Statistical Analysis Plan I3Y-MC-JPEG Version 2

CYCLONE 3: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abemaciclib in Combination With Abiraterone Plus Prednisone in Men With High-Risk Metastatic Hormone-Sensitive Prostate Cancer

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Protocol Title: CYCLONE 3: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abemaciclib in Combination with Abiraterone plus Prednisone in Men with High-Risk Metastatic Hormone-Sensitive Prostate Cancer

Protocol Number: I3Y-MC-JPEG

Compound Number: Abemaciclib (LY2835219)

Short Title: CYCLONE 3: A Study of Abemaciclib with Abiraterone in Men with High-Risk Metastatic Hormone-Sensitive Prostate Cancer

Acronym: CYCLONE 3

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Version History

The statistical analysis plan (SAP) for Study I3Y-MC-JPEG is based on protocol amendment (c) dated 20 October 2022. Version 1 was approved prior to the first unblinding.

SAP Version 1 was amended due to protocol amendment (d). SAP Version 2 was approved prior to database lock for interim futility analysis.

Table 1. SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	03 November 2022	Not Applicable	Original version
2	See date on Page 1	1. Updated the timing of the futility analysis	1. To ensure adequate follow-up time at the time of the futility analysis, after accounting for actual rate of enrollment to the study
		2. Clarification was added to the censoring rules for new anticancer treatment	2. Clarification
		3. Updated the predefined baseline disease characteristics list of variables	3. Update
		4. Added appendix 2: Notable Patient Criteria	4. Update

1. Introduction

There are no changes to the analyses described in the protocol. This SAP is an extension of the protocol. It contains additional details about the analysis plan for efficacy, safety, pharmacokinetics (PK), patient-reported outcomes (PROs), and exploratory endpoints.

Tables, figures, and listings specifications will be contained in a separate document.

Note that analyses PROs, PK/pharmacodynamics, and biomarkers will be further described in separate SAP addendums.

1.1. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
• To determine whether adding abemaciclib to abiraterone plus prednisone[a] improves radiographic progression-free survival (rPFS).	• rPFS assessed by the investigator.
Secondary	
• To evaluate improvements in other clinically relevant efficacy endpoints with the addition of abemaciclib to abiraterone plus prednisone.	• rPFS by blinded, independent, central review (BICR) • Clinical PFS (cPFS) • Castration-resistant prostate cancer (CRPC)-free survival • Time to symptomatic progression • Time to PSA progression • Time to initiation of new anticancer therapy • Overall survival (OS).
• To characterize the safety of adding abemaciclib to abiraterone 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 characterize the PK of abemaciclib when administered in combination with abiraterone.	• Concentrations of abemaciclib.
• To assess patient-reported pain and HRQoL.	• Time to pain progression • Time to deterioration in HRQoL measured by the FACT-P (Physical Well-Being and PCS scores) and EQ-5D-5L.
Exploratory	
CCI	

Objectives	Endpoints
CCI	

Abbreviations: AE = adverse event; ECG = electrocardiogram; EQ-5D-5L = European Quality of Life – 5 dimensions – 5 level; HRQoL = Health-related quality of life; FACT-P = Functional Assessment of Cancer Therapy-Prostate; PK = pharmacokinetics; PRO-CTCAE = Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events; PSA = prostate-specific antigen; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Prednisone implies prednisone or prednisolone.

Primary estimand

The primary research question is: What is the difference in rPFS when adding abemaciclib or placebo to abiraterone plus prednisone in patients with high-risk mHSPC?

The estimand for the primary objective is described by the following attributes:

- Population: adult men with high-risk metastatic hormone-sensitive prostate cancer (mHSPC) randomized to study arms (primary analysis population). Further details can be found in Protocol Section 5.
- Endpoint: investigator-assessed radiographic progression-free survival (rPFS) in the primary analysis population, which is defined as the time from randomization until
  - first occurrence of documented radiographic disease progression, or
  - death from any cause.
- Treatment condition: Abemaciclib CCI and abiraterone CCI plus prednisone CCI will be compared to placebo CCI and abiraterone CCI plus prednisone CCI Study intervention will be administered until radiographic progression, unacceptable toxicity, or until other discontinuation criteria are met (see Protocol Section 7.1). Further details on study intervention, concomitant therapy, and dose modification, can be found in Protocol Section 6.
- Intercurrent-event strategies (IES):
  - Study intervention discontinuation prior to radiographic progression or death without prior progression is handled with CCI
  - The initiation of new anticancer therapy prior to documented disease progression or death without prior progression is handled with CCI

  - Extended time without adequate assessment prior to documented disease progression or death without prior progression is handled with CCI [redacted]

- Population-level summary measure: Hazard ratio of rPFS in the experimental arm versus the control arm estimated using a stratified Cox regression model (Cox 1972).
- Rationale for IES: The interest lies in the treatment effect regardless of study intervention discontinuation and without the confounding effect of the start of a new anticancer therapy or extended time without adequate assessment.
  - Study intervention discontinuation due to reasons other than documented radiographic disease progression or death without prior progression is handled with CCI [redacted] Time from randomization until documented disease progression or death without prior progression regardless of study intervention discontinuation will be considered in the analysis.
  - The initiation of new anticancer therapy could happen prior to observing an rPFS event and potentially confound the assessment of the primary endpoint. CCI [redacted]
  - Disease progression observed after an extended time without adequate tumor assessment may have occurred much earlier but is not reported because the scheduled assessment was not done. This inadequate observation may introduce bias to rPFS estimates. If extended time without adequate assessment occurs, CCI [redacted]

Secondary estimand

An additional secondary research question is: What is the difference in OS when adding abemaciclib or placebo to abiraterone plus prednisone in patients with high-risk mHSPC?

The estimand for the secondary objectives is described by the following attributes:

- Population: adult men with high-risk mHSPC randomized to study arms (primary analysis population).
- Endpoint: Overall survival (OS), which is defined as the time from randomization until death from any cause.
- Treatment condition: Abemaciclib CCI [redacted] and abiraterone CCI [redacted] plus prednisone CCI [redacted] will be compared to placebo CCI [redacted] and abiraterone CCI [redacted] plus prednisone CCI [redacted] Study intervention will be administered until radiographic progression, unacceptable toxicity, or until other discontinuation criteria are met (see Protocol Section 7.1). Further details on study intervention, concomitant therapy, and dose modification, can be found in Protocol Section 6.

- Intercurrent-event strategies (IES):
  - Study intervention discontinuation prior to death is handled with treatment policy strategy, that is, regardless of whether or not study intervention discontinuation had occurred
  - Initiation of new anticancer therapy prior to death is handled with treatment policy strategy, that is, regardless of whether or not anticancer therapy was initiated post study intervention discontinuation
- Population-level summary measure: Hazard ratio of OS in the experimental arm versus the control arm estimated using a stratified Cox regression model (Cox 1972).

Rationale for IES: The interest lies in the treatment effect regardless of study intervention discontinuation and regardless of any potential confounding effect of the start of a new anticancer therapy.

1.2. Study Design

CYCLONE 3 is a multicenter, multinational, randomized, double-blind, placebo-controlled, Phase 3 study to assess the safety and efficacy of adding abemaciclib to abiraterone plus prednisone in patients with high-risk mHSPC. High-risk is defined as the presence of ≥4 bone metastases and/or ≥1 visceral metastases.

Approximately 900 participants will be randomized in a 1:1 ratio.

Treatment Arms:

Abiraterone and prednisone (or prednisolone):

All participants will receive therapy with abiraterone CCI [redacted] plus prednisone CCI [redacted] per the recommended standard posology in the mHSPC population. Prednisolone may be used in lieu of prednisone per local abiraterone prescribing information or where prednisone is not commercially available.

Blinded study drug:

- Experimental arm: Abemaciclib CCI [redacted] orally CCI [redacted]
- Control arm: Placebo CCI [redacted] orally CCI [redacted]

Abiraterone, prednisone, and abemaciclib/placebo, will be initiated ≤7 days following randomization and administered on Days 1 through 28 of a 28-day cycle until disease progression, unacceptable toxicity, or other discontinuation criteria are met (see Protocol Section 7.1).

Note: Participants who have not undergone bilateral orchiectomy are required to continue background androgen deprivation therapy (ADT) with a luteinizing hormone-releasing hormone (LHRH) agonist/antagonist throughout the study.

Stratification:

Randomization will be stratified according to the following factors:

- de novo metastatic prostate cancer (metastatic disease at initial diagnosis) (Yes vs. No).
- visceral metastases (Yes vs. No).

These stratification criteria were selected because they represent important prognostic factors and/or an imbalance that may bias study results.

In addition, participants 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.

Participants discontinuing treatment due to documented radiographic progression will be followed for the development of symptomatic progression.

All patients will be followed for survival.

A detailed description of the study design is contained in the protocol.

2. Statistical Hypotheses

The primary hypothesis is that the addition of abemaciclib to abiraterone plus prednisone will provide a clinically meaningful increase in rPFS over adding placebo to abiraterone plus prednisone in participants with high-risk mHSPC.

2.1. Multiplicity Adjustment

A gated hypothesis testing procedure will be used to ensure control of the familywise error rate at 0.025 (one-sided) across the 2 endpoints (rPFS and OS). The primary endpoint of rPFS will first be tested; the secondary OS will be tested only if statistical significance is achieved for rPFS. Other endpoints will not be error controlled.

3. Analysis Sets

The populations for analysis are defined below:

Population	Description
Intent-to-treat (ITT)	All randomized participants, regardless of whether they took any doses of study intervention, or if they took the correct treatment. Participants will be analyzed according to the treatment group as randomized and not by actual treatment received.
Safety	All randomized participants who received at least 1 dose of any study intervention. Participants will be analyzed according to the first dose of study intervention they actually received, regardless of the arm to which they were randomized.
Measurable disease population	All randomized patients who have measurable disease in soft tissue at baseline according to RECIST v1.1. This population will be used for efficacy analyses based on soft tissue tumor response related endpoints such as best overall response.
Pharmacokinetic (PK) analysis	All randomized participants who received at least 1 dose of study intervention and at least 1 postbaseline evaluable PK sample.
Biomarker population	The subset of patients from the ITT population from whom a valid assay result has been obtained.

4. Statistical Analyses

4.1. General Considerations

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

Continuous variables will be summarized using descriptive statistics (that is, number of patients, mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized by frequency and its corresponding percentage.

All tests of treatment effects will be conducted at a 1-sided alpha level of 0.025, unless otherwise stated, and all confidence intervals (CIs) will be given at a 2-sided 95% level.

Any change to the data analysis methods described in the protocol will require a protocol 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 (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

4.1.1. Definitions and Conventions

Blinded study drug refers to abemaciclib or placebo.

Study treatment or study intervention refer to any of: abemaciclib, placebo, abiraterone, or prednisone.

The **date of randomization** is the date the patient was randomly assigned to study treatment using the interactive web response system.

The **date of first dose** is the date of the first dose of any study treatment.

The **baseline value of a safety assessment** is the last value observed prior to the first dose of any study treatment.

The **baseline value of an efficacy assessment** is the last value observed prior to the date of randomization. If a patient's first assessment occurs after randomization but prior to the first dose, this assessment will be used as the baseline.

The **study day of a safety event or assessment** will be calculated as:

- the difference between the date of the event or assessment and the date of first dose plus 1 for all events or assessments occurring on or after the day of first dose. For example, if an event occurs on 08 May 2022 and the date of first dose was 06 May 2022, the study day of the event is 3.
- the difference between the date of the event or assessment and the date of first dose for all events or assessments occurring before the day of first dose. For example, if an event occurs on 05 May 2022 and the date of first dose was 06 May 2022, the study day of the event is -1.

The **study day of an efficacy event or assessment** will be calculated as:

- the difference between the date of the event or assessment and the date of randomization plus 1 for all events or assessments occurring on or after the date of randomization.

- the difference between the date of the event or assessment and the date of randomization for all events or assessments occurring before the date of randomization.

One **month** is defined as 365/12 days.

4.1.2. Handling of Dropouts or Missing Data

With the exception of dates, missing data will not be imputed. The method of imputation for any dates that are imputed is described in the relevant section.

For time to event endpoints where a patient death is not considered an event, the impact of deaths occurring prior to the event of interest being observed will be assessed to ensure no significant bias is introduced in the estimates of the hazard ratio (HR) or median. Specifically, a sensitivity analysis will be performed by treating such deaths as events.

4.2. Participant Disposition

A detailed description of participant disposition will be created, including a summary of the number and percentage of participants entered into the study, enrolled in the study, and treated, as well as number and percentage of participants completing the study, as defined in Appendix 1, or discontinuing prior to study completion (overall and by reason for discontinuation).

4.3. Primary Endpoint Analysis

4.3.1. Definition of Endpoint(s)

The primary endpoint of CYCLONE 3 will be investigator-assessed rPFS. Radiographic progression-free survival is defined as the time from the date of randomization to the earliest date of investigator-assessed radiographic disease progression in soft tissue per RECIST 1.1 (Eisenhauer et al. 2009) AND/OR bone disease (per adapted Prostate Cancer Working Group 3 [PCWG3], as described in Protocol Section 8.1), or death from any cause, whichever occurs first. Patients who have neither progressed nor died will be censored at the date of their last adequate radiographic tumor assessment (if available) or the date of randomization (if no post-baseline radiographic assessment is available). The detailed censoring rules are described in Table 4.1.

4.3.2. Main Analytical Approach

Table 4.1 defines the censoring rules for the rPFS primary analysis.

Table 4.1. Radiographic Progression-Free Survival Event/Censoring Scheme

Situation[a]	Event/Censor	Date of Event or Censor
Radiographic disease progression or death	Event	Earliest date of radiographic disease progression or death[b]
No radiographic disease progression and no death	Censored	Date of last adequate radiographic assessment showing no evidence of disease progression or date of randomization (whichever is later)[c]

Situation[a]	Event/Censor	Date of Event or Censor
Unless		
No baseline radiographic tumor assessment available	Censored	Date of randomization
CCI		

Abbreviations: CR = complete response; LHRH = luteinizing hormone-releasing hormone; PD = progressive disease; rPFS = radiographic progression-free survival; PR = partial response; SD = stable disease.

a Clinical/symptomatic deterioration will not be considered as radiographic disease progression.

b CCI

c Adequate radiographic tumor assessment refers to an assessment of one of the following:

- Soft tissue disease with one of the following responses: CR, PR, SD; and adequate bone scan showing no or initial evidence of disease progression. For patients with no soft tissue disease at baseline, an assessment documenting no evidence of disease progression must still be performed and recorded according to the CRF guidelines. Similarly, for patients with no bone disease at baseline, an assessment documenting no evidence of disease progression must still be performed and recorded according to the CRF guidelines.
- Soft tissue disease with a response of PD.
- Bone scan showing disease progression (excluding scans showing initial evidence progression, if confirmation is required for that timepoint).

To be specific, "last adequate radiographic assessment showing no evidence of disease progression" does not include the assessment showing initial/unconfirmed evidence of bone progression, if confirmation of bone progression is required for that timepoint. If tumor scans for one assessment were performed on multiple days, use the earliest scan date for that visit as the date of assessment.

d CCI

e CCI

The primary analysis of rPFS will be performed on the intent-to-treat (ITT) population and will use the log-rank test stratified by the randomization factors. The Kaplan-Meier (KM) method (Kaplan and Meier 1958) will be used to estimate the rPFS survival curves as well as rPFS rates every 6 months for each treatment group. The corresponding HR between treatment groups will be estimated using a stratified Cox regression model (Cox 1972), stratified by the randomization strata.

The overall type I error will be controlled at a 1-sided alpha level of 0.025. There is 1 planned futility analysis, 1 planned efficacy interim analysis, and the primary outcome analysis of rPFS.

Within the analyses of rPFS CCI

The futility analysis is planned to take place after CCI

There are 2 planned efficacy analyses of rPFS. An interim analysis will be performed afte CCI

The cumulative 1-sided type I error rate of 0.025 will be maintained CCI

Table 4.2. Statistical Analysis Milestones

Milestone	rPFS	One-sided Boundary p-value for rPFS Efficacy
CCI		

Abbreviations: CCI

a CCI

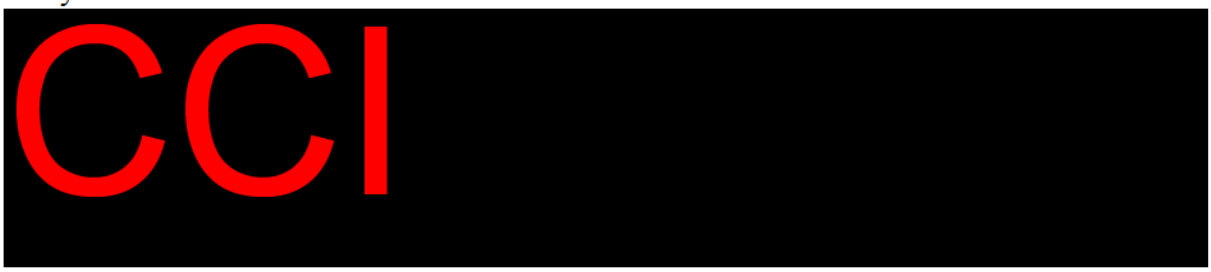
b CCI

4.3.3. Sensitivity Analyses

Sensitivity analyses will be undertaken for calculation of the primary endpoint in order to evaluate the robustness of the analysis. The following sensitivity analyses will be conducted on the primary endpoint, rPFS:

- Under an early version of the protocol, patients were initially randomized using a third randomization factor, whether the patient had received prior docetaxel for mHSPC (Yes vs. No). Patients that had received prior docetaxel for mHSPC were subsequently excluded from the trial by Protocol Amendment (c), and randomization proceeded using only the two remaining randomization factors. Because only a very small proportion of patients that had received prior docetaxel were enrolled prior to the implementation of Protocol Amendment (c), the primary stratified analysis will not consider prior docetaxel as a stratification factor. However, a stratified log-rank test and stratified Cox proportional hazard model (Cox 1972) with stratification by all 3 original randomization

factors will also be performed as a sensitivity analysis providing sufficient numbers of events within each strata.

- An unstratified log-rank test without stratification by randomization factors will be performed.
- An unstratified Cox proportional hazard model (Cox 1972) with treatment as a factor will be used to estimate the HR between the 2 treatment arms and the corresponding CI and p-value.
- A multivariate Cox proportional hazard model constructed by selecting variables among all the potential variables (see specified factors in Section 4.7.14), using a stepwise selection method with an entry p-value of .05 and an exit p-value of .10; the treatment factor will be kept out of the model throughout the covariate selection process and will only be added into the final model.
- 

- **Proportional Hazards:** A formal evaluation of the proportional hazard assumption for rPFS will be conducted. This will be done visually through inspection of the graph of log(–log[S(t)]) versus log(t) for the 2 treatment groups. If the event that the proportional hazards assumption is violated, additional analyses will be performed.

Other sensitivity analyses may be conducted if deemed appropriate.

4.4. Secondary Endpoints Analysis

4.4.1. Key Secondary Endpoint: Overall Survival

4.4.1.1. Definition of Endpoint

OS is defined as the time from randomization until death from any cause. If the participant is alive or lost to follow-up at the time of analysis, OS data will be censored on the last date the participant is known to be alive.

4.4.1.2. Main Analytical Approach

OS in the ITT population will be compared between treatment arms using a stratified log-rank test, stratified by the randomization factors. The corresponding HR between treatment arms will be estimated using a stratified Cox regression model (Cox 1972), stratified by same randomization strata used for the primary rPFS analysis. The OS survival curves, and yearly OS rates with 95% CI for each treatment arm will be estimated using the KM method.

Hypothesis testing for OS will be conducted in a gated fashion. To maintain the experiment-wise type I error rate, OS will be hierarchically tested in the following way: only if the test of rPFS in

the ITT population is significant will OS also be tested inferentially for significance (Glimm et al. 2010).

There are up to 3 planned interim OS analyses and 1 final analysis at the following time points:

- The interim rPFS analysis CCI
- The final rPFS analysis CCI
- CCI
- Final OS analysis: CCI whichever occurs earlier.

If rPFS is not statistically significant at the interim rPFS analysis, OS will not be statistically evaluated at that time point. If rPFS is not statistically significant at either the interim or final rPFS analysis, OS will not be statistically evaluated.

The cumulative 1-sided type I error rate of 0.025 will be maintained using the Lan-DeMets method (DeMets and Lan, 1994). Specifically, an α-spending function corresponding to the following O'Brien-Fleming type stopping boundary will be used for each interim efficacy analysis:

$$\alpha^*(t_k) = 2(1-\Phi(\Phi^{-1}(1-\alpha/2)/\mathrm{sqrt}(t_k)))$$

Here, t_k is the information fraction at time k, Φ is the standard normal cumulative distribution function, and Φ^{-1} is the standard normal quantile function. The boundary p-value at each analysis will be calculated based on the actual number of events observed at the time of analysis using software that implements this alpha-spending function (for example, EAST 6.5 or SAS 9.4).

4.4.1.3. Sensitivity Analyses

The following sensitivity analyses will be conducted on the secondary endpoint, OS:

- Under an early version of the protocol, patients were initially randomized using a third randomization factor, whether the patient had received prior docetaxel for mHSPC (Yes vs. No). Patients that had received prior docetaxel for mHSPC were subsequently excluded from the trial by Protocol Amendment (c), and randomization proceeded using only the two remaining randomization factors. Because only a very small proportion of patients that had received prior docetaxel were enrolled prior to the implementation of Protocol Amendment (c), the primary stratified analysis will not consider prior docetaxel as a stratification factor. However, a stratified log-rank test with stratification by all 3 original randomization factors will also be performed as a sensitivity analysis.
- A log-rank test without stratification by randomization factors will be performed.
- An unstratified Cox proportional hazard model (Cox 1972) with treatment as a factor will be used to estimate the HR between the 2 treatment arms and the corresponding CI and p-value.

4.4.2. Supportive Secondary Endpoints

Radiographic progression-free survival by blinded independent review committee (BIRC) is defined the same way as the primary endpoint of rPFS. For BIRC analysis, scans will be collected and reviewed for all randomized participants based on RECIST version 1.1 and the adapted PCWG3 criteria. BIRC-assessed rPFS intends to evaluate the reliability of the treatment effect based on the investigator-assessed rPFS. BIRC-assessed rPFS will be analyzed using the same methods as the investigator-assessed rPFS. BIRC-assessed rPFS is not intended to provide an alternative means of definitive analysis, but it may be useful to evaluate bias in local assessments. Discordance rates (that is, differences in assessment of progression between investigator and blinded independent central review) will be summarized for each arm (Amit et al. 2011). The agreement between BICR and investigator within a treatment arm is represented in a tabular form (Table 4.3) and will be summarized for each arm and overall. Additionally, differential discordance will be described using early discrepancy rate and late discrepancy rate differences.

Table 4.3. BIRC-assessed Versus Investigator-assessed Disease Progression

	BIRC	
Investigator	PD	No PD
PD	a=a1+a2+a3	b
No PD	c	d

Abbreviations: a1 = number of agreements on timing and occurrence of PD; a2 = number of times investigators declare PD later than BIRC; a3: number of times investigators declare PD earlier than BIRC; BIRC = blinded independent review committee; PD = progressive disease.

The early discordance rate (EDR) quantifies the frequency with which the investigator assessment declares progression earlier relative to BIRC within each arm and is defined as:

$$EDR = (b+a3)/(a+b)$$

The late discordance rate (LDR) quantifies the frequency with which the investigator assessment declares progression later than BIRC within each arm and is defined as:

$$LDR = (c+a2)/(b+c+a2+a3)$$

The EDR and LDR will be summarized for each treatment arm and the differential discordance around each measure can be defined as the rate on the experimental arm minus the rate on the control arm. A negative differential discordance for the EDR and/or positive differential discordance for the LDR are suggestive of a bias in the investigator-assessed rPFS favoring the experimental arm.

Other endpoints using investigator-assessed radiographic response or progression will also be summarized for each arm by BIRC.

Clinical progression-free survival (cPFS) is defined as the time from the date of randomization to the earliest date of investigator-assessed radiographic disease progression, symptomatic progression, or death from any cause, whichever occurs first. The same censoring rules used for

rPFS will be used in the derivation of cPFS. The analysis of cPFS will be performed on the ITT population and will use the log-rank test stratified by the randomization factors. The KM method will be used to estimate the cPFS survival curves as well as landmark survival rates every 6 months for each treatment group. The corresponding HR between treatment groups will be estimated using a stratified Cox regression model (Cox 1972), stratified by the randomization strata.

Prostate-specific antigen 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 prostate-specific antigen (PSA) measurements within 12 weeks since baseline will be ignored in determining PSA progression.

Castration-resistant prostate cancer (CRPC)-free survival is defined as the time from the date of randomization to the earliest date of castration resistance, as demonstrated by any of the following (whichever occurs earliest):

- Confirmed PSA progression with serum testosterone ≤50 ng/dL (≤1.73 nmol/L)
- Investigator-assessed radiographic progression with serum testosterone ≤50 ng/dL (≤1.73 nmol/L)
- Death from any cause.

Patients that do not demonstrate castration-resistance will be censored at the last observed date without castration resistance while serum testosterone is ≤50 ng/dL. The analysis of CRPC-free survival will be performed on the ITT population and will use the log-rank test stratified by the randomization factors. The KM method will be used to estimate the survival curves as well as landmark survival rates every 6 months for each treatment group. The corresponding HR between treatment groups will be estimated using a stratified Cox regression model (Cox 1972), stratified by the randomization strata.

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 (that is, postbaseline) PSA assessment is available. The detailed censoring rules are described in Table 4.4.

Table 4.4. Time to PSA Progression Event/Censoring Scheme

Situation	Event/Censor	Date of Event or Censor
Confirmed PSA progression	Event	Date of first observation of PSA progression[a]
Not known to have had confirmed PSA progression confirmed	Censored	Date of last PSA assessment showing no evidence of PSA progression or date of randomization (whichever is later)[b]
Unless		
No baseline PSA assessment, or no postbaseline PSA assessments available beyond 12 weeks since baseline	Censored	Date of randomization

Abbreviations: PSA = prostate-specific antigen.

[a] To be specific, for confirmed PSA progression, the date of first observation of PSA progression is the date at which initial PSA progression is observed, not the date that the PSA progression is later confirmed by a subsequent assessment.

[b] To be specific, "last PSA assessment showing no evidence of PSA progression" does not include the assessment showing initial/unconfirmed evidence of PSA progression.

The analysis of time to PSA progression will be performed on the ITT population and will use the log-rank test stratified by the randomization factors. The KM method will be used to estimate the survival curves as well as landmark survival rates every 6 months for each treatment group. The corresponding HR between treatment groups will be estimated using a stratified Cox regression model (Cox 1972), stratified by the randomization strata.

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

- Symptomatic skeletal event, defined as cancer-related 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 anticancer 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. The analysis of time to symptomatic progression will be performed on the ITT population and will use the log-rank test stratified by the randomization factors. The KM method will be used to estimate the survival curves as well as landmark survival rates every 6 months for each treatment group. The corresponding HR between treatment groups will be estimated using a stratified Cox regression model (Cox 1972), stratified by the randomization strata.

Time to initiation of new anticancer therapy is defined as the time from randomization until the first initiation of a new systemic anticancer therapy. If the participant has not initiated a new anticancer therapy at the time of analysis, data will be censored on the last date the participant has been observed. The analysis of time to initiation of new anticancer therapy will be performed on the ITT population and will use the log-rank test stratified by the randomization factors. The KM method will be used to estimate the survival curves as well as landmark survival rates every 6 months for each treatment group. The corresponding HR between treatment groups will be estimated using a stratified Cox regression model (Cox 1972), stratified by the randomization strata.

Time to pain progression (using the Brief Pain Inventory – Short Form [BPI-SF] Worst Pain Numeric Rating Scale [NRS] score and Analgesic Quantification Algorithm [AQA] score) is described in Section 4.7.10.

4.5. Exploratory Endpoints Analyses

CCI [redacted]

4.6. Safety Analyses

All participants in the safety analysis set will be evaluated for safety and toxicity.

4.6.1. Extent of Exposure

Drug exposure, dose intensity, and drug adjustment (dose omissions, increases, reductions, interruptions, and delays) for abemaciclib/placebo, abiraterone, and prednisone will be summarized for all treated patients per treatment arm. Drug exposure will include summaries of cycles received per patient, duration on therapy, and cumulative dose. Dose intensity will be calculated as the actual cumulative amount of drug taken divided by the duration of treatment. Relative dose intensity will be calculated as the actual amount of drug taken divided by the amount of drug prescribed times 100% (expressed as a percentage).

For abemaciclib/placebo, extent of exposure will be measured by pill counts and summarized cumulatively. The summary will include total dosage taken, dose intensity, and relative dose intensity. The assigned cumulative dose for each patient during each cycle is CCI

CCI × 28 days = CCI. The assigned cumulative dose while on study is CCI × number of days on treatment.

For abiraterone and prednisone, data are reported on the Exposure Compliance forms of the case report form and will be summarized cumulatively. The summary will include total doses since the previous visit and dose intensity. Dose intensity will be calculated as the ratio of total doses to the assigned number of doses. The assigned number of doses while on study is 1 dose per day × number of days on treatment.

4.6.2. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) derived from the verbatim term will be used when reporting adverse events (AEs) by MedDRA terms. The MedDRA Lower Level Term will be used in the treatment-emergent computation. Toxicity grades will be assigned by the investigator using National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

Preexisting conditions are defined as AEs that either are ongoing at informed consent or end on or after informed consent. Preexisting conditions will be included in the listing of AE so that the history of AEs can be traced.

A treatment-emergent adverse event (TEAE) is defined as any AE that begins between the day of first dose and 30 days after treatment discontinuation (or up to any time if serious and related to study treatment), or any pre-existing condition that increases in CTCAE grade between the day of first dose and 30 days after treatment discontinuation (or up to any time if serious and related to study treatment).

A serious adverse event (SAE) is any AE during 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
- considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment of the investigator, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Consolidated AEs are composite AE terms consisting of synonymous PTs to allow meaningful interpretation of the AE data. The final list of consolidated AE categories and PTs will be maintained at both compound and study level and reported in the CSR.

Safety analyses will include summaries of the following:

- adverse events, including severity and possible relationship to study treatment.
- serious adverse events, including possible relationship to study treatment.

- adverse events leading to dose adjustments.
- discontinuations from study treatment due to adverse events or death.
- treatment-emergent abnormal changes in laboratory values.
- treatment-emergent abnormal changes in vital signs and ECGs.

4.6.3. Deaths

All deaths on study will be listed along with the reason for death, if known. For those deaths attributed to an AE, the listing will include the preferred term of the AE. A summary of deaths including reasons for death will be produced.

4.6.4. Clinical Laboratory Evaluation

The severity of laboratory results will be classified according to NCI-CTCAE. The laboratory toxicity by worst NCI-CTCAE grade and shifts in toxicity grading from baseline to the worst postbaseline grade will be summarized. Abnormal laboratory parameters will be listed.

Shift to low/high tables will include the number and percentage of patients within each baseline category (baseline value is low, normal, high, or missing) versus each postbaseline category (worst value is low, normal, high, or missing) by treatment arm.

4.6.5. Vital Signs and Other Physical Findings

Temperature, blood pressure, pulse rate, respiration rate, oxygen saturation, weight and Eastern Cooperative Oncology Group Performance Status (ECOG PS) will be summarized by visit. Observed values and changes from baseline will be summarized.

4.6.6. Electrocardiograms

Local electrocardiograms (ECGs) will be summarized. The summary will classify patients as having normal or abnormal ECG and summarize AEs identified by ECG.

4.7. Other Analyses

4.7.1. Demographics

Patient demographics will be summarized. Patient demographics will include the following:

- race
- ethnicity
- geography
- age (numerical summary and ≤65 years vs. >65 years)
- height
- weight
- body mass index
- baseline ECOG PS

4.7.2. Baseline Disease Characteristics

Disease characteristics will be summarized. Disease characteristics will include the following:

- initial pathological diagnosis
- disease stage: TNM stage, Gleason score, and PSA at initial diagnosis
- extent of disease: nodal disease only, bone disease (with or without nodal disease), visceral disease (with or without nodal disease and/or bone disease), other
- site(s) of disease (local, nodal-regional, nodal-distant, liver, lung, soft tissue-other, bone)
- bone disease burden at baseline (0, 1-10, >10 bone metastases, or superscan)
- measurable disease at baseline (yes vs. no)
- number of organs involved (1, 2, or 3+)
- high-risk status at baseline (≥4 bone metastases, ≥1 visceral metastases, both)
- site of visceral metastasis (liver vs. lung vs. other)
- de novo metastatic disease (yes vs. no)
- time from diagnosis to randomization
- time from LHRH to randomization
- ALP at baseline
- LDH at baseline
- prior use of bone-modifying agents (yes vs. no)
- prior docetaxel use for mHSPC (yes vs. no, duration of treatment)
- baseline tumor burden as assessed by prostate-specific membrane antigen positron emission tomography (PSMA-PET)/CT

Number of organs involved will be derived from the "Target Tumor: RECIST 1.1", "Non Target Tumor: RECIST 1.1", and "Bone Lesion Identification and Results-Baseline" case report forms at baseline. The number of organs involved will be derived from the location codes the baseline lesions. All patients with at least one lesion on the target lesion form will be counted as having measurable disease.

4.7.3. Medical History

Historical conditions and preexisting conditions (using MedDRA PTs) will be summarized by treatment arm.

4.7.4. Prior Therapy

Prior radiotherapy, surgery, and systemic therapy will be summarized by treatment arm. Prior radiotherapy and surgery will be categorized by reason for regimen. Prior systemic therapies will be categorized by type of regimen (endocrine therapy, chemotherapy, and so on) and reason for regimen ([neo]adjuvant therapy, or therapy for locally advanced, non-metastatic castration resistant, metastatic hormone sensitive). Frequency of each specific therapy will be tabulated within each type of therapy and per reason for regimen.

All ADT use will also be summarized, including prior to randomization, while on study, and poststudy treatment discontinuation.

4.7.5. Concomitant Therapy

All medications will be coded to the generic preferred name according to the current World Health Organization drug dictionary. All concomitant medications will be summarized for the ITT population using the preferred name. If appropriate, concomitant use of anti-diarrheal medication will also be summarized separately.

Palliative radiotherapy and/or surgery performed while patients are on study treatment will also be listed and summarized.

4.7.6. Poststudy Treatment Discontinuation Therapy

The numbers and percentages of participants receiving poststudy 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.

4.7.7. Treatment Compliance

Treatment compliance of abemaciclib/placebo will be measured by tablet/capsule counts and summarized cumulatively. Compliance will be calculated as the ratio of total dose taken to the total assigned dose (plus or minus any dose adjustments and doses omitted/withheld). The total assigned dose for a patient with no adjustments or omissions is as follows:

- CCI [redacted] × number of days on blinded study drug.

Treatment compliance of abiraterone acetate and prednisone will be calculated using the 'Exposure Compliance: Study Treatment Abiraterone Acetate' and 'Exposure Compliance: Study Treatment Prednisone' forms, respectively. Compliance for these drugs will only be collected and calculated on the scale of number of doses, without considering detailed dose level (mg per dose). The estimate of percent compliance will be calculated as ratio of total number of doses taken to the total number of assigned dose (minus number of doses omitted/withheld).

4.7.8. Follow-up Time

Follow-up time is defined as the time from the date of randomization until death from any cause or last date the patient is known to be alive and under follow-up. Median follow-up time will be estimated using Kaplan-Meier estimation of potential follow-up ("reverse Kaplan-Meier") (Schemper and Smith 1996). The inverse of the censoring rules for the OS will be used (that is, considering all censoring times for OS as event times [times when the patient is known to be still alive and under follow-up] and censoring patients who had OS events at the date of death).

4.7.9. Medical Resource Utilization

Frequency counts of hospitalizations, emergency room visits, radiation, surgery, transfusion, and analgesic use will be summarized descriptively by cycle and overall for each arm, as well as by treatment phase.

Duration of hospital stays and average number of emergency room visits will be reported by treatment arm.

4.7.10. Patient-Reported Outcomes

Patient-reported outcomes are measured through the following:

- BPI-SF Worst Pain NRS
- Functional Assessment of Cancer Therapy – Prostate (FACT-P)
- EuroQol 5 Dimension 5 Level (EQ-5D-5L)

For each PRO instrument, percentage compliance will be calculated as the number of completed assessments divided by the number of expected assessments. Data will be separately summarized using descriptive statistics. The Cycle 1 Day 1 (pre-dose) visit will be considered as baseline for all PRO analyses. Analyses for change from baseline will be based on the participants who have baseline and at least 1 post-baseline data. Exploratory analyses may be performed to investigate associations between patient-reported data and clinical efficacy endpoints as appropriate.

Further details on analyses of secondary and exploratory PRO endpoints will be provided in a separate PRO SAP.

4.7.10.1. Worst Pain NRS

The Worst Pain NRS item is a single-item, patient-reported, 11-point horizontal scale (Atkinson et al. 2010), obtained from question #3 of the BPI-SF (Chapman and Loeser 1989) and assesses the participant's pain in the last 24 hours. This scale is anchored at 0 to 10, with 0 representing "no pain" and 10 representing "pain as bad as you can imagine".

Time to pain progression (using the BPI-SF Worst Pain NRS score and AQA score) is defined as the time from randomization to any of the following (whichever occurs earlier):

- an increase from baseline of at least 2 points in Worst Pain NRS score at 2 consecutive assessments at least 3 weeks apart, with no decrease from baseline in opioid use
- initiation of opioid use or increase from baseline in opioid use.

Participants who do not satisfy any of the criteria above will be censored at the time of the last known assessment that showed an absence of pain progression. The analysis of time to pain progression will be performed on the ITT population and will use the log-rank test stratified by the randomization factors. The KM method will be used to estimate the survival curves as well as landmark survival rates every 6 months for each treatment group. The corresponding HR between treatment groups will be estimated using a stratified Cox regression model (Cox 1972), stratified by the randomization strata.

4.7.10.2. FACT-P

Patient-reported health-related quality of life will be measured by FACT-P, which consists of 27 core items from the Functional Assessment of Cancer Therapy – General (FACT-G) to assess health related quality of life in 4 domains (physical well-being [PWB], social/family well-being [SWB], emotional well-being [EWB], and functional well-being [FWB]) and is supplemented by a 12 item prostate cancer subscale (PCS) that assesses symptoms and impacts associated with prostate cancer as well as the trial outcome index (TOI) composite subscale score (PWB + FWB + PCS scores). Descriptive statistics will be summarized by treatment group and cycle, for the 2 total scores (for FACT-P and FACT-G), as well as the 6 subscale scores (for PWB, SWB, EWB,

FWB, PCS, and the TOI). For each FACT-P score, the analysis will include all cycles for which at least 25% of patients in each arm have an assessment. If the above criteria are met, a mixed model will be applied to compare mean change from baseline across treatment arms for each of the FACT-P scores. The model will include baseline score as a covariate and an unstructured covariance matrix will be utilized if it converges. If the model cannot converge with an unstructured covariance matrix, the covariance matrix will be determined based on the Akaike Information Criterion (AIC).

Time to deterioration in health-related quality of life is a set of secondary endpoints defined as the time from randomization to the date of the first clinically meaningful deterioration on 2 consecutive measurements and will be calculated for deterioration in the FACT-G PWB and the FACT-P PCS. Clinically meaningful deterioration thresholds will be based on clinically meaningful changes as defined by Cella (2003, 2009) and Chi (2018).

The Kaplan-Meier analysis will be performed to estimate the time to deterioration survival curves as well as quartiles for each treatment group, for each of the above FACT-P health-related quality of life scores. In addition, the Cox regression stratified by the randomization factors will be used to estimate the HR between the 2 treatment groups, along with CIs.

4.7.10.3. EQ-5D-5L

The EQ-5D-5L will be used to collect information to assess patient-reported health status visual analog scale (VAS) and to develop the index score. The index score is calculated from a set of item weights to derive a score of 0 to 1, with 1 representing the best health status. United Kingdom (UK) weights will be applied for the base case. Scoring will be conducted according to the EuroQoL group user manual (EuroQoL 2019) and will include descriptive summary of the 5 descriptive items and applying a mixed effects repeated measures model to explore the difference between treatment group by cycle for to the VAS and the index score change from baseline. For the EQ-5D-5L VAS and index scores, the analysis will include all cycles for which at least 25% of patients in each arm have an assessment. The model will include baseline score as a covariate and an unstructured covariance matrix will be utilized if it converges. If the model cannot converge with an unstructured covariance matrix, the covariance matrix will be determined based on the AIC.

4.7.11. Biomarker Analyses

Biomarkers assessed from blood or tissue samples and their relationship with clinical outcomes will be analyzed according to a separate translational research analysis plan.

4.7.12. Pharmacokinetic and Exposure-Response Analyses

A separate Population PK and Exposure-Response Analysis Plan will describe the planned PK and exposure-response analyses. Pharmacokinetic analyses will be conducted on all participants who have received at least 1 dose of study intervention and have at least 1 evaluable PK sample.

Abemaciclib PK analyses may include, but are not limited to:

- Summary analyses of individual and/or mean concentrations of abemaciclib, M2, and M20, grouped by analyte, dose level, time point, and so on.
- Comparison of time-matched plasma and micro sampling PK samples.
- Population PK modeling analysis to evaluate population PK parameters and inter-individual PK variability.

Relationships between exposure and measures of efficacy and safety may be explored.

4.7.13. Important Protocol Deviations

Important protocol deviations that potentially compromise the data integrity and participants' safety will be summarized. These deviations will include deviations that can be identified programmatically and those which can only be identified by the clinical research associates during monitoring. Important protocol deviations are described in another document within the study Trial Master File.

4.7.14. Subgroup Analyses

Subgroup analyses of rPFS and OS will be performed for potential prognostic subgroup variables, including

- de novo metastatic disease (Y/N)
- ≥1 visceral metastases (Y/N)
- CCI [redacted]
- baseline bone disease burden CCI [redacted]
- age (≤65, >65)
- region (North America/Europe, Asia, Other)
- baseline ECOG PS (0 vs. ≥1)
- baseline PSA (greater than the median or not)
- Gleason score at initial diagnosis (≤8 vs. >8)

If a level of a factor consists of fewer than 5% of randomized patients, analysis within that level may be omitted.

Analyses will be done within subgroup and, separately, across subgroups with a test of interactions of subgroups with treatment performed. Estimated HRs and CIs for the within subgroup analyses will be presented as a forest plot along with p-values for tests of interactions between subgroup variables and treatment.

If data warrants, other exploratory subgroup analyses may be performed, including subgroups by type of castration (LHRH agonist, LHRH antagonist, surgical), prior therapy for local disease (radical radiotherapy vs. surgery), prior docetaxel for mHSPC (Y/N), bone-modifying agent use at baseline (Y/N), ethnicity, race, measurable disease at baseline (Y/N) and CCI [redacted] If any safety analyses identify important imbalances between arms, subgroup analyses of these endpoints may be performed.

4.8. Interim Analyses

4.8.1. Data Monitoring Committee (DMC)

Interim analyses for safety and efficacy will be conducted under the guidance of an independent DMC. Only the DMC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results only if they need to know for the safety of their participants. Unblinding details are specified in a separate blinding and unblinding plan document.

The DMC will consist of at least 3 members, including 2 clinicians and 1 statistician. The DMC will communicate any recommendations based on interim analysis to the sponsor senior management designee (SMD). If necessary, the SMD may form an IRC to review and act upon the recommendations of the DMC. Details will be provided in a separate DMC charter.

4.8.2. Safety Interim Analysis

The DMC will monitor the overall safety of the study. The DMC members will review unblinded safety data at each 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 sponsor SMD.

In the event that blinded safety monitoring by the study team 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 the sponsor representatives external to the study team may be required for evaluation of selected SAEs for determination of regulatory reporting.

There will be no prespecified rules for stopping the trial due to safety concerns. The DMC will meet and review the overall data approximately every 6 months thereafter while patients remain in the on-study intervention periods. At the recommendation of the DMC, the frequency of safety interim analyses may be modified.

4.8.3. Efficacy Interim Analysis

One futility analysis and one efficacy interim analysis are planned, as described in Section 4.3.2. If the futility boundary is met at the futility analysis, the DMC should recommend that the study be stopped for futility.

The efficacy interim analysis will be conducted to provide early efficacy information and could potentially result in early communication with regulatory agencies. The DMC will be instructed to recommend to the SMD that the sponsor be unblinded if the analysis of rPFS reaches statistical significance as described in Section 4.3.2 and any additional criteria specified in the DMC charter are met. See the separate unblinding plan for details.

The sponsor does not intend to stop the study based on the interim analysis of efficacy and all patients will continue to follow-up for all study objectives until study close. Participants randomized to the control group will not be permitted to cross over to the experimental group, as this will confound the assessment of OS. If the DMC makes a recommendation counter to this at an interim analysis, for example, the DMC recommends crossing all participants over to the experimental treatment, regulatory agencies may be consulted before any action is taken.

Additionally, patients will remain blinded for the duration of the study unless specific unblinding criteria are met.

5. Sample Size Determination

Approximately 900 participants will be randomized into the study using a 1:1 ratio. The primary endpoint is rPFS. CCI [redacted] Accounting for the planned futility and interim analyses, the desired power is achieved under these assumptions when the primary analysis is conducted after approximately CCI rPFS events have occurred in the ITT population.

6. Supporting Documentation

6.1. Appendix 1: Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the clinical trial registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of adverse events (AEs), provided as a dataset which will be converted to an XML file. Both Serious AEs and 'Other' AEs are summarized by treatment group and, by Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT).

- An AE is considered 'Serious' whether or not it is a treatment-emergent adverse event (TEAE).
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each Serious AE and 'Other' AE, for each term and treatment group, the following are provided:
  - the number of participants at risk of an event
  - the number of participants who experienced each event term
  - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of participants/subjects in every treatment group may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- AE reporting is consistent with other document disclosures for example, the clinical study report (CSR), manuscripts, and so forth.

In addition, the following rules apply in order to meet the requirement for participant flow and accurately represent study completion.

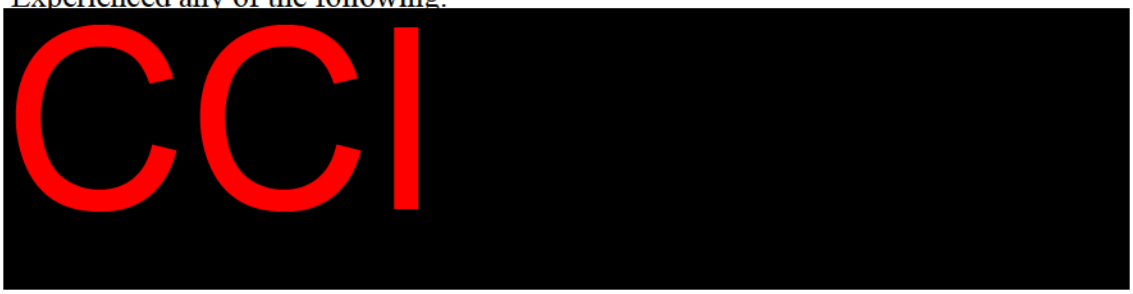
Study Discontinuation Reason	Completed	Not Completed
Participants who had an event (radiographic progression or death)	X	
Participants who were off the treatment and were alive at study conclusion	X	
Lost to follow-up[a]		X
Withdrew consent to study participant (participant or physician)		X
On study treatment at study conclusion		X

[a] Include participants only if not meeting the definition for "Completed."

6.2. Appendix 2: Notable Patient Criteria

Prior to the approval of Version 2 of this statistical analysis plan (SAP), the notable patient criteria were documented in the Patient Narrative Planning Tool. The following notable criteria supersede the ones in the Patient Narrative Planning Tool:

- Discontinued trial treatment (at least 1 of the study drugs) due to an adverse event (AE), serious or nonserious
- Died while on trial treatment or within 30 days after the date of trial treatment discontinuation, regardless of whether the death was due to trial disease
- Experienced a serious adverse event (SAE) not described in Table 7.1 of the investigator's brochure (Serious Adverse Reactions for Abemaciclib Considered Expected for SUSAR Reporting Purposes, as a Single Agent)
- Experienced any of the following:



Narratives will be provided for patients in the safety population with at least 1 notable event.

7. References

Amit O, Mannino F, Stone AM, et al. Blinded independent central review of progression in cancer clinical trials: results from a meta-analysis. *Eur J Cancer*. 2011;47(12):1772-1778. https://doi.org/10.1016/j.ejca.2011.02.013

Atkinson TM, Mendoza TR, Sit L, et al. The brief pain inventory and its "pain at its worst in the last 24 hours" item: clinical trial endpoint considerations. *Pain Med*. 2010;11(3):337-346. https://doi.org/10.1111/j.1526-4637.2009.00774

Cella D, Zagari MJ, Vandoros C, et al. Epoetin alfa treatment results in clinically significant improvements in quality of life in anemic cancer patients when referenced to the general population. *J Clin Oncol*. 2003;21(2):366-373. https://doi.org/10.1200/JCO.2003.02.136

Cella D, Nichol MB, Eton D, et al. Estimating clinically meaningful changes for the functional assessment of cancer therapy-prostate: results from a clinical trial of patients with metastatic hormone-refractory prostate cancer. *Value Health*. 2009;12(1):124-129. https://doi.org/10.1111/j.1524-4733.2008.00409.x

Chapman CR, Loeser JD, editors. Advances in pain research and therapy. Vol 12. *Issues in Pain Measurement*. Raven Press, New York; 1989:391-403.

Chi KN, Protheroe A, Rodríguez-Antolín A, et al. Patient-reported outcomes following abiraterone acetate plus prednisone added to androgen deprivation therapy in patients with newly diagnosed metastatic castration-naïve prostate cancer (LATITUDE): an international, randomised phase 3 trial. *Lancet Oncol*. 2018;19(2):194-206. https://doi.org/10.1016/S1470-2045(17)30911-7

Cox DR. Regression models and life-tables. *J Royal Stat Soc Ser B*. 1972;34(2):187-202. https://doi.org/10.1111/j.2517-6161.1972.tb00899.x

DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. *Stat Med*. 1994;13(13-14):1341-1352. https://doi.org/10.1002/sim.4780131308

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247. https://doi.org/10.1016/j.ejca.2008.10.026

EuroQol Research Foundation. EQ-5D-5L User Guide. Version 3.0. Published September 2019. Accessed February 23, 2021. https://euroqol.org/publications/user-guides

Glimm E, Maurer W, Bretz F. Hierarchical testing of multiple endpoints in group-sequential trials. *Stat Med*. 2010;29(2):219-228. https://doi.org/10.1002/sim.3748

Kaplan EL, Meier P. Nonparametric estimation of incomplete observations. *J Amer Stat Assoc*. 1958;53:457-481. https://doi.org/10.1007/978-1-4612-4380-9_25

Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials*. 1996;17(4):343-346. https://doi.org/10.1016/0197-2456(96)00075-x

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