Statistical Analysis Plan GU 115/I6A-MC-CBBD (V2)

A Double-Blinded, Placebo-Controlled, Randomized Phase II Study of Enzalutamide With or Without the PI3 Kinase/mTOR Inhibitor LY3023414 in Men with Metastatic Castration Resistant Prostate Cancer

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Statistical Analysis Plan

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Sponsor:	Eli Lilly and Company Indianapolis, Indiana, USA 46285
Study Drug:	LY3023414
SCRI Protocol Number:	GU 115
Sponsor Protocol Number:	16A-MC-CBBD
Prepared By:	SCRI Development Innovations (Innovations)

History of Changes

This document has undergone the following changes:

Version Number	Version Date	Description of Changes
1.0	July 16 2015	Original document
2.0	Mar 8 2017	Updated with futility interim at 36 PFS events
	Mar 8 2017	Updated Section 3.1 by additional details on censor dates
	Mar 8 2017	Updated the Sign Off Page
	Apr 17 2017	Miscellaneous updates

Statistical Analysis Plan Review and Approval

PPD

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Glossary

ADT	Androgen deprivation therapy
AE	Adverse event
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Adverse reaction
AST (SGOT)	Aspartate aminotransferase
BID	Twice daily
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CMP	Comprehensive metabolic profile
CR	Complete remission
CRPC	Castration Resistant Prostate Cancer
CT	Computerized tomography
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IP	Investigational product
IRB	Institutional Review Board
LHRH	Luteinizing hormone-releasing hormone
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OR	Objective response
ORR	Overall response rate
OS	Overall survival
PCWG2	Prostate Cancer Clinical Trials Working Group
PD	Progressive disease
PDx	Pharmacodynamic
PHI	Protected health information
PI3K	Phosphatidylinositol-3-kinase
PFS	Progression-free survival

PK	Pharmacokinetic
PR	Partial response
PSA	Prostate specific antigen
PTEN	Phosphatase and tensin homolog (gene)
QA	Quality assurance
QD	Once daily
RANK-L	Receptor activator of nuclear factor kappa-B ligand
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response rate
SAE	Serious adverse event
SAR	Suspected adverse reaction
SCRI	Sarah Cannon Research Institute
SD	Stable disease
SUSAR	Suspected Unexpected Serious Adverse Reaction
TTP	Time to progression
UAE	Unexpected adverse event
ULN	Upper limit of normal

1 Introduction

This document describes the Statistical Analysis Plan for study 16A-MC-CBBD, *A Double-Blinded, Placebo-Controlled, Randomized Phase II Study of Enzalutamide With or Without the PI3 Kinase/mTOR Inhibitor LY3023414 in Men with Metastatic Castration Resistant Prostate Cancer*, sponsored by Eli Lilly & Company.

1.1 Objectives

Primary Objective

- The primary objective of this study is to compare progression-free survival (PFS) - PSA, radiographic, or Prostate Cancer Clinical Trials Working Group (PCWG2) symptomatic progression -in men with mCRPC who are receiving enzalutamide plus LY3023414 versus enzalutamide plus placebo using Prostate Cancer Clinical Trials Working Group (PCWG2) criteria.

Secondary Objectives

The secondary objectives of this study are:

- To compare the clinical response rates (RRs) in men with mCRPC who are receiving enzalutamide plus LY3023414 versus enzalutamide plus placebo and who have measurable disease at baseline using Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 (Eisenhauer et al. 2009).
- To compare time to clinical (symptomatic or radiographic) and/or PSA progression (TTP) in men with mCRPC who are receiving enzalutamide plus LY3023414 versus enzalutamide plus placebo using PCWG2 criteria.
- To compare the maximum decline in PSA that occurs following treatment in men with mCRPC who are receiving enzalutamide plus LY3023414 versus enzalutamide plus placebo.
- To demonstrate the safety and tolerability of 200 mg twice daily (BID) oral LY3023414 given in combination with 160 mg once daily (QD) oral dose of enzalutamide.
- To evaluate potential pharmacokinetic (PK) drug interactions (i.e. impact of enzalutamide on LY3023414 exposure) and to further characterize LY3023414 PK properties.
- To characterize the safety profile of enzalutamide plus LY3023414 as compared to enzalutamide plus placebo in this patient population.

Exploratory Objectives

The exploratory objective of this study is:

- To collect blood and archival tissue for exploratory studies to identify biomarkers predictive of clinical efficacy and disease progression in this patient population.

1.2 Study Design

This is a double-blinded, placebo-controlled, randomized Phase II study of the combination of enzalutamide plus LY3023414 versus enzalutamide plus placebo in medically or surgically castrated men with mCRPC who have shown disease progression on abiraterone.

Cycles will be 28 days in length. Patients will be treated until disease progression (radiographic or PCWG2 symptomatic progression), or until they develop an unacceptable adverse event (AE) requiring discontinuation of the drug, or patient/physician choice. Patients with PSA progression are allowed and encouraged to continue treatment until clinical (symptomatic or radiographic) progression.

Lead-In (Part A)

A lead-in (Part A) of approximately 6-12 patients will be conducted prior to the randomized Phase II portion of the study to assess safety, tolerability, and potential PK interaction. Prior to starting this combination therapy on Cycle 1 Day 1, patients in Part A will be given single agent LY3023414 200 mg every 12 hours (BID) during the initial week (called Week •1) to assess LY3023414 PKs at a steady state on Day -1 (last day of that Week -1).

Double-blinded, Placebo-Controlled Randomized Study (Part B)

After safety and tolerability of the dose is established in Part A, a total of approximately 132 patients will be randomized in a 1:1 ratio to enzalutamide 160 mg orally QD in combination with LY3023414 200 mg or matching placebo orally BID (Part B). Randomization will be stratified based on two factors: 1) the presence or absence of visceral disease (i.e. non-lymph node soft tissue disease), and 2) if patients previously received chemotherapy in the hormone-sensitive setting when commencing androgen deprivation therapy (ADT). Interim efficacy analyses will be performed at the points indicated in Section 1.3

Treatment Groups

Patients will be randomized in a 1:1 ratio to enzalutamide 160 mg orally QD in combination with LY3023414 200 mg or matching placebo orally BID in Part B. The two treatment groups displayed in data summaries as 'LY3023414' and 'Placebo' given that all patients will receive enzalutamide.

1.3 Statistical Considerations

CCI

[redacted]

CCI [redacted]

Randomization

Patients will be randomly assigned treatment (1:1) to LY3023414 plus enzalutamide or placebo plus enzalutamide stratified by visceral disease status (present or absent) and prior chemotherapy in the hormone-sensitive setting when commencing ADT (yes or no). Randomization will be performed using an IWRS.

1.4 Timing Of Analysis

A Safety Internal Monitoring Committee (SIMC) will conduct a review of the safety and PK data of the lead-in phase (part A) patient prior to the initiation of the randomized phase part B of the study. The SIMC will review the results of the safety data at timepoints specified in the safety management plan for the study. The data cut-off date for table, listing and graph production will be based on the last lead-in patient's completion of his/her first cycle of treatment.

CCI [redacted]

CCI [redacted] will be used as the boundary to assess the efficacy of enzalutamide plus LY3023414 versus enzalutamide plus placebo in the final analysis.

The results from the interim analyses will be examined by a Lilly internal assessment committee (IAC) that will be established prior to the inclusion of the first patient in the trial. The IAC will consist at least of a Lilly Medical Director, a Lilly CRP or clinical research scientist not associated with the study, PK scientist and a Lilly statistician not associated with the study. IAC will examine the interim results and make recommendations about the trial. The interim analyses will be used to ensure the dose regimen is tolerable in this study and the assessment committee will determine if any changes are needed. They may also serve to get an early read on futility (interim analysis 1) or efficacy (interim analysis 2) through surrogates (e.g. continuous tumor measurements) or clinical efficacy endpoints for future planning. More details will be provided in the IAC Charter.

In addition to the efficacy analysis, the interim analyses will also include disposition, demographics, baseline characteristics, safety summary, and study drug administration. Applicable TFLs to be generated for the interim anlaysis will be marked with an '*IA' in the table of contents.

The final analysis will take place when there are 92 PFS events.

1.5 Responsibilities

The final statistical analysis for the study will be performed by SCRI Development Innovations. Pharmacokinetic parameter estimation and modelling will be performed by Lilly internal pharmacokinetic group. The interim analyses will be performed by statisticians and statistical programmers who are independent of study conduct. The PK parameters generation, summary of PK analysis are the responsibilities of Eli Lilly's pharmacokinetic group.

1.6 Analysis Software

Analyses will be performed using SAS® version 9.4 or higher. The analysis of the concentration data and PK parameters generation is the responsibility of Eli Lilly PK group as per the work plan. The PK parameters will be estimated using WinNonlin® within Phoenix 6.3(or higher) (Pharsight.a Certara ™ Company) and any software, approved and validated by Eli Lilly global PKPD organisation, to analyse the PK data using non-linear mixed effect modelling technics. A separate PK analysis plan is developed by Eli Lilly for the PK analysis.

2 Definition of Analysis Sets

The following analysis sets will be used in this study.

2.1 All Patients

All patients who have signed the informed consent form (i.e. screening failures plus patients enrolled) will comprise the All Patients Set (APS). The APS will be used to describe the patient disposition and all-cause deaths in both Part A and Part B

2.2 Full Analysis Set (FAS)

All enrolled patients randomized to a treatment arm in Part B will comprise the Full Analysis Set (FAS) regardless of receipt of treament. Information using this population will be tabulated by treatment arm, as randomized (Intent to Treat) according to the IWRS, unless otherwise indicated. This population will be used for the primary analyses of the efficacy endpoints.

2.3 Per Protocol Analysis Set (PPAS)

The Per Protocol population is a subset of the FAS population and consists of the randomized and treated patients who do not have a major protocol violation (e.g. clinically important and potentially impact efficacy evaluations) as listed below:

- Patient has not met the inclusion/exclusion criteria
- Patient has received certain non-permitted therapies during study
- Patient was not allocated to the treatment group determined by the randomization, or received incorrect study drug

Prior to database lock, there will be a (blinded) review of all reported protocol violations to determine the inclusion/exclusion of patients in each analysis set.

2.4 Safety Analysis Set (SAF)

All patients who have received at least one (full or partial) dose of study treatment will comprise the Safety Analysis Set (SAF). In the event of misrandomization, patients will be assigned to treatment groups based on what was actually received for all safety evaluations.

Part A patients who have received at lease one dose of study treatment are considered the Safety Analysis Set (SAF).

2.5 Pharmacokinetics Analysis Set (PKAS)

Pharmacokinetics analysis will be addressed in a separate SAP.

3 Efficacy Parameters / Endpoints

3.1 Efficacy Endpoints

Primary Efficacy Parameter / Endpoint

The primary efficacy endpoint is progression-free survival (PFS), which is defined as the time from randomization until the date of disease progression (PD) according to Prostate Cancer Clinical Trials Working Group (PCWG2) criteria or death.

To evaluate the robustness of PFS, the progression by categories according to PCWG2, PFS defined by radiological progression (rPFS), PFS defined by radiological progression and symptomatic disease progression, and PFS defined by PSA progression will be analyzed for sensitivity of the primary analysis. The first two

endpoints above are direct measurement of clinical benefit in tumor assessment rather than PSA progression.

Secondary Efficacy Parameters / Endpoints

- Overall Response Rates (ORRs) using Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1
- Time to disease progression (TTP) per PCWG2 criteria is defined as time from randomization until the date of disease progression (PD) according to PCWG2 criteria
- Radiological Progression-free survival (rPFS), which is defined as the time from randomization until the date of radiological disease progression (PD) or death
- Percentage change in PSA from baseline to 12 weeks, and the maximum decline in PSA that occurs following treatment according to PCWG2 criteria
- Time to symptomatic disease progression defined by PCWG2
- The event types under symptomatic progression
- Safety endpoints includes Adverse Events, Laboratory Evaluations, Vital Signs, ECG, Physical examination findings, and ECOG
- Drug exposure.
- Pharmacokinetic (PK) parameters of LY3023414 alone and with enzalutamide

3.1.1 Exploratory Endpoints

- Biomarkers collected from blood and archival tissue will be used in ad-hoc analysis to identify potential predictive factors in clinical efficacy and disease progression in this patient population.

3.2 Definition of Endpoints

3.2.1 Progression Free Survival based on PCWG2 criteria

PCWG2 Disease Progression Date:

The PCWG2 progression date for the primary endpoint will be the earliest date among any of the three event dates described by the Prostate Cancer Clinical Trials Working Group (PCWG2) criteria:

1) Date of Radiographic Progression

Appearance of 2 or more new lesions on bone scan, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions. The date of progression is the date of the first scan that shows the change.

Or

Soft tissue disease target lesion progression by modified RECIST v.1.1 to report changes in lymph nodes that were ≥ 20 mm in diameter at baseline with additional

requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later. The date of progression is the date of the first scan that shows the change. Note that for some treatments, a lesion may increase in size before it decreases.

The earlier date of above two progression date is the date of radiological progression.

2) Date of PSA Progression

For patient with a decrease on treatment, PSA progression is defined as ≥25% increase and ≥2 ng/mL increase above the nadir.

For patients without a decrease on treatment, PSA progression is defined as ≥25% and a ≥2 ng/mL from baseline after 12 weeks.

PSA progressions must be confirmed at the next study visit 3 or more weeks later. PSA will be collected at screening and on Day 1 of each treatment cycle.

PSA progression alone will not be considered diagnostic of disease progression,

therefore it will not be used as a reason to discontinue study treatment.

3) Date of Symptomatic Progression

Symptomatic progression is defined as evidence of unequivocal symptomatic or clinical progression defined by at least 1 of the following:

- A marked escalation in cancer-related pain that is assessed by the Investigator to indicate the need for other systemic therapy or palliative radiotherapy. Ignore early changes (≤ 12 weeks) in pain or health-related quality of life in absence of compelling evidence of disease progression. Confirm progression of pain or health-related quality of life ≥ 3 weeks later,
- An immediate need for initiation of new anticancer treatment, surgical or radiological intervention for complications due to tumor progression,
- A marked deterioration in ECOG performance status to Grade 3 or higher, or
- It is felt to be in the best interest of the patient to come off study due to clinical progression

Progression Free Survival based on PCWG2

Progression-free survival (PFS) is defined as the time from randomization until the date of disease progression (PD) according to Prostate Cancer Clinical Trials Working Group (PCWG2) criteria or death. PFS will be censored in the following senarios:

- If patient has neither PD nor death, the PFS will be censored at last radiological tumor assessment date or PSA lab assessment date.

- If patient had PD or Death occurred more than 84 days (3 tumor assessment intervals) after previous tumor radiological assessment or PSA lab assessment. The PFS will be censored at last radiological tumor assessment date or PSA lab assessment date.
- If patient does not have post baseline tumor assessment, PSA assessment, nor death within 84 days after randomization, the PFS will be censored at Day 1.
- If patient does not have valid baseline tumor assessment or PSA assessment, the PFS will be censored at Day 1.

Progression Free Survival Sensitivity Analysis For Primary Endpoints

Similiarly, the PFS time to event endpoints will be defined and evaluated for the following categories as sensitivity analysis:

- Radiological Progression-free survival (rPFS), which is defined as the time from randomization until the date of radiological disease progression (PD) or death. Patients who do not have an event or have started on any subsequent anti-cancer therapy without any documentation of progression will be censored on the date of previous radiological tumor assessment date.
- Progression Free Survival defined by both radiological progression and symptomatic disease progression defined by PCWG2.
- Progression Free Survival defined by RECIST, patient without documented progression will be censored on last tumor assessment date with SD, PR or CR.

Above time to event variable is generally defined as the time from date of randomization to the first event of interest. Patients who have started on any subsequent anti-cancer therapy without any documentation of progression will be censored on the date of previous radiological assessment date.

Tumor Respones and Response Rate

Timepoint Overall Tumor Response

Timepoint overall tumor response will be evaluated, using the RECIST 1.1 criteria, every 2 weeks until disease progression (as determined by the investigator). The categories are as follows:

- Complete response (CR)
- Partial response (PR)
- Stable disease (SD)
- Progressive disease (PD)
- Not Evaluable (NE)

The timepoint overall response at each assessment and the best overall response may be determined by Investigator and will be derived programmatically.

Discrepancies will be queried, but Investigator assessment will be used for analytical purposes.

Overall Response Rate

Overall Response Rate (ORR) is the proportion of patients whose best overall response is Complete Response (CR) or Partial Response (PR). Only patients with measurable disease at baseline will be included in the analysis of ORR.

Best Overall Response is derived based on the time point response information on the CRF according to RECIST criteria:

- If a patient has at least two CR and the first and the last CR dates are more than 28 days apart, then the best overall response is defined as CR.
- If a patient has PR and another CR/PR with more than 28 days apart, then the best overall response for this patient is PR.
- For those patients who do not have confirmed CR or PR, if the patient's last tumor assessment record of CR/PR/SD is at least 42 days after date of randomization, then best overall response is defined as SD.
- For those patients who do not have SD defined as above, but they have PD, their best overall response is PD.
- Otherwise, best overall response is defined as NE.

The derivation above will be implemented using SAS to evaluate the accuracy of the best overall response in the CRF.

Based on patients' best overall response during the study, the following rates are calculated:

- Disease Control Rate (DCR) = Proportion of patients with a best overall response of CR, PR, or SD.
- Early Progression Rate (EPR) = Proportion of patients with progressive disease within 12 weeks of randomization

PSA Response

PSA response is defined as more than 50% and 90% reduction from baseline to lowest post baseline value after 70 days (12 weeks – 2 weeks) of treatment.

Time to Progression (TTP)

TTP is defined as the time from date of randomization to the first documented observation of disease progression in radiological exam which was defined in the PCWG2 criteria as above. Time to symptomatic progression and time to PSA progression will be defined in the same manner. Patient without progression will be censored on last radiological assessment date.

Time to PSA progression will be defined in the same manner as PCWG criteria as above. Patient without progression will be censored on last PSA assessment date.

Overall Survival (OS)

Overall Survival (OS) is the time from date of randomization to death due to any cause. If a patient has not died, overall survival is censored at the last known alive date.

Percent Change from Baseline in PSA Levels

The percent change from baseline in PSA levels after 12 weeks on study and the maximum percent change from baseline will be summarized using waterfall plots for each treatment arm. To define the Week 12 visit, a visit window of 84 +/- 14 days will be used, hence any PSA level after 70 days is considered as PSA level after 12 weeks. For patients who discontinue on or before the 12 week assessment or for whom the 12 week assessment is missing, the last observation prior to the week 12 assessment will be utilized. Patients with no post-baseline PSA data will be excluded from the summaries.

Pharmacokinetics Parameters

Lilly PKPD group will be responsible for the PK analysis. SCRI will be responsible for providing the PK data set (at the interim analysis in part B and for the final analysis) and also providing QC data from the lab (at the end of the lead–in safety cohort of 6 to 12 patient).

During Part A of the study, PK blood samples will be collected **on Day -1** (last day of LY3023414 monotherapy week treatment), at pre-dose, 1.5 , 3, and 6 hours post LY3023414 dose; **on Day 1 of cycle 1** at pre-dose of LY3023414 and enzalutamide; **on any day X of cycle 1** (between Day 15 and Day 28), at pre-dose of LY3023414 and enzalutamide, 1.5 , 3, and 6 hours post LY3023414 dose (note : cycle duration 28 days); **on day 1 of cycle 2 and cycle 3** (i.e study day 29 and 57) pre-dose of LY3023414 and enzalutamide and 1.5 h post dose).

Table 1 Pharmacokinetic Sample Collection Times – Part A Patients only

Study Visit	Collection Time (± 15 minutes)	LY3023414 PK-DBS/Plasma Sample	Enzalutamide PK Plasma Sample
Week •1, Day -1[a]	Pre-dose 1.5, 3, and 6 hours post LY3023414 dose	✓	
Cycle 1, Day 1 [a]	Pre-dose of LY3023414 and enzalutamide	✓	
Cycle 1, Day X (Day 15 –Day 28)[b, c]	Pre-dose of LY3023414 and enzalutamide 1.5, 3, and 6 hours post LY3023414 dose	✓	✓
Cycle 1, Day X + 1[b, c]	Pre-dose of LY3023414 and enzalutamide	✓	✓
Cycle 2, Day 1 [b]	Pre-dose of LY3023414 and enzalutamide 1.5 hours post LY3023414 and enzalutamide dose	✓	✓
Cycle 3, Day 1 [b]	Pre-dose of LY3023414 and enzalutamide 1.5 hours post LY3023414 and enzalutamide dose	✓	✓

a: On Day -1, last day of Week -1, the morning LY3023414 dose is given and PK samples taken to estimate the exposure of LY3023414 as monotherapy. On Day 1, a pre-dose sample is taken prior to initiation of the combination treatment LY3023414 + enzalutamide (this sample is about 12 hours post the Day-1 evening LY3023414 dose)

b: It is planned that the morning dose of LY3023414/placebo will be taken together/concomitantly with the daily dose of enzalutamide.

c: Day X of Cycle 1 is any day between Day 15 and Day 28.

The Plasma concentration versus time profiles of LY3023414, enzalutamide and its metabolites will be obtained from the analysis of plasma samples. Pharmacokinetic parameters will be calculated for each patient in the lead in phase part A. Pharmacokinetic parameters for LY3023414 will include but are not limited to AUC_{0-6}, C_{max}, and T_{max}. at steady state after 7 days monotherapy and at steady state after at least 15 days combination therapy with Enzalutamide. Pharmacokinetics parameters for enzalutamide and its metabolite will include, but are not limited to, AUC_{0-6}, C_{max}, and T_{max} at steady state.

For part B patient, only sparse sampling PK will be carried out and steady state trough and Cmax LY3023414 concentraton will be reported.

As stated in section 1.6 of this document: the analysis of the concentration data and PK parameters generation is the responsibility of Eli Lilly PK group as per the work plan. The PK parameters will be estimated using WinNonlin® within Phoenix 6.3 (or higher) (Pharsight.a Certara ™ Company) and any software, approved and validated by Eli Lilly global PKPD organisation, to analyse the PK data using non-linear mixed effect modelling techniques. A separate PK analysis plan is developed by Eli Lilly for the PK analysis.

Exploratory Endpoints

Blood and archival tissue will be collected for exploratory studies to identify potential biomarkers predictive of clinical efficacy and disease progression in this patient population. Analysis may be performed on biomarker variants hypothetically playing a role in PI3K pathways or enzalutamide metabolism, including, but not limited to, PIK3CA, PTEN, or AR-V7, to evaluate their association with observed clinical outcomes to study treatment.

Additional exploratory analysis may be performed, if appropriate and allowed by the collected data. The details of the analysis plan are documented in a separate document. Results will be included in a separate report.

3.3 General Rules in Deriving Time To Event Variables

The general rule for time to event analysis is described below:

Time To Event = Date of event with interest (with event) – Start Date + 1 day, if there is an event.

Time To Event = Last Date of event with interest (no event) – Start Date + 1 day, if there is no event.

If dates of event of interests are not available, the date of randomization will be used as event date (ie censored on day 1).

Start Date

Date of randomization is the start date to calculate the event.

Event Dates

For Overall Survival (OS), Progression-Free Survival (PFS) and Time To Progression (TTP), multiple dates will be used to derive the event dates for these endpoints, with the following rules:

- Events always take precedence to Censoring
- If multiple event dates are applicable, the earliest date will be used.
- If multiple censoring dates are applicable, the last date will be used.

Cut-off Date

Any Event of interest after cut-off date will not be considered in the primary analyses. If the first event of interest is after cut-off date, the time to event variable will be censored to the previous date associated with the event of interest date. Follow-up evaluations of time to event measures may be conducted at a later date and appended to the CSR as appropriate.

3.4 Handling of Missing Efficacy Data

No imputation will be conducted for the efficacy data.

4 Safety Parameters / Endpoints

4.1 Adverse Events

Adverse events will be coded using MedDRA version 18.0. Particular preferred terms will be summarized in consolidation when appropriate.

For example, anaemia, haematocrit decreased, haemoglobin decreased, hypochromic anaemia and red blood cell count decreased will be summaried as anemia.

A treatment-emergent adverse event is defined as any adverse event that has started or worsened after the start of the first dose of study treatment up to 30 days after discontinuation of study drug. Adverse events will be graded using the NCI-CTCAE version <4.03> where applicable, or using the 5-point severity scale:

NCI-CTCAE Grade	Severity scale
1	Mild
2	Moderate
3	Severe
4	Life-Threatening
5	Death

In cases of multiple occurences of adverse event, the most severe grade observed is to be reported.

4.2 Laboratory Parameters

Laboratory toxicity grading will be derived from the laboratory values using NCI-CTCAE version <4.03>.

4.3 Other Variables

The duration of exposure
For each subject, the Length of Time on double-blind treatment will be calculated in days, using the following formula:

('Date last dose of study drug'# - 'Date first dose*) + 1

Total Dose Consumed
For each subject, the total dose on double-blind treatment will be calculated.

Dose Intensity

Dose Intensity on Dosing Days will be calculated as:

$$\frac{\text{[Total Dose Consumed]}}{\text{[Sum of all Dosing Intervals]}}$$

Relative Dose Intensity

Dose Intensity will be calculated as:

$$\frac{\text{[Total Dose Consumed]}}{\text{[Last Dose Date-First Dose Date+1]}}$$

Compliance

Compliance will be calculated as:

$$\frac{\text{[Total Dose Consumed]}}{\text{[Planned Dose]}} * 100\%$$

Prior and concomitant medication

Prior medication is defined as medication with a stop date before the date of the first dose of study drug.

Concomitant medication is defined as medication with at least one dose taken between the date of first dose (inclusive) and the date of last dose (inclusive) of study drug.

4.4 Handling of Missing Safety Data

If a patient's birthdate is a partial date with month and year available, the 15th of the month will be used to calculate the age. If a patient's birthdate is a partial date with only year available, the July 1st will be used to calculate the age.

When defining treatment emergent adverse event, if the adverse event onset date is missing in day, the last date of the month will be used. Therefore, any adverse event with onset in the same month of the first dose, is considered as treatment emergent. If the adverse event onset date is missing in both day and month, the last date of the year will be used.

For any concomitant medication, if the first use date is prior to the first dose of study medication, then the medication is defined as prior medication. If the first use of concomitant medication is missing in day, the last date of the month will be used. Therefore, any concomitant medication with first use in the same month of the first dose, is considered as the concomitant medication. If the first use date of

concomitant medication is missing in both day and month, the last date of the year will be used.

Missing relationship to study medication of any adverse event, if the adverse event onset date is after the first dose of study medication, the relationship will be considered as probably related.

5 Statistical Methods

5.1 Definition of Dates / Days

Deriving Study Day

- Date of first dose will be used in all Part A analysis
- Date of randomization will be used in all Part B efficacy analysis in dispositions, ECOG and efficacy related endpoints to ensure the consistency with the efficacy analysis.
- Date of first dose will be used in all Part B safety analysis in Exposure, Adverse Events, Laboratory Evaluations, Vital Signs, ECG, and Physical examination findings

5.2 General Consideration

For continuous variables, descriptive statistics will include the number of patients (n), mean, standard deviation, median, minimum and maximum. In addition, for continuous PK parameters, the coefficient of variation will be calculated and for Cmax and AUC the geometric mean will also be calculated. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of patients with no missing data, i.e. will add up to 100%.

All statistical comparisons will be made using two sided tests at the alpha=0.05 significance level unless specifically stated otherwise. All null hypotheses will be of no treatment difference. All alternative hypotheses will be two-sided unless specifically stated otherwise.

All data processing, summarization, and analyses will be performed using SAS Version 9.4 or higher. Specifications for table, graphs, and data listing formats can be found in the TLG specifications for this study.

5.3 Study Population

5.3.1 Disposition of Patients

The following patient data will be summarized and presented for Part A, and each treatment group in Part B:

- Number and percentage of patients randomized, and randomized but were not treated, by treatment group and overall;
- Number and percentage of patients in each analysis set, by treatment group, and overall;
- Number and percentage of patients in each stratum, by treatment group and overall for the FAS, and Safety Population;

- Number and percentage of patients who prematurely discontinued from investigational period, by reason for discontinuation and by treatment group. Reasons for study treatment discontinuation will be summarized by the following categories: disease progression based on RECIST version 1.1, adverse event (AE), medical or ethical reasons, including non-compliance, following discussion between the investigator and sponsor, and subject request (excluding AEs).

5.3.2 Protocol Violations

The number of protocol deviations/unevaluable criteria and the number of patients with at least one protocol deviation or unevaluable subjects will be summarized by each treatment group and overall for the FAS. The protocol deviation/unevaluable criteria types will also be summarized, which may include any of the following: Not Done, Outside of Window, Excluded Prior Therapy, Excluded Concomitant Medication, Value Out of Range, Same Method Not Used, Incorrect Dose Level, Dose Not Held, Dose Not Reduced, Incorrect Drug Dispensed, Incorrectly Stratified, and Other.

Major protocol violations/unevaluable criteria as defined in section 2.4 will also be summarized by violation type/unevaluable criterion and treatment group for the FAS.

5.3.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by descriptive statistics for each treatment group and overall for the PKAS for Part A, and for FAS each treatment group in Part B:

Descriptive statistics for age, weight, height and Time from initial diagnosis at study entry will be presented. Age will be calculated as the integer part of (Date of Randomization – Date of Birth + 1)/365.25. Age will also be categorized using the categories < 65 and ≥ 65 and will be presented using frequencies and percentages. Frequency tabulations for race and Cigarette Smoking History will be presented.

Frequency tabulation for the randomization stratification factor will also be presented. The factors are:

- visceral disease status (present or absent)
- prior chemotherapy in the hormone-sensitive setting when commencing ADT (yes or no).

5.3.4 Concomitant Medication

Previous medications are coded with WHODrug, Version March 2015 and will be summarized by therapeutic category, ATC class (4th level, chemical subgroup) and coded term by treatment group for the SAF.

All medications received during the treatment period (i.e. overlapping with the administration of study medication including enzalutamide) other than study drug will be considered concomitant medications. As with previous medication, concomitant medication will be summarized for each treatment group by ATC class (level 2 and 4) and WHO-DRL reference for the SAF. Patients taking the same medication multiple times will be counted once per medication and investigational period. Patients who received concomitant medications will be listed as well.

5.4 Efficacy Analysis

5.4.1 Analysis of Primary Variable

In order to compare the Progression Free Survival (PFS) distribution between any of the 2 arms, the null hypothesis will be constructed:

H_0: Duration of PFS is equal between LY3023414 and Placebo

The accompanying alternative hypothesis is:

H_1: Duration of PFS is prolonged in LY3023414

The one-sided p-values for the above hypothesis tests will be calculated using an unstratified log-rank test.

The hazard ratio of the treatment effect along with 2-sided, 60%, 80% and 95% confidence intervals will be calculated using a Cox proportional hazard model.

Kaplan-Meier survival plots will be used to describe the PFS in each treatment arm. Median PFS and 60%, 80%, and 95% confidence intervals will be estimated from the Kaplan-Meier curve.

The secondary analyses of primary efficacy variable include:

Sensitivity Analysis: A stratified log-rank test based on the stratification factors at randomization will be performed if the data within each stratum is sufficient to support a stratified analysis. A Cox proportional hazard model stratified by the stratification factors at randomization will also be used to estimate hazard ratio and to create 60%, 80% and 95% confidence intervals for the hazard ratio.

Stratification variables will include: a, visceral disease status (present or absent) b, prior chemotherapy in the hormone-sensitive setting when commencing ADT (yes or no).

The primary variable (PFS based on PCWG) of each treatment arm comparisons will be analyzed as described above and they will also be displayed in the figure.

The median of PFS time, the p-value of Log-Rank Test, the hazard ratio and its 80% CI and number of patients at risk at each time point will be displayed in the figure.

The derived endpoints for the sensitivity analysis of the primary endpoint, such as, Radiological Progression-free survival (rPFS) and Progression Free Survival defined by both radiological progression and symptomatic disease progression defined by PCWG2, will be analysed in the same manner as the primary efficacy endpoint.

5.4.2 Analysis of Secondary Efficacy Variables

All secondary endpoints will be analyzed in the same way as the primary analysis by the same the cut-off date.

rPFS, PFS based on symptomatic progression, PFS based on PSA progression, PFS based on RECIST criteria, time to Progression endpoints, and Overall Survival will be analyzed in the same manner as those for the primary efficacy variable including the graphics, the unstratified analysis and the stratified sensitivity analysis based on the stratification factors at randomization. Due to the study design, once a patient experiences PCWG2 progression, the patient will be discontinued from the study. The patient lost-to-follow-up pattern can be treatment related, hence above analyses are only for reference.

Response rate variables (PSA Response, DCR, EPR and ORR) will be summarized for each treatment group. The response rate along with exact 60%, 80% and 95% confidence intervals (Clopper-Pearson) will be calculated for each treatment arm.

Percent Change from Baseline in PSA levels will also be summarized by each treatment group over time. The maximum percent change from baseline after Week 12 will be summarized using waterfall plots for each treatment arm. No statistical testing will be conducted.

Categorical of change in ECOG will be summarized by shift table.

5.4.3 Subgroup Analysis

Primary analyses will be conducted for patient subgroups as defined by the stratification factors and other patient characteristics. A Cox proportional hazard model will be used to estimate hazard ratio and to create 60%, 80% and 95% confidence intervals for the hazard ratio in each subgroup.

5.4.4 Analysis of Other Variables

Exploratory analysis will be conducted for key efficacy endpoints in subgroups in addition to the stratification factors or patient baseline characteristics. Variables that may be considered include, but are not limited to age, disease history, and previous treatment history. Both univariate and multivariate analysis by the Cox proportional hazard model will be used to examine the association between the key efficacy endpoint and prognostics factor. The logistic regression analysis may be performed to examine the association between the stratification factors, baseline variables and response rates. All exploratory or post hoc analyses will be identified in the approapriate sections of the clinical study report.

5.5 Safety Analysis

The primary analysis population for safety is the safety population.

All Part A SAF patients will be summarized for safety analysis and baseline characteristics.

All safety analyses will be performed on the SAF, and all safety data will be presented by cohort or treatment group for each study period.

Treatment-emergent adverse events (TEAEs) are defined as adverse events that begin or worsen in severity on or after the date of the first dose of study drug and within 30 days of the date of the last dose of study drug. If date of last dose of study drug is missing but first dose date is non-missing, AEs that begin after the first dose of study drug will be considered as TEAEs.

5.5.1 Adverse Events

The coding dictionary for this study will be MedDRA Version 18.0 or higher. It will be used to summarize AEs by system organ class (SOC) and/or preferred term (PT).

Toxicity grade is defined according to the version 4.03 or later of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

The number and percentage of patients with TEAEs, as classified by SOC and PT, will be summarized for each treatment group. Similar summaries will also be provided for drug related TEAEs, treatment-emergent SAEs, drug related serious TEAEs and TEAEs that lead to study drug discontinuation or death. The TEAE leading to death is defined by the CTCAE grade=5. A drug-related TEAE is defined as any TEAE related to study medication as assessed by the investigator, or with missing assessment of the causality relationship.

TEAEs will also be summarized by severity in CTCAE grade. If an adverse event changes in severity, then the adverse event will be counted only once with the worst severity. If CTCAE grade is missing, the adverse event will be summarized as Grade "3".

All AEs and SAEs occurring throughout the conduct of the study, including all-cause deaths, will be summarized in listings. Treatment-emergent SAEs will be summarized by MedDRA SOC and PT.

Tables will include the following details:

- Number and percentage of patients with TEAEs
- Number and percentage of patients with drug related TEAEs
- Number and percentage of patients with treatment-emergent SAEs
- Number and percentage of patients with drug related treatment-emergent SAEs

- Number and percentage of patients with TEAEs by maximum CTCAE grade
- Number of TEAEs leading to permanent discontinuation of study drug.
- Number of drug related TEAE leading to permanent discontinuation of study drug.
- Number of deaths.

5.5.2 Clinical Laboratory Evaluation

The following clinical laboratory parameters will be summarized:

- Hematology –full blood count with hemoglobin, platelets, 3-part differential, prothrombin time (PT) and INR.
- Biochemistry – blood glucose, HbA1c, electrolytes (Ca, Cl, Mg, Na, phosphate, and K), BUN, creatinine, total bilirubin, alkaline phosphatase, AST, ALT, LDH, total protein, albumin.
- Urine Analysis.

Means, standard deviation, minimum, maximum and median for numeric results will be summarized at each visit by treatment group.

Biochemistry and hematology lab tests will be graded according to NCI CTCAE v4.03 or later where applicable. Shift from baseline to the worst grade on study by CTCAE grades will be presented. Shifts from baseline to worst value on study will be presented for categorical or ordinal lab parameters. Incidence of patients with laboratory values outside laboratory supplied normal range will also be presented.

Microscopic urinalysis results will be summarized by categoricals and will also presented in the listing only.

The potential for drug-induced liver injury (DILI) will be evaluated via liver function tests as outline in the FDA guidance on DILI. Summary tables will be presented for the following:

- Shifts from baseline to maximum post baseline value as a function of the upper limit of normal (ULN) as follows:
  - AST, ALT and either ALT or AST >= (3xULN, 5xULN, 10xULN, 20xULN, exclusively)
  - Total bilirun >= (1.5xULN and 2xULN, exclusively)
  - ALP >= 1.5xULN.
- The incidence of subject's meeting the criteria for Hy's Law defined as elevations in ALT and/or AST of >= 3xULN with accompanying elevations in total bilirubin of >= 2xULN.

5.5.3 Vital Signs

Vital signs and change from baseline for vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, temperature and weight) will be summarized using mean,

standard deviation, minimum, maximum and median by treatment group and visit. Additionally, change from baseline at end of treatment will be summarized.

5.5.4 Physical Examination Findings

Physical examination findings will be provided in a listing.

5.5.5 Electrocardiograms (ECGs)

Number and percent of subjects with normal, not clinically significant abnormal, and clinically significant abnormal results for the 12 lead ECG will be tabulated by treatment group at each treatment visit. A 2 x 3 shift table showing investigator's assessment of changes in normal, abnormal, and abnormal and clinically significant results during the study will be displayed. Abnormal and clinically significant results will be documented as AEs.

5.5.6 Exposure

Patients will be randomized in a 1:1 ratio to enzalutamide 160 mg orally QD in combination with LY3023414 200 mg or matching placebo orally BID in Part B.

Extent of Exposure

Duration of exposure of both LY3023414 and enzalutamide will be summarized in two ways.

Descriptive statistics will be presented for duration of exposure in months by treatment group for the SAF.

Exposure time will be categorized according to the following categories by treatment group:

- <=1 Cycle completed
- 2 Cycle completed
- 3 Cycle completed
- 4 Cycle completed
- Etc

Counts and percentages of subjects in each of these categories will be summarized for each treatment group for the SAF.

Treatment Compliance

Overall compliance with the dosing schedule will be examined for subjects in the SAF whose total study drug count and first and last days of treatment are known. Descriptive statistics will be presented by treatment group for cumulative dose, duration of exposure, dose intensity and relative dose intensity.

Treatment Modifications

Treatment modifications will be summarized by each treatment group and overall for the SAF. The number of subjects with dose interruptions and /or dose reductions will be summarized by treatment groups using frequency counts and percentages.

5.6 Prior/Concurrent Medications and Concomitant Medications

All medications will be coded using the WHODrug Dictionary <Mar. 2015>. The number of patients receiving each class of concomitant medication will be summarized by treatment group by ATC levels and preferred term. Medications stopped prior to initiation of study drug and/or started after discontinuation of study drug will be summarized in listings.

5.7 Pharmacokinetic Analysis responsibility of Lilly PKPD group

Pharmacokinetic Analysis will be performed under a separate SAP written by Lilly PK scientist.

5.8 Pharmacodynamic Analyses

Not Applicable.

5.9 Quality of Life Analyses

Not Applicable.

5.10 Pharmacoeconomics Analyses

Not Applicable.

5.11 Pharmacogenetics Analyses

The biomarker analysis will be performed under a separate SAP written by Lilly team.
Predictive biomarkers will be sought by including them, and their interactions with the Treatments, in the efficacy models described above, and examing their impact on the models' fit. Biomarkers will include mutations and amplifications of PI3K/AKT/mTOR related genes from targeted exome sequencing of tissue and blood samples. Further exploratory biomarker analysis might be done if considered of interest by the sponsor.

6 References

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7 Appendices

7.1 Appendix 1: Schedule of Assessments

Assessments	Screening	Study Treatment						Off-Treatment	Follow-Up
		Single Agent Week -1 LY302414 (Part A only)		Cycle 1		Cycle 2 & All Subsequent Cycles (±72 hrs)	Response Assessments Prior to Cycle 3 & every 2nd Cycle thereafter (i.e. 5,7, etc.)	End of Study Treatment[q]	Off Treatment Prior to Progression[r]
	Baseline[a]	D -7	D -1	D1	D15[p]	D1			
TESTS AND OBSERVATIONS									
Informed consent	X								
Medical history	X								
Physical exam[b]	X	X		X		X		X	X
Vital Signs[c]	X	X		X	X	X		X	X
ECOG PS	X	X		X	X	X		X	X
12-lead ECG[d]	X			X		X[d]		X	
Adverse event evaluation		X		X	X	X		X	
Concomitant medication review	X	X		X	X	X		X	
Study drug compliance assessment					X	X		X	
STUDY TREATMENT (Continuous Dosing)									
LY3023414 or matching placebo BID[j]		X[n]	X[n,o]	X	X	X			
Enzalutamide 160 mg[j] QD				X	X	X			
LABORATORY EVALUATIONS									
CBC, 3-part differential, and platelets	X	X		X	X	X		X	
Fasting CMP[e] plus LDH	X	X		X	X	X		X	
PT/INR[f]	X	X[f]		X[f]		X[f]			
Urine dipstick	X	X		X	X	X		X	
Biomarker blood sample[g]	X[g]			X[g]		X[g]		X	
Testosterone blood sample	X								
HbA_{1c} blood sample[h]	X					X[h]		X[h]	
PK blood sample[i,j]			X[i,j]	X[i,j]	X[i,j]	X[i,j]			

Assessments	Screening	Study Treatment					Response Assessments Prior to Cycle 3 & every 2nd Cycle thereafter (i.e. 5, 7, etc)	Off-Treatment	Follow-Up
		Single Agent Week -1 LY302414 (Part A only)		Cycle 1		Cycle 2 & All Subsequent Cycles (±72 hrs)		End of Study Treatment[q]	Off Treatment Prior to Progression[r]
	Baseline[a]	D -7	D -1	D1	D15[p]	D1			
LABORATORY EVALUATIONS									
Archived or fresh tumor tissue (optional)	X								
STAGING									
PSA[l]	X	X[l]		X		X[l]		X[l]	X[l]
Bone scan[m]	X						X[k,m]	X[k,m]	X[k,m]
CT scan of chest, abdomen and pelvis[n]	X						X[k,n]	X[k,n]	X[k,n]

a The physical examination, medical history, concomitant medications recorded ≤30 days prior to study entry, ECOG PS, CBC including differential and platelets, CMP, urinalysis, and PT/INR should be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours prior to the initiation of treatment they do not have to be repeated. Scans to document evaluable disease (i.e., tumor measurement), 12-lead ECG, and PSA should be performed ≤4 weeks prior to initiation of treatment.

b Physical examination will include measurements of height and weight at the baseline visit. Physical examinations (PE) done at all other times during the study will include only weight. Only Part B patients will need a physical exam on Cycle 1 Day 1.

c Vital signs include resting heart rate, blood pressure, oral temperature

d ECG performed locally at baseline, predose on Cycles 1 -4, and at the End of Treatment visit. Repeat if clinically indicated.

e Fasting CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO2, ALP, AST, ALT, total bilirubin, total protein, albumin, phosphorus, and LDH.

f PT/INR will only need to be repeated if abnormal at baseline or if clinically indicated. Patients requiring the initiation of an anti-coagulation therapy during study treatment should have their coagulation test performed on a weekly basis.

g Biomarker blood samples will be taken at baseline and pre-dose on Day 1 of Cycles 1, and 3 and every 2 cycles thereafter, and at the End of Treatment visit.

h HbA_{1c} blood sample will be taken at baseline, Cycle 3 and every 2 cycles thereafter, and at the End of Treatment visit.

Schedule of Assessments (continued)

i PK blood samples will have a window of ± 15 minutes. PK blood samples for patients who are participating in Part A will be **Day -1**, pre-dose, 1.5, 3, and 6 hours post LY3023414 dose; **Cycle 1 Day 1** pre-dose of LY3023414 and enzalutamide; **Cycle 1 Day X** - any day between Day 15 and Day 28, pre-dose of LY3023414 and enzalutamide, 1.5, 3, and 6 hours post LY3023414 dose; and **Cycle 1 Day X + 1**- between Day 16 and Day 29, pre-dose of LY3023414 and enzalutamide. PK blood samples for all patients will be taken pre-dose of LY3023414/placebo and enzalutamide and 1.5 hours post LY3023414/placebo dose on Cycle 2 Day 1 and Cycle 3 Day 1 .

j On PK days, pre-dose measurements and dose administration will be done in a fasted state. Patients should remain fasted for 1 hour post- dose.

k Patients will be restaged prior to Cycle 3 and after every 2 cycles of treatment thereafter (every 8 weeks). Patients with progressive disease or unacceptable toxicity should be discontinued from treatment; patients with stable disease or response to therapy will continue treatment.

l PSA blood samples will be taken ≤4 weeks prior to initiation of treatment, on Week -1 Day -7 for Part A patients, Cycle 1 Day 1 (unless collected within the previous 72 hours) Day 1 of every cycle, and at the End of Study visit if not taken in the previous 4 weeks. Patients with PSA progression are allowed and encouraged to continue treatment until symptomatic or radiographic progression.

m Bone scans- technetium only - ≤4 weeks prior to initiation of treatment, prior to Cycle 3 and after every 2 cycle s of treatment thereafter, and at the End of Study visit if scans were not taken in the previous 8 weeks. Bone lesions should be evaluated using PCWG2 criteria and not RECIST v 1.1.

n CT scans of the chest, abdomen and pelvis ≤4 weeks prior to initiation of treatment. CT scan of the chest should be repeated only if abnormal at baseline. CT scans of the abdomen and pelvis should be taken prior to Cycle 3 and after every 2 cycles of treatment thereafter, and at the End of Study visit (if scans were not taken in the previous 8 weeks). Lymph nodes should be evaluated using PCWG2 criteria and not RECIST v 1.1.

o Part A patients do not receive a placebo.

p Only Part A patients come in on Cycle 1 Day 15.

q After patients complete therapy or are discontinued from treatment they will visit the study center 30 days (+3) after finishing treatment for end of treatment assessments. Patients must be followed for AEs for 30 calendar days after the last dose of study drug.

r Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 3 months (±1 month) from the date of last dose of study drug until disease progression or for up to 3 years whichever comes first.

7.2 Appendix 2: Tables, Figures and Listings Shells

7.3 Appendix 3: In-Text Tables and Figures Specifications

7.4 Appendix 4: Derived Variables and Datasets Specifications