Statistical Analysis Plan I3Y-MC-JPBJ Version 2

A Phase 1b Study of Abemaciclib in Combination with Multiple Single Agent Options for Patients with Stage IV NSCLC

NCT02079636

Approval Date: 22-Apr-2016

1. Statistical Analysis Plan: I3Y-MC-JPBJ: A Phase 1b Study of Abemaciclib in Combination with Multiple Single Agent Options for Patients with Stage IV NSCLC

Abemaciclib (LY2835219)

This Phase 1 study is a multicenter, nonrandomized, open-label, dose-escalation study followed by cohort expansion of oral abemaciclib in patients with metastatic non-small cell lung cancer.

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Protocol I3Y-MC-JPBJ
Phase 1

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 13 Feb 2014
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

Approval Date: 22-Apr-2016 GMT

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to first patient visit on 13-February-2014.

Statistical Analysis Plan (SAP) Version 2 was approved on 25-April-2016 incorporating changes due to protocol amendment JPBJ(d).

4. Study Objectives

4.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of abemaciclib when administered orally in combination with multiple single-agent options to patients with Stage IV NSCLC using Common Terminology Criteria for Adverse Events (CTCAE version 4.0,NCI 2009).

4.2. Secondary Objectives

The secondary objectives of this study are:

- To determine the pharmacokinetics (PK) of abemaciclib and pemetrexed, gemcitabine, ramucirumab,or LY3023414, when given in combination.
- To document the antitumor activity of abemaciclib when given in combination with multiple single-agent options.
- To characterize changes in patient-reported pain and disease-related symptoms collected via the MD Anderson Symptom Inventory-Lung Cancer (MDASI-LC) (Mendoza et al. 2011).

4.3. Exploratory Objectives

The exploratory objectives of this study are:

- To explore biomarkers relevant to abemaciclib and the disease state and to correlate these markers to clinical outcome and to abemaciclib.
- To explore the relationship between pathways and signatures of sensitivity developed in preclinical models based on gene expression and response to therapy using archival tumor specimens (as samples are available).
- To explore the relationship between genetic variants and the role in regulation of the cell cycle and association with observed clinical outcomes to abemaciclib.

5. Study Design

5.1. Summary of Study Design

This study is a multicenter, nonrandomized, open-label, dose-escalation Phase 1b trial in approximately 180 patients with Stage IV non small cell lung cancer (NSCLC) to receive abemaciclib in combination with 1) pemetrexed (Part A), 2) gemcitabine (Part B), 3) ramucirumab (Part C), 4) LY3023414 (Part D), and 5) pembrolizumab (Part E) as shown in Figure JPBJ.5.1. Patients will be enrolled into 1 of 5 study parts based on prior therapy or histology. During dose escalation, cohorts of atleast 3 patients will be enrolled at each of the planned dose levels. Abemaciclib will be administered orally at 100 mg, 150 mg, and 200 mg every Q12H on Days 1 through 21 of a 21-day cycle. Contingency for de-escalation to abemaciclib at 100 mg orally Q12H on Days 1 through 21 of a 21-day cycle will be permitted. In study Parts A and B at least 18 and up to 24 patients, in study Part C at least 30 and up to 42 patients, in study Part D, at least 30 and up to 48 patients, and in study Part E, at least 21 and up to 30 patients will be treated on the twice-daily schedule at a dose no greater than the established single-agent MTD (200 mg Q12H) with administration of abemaciclib on Days 1 through 21 of a 21-day cycle.

All patients in the study will continue to receive abemaciclib unless 1 or more of the criteria for discontinuation are fulfilled; the follow-up period for poststudy evaluation is 30 the criteria the date of the last dose of study drug received.

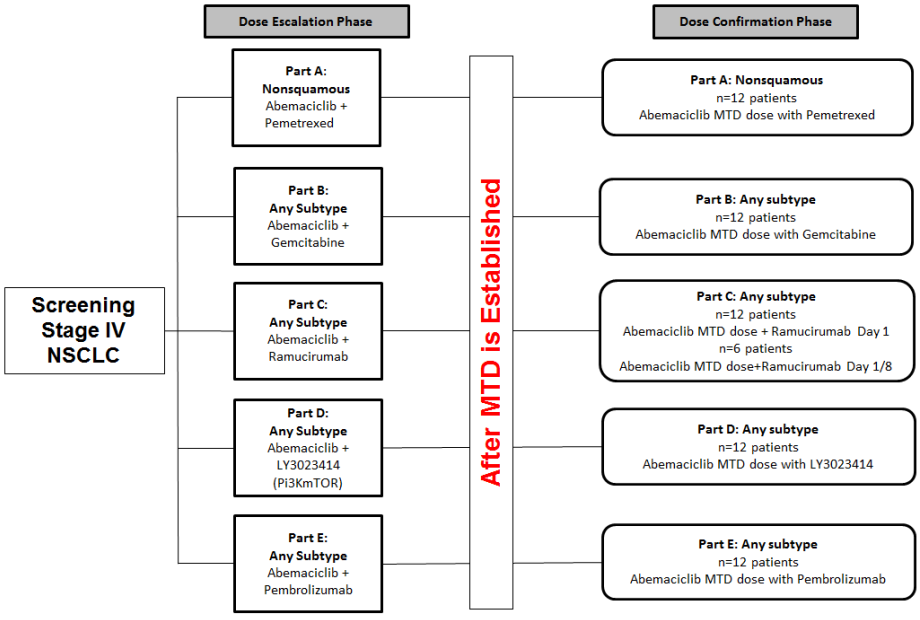

Figure JPBJ.5.1. Study design for I3Y-MC-JPBJ.

6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of the sponsor. The analyses for this study will be descriptive, except for possible exploratory analysis as deemed appropriate. Exploratory analyses of the data not described in this SAP will be conducted as deemed appropriate.

Data analyses will be provided by study part, dose group, 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.

The following data handling conventions will be used in the analysis (see Table 6.1).

Table 6.1. Data Handling Conventions

Term	Definition or Rule
Relative Study Day	If assessment is on or after date of first dose then (date of assessment) – (date of first study drug dose) +1
	If assessment precedes first dose of drug then (date of assessment) – (date of first study drug dose)
	There is no study day 0. Study day 1 is the date of first dose and study day -1 is the day before the first dose.
Baseline	For change from baseline analyses, baseline value is defined as the last reported measure on or before the first dose date (prior to the dose administration), unless otherwise specified. For change from baseline within a cycle, baseline value is defined as the measure prior to the first dose of that cycle, unless otherwise specified.
Entered	Patients who have signed the informed consent document directly.
Treated Paient (enrolled patient)	Patients who have been assigned to study treatment and have received at least one dose of any study treatment.
Screen Failures	Patients who have signed informed consent, do not meet eligibility criteria and are not enrolled.

All entered patients will be used in summarizing patient disposition. All treated patients (patients who took at least one dose of study drug) will be used in analyzing patient characteristics, safety and efficacy data. All treated patients with a baseline and at least one post baseline observation will be used in analyzing the MDASI-LC score.

6.2. Handling of Dropouts or Missing Data

Missing data will not be imputed.

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, enrolled 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 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.

All clinically relevant protocol deviations will be listed by pre-determined categories (for example, inclusion/exclusion criteria, non-compliance with protocol procedures, drug dosage/intervention, use of excluded treatments, informed consent/assent process, continuing after meeting withdrawal criteria, or other).

6.4. Patient Characteristics

6.4.1.1. Demographics and Baseline Disease Characteristics

Patient demographics and baseline disease characteristics will be listed for all treated patients and summarized by dose level and by overall study part.

Patient demographics will include sex, race, age, height, weight, and body mass index (BMI). Baseline disease characteristics will include basis for diagnosis, initial pathological diagnosis and Eastern Cooperative Oncology Group (ECOG) performance status.

6.4.1.2. Historical Illnesses

Historical illnesses are clinically relevant events in the past that ended before the screening visit. Historical illnesses (using Preferred Term(s) [PTs] from the most current version of the Medical Dictionary for Regulatory Activities [MedDRA]) will be listed for all patients on therapy.

6.4.1.3. Prior and Post Discontinuation Therapies

Prior systemic therapy, radiotherapy, and surgeries will be listed and summarized for all patients on therapy. Any post-treatment therapies occurring during the study follow up period will also be listed.

6.5. 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 dose level and overall study part. If concomitant medication use is due to an AE, the associated National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (NCI 2009) term will be listed.

6.6. Efficacy Analyses

The study was not designed to make an inferential efficacy assessment. However, tumor response data and progression free survival (PFS) data will be listed and summarized.

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. Best overall response will be derived based on investigator assessment of response and Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (Eisenhauer et al. 2009). 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 90% confidence intervals (CIs) for each of these measures will be calculated.

Progression-free survival time will be defined as the time from first dose of any study drug to progressive disease (either due to objective progression or symptomatic progression) or death, whichever occurs first. Patients are not known to have progressed or died while on study will have their PFS time censored at the date of the last post baseline radiographic assessment while on study. Patients for which there is no record for progression, death, or post baseline radiographic assessment will have their PFS time censored on the day of first dose of any study drug. Progression-free survival time will be summarized by overall study part using the Kaplan-Meier method after the end of the study. Progression-free survival quartiles and PFS rates at 3 and 6 months will be estimated along with 90% CIs. Month is defined as days/30.4375.

6.7. Health Outcomes/Quality-of-Life Analyses

The MDASI-LC scores and changes from baseline in scores will be listed. Changes from baseline will be summarized at each postbaseline time point specified in the study schedule. The summary at each post baseline timepoint will include mean, median, and standard deviation.

Hospitalization data will be listed.

6.8. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

Pharmacokinetic parameter estimates will be computed for abemaciclib, its metabolites, and whenever possible, for other anticancer agents used in the combination (pemetrexed, gemcitabine, ramucirumab, and trametinib). These PK parameters will be computed by standard noncompartmental methods of analysis using WinNonlin Professional Edition on a computer that meets or exceeds the minimum requirements for this program.

The primary parameters for analysis will be maximum concentration (C_{max}) and area under the concentration-time curve ($AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}tau}$). Other noncompartmental parameters, such as time of half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (V/F) may be reported.

In addition to a standard noncompartmental assessment, the plasma concentration data of abemaciclib will also be analyzed by means of a compartmental approach using NONMEM. Plasma data from all patients will be pooled for analyses to determine the compartmental PK parameters and between- and within-patient variability. Covariates analysis will be also

performed. Once a structural and statistical model has been established, the effect of patient factors will be assessed. Covariate data distributions will be assessed.

Additional exploratory analyses may 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 Eli Lilly and Company (Lilly) requirements of software validation.

6.9. Biomarker Analyses

Biomarker analyses related to the exploratory objectives of this study will be described in a separate SAP.

6.10. Safety Analyses

6.10.1. Extent of Exposure

The number of cycles of treatment received, dose delays, and dose intensity (for both abemaciclib and combination therapies) will be summarized. Dose intensity will be defined as the percentage of the planned cumulative dose (based on treatment assignment) administered during the cycle. Dose adjustments including the reasons for dose adjustment will also be listed and summarized.

6.10.2. Dose Limiting Toxicities

A dose-limiting toxicity (DLT) is defined as an AE occurring between Day 1 and Day 21 of Cycle 1 for a patient enrolled in the dose escalation phase that is possibly related to the study regimen (either abemaciclib or the combination therapy) and fulfills any 1 of the following criteria:

- Grade 3 or 4 nonhematological toxicity according to the NCI CTCAE V4.0 except for nausea, vomiting, diarrhea, or electrolyte disturbance.
- Grade 3 or 4 nausea, vomiting, diarrhea, or electrolyte disturbance that persists more than 2 days despite maximal supportive intervention.
- Grade 4 hematological toxicity that persists more than 5 days.
- Grade 3 or 4 thrombocytopenia with bleeding.
- Grade 3 or 4 neutropenia with fever.

Investigators, together with the Lilly clinical research physician (CRP), can declare a DLT if a patient is experiencing increasing toxicity during treatment, and it becomes clear that it is not going to be possible to complete the treatment without exposing the patient to excessive risk.

A DLT-equivalent is defined as an AE that would have met the criteria for DLT if it had occurred during Cycle 1 for a patient enrolled in the dose escalation phase, but that occurs

between 1) Day 1 and Day 21 of Cycle 2 and beyond for a patient enrolled in the dose escalation phase and 2) at any time for a patient in the dose expansion phase.

Investigator-reported DLTs will be listed for all patients on therapy in the dose escalation portions of each study part. Investigator reported DLT-equivalent toxicities will also be listed for all patients on therapy.

6.10.3. Adverse Events

All patients who receive at least 1 dose of any study drug will be evaluated for safety and toxicity. Adverse event terms and severity grades will be assigned by the investigator using CTCAE, v4.0. In addition, AE verbatim text will also be mapped by the sponsor or designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Adverse events will be reported using a unified CTCAE/MedDRA reporting process:

- The CTCAE v4.0 term reported by the investigator will be mapped to the MedDRA PT and system organ class (SOC) of the corresponding MedDRA lowest 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 on or after the day of the first dose of abemaciclib or any pre-existing condition that increases in CTCAE grade on or after the day of the first dose of abemaciclib. 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 (except for study drug administration)
- 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 drug, 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 all "related" and "possibly related" AEs and SAEs will be defined as related to study drug.

The following AE listings and summaries will be produced:

- List of pre-existing conditions and AEs,
- List of SAEs,
- Summary of all pre-existing conditions,
- Summary of all TEAEs,
- Summary of related TEAEs,
- Summary of all SAEs,
- Summary of related SAEs.

6.10.4. Deaths

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

6.10.5. Clinical Laboratory Evaluation

Laboratory data will be listed for all patients on therapy. Abnormal results will be listed separately for all patients on therapy. In addition to the Investigator reported AEs, all relevant hematology and chemistry laboratory values will be graded according to CTCAE v4.0. These calculated grades will be included on the listing and summarized by maximum post-baseline grade over the entire study.

6.10.6. 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.

6.10.7. Electrocardiograms

All electrocardiogram (ECG) data will be listed.

6.10.8. Left Ventricular Ejection Fraction (Part D Only)

Left ventricular ejection fraction (LVEF) results and change from baseline values will be listed. Change from baseline will also be summarized by cycle. Per protocol, LVEF can be assessed using either echocardiogram (ECHO) or multi-gated acquisition (MUGA) scans provided the assessment modality is consistent across all assessments. Thus, change from baseline will only be calculated and reported for assessment time points where the method of assessment (ECHO or MUGA) is consistent with the method used at baseline.

6.10.9. Ophthalmic Exams (Part D Only)

All ophthalmic exam data will be listed.

6.11. Protocol Violations

Protocol violations that can be derived from the data and are related to inclusion/exclusion criteria or treatment will be listed. These violations will include those defined by:

- Inclusion/Exclusion Criteria
    - Diagnosis
    - Age
    - Baseline hematologic, hepatic, and renal labs
    - Performance Status
    - Baseline QTC interval
- Treatment
    - Initial dosing
    - Dose delays
    - Dose reductions

6.12. Interim Analyses and Data Monitoring

Since this is a dose-finding study, data will be reviewed on a cohort-by-cohort basis during the study, until the MTDs are determined for each combination therapy. The purpose of these cohort-by-cohort reviews is to evaluate the safety data at each dose level and determine if a DLT has been observed that would suggest MTD for each combination therapy has been met orexceeded. The investigators and the Lilly study team will make the determination regarding dose escalation based upon their review of the safety and tolerability data as described in this protocol.

During the dose-confirmation portion of each study part, interim analyses may be conducted to review available safety, PK, PD, and efficacy data once enrollment to that particular part (A, B,C, D, or E) has completed and all patients in that part have either completed 2 cycles of therapy or discontinued from the treatment.

6.13. Development Safety Update Report Analyses

The following reports will be produced for the Development Safety Update Report (DSUR):

- Summary of patient demographics by age and gender
- Summary of patient demographics by racial groups
- Summary of cumulative patient exposure information
- Listing of patients who discontinued study treatment due to AEs
- Listing of patients who discontinued study treatment due to death, with the exception of those patients who discontinued due to study disease.

6.14. 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 AEs, provided as a dataset which will be converted to an XML file. Both SAEs and 'Other' AEs are summarized by treatment group and 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 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).
- Adverse event reporting is consistent with other document disclosures for example, the clinical study report (CSR), manuscripts, and so forth.

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 on the study discontinuation eCRF only after completing the follow up visit.

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.

Mendoza TR, Wang XS, Lu C, Palos GR, Liao Z, Mobley GM, Kapoor S, Cleeland CS. Measuring the symptom burden of lung cancer: the validity and utility of the lung cancer module of the M. D. Anderson Symptom Inventory. *Oncologist*. 2011;16(2):217-227.

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