Protocol 14D-MC-JTJH A Phase 2 Study of LY2606368 in Patients with Extensive Stage Disease Small Cell Lung Cancer

NCT# NCT02735980

Approval Date: 16-May-2016

1. Statistical Analysis Plan:
I4D-MC-JTJH: A Phase 2 Study of LY2606368 in Patients with Extensive Stage Disease Small Cell Lung Cancer

LY2606368

This is a multicenter, nonrandomized, parallel-cohort Phase 2 study of LY2606368 in patients with extensive-stage disease small cell lung cancer (ED-SCLC) who have either platinum-sensitive or platinum-resistant/refractory disease.

Eli Lilly and Company
Indianapolis, Indiana USA 46285
Protocol I4D-MC-JTJH
Phase 2

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

Approval Date: 16-May-2016 GMT

2.   Table of Contents

LY2606368

Table of Contents

3. Revision History

SAP Version 1 was approved prior to the first visit when a subject receives study drug or any other protocol intervention.

4. Study Objectives

4.1. Primary Objective

- Cohort 1: To estimate the overall response rate (ORR) when a dose of 105 mg/m^2 LY2606368 every 14 days is administered to patients with ED-SCLC that have platinum-sensitive disease

- Cohort 2: To estimate the ORR when a dose of 105 mg/m^2 LY2606368 every 14 days is administered to patients with ED-SCLC that have platinum resistant/refractory disease

4.2. Secondary Objectives

- To characterize the safety and toxicity profile of LY2606368

- To characterize the pharmacokinetics (PK) of LY2606368

- To estimate secondary efficacy measures including disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), and overall survival (OS)

- To evaluate the association between best tumor response and change from baseline in lung cancer specific-symptoms, symptomatic distress, activity status, overall quality of life, total Lung Cancer Symptom Scale (LCSS) score, and Average Symptom Burden Index (ASBI) for patients who have platinum-sensitive or platinum resistant/refractory SCLC

4.3. Exploratory Objectives

- To explore biomarkers associated with the efficacy and safety of LY2606368, the exposure (PK) of LY2606368, the mechanism of action of CHK1, DNA damage response pathways or downstream effects, cell cycle markers, immune function, or cancer pathobiology

- To explore whether ongoing measurement of tumor shrinkage (such as changes in tumor size) correlate with efficacy measures

5. A Priori Statistical Methods

5.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company. The interpretation of the study results will be the responsibility of the Lilly Clinical Research Physician/Clinical Research Scientist (CRP/CRS) and statistician. The CRP/CRS and statistician will also be responsible for the appropriate conduct of internal reviews 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.

The study will enroll approximately 116 patients (58 platinum-sensitive patients, 58 platinum-refractory/resistant patients).

For the platinum-sensitive cohort, it is assumed that a true ORR of less than 20% indicates inadequate antitumor activity. Given that a futility interim analysis will be conducted on the first 29 patients' response data, then with a one-sided significance level of 0.1, a sample size of 58 patients will provide approximately 90% power to detect a true ORR of at least 35%.

For the platinum-refractory/resistant cohort, it is assumed that a true ORR of less than 5% indicates inadequate anti-tumor activity. Given that a futility interim analysis will be conducted on the first 29 patients' response data, then with a one-sided significance level of 0.1, a sample size of 58 patients will provide approximately 90% power to detect a true ORR of at least 15%.

The stopping rule for interim analysis and decision rule for final analysis are defined as follows:

- Platinum-sensitive cohort:

  - If 4 or fewer overall responses of confirmed CR or PR are observed in the first 29 patients, then the cohort will be terminated for futility; otherwise, the cohort will continue

  - If 16 or more overall responses of confirmed CR or PR are observed in all 58 patients, then the ORR is statistically significantly greater than 20%

- Platinum-refractory/resistant cohort:

  - If no overall response of confirmed CR or PR is observed in the first 29 patients, then the cohort will be terminated; otherwise, the cohort will continue

  - If 6 or more overall responses of confirmed CR or PR are observed in all 58 patients, then the ORR is statistically significantly greater than 5%

For each cohort, the overall type II error rate, i.e. the probability of terminating an effective cohort, will be controlled using a Lan-DeMets spending function (Lan and DeMets 1983), which generates boundaries that are very similar, though not identical, to the classical stopping

boundaries of O'Brien and Fleming (1979). The type II error rate spent at interim analysis after the first 29 patients for each cohort is approximately 2%; the cumulative type II error rates spent at final analysis for platinum-sensitive cohort and platinum-refractory/resistant cohort are 9.9% and 9.4%, respectively.

The following patient populations will be analyzed in this study:

- **Full analysis set**: will include all enrolled patients. This population will be used for all baseline, efficacy, health economics, dosing/exposure, and safety analyses

- **Per-protocol population**: will include all enrolled patients who do not have any major protocol violations that could potentially affect the efficacy conclusions of the study. This population will be determined after study team review of the list of important protocol deviations at end of the study, following the guideline below:

  o Patients who either have a post-baseline tumor assessment (radiological imaging and/or tumor measurement [palpable or visible]) of any level of response (excluding "not evaluable"), or discontinue from study treatment prior to tumor assessment due to an AE

  o The absence of the violation of inclusion/exclusion criteria, significant deviations in efficacy assessments, and instances of suspected misconduct

- **Pharmacokinetic population**: will include all enrolled patients who received at least 1 full infusion (dose) of LY2606368 and have evaluable PK samples collected

- **Biomarker population**: will include the subset of patients from the full analysis set from whom a valid assay result has been obtained

Unless otherwise stated, all confidence intervals (CIs) will be given at a 2-sided 95% level.

Summary statistics for continuous variables will include number of patients (N), mean, median, standard deviation (SD), minimum, and maximum. Summary statistics for categorical endpoints will include N, frequency, percentages, and associated SE and 95% CI. Exploratory analyses will be conducted as deemed appropriate. Time-to-event variables will be summarized using the Kaplan-Meier (KM) method. Kaplan-Meier estimates of median and quartiles will be reported along with 95% CIs.

Analyses will be implemented using Statistical Analysis System (SAS®, SAS Institute) version 9.1 or higher; any exceptions will be documented in the outputs.

The following data handling conventions will be used in the analysis (see Table JTJH.5.1).

Table JTJH.5.1.   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 treatment dose) +1
	If assessment precedes first dose of drug then (date of assessment) – (date of first study treatment 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 form directly or through their legally acceptable representatives.
Enrolled	Patients who have been assigned to study treatment and have received at least one dose of study treatment.
Screen Failures	Patients who have signed informed consent, do not meet eligibility criteria and are not enrolled.

5.2. Adjustments for Covariates

Please refer to Sections 5.11 and 5.17.1 for analyses with adjustments for covariates.

5.3. Handling of Dropouts or Missing Data

The full analysis set, which includes all enrolled patients, will be used for all baseline, efficacy, health outcomes, dosing/exposure, and safety analyses.

Baseline will refer to the last non-missing observation prior to first administration of any treatment unless stated otherwise. Missing data, except for dates, will not be imputed. When dates are used in calculations, missing days will be replaced with 15th of the month and missing day/month with 01 JULY. Where windows are allowed for data collection and there is more than one reading in any window, appropriate consideration will be given as to whether only one value from the window should be used, and if so how it should be chosen. This could either be the mean (geometric mean) or the value closest to the mid-point of the window or the value closest to the data collection time of another variable if the analysis involves time-matched analyses.

If a patient discontinues from study treatment for any reason other than becoming lost to follow-up or death, regular follow-up visits will be conducted to collect information on subsequent non-protocol defined therapy, first disease recurrence, and death. Therefore, it is possible to obtain information for time-to-event endpoints for these patients.

In the primary efficacy analysis, a patient with a tumor response of "not evaluable" will be included in the denominator for the purpose of calculating ORR.

In the health outcomes/quality-of-life analyses, if any of the 6 symptom-specific questions have not been completed, the ASBI will not be calculated. Similarly, if any of the 9 LCSS questions have not been completed, the total LCSS score will not be calculated.

5.4. Multicenter Studies

This is a multicenter study. Enrollment by center will be summarized. Due to limited sample size, analyses will not be conducted by center.

5.5. Multiple Comparisons/Multiplicity

The error spending for interim analysis is described in Section 5.16. No other multiple comparison/multiplicity adjustments will be made.

5.6. 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.

5.7. Patient Characteristics

Patient characteristics will be listed for all patients on therapy by cohort, including:

- Patient demographics (including age, sex, race, screening height and weight, and screening derived body surface area)

- Baseline disease characteristics (including basis for initial diagnosis, initial pathological diagnosis, stage at initial diagnosis, baseline Eastern Cooperative Oncology Group performance status)

5.8. Treatment Compliance

The study treatment will be administered only at the investigational sites by the authorized study site personnel. As a result, treatment compliance is ensured. Patients should attend scheduled clinic visits and must comply with study criteria under their control. Deviations from the prescribed dosage regimen should be recorded on the case report form and listed.

5.9. Concomitant Therapy

All medications will be coded to the generic preferred name according to the current World Health Organization drug dictionary. All concomitant medications will be listed and summarized using the preferred name for all patients on therapy by cohort. If concomitant medication use is due to an AE, the associated National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v4.0 (NCI 2009) term will be listed.

5.10. Efficacy Analyses

5.10.1. Primary Outcome and Methodology

Best overall response (BOR) is defined as the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation, and will be derived based on investigator assessment of response and Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (Eisenhauer et al. 2009).

Overall response rate is defined as the number of patients who achieve a BOR of CR or PR, divided by the total number of patients enrolled to the corresponding cohort (full analysis set). Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point (greater than 4 weeks). The ORR, with exact 95% and 80% CIs, will be summarized for each cohort using the Clopper-Pearson method.

5.10.2. Secondary Efficacy Analyses

Secondary efficacy variables are defined as follows:

Disease control rate is defined as the number of patients who achieve a BOR of CR, PR, or stable disease (SD) divided by the total number of patients enrolled to the corresponding cohort (full analysis set). The confirmation of CR and PR is required. The BOR for patients with an unconfirmed PR or CR observation will be classified as SD, as long as they otherwise meet those requirements (see following sentence). In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (not less than 5 weeks). The DCR, with exact 95% CI, will be summarized for each cohort using the Clopper-Pearson method.

Duration of response is defined as the time from the date measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that disease is recurrent or objective progression is observed, per RECIST 1.1 criteria, or the date of death from any cause in the absence of objectively determined disease progression or recurrence.

Overall survival is defined as the time from enrollment until 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 curves, median OS, and OS rates at various time points with 95% CI, for each cohort will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958).

Progression-free survival is defined as the time from enrollment until the first radiographic documentation of progression or death from any cause in the absence of PD. Patients known to be alive and without disease progression will be censored at the time of the last adequate tumor assessment prior to study completion (a detailed PFS event/censoring scheme is provided in Table JTJH.5.2). Progression-free survival curves, median PFS, and PFS rates at various time points with 95% CI for each cohort will be estimated using the Kaplan-Meier method (Kaplan and Meier 1958).

Table JTJH.5.2.   **PFS Event/Censoring Scheme**

Situation[a]	Event/Censor	Date of Event or Censor
Tumor progression or death	Event	Earliest date of PD or death
No tumor progression and no death	Censored	Date of last adequate radiological assessment or date of enrollment (whichever is later)[b]
Unless		
No baseline radiological tumor assessment available	Censored	Date of enrollment
No adequate postbaseline radiological tumor assessment available <u>and</u> death reported after 2 scan intervals following enrollment[b,c]	Censored	Date of enrollment
Tumor progression or death documented <u>immediately after</u> 2 or more scan intervals following last adequate radiological tumor assessment or enrollment (whichever is later)[b,c]	Censored	Date of last adequate radiological assessment or date of enrollment (whichever is later)[b]

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

[a] Symptomatic deterioration (that is, symptomatic progression that is not radiologically confirmed) will not be considered as tumor progression.

[b] Adequate radiological tumor assessment refers to an assessment with one of the following responses: CR, PR, SD, or PD.

[c] For the first 52 weeks following enrollment, radiologic imaging for tumor assessment will be performed approximately every 6 weeks (that is, every 3 cycles) starting at the end of Cycle 3. Thereafter, it will be performed approximately every 12 weeks. The same method of imaging used at baseline should be used for each subsequent assessment. Scans should also be obtained as clinically indicated.

5.11. Health Outcomes/Quality-of-Life Analyses

For the LCSS, the compliance rate by cohort will be calculated as the number of completed assessments divided by the number of expected assessments (that is, patients still on study). Compliance rates, reasons for noncompliance, and data collected will be summarized for all patients (cohort 1 and 2) and by cohort.

The ASBI will be calculated as the mean of 6 symptom-specific questions; the total LCSS score will be calculated as the mean of 9 questions from the LCSS. For a given assessment, if any of the 6 symptom-specific questions have not been completed, the ASBI will not be calculated. Similarly, if any of the 9 LCSS questions have not been completed, the total LCSS score will not be calculated.

Change in tumor size (defined as the percent change in tumor size from the baseline evaluation to the evaluation at the time point where BOR is observed. The correlation between CTS and LCSS score and ASBI will be tested using the Spearman's correlation coefficient.

Descriptive statistics for each of the domain scores/items of interest by category of BOR (that is, CR, PR, SD, PD) will be summarized and a linear model will be fitted for each cohort in order to evaluate the association between BOR and change from baseline/the maximum improvement

from baseline in lung cancer-specific symptoms, symptomatic distress, activity status, overall quality of life, total LCSS score, and ASBI for patients who have platinum-sensitive or platinum-resistant/refractory SCLC. The model will include change from baseline/maximum change from baseline as the response variable and category of best overall response as an independent variable.

5.12. Pharmacokinetic/Pharmacodynamic Analyses

Planned pharmacokinetic and PK/pharmacodynamic (PD) analyses are specified in a separate standalone population based PK/PD analysis plan.

5.13. Safety Analyses

All patients who receive at least one dose of study treatment will be evaluated for safety and toxicity. Adverse event terms and severity grades will be assigned by the investigator using CTCAE, version 4.0.

5.13.1. Extent of Exposure

A summary of drug exposure for study treatment will be presented.

A summary of the dose administration, detailing the number of doses given as planned, reduced, omitted, and delayed will be presented for study treatment. Reasons for dose adjustments will also be summarized.

Dose intensity and relative dose intensity will be summarized for study treatment. Dose intensity is defined as actual cumulative amount of drug taken (mg/m^2)/ duration of treatment (week).

5.13.2. Adverse Events

All patients who receive at least one dose of study treatment will be evaluated for safety and toxicity. Adverse event terms and severity grades will be assigned by the investigator using CTCAE v4.0X. 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). 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 preferred term (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 MedDRA LLT and the MedDRA PT resulting from this process.

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened in CTCAE grade after the first dose of study treatment. The MedDRA LLT will be used in the treatment-emergent computation.

All observed AEs will be graded using CTCAE version 4.0. Adverse events, deaths and serious adverse events (SAEs) will be listed and summarized. Summaries for patients on therapy will include:

- Summary of all pre-existing conditions and AEs

- Summary of all TEAEs

- Summary of TEAEs possibly related to study treatment

- Summary of all TEAEs by maximum CTCAE grade

- Summary of TEAEs possibly related to study treatment by maximum CTCAE grade

- Summary of deaths on treatment or post-study treatment deaths possibly related to study treatment.

5.13.3. Deaths

All deaths recorded in this study will be included as part of the complete AE listing, where appropriate, and listed separately. A summary of deaths may be presented for all patients on therapy if there are a sufficient number of events for this to be deemed useful.

5.13.4. Clinical Laboratory Evaluation

Laboratory data (hematology, chemistry) 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 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 AEs.

5.13.5. Vital Signs and Other Physical Findings

All vital signs including blood pressure, pulse, and temperature will be listed for all patients on therapy.

5.13.6. Electrocardiograms

For each patient, single local electrocardiogram (ECG) will be collected according to the study schedule. The ECG data will be summarized and listed.

5.14. Subgroup Analyses

The selected primary and secondary endpoints may be analyzed in the following subgroups:

- Performance status (0 vs. 1)

- Number of prior treatments (2 vs. 3)

- Nature of prior treatments (e.g. cisplatin vs. carboplatin, etoposide/no etoposide, adjuvant radiation/no radiation)

- CNS metastasis (present/absent)

- Geographic region (North America, Europe, Asia)

5.15. Important Protocol Deviations

Important protocol deviations that potentially compromise the data integrity and patients' safety will be listed. These deviations will include those defined by:

- Informed consent

- Inclusion/Exclusion Criteria

- Investigational Product

- Study Procedures

- Administrative/Oversight

- Safety

- Other

Based on the discussion with study team, the detailed description of each deviation within the above category and the method to identify each deviation will be documented.

5.16. Interim Analyses and Data Monitoring

For each cohort, one interim analysis of futility will be conducted after the 29th patient in the cohort has completed Cycle 3, and, if required, the response is confirmed. The interim analysis will be conducted to assess whether the respective cohort is unlikely to achieve statistical significance on its primary endpoint and may also include PK data in order to confirm that patients are in the expected systemic exposure range.

5.17. Planned Exploratory Analyses

5.17.1. Biomarker Analyses

Descriptive summaries and statistical analyses results will be provided to support the biomarker research objectives outlined in the protocol.

For biomarkers obtained from whole-blood samples, descriptive statistics will be reported at pre-treatment (baseline), post-treatment and post-regression time points. Each biomarker will be described using summary statistics at the study, cohort, and at the level of other patient subgrouping of interest. Any correlations or associations between the biomarkers measured on the same patient will also be looked at.

For biomarkers obtained from biopsies done on lesions, descriptive statistics will be reported at pre-treatment (baseline), post-treatment and post-regression time points as described in the paragraph above. In addition, descriptive statistics on lesions that regressed after treatment will be provided. Provided a sufficient number of patients with such biopsies are available, additional

analyses may be undertaken to investigate the correlation between the change in the status/level of the biomarker and the change in the size of the lesion.

All biomarkers deemed relevant may be specifically investigated with the aim of understanding the biomarker profile of patients who receive the greatest clinical benefit from LY2606368. These investigations will look at the correlation/association between the baseline (archival or pre-treatment) status/level of the biomarker(s) and measures of clinical benefit such as objective clinical response status (CR/PR or no-CR/PR) or disease control status (CR/PR/SD or no-CR/PR/SD). Where a change in the status/level of a biomarker over time can be ascertained, additional exploratory analyses may be undertaken to assess the effect of the change or its magnitude on the same clinical efficacy endpoints. For secondary efficacy measures of PFS and OS, parametric and semi-parametric survival analysis will be undertaken to quantify the association between the biomarker status and the time-to-event efficacy measure.

For serially measured plasma-based biomarkers, change from baseline to subsequent time points may be associated with clinical response outcomes. In addition, the time-course relationship of these biomarkers with safety and/or PK parameters (systemic exposure) may also be investigated.

Biomarker results may also be analyzed to elucidate the associations between the baseline status/level, or change in status/level and including, but not limited to, the mechanism of action of LY2606368, sensitivity to CHK1 inhibition, and sensitivity or resistance to platinum-based therapies.

5.17.2. Correlation between Change in Tumor Size and Efficacy Measures

Change in tumor size (CTS) will be assessed in each patient using radiographic imaging. This endpoint will be based on tumor measurements collected by the centers according to RECIST 1.1. Tumor size is the sum of the tumor measurements for target lesions at each tumor evaluation. Change in tumor size is defined as the percent change in tumor size from the baseline evaluation to the evaluation at the end of Cycle 3.

$$CTS = (\text{tumor size at Cycle 3} - \text{tumor size at baseline})/(\text{tumor size at baseline})$$

The correlation between CTS and PFS will be tested using the Spearman's correlation coefficient.

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

5.18. 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 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:

    o the number of participants at risk of an event

    o the number of participants who experienced each event term

    o 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.

6. References

Eisenhauer EA, Therasse P, Bogaert 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.

Lan KKG, DeMets DL. Discrete Sequential Boundaries for Clinical Trials. *Biometrika*. 1983; 70:659 ts DL.

O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979;35:549-56.