I3Y-MC-JPCY Statistical Analysis Plan

CYCLONE 1: A Phase 2 Study of Abemaciclib in Metastatic Castration-Resistant Prostate Cancer Patients Previously Treated with a Novel Hormonal Agent and Taxane-based Chemotherapy

NCT04408924

Approval Date: 10-Dec-2020

1. Statistical Analysis Plan: I3Y-MC-JPCY: CYCLONE 1: A Phase 2 Study of Abemaciclib in Metastatic Castration-Resistant Prostate Cancer Patients Previously Treated with a Novel Hormonal Agent and Taxane-based Chemotherapy

Abemaciclib (LY2835219)

Study I3Y-MC-JPCY is an open-label, single-arm, Phase 2 study to assess the safety and efficacy of abemaciclib monotherapy in heavily pretreated mCRPC patients who received at least 1 novel hormonal agent and 2 taxane regimens.

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Indianapolis, Indiana USA 46285

Protocol I3Y-MC-JPCY
Phase 2

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

Approval Date: 10-Dec-2020 GMT

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to the first visit when a subject receives study treatment or any other protocol intervention.

4. Study Objectives

Table JPCY.4.1. Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize the efficacy of abemaciclib monotherapy	• Investigator-assessed ORR per RECIST 1.1
Secondary	
• To further characterize the clinical activity of abemaciclib monotherapy	• rPFS • OS • DoR • DCR • PSA response rate • Time to PSA progression • Time to symptomatic progression
• To characterize the safety profile of abemaciclib	• Assessment of safety including, but not limited to, the following: AEs, SAEs, physical examination, and clinical laboratory abnormalities per CTCAE v5.0
• To explore patient-reported tolerability of abemaciclib monotherapy (including symptomatic AEs and overall side-effect burden), patient-reported pain intensity, physical functioning, and overall health-related quality of life	• PRO-CTCAE • FACT-GP5 • 7-day Worst Pain Numeric Rating Scale • EORTC QLQ-C30 Physical Functioning Scale • EORTC QLQ-C30 Global Health Status/QoL Scale
• To characterize the PK of abemaciclib and its metabolites	• Concentrations of abemaciclib and its metabolites
• To characterize Ki-67 baseline expression	• Percentage of cells expressing Ki-67 by IHC
Exploratory	
CCI	

Study Objectives and Endpoints

Abbreviations: AE = adverse event; CTCAE v5.0 = Common Terminology Criteria for Adverse Events version 5.0 (NCI 2017); DCR = disease control rate; DoR = duration of response; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; FACT-GP5 = Functional Assessment of Cancer Therapy-General; IHC = immunohistochemistry; ORR= objective response rate; OS = overall survival; PK = pharmacokinetics; PRO-CTCAE = Patient-Reported Outcome Common Terminology Criteria for Adverse Events version 5.0 (NCI 2017); PSA = prostate-specific antigen; QoL = quality of life; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1 (Eisenhauer et al. 2009); rPFS = radiographic progression-free survival; SAE = serious adverse event; SSE = symptomatic skeletal event.

5. Study Design

5.1. Summary of Study Design

I3Y-MC-JPCY (CYCLONE 1) is a Phase 2, open-label, single-arm, multicenter study to assess the efficacy of abemaciclib monotherapy in participants with metastatic castration-resistant prostate cancer (mCRPC) whose disease progressed on or after at least 1 androgen-axis therapy (abiraterone acetate, apalutamide, darolutamide or enzalutamide) and 2 taxane-based chemotherapy regimens (docetaxel and cabazitaxel). Participants may have received up to 3 prior systemic treatments for mCRPC, must have measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), and a have metastatic lesion amenable to biopsy. Androgen deprivation therapy with a gonadotropin-releasing hormone agonist must be continued throughout the study for participants who have not undergone bilateral orchiectomy. Abemaciclib 200 mg twice daily will be administered on a continuous dosing schedule until disease progression, unacceptable toxicity, or other discontinuation criteria are met.

This study will initially treat approximately 40 participants.

5.2. Determination of Sample Size

All treated patients will be included in the assessment of objective response.

An observed response rate of at least 12.5% will be considered as evidence of clinically relevant activity. Applying this rule to a 40-patient cohort yields an adequate Type I error rate and power. As an illustration of Type I error control, assuming a true response rate of 5%, the probability of observing an objective response rate (ORR) of at least 12.5% in a cohort of 40 participants is 4.8%. As an illustration of power, assuming a true response rate of 15%, the probability of observing an ORR of at least 12.5% is 73.7%.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly) or its designee. The analyses for this study will be mostly descriptive, except for possible exploratory analysis as deemed appropriate. For continuous variables, summary statistics will include the number of patients, mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized using number of patients, frequency, and percentages. Missing data will not be imputed, except for missing date of birth for analysis purpose. If birth year and month are available and date is not available or missing, date will be imputed to the 15th of that month.

The interpretation of the study results will be the responsibility of the investigator with the Lilly clinical research physician (CRP)/clinical research scientist (CRS), pharmacokineticist, and statistician. The Lilly CRP/CRS and statistician will also be responsible for the appropriate conduct of an internal review for both the final study report and any study-related material to be authorized by Lilly for publication.

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

6.1.1. Populations

For the purpose of statistical analysis, following populations are defined:

Population	Description
Entered	All participants who sign the ICF
Treated/Safety	All participants who have initiated study intervention, regardless of how many doses of study intervention they receive or how many on-study research procedures are performed
Biomarker-Evaluable	All participants within the subset of participants from the treated population from whom a valid pretreatment tumor assay result has been obtained
Pharmacokinetic Analysis	All treated participants who received at least 1 dose of abemaciclib and have at least 1 evaluable PK sample

Abbreviations: ICF = informed consent form; PK = pharmacokinetics.

6.1.2. Definitions and Conventions

Study drug or **study treatment** refers to abemaciclib.

Date of first dose is the date of the first dose of study drug.

Study day 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 (eg, if an event occurs on 08 January 2021 and the date of first dose was 06 January 2021, 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 (eg, if an event occurs on 05 January 2021 and the date of first dose was 06 January 2021, the study day of the event is -1).

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

Unless otherwise noted, **summaries of continuous variables** will include a mean, median, standard deviation, minimum, and maximum.

Unless otherwise noted, **summaries of categorical variables** will include the frequency and percentage (relative to the population being analyzed) of each category.

The assumptions for each statistical method will be evaluated. If there is violation of assumptions, alternative statistical methods may be used. Additional exploratory analyses of the data will be conducted as deemed appropriate. Unless otherwise stated, all tests of treatment effects will be conducted at a 1-sided alpha level of .025, and all confidence intervals (CIs) will be given at a 2-sided 95% level.

6.2. 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.

6.3. Patient Disposition

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of patients entered into the study, treated in the study, reasons for discontinuation from study treatment, and reasons for discontinuation from study. Reason for discontinuation from both study treatment and the study will be summarized by predetermined categories. If the reason for discontinuation is an adverse event (AE), the associated AE term will be reported.

6.4. Patient/Subject Characteristics

6.4.1. Demographics

Patient demographics will be summarized for all treated patients. Patient demographics will include sex, race, ethnicity, country, age, height, weight, and body mass index.

6.4.2. Baseline Disease Characteristics

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

- initial pathological diagnosis

- disease stage - TNM stage, Gleason score and prostate-specific antigen (PSA) at initial diagnosis
- time from initial diagnosis to:
    - castration-resistant prostate cancer (CRPC)
    - study treatment start date
- PSA doubling time prior to study treatment
- type of progression at study entry (PSA progression and/or radiographic progression)
- nature of disease (bone/nodal disease only, visceral metastases, or other)
- number of organs involved (1, 2, or 3 or more)
- metastatic site(s)
- baseline Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), and
- baseline laboratory values (PSA, testosterone, lactate dehydrogenase [LDH], alkaline phosphatase [ALP], hemoglobin [Hb], albumin).

Disease stage (I-IV) at initial diagnosis will be derived based on TNM stage, Gleason score, and PSA.

Nature of disease and number of organs involved will be derived from the baseline electronic clinical (case) report forms: 'Target Tumor: RECIST 1.1 (Tumor Assessment)' and 'Non-Target Tumor: RECIST 1.1 (Tumor Assessment)' for soft tissue, and 'Bone Lesion – Baseline (Tumor Assessment)'. The number of organs involved in soft tissue will be derived from the location codes of the target and non-target lesions.

6.4.3. Historical Illnesses

Historical illnesses are clinically relevant events in the past that ended before the screening visit. Historical illnesses (using Preferred Terms [PTs] from the most current version of the Medical Dictionary for Regulatory Activities [MedDRA]) will be summarized.

6.4.4. Prior Therapies

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

6.4.5. Therapies After Study Treatment Discontinuation

The numbers and percentages of participants receiving anticancer therapies after study treatment discontinuation 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.

Systemic therapies received following study treatment discontinuation will be summarized. Therapies will be summarized overall and by category:

- endocrine therapy
- chemotherapy
- targeted therapy, or
- other.

6.5. Treatment Compliance

Treatment compliance for abemaciclib will be measured by pill 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:

- 200 mg per dose × 2 doses per day × number of days on study drug

6.6. Concomitant Therapy

All medications will be coded to the generic preferred name according to the current World Health Organization (WHO) drug dictionary. All concomitant medications will be summarized by number and percentage of patients for the treated population using the base name (without esters or salts).

6.7. Efficacy Analyses

Unless otherwise noted, all efficacy analyses will be performed on the treated population. Patients with a nonevaluable or unknown response per each specified criteria will be considered nonresponders for the purpose of calculating response rates.

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

Objective response rate is the primary endpoint for this study. The study will be considered positive if ORR is positive at its primary analysis, as described below.

6.7.1. Primary Outcome and Methodology

The primary endpoint for this study is ORR, defined as the proportion of participants who have a soft tissue best overall response (BOR) of complete response (CR) or partial response (PR) per RECIST 1.1 and do not have concurrent bone disease progression per Prostate Cancer Working Group 3 (PCWG3) criteria, as assessed by the investigator/local radiologist. The primary analysis will require confirmation of responses, but, when appropriate, response rates including

both confirmed and unconfirmed responses may also be reported. Calculation of BOR will be done for each patient in the treated population and will include all response evaluations through the short-term follow-up visit and before the initiation of poststudy-treatment discontinuation therapy.

The primary analysis of the primary endpoint of ORR will be performed approximately 6 months after the last patient enters treatment. In certain circumstances, it may be appropriate to perform the primary analysis earlier (for instance, if all treated patients have experienced objective disease progression). All secondary endpoints will be evaluated at this time. Additional updated analyses of efficacy and safety may be conducted at later times if deemed appropriate by the sponsor.

The ORR will be evaluated against a null hypothesis of 5%. At the time of primary analysis, if 5 or more responders are observed in the planned 40 patients, the study will be considered positive. This is equivalent to a p-value <.05 for the exact test of a null hypothesis of an ORR of 5% against an alternative of ORR >5%.

Lilly or its designee will collect and store tumor assessment images, and an independent review of imaging scans may be performed by Lilly or its designee. Analyses of ORR may be repeated using independently reviewed BOR and presented as sensitivity analyses.

6.7.2. Secondary Efficacy Analyses

6.7.2.1. Radiographic Progression-Free Survival

The radiographic progression-free survival (rPFS) time is measured from the date of first dose to the earliest date of investigator-determined radiographic disease progression (by objective radiographic disease assessment per RECIST 1.1 for soft tissue AND/OR radionuclide bone scan using PCWG3 criteria for bone) or death from any cause, whichever occurs first. Patients who have neither progressed nor died will be censored at the day of their last radiographic tumor assessment (if available) or date of first dose if no postinitiation (ie, postbaseline) radiographic assessment is available. The detailed censoring rules are described in Table JPCY.6.1.

Radiographic progression-free survival will be summarized and listed for all treated patients. The Kaplan-Meier (KM) method (Kaplan and Meier 1958) will be used to estimate the rPFS curve as well as rPFS rates at 3, 6, 9, and 12 months.

Table JPCY.6.1. rPFS 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 first dose (whichever is later)[c]
Unless		
No baseline radiographic tumor assessment available	Censored	Date of first dose
No adequate postbaseline radiographic tumor assessment available and death reported after 2 scan intervals following first dose[c,d]	Censored	Date of first dose
New anticancer treatment started and no radiographic disease progression or death within 14 days	Censored	Date of last adequate radiographic assessment showing no evidence of disease progression prior to (start of new therapy +14 days) or date of first dose (whichever is later)[c]
Radiographic disease progression or death documented after 2 or more scan intervals following last adequate radiographic tumor assessment or first dose (whichever is later)[c,d]	Censored	Date of last adequate radiographic assessment showing no evidence of disease progression or date of first dose (whichever is later)[c]

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

[a] Clinical/symptomatic deterioration that is not radiologically confirmed will not be considered as radiographic disease progression.

[b] To be specific, once the radiographic disease progression is observed, especially for confirmed bone progression, the date of disease progression is the date at which initial bone progression (or soft tissue progression, whichever is earlier) is observed, not the date that the bone progression is confirmed by a subsequent assessment.

[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.
- Soft tissue disease with a response of PD.
- Bone scan showing confirmed disease progression.

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 tumor scans for 1 assessment were performed on multiple days, use the earliest scan date for that visit as the date of assessment.

[d] Two scan intervals refer to the time period of next 2 protocol-scheduled radiographic tumor assessments. Time is measured from the last adequate radiographic tumor assessment date. The window of the tumor assessment is also considered. For example, if the last adequate assessment occurs during Cycle 3, the next 2 protocol-mandated assessments are Cycle 5 and Cycle 7, and the window around each assessment is 7 days, then 2 scan intervals will be considered as 2*(28*2 + 7) = 126 days.

6.7.2.2. Overall Survival

The overall survival (OS) time is measured from the date of first dose to the date of death from any cause. If the patient is alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the patient is known to be alive. Overall survival will be summarized

and listed for all treated patients. The KM method (Kaplan and Meier 1958) will be used to estimate the OS curve as well as OS rates at 3, 6, 9, 12, and 18 months.

6.7.2.3. Duration of Response

Duration of Response (DoR) is defined only for confirmed responders (patients with a soft tissue BOR of CR or PR). It is measured from the date of first evidence of soft tissue CR or PR to the earliest date of investigator-determined radiographic disease progression (by objective radiographic disease assessment per RECIST 1.1 for soft tissue AND/OR radionuclide bone scan using PCWG3 criteria for bone) or death from any cause, whichever is earlier. It is calculated as date of radiographic progression or death minus date of first soft tissue response evaluation of CR or PR plus 1. The DoR will be censored according to the same rules as rPFS.

Duration of response will be summarized and listed for all treated patients, and a KM analysis of DoR will be performed to estimate the DoR curve. Point estimates and CIs for DoR quartiles and DoR rates will be calculated every 3 months for the first 18 months.

6.7.2.4. Disease Control Rate

The disease control rate (DCR) is the percentage of all treated patients with a best response of CR, PR, or stable disease (SD) that do not have concurrent bone disease progression per PCWG3. The DCR will be summarized for all treated patients.

6.7.2.5. Time to Prostate-Specific Antigen Progression

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 postbaseline PSA measurements within 12 weeks since baseline will be ignored in determining PSA progression. Time to PSA progression is measured from the date of first dose 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 first dose if no postinitiation (ie, postbaseline) PSA assessment is available. The detailed censoring rules are described in Table JPCY.6.2.

Time to PSA progression will be summarized and listed for all treated patients. The KM method (Kaplan and Meier 1958) will be used to estimate the time to PSA progression curve as well as landmark survival rates at 3, 6, 9, and 12 months.

Table JPCY.6.2. 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 first dose (whichever is later)[b]
Unless		
No baseline PSA assessment or no postbaseline PSA assessments available beyond 12 weeks since baseline	Censored	Date of first dose

Abbreviation: 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.

6.7.2.6. Prostate-Specific Antigen Response Rate

The PSA response rate is defined as the proportion of participants with a reduction in PSA level ≥50% from baseline, confirmed with a second assessment conducted at least 3 weeks later. The PSA response rate will be listed and summarized for all treated patients.

6.7.2.7. Time to Symptomatic Progression

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

- symptomatic skeletal event, defined as symptomatic fracture, surgery or radiation to bone, or spinal cord compression
- pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anticancer therapy, and
- development of clinically significant symptoms due to locoregional 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.

Time to symptomatic progression will be summarized and listed for all treated patients. A KM analysis will be performed to estimate the time to symptomatic progression survival curve as well as quartiles and rates at 3-month intervals. As appropriate, these analyses will be repeated for each of the individual components of time to symptomatic progression.

6.7.3. Sensitivity Analyses

Sensitivity analyses will be undertaken for calculation of the primary or key secondary endpoints in order to evaluate the robustness of the analysis. The following sensitivity analysis will be performed:

- **Blinded Independent Central Review** - as appropriate, imaging-based endpoints (including ORR, DoR, and rPFS) will also be assessed by a blinded independent review of centrally stored imaging.

6.7.4. Exploratory Analyses

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6.8. Health Outcomes/Quality-of-Life Analyses

Patient-reported outcomes (PRO) are measured through the following:

- single-item worst Pain Numerical Rating Scale (NRS)
- the National Cancer Institute's PRO version of the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE) (PRO-CTCAE)
- item GP5 of the Functional Assessment of Cancer Therapy-General (FACT-G), and
- European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLC-C30).

Additionally, analgesic use will be classified into categories (eg, according to the WHO analgesic ladder or the Analgesic Quantification Algorithm scale).

For each instrument, the compliance rate will be calculated by visit. Reasons for noncompliance will also be summarized.

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6.9. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Pharmacokinetic (PK) and pharmacodynamic analyses will be performed according to a separate PK analysis plan.

6.10. Biomarker Analyses

Protocol Section 8.8 describes the biomarker samples that will be collected during the course of the study and will be used to carry out biomarker-specific exploratory analyses. In addition to characterizing the biomarker data distribution, these analyses may include the assessment of prognostic or predictive relationships between the biomarker(s) being investigated and the clinical efficacy endpoints of the study.

In particular, the percentage of cells expressing Ki-67 by immunohistochemistry for each participant in the biomarker-evaluable population will be summarized and listed. Additionally, Ki-67 expression values will be classified into a series of binary variables (eg, <10%, <25%, etc.), and the proportion of participants in each group will be reported with corresponding exact 95% CIs.

If deemed necessary, further analysis of biomarkers may be described in a separate biomarker SAP.

6.11. Safety Analyses

Safety analyses will be completed on the safety population as specified below, unless COVID-19 impact creates a situation requiring a change to an existing analysis or a need for additional analyses as outlined by Nilsson et al. (2020).

6.11.1. Extent of Exposure

Drug exposure, drug adjustments, and omissions for abemaciclib will be summarized for all treated patients. Drug exposure will include summaries of cycles received per patient, duration on therapy, and cumulative dose. The summary of dose adjustments and omissions will include the reason for adjustment or omission. Dose intensity will be summarized for all treated patients. 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 assigned times 100% (ie, expressed as a percentage).

Extent of exposure will be measured by pill counts. Dose intensity will be expressed in mg/day. The assigned cumulative dose for abemaciclib while on study is

- 200 mg per dose × 2 doses per day × number of days on study drug.

6.11.2. Adverse Events

Adverse event verbatim text will be mapped by the sponsor or designee to corresponding terminology within the MedDRA. Severity grades will be assigned by the investigator using CTCAE version 5.0. Medical Dictionary for Regulatory Activities PTs, identified by Medical as clinically identical or synonymous, will be grouped together under a single, consolidated PT. For example, ‘Neutropenia’ and ‘Neutrophil count decreased’ will be reported as ‘Neutropenia’. Adverse events will be reported according to PTs resulting from this process.

Preexisting conditions are defined as AEs that begin prior to the first dose of study drug.

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 preexisting condition that increases in CTCAE version 5.0 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).

The MedDRA Lowest-Level Term will be used for comparisons of preexisting conditions to on-treatment events in the treatment-emergent computation.

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 (ie, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect, and
- is 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, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The following AE listings and summaries will be produced:

- Overview of TEAEs
- Summary of TEAEs by PT (all grade and Grade ≥3)
- Summary of TEAEs by System Organ Class (SOC) and PT (all grade and Grade ≥3)
- Summary of TEAEs by PT and maximum grade (1-5)
- List of SAEs
- Summary of SAEs by SOC and PT (all grade and grade ≥3), and
- Summary of AEs as reason for study treatment discontinuation by PT.

The TEAE and SAE summaries will be produced for all TEAEs/SAEs and repeated for TEAEs/SAEs related to study treatment, where relationship of the AE to the study treatment will be assessed by the investigator (yes or no).

6.11.3. Deaths

All deaths on study not attributed to study disease by the investigator will be listed along with the reason for death, if known. For those deaths attributed to an AE, the listing will include the PT of the AE. A summary of deaths including reasons for death will be produced.

6.11.4. Clinical Laboratory Evaluation

All relevant hematology and chemistry laboratory values will be graded according to CTCAE version 5.0. These calculated grades will be summarized by cycle and maximum postbaseline grade over the entire study. Treatment-emergent changes will be summarized by the maximum postbaseline grade, and a shift table of baseline grade by maximum postbaseline grade will be produced.

6.11.5. Vital Signs and Other Physical Findings

Temperature, blood pressure, pulse rate, respiration rate, weight, and ECOG PS will be summarized by cycle.

6.12. Subgroup Analyses

If results are suggestive of isolated efficacy or toxicity, subgroup analyses may be performed to identify hypotheses requiring further research.

6.13. Protocol Violations

Significant protocol violations that potentially compromise data integrity and patient safety will be summarized for all treated patients. These violations will include deviations that can be identified programmatically and those that can only be identified by the clinical research associate during monitoring. Significant protocol deviations are described in another document within the study Trial Master File.

6.14. Interim Analyses and Data Monitoring

There is 1 planned futility analysis and 1 planned interim analysis of efficacy for this study. Interim analyses will be conducted by an assessment committee including, at a minimum, the study statistician, CRP/CRS, and Global Patient Safety physician.

The futility analysis will be conducted approximately 2 months after the 15th participant has entered treatment. Trial enrollment will continue while awaiting the results of the futility analysis. The study team will consider the totality of safety, efficacy, and PK data. As guidance, futility should be declared and trial enrollment stopped if 0 patients have achieved an unconfirmed PR or CR per RECIST 1.1 AND <5 participants have achieved a BOR of SD per RECIST 1.1 at the time of the futility analysis.

One additional interim analysis of efficacy will be conducted approximately 2 months after all participants have entered treatment. Endpoints using RECIST 1.1 will be analyzed considering both confirmed and unconfirmed responses. The interim analysis will be conducted to evaluate the initial evidence of antitumor activity but will not formally test for significance. The sponsor has no intent to stop the study based on the interim analysis of antitumor activity, and all participants will continue follow-up for all study objectives until study close. At a minimum, all analyses described above of the primary efficacy endpoint, secondary efficacy endpoints, and safety will be conducted at this interim analysis.

Additional interim analyses may be conducted as deemed appropriate by the sponsor.

6.15. Annual Report Analyses

Annual report analyses, including Developmental Safety Update Report and Investigator's Brochure analyses, are described in the LY2835219 Program SAP.

6.16. Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling Clinical Trial Registry (CTR) requirements.

Analyses provided for CTR requirements include the following:

- Summary of AEs, provided as a dataset which will be converted to an XML file; both SAEs and 'Other' AEs will be summarized by MedDRA PT
    - An AE is considered 'Serious' whether or not it is a TEAE.
    - An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term, the following are provided:
        - the number of participants at risk of an event
        - the number of participants who experienced each event term, and
        - the number of events experienced.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in <5% of patients/subjects may not be included if a 5% threshold is chosen (5% is the minimum threshold).
- Adverse event reporting is consistent with other document disclosures (eg, the CSR, manuscripts, etc.).

In addition, a participant flow will be created that will describe how many enrolled patients completed the study and, for those who did not, the frequency of each reason for not completing. This analysis will be based on study discontinuation not treatment discontinuation. A patient will be identified as having completed the study if the patient dies while on the study or the patient had discontinued study treatment and is in follow-up at the time of the final OS analysis. Patients who withdraw consent before the final OS analysis or who are still on treatment at the time of the final OS analysis will be identified as not completing the study.

7. References

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Leo Document ID = bbf28a95-1e8a-45c3-88f8-cfde53b81da1

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Approval Date & Time: 10-Dec-2020 09:14:47 GMT

Signature meaning: Approved