I3Y-MC-JPBX Statistical Analysis Plan Version 1

A Randomized Phase 2 Study of Abemaciclib (LY2835219) versus Docetaxel in Patients with Stage IV Squamous Non-Small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy

NCT02450539

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1. Statistical Analysis Plan: I3Y-MC-JPBX: A Randomized Phase 2 Study of Abemaciclib (LY2835219) versus Docetaxel in Patients with Stage IV Squamous Non-Small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy

Abemaciclib (LY2835219)

Study JPBX is a multicenter, randomized, open-label, parallel, comparator-controlled, Phase 2 trial in Stage IV squamous non-small cell lung cancer patients who have progressed after platinum-based chemotherapy, evaluating second-line treatment with abemaciclib versus docetaxel.

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

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3. Revision History

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

4. Study Objectives

4.1. Primary Objective

The primary objective of this study is to compare treatment with abemaciclib versus docetaxel therapy with respect to investigator-assessed PFS in patients with Stage IV squamous cell carcinoma NSCLC who have relapsed after prior platinum-based therapy for advanced disease.

4.2. Secondary Objectives

The secondary objectives of the study are as follows:

- To evaluate the pharmacokinetic (PK) parameters including abemaciclib and its active metabolites
- To compare treatment of abemaciclib versus docetaxel with respect to the following:
    - Overall survival (OS)
    - Overall response rate (ORR) [complete response (CR) + partial response (PR)]
    - Disease control rate (DCR) [CR + PR + stable disease (SD)]
    - Time to worsening of Performance Status (PS)
    - The safety and tolerability using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 4.0)
    - Change from baseline in patient-reported outcomes (PROs), including: 1) the MD Anderson Symptom Inventory Lung Cancer (MDASI-LC) questionnaire pain and disease-related symptoms scores; and 2) the EuroQol Group's EQ-5D-5L questionnaire index score, derived from the 5-item descriptive system, and visual analog scale (VAS) self-rated health score.

4.3. Exploratory Objectives

- To explore potential biomarkers related to the cell cycle pathway components, abemaciclib, and/or the pathogenesis of lung cancer, and their associations with clinical outcomes
- To explore the relationship between abemaciclib exposure and response
- To explore if change in tumor size is associated with PFS and OS

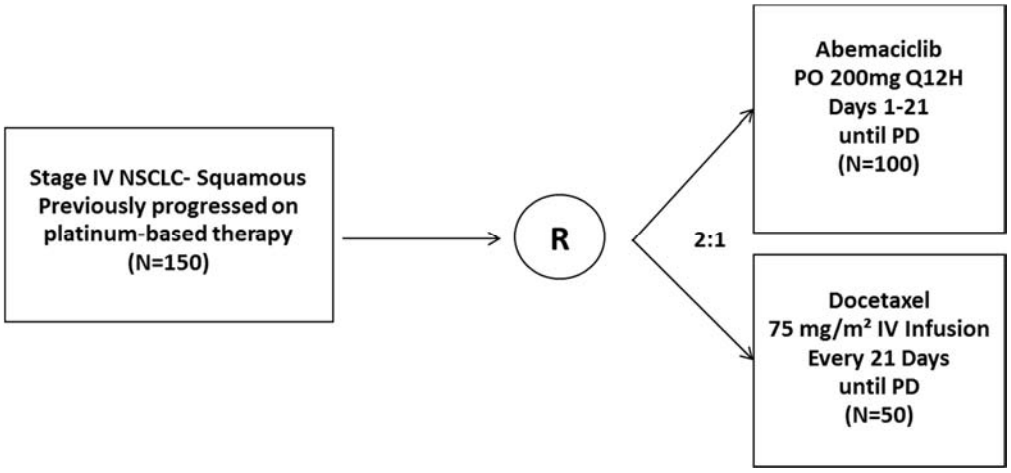
5. Study Design

5.1. Summary of Study Design

Study I3Y-MC-JPBX (JPBX) is a multicenter, randomized, open-label, parallel, comparator-controlled, Phase 2 trial in Stage IV squamous NSCLC patients who have progressed after platinum-based chemotherapy for advanced disease, evaluating treatment with abemaciclib versus docetaxel.

Patients will be stratified at randomization according to the following: ECOG PS (0 vs. 1); number of prior therapies (received only platinum-based therapy vs. platinum-based therapy plus immune checkpoint inhibitor); and time since the initiation of first-line therapy (≤ 9 vs. >9 months).

Figure JPBX.5.1. illustrates the study design.



Abbreviations: IV = intravenous; N = number; NSCLC = non-small cell lung cancer; PD = progressive disease; PO = orally; Q12H = every 12 hours; R = randomized.

Figure JPBX.5.1. Illustration of study design.

5.2. Determination of Sample Size

The primary objective of this study is to compare abemaciclib versus docetaxel in terms of PFS in patients with Stage IV squamous cell carcinoma NSCLC after progression with a platinum-based therapy for advanced disease. The study will enroll approximately 150 patients in 2:1 randomization (100 patients in abemaciclib and 50 patients in docetaxel). The primary PFS analysis will be performed after 120 PFS events are observed. Historical information will be incorporated into control arm during the primary analysis by using a Bayesian approach. Assuming a hazard ratio (HR) of 0.64, with 150 patients and the proposed Bayesian design, power of 90.5% was estimated by simulation. Under a frequentist design, this sample size yields roughly 75% power with 1-sided type I error of 0.05.

If the true median PFS for the docetaxel arm is 3 months, the HR of 0.64 amounts to an approximately 1.7-month improvement in median PFS for the abemaciclib arm under an additional assumption of exponential survival distribution.

Refer to Protocol Attachment 6 for more detail on the statistical model and simulations.

6. A Priori Statistical Methods

6.1. General Consideration

Statistical analysis of this study will be the responsibility of Lilly.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All tests of interactions will be conducted at a 2-sided alpha level of 0.1, and all CIs will be given at a 2-sided 95% level, unless otherwise stated.

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.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

6.1.1. Populations

The **entered** population includes all patients who sign the informed consent document.

The **enrolled** or **intent-to-treat (ITT)** population includes all randomized patients.

The **randomized and treated (RT)** population includes all randomized patients who received at least 1 dose of abemaciclib or Docetaxel.

All efficacy analyses will be based on the intent-to-treat population, unless otherwise stated.

Safety analyses will be based on the randomized and treated population.

Pharmacokinetic analyses will be conducted on all patients who have received at least 1 dose of abemaciclib and have had samples collected.

Pharmacodynamic and/or tailoring biomarker analyses will be based on the subset of patients from the above populations from whom a valid assay result (according to laboratory guideline) has been obtained.

6.1.2. Definitions and Conventions

Study drug refers to LY2835219 (abemaciclib).

The **date of first dose** is the date of the first dose of study drug.

The **baseline** value of an assessment is the last value observed prior to the first dose of study drug.

The **study day** of an event or assessment will be calculated as the difference between the day of the event or assessment and the date of first dose plus 1. For example, if an event occurs on 08JUN2014 and the date of first dose was 06JUN2014, the study day of the event is 3.

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

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 pre-determined categories. If the reason for discontinuation is adverse event (AE), the associated AE term will be reported.

A summary of all important protocol deviations will be provided.

6.4. Patient Characteristics

6.4.1. Baseline Demographics and Patient

Patient demographics and baseline disease characteristics will be listed for all patients on therapy and summarized by 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 (histological or cytological), disease stage and Eastern Cooperative Oncology Group (ECOG) performance status.

6.4.2. 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 summarized by treatment arm.

6.4.3. Prior Therapies

Prior systemic therapies will be summarized by drug name and treatment arm.

6.4.4. Post Study Treatment Discontinuation Therapies

The numbers and percentages of patients reporting postdiscontinuation therapies will be provided overall, by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug name.

6.5. Treatment Compliance

The number of dose omissions, reductions, and delays, cycles received, and dose intensity will be summarized for all treated patients per treatment arm.

Treatment compliance of abemaciclib will be measured by pill counts and summarized by cycle. Within each cycle, 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 reasons).

The total assigned dose for a patient with no adjustments or omissions is 200 mg per dose × 2 doses per day × 21 days = 8400 mg.

Docetaxel will be administered only by trained medical personnel at the investigational sites and under the direction of the investigator. As a result, monitoring of patient compliance is ensured. Patients who require a delay of more than 14 days in starting a new cycle of docetaxel (>35-day interval between consecutive cycles) should be considered as protocol violation.

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 treatment arm using the preferred name.

6.7. Efficacy Analyses

6.7.1. Stratification Factors

The stratification factors for the analysis are: ECOG PS (0 vs 1); number of prior therapies (received only platinum-based therapy vs. platinum-based therapy plus immune checkpoint inhibitor); and time since the initiation of first-line therapy (≤ 9 vs. >9 months)

The stratification factors are captured in the IWRS and on electronic clinical (case) report forms (eCRFs). Unless otherwise stated, all stratification analyses will be based on the stratification factors per CRF.

6.7.2. Primary Outcome and Methodology

The primary efficacy measure is investigator-assessed progression-free survival (PFS) as defined as the time from randomization until the first evidence of objective progression as defined by RECIST 1.1 (Eisenhauer et al. 2009) or death from any cause, whichever is earlier. Patients who have neither progressed nor died will be censored at the day of their last radiographic tumor assessment, if available, or the date of randomization if no postbaseline radiographic assessment is available. The detailed censoring rules are described in Protocol Table JPBX.10.1.

The primary analysis of PFS will be performed after at least 120 investigator-assessed PFS events have occurred. PFS will be compared between treatment arms by using a Bayesian exponential-likelihood model with a hierarchical random effects distribution on treatment effects. The final model will incorporate historical data from a completed study (Garon et al. 2014) to augment the prospective control-arm data. If the Bayesian posterior probability of superiority of abemaciclib arm to docetaxel arm (that is, HR <1) exceeds 0.95, then it will be concluded that the experimental arm is superior. See Protocol Attachment 6 for more details.

In addition to the primary analysis of PFS, following analysis will also be conducted:

- Log-rank test will be used to compare the PFS distribution between treatment groups with and without adjustment using the same factors as the randomization scheme. The p-value will be compared with the traditional threshold of 0.05.

- Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the PFS curve for each treatment group.
- The Cox proportional hazard model (Cox 1972) will be used to estimate the HR and corresponding 95% CI with and without stratified by randomization factors.

6.7.3. Secondary Outcome and Methodology

Secondary efficacy objective for this study include comparison of OS, ORR, DCR, and time to worsening of PS. The definition of secondary efficacy measures are listed in Protocol Section 10.1.4.

Kaplan-Meier analysis will be performed on the observed distribution of OS. Parameter estimates of the OS median and quartiles will be reported for each treatment group. All parameter estimates will be quoted together with their 95% confidence limits. Overall survival will be compared between treatment arms using the log-rank test adjusted by randomization factors. The adjusted Cox proportional hazard model (Cox 1972) will be used to estimate the HR and corresponding 95% CI.

The ORR and DCR of each treatment arm will be calculated as defined by RECIST v1.1. All rates will be compared between treatment arms based on a normal approximation for the difference between the rates.

Exploratory analysis may be performed to investigate associations between change in tumor size data and PFS and OS data.

6.7.4. Sensitivity Analyses

Sensitivity analyses will be undertaken for calculation of the primary endpoint in order to evaluate the robustness of the analysis by changing one or more of the censoring rules stated in the primary analysis. The following sensitivity analyses will be performed for PFS:

Progression-Free Survival Sensitivity Analysis 1 (forward-dating progressions at unscheduled assessments): if a patient has objective progression at an unscheduled disease assessment, then the PFS time for that patient will be forward-dated to the next scheduled disease assessment. The definition of PFS for this sensitivity analyses is presented in Table JPBX.6.1. Those items that differ from Protocol Table JPBK.12.1. are underlined.

Table JPBX.6.1. Progression-Free Survival Sensitivity Analysis 1

	Situation	Date of Progression or Censor	Outcome
1	No baseline tumor assessments	Date of Randomization	Censored
2	No post baseline assessments and no death	Date of Randomization	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	Death or documented progression after missed ≥2 consecutively post-baseline tumor assessment visits	Date of last adequate tumor assessment before missed assessments or date of randomization, whichever is later	Censored
8	Objective progression at an unscheduled disease assessment	Date of next scheduled disease assessment	Progressed

6.8. Health Outcomes/Quality-of-Life Analyses

Patient-reported outcomes are measured through paper versions of the following:

- MD Anderson Symptom Inventory- Lung Cancer (with 11 exploratory items for brain metastases (9) and potential toxicities (2))
- EuroQol 5-Dimension 5 Level (EQ-5D 5L).

Percentage of compliance and reasons for non-compliance will be summarized by treatment arm and time point. Percentage of compliance will be calculated as the number of completed assessments divided by the number of expected assessments (that is, patients still on study and alive).

Data from the MDASI-LC instrument will be scored as described by Mendoza and colleagues (Mendoza et al. 2011). Descriptive statistics will be used to describe several subscales and individual items by treatment arm: symptom severity (13 core items plus lung-cancer items), core severity (13 core items only), interference (6 interference items), brain symptoms (weakness, understanding, speaking, seizures, concentrating, appearance, irritability) as well as individual items headache, diarrhea and rash. Additionally, a composite score based on the 5 most severe baseline symptoms from items 1 through 16 will be described using descriptive statistics by treatment arm and cycle.

If a patient does not complete all items on the MDASI-LC, the mean score for a subscale will be calculated when at least 50% of the items for that subscale were answered.

The EQ-5D 5L data will be scored as described in literature (van Hout et al. 2012). The index score is calculated from a set of item weights to derive a score of 0 to 1, with 1 representing the best health status. United Kingdom (UK) weights will be applied for the base case.

The EQ-5D 5L responses for each item will be summarized by frequency and corresponding percentages by treatment arm and best response category. Descriptive statistics for the index and VAS will be calculated by arm and best response category.

Additional exploratary analysis will be described in a separate health outcome analysis plan.

6.9. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

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

6.10. Tailoring Biomarker Analyses

Analysis of biomarkers will be described in a separate biomarker analysis plan

6.11. Safety Analyses

Safety analyses will be based on the RT Population as defined in Section 6.1.1. Patients will be grouped according to treatment received in Cycle 1.

6.11.1. Extent of Exposure

Extent of exposure will be measured by dose intensity and relative dose intensity and summarize by treatment arm. For abemaciclib, dose intensity is defined as actual cumulative amount of drug taken (pill dispensed – pill returned) in treatment divided by duration of treatment in days. Relative dose intensity will be calculated as ratio of actual cumulative amount of drug taken in treatment to the assigned cumulative drug in treatment.The assigned cumulative dose for each patient during each cycle is 200 mg per dose × 2 doses per day × 21 days = 8400 mg. The assigned cumulative dose while on study is 8400 mg × number of cycles started.

For docetaxel, exposure will be measured in a similar approach. Daily dose intensity and relative dose intensity in treatment will be calculated based on the planned dosage and actually administrated dosage that captured in CRF page.

Dose adjustments and omissions, along with the reason for adjustment or omission, will be summarized.

6.11.2. Adverse Events

Verbatim text for the adverse events will be entered by the investigator , as well as the adverse event (AE) terms and severity grades per CTCAE Version 4.0.

Since all the terms in CTCAE Version 4.0 are themselves LLTs of MedDRA, adverse events will be handled in the following manner:

- The CTCAE Version 4 term reported by the investigator will be mapped to the corresponding MedDRA PT and system organ class (SOC), 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.

Serious adverse event (SAE) and relationship of AE to the study drug are defined in Protocol Section 10.3.1.1. The derivation of treatment emergent adverse event (TEAE) is described in Protocol Section 12.2.11.

Overview of adverse event will be summarized for abemaciclib. The following TEAE/SAE listings and summaries will be produced:

- 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)

The four summaries will be produced for all TEAEs/SAEs and repeated for TEAEs/SAEs related to study treatment.

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 4. These calculated grades will be summarized by cycle and maximum post-baseline grade over the entire study.

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.

6.11.6. Electrocardiograms

Local electrocardiograms (ECGs) will be summarized by cycle and overall. The summary by cycle will classify patients as having normal or abnormal ECG and summarize AEs identified by ECG within each cycle. The overall summary will classify patients as having an abnormal ECG at any point and summarize all AEs identified by ECG.

6.11.7. Hospitalizations and Transfusions

The frequency and percentage of patients with any hospitalizations and Transfusions experienced during the study treatment period or 30-day post discontinuation follow-up period will be summarized by treatment arm.

6.12. Subgroup Analysis

Subgroup analyses of PFS and OS will be performed for each of following potential prognostic subgroup variables:

- All baseline stratification factors
- Age (<65 years vs. ≥65 years)
- Region (North America vs. Europe vs. Other)
- Race (Caucasian vs. Asian vs. Other)

If a level of a factor consists of fewer than 10% of randomized patients, analysis within that level will be omitted.

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

Other subgroup analyses may be performed as deemed appropriate. If any safety analyses identify important imbalances between arms, subgroup analyses of these endpoints may be performed.

6.13. Interim Analysis

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

6.14. Protocol Violation

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

- Inclusion/Exclusion Criteria
    - Diagnosis
    - Prior treatments received
    - Age
    - Performance Status
- Treatment
    - Dose delays

- Dose reductions

6.15. Annual Report Analysis

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

6.16. 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 will be summarized by MedDRA PT.

- An AE is considered 'Serious' whether or not it is a treatment emergent adverse event (TEAE).
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each 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 (AE) reporting is consistent with other document disclosures for example, the clinical study report (CSR), manuscripts, and so forth.

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. Unblinding Plan

JPBX is an open-label study.

8. References

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