, Zarkar A, Parmar MKB, Sydes MR; STAMPEDE Investigators. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med*. 2017;377:338-351.

Kaplan EL, Meier P. Nonparametric estimation of incomplete observations. J Amer Stat Assoc. 1958;53:457-481.

CCI [redacted]

Lonergan, PE, Tindall, DJ. Androgen receptor signaling in prostate cancer development and progression. *J Carcinog.* 2011;10:20.

[NCI] National Cancer Institute. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 5.0, DCTD, NCI, NIH, DHHS. 2017. Publish date: 27 November 2017.

Noonan KL, North S, Bitting RL, Armstrong AJ, Ellard SL, Chi KN. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. *Ann Oncol.* 2013;24(7):1802-1807.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

Ortega S, Malumbres M, Barbacid M. Cyclin D-dependent kinases, INK4 inhibitors and cancer. *Biochim Biophys Acta*. 2002;1602(1):73-87.

CCI

Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Arcasoy MO, Spivak JL, Bennett CL, Bohlius J, Evanchuk D, Goode MJ, Jakubowski AA, Regan DH, Somerfield MR; American Society of Clinical Oncology; American Society of Hematology. American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *J Clin Oncol.* 2010;28(33):4996-5010.

Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, Fizazi K, Mainwaring P, Piulats JM, Ng S, Carles J, Mulders PF, Basch E, Small EJ, Saad F, Schrijvers D, Van Poppel H, Mukherjee SD, Suttmann H, Gerritsen WR, Flaig TW, George DJ, Yu EY, Efstathiou E, Pantuck A, Winquist E, Higano CS, Taplin ME, Park Y, Kheoh T, Griffin T, Scher HI, Rathkopf DE; COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med.* 2013;368(2):138-148.

Sartor O, de Bono JS. Metastatic prostate cancer. *N Engl J Med*. 2018;378(17):1653-1654.

Scher HI, Morris MJ, Basch E, Heller G. End points and outcomes in castration-resistant prostate cancer: from clinical trials to clinical practice. *J Clin Oncol.* 2011;29(27):3695-3704.

Scher HI, Morris MJ, Stadler WM, Higano C, Basch E, Fizazi K, Antonarakis ES, Beer TM, Carducci MA, Chi KN, Corn PG, de Bono JS, Dreicer R, George DJ, Heath EI, Hussain M, Kelly WK, Liu G, Logothetis C, Nanus D, Stein MN, Rathkopf DE, Slovin SF, Ryan CJ, Sartor O, Small EJ, Smith MR, Sternberg CN, Taplin ME, Wilding G, Nelson PS, Schwartz LH, Halabi S, Kantoff PW, Armstrong AJ; Prostate Cancer Clinical Trials Working Group 3. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. *J Clin Oncol.* 2016;34(12):1402-1418.

Schrader AJ, Boegemann M, Ohlmann CH, Schnoeller TJ, Krabbe LM, Hajili T, Jentzmik F, Stoeckle M, Schrader M, Herrmann E, Cronauer MV. Enzalutamide in castration-resistant prostate cancer patients progressing after docetaxel and abiraterone. *Eur Urol*. 2014;65:30-36.

[SEER] SEER Cancer Stat Facts: Prostate Cancer. National Cancer Institute. Bethesda, MD 2017. Available at: https://seer.cancer.gov/statfacts/html/prost.html. Accessed 18 June 2018.

Sherr CJ. Cancer Cell Cycles. *Science*. 1996;274:1672-1677.

Sledge GW Jr, Toi M, Neven P, Sohn J, Inoue K, Pivot X, Burdaeva O, Okera M, Masuda N, Kaufman PA, Koh H, Grischke EM, Frenzel M, Lin Y, Barriga S, Smith IC, Bourayou N, Llombart-Cussac A. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2− advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol.* 2017;35(25):2875-2884.

Slud E, Wei LJ. Theory and Method: Two-Sample Repeated Significance Tests Based on the Modified Wilcoxon Statistic. J Amer Stat Assoc. 1982;77(380):862-868.

Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, Goldberg JM, Khatcheressian JL, Leighl NB, Perkins CL, Somlo G, Wade JL, Wozniak AJ, Armitage JO; American Society of Clinical Oncology. Recommendations for the Use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol.* 2015;33(28):3199-3212.

Smith MR, Saad F, Rathkopf DE, Mulders PFA, de Bono JS, Small EJ, Shore ND, Fizazi K, Kheoh T, Li J, De Porre P, Todd MB, Yu MK, Ryan CJ. Clinical outcomes from androgen signaling-directed therapy after treatment with abiraterone acetate and prednisone in patients with metastatic castration-resistant prostate cancer: post hoc analysis of COU-AA-302. *Eur Urol.* 2017;72(1):10-13.

Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, Wong YN, Hahn N, Kohli M, Cooney MM, Dreicer R, Vogelzang NJ, Picus J, Shevrin D, Hussain M, Garcia JA, DiPaola RS. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med.* 2015;373(8):737-746.

[WHO] World Health Organization. *WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents*. Geneva: World Health Organization; 2018.

CCI [redacted]

Appendix 1. Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
ADT	androgen-deprivation therapy
AE	Adverse event: any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration-versus-time curve
BICR	blinded, independent, central review
blinding/masking	A procedure in which one or more parties to the study are kept unaware of the treatment assignment. Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
BP	blood pressure
BPI-SF	Brief Pain Inventory Short Form
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase

CMV	cytomegalovirus
CNS	central nervous system
collection database	a computer database where clinical study data are entered and validated.
CR	complete response
CRF	case report form
CRP/CRS	Clinical Research Physician/Clinical Research Scientist: Individual responsible for the medical conduct of the study.
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCSI	Developmental Core Safety Information
DBL	direct bilirubin
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
effective method of contraception	For all countries except Japan, effective method of contraception means male condom with spermicide, female condom with spermicide, diaphragm with spermicide, cervical sponge, or cervical cap with spermicide. For Japan, effective method of contraception means bilateral tubal ligation, male condom with spermicide, intrauterine device that has been in place for at least 3 months before the first dose of study treatment, or an oral contraceptive pill taken for at least 3 months before the first dose of study treatment.
end of study	date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
CCI	[redacted]
ERB	ethical review board
ESA	erythropoiesis-stimulating agent

ET	endocrine therapy
EU	European Union
CCI	[redacted]
FDA	Food and Drug Administration
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factor
GDPR	EU General Data Protection Regulation
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
HER2−	human epidermal growth factor receptor 2-negative
HR+	hormone receptor–positive
HR	hazard ratio
HRQoL	health-related quality of life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation (formerly the International Conference on Harmonisation)
interim analysis	an analysis of clinical study data conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	institutional review board
ITT	intention-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IV	intravenous
IWRS	interactive Web-response system

LC-MS/MS	liquid chromatography with tandem mass spectrometry
LHRH	luteinizing hormone-releasing hormone
MATE	multidrug and toxin-extrusion protein
MBC	metastatic breast cancer
mCRPC	metastatic castration-resistant prostate cancer
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involves a failure to uphold one or more of the five "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
MedDRA	Medical Dictionary for Regulatory Activities
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
mTOR	mammalian target of rapamycin
MUGA	multigated acquisition scan
NCI	National Cancer Institute
NONMEM	nonlinear mixed-effect modeling
NRS	Numerical Rating scale
NSAI	nonsteroidal aromatase inhibitor
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association

OCT2	organic cation transporter 2
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PCa	prostate cancer
PCS	prostate cancer subscale
PCWG2	Prostate Cancer Working Group 2
PCWG3	Prostate Cancer Working Group 3
PD	pharmacodynamic(s)
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PS	performance status
PT	MedDRA Preferred Term
randomize	the process of assigning patients to an experimental group on a random basis.
Rb	retinoblastoma
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
rescreen	to screen a patient who was previously declared a screen failure for the same study
RNA	ribonucleic acid
rPFS	radiographic progression-free survival
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.

screen failure	patient who does not meet one or more criteria required for participation in a study
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SOC	MedDRA System Organ Class
SSE	symptomatic skeletal event
study completion	occurs following the final analysis of overall survival, as determined by Lilly.
SUSARs	suspected unexpected serious adverse reactions Refers to an adverse event that occurs in a clinical trial participant, which is assessed by the sponsor and or study investigator as being unexpected, serious, and as having a reasonable possibility of a causal relationship with the study intervention.
TBL	total bilirubin
TEAE	treatment-emergent adverse event: an untoward medical occurrence that emerges during a defined treatment period, having been absent at baseline, or worsens relative to the baseline state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
VTE	venous thromboembolic event
WHO	World Health Organization
WHO-AL	World Health Organization - Analgesic Ladder

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology: laboratory[a]	**Local**	**Central**
Leukocytes (WBC)		X
Neutrophils[b]		X
Lymphocytes		X
Monocytes		X
Eosinophils		X
Basophils		X
Erythrocytes (RBC)		X
Hemoglobin (HGB)		X
Hematocrit (HCT)		X
Mean corpuscular volume (MCV)		X
Mean corpuscular hemoglobin concentration (MCHC)		X
Platelets (PLT)		X

Coagulation: laboratory	**Local**	**Central**
Activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT)	X	
International normalized ratio (INR) or Prothrombin time (PT)	X	

Clinical Chemistry: laboratory[a]	**Local**	**Central**
Serum Concentrations of:		
Alanine aminotransferase (ALT)		X
Albumin		X
Alkaline phosphatase		X
Aspartate aminotransferase (AST)		X
Bilirubin, direct		X
Bilirubin, total		X
Blood urea nitrogen (BUN) or blood urea		X
Calcium		X
Cholesterol		X
Creatine kinase (CK)		X
Cystatin C		X
Creatinine		X
Glucose, nonfasting		X
High-density lipoproteins (HDL)		X
Lactate dehydrogenase (LDH)		X
Low-density lipoproteins (LDL)		X
Magnesium		X
Phosphate		X
Potassium		X
Protein		X
Sodium		X
Triglycerides		X
Urate		X

Urinalysis: laboratory	**Local**	**Central**

Blood	X
Glucose	X
Ketones	X
pH	X
Protein	X
Specific gravity	X
Urine leukocyte esterase	X

Other Tests: laboratory[a]	**Local**	**Central**
PSA		X
Testosterone		X

Abbreviations: CRF = case report form; PSA = prostate-specific antigen; RBC = red blood cells; WBC = white blood cells.

[a] Enrollment and treatment decisions may be based on local laboratory results. A duplicate sample must still be sent to the central laboratory. Differences between these samples will not constitute a protocol deviation.

[b] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. When a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

Appendix 3. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for:

ensuring that the patient/patient's legal representative understands the nature of the study, the potential risks and benefits of participating in the study, and that the patient's participation is voluntary

ensuring that informed consent is given by each patient/patient's legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any study procedures and prior to the administration of study treatment.

providing a copy of the signed ICF(s) to the patient/patient's legal representative and retaining a copy of the signed ICF in the site file

answering any questions the patient/patient's legal representative may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's/patient's legal representative's willingness to continue the patient's participation in the study.

Ethical Review

Documentation of ERBs/IRBs approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs/IRBs, before it is used at the investigative site(s). All ICFs must be compliant with the International Council for Harmonisation (ICH) guideline on good clinical practice (GCP).

The study site's ERBs/IRBs should be provided with the following:

the protocol, protocol amendments, and relevant protocol addenda and the current Investigator's Brochure (IB) or package labeling, Patient Information Leaflet, Package Insert, or Summary of Product Characteristics and updates during the course of the study

ICF

other relevant documents (for example, curricula vitae advertisements).

Regulatory Considerations

This study will be conducted in accordance with the protocol and with:

consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

applicable ICH GCP Guidelines

applicable laws and regulations.

Some obligations of Lilly may be assigned to a third-party organization.

Investigator Information

Physicians with a specialty in oncology or urology will participate as investigators in this clinical study.

Investigator Reporting Requirements

The investigator will be responsible for reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.

Protocol Signatures

Lilly's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Final Report Signature

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

If the lead investigator is unable to serve as the clinical study report coordinating investigator, another investigator will be chosen by Lilly to fulfill this role.

The Lilly responsible medical officer and statistician will approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and verify data reported to detect potential errors.

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data-capture system (EDC) will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered a source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, clinical outcome assessment (COA) data (questionnaires, scales, self-reported diary data, etc.) will be collected by the subject, via a paper source document and will be transcribed by the investigator site personnel into the EDC system.

Data collected via the sponsor-provided data capture system(s) will be stored at third-party organizations (at third parties). The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports/electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

Data Protection

Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as

described in the informed consent. This is done by the site personnel through the informed consent process.

The participant must be informed through the informed consent by the site personnel that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration, or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations, including the General Data Protection Regulation.

Study and Site Closure

Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Discontinuation of the Study

The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Communication of Suspended or Terminated Dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by Lilly to all investigators (for example, by phone and/or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be followed up by Lilly personnel prior to any further planned dosing. If a dose is planned imminently, Lilly personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the

integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Appendix 4. Sampling Schedule for Pharmacokinetics/Pharmacodynamics

Dosing dates and times are required to be collected on the appropriate form 1 day prior to the PK samples. The exact date and time of collection of each venous blood sample must also be recorded on the laboratory requisition.

Due to practical and logistical concerns, some deviation from the specified sampling is possible. Sites should keep in mind that drawing the sample and recording the actual time on the appropriate form are of principal importance. Differences from the time specified in the protocol are not considered protocol deviations as long as samples are collected and accurate dates and times are recorded in a timely manner on the appropriate forms. The schedule for PK sampling is summarized in the table below. The date and exact time of collection for each venous blood sample should be documented on the laboratory requisition. The intention of this sampling schedule beyond the first dose is to coincide with standard laboratories, for example, those that are used to determine how to begin the next cycle of dosing (e.g., hepatic monitoring, hematology, and clinical chemistry that can be done ≤3 days before the first day of a cycle). Hence, these samples should be taken close in time to those other laboratories. This should avoid difficulties or questions associated with how to handle sampling if the decision is made to hold or delay the dose.

Pharmacokinetic Sampling Schedule

Cycle(C) and Day(D)	PK Sample Number	Sampling Time PK from Blood[a]
C1D1	1	Pre dose
C1D1	2	Any time 30 minutes or more after blinded study treatment dose
C1D15	3	Any time after blinded study treatment dose
C2D1	4	Any time after blinded study treatment dose
C2D15	5	Any time after blinded study treatment dose
C3D1	6	Any time after blinded study treatment dose

Abbreviation: PK = pharmacokinetic.

[a] Samples of approximately 4 mL of whole blood will be drawn for measurement of abemaciclib and its metabolites LSN3106726, LSN2839567, abiraterone and prednisone.

Note: The time of abiraterone acetate, prednisone, and blinded study drug dose taken before the sample must be recorded on the day the PK sample is drawn.

Biomarker Sampling Schedule

Cycle(C) and Day(D)	Tumor Tissue	Plasma Biomarker	Blood	PGx Whole blood
Baseline (Day -28 to Day -1)	X[a] (mandatory for Part 1 and Part 2, optional for Part 3)			
C1D1		Predose	Predose	Predose[c]
C2D1		X	X	
C3D1		X	X	
Short-term follow-up (Visit 801)	X[b] (optional)	X		

Abbreviation: PGx = pharmacogenetics.

[a] To meet study eligibility criteria for Part 1 and Part 2, patients must have metastatic disease amenable to biopsy of at least 1 metastatic site for biomarker analysis. Soft-tissue as well as bony metastatic lesions will be considered acceptable. Soft-tissue biopsy is preferred to bone biopsy whenever possible. Adequate archival metastatic tissue can be used in lieu of a new biopsy if the biopsy was done within 12 weeks prior to randomization and no treatment was initiated from biopsy to study entry.

[b] Optional biopsy of metastatic lesion at the time of disease progression (the progressing metastatic lesion preferred) or if the patient discontinues study treatment for reasons other than progressive disease and have been on study treatment for ≥6 cycles.

[c] Collect once. Sample can be collected at a subsequent timepoint if not collected on Cycle 1 Day 1.

Appendix 5. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly clinical research physician.

Hepatic Evaluation Testing Refer to protocol Hepatic Safety Monitoring Section 9.4.2 for guidance on appropriate test selection. **For testing selected, analysis is required to be completed by the Lilly designated central laboratory except for Microbiology.** **Local testing may be performed <u>in addition to central testing</u> when required for immediate patient management.** **Results will be reported if a validated test or calculation is available.**	
Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - Red Blood Cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - White Blood Cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen Protein Adducts
Platelets	Alkaline Phosphatase Isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Coagulation	Copper
	Ethyl Alcohol (EtOH)
Prothrombin Time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (Quantitative)
Hepatitis A Virus (HAV) Testing:	Immunoglobulin IgG (Quantitative)
HAV Total Antibody	Immunoglobulin IgM (Quantitative)
HAV IgM Antibody	Phosphatidylethanol (PEth)
Hepatis B Virus (HBV) Testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug Screen
Hepatitis B surface antibody (Anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (Anti-HBc)	**Other Serology**

Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]
HBV DNA [d]	Anti-actin antibody [b]
Hepatis C Virus (HCV) Testing:	Epstein-Barr Virus (EBV) Testing:
HCV antibody	EBV antibody
HCV RNA [d]	EBV DNA [d]
Hepatitis D Virus (HDV) Testing:	Cytomegalovirus (CMV) Testing:
HDV antibody	CMV antibody
Hepatitis E Virus (HEV) Testing:	CMV DNA [d]
HEV IgG antibody	Herpes Simplex Virus (HSV) Testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [d]	HSV (Type 1 and 2) DNA [d]
Microbiology [c]	Liver Kidney Microsomal Type 1 (LKM-1) Antibody
Culture:	
Blood	
Urine	

[a] This is not required if Anti-Actin Antibody is tested.
[b] This is not required if Anti-smooth muscle antibody (ASMA) is tested.
[c] Assayed by Investigator-designated local laboratory ONLY; no Central Testing available.
[d] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Appendix 6. Protocol JPCM ECOG Performance Status

ECOG Performance Status

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

Source: Oken et al. 1982

Appendix 7. Protocol JPCM RECIST Criteria 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the new Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1; Eisenhauer et al. 2009).

Measurability of Tumor at Baseline

Tumor lesions/lymph nodes will be categorized at baseline as measurable or nonmeasurable. Measurable disease is defined by the presence of at least 1 measurable lesion. If a metastatic lymph node is more amenable to biopsy than the primary breast lesion, the lymph node can be used for study biopsies.

Measurable

Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness 5 mm)

10 mm caliper measurement by clinical exam (non-measurable lesions if cannot be accurately measured with calipers)

20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be 15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be 5 mm).

Nonmeasurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special Considerations for Lesion Measurability

Bone lesions:

Bone scan, positron emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure 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.

Blastic bone lesions are non-measurable.

Cystic lesions:

Simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable)

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability. If noncystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are non-measurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Non-nodal Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and can be reproduced in repeated measurements. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of 15 mm by CT scan. All measurements are to be recorded in the eCRF in millimeters (or decimal fractions of centimeters [cm]).

Nontarget Lesions

All other lesions (or sites of disease) are identified as nontarget lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as 'present,' 'absent,' or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the eCRF (for example, multiple liver metastases recorded as 1 liver lesion).

Lymph nodes with short axis 10 mm but <15 mm should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and are not recorded or followed.

Specifications by Methods of Measurement

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is

should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical exam.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. If prior to enrollment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the patient at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial and 10 mm diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray when progression is an important endpoint. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI: CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm. When CT scan have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Ultrasound: Ultrasound should not be used to measure lesion size. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response (CR). Specific guidelines for both prostate-specific antigen (PSA) response (in recurrent prostate cancer) and CA-125 response (in recurrent ovarian cancer) have been published. *Cytology, Histology*: These techniques can be used to differentiate between partial responses (PR) and CR in rare cases, if required by protocol (for example, residual lesions in

tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease.

Pet Scan (FDG-PET, PET CT): PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

Bone Scan: If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a CR or PR in target disease or when progression in bone is suspected.

Response Criteria

Evaluation of Target Lesions

Complete Response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Tumor marker results must have normalized.

Partial Response: At least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters.

Progressive Disease: At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

For equivocal findings of progression (for example, 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.

Stable Disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Not Evaluable: When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

Evaluation of Nontarget Lesions

Complete Response: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be non-pathological or normal in size (<10 mm short axis).

Non-CR/non-PD: Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing nontarget lesions. The appearance of 1 or more new lesions is also considered progression.

Not Evaluable: When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. The Best Overall Response will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. Table APP.7.1 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

Table APP.7.1. Time Point Response: Patients with Target (Nontarget) Disease

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

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = inevaluable.

Table APP.7.2 is to be used when patients have nonmeasurable disease only.

Table APP.7.2. Time Point Response: Patients with Nontarget Disease Only

Nontarget 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

Abbreviations: CR = complete response; NE = nonevaluable; PD = progressive disease.

[a] non-CR/non-PD is preferred over stable disease for nontarget disease.

Frequency of Tumor Re-Evaluation

A baseline tumor evaluation must be performed within 4 weeks before patient begins study treatment. Frequency of tumor re-evaluation while on and adapted to treatment should be protocol-specific and adapted to the type and schedule of treatment. In the context of Phase 2 studies in which the beneficial effect therapy is not known, follow-up every 6 to 8 weeks is reasonable. Normally, all target and nontarget sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Confirmatory Measurement/Duration of Response

Confirmation:
The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in *nonrandomized trials* in which response (CR/PR) is the primary end point. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontargets is not required.

However, in *randomized trials* (Phase 2 or 3) or studies in which SD or progression is the primary endpoint, confirmation of response is not required. However, elimination of the requirement may increase the importance of central review to protect against bias, in particular of studies that are not blinded.

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 6 weeks measured from first dose.

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease
Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of PD).

Independent Review of Response and Progression

When objective response (CR+PR) is the primary end point, and when key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment.

Appendix 8. Protocol JPCM Strong and Moderate Inducers of CYP3A4, Strong Inhibitors of CYP3A4, Substrates of CYP2D6 with Narrow Therapeutic Range, and Transporter Substrates with Narrow Therapeutic Range

The information in this attachment is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated. Please refer to Section 7.7 Concomitant Therapy.

This list is not intended to be exhaustive. With available information continually evolving, the status of every relevant drug cannot be guaranteed. Please consult with the medical monitor in case of any doubt about a potential drug-drug interaction.

Strong Inducers of CYP3A4

Aminoglutethimide
Apalutamide
Carbamazepine (daily dose exceeding 600 mg)
Enzalutamide
Fosphenytoin (see also phenytoin)
Ivosidenib
Lumacaftor
Mitotane
Phenobarbital
Phenytoin
Rifabutin
Rifampicin (rifampin)
Rifapentine
St. John's wort

Moderate Inducers of CYP3A4

Bosentan
Carbamazepine (daily dose 600 mg or lower)
Cenobamate
Dabrafenib
Danshen (*Salvia miltiorrhiza*)
Efavirenz
Elagolix
Encorafenib
Etravirine
Genistein
Lopinavir (alone)
Lorlatinib
Modafinil

Nafcillin (intravenous)
Pentobarbital
Primidone
Sotorasib
Thioridazine
Tocilizumab (atlizumab)

Strong inhibitors of CYP3A4

Atazanavir and cobicistat
Boceprevir
Ceritinib
Clarithromycin
Cobicistat (see atazanavir and cobicistat)
Conivaptan
Danoprevir and ritonavir
Elvitegravir and ritonavir
Fosamprenavir and ritonavir
Grapefruit juice
Idelalisib
Indinavir and ritonavir
Itraconazole
Josamycin
Ketoconazole

CYP2D6 Substrates with Narrow Therapeutic Range

Astemizole
Flecainide
Mexiletine
Pimozide
Propafenone
Thioridazine

Transporter Substrates with Narrow Therapeutic Range

Dabigatran
Digoxin
Dofetilide
Metformin

Appendix 9. Protocol JPCM CTCAE 5.0 Diarrhea/Pneumonitis/ALT and AST Increased Definitions

Diarrhea/Pneumonitis/ALT and AST increased will be evaluated in this study using the criteria proposed by CTCAE v5.0 revised: Gastrointestinal disorders, Respiratory, Thoracic, and Mediastinal Disorders, and Investigations.

Grade					
Adverse Event	**1**	**2**	**3**	**4**	**5**
Gastrointestinal Disorders					
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: a disorder characterized by an increase in frequency and/or loose watery bowel movements.					
Respiratory, Thoracic, and Mediastinal Disorders					
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: a disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.					

Investigations					
Alanine aminotransferase (ALT) increased	>ULN through 3.0 x ULN if baseline was normal; 1.5 through 3.0 x baseline if baseline was abnormal	>3.0 through 5.0 x ULN if baseline was normal; >3.0 through 5.0 x baseline if baseline was abnormal	>5.0 through 20.0 x ULN if baseline was normal; >5.0 through 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Death
Definition: a finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.					
Aspartate aminotransferase (AST) increased	>ULN through 3.0 x ULN if baseline was normal; 1.5 through 3.0 x baseline if baseline was abnormal	>3.0 through 5.0 x ULN if baseline was normal; >3.0 through 5.0 x baseline if baseline was abnormal	>5.0 through 20.0 x ULN if baseline was normal; >5.0 through 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Death
Definition: a finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.					

Abbreviation: ADL = activities of daily living; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; ULN = upper limit of normal.

Appendix 10. Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this Appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in consultation with the investigator.

Exceptional Circumstances

Exceptional circumstance are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing Changes under Exceptional Circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

Additional notification to these groups will not typically be required unless they have specific conditions in which notification is required. To protect the safety of study participants, urgent changes may be implemented before approval but need to be reported as soon as possible. All approvals must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for Making a Change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making such changes are compliance with Good Clinical Practice, enabling participants to continue safely in the study, and maintaining the integrity of the study.

Informed Consent

Additional consent from the participant will be obtained, if required, for:

participation in remote visits, as defined below in Section 1, Remote visits,
alternate delivery of study treatment and ancillary supplies, and
provision of their personal or medical information required prior to implementation of these activities.

Changes in Study Conduct During Exceptional Circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct (e.g., telemedicine versus on-site) will not be considered protocol deviations.

1. Remote visits

In exceptional circumstances, study visits may be done remotely using telemedicine. In source documents and the eCRF, the study site must capture the visit method, with a specific explanation for any data missing and document as protocol violations, when applicable.

Telemedicine:

Telemedicine visits using interactive technology-assistance (that is, at a minimum video and/or audio technology) may be performed by an investigator in lieu of on-site visits to complete required study assessments as outlined in Section 2.

Study procedures that may be performed by an investigator using telemedicine include the following:

Informed consent
Inclusion/exclusion assessments; medical history
Telehealth physical examination (if allowed by local regulation)
AE assessments; review and update on concomitant medications
ECOG performance status
Evaluation of symptomatic progression
PRO assessments; review of patient diary; drug compliance evaluations for all study treatment
Survival status; post-discontinuation anticancer therapies.

Other alternative locations:

In exceptional circumstances, imaging procedures required during screening, on-study treatment, or follow-up may be performed at an alternate location than the study site or designated facility. Imaging includes: CT or MRI scan (of chest, abdomen, and pelvis), radionuclide bone scan, MRI/CT (MRI preferred) of the brain (if clinically indicated), and ECHO/multigated acquisition scan (MUGA) scans. See Section 2 for details.

The protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged. Furthermore, every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participant and the site staff.

2. Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. The local laboratory must be qualified in accordance with applicable local regulations.

3. Study treatment and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study treatment or study tools (e.g., participant diaries) during regularly scheduled on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

asking the participant's caregiver or designee to go to the site and receive study treatment or study tools on a participant's behalf, or
arranging delivery of study treatment and/or study supplies.

These requirements must be met and documented in the participant's medical records before action is taken:

Alternate delivery of study treatment should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study treatment.
When delivering study treatment to a location other than the study site (for example, participant's home), the investigator or designated site staff should follow local regulation and ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
Instructions should be provided to the participant or caregiver on the final disposition of any unused study treatment, empty product bottles, or completed patient diaries.

4. Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments completed during screening are required as outlined in the protocol.

In exceptional circumstances, Cycle 1 Day 1 visit must occur within 35 days from date of signed informed consent and will not constitute as a protocol violation. Any screening procedures that fall outside of the required windows per the Schedule of Activities (Section 2) must be repeated. See Protocol JPCM Section 6.4 for additional details on screen failures.

Participants who are unable to complete screening within the 35-day window and are not able to repeat screening procedures will be documented in eCRF as a screen failure due to exceptional circumstances.

5. Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual Schedule of Activities outlined in Section 2. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

This table describes the allowed adjustments to visit windows.

Visit Number	Tolerance
Day 1 of all cycles	The relative day within dosing cycle and visit window may be adjusted to ±5 days.
All other treatment visits	Follow Protocol JPCM; Schedule of Activities Section 2.

For participants whose visits have extended windows, additional study treatment may need to be provided to avoid interruption and maintain overall integrity of the study.

Documentation

Changes to study conduct will be documented:

Sites will document all remote visits in the study files and eCRF (where applicable) including telemedicine, local imaging and procedures, study treatment, or screening period guidance. Documentation should include details of which participants, visits type, and study procedures were affected by exceptional circumstances. Dispensing/shipment records of study treatment and relevant communications, including delegation, should be filed with site study records.

Source documents generated during a telemedicine visit should be part of the investigator's source documentation.

Appendix 11. Protocol Amendment History

Amendment Summary of Changes Table for the current amendment is located before the Table of Contents (TOC).

Amendment [e]: (08-Sep-2023)
This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment e:

The protocol was amended to correct the EudraCT Number.

Section # and Name	Description of Change	Brief Rationale
Cover Page	Revised incorrect EudraCT Number: 2014-001502-18 to the correct EudraCT Number: 2016-004276-21	Correction
1. Synopsis		
3.1.4. Rationale for Amendment (d)	Added rationale for Amendment (d)	Addition
11. Appendix 11: Protocol Amendment History	Added amendment (d) summary of changes table	To update the amendment history

Amendment [d]: (30-Aug-2023)
This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The protocol was amended to comply with the new European Union Clinical Trial Regulation (EU-CTR). The table listing strong and moderate inducers and strong inhibitors of CYP3A4 in Appendix 8 was updated.

Changes and rationale are summarized in the table below; minor typographical or formatting edits are not presented in the table.

Section # and Name	Description of Change	Brief Rationale
1. Synopsis	Added subsections Regulatory Agency Identifier Numbers (Eudra CT and EU CT numbers)" Study Population Ethical Considerations of Benefit/Risk Data Monitoring Committee	Compliance with EU-CTR
7.1. Treatments Administered	Added table describing	

Section # and Name	Description of Change	Brief Rationale
	authorization as defined by EU-CTR for abemaciclib, abiraterone acetate, and prednisone, and the definition for study treatment	
7.1.1. Packaging and Labeling	Updated language on packaging and labeling	
9.2. Adverse Events	Updated events meeting the AE definition	
9.2.1. Serious Adverse Events	Updated regulatory reporting of SAEs	
10.3. Statistical Analyses	Added a statement on handling of missing, unused, and spurious data	
Appendix 1. Abbreviations and Definitions	Added new abbreviations to the list	
Appendix 3. Study Governance, Regulatory, and Ethical Considerations	Added required language on investigator reporting requirements	
	Added required language on data protection	
	Added required language for communication of suspended or terminated dosing and time frame for posting of summary of results as specified by local law or regulation	
Appendix 8. Protocol JPCM Strong and Moderate Inducers of CYP3A4, Strong Inhibitors of CYP3A4, Substrates of CYP2D6 with Narrow Therapeutic Range, and Transporter Substrates with Narrow Therapeutic Range	Updated table listing strong and moderate inducers and strong inhibitors of CYP3A4	Update
	Added back the list of transporter substrates with narrow therapeutic range which was inadvertently omitted in Amendment c	Correction

Amendment [c]: (11-Mar-2021)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

See Section 3.1.3.

Section # and Name	Description of Change	Brief Rationale
Synopsis, Section 5.1. Overall Design, Section 5.2. Number of Patients, Section 7.2. Method of Treatment Assignment	Addition of Part 3 of the study: Part 3 will open if the prespecified expansion criteria in an adaptive interim analysis are met and will randomize approximately 170 additional patients to Arm A or Arm B, for a total of 350 patients to be enrolled.	Adaptive Design
Synopsis, Section 4. Objectives and Endpoints, Section 5.4.4. PSA Progression as an Efficacy Endpoint, Section 9.1.2. Definitions of Efficacy Measures, Section 10.3.1.3. Time to Prostate-Specific Antigen Progression	Time to prostate-specific antigen (PSA) progression was changed from a coprimary objective to a secondary objective. Accordingly, PSA Progression as an Efficacy Endpoint is removed from Section 5.4.4 and the planned primary analysis for time to PSA progression was removed from Section 10.3.1.3.	Adaptive Design
Synopsis, Section 4. Objectives and Endpoints, Section 5.4.3. Radiographic PFS as an Efficacy Endpoint	Added “rPFS by blinded, independent, central review (BICR)” as a secondary objective if Part 3 is opened for enrollment.	Addition
Synopsis, Section 4. Objectives and Endpoints	Patient-reported pain was changed from an exploratory to a secondary objective, and “time to worst pain progression” was added as a secondary endpoint.	Addition
Synopsis, Section 7.3.1. Unblinding at Interim Analyses, 10.3.5 Interim Analyses	Duplication of preexisting language from Section 5.1. Overall Design and Section 10.3.5. Interim Analyses, to reinforce that the assessment committee (AC) is composed of Lilly members not involved in the day-to-day study conduct	Clarification
Synopsis, Section 5.1. Overall Design, Section 7.3.1. Unblinding at Interim Analyses	Clarification regarding the independent data monitoring committee (DMC) conducting interim analyses	Clarification
Section 2. Schedule of Activities	Deletion of Urinalysis during the ‘on treatment’ period Reinforcing that ‘on treatment’ tumor imaging should be performed at specified	Deletion Clarification

Section # and Name	Description of Change	Brief Rationale
	intervals independent of treatment delays • CCI [redacted]	• Addition related to exploratory objective for Part 3, Clarification of instructions
Section 3.1.3. Rationale for Amendment C	Addition of rationale for Amendment C	Addition
Section 4. Objectives and Endpoints, Section 9.9.1.1. Definitions of Patient-Reported Outcome Endpoints	CCI [redacted]	Addition/Clarification
Section 5.1. Overall Design	Addition of timelines and details for planned analyses	Addition
Section 5.1. Overall Design, Section 7.1. Treatments Administered	Added that the AC has determined the recommended Phase 2 dose (RP2D) of abemaciclib to be CCI [redacted]	Addition
Section 5.1. Overall Design	Updated Figure JPCM.1. study design.	Adaptive Design
Section 6.1. Inclusion Criterion 7; Section 9.8.1. Tissue Samples for Biomarker Research	Stipulated that baseline tumor tissue collection is optional for Part 3.	Addition
Section 6.1. Inclusion Criterion 5	Clarified that Prostate Cancer Working Group 3 (PCWG3) criteria for bone progression at trial entry refers to the appearance of ≥2 new bone lesions	Clarification
Section 6.2. Exclusion	Exclusion Criterion 15: 3 months or 5 half-lives washout for prior investigational product changed	Clarification

Section # and Name	Description of Change	Brief Rationale
Criteria	"whichever is longer" to "whichever is shorter"	
Section 6.4. Screen Failures	Interval between rescreenings changed from "at least 4 weeks" to "at least 2 weeks"	Update
Section 7.2.1. Selection and Timing of Doses	Added language regarding additional study treatment to be dispensed for planned cycle delays after discussion with Lilly Clinical Research Physician/Clinical Research Scientist (CRP/CRS).	Addition
Section 7.3. Blinding, Section 7.3.2. Emergency Unblinding	Moved text from Section 7.3.2 Emergency Unblinding to Section 7.3 Blinding and updated language to reinforce that unblinding of the investigator and the patient at the time of documented objective disease progression is permitted to ensure optimal patient management and/or facilitate selection of subsequent treatment.	Addressing regulatory feedback
Section 7.4.1.2 Abemaciclib/Placebo and Abiraterone acetate and Dose Adjustments and Delays - Increased ALT/AST	Added Table JPCM.8. and corresponding text for abemaciclib/placebo and abiraterone acetate and dose adjustments and delays for increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST).	To condense text and to update dose adjustments for ALT/AST increase from language previously in Section 7.7.2.3
Section 7.7. Concomitant Therapy	Updated language for CYP3A modulators and transporter substrates.	Update to align with current guidance
Section 7.4.1.2. Abemaciclib/Placebo and Abiraterone acetate Dose Adjustments and Delays for Increased ALT/AST, Section 7.7.2 Supportive Care, Section 9.4.2 Safety Monitoring	Moved Guidance for Monitoring Renal Function from Section 7.7.2.2 to Section 9.4.2.3 under Safety Monitoring. Updated and moved Guidance for Abnormal Liver Function Test from Section 7.7.2.3 to: - Section 7.4.1.2. Abemaciclib/Placebo and Abiraterone acetate Dose Adjustments and Delays for Increased ALT/AST and to - Section 9.4.2.1 Hepatic Safety Monitoring under Safety Monitoring Added Section 9.4.2.4 Guidance for Venous Thromboembolic Events under Safety Monitoring Moved Guidance for Interstitial Lung Disease (ILD)/Pneumonitis from Section 7.7.2.4 to Section 9.4.2.5 under Safety Monitoring Updated and moved Guidance for Hypertension,	These changes were made to group all guidances previously under Section 7.7.2 Supportive Care to Section 9.4.2 Safety Monitoring. Updates were made to align with Abemaciclib Investigator's Brochure (IB) and/or Abiraterone prescribing information updates.

Section # and Name	Description of Change	Brief Rationale
	Hypokalemia, and Fluid Retention Due to Mineralocorticoid Excess from Section 7.7.2.7 to Section 9.4.2.6 under Safety Monitoring Added Section 9.4.2.7 Guidance for Adrenocortical Insufficiency under Safety Monitoring Added Section 9.4.2.8 Guidance for Hypoglycemia under Safety Monitoring	
Section 9.1.2. Definitions of Efficacy Measures, Section 10.3.1.1. Radiographic Progression Free Survival	Added language regarding Radiographic progression-free survival (rPFS) by BICR; moved language regarding worst pain NRS to Section 9.9.1.	Update
Section 9.8.1. Tissue Samples for Biomarker Research	Deleted the requirement for discussion with the Lilly CRP/CRS for use of archival metastatic tissue.	Deletion
Section 9.9.1 Patient-reported Outcomes, Section 9.9.1.1. Definitions of Patient-Reported Outcome Endpoints	Added section and corresponding subsection.	Addition
Section 9.9.2. Health Care Resource Utilization	Added section.	Addition
Section 10. Statistical Considerations	Revised planned statistical analyses to account for changes to primary endpoint, interim analyses, and the addition of Part 3.	Adaptive Design
Section 10.3.1.2. Overall Survival	Moved subsection from Section 10.3.1.4 to Section 10.3.1.2.	Editorial
Section 10.3.3.9. Health Outcome/Quality-of-Life Analyses	Revised section.	Revision
Section 10.3.5.2. Futility/Adaptive	Revised section title and text to describe adaptive interim analyses and criteria for opening	Adaptive Design

Section # and Name	Description of Change	Brief Rationale
Interim Analyses	enrollment to Part 3.	
Appendix 4	Updated table and footnote to align with changes throughout the protocol. Added Footnote c to clarify that pharmacogenetics (PGx) whole blood sample can be collected at subsequent timepoints if not collected at Cycle 1 Day 1.	Update/Clarification
Appendix 8	Deleted medications to align with current CYP3A guidance	Deletion
Appendix 9	Added ALT and AST to the Common Terminology Criteria for Adverse Events (CTCAE 5.0) grading table and updated Appendix title and summary text.	Addition
Appendix 10	Added provision for changes in study conduct during exceptional circumstances.	Addition
Throughout	Minor editorial and formatting changes made for clarity; changed Phase 2 to Phase 2/3; changed "solid oral dosage units" to "tablets/capsules"	Other

Amendment [b]: (28-Feb-2020)

The overall changes and rationale for the changes made to this protocol are as follows:

An update to the title including the name of the study, CYCLONE 2.

A clarification was made in the synopsis outlining the time of treatment initiation from randomization.

The protocol was updated to bring references to abemaciclib into alignment with the sponsor's standard language.

A data monitoring committee was added to perform unblinded safety and futility/efficacy analyses.

A clarification was added to the SoA defining baseline procedure timing as days prior to randomization consistent with the synopsis.

A clarification was added to the SoA confirming procedures will be performed according to calendar days, regardless of treatment delays.

A clarification was added to the instructions of ECOG PS, hematology, chemistry, and urinalysis further clarifying procedures assessed at baseline do not need repeated at C1D1 if assessed ≤3 days prior to treatment initiation.

Section 3.1.1 and Section 3.1.2 was added to provide the rationale for Amendment a and Amendment b respectively.

A clarification was made to Section 5.4.2 to prior treatments and text was updated with recent approvals.

A clarification was made to Exclusion Criteria 14 to update text with recent approvals.

A clarification was made to Section 6.3 and Section 7 further clarifying patients should refrain from grapefruit, pomegranate, and their juice while on study.

A clarification was made to Section 7.2.1 confirming a delay or earlier start due to holiday, weekend, bad weather, or unforeseen circumstances will be permitted up to 7 days.

An update was made to the dose modification guidance and the safety language for ILD/pneumonitis. These updates are in alignment with changes made in the development core safety information of the Investigator's Brochure. In addition, the hepatic safety monitoring guidance was updated.

Changes to Section 7.7.2.3, the Special Hepatic Safety Data Collection, and Appendix 5 were done to ensure a comprehensive evaluation of patients with treatment emergent abnormal liver tests and to align with current guidance from the Lilly Liver and Gastrointestinal (GI) Safety Advisory Committee.

A clarification was made to PSA and testosterone labs in Appendix 2 ensuring consistency with other labs.

The pneumonitis CTCAE definition was added for investigator convenience.

Other minor editorial changes were made to add clarity.

Amendment [a]: (31-Oct-2018)

The overall changes and rationale for the changes made to this protocol are as follows:

An update the synopsis to reflect changes made throughout the protocol.

Clarifications were made to the schedule of activities including the timing of chemistry labs and confirming hypokalemia correction prior to ECG collection.

A deletion of ECOG performance score on Day 15 of Cycle 1 and 2.

An addition of symptomatic progression assessment to the Schedule of Activities.

An update of the CTCAE version throughout the protocol.

An update throughout the protocol allowing the use of prednisolone where prednisone is not commercially available.

A clarification to the timing of when short-term follow-up begins.

An update to the background on abemaciclib with new approvals globally.

An addition of the endpoint symptomatic skeletal event to the time to symptomatic progression objective.

A clarification in Section 5.1 to further clarify where blinded study treatment has been dose reduced below the selected RP2D.

A clarification in Section 5.1 to further clarify why stratification factors were chosen.

A change to inclusion criteria 2 to exclude patients with large cell neuroendocrine carcinoma and carcinoid tumors.

A clarification to exclusion criteria 17 to allow for investigator judgment instead of Lilly CRP.

A clarification to exclusion criteria 23 to further clarify infections.

An update to exclusion criteria 27 as well as throughout the protocol updating excluded concomitant medications.

A change to Section 7.4.1.1 with updated toxicity dose adjustments and delays to blinded study treatment.

A change to Section 7.7 adding dabigatran to the list of medications to be avoided or substituted if possible.

A clarification was made to Section 7.7.2.2 for guidance for monitoring renal function.

An update was made to Section 7.7.2.6 guidelines for hypertension, hypokalemia, and fluid retention due to mineralocorticoid excess.

An update to Section 8.1.1 to further clarify and reinforce that the protocol is not intended to permit the enrollment of patients who do not meet eligibility criteria.

A clarification to Table JPCM.7. was made to the confirmatory scan for progressed patients at week 17 or greater.

A clarification to Section 9.1.2 defining secondary objectives, DoR and ORR.

A clarification to Section 9.4.2 was made to clarify hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities.

A change to Section 9.4.2.1. was made to update requirements for special hepatic safety data collection.

A clarification to Section 9.8.1 to further clarify the collection of required tumor tissue samples.

An addition to clinical chemistry clinical laboratory test in Appendix 2 adding Cystatin C, HDL, LDL, and triglycerides.

Other minor editorial changes were made to add clarity.

Signature Page for VV-CLIN-151605 v1.0

Approval	PPD 30-Apr-2024 09:22:25 GMT+0000

Approval	PPD 30-Apr-2024 17:53:12 GMT+0000

Signature Page for VV-CLIN-151605 v1.0