I3Y-CR-JPBR Statistical Analysis Plan Version 2

I3Y-CR-JPBR: A Phase 1 Study of Abemaciclib in Native Chinese Patients with Advanced and/or Metastatic Cancers

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1. Statistical Analysis Plan: I3Y-CR-JPBR: A Phase 1 Study of Abemaciclib in Native Chinese Patients with Advanced and/or Metastatic Cancers

Abemaciclib (LY2835219)

This Phase 1 study is a multicenter, randomized, open-label study of oral abemaciclib in native Chinese patients with advanced and/or metastatic cancers.

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Protocol I3Y-CR-JPBR
Phase 1

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to first patient visit.

Statistical Analysis Plan Version 2 was approved prior to the study completion lock. The SAP Version 2 clarified analysis population, analysis plan for treatment compliance, and details for efficacy analyses including censoring rules for PFS and OS.

4. Study Objectives

4.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of abemaciclib in Chinese patients with advanced and/or metastatic cancers.

4.2. Secondary Objectives

The secondary objectives of this study are:

- to assess the PK of abemaciclib and its metabolites in Chinese patients with advanced and/or metastatic cancers
- to assess the antitumor activity of abemaciclib

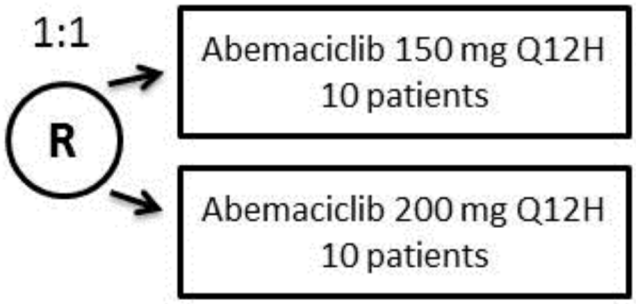
5. Study Design

5.1. Summary of Study Design

This study is a multicenter, open-label, Phase 1 trial of abemaciclib in Chinese patients with advanced and/or metastatic cancers.

The study will be focused on safety evaluation and PK data collection in patients with all advanced and/or metastatic cancers. Patients will be randomized into 2 dose cohorts, and orally receive abemaciclib 150 mg or 200 mg every 12 hours (Q12H). One cycle is defined as 28 days (Cycle 1: 32 days), with modifications during Cycle 1 to enable PK sampling following a single dose and repeated doses. The treatment of abemaciclib will continue until disease progression, development of unacceptable toxicity, or fulfillment of the other discontinuation criteria. In case of patient discontinuation during Cycle 1, the enrollment will be extended until at least 10 patients with completed PK data accrued in each cohort. Analysis on available PK and safety data will be conducted after study completion.

All patients in the study receive at least 2 cycles of abemaciclib unless one or more of the criteria for discontinuation (refer to Protocal Section 6.3.1) are fulfilled; the short-term follow-up period for poststudy evaluation is 30 ±7 days after the decision to discontinue treatment. Figure JPBR 5.1 shows the study design for Study JPBR.



Abbreviations: Q12H = every 12 hours; R = randomization.

Figure JPBR 5.1 Study design for JPBR.

5.2. Determination of Sample Size

There are no formal sample size calculations. Twenty or more patients may be enrolled to ensure 10 completers (that is, obtained the full set of PK samples for appropriate PK evaluation) in each dose cohort.

5.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive abemaciclib in this study. Before each patient's enrollment into the study, an eligibility check must be conducted at the investigational site to confirm that each patient meets all enrollment criteria. Upon confirmation

of eligibility, the sponsor will confirm the dose and identification number assignment for each patient using the interactive web response system (IWRS).

Upon obtaining informed consent, site personnel should access the IWRS, which will enter a patient number. Patients who meet all criteria for enrollment will be randomly assigned to receive either 150-mg or 200-mg abemaciclib. A simple randomization method will be adopted. Assignment to treatment groups will be determined by a computer-generated random sequence using the IWRS. Site personnel will confirm that they have located the correct dosage by entering a confirmation number found on the packages into the IWRS.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company. The analyses for this study will be descriptive, except for possible efficacy analysis as deemed appropriate. Exploratory analyses of the data will be conducted as deemed appropriate.

Safety analyses and all efficacy analyses will be conducted using the treated analysis set , which will include the data from all patients who randomized and received at least one dose of any study drug.

Data analyses will be provided by cohort, and for all study patients combined wherever appropriate. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of patients, frequency, and percentages.

6.2. Adjustments for Covariates

No adjustments for covariates.

6.3. Handling of Dropouts or Missing Data

Missing data will not be imputed.

6.4. Multiple Comparisons/Multiplicity

No adjustments for multiplicity.

6.5. Use of an "Efficacy Subset" of Patients

Not applicable.

6.6. 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, enrolled in the study, reasons for discontinuation from study treatment, and reasons for discontinuation from the study. Reason for discontinuation from both study treatment and the study will be listed by the pre-determined categories. If the reason for discontinuation is adverse event (AE) or death, the associated AE or cause of death will be reported. All patients entered in the study will be included in the summary.

6.7. Patient Characteristics

Patient characteristics will include the analysis of the following:

- Patient demographics will be reported
- Baseline disease characteristics
- Prior disease-related therapies.

Patient demographics and baseline disease characteristics will be listed for all patients on therapy and summarized by cohort. Patient demographics will include sex, race, age, height, weight, and body mass index (BMI). Baseline disease characteristics will include initial pathological diagnosis and Eastern Cooperative Oncology Group (ECOG) performance status.

Prior systemic therapy, radiotherapy, and surgeries will be listed and summarized for all patients on therapy.

Other patient characteristics will be analyzed as deemed appropriate.

6.8. Treatment Compliance

Treatment compliance of abemaciclib will be measured by capsule counts and summarized over the whole treatment period. Compliance will be calculated as the ratio of total dose taken to the total assigned dose (minus any dose adjustments and doses omitted/withheld for medical or logistical reasons). The total assigned dose for a patient with no adjustments, omissions, or extensions for logistical reasons is 150 mg per dose × 2 doses per day × 28 days = 8400 mg for lower dose cohort and 200 mg per dose × 2 doses per day × 28 days = 11200 mg for higher dose cohort.

6.9. 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 listed and summarized using the preferred name for all patients on therapy by cohort.

6.10. Efficacy Analyses

The study was not designed to make an efficacy assessment. However, tumor response data, progression-free survival (PFS) data and overall survival (OS) data will be analyzed. Tumor response and progression will be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST v1.1, Eisenhauer et al. 2009).

Reported lesion data (target/ non-target or measurable/ nonmeasurable) will be listed for all enrolled patients. Change from baseline in the sum of target lesion size will be listed by cycle and depicted as a waterfall plot. The waterfall plot will depict each patient's best change from baseline in the sum of target lesion size while on study.

Investigator-determined response by cycle and best overall response for each patient will be listed. Response will be summarized using the Overall Response Rate (ORR) and Disease Control Rate (DCR). Overall Response Rate will be defined as the percentage of enrolled patients with a best response of partial response (PR) or complete response (CR). Disease Control Rate will be defined as the percentage of enrolled patients with a best response of PR, CR, or stable disease (SD). Exact 95% confidence intervals (CIs) for each of these measures will be calculated.

Progression-free survival (PFS) time will be measured from the date of the first dose to the date of investigator-determined objective progression as defined by RECIST v1.1, or death from any

cause. If a patient is not known to have progressed or died at the time of analysis, PFS time will be censored at the last known progression-free assessment. The detailed censoring rules are desc ribed in the table below (Table JPBR.6.1). PFS for each patient will be calculated and listed. Swimmer plot will be applied to present the time to event for each patient.

Table JPBR.6.1. Rules for Determining Date of Progression or Censor for Progression-Free Survival

Rule	Situation	Date of Progression or Censor	Outcome
1	No baseline tumor assessments	Date of first dose	Censored
2	No post baseline assessments and no death	Date of first dose	Censored
3	No documented progression and no death (with a post-baseline tumor assessment)	Date of last adequate tumor assessment	Censored
4	Patient lost to follow-up (or withdrew consent from study participation) before documented progression or death	Date of last adequate tumor assessment	Censored
5	Documented progression	Date of documented progression. If a tumor assessment was done on multiple days, use the earliest date for that visit.	Progressed
6	Death without documented progression	Date of death	Progressed
7	Documented progression or death after missing ≥2 consecutive post-baseline tumor assessments	Date of last adequate tumor assessment before missed assessments or date of first dose, whichever is later	Censored

Note: Progression-free survival and associated outcome is determined by the earliest of the dates above, if more than 1 situation applies.

Overall survival (OS) duration will be measured from the date of the first dose to the date of death from any cause. For each patient who is not known to have died, OS will be censored at the date of last day known alive.

6.11. Bioanalytical and Pharmacokinetic Methods

Pharmacokinetic analyses will be conducted on patients who have received at least one dose of the study drug and have had samples collected to allow the estimation of abemaciclib PK parameters.

Plasma concentrations of abemaciclib and its major metabolites, LSN2839567 (M2) and LSN3106726 (M20), will be determined using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method.

Pharmacokinetic parameter estimates for abemaciclib and its major metabolites will be calculated by standard noncompartmental methods of analysis using Phoenix WinNonlin on a computer that meets or exceeds the minimum system requirements for this program. The primary parameters for analysis will be C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty}$ Other noncompartmental parameters, such as $t_{1/2}$, $C_{L/F}$, and V/F may be reported. The PK profiles will be graphically presented and summary statistics of PK parameters will be obtained.

Additional exploratory analyses will be performed if warranted by data and other validated PK software programs (for example, NONMEM) may be used if appropriate and approved by Global Pharmacokinetic management. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

6.12. Safety Analyses

6.12.1. Extent of Exposure

The number of cycles of treatment received, dose delays, and dose intensity will be summarized.

Extent of exposure will be measured by pill counts and summarized by cycle. The summary will include total dosage taken and dose intensity. Dose intensity will be calculated as the ratio of total dose taken to the assigned cumulative dose. The assigned cumulative dose for each patient during each cycle is 150 mg per dose × 2 doses per day × 28 days = 8400 mg for lower dose cohort and 200 mg per dose × 2 doses per day × 28 days = 11200 mg for the higher dose cohort. The assigned cumulative dose while on study for lower and higher dose cohort is 2 × 150 mg × number of days and 2 × 200 mg × number of days on treatment, accordingly.

Dose adjustments including the reasons for dose adjustment will also be listed and summarized.

6.12.2. Adverse Events

Adverse event (AE) terms and severity grades will be assigned by the investigator using Common Terminology Criteria for Adverse Events (CTCAE version 4.0, NCI 2009) In addition, AE verbatim text will also be mapped by the sponsor or designee to corresponding terminology within MedDRA. Adverse events will be reported using the following reporting process:

- The CTCAE Version 4 term reported by the investigator will be mapped to the MedDRA PT and system organ class (SOC) of the corresponding MedDRA lower level term (LLT), unless the reported CTCAE term is 'Other – specify'.
- If the reported CTCAE term is 'Other – specify' the MedDRA LLT, PT and SOC mapped from the verbatim AE term will be used.
- All listings and summaries will use the PT resulting from this process.

Pre-existing 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 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). Comparisons of pre-existing conditions to on-treatment events at the LLT level will be used 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 (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, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

To assess the relationship of the AE to the study treatment, the following terminologies are defined (in Protocol Section 8.1.2):

- Related: a direct cause and effect relationship between the study treatment and the AE is likely.
- Possibly related: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible.
- Unrelated: without question, the AE is definitely not associated with the study treatment.

As per Lilly's standard operating procedures (SOPs), all "related" and "possibly related" AEs and SAEs will be defined as related to study treatment.

The following TEAE/SAE listings and summaries will be produced:

- List of pre-existing conditions and AEs
- Overview of TEAEs
- Summary of TEAEs by PT (all grade and grade ≥ 3)
- Summary of TEAEs by 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)
- List of DLT-equivalent toxicity.

The four summaries will be produced for all TEAEs/SAEs and repeated for TEAEs/SAEs related

to study treatment.

6.12.3. Deaths, Other Serious Adverse Events, and Other Notable Adverse Events

All deaths on study will be listed along with the reason for death, if known. A summary of deaths will also be produced.

6.12.4. Clinical Laboratory Evaluation

Laboratory data will be listed and summarized by each cohort. Abnormal results will be listed separately. In addition to the investigator reported adverse events, all relevant hematology, chemistry laboratory values, and hepatic monitoring test results will be graded according to CTCAE version 4.0. These derived values will be included on the listings of laboratory data and summary tables will be produced in a similar manner to those created for the investigator reported adverse events.

6.12.5. Vital Signs and Other Physical Findings

Temperature, blood pressure, pulse rate, respiration rate, weight and ECOG performance status will be listed and summarized for all patients on therapy.

6.12.6. Electrocardiograms

All electrocardiogram (ECG) data will be listed.

6.13. Protocol Violations

Protocol violations that can be derived from the data and are related to inclusion/exclusion criteria or treatment will be listed.

6.14. Annual Report Analyses

Annual report analyses, including Developmental Safety Update Report (DSUR) and Investigational Brochure (IB) analyses, are described in the LY2835219 Program Safety Analysis Plan.

6.15. 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, provided as a dataset which will be converted to an XML file. Both Serious Adverse Events and ‘Other’ Adverse Events are summarized: by treatment group, by MedDRA preferred term.

- An adverse event is considered ‘Serious’ whether or not it is a treatment emergent adverse event (TEAE).

- An adverse event 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 patients/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 CSR, manuscripts, and so forth.

7. References

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, v4.0, DCTD, NCI, NIH, DHHS. 2009. Publish date: 29 May 2009.

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