I4X-MC-JFCU Statistical Analysis Plan

A Single-Arm, Multicenter, Phase 1b Study with an Expansion Cohort to Evaluate Safety and Efficacy of Necitumumab in Combination with Abemaciclib in Treatment of Patients with Stage IV Non-Small Cell Lung Cancer (NSCLC)

NCT02411591

Approval Date: 13-Dec-2016

1. Statistical Analysis Plan: I4X-MC-JFCU A Single-Arm, Multicenter, Phase 1b Study with an Expansion Cohort to Evaluate Safety and Efficacy of Necitumumab in Combination with Abemaciclib in Treatment of Patients with Stage IV Non-Small Cell Lung Cancer (NSCLC)

Necitumumab (LY3012211), Abemaciclib (LY2835219)

This is a single-arm Phase 1b study with an expansion cohort in patients with Stage IV non-small cell lung cancer (NSCLC). The study consists of 2 parts (Part A and Part B). Part A is a single-arm, open-label, dose-escalation study to determine the recommended dose of abemaciclib in combination with necitumumab for Part B (expansion cohort). Part B is an open-label study to evaluate the efficacy and safety of necitumumab in combination with abemaciclib.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 14 May 2015
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

Approval Date: 13-Dec-2016 GMT

2. Table of Contents

Section **Page**

Table of Contents

Table **Page**

3. Revision History

SAP Version 1 was approved on 15 May 2015.

Major changes from Version 1:

- interim efficacy analyses have been added according to the protocol JFCU(b)
- various sections modified according to the new TAFFY standard Tables, Figures, and Listings shells.

4. Study Objectives

4.1. Primary Objective

This study is divided into 2 parts:

Part A: to determine the dose-limiting toxicity (DLT) of abemaciclib at doses up to 200 mg when combined with necitumumab 800 mg, in patients with Stage IV non-small cell lung cancer (NSCLC) as measured by the number of patients with a DLT in Cycle 1.

Part B: to evaluate the efficacy of necitumumab in combination with abemaciclib in terms of progression-free survival (PFS) rate at 3 months in patients with Stage IV NSCLC.

4.2. Secondary Objectives

The secondary objectives of the study are as follows:

Part A:

- to investigate the safety profile as assessed by clinical and laboratory significant events of necitumumab in combination with abemaciclib
- to determine the overall response rate (ORR)
- to determine pharmacokinetics (PK) of necitumumab and abemaciclib
- to determine the immunogenicity of necitumumab

Part B:

To demonstrate the safety, efficacy, and feasibility of necitumumab in combination with abemaciclib at the recommended dose by:

- determining PFS
- determining ORR and disease control rate (DCR)
- estimating overall survival (OS)
- investigating the safety profile as assessed by clinical and laboratory significant events
- determining PK of necitumumab and abemaciclib
- determining the immunogenicity of necitumumab

The exploratory objectives of the study are to correlate biomarkers with clinical outcomes, including, but not limited to *KRAS* mutation assessment, epidermal growth factor receptor (EGFR) protein expression, and/or other biomarkers associated with the disease pathobiology, the cell cycle, EGFR pathway, and/or the mechanism of action of the therapeutic molecules. The biomarker-based analyses will be described in a separate Translational Research Statistical Analysis Plan.

5. A Priori Statistical Methods

5.1. Determination of Sample Size

A total of approximately 68 patients evaluable for either the Part A or Part B portions of the study will be enrolled. Part A requires up to 18 treated patients (3 to 6 per dosage cohort). Patients with squamous and nonsquamous NSCLC who received the recommended abemaciclib dose for Part B in Part A will also be part of the Part B portion of the trial. These patients will also be included in the interim safety analysis as described in Section 5.10.

An evaluable patient for Part B will include any patient enrolled in Part A and treated at the recommended doses of necitumumab and abemaciclib. In addition, patients will be entered strictly to Part B (with a total of 50 evaluable patients in Part B). To be evaluable for Part B of the study, these additional patients entered must meet the following criteria:

- The patient has received at least 1 dose each of necitumumab and abemaciclib.
- The patient has a complete radiographic assessment at baseline.

The final analysis of the study will take place approximately 5 months after the last patient evaluable for Part B portion of the study has been enrolled. The primary Part B outcome variable in this study will be the 3-month PFS rate. The Part B statistical null hypothesis states that the true 3-month PFS rate is 50%, whereas the research hypothesis states that the true 3-month PFS rate is 65%. Assuming the Part B portion of the study continues to a full enrollment of 50 evaluable patients, the null hypothesis will be rejected at the final analysis only if at least 60% of evaluable patients experience PFS $\geq$3 months.

If the research hypothesis is true, there is an 81% chance of reaching full Part B enrollment and rejecting the null hypothesis. If the null hypothesis is true, then there is a 10% chance of reaching full Part B enrollment and rejecting the null hypothesis. Therefore, the Part B portion of this study has a one-sided alpha level of 0.10, with statistical power of 81%.

5.2. General Considerations

The following populations will be defined for this study:

- **All enrolled population:** anyone who signed the informed consent will be included in this population.
- **Safety population:** all patients who have received any amount of study drug [necitumumab, and/or abemaciclib]
- **Evaluable population:** all patients who have received at least 1 dose each of necitumumab and abemaciclib and have had a complete radiographic assessment at baseline

Unless otherwise specified, for continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized using frequency and percentages.

- **Age (years):** (Informed Consent Date - Date of Birth + 1)/365.25, if only year of birth is collected, see Section 5.3 for date imputation.
- **Missing Data:** All analyses and descriptive summaries will be based on the observed data. Unless otherwise specified, missing data will not be imputed or "carried forward."
- **Baseline Measurement:** Unless otherwise specified, the last nonmissing measurement prior to the first dose of study drug will serve as the baseline measurement.
- **Study Day:** Study day is calculated as assessment date – first dose date + 1 day if the assessment is done on or after the first dose day. If the assessment is done prior to the first dose day, study day will be calculated as assessment date – first dose date. Date of first dose is defined as study day 1.
- **Duration:** Duration is calculated as:

  Duration (days): (End Date – Start Date + 1)

  Duration (weeks): (End Date – Start Date + 1)/7

  Duration (months): (End Date – Start Date + 1)/30.4375 (Days in months = (1/12)*average number of days in a year.)

  Duration (years): (End Date – Start Date + 1)/365.25 (Average days in a year = 365.25, reflecting the Julian Year of 3 years with 365 days each and one leap year of 366 days.)

- **Time-to-event:** The event or censoring time (days) is calculated as:
  Date of event/censoring – Date of first dose of study drug + 1

5.3. Handling of Dropouts or Missing Data

Dates missing the day or both the day and month of the year will adhere to the following conventions:

- The missing day of onset of an adverse event or start date of a concurrent therapy will be set to:
  - first day of the month that the event occurred, if the onset yyyy-mm is after the yyyy-mm of first study treatment
  - the day of the first study treatment, if the onset yyyy-mm is the same as yyyy-mm of the first study treatment
  - the date of informed consent, if the onset yyyy-mm is before the yyyy-mm of the first treatment.

- The missing day of resolution of an adverse event or end date of a concurrent therapy will be set to:
    - the last day of the month of the occurrence. If the patient died in the same month, then set the imputed date as the death date.
- If the onset date of an adverse event or start date of a concurrent therapy is missing both the day and month, the onset date will be set to:
    - 01 January of the year of onset, if the onset year is after the year of the first study treatment
    - the date of the first treatment, if the onset year is the same as the year of the first study treatment
    - the date of informed consent, if the onset year is before the year of the first treatment
- If the resolution date of an adverse event or end date of a concurrent therapy is missing both the day and month, the date will be set to:
    - 31 December of the year of occurrence. If the patient died in the same year, then set the imputed date as the death date
- If date is completely missing, then no imputation will be done and the event will be considered as treatment emergent unless the end date rules out the possibility.

For initial diagnosis date, birthday, and death date, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, "Jul 1" will be used to replace the missing information.

5.4. Patient Disposition

A detailed description of patient disposition will be provided.

The number and percentage of patients never treated and still under treatment (that is, have not completed the End of Treatment visit) at data cut-off date will be summarized. Patients discontinued from treatment will be presented by reason.

The number and percentage of patients with any important protocol violation will be summarized overall and by type of violation. The predefined important protocol violations are listed below; in addition, any other protocol violations reported from monitoring visits or other sources will be reviewed by the clinical research physician (CRP) and if deemed important will be included in the summary.

- Patient failed to meet study inclusion/exclusion criteria

- Study treatment continued after progressive disease (PD) occurred
- Patient received concurrent prohibited therapy (Listing to identify Anatomical Therapeutic Chemical codes is to be provided for medical review) while receiving study treatment.
- Necitumumab continued after Grade 3 to Grade 4 infusion reaction occurred (as defined by dictionary term "Infusion related reaction")
- Actual doses of necitumumab were more than 10% greater than protocol defined dose (800 mg), at any of dose administration
- Patient started next cycle less than 18 days later after Day 1 of the most recent treatment cycle
- Patient received more than 2 dose reductions within necitumumab; or for patients starting at abemaciclib 100 mg every 12 hours (Q12H), received 1 or more dose reductions; or for patients starting at abemaciclib 150 mg Q12H, received 2 or more dose reductions; or for patients starting at abemaciclib 200 mg Q12H, received 3 or more dose reductions
- dose-limiting toxicity not reported

5.5. Patient Characteristics

5.5.1. Demographics and Baseline Characteristics

- age (years)
- age group (<65, ≥65 to <70, ≥70 years)
- race (In case of multiple races checked in the case report form [CRF] [for example, "White" and "Asian"], patients will be counted only once in the summary and will be presented as multiple.)
- gender
- ethnicity
- height (cm)
- weight (kg)
- body mass index (BMI)
- Eastern Cooperative Oncology Group (ECOG) performance status

Demographics and baseline characteristics will be summarized.

5.5.2. Disease Characteristics (Pretreatment)

- initial pathological diagnosis basis of determination: histopathological or cytological

- Histology: squamous cell carcinoma of lung, nonsquamous (adenocarcinoma lung + large cell lung cancer), non-small cell lung cancer NOS
- duration of disease (defined as time from diagnosis date to first dose of study drug)
- disease stage

Previous systemic anticancer therapy will be summarized.

5.5.3. Medical History

Preexisting conditions and medical history will be summarized by the number and percentage of patients reporting at least 1 diagnosis and by Medical Dictionary of Regulatory Activities (MedDRA™) preferred term (PT).

5.6. Efficacy Analyses

Efficacy analyses will be performed for the evaluable population. For all time-to-event variables (OS and PFS), the Kaplan-Meier product limit method will be used to estimate the survival curve as well as survival rates at various time points (3-month, 6-month, and 1-year). A 2-sided, 95% confidence interval (CI) for median PFS, median OS, and survival rate at time point will be computed by the Brookmeyer and Crowley method.

5.6.1. Primary Efficacy Endpoint

The primary endpoint for Part B is the PFS rate at 3 months. Progression-free survival rate at 3 months is defined as the rate of PFS at 3 months from the date of first dose of study drug and is determined using the distribution of overall PFS times. The PFS rate at 3 months is estimated using the Kaplan-Meier method.

Progression-free survival is defined as the time from the date of first dose of study drug until first observation of objective (radiographically documented) PD as defined by Response Evaluation Criteria In Solid Tumors Version 1.1 (RECIST 1.1) or death from any cause, whichever comes first. The censoring is taken in the following order:

- If a patient does not have an adequate baseline radiological tumor assessment, then the PFS time will be censored at the date of first study drug, regardless of whether or not objectively determined disease progression or death has been observed for the patient; otherwise,
- If a patient is not known to have died or have objective progression as of the data inclusion cutoff date for the analysis, the PFS time will be censored at the last adequate objective progression-free disease assessment date.

Adequate radiological tumor assessment refers to an assessment with 1 of the following responses: complete response (CR), partial response (PR), stable disease (SD), or PD. If a tumor assessment was done on multiple days, the earliest date for that visit will be used if overall response is PD, and the last date will be used otherwise (censor).

Progression-free survival sensitivity analysis will be performed. The censoring rules for PFS sensitivity analysis are listed in Table JFCU.5.1.

Table JFCU.5.1. Rules for Determining Date of Progression or Censor for PFS Sensitivity Analysis

Situation	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 first dose (whichever is later)
unless		
No baseline radiological tumor assessment available	Censored	Date of first dose
No adequate postbaseline radiological tumor assessment available and death reported after 2 scan intervals following first dose	Censored	Date of first dose
New anticancer treatment started and no tumor progression or death within 14 days	Censored	Date of adequate radiological assessment prior to (start of new therapy +14 days) or date of first dose (whichever is later)
Tumor progression or death documented immediately after 2 or more scan intervals following last adequate radiological tumor assessment or first dose (whichever is later)	Censored	Date of last adequate radiological assessment or date of first dose (whichever is later) prior to the missed assessment

Abbreviations: PD = progressive disease; PFS = progression-free survival.
Notes:
(1) Symptomatic deteriorations (that is, symptomatic progressions, which are not radiologically confirmed) will not be considered as progressions
(2) 2 scan intervals = 90 days# for this trial.
#: 2*(6 weeks+3 days window).

5.6.2. Secondary Efficacy Endpoints

5.6.2.1. Overall Response Rate

The denominator of overall response rate (ORR) includes all evaluable patients and the numerator includes those patients counted in the denominator with a best overall tumor response of PR or CR per RECIST 1.1. Confirmation of objective response is required for this trial. To be assigned a best overall response status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. In this circumstance, the best overall response can be interpreted as in Table JFCU.5.2. In the case of SD, measurements must have met the SD criteria at least once after first dose at a minimum interval of 6 weeks. Patients' responses after objective progression or start of new anticancer therapy are excluded from the determination of best response. The ORR and its exact 95% CIs will be estimated.

Table JFCU.5.2. Best Overall Response when Confirmation of CR and PR Required

Overall Response First Time point	Overall Response Subsequent Time point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration are met. Otherwise, PD
CR	PD	SD provided minimum criteria for SD duration are met. Otherwise, PD
CR	NE	SD provided minimum criteria for SD duration are met. Otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration are met. Otherwise, PD
PR	NE	SD provided minimum criteria for SD duration are met. Otherwise, NE
NE	NE	NE

Abbreviations: CR = complete response; NE = inevaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

5.6.2.2. Disease Control Rate

Disease control rate (DCR) will be analyzed, with the same denominator as defined in ORR. Among patients counted in the denominator, the numerator counts those with a confirmed best tumor response of SD, PR, or CR per RECIST 1.1. The DCR and its exact 95% CI will be estimated.

5.6.2.3. Overall Survival

Overall survival duration is measured from the date of first dose of study drug to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cut-off date for a particular analysis, OS will be censored for that analysis at the date of last contact prior to the data inclusion cutoff date (contacts considered in the determination of last contact date include adverse event date, lesion assessment date, visit date, and last known alive date).

5.7. Analysis of Safety Data

5.7.1. Extent of Exposure

5.7.1.1. Necitumumab

- number of cycles received by patient
- number of patients treated by cycle
- duration of treatment (in weeks) = [(Date of last dose – date of first dose)+14]÷7
- cumulative dose (mg) = sum of all doses administered
- dose intensity (mg/week) = (cumulative dose) ÷ (duration of treatment)
- relative dose intensity (%) = dose intensity (mg/week) ÷ (800 mg *2 / 3 weeks)
- number of dose reductions = total number of reduction steps comparing the planned dose level before each infusion (as entered in the electronic CRF) to the protocol planned dose level as referenced in Table JFCU.5.3.
- dose delay as recorded on the CRF.

5.7.1.2. Abemaciclib

- duration of treatment (in weeks) = [(date of last dose – date of first dose)+1]÷7
- cumulative dose (mg) = sum of all pills (in mg) taken
- dose intensity (mg/week) = (cumulative dose) ÷ (duration of treatment)
- relative dose intensity (%) = dose intensity (mg/week) ÷ (7* 2*starting dose (in mg)) where starting dose is 100 mg, 150 mg, or 200 mg according to the patient assignment to the cohorts or Part B
- number of dose reductions = total number of reduction steps comparing the dose entered at the Abemaciclib Dose Adjustment CRF page to the protocol planned dose level as referenced in Table JFCU.5.3.

Table JFCU.5.3. Dose Reductions for Necitumumab and Abemaciclib

Dose Level	Necitumumab	Abemaciclib	Abemaciclib	Abemaciclib
Starting Dose	800 mg	200 mg	150 mg	100 mg
First Dose Reduction	600 mg	150 mg	100 mg	na
Second Dose Reduction	400 mg	100 mg	na	na

Abbreviations: CRF = case report form; na = not applicable.

Note: Actual dose levels entered in the CRF will be rounded to the nearest dose level listed in this table (for example, any necitumumab dose level ≥700 mg will be rounded to 800 mg for the purpose of the dose reduction calculation; any necitumumab dose level <400 mg will be rounded to 400 mg).

The relative dose intensity will be additionally presented categorized (that is, number and percentage of patients with relative dose intensity of <60%, ≥60 to <80%, ≥80 to <90%, ≥90 to <100%, 100%, >100 to <110%, and ≥110%).

Moreover, for necitumumab, the number and percentage of patients with any dose delay, any dose reduction (reduction to first or second dose level) will be presented, along with the reason, as well as the number and percentage of patients with infusion modifications (infusion interrupted); and for abemaciclib, dose adjustments and dose withheld, along with the reason, will be summarized.

Patients who did not receive any amount of a given treatment will be assigned a value of 0 for exposure to that treatment (that is, number of infusions, duration of treatment, cumulative dose, dose intensity, and relative dose intensity).

5.7.2. Adverse Events

Adverse events (AEs) will be summarized by MedDRA System Organ Class (SOC) and PT, classified from verbatim terms. The incidence and percentage of patients with at least 1 occurrence of a PT will be included, according to the most severe National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0 grade.

If more than 1 AE is recorded for a patient within any PT, the patient will only be counted once on the most severe grade. Missing classifications concerning study treatment relationship will be considered as related to study treatment.

A treatment-emergent adverse event (TEAE) is defined as an event that first occurred or worsened between the first dose of study treatment and 30 days after the last dose of study treatment and related serious AEs (SAEs) reported beyond 30 days after the last dose of study treatment.

5.7.2.1. Overall Summary of Adverse Events

An overall summary of AEs will be provided to summarize the following categories using frequency counts and percentages:

- patients with at least 1 TEAE, or SAE
- deaths
- subjects who discontinued study treatment due to AE
- treatment-emergent adverse event related to study treatment
-

5.7.2.2. Treatment-Emergent Adverse Events

The following summaries of TEAEs will be provided and repeated for events deemed by the investigator to be possibly related to study medication:

- by PT

- by SOC and PT, and by maximum CTCAE grade

A patient listing of all AEs will be provided.

5.7.2.3. Adverse Event of Special Interest

Adverse events of special interest (AESI) include events related to arterial thromboembolism (ATE), venous thromboembolism (VTE), skin reactions (rash will be identified as a separate category as well as included under skin reactions), conjunctivitis, hypersensitivity/infusion related reaction (IRR), hypomagnesemia, and interstitial lung disease (pneumonitis). Each AESI is defined by a set of MedDRA PTs and the PT lists were identified by the medical and safety physicians for the compound based on the (blinded) review of all PTs (without looking at the number of patients/events for that PT) reported.

The incidence of treatment-emergent AESI will be summarized by AESI category and PT.

5.7.2.3.1. Thromboembolic Adverse Events

Thromboembolic AEs according to the AESI criteria outlined above are classified as arterial thromboembolic AE and venous thromboembolic AE. Treatment-emergent thromboembolic SAEs will be tabulated by overall, arterial thromboembolic AE, and venous thromboembolic AE. A listing of all treatment-emergent thromboembolic AEs will be generated.

In order to further assess the thromboembolic AEs observed in the study, an additional analysis examining possible risk factors for such events will be performed. Identification of these risk factors will be based on a literature search (Scappaticci et al. 2007; Khorana et al. 2008; Choueiri et al. 2010; Hurwitz et al. 2011; Petrelli et al. 2012; Lyman et al. 2013).

5.7.2.4. Consolidated Adverse Event

Consolidated AE categories include Anemia, Fatigue, Hypercalcaemia, Hyperkalaemia, Hypermagnesaemia, Hypernatraemia, Hyperphosphataemia, Hypocalcaemia, Hypokalaemia, Hypomagnesaemia, Hyponatraemia, Hypophosphataemia, Leukopenia, Neutropenia, and Thrombocytopenia. Each category contains PTs identified as clinically identical or synonymous, and PT lists were identified by the medical and safety physicians for the compound based on the (blinded) review of all PTs (without looking at the number of patients/events for that PT) reported.

The incidence of treatment-emergent consolidated AEs will be summarized by consolidated category and PT.

5.7.3. Deaths, SAEs, and Other Significant AEs

Reasons for deaths (study disease, AE [any AE, study treatment-related AE], etc.) will be summarized separately for 1) all deaths, 2) death on therapy, 3) deaths within 30 days of discontinuation of study therapy, 4) deaths on therapy or within 30 days of discontinuation of study therapy, and 5) deaths after 30 days of discontinuation of study therapy.

Serious adverse events will be summarized by SOC and PT, by maximum CTCAE grade, and by SOC and PT, and repeated for events deemed by the investigator to be possibly related to study medication. A listing of SAEs will be produced.

In addition, the following analyses will be performed:

- listing of adverse events leading to death
- listing of adverse events leading to study treatment discontinuations
- adverse events leading to study treatment dose modification by SOC and PT

Patients in Part A who experienced a DLT will be listed.

5.7.4. Weight, Performance Status, and Vital Signs

5.7.4.1. Weight and ECOG Performance Status

Weight observed value and change from baseline will be presented by scheduled visit.

The ECOG performance status results will be summarized using frequency distributions for each scheduled visit, including also the best postbaseline value.

5.7.4.2. Vital Signs

Vital sign observed value and change from baseline will be presented by scheduled visit.

5.7.5. Laboratory Evaluations

Laboratory results will be converted to standard (SI) units, as referenced in the NCI-CTCAE v.4.0. Laboratory results not corresponding to a NCI-CTCAE v.4.0 term will not be graded.

Shift tables showing the change from baseline to the worst CTCAE toxicity grade (first dose up to 30 days after the last dose of study treatment) will be presented.

Laboratory results will also be presented in a data listing to include a flag for values outside of the laboratory normal range. A listing of patients who had laboratory toxicities of CTCAE Grade 3 or greater will be presented.

5.7.6. Electrocardiogram

Electrocardiogram (ECG) results will be listed.

5.8. Other Analyses

5.8.1. Pharmacokinetic (PK) Analyses

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

5.8.2. Immunogenicity Analyses

The number and percentage of patients with positive anti-necitumumab response will be summarized. Additional efficacy and/or safety analyses may be performed in the subgroup of patients with positive anti-necitumumab responses, if appropriate.

5.8.3. Concomitant Therapy and Post-Study Anticancer Treatments

Prior and concomitant therapy will be summarized separately by frequency tables. A medication will be regarded as **prior** if it started within 28 days prior to first dose of study treatment and stopped prior to first dose of study treatment (medication stop date < first dose date). A medication will be regarded as **concomitant** if:

- it started on or after the date of first dose of study treatment and within 30 days after the date of last study treatment; or
- it started prior to first dose of study treatment but was ongoing at the time of the first dose of study treatment.

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

Transfusions during the study treatment or within 30 days of the last dose of study drug will be summarized.

5.9. Hospitalizations

Patient hospitalizations during the study treatment or within 30 days of the last dose of study drug will be summarized.

5.10. Interim Analyses

An interim safety analysis will be performed after the first 15 evaluable patients in the Part B portion of the trial have completed 2 cycles of study treatment (or otherwise discontinued study treatment). Patients with squamous and nonsquamous NSCLC who received the recommended abemaciclib dose for Part B in Part A will be taken into account for the safety interim analysis.

The interim safety analysis will be conducted to permit evaluation of safety data by Lilly.

The results from the safety interim analyses will be examined by an internal assessment committee, which will be established prior to enrollment of the first patient in the trial. The internal assessment committee will consist of a Lilly medical director, a Lilly CRP/clinical research scientist, a PK scientist, and a statistician and will make recommendations about the trial. Enrollment will continue while the interim analysis is being performed. Interim analysis results will not be disseminated outside of the assessment committee, unless emerging safety outcomes warrant such a disclosure. In case a disclosure is warranted, the outcome of the interim analyses will be documented, and a written letter will be submitted to the ethical review board(s) and the investigators for documentation purposes.

Interim safety analysis will be performed by Spotfire. Patient disposition, AE, lab and other data, if needed, will be reviewed at the interim.

Interim efficacy analyses may be performed as needed to aid in the planning of future trials. There is no plan to stop the study for positive efficacy, the type-1 error for final primary analysis will not be affected and hence is not adjusted. An interim efficacy analysis for the nonsquamous patients may be performed to evaluate the preliminary results for PFS rate at 3 months and the ORR approximately 4 months after the last nonsquamous patient has been enrolled. Patients with nonsquamous NSCLC in Part A who received the recommended abemaciclib dose for Part B will be taken into account for the interim analyses.

6. References

Choueiri TK, Schutz FA, Je Y, Rosenberg JE, Bellmunt J. Risk of arterial thromboembolic events with sunitinib and sorafenib: a systematic review and meta-analysis of clinical trials. *J Clin Oncol*. 2010;28(13):2280-2285.

Hurwitz HI, Saltz LB, Van Cutsem E, Cassidy J, Wiedemann J, Sirzén F, Lyman GH, Rohr UP. Venous thromboembolic events with chemotherapy plus bevacizumab: a pooled analysis of patients in randomized phase II and III studies. *J Clin Oncol*. 2011;29(13):1757-1764.

Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*. 2008;111(10):4902-4907.

Lyman GH, Eckert L, Wang Y, Wang H, Cohen A. Venous thromboembolism risk in patients with cancer receiving chemotherapy: a real-world analysis. *Oncologist*. 2013;18(12):1321-1329.

Petrelli F, Cabiddu M, Borgonovo K, Barni S. Risk of venous and arterial thromboembolic events associated with anti-EGFR agents: a meta-analysis of randomized clinical trials. *Ann Oncol*. 2012;23(7):1672-1679.

Scappaticci FA, Skillings JR, Holden SN, Gerber HP, Miller K, Kabbinavar F, Bergsland E, Ngai J, Holmgren E, Wang J, Hurwitz H. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst*. 2007;99(16):1232-1239.