I3Y-MC-JPBK

# I3Y-MC-JPBK: A Randomized Phase 3 Study of Abemaciclib plus Best Supportive Care versus Erlotinib plus Best Supportive Care in Patients with Stage IV NSCLC with a Detectable *KRAS* Mutation Who Have Progressed After Platinum-Based Chemotherapy

NCT02152631

Approval Date: October 2, 2017

# 1. Statistical Analysis Plan: I3Y-MC-JPBK: A Randomized Phase 3 Study of Abemaciclib plus Best Supportive Care versus Erlotinib plus Best Supportive Care in Patients with Stage IV NSCLC with a Detectable *KRAS* Mutation Who Have Progressed After Platinum-Based Chemotherapy



Abemaciclib (LY2835219)
Non-Small Cell Lung Cancer

This study is a global, multicenter, randomized, open-label, Phase 3 trial in patients with Stage IV NSCLC whose tumors have a detectable *KRAS* mutation in codons 12 or 13 and who have progressed after platinum-based chemotherapy and received 1 other prior therapy or are ineligible for further chemotherapy randomized to receive either abemaciclib (LY2835219) plus best supportive care or erlotinib plus best supportive care.


Eli Lilly and Company
Indianapolis, Indiana USA 46285


Protocol I3Y-MC-JPBK
Phase 3

Statistical Analysis Plan Version 1 electronically signed and approved by Lilly: 28 August 2014
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly: 13 July 2017
Statistical Analysis Plan Version 3 electronically signed and approved by Lilly on date provided below.

Approval Date: 02-Oct-2017 GMT

# 2. Table of Contents

**Section** **Page**

## Table of Contents

**Table** **Page**

## Table of Contents

**Figure** **Page**

## Table of Contents

**Appendix** **Page**

# 3. Revision History

SAP Version 1 was approved prior to first patient visit.

SAP Versions 2 reflected the following changes in the protocol amendment (e):

1. PFS is removed as a co-primary endpoint and changed to a secondary endpoint. With this change OS becomes the sole primary endpoint.
2. The final OS analysis occurs when approximately 304 OS events have been observed, a reduction from the current protocol requirement of 407 OS events. With this change, the study provides 80% statistical power for a new targeted hazard ratio of 0.72.
3. Due to the reduced number of targeted OS events, a smaller sample size of approximately 450 patients will be sufficient to reach the 304 OS events for the final analysis.

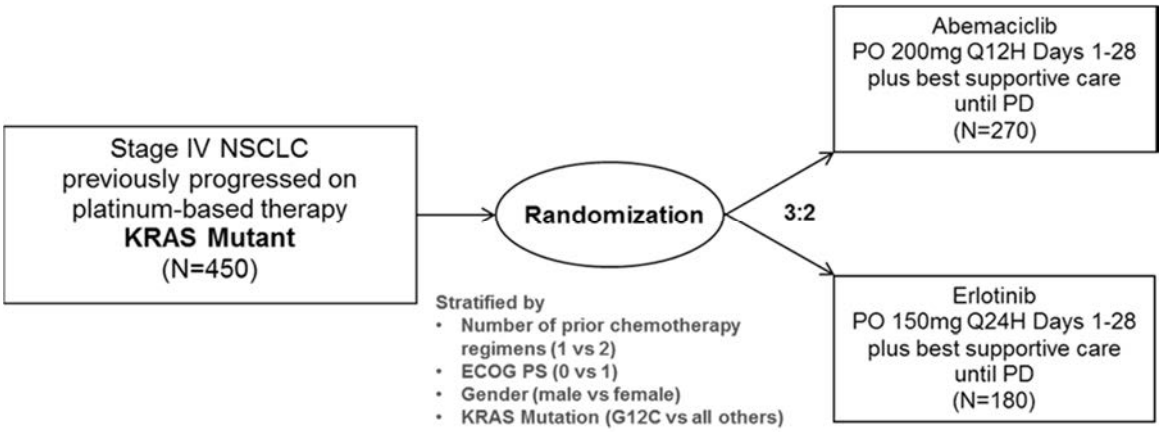
SAP Version 3 made some changes in Exploratory Objectives (Section 5.3) and Biomaker (Rb Expression) Analyses (Section 6.2.12).

SAP Version 3 was approved prior to the final database lock.

# 4. Study Design

Study I3Y-MC-JPBK is a multicenter, randomized, open-label, parallel, comparator-controlled trial in patients with Stage IV NSCLC whose tumors have a detectable KRAS mutation in codons 12 or 13 by an investigational assay at the Study JPBK central laboratory and who have progressed after platinum-based chemotherapy and received 1 other prior therapy or are ineligible for further chemotherapy after platinum-based therapy.

Figure JPBK.4.1 illustrates the study design.



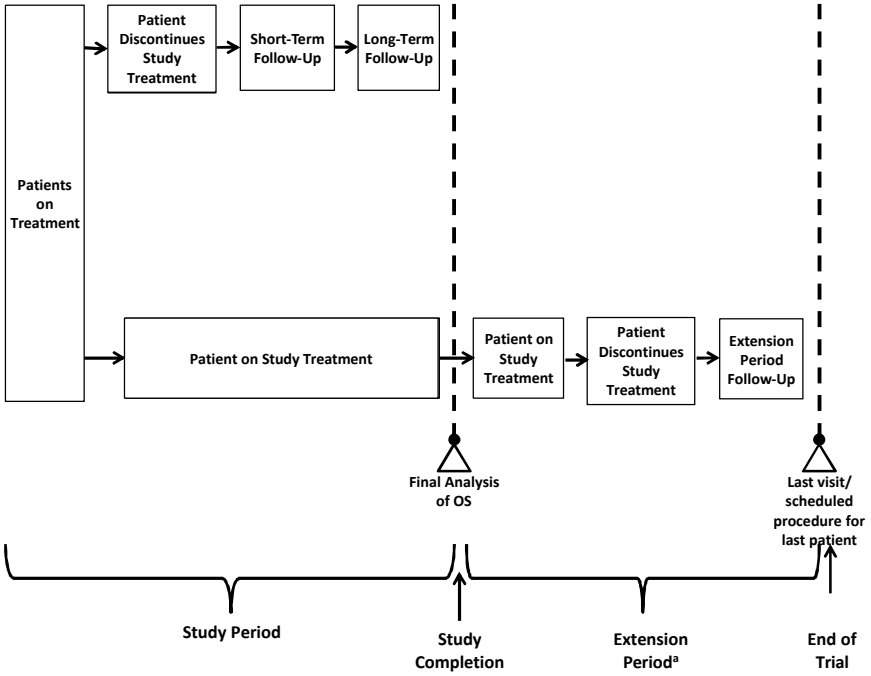

Abbreviations: ECOG = Eastern Cooperative Oncology Group; NSCLC = non-small cell lung cancer; PD = progressive disease; PO = orally; Q12H = every 12 hours; Q24H = every 24 hours; PS = performance status.

**Figure JPBK.4.1. Illustration of study design.**

Approximately 450 patients will be randomized 3:2 between the 2 arms:

- LY2835219-200mg: Abemaciclib 200 mg orally every 12 hours plus BSC on Days 1 to 28 of a 28-day cycle
- ERLOTINIB-150mg: Erlotinib 150 mg orally every 24 hours plus BSC on Days 1 to 28 of a 28-Day Cycle

Patients will be randomized using the following stratification factors: number of prior chemotherapy regimens (1 versus 2), performance status (ECOG 0 versus 1), Gender (male versus female), and KRAS mutation (G12C versus all others).




Abbreviations: OS = overall survival

[a] Lilly will notify sites when this begins and ends.

**Figure JPBK.4.2. Study period and extension period diagram.**

# 5. Study Objectives

## 5.1. Primary Objective

The primary objective of this study is to compare Abemaciclib plus BSC versus erlotinib plus BSC in patients with Stage IV NSCLC whose tumors have detectable *KRAS* mutations (specifically, in codons 12 or 13 of the KRAS oncogene) and who have progressed after prior platinum-based therapy and 1 additional therapy which may include an immune checkpoint inhibitor and/or other anti-cancer therapy; or are not eligible for further chemotherapy with respect to:

- Overall Survival (OS)

## 5.2. Secondary Objectives

The secondary objectives of the study are to compare Abemaciclib plus BSC versus erlotinib plus BSC with respect to:

- Progression-free survival (PFS)
- overall response rate (complete response [CR] + partial response [PR]).
- changes in patient-reported pain and disease-related symptoms collected via the MD Anderson Symptom Inventory (MDASI-LC) and changes in health status via European Quality of Life – 5 Dimensions – 5 Level (EQ-5D-5L).
- safety and tolerability
- resource utilization (for example, analgesic type, hospitalization, transfusion)
- pharmacokinetic (PK) and pharmacodynamic (PD) properties of Abemaciclib

## 5.3. Exploratory Objectives

The exploratory objective of primary interest is the exploration of the relationship between retinoblastoma (Rb) protein expression and the clinical response observed in the Abemaciclib arm of the study. The post hoc exploration of other biomarkers relevant to Abemaciclib, the disease state, or clinical outcomes to study treatments may also be undertaken.

# 6. A Priori Statistical Methods

## 6.1. Determination of Sample Size

The primary objective of this study is to compare Abemaciclib versus erlotinib with respect to OS in patients with Stage IV NSCLC whose tumors have detectable *KRAS* mutations (specifically, in codons 12 and 13 of the KRAS oncogene) and who have progressed after prior platinum-based therapy and received 1 additional therapy which may include an immune checkpoint inhibitor and/or other anti-cancer therapy; or are not eligible for further chemotherapy

The study will enroll approximately 450 patients in 3:2 randomization (270 patients in the Abemaciclib arm and 180 patients in the erlotinib arm). The final OS analysis will occur when approximately 304 OS events have been observed.

The comparison of the OS distributions between treatment groups will be conducted using a stratified log-rank test adjusted by all stratification factors. Following statistical hypotheses about OS hazard ratio (HR) will be tested for Abemaciclib over erlotinib:

$H_0$: HR $\geq$ 1 (Abemaciclib arm not superior to erlotinib arm)

$H_1$: HR < 1 (Abemaciclib arm superior to erlotinib arm)

Assuming an OS HR of 0.72, this sample size yields approximately 80% statistical power to detect superiority of the Abemaciclib arm over erlotinib arm with the use of a 2-sided log-rank test and a type I error of 0.05.

If the true median OS for the erlotinib arm is 6.5 months, then the HR of 0.72 amounts to an approximately 2.5-month improvement in median OS for the Abemaciclib arm under an additional assumption of exponential survival distribution.

## 6.2. Statistical and Analytical Plans

### *6.2.1. General Considerations*

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 confidence intervals (CIs) will be given at a 2-sided 95% level, unless otherwise stated. P-values will be rounded at three significant digits. P-values less than 0.001 will be presented as p <0.001.

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.

Before unblinding of the aggregate database, minor modifications or clarifications to the data analysis methods may be described and justified in the statistical analysis plan (SAP).

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.

### 6.2.2. 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 ITT analysis of efficacy data will consider allocation of patients to treatment groups as randomized and not by actual treatment received. This population will be used for all baseline, efficacy, and health economics analyses.

**Safety population** will include all randomized patients who received any quantity of study treatment, regardless of their eligibility for the study. The safety evaluation will be performed based on the first dose of study treatment a patient actually received, regardless of the arm to which he or she was randomized. The safety population will be used for all dosing/exposure, safety, and resource utilization analyses.

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.

### 6.2.3. Definitions and Conventions

**Study drug** refers to Abemaciclib or erlotinib.

**Study treatment** refers to Abemaciclib + best supportive care or erlotinib + best supportive care.

The **date of randomization** is the date the patient was randomly assigned to Abemaciclib + best supportive care or erlotinib + best supportive care using the interactive web response system (IWRS).

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

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

The **baseline value of an efficacy assessment** is the last value observed prior to the date of randomization. If a patient's first assessment occurs after randomization but prior to the first dose, this assessment will be used as the baseline.

The **study day of a safety event or assessment** will be calculated as:

- the difference between the date of the event or assessment and the date of first dose plus 1 for all events or assessments occurring on or after the day of first dose. For example, if an event occurs on 08JUN2014 and the date of first dose was 06JUN2014, the study day of the event is 3.
- the difference between the date of the event or assessment and the date of first dose for all events or assessments occurring before the day of first dose. For example, if an event occurs on 05JUN2014 and the date of first dose was 06JUN2014, the study day of the event is -1.

The **study day of an efficacy event or assessment** will be calculated as:

- the difference between the date of the event or assessment and the date of randomization plus 1 for all events or assessments occurring on or after the date of randomization.
- the difference between the date of the event or assessment and the date of randomization for all events or assessments occurring before the date of randomization.

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

Unless otherwise noted, **summaries of continuous variables** will include a mean, median, standard deviation, minimum, and maximum.

Unless otherwise noted, **summaries of categorical variables** will include the frequency and percentage (relative to the population being analyzed) of each category.

### *6.2.4. 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.

### *6.2.5. 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, and treated (including number of patients still on treatment as of the data-inclusion cutoff date) as well as number and percentage of patients completing the study, or discontinuing (overall and by reason for discontinuation).

A summary of all important protocol deviations will be provided.

### *6.2.6. Baseline Demographics and Patient Characteristics*

Patient demographics including age, sex, screening height and weight, screening body mass index, and smoking status will be reported using descriptive statistics.

Baseline disease characteristics will be summarized by presenting frequency counts and percentages for pathological diagnosis (histological or cytological), disease stage, or performance status.

Patient preexisting condition, historical illness, and prior chemotherapy (including both cytotoxic and targeted agents) will be summarized by treatment arm.

### 6.2.7. Prior and Post Discontinuation Therapies

Prior Therapies: Prior radiotherapy, surgery, and systemic therapy will be summarized. Prior radiotherapy and surgery will be categorized by reason for regimen. Prior systemic therapies will be categorized by reason for regimen ([neo]adjuvant therapy or therapy for locally advanced or metastatic disease), number of regimens for locally advanced or metastatic disease and specific therapy. Frequency of each specific therapy will be tabulated within each reason for therapy.

Prior immunotherapy will be categorized by time on therapy (<4 months or >=4 months). For patients who had one prior chemotherapy based on eCRF, reason for patient being not eligible for further chemotherapy will be summarized by study treatment arms.

Post Discontinuation Therapies: The numbers and percentages of patients reporting post-discontinuation therapies will be provided overall, by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug name.

### 6.2.8. 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 information for Abemaciclib or erlotinib will be collected through capsule (Abemaciclib) or tablet (erlotinib) counts at each tumor assessment visit. The estimate of percent compliance will be given by:

$$\text{Percent Compliance} = \frac{\text{Actual cumulative dose taken}}{\text{Expected cumulative dose to be taken}} \text{ x } 100$$

The actual cumulative dose taken will be determined based on counting the number of capsules returned at each visit and subtracting that number from the number of capsules dispensed. The expected cumulative dose to be taken will be determined based on the assigned dose and taking into account any dose reductions or omissions.

### 6.2.9. Concomitant Therapy

Concomitant medication will be summarized by treatment arm in a frequency table listing the terms recorded on the electronic clinical (case) report form (eCRF).

### 6.2.10. Efficacy Analyses

#### 6.2.10.1. Stratification Factors

The stratification factors for the analysis are: number of prior chemotherapy regimens (1 versus 2), performance status (ECOG 0 versus 1), gender (male versus female), and *KRAS* mutation (G12C versus all others).

The stratification factors are captured in the IWRS and eCRFs. KRAS mutation status is also captured through central laboratory system. Unless otherwise stated, all stratification analyses will be based on the stratification factors per IWRS.

### 6.2.10.2. Primary Efficacy Endpoint

The primary efficacy endpoint in JPBK is OS.

**Overall Survival (OS)** time is defined as the time from the date of randomization (Day 1) to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cutoff 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.

The comparison of the OS distributions between treatment groups will be conducted using a stratified log-rank test with the following stratification variables: number of prior chemotherapy regimens (1 versus 2), ECOG PS (0 versus 1), gender (male versus female), and *KRAS* mutation (G12C versus all others). The sources of the stratification factors will be IWRS.

The Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the OS survival curves as well as survival rates at 3, 6, 9, and 12 months for each treatment group. These rates will be compared based on a normal approximation for the difference between the arms. The Cox proportional hazard model (Cox 1972) with treatment as a factor, stratified by the stratification factors used in the randomization (as per the primary analysis) will be used to estimate the HR and corresponding 95% CI.

### 6.2.10.3. Secondary Efficacy Endpoints

**Progression-free survival (PFS)** time is defined as the time from the date of randomization (Day 1) to the date of investigator-determined objective progression as defined by RECIST 1.1 (Eisenhauer et al. 2009) or the date of death due to 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 date of randomization if no post initiation (i.e., post baseline) radiographic assessment is available. The detailed censoring rules are described in the Table JPBK.6.1.

The statistical comparison of PFS between treatment groups will be conducted using the same methods for OS as described in Section 6.2.10.2.

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

| | 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 immediately after missed ≥2 consecutive post-baseline tumor assessment visits | Date of last adequate tumor assessment before missed assessments or date of randomization, whichever is later | Censored |

Note: PFS and associated outcome is determined by the earliest of the dates above, if more than one situation applies

Other secondary efficacy measures include response rate as defined by RECIST 1.1 (Eisenhauer et al. 2009).

Best overall response (BOR) will be derived to encompass all tumor assessments (according to RECIST v1.1) from baseline until the earliest of objective progression or start of new anticancer therapy. Any responses observed after objective progression or the start of new anticancer therapy are excluded from the determination of best response. Each patient's BOR will categorized as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or not evaluable (NE).

Overall Response Rate (ORR) is defined as the proportion of patients with BOR of CR or PR (according to RECIST v1.1). Disease control rate (DCR) is defined as the proportion of patients with BOR of CR, PR or SD (according to RECIST v1.1).

Point estimates and 95% confidence intervals (using the normal approximation to the binomial) will be calculated for ORR and DCR by treatment arm. Stratified tests comparing these rates between treatment arms will be conducted using a Cochran-Mantel-Haenszel (CMH) test adjusted by all stratification factors.

Duration of response (DoR) will be presented for responders (patients with a BOR of CR or PR according to RECIST 1.1). DoR is defined as the time from the date of the first evidence of CR or PR to the date of investigator-determined objective progression or the date of death due to any cause, whichever is earlier. DoR will be censored according to the same rules as PFS (presented in Table JPBK.6.1). The median duration of response will be summarized using K-M

techniques. The statistical comparison of DoR between treatment groups will be conducted using unstratified log-rank test and HR will be estimated using an unstratified Cox model with only the treatment factor in the model.

### 6.2.10.4. Sensitivity Analyses

Sensitivity analyses may be undertaken in order to evaluate the robustness of the analysis.

**Restricted Mean Difference:** The common method for describing benefit on the time scale is to calculate the difference in median event time between the two treatment arms. An alternative method for describing benefit on the time scale is to estimate the average difference between the KM curves. This corresponds to calculating the difference in the average time to event for the two treatment arms (Irwin 1949; Karrison 1997; Meier et al. 2004). Similar to the HR, this method uses all of the available information across the KM curves, but has the additional advantage of assessing benefit on the time scale.

To estimate an improvement in OS with Abemaciclib, we will follow the method of Irwin (1949) detailed in Karrison (1997) and Meier (2004) for estimating the "difference in average OS", which we will refer to more formally as the restricted mean difference in OS. The area under each KM curve will be calculated using numerical integration (trapezium rule) per Karrison and implemented in SAS using PROC LIFETEST. The difference between treatment arms and a CI for the difference will be formed.

Since the KM curve may be ill-determined beyond a certain range, or even undefined (if the longest observation is censored), for evaluation and comparison of means, the area under each KM curve will be calculated between time 0 and restriction time T, which is why this is referred to as a "restricted mean". Following the suggestion of Karrison, the restriction time T will be chosen as largest time point t such that the standard error (SE) of the survival estimate at time t in each treatment group is no more than 0.075. For this purpose, we will use the simple, albeit conservative, formula proposed by Peto et al. (1977) for calculating the SE of S(t) as $SE\big(S(t)\big) = S(t)\sqrt{(1 - S(t))/n(t)}$, where $n$(t) is the number of patients still at risk at time t.

The following sensitivity analyses will be performed for OS:

**Overall Survival Sensitivity Analysis 1:** The comparison of the OS distributions between treatment groups will be conducted using a log-rank test without stratification factors as secondary analysis.

**Overall Survival Sensitivity Analysis 2:** A stratified log-rank test with stratification factors the number of prior chemotherapy regimens (1 versus 2), ECOG PS (0 versus 1), and gender (male versus female) from eCRF, and *KRAS* mutation (G12C versus all others) from central lab will be conducted.

The following sensitivity analyses will be performed for PFS:

**Progression-Free Survival Sensitivity Analysis 1** (censoring for receiving subsequent systemic anticancer therapy): if a patient is initiated on another anticancer therapy prior to objective

progression including any postdiscontinuation treatment systemic therapy, PFS will be censored at the date of the last complete objective progression-free disease assessment before initiation of the new therapy, regardless of whether or not this patient subsequently had objective progression or died. The definition of PFS for this sensitivity analyses is presented in Table JPBK.6.2. Those items that differ from Table JPBK.6.1 are underlined.

**Progression-Free Survival Sensitivity Analysis 2** (nonobjective progression as a PFS event): if a patient is discontinued from study treatment due to investigator determined non-objective progression (for example, symptomatic deterioration), then the patient's PFS time will be calculated using the date of non-objective progression as the progression date. The definition of PFS for this sensitivity analyses is presented in Table JPBK.6.3. Those items that differ from Table JPBK.6.1 are underlined.

**Progression-Free Survival Sensitivity Analysis 3** (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 JPBK.6.4. Those items that differ from Table JPBK.6.1 are underlined.

**Table JPBK.6.2. 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 immediately after missed ≥2 consecutive post-baseline tumor assessment visits | Date of last adequate tumor assessment before missed assessments or date of randomization, whichever is later | Censored |
| 8 | New anticancer treatment started | last complete objective progression-free disease assessment before initiation of the new therapy | Censored |

Note: PFS and associated outcome is determined by the earliest of the dates above, if more than one situation applies

### Table JPBK.6.3. Progression-Free Survival Sensitivity Analysis 2

| | 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 immediately after missed ≥2 consecutive post-baseline tumor assessment visits | Date of last adequate tumor assessment before missed assessments or date of randomization, whichever is later | Censored |
| 8 | Investigator determined non-objective progression | Date of non-objective progression | Progressed |

Note: PFS and associated outcome is determined by the earliest of the dates above, if more than one situation applies

### Table JPBK.6.4. Progression-Free Survival Sensitivity Analysis 3

| | 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 immediately after missed ≥2 consecutive 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 |

Note: PFS and associated outcome is determined by the earliest of the dates above, if more than one situation applies

Additional sensitivity analyses for OS and PFS may be carried out for patients who are *KRAS* positive based only on central test result. Patients who are enrolled with their *KRAS* mutation status based only on local lab reported in the eCRF are excluded in these analyses. For these analyses, the statistical analysis model described in Section 6.2.10.2 will be applied.

### 6.2.11. Bioanalytical and Pharmacokinetic/Pharmacodynamic Methods

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

### 6.2.12. Rb Expression Analyses

Rb protein which governs cell-cycle progression in mid-G1 is a major target of CDK4 and CDK6. Cancer cells must express wild-type Rb in order for a CDK4/6 inhibitor to be able to dephosphorylate Rb and thereby cause cell-cycle arrest. Therefore, it is hypothesized that tumors lacking in Rb expression are less likely to respond to abemaciclib relative to the response that is seen in tumors that do express Rb. In the comparator arm, Rb expression is not expected to affect the observed clinical response.

In this study, Rb expression in the nucleus of target cells obtained from formalin-fixed, paraffin embedded tumor tissue was assessed using an immunohistochemistry assay (IHC). The assay as validated is scored qualitatively, with "Positive" expression defined as a tumor showing minimal (1+) specific staining for Rb in at least 10% of target cells and "Negative" expression defined as less than 10% of cells with specific staining, or no specific staining present.

All patients for whom valid IHC results are available at the time of study database lock (hereafter referred to as the Rb population) will be analyzed in the following ways:

- Rb protein expression status will be summarized for all patients in the Rb population by treatment arm as well as overall.
- The patient and disease characteristics obtained at the baseline visit will be summarized and compared between the Rb population and the ITT population.
- Assess if the dichotomized (Positive/Negative) Rb protein expression status observed in tumor tissue is predictive of Abemaciclib treatment benefit with respect to OS, PFS and ORR.

### 6.2.13. Health Outcomes and Quality of Life Evaluations

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)

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 and cycle: symptom severity (13 core items plus lung-cancer items), core severity (13 core items only), interference (6 interference items), 6 individual brain symptom items: irritability (affective); understanding, speaking, concentrating (cognitive); seizures (focal neurologic); appearance (generalized/ disease status) as well as 3 individual items headache, diarrhea and rash.

For each instrument, the analysis will include all cycles for which instrument is planned to measure and at least 25% of patients in each arm have an assessment. If the above criteria are met, a mixed model will be applied to compare treatment arms for symptom severity, core severity, interference subscales, each of 6 individual brain symptom items (irritability, understanding, speaking, concentrating, seizures, and appearance) as well as 3 individual items: headache, diarrhea and rash. The model will include baseline score as a covariate and an unstructured covariance matrix will be utilized if it converges. If the model cannot converge with an unstructured covariance matrix, the covariance matrix will be determined based on the Akaike Information Criterion (AIC).

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).

Based on literature (Farrar et al. 2001), it is suggested that worsening of pain by 2 points may be clinically relevant. Time to worsening in pain (worsening by 2 or more points in MDASI pain item or in WHO ladder code based on Table JPBK.6.5 whichever occurs first) will be described using the method of Kaplan and Meier and will be compared between 2 arms by a log-rank test. Worsening-free pain rate at 3, 6, 9, and 12 months (if available) will be compared between treatment arms.

**Table JPBK.6.5. World Health Organization Pain Scale**

| Code | Description |
|---|---|
| 0 | No analgesia |
| 1 | Aspirin (for pain, not cardiovascular prophylaxis), acetaminophen, nonsteroidal anti-inflammatory drugs |
| 2 | Codeine, hydrocodone, pentazocine, oxycodone |
| 3 | Oral morphine, hydromorphone, methadone, transdermal fentanyl |
| 4 | Parenteral opiates |
| 5 | Neurosurgical procedures (blocks) |

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. Index score and VAS, will be

compared using mixed models. The model will include baseline score as a covariate and an unstructured covariance matrix will be utilized. The analysis will include all cycles for which at least 25% of patients in each arm have an assessment.

#### 6.2.13.1. Resource Utilization

Utilization data will be summarized by category across arms. The following resource utilizations will be described:

- Analgesics (on study treatment and during short term follow up)
- Transfusions (on study treatment and during short term follow up)
- Growth factors (on-study treatment and during short term follow-up)
- Surgery (on study treatment and during short term follow up)
- Hospitalizations (on study treatment and during short term follow up)
- Post discontinuation radiotherapy and systemic therapy.

For categorical variables, frequency and the corresponding proportions will be calculated. Continuous variables will be described by the mean, median, and standard deviation.

### *6.2.14. Safety Analyses*

Safety analyses will be based on the Safety Population as defined in Section 6.2.2. Patients will be grouped according to treatment received in Cycle 1.

#### 6.2.14.1. Extent of Exposure

For Abemaciclib, extent of exposure will be measured by pill counts and summarized by cycle and cumulatively. The summary will include total dosage taken and dose intensity. Dose intensity will be calculated as the ratio of total dose taken to the assigned cumulative dose. The assigned cumulative dose for each patient during each cycle is 200 mg per dose $\times$ 2 doses per day $\times$ 28 days = 11200 mg. The assigned cumulative dose while on study is 11200 mg $\times$ number of cycles started.

For erlotinib, exposure will be measured in a similar approach. The assigned cumulative dose for each patient during each cycle is 150 mg per day $\times$ 28 days = 4200 mg. The assigned cumulative dose while on study is 4200 mg $\times$ number of cycles started.

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

#### 6.2.14.2. Adverse Events

Verbatim text for the adverse events (AEs) will be entered by the investigator, as well as the AE terms and severity grades per CTCAE Version 4.0. In addition, AE verbatim text will also be mapped by the sponsor or designee to corresponding terminology within MedDRA.

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.
- Preferred terms identified by Medical as clinically identical or synonymous will be grouped together under a single consolidated term. For example, 'Asthenia' and 'Fatigue' will be reported as 'Fatigue.' See Appendix 1 for a complete listing. This listing may be updated prior to database lock as new synonymous terms are observed.
- Additional 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. A treatment emergent adverse event (TEAE) is defined as any AE that begins between the day of first dose and thirty days after treatment discontinuation (or up to any time if serious and related to study treatment), or any pre-existing condition that increases in CTCAE grade between the day of first dose and thirty days after treatment discontinuation (or up to any time if serious and related to study treatment).

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

- Overview of TEAEs
- Summary of TEAEs by PT (all grade and grade $\geq 3$)
- Summary of TEAEs by SOC and PT (all grade and grade $\geq 3$)
- Summary of TEAEs by PT and maximum grade (1-5)
- List of SAEs
- Summary of SAEs by SOC and PT (all grade and grade $\geq 3$)

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

In addition, summaries will be produced for TEAEs as a reason for study treatment discontinuation, dose adjustment/withholding or hospitalization by SOC and PT.

### 6.2.14.3. 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.

### 6.2.14.4. 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.

#### 6.2.14.5. Vital Signs and Other Physical Findings

Temperature, blood pressure, pulse rate, respiration rate, weight and ECOG PS will be summarized by cycle.

#### 6.2.14.6. 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.

#### 6.2.14.7. Hospitalizations and Transfusions

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

### *6.2.15. Subgroup Analyses*

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

- All baseline stratification factors, including the number of prior chemotherapy regimens (1 vs. 2), performance status (ECOG 0 vs. 1), gender (male vs. female), and *KRAS* mutation (G12C vs. all others).
- Age (<65 years vs. ≥65 years). Additional age cutoffs may be explored.
- Smoking status (current vs. former vs. never).
- Region (North America vs. Europe vs. Asia vs. Other).
- Race (Caucasian vs. Asian vs. Other).
- Prior immunotherapy (with vs. without).

If a level of a factor consists of fewer than 5% 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. Cox proportional model in analyzing each of the subgroup will contain a term for treatment, the subgroup covariate of interest and the treatment by subgroup interaction term. The stratification factors will not be included in the model unless stratification factor is the subgroup being analyzed.

Analyses conducted specifically for the Japan Pharmaceuticals and Medical Devices Agency (PMDA) will be described in a separate SAP.

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.

## 6.2.16. Interim Analyses and Data Monitoring

### 6.2.16.1. Safety Interim Analyses

The data monitoring committee (DMC) is responsible for providing external oversight of patient safety in Study JPBK independently of the Lilly study team and Lilly GPS.

During the study, safety interim analyses will be performed approximately every 6 months. The safety interim analyses will be conducted to evaluate the overall safety profile of Abemaciclib. At the recommendation of the DMC, the frequency of safety interim analyses may be modified.

At each interim analysis, the DMC may recommend the trial continue without modifications, continue with specific modifications, or be stopped for safety concerns. There will be no prespecified rules for stopping the trial due to safety concerns. The DMC members will review unblinded safety data at each interim analysis. If a significant safety signal is identified, the DMC may recommend a protocol amendment, termination of enrollment, and/or termination of study treatment. The recommendations of the DMC will be communicated to the Lilly Senior Management Designee and, if necessary, an Internal Review Committee.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the treatment group level, members of the DMC can conduct additional analyses of the safety data. Additionally, unblinding of a limited number of Lilly representatives external to the study team may be required for evaluation of selected SAEs for determination of regulatory reporting.

### 6.2.16.2. Futility and Efficacy Interim Analyses

One interim efficacy analysis is planned based on PFS endpoint and is for futility only. This interim analysis will be conducted by the DMC. There is no plan for interim efficacy analysis based on the OS endpoint. The DMC may call for additional, unplanned, interim efficacy analyses. Details of the DMC communication plan can be found in the DMC charter. The analysis will occur after approximately100 PFS events have been observed. The DMC will be instructed to recommend stopping the study for futility if the observed hazard ratio for PFS (as calculated using a stratified Cox proportional hazards model) is greater than 0.95. Only the DMC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

## 6.2.17. Protocol Violations

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
- Inconsistency in stratification factors: number of prior chemotherapy regimens (1 vs. 2), performance status (ECOG 0 vs. 1) and gender (male vs. female) between values captured in IWRS vs eCRF.
- Inconsistency in stratification factor, *KRAS* mutation (G12C vs. all others) between values captured in the IWRS vs the central laboratory system.
- Treatment
  - Dose delays
  - Dose reductions

### *6.2.18. Annual Report Analyses*

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

### *6.2.19. 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: treatment group, 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

Study JPBK is a randomized, open label study. Randomization will occur using an IWRS system. Assignment to treatment groups will be determined by a computer-generated random sequence. Each patient in this study will be aware of his or her own assigned treatment group. At each investigative site, all staff involved in treating and caring for study patients will have full knowledge of treatment assignments for the patients under their care.

In order to maintain the scientific integrity of this trial, access to study data will be strictly controlled prior to the interim and final analyses. For the accumulated group-level data, treatment assignment will not be included, and other parameters that can disclose treatment assignment will be scrambled. Therefore, the sponsor and all investigative sites will remain blinded to treatment group assignments for the summary statistics and reports until the database lock for the final analysis. Dummy treatment assignment will be used in the reporting database for Lilly trial-level safety review until the database lock for the final analysis of overall survival. Interim analyses will be carried out approximately every 6 months by an independent DMC (external to Lilly) to monitor safety and efficacy. The DMC is unblinded and only the Statistical Analysis Center (SAC), which is independent of the sponsor, will perform analyses on unblinded data. Until the primary analyses, only the SAC and the DMC will be unblinded to the summary statistics and reports.

For the interim PK analysis to occur prior to the interim/primary analyses, the list of individuals that will have access to unblinded data will be provided with the PK/pharmacodynamic analysis plan, and documentation concerning their access to the data will be retained.

# 8. References

Cox DR. Regression models and life-tables. *J Royal Stat Soc Ser B*. 1972;74(2):187-220.

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.*Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*. Rockville, Md: US Dept of Health and Human Services, Food and Drug Administration; May 2007.

Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole M. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain.* 2001;94:149-158.

Irwin JO. The standard error of an estimate of expectational life. *Journal of Hygiene.* 1949;47:188-189.

Kaplan EL, Meier P. Nonparametric estimation of incomplete observations. *J Amer Stat Assoc*. 1958;53:457-481.

Karrison T. Use of Irwin's restricted mean as an index for comparing survival in different treatment groups-- interpretation and power considerations. *Controlled Clinical Trials.* 1997;(18):151-167.

Meier P, Karrison T, Chappell R, Xie H. The Price of Kaplan-Meier. *J Amer Stat Assoc*. 2004;99:467:890-896.

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.

Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. *Br J Cancer.* 1977;35(1):1-39.

van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, Lloyd A, Scalone L, Kind P, Pickard AS. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health*. 2012;15(5):708-715.

# Appendix 1. Abemaciclib Consolidated AE Terms

| Consolidated Preferred Term / Consolidated System Organ Class | MedDRA Preferred Terms from CTCAE Mapping |
|---|---|
| Abdominal pain / Gastrointestinal disorders | Abdominal pain, Abdominal pain lower, Abdominal pain upper, Gastrointestinal pain |
| Anaemia / Blood and lymphatic system disorders | Anaemia, Haematocrit decreased, Haemoglobin decreased, Red blood cell count decreased |
| Fatigue / General disorders and administration site conditions | Asthenia, Fatigue |
| Haematuria / Renal and urinary disorders | Blood urine present, Haematuria |
| Hypercalcaemia / Metabolism and nutrition disorders | Blood calcium increased, Hypercalcaemia |
| Hypercholesterolaemia / Metabolism and nutrition disorders | Blood cholesterol increased, Hypercholesterolaemia |
| Hyperglycaemia / Metabolism and nutrition disorders | Blood glucose increased, Hyperglycaemia |
| Hyperkalaemia / Metabolism and nutrition disorders | Blood potassium increased, Hyperkalaemia |
| Hypermagnesaemia / Metabolism and nutrition disorders | Blood magnesium increased, Hypermagnesaemia |
| Hypernatraemia / Metabolism and nutrition disorders | Blood sodium increased, Hypernatraemia |
| Hyperphosphataemia / Metabolism and nutrition disorders | Blood phosphorus increased, Hyperphosphataemia |
| Hypertension / Vascular disorders | Blood pressure diastolic increased, Blood pressure increased, Blood pressure systolic increased, Hypertension |
| Hypertriglyceridaemia / Metabolism and nutrition disorders | Blood triglycerides increased, Hypertriglyceridaemia |
| Hypoalbuminaemia / Metabolism and nutrition disorders | Blood albumin decreased, Hypoalbuminaemia |
| Hypocalcaemia / Metabolism and nutrition disorders | Blood calcium decreased, Hypocalcaemia, Calcium deficiency |
| Hypoglycaemia / Metabolism and nutrition disorders | Blood glucose decreased, Hypoglycaemia |
| Hypokalaemia / Metabolism and nutrition disorders | Blood potassium decreased, Hypokalaemia |
| Hypomagnesaemia / Metabolism and nutrition disorders | Blood magnesium decreased, Hypomagnesaemia |
| Hyponatraemia / Metabolism and nutrition disorders | Blood sodium decreased, Hyponatraemia |
| Hypophosphataemia / Metabolism and nutrition disorders | Blood phosphorus decreased, Hypophosphataemia |
| Hypotension / Vascular disorders | Blood pressure diastolic decreased, Blood pressure decreased, Blood pressure systolic decreased, Hypotension |
| Intestinal obstruction / Gastrointestinal disorders | Gastrointestinal obstruction, Intestinal obstruction, Large intestinal obstruction, Small intestinal obstruction |
| Leukocytosis / Blood and lymphatic system disorders | Leukocytosis, White blood cell count increased |
| Leukopenia / Blood and lymphatic system disorders | Leukopenia, White blood cell count decreased |
| Lymphopenia / Blood and lymphatic system disorders | Lymphopenia, Lymphocyte count decreased |
| Myocardial infarction / Cardiac disorders | Acute myocardial infarction, Myocardial infarction |

| Consolidated Preferred Term / Consolidated System Organ Class | MedDRA Preferred Terms from CTCAE Mapping |
|---|---|
| Neuropathy / Nervous system disorders | Acute polyneuropathy, Anaesthesia, Axonal neuropathy, Burning sensation, Dysaesthesia, Hypoaesthesia, Neuralgia, Neuritis, Neuropathy peripheral, Paraesthesia, Peripheral sensory neuropathy, Polyneuropathy, Sensory disturbance, Sensory loss, Skin burning sensation, Toxic neuropathy |
| Neutropenia / Blood and lymphatic system disorders | Neutropenia, Neutrophil count decreased |
| Rash / Skin and subcutaneous tissue disorders | Exfoliative rash, Mucocutaneous rash, Rash, Rash erythematous, Rash follicular, Rash generalized, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash morbilliform, Rash papular, Rash papulosquamous, Rash pruritic, Rash pustular, Rash vesicular, Vulvovaginal rash |
| Thrombocytopenia / Blood and lymphatic system disorders | Platelet count decreased, Thrombocytopenia |
| Urticaria / Skin and subcutaneous tissue disorders | Urticaria, Urticaria papular |

CCI

**Approver:** PPD
**Approval Date & Time: 02-Oct-2017 16:20:04 GMT**
**Signature meaning: Approved**

**Leo Document ID = d202fb58-0ef1-4ff3-8238-87744fcd32b1**

**Approver:** PPD
**Approval Date & Time: 10-Jul-2018 09:10:11 GMT**
**Signature meaning: Approved**

**Leo Document ID = d202fb58-0ef1-4ff3-8238-87744fcd32b1**

**Approver:** PPD
**Approval Date & Time: 11-Jul-2018 20:06:14 GMT**
**Signature meaning: Approved**

**Leo Document ID = 6a4bff96-aad0-4dde-abcb-d607cb1615b2**

**Approver:** PPD
**Approval Date & Time: 23-Aug-2018 14:44:33 GMT**
**Signature meaning: Approved**