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

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Approval Date: December 20, 2016

1. Protocol I3Y-MC-JPBK(e)
JUNIPER: 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)

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 plus best supportive care or erlotinib plus best supportive care.

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Protocol Approved by Lilly: 13 May 2014
Amendment (a) Approved by Lilly: 19 December 2014
Amendment (b) Approved by Lilly: 20 July 2015
Amendment (c) Approved by Lilly: 16 June 2016
Amendment (d) Approved by Lilly: 19 September 2016
Amendment (e) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 20-Dec-2016 GMT

2. Synopsis

Study Rationale

Patients with metastatic non-small cell lung cancer (NSCLC) that harbor *KRAS* mutations (25%) have a poor prognosis compared to NSCLC patients who are *KRAS* wild-type. The p16INK4A-cyclin D-cyclin-dependent kinases (CDK) 4 and 6-retinoblastoma pathway is frequently dysregulated in NSCLC and therefore this pathway represents an attractive therapeutic target. Abemaciclib is a potent and selective small molecule inhibitor of CDK4 and CDK6 that has shown acceptable safety/tolerability as well as evidence of clinical activity in multiple tumor types.

The Phase 3 Study I3Y-MC-JPBK (JPBK) study will evaluate the clinical activity of abemaciclib plus best supportive care (BSC) versus erlotinib plus BSC for patients with Stage IV NSCLC whose tumors have a detectable *KRAS* mutation and who have progressed after prior platinum-based therapy and received 1 other prior therapy or are not eligible for further chemotherapy.

Clinical Protocol Synopsis: Study I3Y-MC-JPBK

<table>
<tr><td colspan="2">Name of Investigational Product: Abemaciclib</td></tr>
<tr><td colspan="2">Title of Study: JUNIPER: 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.</td></tr>
<tr><td>Number of Planned Patients:
Entered: 2500
Enrolled/Randomized: approximately 450
Completed: approximately 450</td><td>Phase of Development: 3</td></tr>
<tr><td colspan="2">Length of Study: Approximately 47 months
Planned first patient visit: September 2014
Planned last patient visit: excluding the extension period: November 2017
Planned interim analysis: Analysis for safety will occur every 6 months. One futility analysis will occur after approximately 100 progression-free survival (PFS) events have been observed.</td></tr>
<tr><td colspan="2">Objectives: 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 and who have progressed after prior platinum-based therapy and 1 other prior therapy or are not eligible for further chemotherapy with respect to:
• overall survival (OS)
The secondary objectives of the study are to compare abemaciclib plus BSC to erlotinib plus BSC with respect to:
• overall response rate (complete response + partial response)
• progression-free survival (PFS)
• 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)
An additional secondary objective is to examine the pharmacokinetic (PK)/pharmacodynamic (PD) properties of abemaciclib.</td></tr>
<tr><td colspan="2">The exploratory objectives of the study are as follows:
• to explore biomarkers relevant to abemaciclib and the disease state and to correlate these markers to clinical outcome and to abemaciclib</td></tr>
</table>

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 and who have progressed after platinum-based chemotherapy and received 1 other prior therapy or are ineligible for further chemotherapy after platinum-based therapy.

Diagnosis and Main Criteria for Inclusion and Exclusions: Patients will be males or females who are ≥18 years of age with a confirmed diagnosis of stage IV NSCLC according to American Joint Committee on Cancer Staging Handbook 7th edition. The patient's tumor will have a mutation in codon 12 or 13 of the *KRAS* oncogene, and the patient must have progressed after platinum-based chemotherapy (with or without maintenance therapy), AND have received 1 additional therapy, which may include an immune checkpoint inhibitor or other anti-cancer therapy for advanced and/or metastatic disease, OR is judged by the physician as ineligible for further standard second-line chemotherapy. Patients may not have received prior epidermal growth factor receptor (EGFR)-targeted therapy, including any multi-target tyrosine kinase inhibitors, which may inhibit EGFR. Patients will have measureable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1), adequate tumor-derived material from biopsy or surgery for analysis of *KRAS* status, an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, and adequate organ function. Patients will be excluded from the study if they have a personal history of certain heart disease, presence of unstable central nervous system metastasis, or history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix) unless in complete remission with no therapy for a minimum of 3 years.

Test Product, Dosage, and Mode of Administration: Abemaciclib 200 mg administered orally as capsules every 12 hours

Planned Duration of Treatment:
Treatment period: until disease progression or unacceptable toxicity occurs (or both)
Short-term follow-up (postdiscontinuation): 30 days
Long-term follow-up (postdiscontinuation): until death or study completion

Reference Therapy, Dose, and Mode of Administration: Erlotinib 150 mg administered orally as a tablet every 24 hours

Criteria for Evaluation:
Efficacy: Efficacy assessments include imaging studies/tumor assessments, according to RECIST v. 1.1, performed every 8 weeks, and survival.
Safety: Safety will be evaluated based on recorded adverse events (AEs), physical examinations, vital sign measurements, and clinical laboratory assessments. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™). Adverse events and clinical laboratory values will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (NCI-CTCAE v. 4.03).
Health Outcomes: Health outcomes will be assessed using standardized instruments, MDASI-LC and EQ-5D 5L. Investigators will report resource utilization such as concomitant medications, transfusions, radiation therapy, surgery, and treatment-related hospitalization days.
Pharmacokinetics: The plasma concentrations of abemaciclib and its metabolites LSN2839567, LSN3106726, and LSN3106729 will be measured for patients receiving abemaciclib.
Biomarkers:
KRAS mutation assessment: all tumor tissue samples (surgical resection, core needle biopsy, or fine needle aspirate) will be analyzed for *KRAS* mutation status. The same sample may also be used for evaluation of codons 12 and 13 via Sanger sequencing.
Other biomarkers: additionally, whole blood, plasma, and tissue samples will be tested for biomarkers relevant to abemaciclib and the disease state and to correlate these markers to clinical outcome and to abemaciclib.

Statistical Methods:

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

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 .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.

Efficacy: Efficacy analyses will be based on the intention-to-treat (ITT) analysis set. This population is defined as all patients randomized to study treatment. For OS and PFS, the comparison of the survival curves between treatment groups will be conducted by 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 (GLY12CYS [G12C] vs. all others). In addition, the Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the survival curves as well as survival rates at 3, 6, 9, and 12 months for each treatment group. As supportive analysis of OS and PFS, the Cox proportional hazard model will be used to estimate treatment HR and corresponding 95% confidence interval (CI) after adjusting for the same randomization variables specified for the primary analysis. All randomized patients, according to the ITT principle, will be included in the analysis of this endpoint.

Safety: All safety summaries and analyses will be based upon the Safety Population, defined as all enrolled patients receiving at least 1 dose of any study drug. Overall exposure to study drug, the numbers of patients completing each cycle, and the dose intensity will be summarized using descriptive statistics. An overall summary of AEs will be provided for AEs deemed by the investigator to be possibly related to study drug, and repeated for events regardless of study drug causality. Incidence rates of these events will be compared between treatment arms using Chi square test. CTCAE v 4.03 will be used to report AEs by CTCAE terms. Laboratory and nonlaboratory CTCAEs will be summarized by CTCAE term and maximum CTCAE grade, including the total for maximum Grade 3 and 4. The MedDRA Version 17.0 (or higher) will be used when reporting AEs by MedDRA terms. The MedDRA Lower Level Term will be used in the treatment-emergent computation. Treatment-emergent AEs will be summarized by System Organ Class (SOC) and by decreasing frequency of Preferred Term (PT) within SOC.

Health Outcomes: The MDASI-LC will be summarized for each assessment period. EQ-5D 5L responses for each item will be summarized by frequency and corresponding percentages. Descriptive statistics for the index and visual analog scale will be calculated.

Pharmacokinetics: Mean population PK parameters for abemaciclib in plasma (clearance, exposure, volume of distribution, and half-lives) and inter-individual PK variability will be computed using nonlinear mixed effect modeling (NONMEM). Covariate effects (such as age, weight, sex, creatinine clearance, and plasma protein levels) on the PK parameters of abemaciclib in plasma will also be investigated. The mean population PK properties of abemaciclib metabolites LSN2839567, LSN3106726, and LSN3106729 in plasma may also be analyzed by means of NONMEM.

Biomarkers:
KRAS mutation assessment: Concordance (agreement) analysis will be performed on samples with valid *KRAS* status (mutation positive and mutation negative) using both the investigational assay and the reference method (Sanger sequencing). Measures of agreement between the investigational *KRAS* assay and the reference method, including positive percent agreement, negative percent agreement, and overall percent agreement, and their corresponding exact 2-sided 95% CI, will be estimated for the overall mutation status; that is, mutation detected or not detected for the 7 mutations of *KRAS* gene. A secondary agreement analysis between the investigational *KRAS* assay and the reference method will be performed for each of the tumor tissue sample types (surgical resection, fine needle aspirate, and core needle biopsy). The data will also be summarized for each of the 7 *KRAS* mutations separately.

Other biomarkers: the distributions of biomarkers will be summarized for the patient population for which samples are available. Associations between clinical endpoints and biomarker will be evaluated using data from patients who have an evaluable sample for each biomarker of interest, and such evaluation will be done on an individual marker basis.

3. Table of Contents

JUNIPER: 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

Section **Page**

List of Tables

List of Figures

Figure **Page**

List of Attachments

4. Abbreviations and Definitions

Term	Definition
AE	adverse event Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study (required by some institutional review boards [IRBs]).
AST	aspartate aminotransferase
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BOR	best overall response
BSC	best supportive care
CDK	p16INK4A-cyclin D-cyclin-dependent kinases
CI	confidence interval
CNS	central nervous system
collection database	A computer database where clinical trial data are entered and validated.
companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
CRF/eCRF	case report form/electronic case report form Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	clinical research physician Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.

CNS	central nervous system
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
CR	complete response
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DMC	data monitoring committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
EQ-5D 5L	European Quality of Life – 5 Dimensions – 5 Level
extension period	The period between study completion and end of trial during which patients on study therapy who continue to experience clinical benefit may continue to receive study therapy until one of the criteria for discontinuation is met.
FDA	US Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
G12C	GLY12CYS: a mutation in codon 12 of the *KRAS* gene resulting in an amino acid substitution from glycine to cysteine

GCP	good clinical practice
G-CSF	Granulocyte-Colony Stimulating Factors
GPS	(Lilly) Global Patient Safety
HIV	human immunodeficiency virus
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial.
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
ITT	intention-to-treat The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IV	intravenous
KRAS	kirsten rat sarcoma
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
LLT	Lower Level Term
MDASI-LC	MD Anderson Symptom Inventory – Lung Cancer

MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NONMEM	nonlinear mixed effect modeling
NSCLC	non-small cell lung cancer
OS	overall survival
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PD	progressive disease
PET	positron emission tomography
PK	pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
PFS	progression-free survival
PO	orally
PR	partial response
pRb	phosphorylated retinoblastoma
Pre-screen	The act of determining if an individual meets minimum requirements to be an appropriate candidate for screening for a clinical study. In this study, prescreening involves diagnostic testing of an archived NSCLC tumor sample for mutations in codons 12 and 13 of the *KRAS* oncogene. Informed consent for this prescreening test shall be obtained; this consent may be separate from obtaining consent for the study.
PS	performance status
PT	Preferred Term
Q12H	every 12 hours
QTc	corrected QT interval
RANKL	nuclear factor kappa B ligand
randomize	the process of assigning patients to an experimental group on a random basis
RECIST	Response Evaluation Criteria in Solid Tumors

reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	to screen a patient who was previously declared a screen failure for the same study
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets the requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, x-rays, blood draws). Informed consent for these screening procedures and/or tests shall be obtained
screen failure	patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
SmPC	Summary of Product Characteristics
SOC	System Organ Class
study completion	This study will be considered complete after the final analysis of overall survival is performed.
SUSARs	suspected unexpected serious adverse reactions
TEAE	treatment-emergent adverse event Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
topoIIα	topoisomerase II alpha
TKI	tyrosine kinase inhibitor
ULN	upper limits of normal
US	United States
VAS	visual analog scale
WBC	white blood cells

JUNIPER: 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

5. Introduction

Patients with metastatic non-small cell lung cancer (NSCLC) that harbor *KRAS* mutations (25%) have a poor prognosis compared to NSCLC patients who are *KRAS* wild-type (Guan et al. 2013). The p16INK4A-cyclin D-cyclin-dependent kinases (CDK) 4 and 6-retinoblastoma pathway is frequently dysregulated in NSCLC and therefore this pathway represents an attractive therapeutic target. Importantly, synthetic lethal interaction between *KRAS* mutation and CDK4 inhibition indicates a potential therapeutic application for CDK4 and CDK6 inhibitors in NSCLC (Puyol et al. 2010).

LY2835219 (hereafter, abemaciclib) is a potent and selective small molecule inhibitor of CDK4 and CDK6. Abemaciclib administered orally demonstrates single-agent activity in xenograft models of human NSCLC. In the Phase 1 study I3Y-MC-JPBA (JPBA), abemaciclib has shown acceptable safety/tolerability, as well as evidence of clinical activity in multiple tumor types. In addition, Study JPBA included a NSCLC expansion cohort that enrolled 57 patients with advanced and/or metastatic NSCLC. The *KRAS* status of the tumors from 53 of the 57 patients has been identified. For patients with *KRAS* mutant tumors (N=29), 16 patients had a Response Evaluation Criteria In Solid Tumors (RECIST) response of stable disease (SD) or better (disease control rate [DCR=55.2%]); for patient with *KRAS* wild-type tumors (N=24), 9 had a response of SD or better (DCR=37.5%).

In clinical trials, the most frequently reported adverse events (AEs) related to abemaciclib have been diarrhea, nausea, fatigue, and vomiting. These AEs have generally been low-grade events.

More information about the known and expected benefits, risks, and reasonably anticipated AEs of abemaciclib may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to abemaciclib may be found in Section 7 (Development Core Safety Information) of the IB. Information on serious adverse events (SAEs) expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

More detailed information about the known and expected benefits and risks of erlotinib may be found in the following: Tarceva Package Insert or Summary of Product Characteristics (SmPC).

An investigational in vitro diagnostic medical device, or companion diagnostic, will be used to evaluate *KRAS* mutations in formalin-fixed paraffin-embedded (FFPE) NSCLC tumor tissue. The QIAGEN® *therascreen*® *KRAS* Rotor-Gene Q (RGQ) Polymerase Chain Reaction (PCR) Kit NSCLC is a real-time qualitative PCR assay used for the detection of 7 somatic mutations in codons 12 and 13 in the *KRAS* oncogene. Potential risks to patients have been evaluated by

Eli Lilly and Company's (Lilly's) Global Patient Safety (GPS). Physicians will consider each patient's disease, *KRAS* test result, and other factors to reach the appropriate therapeutic decision. No treatment decision shall be made solely on the basis of the *KRAS* test result. In the event abemaciclib would be administered to a patient for whom it is not indicated based on the result of the *KRAS* test result, there is no evidence from clinical studies indicating that this might cause or contribute to any serious harm of a patient, other than potentially delaying another treatment option for a patient. It is unlikely that an incorrect result would be generated by the in vitro diagnostic medical device and highly likely that an incorrect result would be detected by laboratory personnel.

Erlotinib is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen (Tarceva United States [US] package insert [USPI], 2010). Until recently, unlike the use of erlotinib for first-line treatment of patients with NSCLC, second- and third-line treatment has no limitation with regard to epidermal growth factor receptor (*EGFR*) or *KRAS* mutation status. In October 2016 the FDA modified the erlotinib label to include only those patients with tumors with common *EGFR* mutations, del 19 and exon 21 L858R substitutions. Before this action, there had been some concern regarding the activity of erlotinib in treating NSCLC with *KRAS* mutations due to results from 3 studies. First, in the original BR-21 study, a subgroup evaluation of 30 patients with *KRAS* mutant tumors randomized between placebo and erlotinib demonstrated a nonsignificant better survival outcome in the placebo group (Zhu et al. 2008). Second, in TITAN, a second-line study of erlotinib versus chemotherapy, 35 patients with *KRAS* mutant tumors had inferior outcome on erlotinib compared to chemotherapy (Ciuleanu et al. 2012). Lastly, a meta-analysis of response rate showed numerically inferior response rate in patients with *KRAS* mutant tumors treated with EGFR tyrosine kinase inhibitors (TKIs, such as erlotinib and gefitinib) (Linardou et al. 2008). In the TAILOR study comparing docetaxel to erlotinib as second-line therapy, overall survival (OS) favored docetaxel treatment in patients with both *KRAS* wild-type and *KRAS* mutant tumors (hazard ratio [HR] = 0.79 and 0.81, respectively); similarly, progression-free survival (PFS) favored docetaxel (HR = 0.68 and 0.89) for *KRAS* wild-type and *KRAS* mutant, respectively (Garassino et al. 2013). There was not a significant treatment interaction based on *KRAS* status. However, the SATURN study of erlotinib maintenance therapy demonstrated that improved PFS was preserved in a subset of 90 patients with *KRAS* mutant tumors (HR = 0.77 erlotinib compared to placebo) (Brugger et al. 2011). Overall, the data remain conflicting and after extensive review of the literature, Langer stated, "*KRAS* mutation cannot be used at this time to preclude NSCLC patients from receiving anti-EGFR TKI's" (Langer 2011). A more recent evaluation of pooled results from four Phase 3 studies of erlotinib showed that *KRAS* mutation was not predictive of treatment outcome with tyrosine kinase inhibitors (Zer et al. 2015). The selection of treatment depends on the overall benefit/risk for the patient. Given the differences in toxicity profile for available treatments, and the limited treatment options for patients, erlotinib is an acceptable control arm as the only oral drug available for patients with lung cancer, and only approved drug for treatment of third-line patients in selected geographies.

The Phase 3 Study I3Y-MC-JPBK (JPBK) study will evaluate the clinical activity of abemaciclib plus best supportive care (BSC) versus erlotinib plus BSC for patients with Stage IV NSCLC

whose tumors have a detectable *KRAS* mutation and who have progressed after prior platinum based therapy and received 1 other prior therapy or are not eligible for further chemotherapy.

5.1. Rationale for Amendment (a)

The protocol was amended based on the US Food and Drug Administration (FDA) feedback to provide a rationale for the selected dose and schedule of abemaciclib for the intended patient population and to add specified provider-conducted history and physical examination to be performed during screening and before each cycle.

Further modifications were performed for clarity: 1) Inclusion Criterion [4] revised to include adjuvant, neoadjuvant, and chemoradiation for locally advanced disease; furthermore, prior immunotherapy, such as anti-PD-1 therapy, does **NOT** count as a prior line of therapy 2) Exclusion Criterion [18] modified to replace LY2835219 to a CDK4 and CDK6 inhibitors; 3) the extension period is also applicable for patients randomized to the erlotinib arm and who are experiencing ongoing clinical benefit; 4) supportive management for diarrhea modified; and 5) clarification with respect to the timing and purpose of the interim analyses added.

Minor typographical and formatting edits were made throughout the document for clarity and consistency.

5.2. Rationale for Amendment (b)

This protocol was amended to clarify the allowed use of immunotherapy as prior line of therapy. Nivolumab, a fully human IgG4 immune checkpoint inhibitor antibody, was recently approved in the US for treatment of patients with advanced (metastatic) squamous NSCLC who have progressed after a platinum-based chemotherapy. In the CheckMate 017 study, 272 patients received either nivolumab (135 patients) or docetaxel (137 patients). The interim analysis showed a median OS of 9.2 months and 6 months (HR 0.59; 95% CI: 0.44 to 0.79; p<.0.001) and PFS 3.5 months and 2.8 months (HR 0.62; 95% CI: 0.47 to 0.81; p<0.001) with nivolumab and docetaxel, respectively (Brahmer et al. 2015). The results of this study and ongoing studies with nivolumab and other immune checkpoint inhibitors demonstrate that an immune checkpoint inhibitor may be a suitable second-line treatment option for patients with metastatic NSCLC. Inclusion Criterion [4] has been updated to include an immune checkpoint inhibitor as one of the possible second-line therapies for inclusion into Study JPBK. In addition, it has been clarified that patients who have received first-line platinum-based therapy followed by standard chemotherapy and subsequently an immune checkpoint inhibitor are also eligible for enrollment in Study JPBK in the third-line setting.

Further modifications were performed for clarity: 1) supportive management for diarrhea; 2) rescreening of patients; 3) dose delays related to toxicity; 4) the timing of study procedures and 5) potential CYP interactions.

Minor typographical and formatting edits were made throughout the document for clarity and consistency.

5.3. Rationale for Amendment (c)

This protocol was amended to address the challenges identified with tissue for *KRAS* testing by the central laboratory. As multiple biomarker targets are recognized within NSCLC (for example, *EGFR, ALK*, and *KRAS*) and tested locally, obtaining tissue of sufficient quality and quantity to enable eligibility testing with the QIAGEN® *therascreen*® *KRAS* RGQ PCR Kit NSCLC at the Study JPBK central laboratory has been a challenge, and ultimately has impacted enrollment. This protocol amendment will permit study inclusion for no more than 10% of randomized patients with a positive local *KRAS* result. A review of approximately 1740 *KRAS* sample submissions indicated that approximately 260 samples were resulted as "indeterminate", "no neoplastic cell in tissue", or "insufficient sample" or 'quantity not sufficient". In many cases, additional tissue to submit for re-testing is not available and the patient is not a candidate for re-biopsy to obtain more tissue. Those patients who have a positive local *KRAS* result for one of the 7 specific mutations identified by the QIAGEN® *therascreen*® *KRAS* RGQ PCR Kit NSCLC will be allowed to enter into the study with this result in the absence of a central laboratory *KRAS* positive result. Additionally, patients with no tissue available for testing with the QIAGEN® *therascreen*® *KRAS* RGQ PCR Kit NSCLC will be allowed to enter into the study with a positive local *KRAS* result. The investigator will require approval from the study team to confirm patient eligibility prior to randomization to study treatment as outlined in Section 10.4.2.2. Inclusion Criterion [3] has been modified to include local *KRAS* mutation results.

This protocol amendment also revises the timing of primary PFS analysis to allow for adequate time to observe additional OS events. The primary PFS analysis will be performed after approximately 338 PFS events have occurred, or approximately 1 month after study enrollment completion, whichever comes later. The interim OS analysis will be conducted at the time of primary PFS analysis. The final OS analysis will be conducted after approximately at least 407 OS events have been observed. If the primary PFS analysis is significant, two-sided alpha=0.0112 will be spent in the interim OS analysis and alpha=0.0466 will be used in the final OS analysis based on O'Brien and Fleming alpha-spending approach using East® 6.3 (Lan and DeMets 1983). If the primary PFS is not significant, two-sided alpha=0.0096 will be spent in the interim OS analysis and alpha= 0.0420 will be used in the final OS analysis. A fallback procedure (Wiens 2003) will be used to maintain a study-wise alpha level of .05.

Additional clarity was added in the unblinding plan for potential positive interim efficacy results. If the data monitoring committee (DMC) recommends to stop the trial based on positive outcome of OS interim analysis, in light of the critical importance of obtaining unbiased results of final OS analysis in the study, the unblinded database will be accessible to a limited number of individuals who need to have such access to perform analyses and make critical decisions (for example, regulatory submission).

An extra plasma biomarker sample was added at baseline prior to randomization. This additional sample will be obtained for the biomarker exploratory analysis and may assist in future development of a liquid biopsy test for *KRAS*. Further information regarding plasma biomarker samples is discussed in Section 10.4.3.3.

Lastly, updates to the dose adjustments for abemaciclib in case of hematologic toxicities were completed for consistency with the abemaciclib program. These updates include specific guidelines for managing Grade 3 hematologic toxicities, including dose omission and reductions, and the use of blood cell growth factors.

Minor typographical and formatting edits were made throughout the document for clarity and consistency.

5.4. Rationale for Amendment (d)

According to the US label and EU SmPC of immune checkpoint inhibitors nivolumab and pembrolizumab, delayed immune-related adverse reactions (AE) such as hepatitis, pancreatitis, hypophysitis, or thyroiditis may occur in patients, even after discontinuation of therapy. Wide variation exists in the reported times of onset of immune-mediated AEs with PD-1 inhibitors (Medina and Adams 2016). For example, pembrolizumab's FDA label reports a delayed immune-related adverse event of autoimmune nephritis that occurred in 1 patient 11.6 months after the first dose of pembrolizumab (5 months after the last dose).

Study JPBK was amended to include the following recommendations for monitoring and treatment of potential delayed immune-related adverse reactions associated with immune checkpoint inhibitors:

- Patients who have received prior immune checkpoint inhibitor or other immunotherapy should be monitored for potential signs of a delayed toxicity after discontinuation of immunotherapy.
- Treatment of a suspected toxicity should be according to the immune checkpoint inhibitor's label and may include immediate use of corticosteroids, an immune-suppressive therapy, and increased laboratory monitoring and physical assessments.
- Current recommendations for monitoring for delayed toxicity range between 90 days and 1 year after treatment discontinuation (Champiat et al. 2016).

In addition, updates to the frequency of the hematological and clinical chemistry laboratory tests during Cycles 1 and 2 were made to align with newer studies within the abemaciclib program. For patients enrolled in Amendment (d), hematological and chemistry samples will be collected on Days 1 and 15 during Cycles 1 and 2. Beginning with Cycle 3, these samples will be collected on Day 1 of each cycle.

Minor typographical and formatting edits were made throughout the document for clarity and consistency.

5.5. Rationale for Amendment (e)

Due to recent changes in the FDA ertlotinib label and National Comprehensive Cancer Network (NCCN) Guidelines, the Sponsor amended the protocol to address the impact on study enrollment completion, and the need for a larger improvement in OS than that historically targeted for NSCLC patients. In addition, OS is considered the preferred primary endpoint for regulatory approval and hence PFS is removed from the primary objective so all

statistical power can be reallocated to enhance the success for OS. The amendment updates include the followings:

- PFS is removed as a co-primary endpoint and changed to a secondary endpoint. With this change OS becomes the sole primary endpoint.
- The final OS analysis will occur when approximately 304 OS events have been observed, a reduction from the current protocol requirement of 407 OS events. With this change, the study will provide 80% statistical power for a new targeted hazard ratio of 0.72.
- 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 (note that current protocol requires 550 patients).

While amending the protocol, the Lilly study team remains blinded to aggregate data and will not be unblinded until the final OS analysis per Section 9.5.

Previously, erlotinib was indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen (Tarceva® United States [US] package insert [USPI], 2010) based upon the BR-21 study. In addition, NCCN Guidelines (April 2015) supported erlotinib use as an option for subsequent second line or third line treatment in NSCLC patients (all histologies) for PS 0-3.

On 18 October 2016, the FDA modified the indication for erlotinib (Tarceva®) for treatment of NSCLC, limiting the use to patients whose tumors have specific *EGFR* mutations (exon 19 deletions or exon 21 L858R substitutions). This labeling supplement occurred based on study results of the IUNO Study (a randomize, double-blind, placebo controlled, trial of erlotnib administered as maintenance therapy in advanced NSCLC patients who had not experienced disease progression or unacceptable toxicity during four cycles of platinum-based first-line chemotherapy). The results showed no observed benefits in PFS, ORR, DCR or OS (median OS was 9.7 and 9.5 months with 'early' and 'late erlotinib', respectively (HR, 1.02, 95% CI: 0.85−1.22; log-rank p = 0.82) in patients receiving erlotinib as maintenance therapy ("early erlotinib") compared to second-line treatment ("late erlotinib") in patients whose tumor did not harbor an *EGFR*-activating mutation. However, safety results were consistent with the established safety profile of erlotinib. Furthermore, in light of the FDA labeling supplement, the NCCN Guidelines removed erlotinib from recommended therapies in patients who progress on platinum therapy and who do not have *EGFR* mutations (NCCN Guidelines October 2016).

Minor typographical and formatting edits were made throughout the document for clarity and consistency.

6. Objectives

6.1. 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 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 treatment; or are not eligible for further chemotherapy with respect to:

- overall survival (OS)

6.2. Secondary Objectives

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

- overall response rate (complete response [CR] + partial response [PR])
- progression-free survival (PFS)
- 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)

An additional secondary objective is to examine the pharmacokinetic (PK)/pharmacodynamic (PD) properties of abemaciclib.

6.3. Exploratory Objectives

The exploratory objectives of the study are as follows:

- to explore biomarkers relevant to abemaciclib and the disease state and to correlate these markers to clinical outcome and to abemaciclib

7. Study Population

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. When re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number. Patients may only be rescreened once.

Patients may be eligible for rescreening in any of the following circumstances:

- Patients who have become eligible to enroll in the study as the result of a protocol amendment.
- Patients whose status has changed such that the eligibility criterion that caused the patient to screen fail would no longer cause the patient to screen fail again.
- Patients who complete screening and meet all inclusion and exclusion requirements but are unable to be enrolled due to extenuating circumstances (such as severe weather, death in family, or child illness).

The investigator should contact the Lilly clinical research physician (CRP) prior to re-screening a patient.

If a *KRAS* mutation positive result was obtained for an individual under their first patient number, this result can be linked to their new number in an effort to preserve patient tissue. If a *KRAS* mutation result was not successfully obtained for an individual under their first patient number, then the investigator can submit a new sample for this individual (as well as one repeat if needed) to the central lab with the new patient number.

Repeating laboratory tests (including one re-test for *KRAS*) during the pre-screening and screening period does not constitute re-screening. Patients who prescreened for *KRAS* mutation and their result was either indeterminate or insufficient tissue will be permitted to resubmit tissue if adequate tissue is available.

Prospective approval of protocol deviations to recruitment and enrollment criteria (also known as protocol waivers or exemptions) is not permitted.

7.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria:

[1] have confirmed diagnosis of stage IV NSCLC according to the American Joint Committee on Cancer Staging Handbook (Edge et al. 2009).

[2] have availability of adequate FFPE tumor-derived material (tumor blocks or slides) from a biopsy, surgery or fine needle aspirate for analysis of *KRAS* mutation status. This sample should be the most recent available sample containing adequate material. Tumor sample requirements are described in Section 10.4.2.1. The sponsor will not request re-biopsy solely for the purpose of testing of *KRAS* status.

[2A] For patients who do not have adequate FFPE tumor-derived material for *KRAS* mutation status analysis, eligibility may be considered based upon a local

KRAS mutation result as described in Section 10.4.2.2. The sponsor will not request re-biopsy solely for the purpose of testing of *KRAS* status.

[3] determined to have detectable mutations in codons 12 or 13 of the *KRAS* oncogene by an investigational assay at the Study JPBK central laboratory

[3A] A *KRAS* positive mutation result in codons 12 or 13 of the *KRAS* oncogene from tumor tissue per local laboratory will be permitted in no more than 10% of the randomized patients; thus, requirement of a central laboratory *KRAS* positive mutation result is waived. No serum or plasma *KRAS* mutation results are permitted for consideration.

[4] have progressed after platinum-based chemotherapy (with or without maintenance therapy [see below]) AND have received 1 additional therapy which may include an immune checkpoint inhibitor or other anti-cancer therapy for advanced and/or metastatic disease; OR is judged by the physician as ineligible for further standard second-line chemotherapy. Patients who have progressed after platinum-based chemotherapy and an immune checkpoint inhibitor (immunotherapy) e.g. pembrolizumab or nivolumab alone or in combination with other agents are eligible.

- Prior adjuvant or neoadjuvant therapy for an earlier stage of NSCLC counts as an appropriate line of therapy in case the patient progressed within 6 months of completing the platinum-based adjuvant or neoadjuvant therapy. The time from the completion of the last cycle of adjuvant or neoadjuvant therapy to progression must be less than 6 months. For radiotherapy for locally advanced disease with curative intent with platinum-based chemotherapy, the time of completion of platinum-based chemotherapy or radiotherapy, whichever finishes last, to progression must be less than 6 months to count as a line of therapy.
- The patient may not have received prior EGFR-targeted therapy, including any multi-target TKIs, which may inhibit EGFR (for example, vandetanib) in any setting for NSCLC.
- The patient may have received prior therapy with bevacizumab.
- The patient may have received maintenance therapy. Maintenance treatment is defined as therapy given approximately within 42 days after the last dose of platinum-based chemotherapy in patients that have not progressed (complete response, partial response, or stable disease) after platinum-based, first-line induction chemotherapy. A minor delay eg. up to 30 additional days in the start of maintenance therapy is acceptable.
- If the patient has received prior immunotherapy, such as anti-PD-1 therapy, after platinum-base therapy plus 1 additional line of therapy, the patient is eligible to participate in study. The immunotherapy does not count as a prior line of therapy in this case. This patient would be entering the study as third line treatment.

[5] have measureable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1, Eisenhauer et al. 2009)

[6] have a performance status (PS) of 0 to 1 on the Eastern Cooperative Oncology Group (ECOG) scale (see Attachment 3)

[7] have discontinued all previous therapies for cancer (including chemotherapy, radiotherapy, immunotherapy, and investigational therapy) for at least 21 days for myelosuppressive agents or 14 days for nonmyelosuppressive agents prior to receiving study drug

[8] recovered from the acute effects of therapy (treatment related toxicity resolved to baseline) except for residual alopecia

[9] have adequate organ function, including:

- hematologic: absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and hemoglobin ≥8 g/dL. Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator. Initial treatment must not begin until the day after the erythrocyte transfusion.
- hepatic: bilirubin ≤1.5 × the upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate transaminase (AST) ≤3.0 times ULN. For patients with hepatic metastases, ALT and AST equaling ≤5.0 times ULN are acceptable.
- renal: serum creatinine ≤1.5 × ULN

[10] are ≥18 years of age

[11a] are a man and agree to use a reliable method of birth control and to not donate sperm during the study and for at least 3 months following the last dose of study drug(s) or country requirements, whichever is longer, OR

[11b] are a woman of child-bearing potential who tests negative for pregnancy at the time of enrollment based on a serum pregnancy test and agrees to use a reliable method of birth control during the study and for 3 months following the last dose of the study drug(s) or country requirements, whichever is longer

[12] have an estimated life expectancy of at least 12 weeks

[13] have given written informed consent/assent prior to any study-specific procedures

[14] are able to swallow oral medications

[15] are reliable and are willing to follow study procedures

7.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

[16] are currently receiving treatment in a clinical trial involving an investigational product or non-approved use of a drug or device (other than the study drug/device used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study

[17] have received treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days of the initial dose of study drug for a nonmyelosuppressive or myelosuppressive agent, respectively

[18] have previously completed or withdrawn from this study or any other study investigating a CDK4 and CDK6 inhibitors, or have received treatment with a prior CDK4 and CDK6 inhibitors

[19] have a personal history of any of the following conditions: presyncope or syncope of either unexplained or cardiovascular etiology, ventricular arrhythmia (including but not limited to ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest

[20] have the presence of unstable central nervous system (CNS) metastasis. History of CNS metastasis or stable CNS metastases is allowed (no longer requiring active therapy such as steroid medications). Patients with a history of CNS metastases must have a brain scan (for example, MRI) within 28 days of randomization to document stability, even if there have been no changes in symptoms. A brain MRI performed up to 45 days is permitted and does not need to be repeated during baseline.

[21] have a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for that disease for a minimum of 3 years

[22] have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study

[23] females who are pregnant or lactating

[24] have active bacterial, fungal, and/or known viral infection (for example, human immunodeficiency virus [HIV] antibodies, hepatitis B surface antigen, or hepatitis C antibodies). Screening for active infections is not required for enrollment.

7.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion Criterion [19] is necessary because the effects of abemaciclib on corrected QT (QTc) prolongation are unknown; these conditions may put the patient at additional risk. Exclusion Criterion [20] is necessary because patients with unstable CNS metastasis are not likely to receive sufficient study treatment, preventing a full assessment of the agents administered in this

study. Exclusion Criterion [23] is necessary because the effects of abemaciclib on the developing fetus are unknown.

7.3. Discontinuations

7.3.1. Discontinuation of Patients

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor clinical research physician (CRP) and the investigator to determine whether the patient may continue in the study, with or without study drug. Inadvertently enrolled patients may be maintained in the study and on study drug when the Lilly CRP agrees with the investigator that it is medically appropriate for that patient. The patient may not continue in the study with or without study drug if the Lilly CRP does not agree with the investigator's determination it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without study drug.

In addition, patients will be discontinued from the study drugs and/or from the study in the following circumstances:

- disease progression
- unacceptable toxicity
- the patient has had 2 dose reductions and experiences an AE that would cause a third dose reduction.
- the patient is significantly noncompliant with study procedures and/or treatment
- investigator decision
    - the investigator decides that the patient should be discontinued from the study or study drug for any reason (for example, the patient becomes pregnant)
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drug occurs prior to introduction of the new agent
- patient decision
    - the patient or the patient's designee (for example, parents or legal guardian) requests to be withdrawn from the study or study drug
- sponsor decision
    - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice
- enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study

The reason for and date of discontinuation will be collected for all patients. All randomized patients who discontinue regardless of whether or not they received study drug will have procedures performed as shown in the Study Schedule (Attachment 1).

7.3.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ethical review board (ERB) of the study site judges it necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).

7.3.3. Discontinuation of the Study

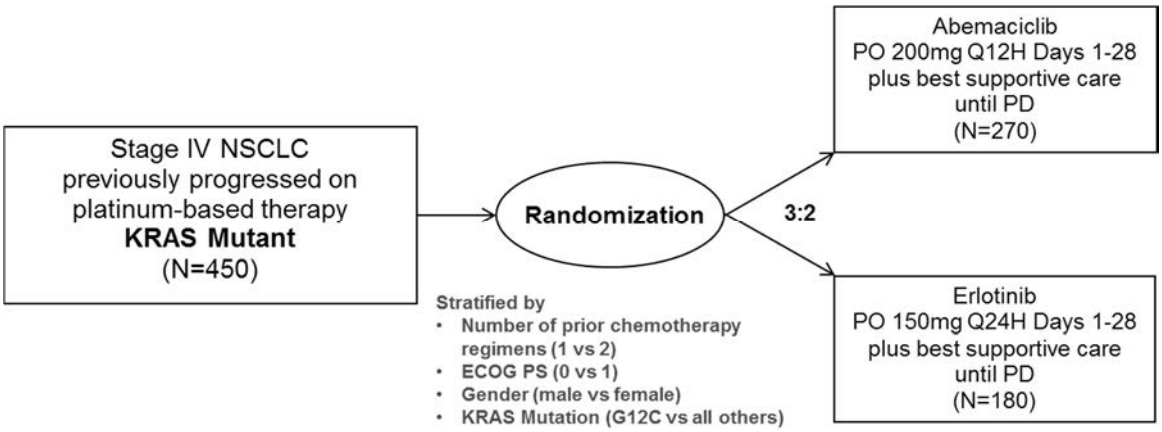
The study will be discontinued if Lilly judges it necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

8. Investigational Plan

8.1. Summary of 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 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.8.1 illustrates the study design.



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

Figure JPBK.8.1. Illustration of study design.

Terms used to describe the periods during the study are defined below:

- **Pre-screening:** begins when the pre-screening informed consent form (ICF) is signed for evaluation of FFPE tissue by Study JPBK central laboratory and ends once the *KRAS* mutation status of the tissue is determined (or at discontinuation, if the study ICF is not signed). Pre-screening for *KRAS* mutation status determination is optional. If pre-screening did not occur, determination of *KRAS* mutation status will occur at baseline.
- **Baseline:** begins when the study ICF is signed and ends at the first study treatment (or at discontinuation, if no treatment is given).
- **Study Period:** begins at the first study treatment and ends at study completion. The study period does not include the extension period.
    - **Study Treatment Period:** begins at the first study treatment and ends when the patient and the investigator agree that the patient will no longer continue study treatment. The date of this agreement is to be reported on the case report form (CRF) as the Date of Discontinuation from study treatment.
    - **Postdiscontinuation Follow-Up:** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment. All

randomized patients must be followed during postdiscontinuation regardless of whether study treatment was received.

Short-term follow-up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days.

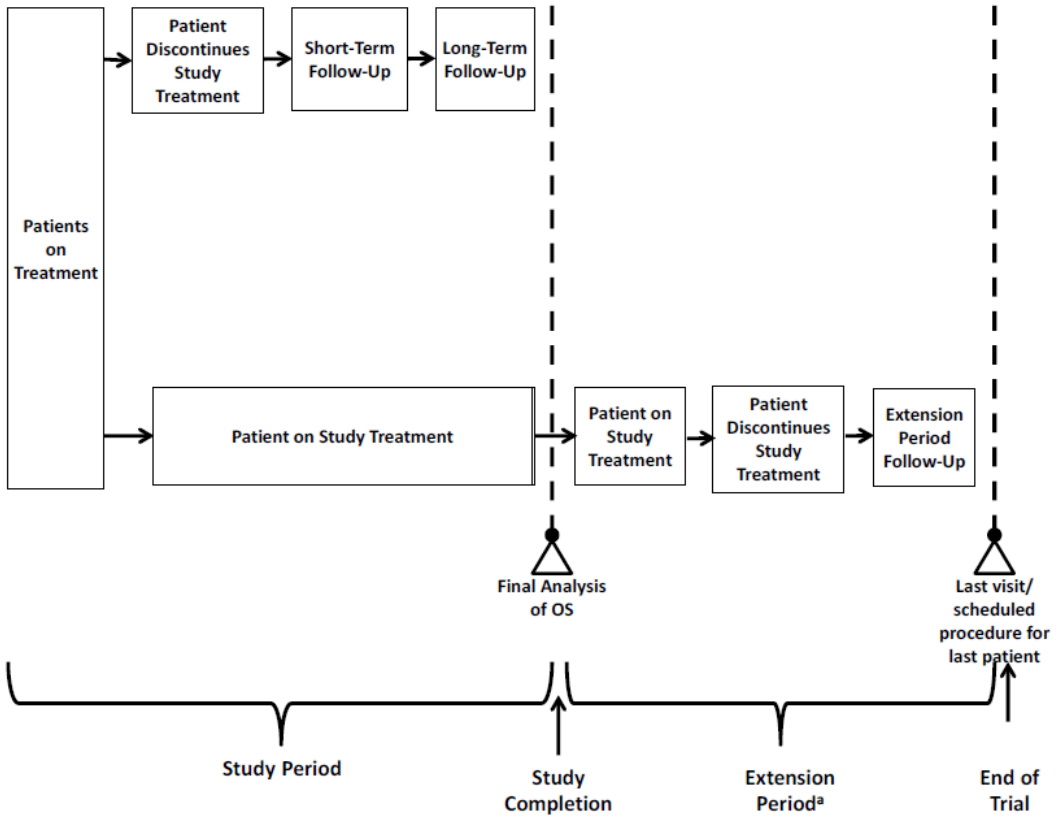
Long-term follow-up begins the day after short-term follow-up is completed and continues until the patient's death or overall study completion. During long-term follow-up, patients will have a follow-up visit every 60 days (±14 days).

- **Extension Period:** begins after study completion and ends at the end of trial. During the extension period, patients on study therapy who continue to experience clinical benefit may continue to receive study therapy until one of the criteria for discontinuation is met. The extension period includes extension period follow-up.
    - Extension period follow-up: begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the extension period and lasts approximately 30 days.

8.1.1. Study Completion and End of Trial

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the final analysis of overall survival, as determined by Lilly. Investigators will continue to follow the study schedule for all patients until notified by Lilly that study completion has occurred.

"End of trial" refers to the date of the last visit or last scheduled procedure for the last patient (Figure JPBK.8.2). The end of trial occurs after study completion and after the last patient has discontinued study treatment and completed extension period follow-up (if applicable).



Abbreviations: OS = overall survival.

a Lilly will notify sites when this begins and ends.

Figure JPBK.8.2. Study period and extension period diagram.

8.1.2. Extension Period

Patients experiencing ongoing clinical benefit may continue to receive abemaciclib or erlotinib in the extension period until 1 of the criteria for discontinuation is met (Section 7.3). There is no cross-over between the 2 study treatment arms. Lilly will notify investigators when the extension period begins.

Patients who are in short-term follow-up when the extension period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply.

Patients who are in long-term follow-up when the extension period begins will be discontinued from long-term follow-up.

During the extension period, all AEs, SAEs, and study drug exposure will be reported on the CRF. Serious adverse events will also be reported to Lilly GPS (see Section 10.3.1). In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE.

Investigators will perform any other standard procedures and tests needed to treat and evaluate patients; however, the choice and timing of the tests will be at the investigator's discretion. Lilly will not routinely collect the results of these assessments.

8.2. Discussion of Design and Control

A randomized, controlled design is being used in this study. Randomization minimizes systematic bias in the selection and assignment of patients to study therapy and provides justification for inferential statistical methods to be used on data from this study. It is expected that abemaciclib will produce better efficacy outcomes than the control; therefore, this study uses a 3:2 randomization. Using an appropriate concurrent control arm enables direct statistical estimation of benefits and harms due to study therapy and minimizes bias in the assessment and interpretation of observed treatment effects. Patients will be stratified for differences in factors thought to be associated with clinical outcomes to further reduce the potential for bias and improve the power of the analyses.

9. Treatment

9.1. Treatments Administered

The following treatments will be administered in this study:

- Experimental Arm A: Abemaciclib 200 mg orally every 12 hours plus BSC on Days 1 to 28 of a 28-day cycle. The total daily dose of abemaciclib is 400 mg.
- Control Arm B: Erlotinib 150 mg orally every 24 hours plus BSC on Days 1 to 28 of a 28-day cycle.

Table JPBK.9.1 shows the treatment regimens.

Table JPBK.9.1. Treatment Regimens/Dosing Schedule

Regimen	Period/Cycle	Dose Day 1-28
Abemaciclib	Treatment/28-day cycle	200 mg PO Q12H
Erlotinib	Treatment/28-day cycle	150 mg PO Q24H

Abbreviations: PO = orally; Q12H = every 12 hours; Q24H = every 24 hours.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the drugs and the planned duration of each individual's treatment to the patient, site personnel, and/or the patient's legal representative,
- verifying that instructions are followed properly,
- maintaining accurate records of study drug dispensing and collection,
- and returning all unused drug to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the study drug if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose clinical trial materials.

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug so that the situation can be assessed.

9.2. Materials and Supplies

Abemaciclib will be supplied by Lilly as capsules for oral administration. Abemaciclib capsules should be stored according to the temperature range listed on the product label, and should not be opened, crushed, or chewed.

Erlotinib will be supplied where required as tablets for oral consumption. Erlotinib should be stored according to the temperature range listed on the product label.

All study drug provided by Lilly will be labeled according to local country regulatory requirements. All medication should be kept out of the reach of children and stored in the original packaging/container provided.

9.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomly assigned to receive either abemaciclib or erlotinib. If possible, treatment should begin as soon as possible when study drug is available.

Randomization will be stratified by the following factors:

- number of prior chemotherapy regimens (1 versus 2)
    - For purposes of stratification, immunotherapy does not count as a chemotherapy regimen. However, immunotherapy may be considered a prior treatment for eligibility as described in Section 7.1 (for example, if a patient received platinum-based therapy followed by immunotherapy, the number of prior chemotherapies for stratification is one).
- performance status (0 versus 1)
- gender (male versus female)
- *KRAS* mutation (GLY12CYS [G12C] versus all others)

Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web response system.

The chosen stratification factors have been identified as variables with the foremost influence on the primary objective of OS. Randomization will be performed separately within each of the 16 strata (or cells) defined by all combinations of these 4 variables.

9.4. Selection and Timing of Doses

Abemaciclib will be taken orally every 12 (±approximately 2) hours on Days 1 through 28 of a 28-day cycle, for a total of 56 doses per cycle. On Cycle 1 Day 1, only one 200-mg dose of abemaciclib will be taken. Chronic oral administration of abemaciclib approximately every 12 hours will be initiated on Cycle 1 Day 2 and continue throughout every cycle. During all cycles, abemaciclib should be taken at approximately the same times each day. If a patient misses or vomits a dose, that dose should be omitted.

Erlotinib will be taken orally once daily (approximately every 24 hours) on Days 1 through 28 of a 28-day cycle, for a total of 28 doses per cycle. During all cycles, erlotinib should be taken at approximately the same time each day. If a patient misses or vomits a dose, that dose should be omitted.

A cycle is defined as the planned treatment interval of 28 days plus any subsequent delay prior to the start of the next cycle. A delay of a cycle due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 7 days and not counted as a protocol deviation. Abemaciclib will be dispensed for 56 doses (28-day supply). Erlotinib will be dispensed with a 30 day supply, but only 28 doses should be taken per cycle.

A patient may continue to receive study drug until he or she meets 1 or more of the specified reasons for discontinuation (as described in Section 7.3.1).

9.4.1. Dose Rationale

The abemaciclib dose of 200 mg administered every 12 hours corresponds to the maximum tolerated dose (MTD) determined in I3Y-MC-JPBA (hereafter designated Study JPBA). Study JPBA is the Phase 1 dose-escalation and tumor cohort-expansion study in advanced cancer patients that included a cohort expansion in NSCLC patients. Selection of 200 mg every 12 hours for assessment during the Phase 3 Study JPBK is based on safety, clinical activity, and PK and PD data from patients with NSCLC enrolled in the ongoing Study JPBA.

The safety profile of abemaciclib is acceptable, with manageable and monitorable toxicities. The most common treatment-emergent adverse events (TEAEs) possibly related to study drug for patients in Study JPBA included diarrhea, nausea, fatigue, neutropenia, vomiting, leukopenia, thrombocytopenia, anemia, decreased appetite, and blood creatinine increased. For the patients enrolled in the Study JPBA NSCLC expansion cohort, the safety profile was similar to that for all patients in the study.

Preliminary analysis of the PK data obtained in Study JPBA for abemaciclib from a total of 124 patients dosed repeatedly with abemaciclib at 150 and 200 mg every 12 hours suggests that the dose of 200 mg administered every 12 hours yields slightly higher and more consistent steady-state plasma concentration levels for abemaciclib. In particular, the mean minimum steady-state concentration for abemaciclib is more consistently maintained at a value of approximately 200 ng/mL, which represents a threshold value associated with more robust and sustained CDK4 and CDK6 inhibition and cell cycle arrest, as indicated by the decrease in phosphorylated retinoblastoma (pRb) and topoisomerase II alpha (topoIIα) expression measured in skin biopsies. Furthermore, these findings are in agreement with PK/PD analyses previously performed on data obtained from mouse xenograft tumor models.

Importantly for patients who may require a dose reduction, there was no apparent difference in the magnitude of the decrease in pRb and topoIIα expression between the 150-mg and 200-mg dose groups. In addition, given the variability in abemaciclib pharmacokinetics, there is overlap in exposures across the dose range of 50 to 200 mg.

Collectively, these findings indicate that the MTD of 200 mg orally every 12 hours demonstrates an acceptable safety profile, evidence of target inhibition and cell cycle arrest in skin, and clinical activity against NSCLC. The dose of 200 mg administered every 12 hours is therefore recommended for further assessment in the Phase 3 Study JPBK.

9.4.2. Special Treatment Considerations

9.4.2.1. Immune Checkpoint Inhibitors

Immune therapies are potentially associated with delayed toxicity (see Section 5.4). Patients who have received prior immune checkpoint inhibitor or other immunotherapy should be monitored for potential signs of a delayed toxicity after discontinuation of immunotherapy. If a suspected delayed immune-mediated toxicity associated with prior immunotherapy occurs while participating in Study JPBK, additional treatment may be considered in addition to the dose adjustment recommendations listed in Section 9.4.2.2. Treatment of a suspected toxicity should

be according to the immune checkpoint inhibitor's label and may include immediate use of corticosteroids, an immune-suppressive therapy, and increased laboratory monitoring and physical assessments. Current recommendations for monitoring for delayed toxicity range between 90 days and 1 year after treatment discontinuation (Champiat et al. 2016).

9.4.2.2. Dose Adjustments and Delays

9.4.2.2.1. Abemaciclib

Table JPBK.9.2. Toxicity Dose Adjustments and Delays of Abemaciclib for Study JPBK

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity Section 9.4.2.2.1	Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Hematologic Toxicity Section 9.4.2.2.1	Recurrent Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic Toxicity Section 9.4.2.2.1	Grade 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic toxicity: Patient requires administration of blood cell growth factors Sections 9.4.2.2.1 and 9.6.1.7	Regardless of severity (Growth factors use according to ASCO Guidelines)	Dose **MUST** be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level unless already performed for incidence of toxicity that lead to the use of growth factor.
Nonhematologic Toxicity (except diarrhea) Section 9.4.2.2.1	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose **MAY** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Nonhematologic Toxicity Section 9.4.2.2.1	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea Section 9.4.2.2.1	Requires hospitalization or Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea Sections 9.4.2.2.1 and 9.6.1.2	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 24 hours to at least Grade 1	Dose **SHOULD** be suspended until toxicity resolves to at least Grade 1.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Diarrhea Sections 9.4.2.2.1 and 9.6.1.2	Diarrhea recurs despite maximal supportive measures after resuming same dose level after initial Grade 2 diarrhea	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.

Abbreviation: ASCO = American Society of Clinical Oncology.

Before the start of each cycle, hematologic toxicity possibly related to abemaciclib must resolve to at least Grade 2. If a patient experiences Grade 4 hematologic toxicity possibly related to

abemaciclib, then dosing must be suspended (until the toxicity resolves to at least Grade 2) and the dose of abemaciclib must be reduced by 1 dose level as outlined in Table JPBK.9.3. If a patient experiences Grade 3 hematologic toxicity, then dosing must be suspended (until the toxicity resolves to at least Grade 2) and the dose of abemaciclib may be reduced by 1 dose level as outlined in Table JPBK.9.3 at the discretion of the investigator. If the patient experiences a recurrent episode of Grade 3 hematologic toxicity, then dosing must be suspended (until the toxicity resolves to at least Grade 2) and the dose of blinded study must be reduced by 1 dose level.

If a patient requires administration of blood cell growth factors, the dose of abemaciclib must be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2, then must be reduced by 1 dose level, if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred.

Before the start of each cycle, nonhematologic toxicity (except alopecia and fatigue) possibly related to abemaciclib must resolve to either baseline or at least Grade 1. Refer to Section 9.6.1.2 for guidance and supportive measures of diarrhea toxicity possibly related to abemaciclib. If a patient experiences ≥Grade 3 nonhematologic toxicity (except diarrhea: refer to Section 9.6.1.2) possibly related to abemaciclib, then dosing must be suspended (until the toxicity resolves to either baseline or Grade 1) and the dose of abemaciclib must be reduced by 1 dose level as outlined in Table JPBK.9.3.

If a patient experiences persistent or recurrent Grade 2 nonhematologic toxicity (except diarrhea, refer to Section 9.6.1.2) possibly related to abemaciclib that does not resolve with maximal supportive measures within 7 days to either baseline or Grade 1, then dosing may be suspended (until the toxicity resolves to either baseline or Grade 1) and the dose of abemaciclib may be reduced by 1 dose level as outlined in Table JPBK.9.3.

The start of a cycle may be delayed to allow sufficient time for recovery from toxicity possibly related to study drug. Patients not recovering from such toxicity within 14 days beyond the last day of the prior cycle will be considered for discontinuation from the study. In rare circumstances, a delay >14 days may be permitted before discontinuing the patient from treatment as long as the patient demonstrates clinical benefit without objective progression and is recovering from the toxicity. Such circumstances should be discussed and documented with the Lilly CRP.

If a patient receiving the 100-mg dose of abemaciclib requires a further dose reduction, the patient should be discontinued from study treatment. If a patient who, in the judgment of the investigator, is receiving clinical benefit from study therapy requires further dose reduction than is outlined in Table JPBK.9.3, then the investigator must discuss with the Lilly CRP prior to any further dose reduction.

Dose omissions are allowed within a cycle. If a patient requires omission of more than 25% of doses during a cycle for tolerability, then treatment may continue if the investigator determines the patient is receiving clinical benefit. If the patient does well after a dose reduction and is

receiving clinical benefit, the investigator may contact the Lilly CRP to discuss possible dose re-escalation. After re-escalation, subsequent dose adjustments should be based on the dose of abemaciclib that the patient is currently receiving.

Table JPBK.9.3. Dose Adjustments of Abemaciclib for Study I3Y-MC-JPBK

Dose Adjustment	Oral Dose	Frequency
0	200 mg	Every 12 hours
1	150 mg	Every 12 hours
2	100 mg	Every 12 hours

A patient experiencing diarrhea requiring hospitalization (irrespective of grade that is, requiring intravenous [IV] rehydration) or severe diarrhea (Grade 3 or 4; see Attachment 9) must have study treatment suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of abemaciclib must be reduced by 1 dose level as outlined in Table JPBK.9.3. If a patient experiences persistent or recurrent Grade 2 diarrhea that does not resolve with maximal supportive measures (refer to Section 9.6.1.2) within 24 hours to at least Grade 1, then study treatment should be suspended (until the toxicity resolves to at least Grade 1) and the dose of abemaciclib may be reduced by 1 dose level as outlined in Table JPBK.9.3. If the same dose level was resumed and diarrhea recurs despite maximal supportive measures, the dose of abemaciclib must be reduced by 1 dose level as outlined in Table JPBK.9.3.

9.4.2.2.2. Erlotinib

Patients should be treated following the recommendations, warnings, and precautions given for erlotinib in the SmPC of erlotinib. Patients receiving erlotinib can have the erlotinib dose reduced if the toxicity is specifically attributable to erlotinib.

The daily dose of erlotinib will be decreased in 50-mg decrements to a minimum dose of 50 mg daily (Table JPBK.9.4). Re-escalation of erlotinib dosing is allowed at the investigator's discretion, except after Grade 3 diarrhea when re-escalation is not allowed. Dose reductions must be documented within the current cycle so that treatment compliance can be determined.

In addition to the common erlotinib toxicities in Table JPBK.9.5, if a patient experiences other Grade 3 or 4 events that are considered at least possibly related to erlotinib, erlotinib administration may be omitted until the event resolves. Patients not recovering from such toxicity within 14 days beyond the last day of the prior cycle will be considered for discontinuation from the study. In rare circumstances, a delay >14 days may be permitted before discontinuing the patient from treatment as long as the patient demonstrates clinical benefit without objective progression and is recovering from the toxicity. Such circumstances should be discussed and documented with the Lilly CRP.

- If the event resolves to ≤ Grade 1 or baseline, the patient may restart erlotinib treatment at a reduced dose (Table JPBK.9.4).

- If the event has not resolved to ≤ Grade 1 or baseline within 7 days, or another AE occurs during therapy at the reduced dose, a second dose reduction is permitted at the investigator's discretion.

If the patient does not tolerate at least the 50-mg daily erlotinib dose, erlotinib must be discontinued.

Table JPBK.9.4. Erlotinib Dose Reduction Schedule

Dose Adjustment	Oral Dose	Frequency
0	150 mg/day	Daily
1	100 mg/day	Daily
2	50 mg/day	Daily

Table JPBK.9.5 shows the dose modification criteria and guidelines for management of common erlotinib toxicities. The investigator may use judgment on management of Grade 1 toxicities if not specified below.

Table JPBK.9.5. Erlotinib Dose Modification Table

Event and Grade[a]	Erlotinib Dose Modifications	Guidelines for Management
Pulmonary Events		
All grades (acute onset of new or progressive pulmonary symptoms such as dyspnea, cough, or fever)	Interrupt, pending the diagnostic evaluation; if interstitial lung disease is diagnosed, discontinue study treatment and institute appropriate treatment	
Diarrhea		
Grade 1	None	Consider loperamide: 4 mg at first onset, followed by 2 mg every 2 to 4 hours until diarrhea-free for 12 hours
Grade 2	Reduce if diarrhea persists over 48 to 72 hours despite optimal medical management	Manage as for Grade 1
Grade 3 or any grade unresponsive to loperamide, or diarrhea that causes dehydration	Interrupt until resolution to Grade ≤1 and restart at next reduced dose; do not re-escalate	Manage as for Grade 1
Grade 4	Discontinue erlotinib treatment	Manage as for Grade 1
Rash		
Tolerable rash (Grade 2 or 3)	None	Any of the following: minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course)
Intolerable rash	Consider interruption or dose reduction if unresponsive to symptomatic management.	Manage as described for Grade 2 or 3
Grade 4	Discontinue erlotinib treatment	Manage as described for Grade 2 or 3

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.
[a] CTCAE (Version 4.03; NCI 2009).

9.5. Blinding

This is a randomized, open-label study. Randomization will occur using an interactive web response 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. Scrambled treatment assignments will be used in the reporting database for Lilly trial-level safety review until the final database lock. 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 the Statistical Analysis Center (SAC), which is also external to Lilly, will carry out analyses for the DMC. 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/PD analysis plan, and documentation concerning their access to the data will be retained.

9.6. Concomitant Therapy

Appropriate documentation of all forms of premedications, supportive care, concomitant medications, and supplements must be captured at each visit in the CRF. Concomitant medications and supportive care therapies must also be documented at the time of discontinuation and at the 30-day short-term follow-up visit.

The results from an in vitro human recombinant cytochrome P450 (CYP) phenotyping study indicate that oxidative metabolism of abemaciclib is primarily catalyzed by CYP3A4. However, the extent of oxidative metabolism responsible for the systemic clearance of abemaciclib in humans is presently unknown. Based on these in vitro findings, grapefruit juice as well as inducers (for example, phenytoin or carbamazepine) and strong inhibitors of CYP3A4 should be substituted or avoided if possible (Attachment 8). In addition, in vitro studies in cultured human hepatocytes indicate that abemaciclib and its major metabolites LSN2839567 and LSN3106726 down regulate mRNA of 1 or more CYPs, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP3A, at clinically relevant concentrations. The mechanism of down regulation and its clinical relevance are presently not understood. Therefore, care should be taken when coadministering substrate drugs of the above CYPs with narrow therapeutic margin.

Erlotinib is also metabolized predominantly by CYP3A4; therefore, grapefruit juice as well as inducers (for example, phenytoin or carbamazepine) and strong inhibitors of CYP3A4 should be substituted or avoided if possible (Attachment 8).

9.6.1. Best Supportive Care

Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment will be offered to all patients on this trial. Supportive care measures may include but are not limited to antidiarrheal agents, antiemetic agents, opiate and nonopiate analgesic agents, appetite stimulants, and granulocyte and erythroid growth factors. Details of interventions (for example, medications such as sedatives, antibiotics, analgesics, antihistamines, steroids, or erythroid-stimulating agents), procedures (for example, paracentesis or thoracentesis), or blood products (for example, blood cells, platelets, or fresh frozen plasma transfusions) should be recorded on the electronic case report forms (eCRFs). If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult the Lilly CRP. Use of any

supportive care therapy should be reported on the CRFs. Guidelines regarding the use of other specific supportive care agents are presented below.

Additional concurrent chemotherapy, radiation therapy (except as noted in Section 9.6.1.1), biologic response modifiers, or other investigational agents may not be administered to patients on this study.

9.6.1.1. Palliative Radiotherapy

Palliative radiotherapy, unless required due to progressive disease, is permitted during the study.

9.6.1.2. Supportive Management for Diarrhea

At enrollment, patients should receive instructions for diarrhea management. In the event of diarrhea (see Attachment 9), supportive measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the patient should initiate antidiarrheal therapy (for example, loperamide) and notify the investigator for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (for example, 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- If diarrhea does not resolve with antidiarrheal therapy within 24 hours to at least Grade 1, dosing should be suspended until diarrhea is resolved to at least Grade 1.
- When study drug recommences, dosing should be adjusted as outlined for abemaciclib (Section 9.4.2.2.1 and Table JPBK.9.3) or erlotinib (Section 9.4.2.2.2 and Table JPBK.9.4 and Table JPBK.9.5).

In severe cases of diarrhea, the measuring of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered.

If diarrhea is severe (requiring IV rehydration) and/or associated with fever or severe (Grade 3 or 4) neutropenia, broad-spectrum antibiotics such as fluoroquinolones must be prescribed.

Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be carefully monitored and given fluid (IV hydration) and electrolyte replacement.
Sites may also follow local practice for management of diarrhea.

9.6.1.3. Antiemetic Agents

The use of antiemetic agents is permitted during this study and at the discretion of the investigator. However, it is recommended to follow the guidelines of the Multinational Association of Supportive Care in Cancer and American Society of Clinical Oncology (ASCO); dexamethasone may be sufficient, but 5-HT3 antagonists and NK1 antagonists may be used (Kris et al. 2006; Gralla et al. 2010).

9.6.1.4. Analgesic Agents

The use of analgesic agents is permitted at the discretion of the investigator.

9.6.1.5. Appetite Stimulants

The use of appetite stimulants is permitted at the discretion of the investigator. Acceptable agents include, but are not limited to, megestrol acetate and dronabinol.

9.6.1.6. Granulocyte-Colony Stimulating Factors (G-CSF)

The use of granulocyte-colony stimulating factor (G-CSF) is permitted during investigational therapy at the discretion of the investigator. G-CSF or similar agents are strongly recommended following Grade 3 or 4 neutropenia of duration >5 days or following any incidence of febrile neutropenia (ANC $<1.0 \times 10^3/\mu L$ [$1.0 \times 10^9/L$] with a single temperature ≥38.3°C or a sustained temperature of ≥38.0°C for >1 hour).

9.6.1.7. Growth Factors

Growth factors should not be administered to a patient to satisfy study inclusion criteria.

Growth factors may be administered in accordance with ASCO guidelines (Smith et al. 2015). Dosing of abemaciclib must be suspended if the administration of growth factors is required and must not be recommenced within 48 hours of the last dose of growth factors having been administered. Following the administration of growth factors, the dose of abemaciclib must be reduced by 1 dose level on recommencement, if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred.

9.6.1.8. Bone-Modifying Agents

The use of approved bone-modifying agents (for example, bisphosphonates or receptor activator of nuclear factor kappa B ligand [RANKL] targeting agents) is allowed on study if a patient had initiated treatment with such agents at least 14 days prior to randomization. Patients who started the study while receiving bisphosphonates or RANKL targeted agents are not allowed to switch treatments (for example, replace bisphosphonates with denosumab) during study treatment. Patients are not permitted to begin treatment with bisphosphonates or RANKL-targeted agents while receiving study treatment.

9.6.1.9. Therapy for Febrile Neutropenia

Patients experiencing febrile neutropenia, especially with diarrhea or dyspnea, should be managed in a hospital setting according to standard procedures, with the urgent initiation of intravenous antibiotic therapy. Events that require a patient to be hospitalized are considered SAEs (see Section 10.3.1.1).

9.7. Treatment Compliance

Patient compliance with study drug will be assessed at each visit. Compliance will be assessed by counting returned tablets/capsules. Patients may use a diary to record study drug intake.

Patients who are significantly noncompliant will be discontinued from the study. Unless required secondary to toxicity, a patient will be considered significantly noncompliant if he or she misses 8 or more consecutive days of study drug (full doses), or more than 25% of the cumulative days of study drug (full doses) during a cycle. Persistent noncompliance may be a reason for discontinuation from study therapy. Similarly, a patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or

repeatedly taken more than the prescribed amount of medication. Dose suspensions or delays related to toxicity are permitted and will not result in a patient being considered as noncompliant.

10. Efficacy, Health Outcome/Quality of Life Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Written informed consent must be obtained prior to any study-specific pretreatment evaluations.

Study procedures related to efficacy, safety, health outcome/quality of life measures, sample collection, and testing assessments and their timing are described in the sections below and shown in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

10.1.1. Efficacy Assessments at Baseline and during Study Treatment

Imaging studies are performed locally and transmitted for central review.

Baseline tumor measurements will be performed on each patient. Computed tomography (CT), including spiral CT, scans, and magnetic resonance imaging (MRI) are the preferred methods of measurement. Tumor assessments should include the chest and abdominal region. Imaging studies performed ≤30 days from date of first dose are permitted as baseline assessment and do not need repeated.

The CT portion of a positron emission tomography (PET)-CT scan may be used as a method of response assessment if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (with intravenous and oral contrast). A PET scan alone or as part of a PET-CT may be performed for additional analyses but cannot be used to assess response according to RECIST.

The method of assessment used at baseline must be used consistently for tumor assessment and must be repeated every other cycle, beginning with Cycle 3 Day 1 until progressive disease is determined. Radiological assessments may be performed up to ±7 of the scheduled Day 1 visit. If progressive disease is determined per RECIST Version 1.1 after the start of a new cycle, the patient should be notified and treatment discontinued. If a cycle is delayed, tumor assessment should be concurrent with Day 1 of the new cycle. If the assessment was completed before Day 1 of the next cycle and the patient has a delay in starting the next cycle, the radiological scan does not need to be repeated again when Day 1 of the next cycle is resumed.

For patients continuing treatment after study completion (that is, during the extension phase), efficacy assessments (frequency and type of assessments) will be at the discretion of the investigator, based on the standard of care.

10.1.2. Efficacy Assessments during the Study Period Postdiscontinuation Follow-Up

Postdiscontinuation follow-up during the study period will be conducted as described in the Study Schedule (Attachment 1).

For those patients who discontinue study treatment without objectively measured progressive disease (PD), the investigative sites will continue to monitor patients and periodically evaluate tumor response approximately every 8 weeks by the same method used at baseline until the patient has objective disease progression, or study completion. After the patient has objective disease progression, radiologic tests are no longer required and the patient will be followed up approximately every 60 days (±14 days) until the patient's death or overall study completion.

Response (CR or PR) should be confirmed before the initiation of additional anticancer therapy. However, initiation of new therapy should not be delayed solely to confirm response.

Efficacy assessments (frequency and type of assessments) for patients still on treatment during the extension phase will be at the discretion of the investigator, based on the standard of care.

10.1.3. Primary Efficacy Measure

This primary efficacy measure of the study is OS.

Overall survival duration is measured from the date of randomization 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 (contacts considered in the determination of last contact date include adverse event date, lesion assessment date, visit date, and last known alive date).

10.1.4. Secondary Efficacy Measures

Tumor response is defined by RECIST v1.1 (Eisenhauer et al. 2009) provided in Attachment 5. To derive the overall response rate, a responder is defined as any patient who exhibits a confirmed CR or PR. Best response is determined from the sequence of responses assessed.

A second assessment must be performed ≥28 days after the first evidence of response. The next scheduled scan at 56 days (8 weeks) would qualify for response confirmation. Two objective status determinations of CR before progression are required for a best response of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a best response of PR. Best response of SD is defined as disease that does not meet the criteria for CR, PR, or PD and has been evaluated at least 1 time, at least 6 weeks after the start of study treatment.

Best response will be derived to encompass all tumor assessments 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.

Progression-free survival will be defined as the time from randomization until the first evidence of objective progression as defined by RECIST v1.1 (Eisenhauer et al. 2009), or death from any cause, whichever is earlier. Patients who are not known to have either progressed or died at the time of analysis will be censored at the day of their last radiographic tumor assessment, if available, or the date of randomization if no postbaseline radiographic assessment is available. The detailed censoring rules are described in Table JPBK.12.2.

The PFS analysis will be based on the local investigator's tumor assessments.

The date of first documented objective disease progression must be recorded on the CRF even if it occurs after the patient has started a new therapy. Lilly or its designee will collect and store all tumor measurement images on all enrolled patients throughout the study. A central review of imaging scans may be performed by Lilly or its designee.

10.2. Health Outcome/Quality of Life Measures

10.2.1. Patient-Reported Outcomes

Patient-reported outcomes will be measured using standardized instruments, MDASI-LC and EQ-5D 5L.

Patient-reported questionnaires should be completed by patients when a language translation is available in which the patient is fluent or literate.

At each time point identified in the Schedule of Events (Attachment 1), a paper copy of the questionnaire should be administered to the patient prior to extensive interaction with site staff and study drug administration.

10.2.1.1. MDASI-LC

The MDASI-LC (Mendoza et al. 2011) is a 22-item instrument that includes 13 core symptoms, 6 core interference items, and 3 lung-specific symptoms (coughing, constipation, and sore throat). An additional MDASI page will include 11 exploratory items that are not a standard part of the MDASI-LC instrument. Advanced lung cancer is a leading source of brain metastases, and symptoms related to brain metastases are described by 8 of these exploratory items (weakness on 1 side of body, difficulty understanding, difficulty speaking, seizures, difficulty concentrating, vision, change in appearance, and irritability). These 8 exploratory items for this study are also included as brain-specific items in the MDASI-Brain Tumor instrument. The remaining 3 exploratory items address an additional brain symptom (headache) and expected treatment-related toxicities (diarrhea, rash, or skin change).

"Worst pain" is the first MDASI-LC item, and use of pain medication will be assessed in conjunction with the MDASI-LC assessment as described in Section 10.2.2.

Responses for the MDASI-LC items are captured through the use of 11-point numeric rating scales anchored at 0 (*not present* or *does not interfere*) and ranged through 10 (*as bad as you can imagine* or *completely interferes*). The MDASI-LC recall period is 24 hours, and typical completion time for this instrument is less than 5 minutes.

10.2.1.2. EQ-5D 5L

The EuroQol 5-Dimension 5 Level (EQ-5D 5L) is a self-reported standardized measure of health status, and will allow for comparison with other tumor types and disease states (Janssen et al. 2008).

Specifically, this questionnaire is included in this trial to evaluate health-state utilities associated with advanced lung cancer. These utility measures are an important input for economic evaluations concerning the value of treatment interventions.

The EQ-5D 5L is designed to be used in conjunction with other patient-reported measures. Patients will complete the 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), 5-level (no problem, slight, moderate, severe, or extreme problem) assessment according to the Study Schedule (Attachment 1). A visual analog scale "thermometer" measures current health state. EQ-5D 5L responses may be incorporated into cost utility analyses and will be summarized in the clinical study report (CSR).

Administration is preferably scheduled after the MDASI-LC, and before extensive contact with study personnel or clinicians, which could result in biased patient response. The recall period is "today." The EQ-5D 5L is designed for self-completion by respondents and expected completion time is 1 to 2 minutes.

10.2.2. Resource Utilization

Investigators will be asked to report the use of **all** concomitant medications (in particular, analgesics, bisphosphonates, and RANK-L targeted agents), blood product transfusions, radiation therapy, surgery, and hospitalization days.

Data on each individual prescription and over-the-counter analgesic medication will be recorded on the Concomitant Medication eCRF. The use of pain medications from the previous visit should be reviewed with the patient at each subsequent visit. Any changes to analgesic use based on this information should be recorded on the Concomitant Medication eCRF, and the term "any changes" includes new or stopped analgesics. Data on neurosurgical blocks will be recorded on the analgesic and/or surgery forms as appropriate. This information should be collected during the study and at the 30-day follow-up visit.

10.3. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

Investigators must document their review of each laboratory safety report.

The investigator is responsible for the appropriate medical care of patients during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1). Table JPBK.10.1 presents a summary of AE and SAE reporting guidelines. Table JPBK.10.1 also shows which database or system is used to store AE and SAE data.

Table JPBK.10.1. Adverse Event and Serious Adverse Event Reporting Guidelines

Period	Types of AEs/SAEs to be Reported	Collection Database	Lilly Safety System
Baseline (pretreatment)	Preexisting conditions	x	
	All AEs	x	
	SAEs related to protocol procedures	x	x
Study treatment period	All AEs	x	
	All SAEs	x	x
30-day short-term postdiscontinuation follow-up	All AEs	x	
	All SAEs	x	x
Long-term postdiscontinuation follow-up	All SAEs related to protocol procedures or study drug	x	x
Extension period	All AEs	x	
	All SAEs	x	x
Extension period follow-up	All AEs	x	
	All SAEs	x	x
After the patient is no longer participating in the study (that is, no longer receiving study therapy and no longer in follow-up)	All SAEs related to protocol procedures or study drug that the investigator becomes aware of		x

Abbreviations: AEs = adverse events; SAEs = serious adverse events.

10.3.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical event associated with the use of a drug in humans, whether or not it is considered related to that drug.

Lack of drug effect is not an AE in clinical trials, because the purpose of the clinical trial is to establish drug effect.

Any clinically significant findings from electrocardiograms (ECGs; for example, QTc prolongation), labs, vital sign measurements, other procedures, and so on that result in a diagnosis should be reported to Lilly or its designee. All non-clinically significant findings must be documented in the patient record as not clinically significant and therefore will not be documented in the eCRF.

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. All non-clinically significant findings must be documented in the patient record as not clinically significant and therefore will not be documented in the eCRF.

After the study ICF is signed, site personnel will record the occurrence and nature of any AEs and any change in the preexisting condition(s). All AEs related to protocol procedures are reported to Lilly or its designee.

In addition, all AEs occurring after the patient receives the first dose of study drug must be reported to Lilly or its designee via eCRF.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure or study drug via eCRF.

The investigator will decide whether he or she interprets the observed AEs as related to disease, to the study drug, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug or procedure, the following terminologies are defined:

- **Probably related**: a direct cause and effect relationship between the study treatment and the AE is likely
- **Possibly related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible
- **Does not know:** the investigator cannot determine
- **Not related**: without question, the AE is definitely not associated with the study treatment

The investigator should classify all "probably related," "possibly related," or "does not know" AEs and SAEs as related to study drug/study procedure.

Patients will be evaluated for AEs at each visit and will be instructed to call their physician to report any AEs between visits.

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching terminology within the NCI-CTCAE v 4.03 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event.

In addition to collecting the AE verbatim and the CTCAE severity grade, AE verbatim text will also be mapped by Lilly or its designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.3.1.1. Serious Adverse Events

An SAE is any adverse event from this study that results in one of the following outcomes:

- death
- a life-threatening experience (that is, immediate risk of dying)

- persistent or significant disability/incapacity
- initial or prolonged inpatient hospitalization
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse event collection begins after the patient has signed the study ICF and has received study drug. If a patient experiences an SAE after signing informed consent, but prior to receiving study drug, the event will not be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.

Study site personnel must alert Lilly or its designee of any **serious** adverse event (SAE) within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms.

This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Planned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs.

Serious adverse events due to disease progression, including death, should not be reported unless the investigator deems them to be possibly related to the study drug.

If an investigator becomes aware of an SAE occurring after the patient's participation in the trial has ended, and the investigator believes that the SAE is related to a protocol procedure or study drug, the investigator should report the SAE to the sponsor, and the SAE will be entered in the Lilly Safety System.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB.

10.3.1.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the Development Core Safety Information in the IB and that the investigator identifies as related to the abemaciclib or study procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

10.3.2. Other Safety Measures

10.3.2.1. Electrocardiograms

For each patient receiving abemaciclib, 12-lead digital ECGs will be collected according to the Study Schedule (Attachment 1) and Table JPBK.10.2 as single ECGs. For each patient receiving erlotinib, an ECG will be collected at baseline only. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Table JPBK.10.2. Schedule for Electrocardiogram Collection

Electrocardiogram	Cycle and Day	Timing
1	Baseline	≤14 Days
2	Cycle 1 Day 1	Predose[a]
3	Cycle 1 Day 1	4 to 6 hours postdose
4	Cycle 2 Day 1	4 to 6 hours postdose
5	Cycle 7 Day 1	4 to 6 hours postdose
6	Visit 801	30 days after study drug discontinuation

Abbreviations: C1D1 = Cycle 1 Day 1; ECG = electrocardiogram.

[a] If baseline ECG performed with 24 hours of C1D1 predose ECG, the C1D1 predose ECG may be omitted.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high-quality records.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria and for immediate patient management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/QTc interval from baseline, or other clinically significant quantitative or qualitative change from baseline, is present, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, or syncope) and to determine if the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation.

10.3.3. Safety Monitoring

The Lilly CRP will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP will, as is appropriate, consult with the functionally independent GPS therapeutic area physician or clinical scientist, and review:

- trends in safety data
- laboratory analytes
- adverse events
- If a patient experiences elevated ALT >5× ULN and elevated total bilirubin >2× ULN, clinical and laboratory monitoring should be initiated by the investigator.
- Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests (see Attachment 3).

10.3.4. Complaint Handling

Lilly collects product complaints on study drugs used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

If supplied by Lilly, complaints related to unblinded comparator drugs are reported to Lilly. If sourced locally, complaints related to unblinded comparator drugs are reported directly to the manufacturers of those drugs in accordance with the package insert.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.4. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study. For patients enrolling under Amendment (d), hematological and chemistry sample collections will occur on Day 1 and Day 15 during Cycles 1 and 2. Beginning with Cycle 3, hematological and chemistry sample collections will be only on Day 1 of each cycle.

Attachment 2 lists the specific tests that will be performed for this study and whether these will be performed at a central or local laboratory. Enrollment and treatment decisions may be based upon results of tests performed locally. If local laboratory tests are used for this purpose, then a duplicate specimen must be submitted to the central laboratory. Discrepancies between the local

and central laboratory that may have an impact on eligibility or treatment decisions will not be considered protocol violations.

Attachment 6 provides a summary of the estimated maximum number and volume of invasive samples, for all sampling, during the study.

10.4.1. Samples for Study Qualification and Health Monitoring

Blood samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health. Blood samples for chemistry and hematology may be drawn +/-3 days prior to the day of the scheduled visit. If the baseline chemistry and hematology samples were drawn within 3 days of Cycle 1 Day 1, the chemistry and hematology samples do not need to be repeated on Cycle 1 Day 1. During Cycles 1 and 2, chemistry and hematology samples will be drawn on Days 1 and 15 (+/- 3 days). Beginning with Cycle 3, chemistry and hematology samples will be drawn on Day 1 (+/- 3 days) of each cycle.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.4.2. Samples for KRAS Mutation Determination

To meet study eligibility criteria, a *KRAS* mutation determination is mandatory for study participation. *KRAS* mutation results will be obtained by submitting tissue to the Study JPBK central laboratory or, for no more than 10% of randomized patients, a prior local laboratory *KRAS* mutation result that is reviewed and approved by the sponsor.

10.4.2.1. Central Laboratory Result

Patients must have available FFPE tumor sample to submit tissue to the Study JPBK central laboratory for *KRAS* testing. While the tissue can be from either initial diagnosis or later (for example, at relapse), the most recent sample is preferred. The sample can be either 8 serially cut unstained sections (preferred) or a tissue block. Sample collection methods may include surgical resection, core needle biopsy, or fine needle aspirate (FNA). Fine needle aspirate, aspiration of solid tumor cells, is acceptable with subsequent processing to FFPE as a cell block and confirmation of the presence of malignant cells; however, other types of cytology specimens (e.g., pleural effusion) are not acceptable. Due diligence should be used to make sure that tumor specimens (not a normal adjacent or a tumor margin sample) are provided.

KRAS mutation determination for study eligibility is made at the central laboratory using the QIAGEN® *therascreen*® *KRAS* RGQ PCR Kit NSCLC. Part of each patient's tumor tissue may be retained for repeat testing during the development of that investigational assay. The same sample used for *KRAS* mutant determination may also be used for evaluation of codons 12 and 13 via Sanger sequencing, and potentially an additional method, to test concordance with the investigational assay.

Prior local testing of *KRAS* status to informally assess eligibility for Study JPBK is highly discouraged. Submission of the investigational assay for potential regulatory approval requires a dataset containing evaluation of both *KRAS* mutant positive and negative samples. If local testing is completed per a site's standard of care, results should be disregarded when evaluating a patient's eligibility for the study.

Details for the handling and shipping of tumor biopsy samples will be provided in a separate document. Instructions and supplies required for the collection, processing, and shipment of the patients' samples will be provided by the sponsor.

The tumor tissue samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study unless otherwise determined by government or local law, at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drug. Tumor specimens submitted as a FFPE tissue block will be returned to the sites by end of study or upon request.

10.4.2.2. Local Laboratory Result

Local *KRAS* testing is not mandatory or considered a protocol required procedure. To address the challenges identified with tissue for *KRAS* testing by the central laboratory, a local *KRAS* mutation result from tumor tissue may be used for patient eligibility for no more than 10% of the randomized patients. These patients, who have a positive local *KRAS* result for one of the 7 specific mutations listed below, will be allowed to enter into the study with this result in the absence of a central laboratory *KRAS* positive result. Instructions will be provided by the sponsor to request approval to use a local *KRAS* mutation result for patient eligibility. The sponsor will review each request and provide approval to the site prior to the patient being randomized. Once approved and randomized to study using local laboratory *KRAS* result, no additional tumor tissue should be submitted to the central laboratory for *KRAS* testing.

In order for a patient with a local *KRAS* mutation result to be considered eligible, the following circumstances must be present:

(a) The local *KRAS* mutation result is one of the following mutations:

- G12A (35G>C) (GLY12ALA)
- G12S (34G>A) (GLY12SER)
- G12D (35G>A) (GLY12ASP)
- G12R (34G>C) (GLY12ARG)
- G12C (34G>T (GLY12CYS)
- G12V (35G>T) (GLY12VAL)
- G13D (38G>A) (GLY13ASP)

(b) The reason for the request for approval to use local *KRAS* mutation test result for inclusion is due to one or more of the following:

- No tissue available for submission to Study JPBK central laboratory that has a documented confirmation by the investigator

- Indeterminate designation obtained from initial sample submitted to Study JPBK central laboratory
- An inadequate sample designation (for example, Insufficient Tissue Received at Laboratory, No Neoplastic Cells in Tissue) obtained from initial sample submitted to Study JPBK central laboratory

Once enrollment of no more than 10% of randomized patients has been reached, the sponsor will communicate that enrollment by local *KRAS* mutation result has been suspended. No additional patients will be randomized using local *KRAS* mutation results.

10.4.3. Samples for Other Biomarkers

10.4.3.1. Archived Tumor Tissue

An archived tumor sample will be collected on Cycle 1 Day 1 in addition to the sample used to determine *KRAS* mutation status. An FFPE tumor tissue sample OR 20 unstained slides are requested for further biomarker research. The tissue sample will be tested for biomarkers relevant to abemaciclib and the disease state and to correlate these markers to clinical outcome and to abemaciclib. Analyses may include, but are not limited to, nucleic acid and protein profiles to better understand the disease process and to develop predictive biomarkers.

Any whole block submitted will be returned to the site. Any partial blocks or slides will either be returned or discarded within 15 years after last patient visit for the trial unless otherwise determined by government or local law.

Patients enrolled based upon a local *KRAS* mutation result are exempt from submitting additional archived tumor tissue for biomarker testing.

10.4.3.2. Whole Blood Samples for Pharmacogenetic Evaluations

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated.

Where local regulations and ERBs allow, a whole blood sample will be collected for pharmacogenetic analysis (refer to Attachment 1). Samples may be genotyped and analyses may be performed to evaluate a genetic association with response to abemaciclib. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

The samples will be coded with the patient number and stored for up to a maximum 15 years unless otherwise determined by government or local law after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be

linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drug.

Samples will be destroyed according to a process consistent with local regulation.

10.4.3.3. Plasma Samples for Exploratory Biomarker Evaluations

Plasma samples will be collected and analysis may be performed on circulating biomarkers that may play a role in the abemaciclib mechanism of action (refer to Attachment 1). A plasma sample will be collected at baseline prior to randomization. Patients who have entered the study based on a local *KRAS* result may omit this baseline sample; however, it is not a deviation if submitted. This sample will be collected separately at the time of FFPE tumor tissue request. For patients who submitted FFPE tumor tissue in pre-screening, the baseline plasma sample may be drawn at the time of other laboratory blood samples. Additional plasma samples will be collected from all randomized patients on Cycle 1 Day 1 and Cycle 2 Day 1. The evaluation of these samples may involve analysis of DNA, RNA, *KRAS* mutations, and proteins (including any of these components derived from exosomes) to investigate their association with observed clinical outcomes to study drug, and may assist in future development of a liquid biopsy test for *KRAS*. The samples will be coded with the patient number and stored for up to a maximum 15 years unless otherwise determined by government or local law. Details for collecting, processing, and storing the samples are similar to those provided in Section 10.4.3.2.

10.4.4. Samples for Drug Concentration Measurements Pharmacokinetics

At the visits and times specified in the Pharmacokinetic Sampling Schedule (Attachment 7), 5 venous blood samples of approximately 2 mL each will be collected from patients receiving abemaciclib to determine the plasma concentrations of abemaciclib and its metabolites LSN2839567, LSN3106726, and LSN3106729. Patients receiving erlotinib will not have samples collected for PK analysis.

Separate blood samples are not required for the parent and its metabolites. Instructions for the collection and handling of blood samples will be provided by the sponsor. It is preferred that the blood samples be obtained from a peripheral location. Blood samples will be allowed from central access devices but a sample drawn from a central catheter of any type for PK must take precautions to prevent obtaining a dilute sample. If multiple samples are obtained centrally, the PK sample should be the last specimen drawn to reduce the potential for a diluted or improperly drawn sample. The actual date and time (24-hour clock time) of each sampling will be recorded. A maximum of 5 additional samples may be drawn at other time points during the study if warranted and agreed upon between both the investigator and Lilly.

These samples will be analyzed at a laboratory designated by the sponsor. Plasma concentrations of abemaciclib plus its metabolites LSN2839567, LSN3106726 and LSN3106729, will be assayed using a validated liquid chromatography/tandem mass spectrometry method. Bioanalytical samples collected to measure study drug concentration and metabolism and/or protein binding, will be retained for a maximum of 1 year following last patient visit for the study. The PK samples will be stored at a facility designated by the sponsor.

10.5. Appropriateness of Measurements

Efficacy measurements by radiographic imaging are standard, widely used, generally recognized as reliable, accurate, and able to discriminate between effective and ineffective agents.

Safety measurements by laboratory monitoring are standard, widely used, generally recognized as reliable, accurate, and able to discriminate between agents with acceptable and unacceptable safety profiles.

11. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide Lilly, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

An electronic data capture system will be used in this trial. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Case report form data will be encoded and stored in a clinical trial database.

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported outcome measures (for example, a rating scale), a daily dosing schedule, or an event diary.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

12. Sample Size and Statistical Methods

12.1. 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 other prior therapy or are not eligible for further chemotherapy.

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

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 .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.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

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

Efficacy analyses will be based on the intention-to-treat (ITT) analysis set. This population is defined as all patients randomized to study treatment. Patients will be grouped according to randomized treatment.

Safety analyses will be based on the Safety Population, defined as all enrolled patients receiving at least 1 dose of any study drug. Patients will be grouped according to treatment received in Cycle 1.

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.

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated. All confidence intervals (CIs) will be given at a 2-sided 95% level, unless otherwise stated.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol.

Before unblinding of the aggregate database, minor modifications or clarifications to the data analysis methods may be described and justified in the SAP. The assumptions for each statistical method will be evaluated. If there is violation of assumptions, alternative statistical methods

may be used. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the CSR.

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

12.2.2. 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 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.

12.2.3. 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.

12.2.4. Concomitant Therapy

Concomitant medication will be summarized by treatment arm in a frequency table listing the terms recorded on the eCRF.

12.2.4.1. Postdiscontinuation Therapy

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

12.2.5. Treatment Compliance

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

Treatment compliance 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.

12.2.6. Primary Outcome and Methodology

The primary endpoint of this study is OS.Overall survival duration is measured from the date of randomization 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 (contacts considered in the determination of last contact date include AE date, lesion assessment date, visit date, and last known alive date).

The comparison of each 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 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.

12.2.7. Secondary Outcome and Methodology

The secondary objectives for this study are stated in Section 6.2.

Progression-free survival time is measured from the date of randomization to the date of investigator-determined objective progression as defined by RECIST v1.1, or death from any cause. 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 (that is, postbaseline) radiographic assessment is available. The detailed censoring rules for PFS are described in Table JPBK.12.1.

Table JPBK.12.1. 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: Progression-free survival and associated outcome is determined by the earliest of the dates above, if more than 1 situation applies.

The statistical comparison of PFS between treatment groups will be conducted using the same methods for OS as described in Section 12.2.6.

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

Details of the statistical methods for analyzing efficacy outcomes are described in the SAP.

12.2.8. Sensitivity Analysis

Sensitivity analyses may be undertaken for the efficacy endpoints in order to evaluate the robustness of the analysis. The following sensitivity analyses may 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, radiotherapy, or surgical intervention, 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.

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.

Progression-Free Survival Sensitivity Analysis 3 (back-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 back-dated to the prior scheduled disease assessment.

Additional sensitivity analyses may be carried out for patients who are *KRAS* positive based only on central test result. Details are described in the SAP.

12.2.9. Pharmacokinetic Analyses

Pharmacokinetics analyses will be conducted on all patients who have received at least 1 dose of abemaciclib and have had samples collected (see PK sampling schedule in Attachment 7).

Mean population PK parameters for abemaciclib in plasma (clearance, exposure, volume of distribution, and half-lives) and inter-individual PK variability will be computed using nonlinear mixed effect modeling (NONMEM). The current PK model for abemaciclib, which has been developed using plasma concentration data available from the Phase 1 Study JPBA, will be updated using the plasma data collected in this study. Covariate effects (such as age, weight, sex, creatinine clearance, and plasma protein levels) on the PK parameters of abemaciclib in plasma will also be investigated.

The mean population PK properties of abemaciclib metabolites LSN2839567, LSN3106726, and LSN3106729 in plasma may also be analyzed by means of NONMEM.

Finally, pharmacodynamic data (such as neutrophil, lymphocytes, or platelets counts in blood) collected in this study may also be analyzed by means of NONMEM and connected to the population PK model in a PK/pharmacodynamic model.

The version of software used for the analysis will be documented and will meet the Lilly requirements of software validation.

12.2.10. Biomarker Analyses

12.2.10.1. *KRAS* Mutation Assessment

Concordance (agreement) analysis will be performed on samples with valid *KRAS* status (mutation positive and mutation negative) using both the investigational assay and the reference method (Sanger sequencing). Measures of agreement between the investigational *KRAS* assay and the reference method, including positive percent agreement, negative percent agreement, and overall percent agreement, and their corresponding exact 2-sided 95% CIs, will be estimated for the overall mutation status; that is, mutation detected or not detected for the 7 mutations of *KRAS* gene. A secondary agreement analysis between the investigational *KRAS* assay and the reference method will be performed for each of the tumor tissue sample types (surgical resection, fine needle aspirate and core needle biopsy). The data will also be summarized for each of the 7 *KRAS* mutations separately.

12.2.10.2. Other Biomarkers

For other biomarkers relevant to abemaciclib and the disease state, the distributions of biomarkers will be summarized for the patient population for which samples are available.

Associations between clinical endpoints and biomarkers will be evaluated using data from patients who have an evaluable sample for each biomarker of interest, and such evaluation will be done on an individual marker basis.

12.2.11. Health Outcome/Quality of Life Analyses

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

- MDASI-LC (includes additional page with 11 items that will be scored separately)
- EQ-5D 5L (EuroQol 5-Dimension 5 Level)

The reason and number of missing and incomplete questionnaires/assessments by visit will be summarized for each instrument and study arm.

12.2.11.1. MDASI-LC

The MDASI-LC population will include all patients who completed at least 1 baseline followed by at least 1 MDASI-LC assessment after 1 cycle of study drug (Cycle 2 Day 1 or later).

The MDASI-LC will be summarized for each assessment period and scored as described (Mendoza et al. 2011). The instrument will be reported as core symptoms (Items 1-13), interference items (Items 14-19) and lung symptoms (Items 14-16), and the 11 additional items will be reported as brain tumor symptoms (Items 23 through 30) and additional 3 items (31-33), as well as each individual item.

For each patient with data from baseline and at least 1 other visit, the maximum change from baseline score will be calculated and summarized for MDASI-LC composite scores, and "worst pain".

Further analysis details will be described in the SAP.

12.2.11.2. Health State Utility

The EQ-5D 5L population will include all patients who completed at least 1 baseline followed by at least 1 EQ-5D 5L assessment after 1 dose of study drug.

The EQ-5D 5L data will be scored based on EuroQol recommendations. 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. The visual analogue score (VAS) is scored from 0 (worst imaginable health state) through 100 (best imaginable health state) to represent the patient's self-report for each day. EQ-5D 5L responses for each item will be summarized by frequency and corresponding percentages. Descriptive statistics for the index and VAS will be calculated as described in the SAP.

12.2.11.3. Use of Pain Medications

Pain medication will be classified into 1 of 6 categories by the sponsor, using an analgesic ladder approach with medication category based on a World Health Organization scale outlined in Table JPBK.12.2. A therapy category for each cycle will be assigned according to the maximum category of therapy administered based on analgesic data from the Concomitant Form for that cycle. Category of pain medication for each cycle will be determined based on the data collected

on analgesic use by Anatomical Therapeutic Chemical code. Change in categories based on analgesic ladder compared to baseline will be described by arm.

Table JPBK.12.2. 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)

12.2.12. Safety Analyses

All safety summaries and analyses will be based upon the Safety Population as defined in Section 12.2.1.

Overall exposure to study drug, the numbers of patients completing each cycle, and the dose intensity will be summarized using descriptive statistics. The number of patients with dose reductions, dose delays, or dose omissions will also be summarized, as will the reasons for dose adjustments.

AEs will be reported using a unified CTCAE/MedDRA reporting process:

- The CTCAE v4.03 term reported by the investigator will be mapped to the MedDRA Preferred Term (PT) and System Organ Class (SOC) of the corresponding MedDRA Lower Level Term (LLT), unless the reported CTCAE term is 'Other – specify'.
- If the reported CTCAE term is 'Other – specify' the MedDRA LLT, PT, and SOC mapped from the verbatim AE term will be used.
- All listings and summaries will use the PT resulting from this process.

Preexisting conditions are defined as adverse events that begin prior to the first dose of study drug. A TEAE is defined as an event that first occurred or worsened in severity between the day of first dose and 30 days after treatment discontinuation (or up to any time if serious and related to study treatment). Comparisons of preexisting conditions to on-treatment events at the LLT level will be used in the treatment-emergent computation.

An overall summary of AEs will be provided for AEs deemed by the investigator to be possibly related to study drug, and repeated for events regardless of study drug causality. Incidence rates of these events will be compared between treatment arms using Chi square test.

The following summaries will be produced by PT within SOC: preexisting conditions, SAEs, TEAEs, drug-related TEAEs, and procedure-related TEAEs.

The following summaries will be produced by PT within SOC and maximum CTCAE grade: laboratory-based TEAEs, nonlaboratory-based TEAEs, drug-related laboratory-based TEAEs, and drug-related nonlaboratory-based TEAEs.

Reasons for death will be summarized separately for on-therapy and within 30 days of treatment discontinuation.

Hospitalizations and transfusions during the study treatment period or during the 30-day short-term follow-up period will be summarized by treatment group.

12.2.13. Subgroup Analyses

Subgroup analyses of OS will be performed for potential prognostic and predictive subgroup variables (for example, patients with or without prior immunotherapy).

12.2.14. Interim Analyses

12.2.14.1. Safety Interim Analyses

The 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.

12.2.14.2. Efficacy Interim Analyses

One interim efficacy analysis is planned based on the PFS endpoint. This interim analysis is for futility only and 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 interim efficacy analysis will be conducted after approximately 100 PFS events have occurred. This analysis will be based on the PFS endpoint and will be for futility only. The DMC will be instructed to recommend the study be stopped 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.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

There may be 2 ICF used in this study: pre-screening ICF and study ICF.

The pre-screening ICF will provide relevant information and documents that the patient is satisfied with his or her understanding of the genetic testing of the tumor sample for *KRAS* mutation status. No procedures will be conducted or treatment provided to patients after signing this pre-screening ICF. Pre-screening is optional; the determination may also be made during screening under the study ICF.

The study ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study. If determination of *KRAS* mutation status by the Study JPBK central laboratory was not completed during a pre-screening period, then the determination will be made during screening under the study ICF. Prior to submitting a request for approval for study entry using a local *KRAS* test result, the study ICF must be signed.

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drug.

As used in this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at the investigative sites. All ICFs must be compliant with the International Conference on Harmonisation (ICH) guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative sites.

The study site's ERBs should be provided with the following:

- the current IB or package labeling (for example, PI or SmPC) and updates during the course of the study
- ICF
- relevant curricula vitae

13.3. Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- the ICH GCP Guideline (E6)
- applicable laws and regulations.

The investigator or designee will promptly submit the protocol to applicable ERB(s).

Some of the obligations of Lilly will be assigned to a third-party organization.

An identification code assigned to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

13.3.1. Investigator Information

Physicians with a specialty in oncology will participate as investigators in this clinical trial.

13.3.2. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

13.3.3. Final Report Signature

The clinical study report (CSR) coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Lilly will select an investigator to serve as the CSR coordinating investigator.

The Lilly responsible medical officer and statistician will sign/approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Attachment 1. Protocol JPBK Study Schedule

Study Schedule, Protocol I3Y-MC-JPBK

Perform procedure as indicated.

			Pre-Screen[a]	Baseline		Patients on Study Treatment					Postdiscontinuation Follow-Up	
		Cycle	Pre-screening BL	BL		1		2		3 – n	Short-Term Follow-Up[b]	Long-Term Follow-Up
		Visit	PRE0	0		1		2		3 – n	801	802 - 8XX
		Duration (days)		≤28		28		28		28	30	60
		Relative day within a cycle		≤28	≤14	1	15	1	15	1		
Procedure Category	**Procedure**	**Protocol Reference**										
Study Entry /Enrollment	Informed Consent Form signed (prior to performance of any protocol-specific tests/procedures)	**Section 13.1**	X	X[ab]								
	Inclusion/Exclusion evaluation	**Section 7**	X		X							
	Brain scan[c]	**Section 7.1**		X								
Medical History[z]	Initial history/ preexisting conditions				X							
	Historical illnesses				X							
	Smoking/alcohol habits assessment				X							
Physical Examination[z]	Height				X							
	Weight				X			X		X	X	
	Blood pressure/pulse	**Section 10.3.1**			X			X		X	X	
	ECOG performance status	**Attachment 4**			X	X		X		X	X	
Tumor Assessment	Tumor measurement (palpable or visible)[d]	**Section 10.1**			X			X		X		X[e]
	Radiologic imaging according to RECIST[f]	**Section 10.1 Attachment 5**		X						X		X[e]
Survival information		**Section 10.1**									X	X[g]
Adverse Event Collection/CTCAE Grading[h]		**Section 10.3**			X	X		X		X	X	X

			Pre-Screen[a]	Baseline		Patients on Study Treatment					Postdiscontinuation Follow-Up	
		Cycle	Pre-screening BL	BL		1		2		3 – n	Short-Term Follow-Up[b]	Long Term Follow-Up
		Visit	PRE0	0		1		2		3 – n	801	802 - 8XX
		Duration (days)		≤28		28		28		28	30	60
		Relative day within a cycle		≤28	≤14	1	15	1	15	1		
Procedure Category	**Procedure**	**Protocol Reference**										
Concomitant Medication Notation		**Section 9.6**		X		X		X		X	X	
Lab/ Diagnostic Tests	Central hematology[i]	**Attachment 2**			X	X	X	X	X	X	X	
	Central chemistry[i]	**Attachment 2**			X	X	X	X	X	X	X	
	Local serum pregnancy test[j,k]	**Attachment 2**			X			X[k]		X[k]		
	Central pharmacokinetic sampling [l]	**Attachment 7**				X		X		X		
	Pharmacogenetic whole blood sample	**Section 10.4.3.2**				X[aa]						
	Plasma sample for circulating biomarkers	**Section 10.4.3.3**		X[m]		X[m]		X[m]				
	Local ECG [n]	**Section 10.3.2.1**			X[o]	X[p]		X[q]		X[r]	X[s]	
	Archived tumor samples	**Section 10.4.2 and 10.4.3.1**	X[t]	X[u]		X[v]						
Health Outcomes Assessments	MDASI-LC [w]	**Section 10.2**			X			X		X	X	
	EQ-5D 5L [w]	**Section 10.2**			X			X		X	X	
Study Drug	Abemaciclib [x]	**Section 9.1**				X		X		X		
	Erlotinib [y]	**Section 9.1**				X		X		X		

Abbreviations: BL = baseline; C1D1 = Cycle 1 Day 1; CNS = central nervous system; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EQ-5D 5L = European Quality of Life – 5 Dimensions – 5 Level; FFPE = formalin-fixed paraffin-embedded; ICF = informed consent form; MDASI-LC = MD Anderson Symptom Inventory; MRI = magnetic resonance imaging; OS = overall survival; PK = pharmacokinetics; Q12H = every 12 hours; RECIST = Response Evaluation Criteria in Solid Tumors; SAEs = serious adverse events; V = Visit.

a The pre-screening period begins when the pre-screening ICF is signed for evaluation of FFPE tissue by Study JPBK central laboratory and ends once the *KRAS* mutation status of the tissue is determined. This period is optional; *KRAS* mutation status can also be determined during screening under the study ICF.

b Short-term follow up begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days (± 7 days).

c Patients with a history of CNS metastases must have a brain scan (for example, MRI) within 28 days of randomization to document stability of their CNS metastases, even if there have been no changes in symptoms. If a prior brain scan was completed within 45 days of starting C1D1, the brain scan does not need to be repeated at baseline.

Study Schedule, Protocol I3Y-MC-JPBK (continued)

[d] Palpable or visual tumor measurement to be performed within 72 hours of start of each cycle if assessed as target/non-target lesions. For visible lesions, a digital photograph is required with a ruler. If the skin lesion is a target lesion, reassessment is performed at each cycle. If the skin lesion is non-target, repeat photographs should be done at every other cycle. Photographs must be performed to document any changes to skin lesions and are sent to central vendor for review.

[e] For patients who discontinue study treatment without objectively measured progressive disease, continue to evaluate tumor response approximately every 8 weeks by the same method used at baseline and throughout the study until the patient has objective disease progression, or until the study's final analysis of OS. After the patient has objective disease progression, radiologic tests are no longer required and the patient will be followed up approximately every 60 days (±14 days) until the patient's death or overall study completion.

[f] Imaging studies are performed locally and transmitted for central review. Radiological assessment of the chest and abdominal region is performed at baseline (within 28 days of treatment start), then on Day 1 ±7 days of the scheduled Day 1) of every other cycle beginning with Cycle 3 until progressive disease or the start of the next line of anti-tumor treatment. A scan performed up to 30 days prior to the first dose of treatment is permitted as the baseline scan, therefore omitting the baseline scan. If a cycle is delayed, tumor assessment should be concurrent with Day 1 of the new cycle. If the assessment was completed before Day 1 of the next cycle and the patient has a delay in starting the next cycle, the radiological scan does not need to be repeated again when Day 1 of the next cycle is resumed.

[g] Collection of survival data and subsequent antitumor therapies. Every 60 days (±14 days). Whenever possible, survival follow-up is conducted in person. If an in-person visit is not possible, the site may confirm survival by contacting the patient directly via phone.

[h] Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System. During long-term follow-up, only SAEs that are related to protocol procedures or study drug will be collected. All drug- or procedure-related adverse events and serious adverse events should be followed until they resolve, are no longer considered to be drug- or procedure-related, become stable or return to baseline, the patient starts a new therapy, the patient dies, or the patient becomes lost to follow-up. Frequency of evaluation is left to the judgment of the investigator.

[i] Laboratory assessments should occur on Day 1 (±3 days) of each cycle and Day 15 (± 3 days) of Cycles 1 and 2. If the baseline laboratory assessment was conducted ≤3 days prior to Cycle 1 Day 1, reassessment is not required at Cycle 1 Day 1. For central versus local labs, refer to Attachment 2.

[j] Perform pregnancy tests for woman of child-bearing potential.

[k] Perform pregnancy tests once every 28 days (±7 days) prior to administration of study drug, where required by local regulations.

[l] Sparse PK samples will be collected on Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 3 Day 1 (only for patients receiving abemaciclib).

[m] A plasma sample should be collected at baseline at the time FFPE tissue is requested for testing at the Study JPBK central laboratory. Patients who enter the study with a local KRAS test result may omit this baseline sample. Patients that have submitted FFPE tissue during pre-screening may have this baseline sample collected at the time of other blood laboratory samples. Additional samples are collected on all randomized patients at Cycle 1 Day 1 and Cycle 2 Day 1.

[n] Local ECG (no replicates required).

[o] A baseline ECG will be collected from all patients.

[p] ECG will be collected from patients receiving abemaciclib only. Two ECG will be collected on Cycle 1 Day 1. The first ECG will be collected predose; the second will be collected 4 to 6 hours postdose. If the patient had a baseline ECG performed within 24 hours of the predose ECG at Cycle 1 Day 1, the scheduled predose ECG may be omitted.

[q] ECG will be collected from patients receiving abemaciclib only. An ECG will be collected 4 to 6 hours postdose on Cycle 2 Day 1.

[r] If the patient received abemaciclib for 6 months, an additional ECG will be collected 4 to 6 hours postdose Cycle 7 Day 1.

Study Schedule, Protocol I3Y-MC-JPBK (concluded)

[s] ECG will be collected from patients receiving abemaciclib only.

[t] Formalin-fixed paraffin-embedded tumor tissue requested after patient signs pre-screening ICF. Eight slides are mandatory for *KRAS* testing by the Study JPBK central laboratory prior to enrollment. If testing did not occur during pre-screening, sample collection and testing is required during baseline visit.

[u] If the patient was not pre-screened, FFPE tumor tissue is requested after patient signs the study ICF. Eight slides are mandatory for *KRAS* testing by the Study JPBK central laboratory prior to enrollment. If enrollment using a local *KRAS* result is approved, no further tissue should be submitted to the Study JPBK central laboratory for analysis. Approval for local *KRAS* result is required from the sponsor prior to randomization. Local *KRAS* testing is not a required study procedure.

[v] An additional 20 slides or FFPE tumor tissue block requested for biomarker research. If enrollment using a local *KRAS* result is approved, no further tissue should be submitted to the Study JPBK central laboratory for analysis.

[w] MDASI-LC and EQ-5D 5L should be administered at baseline (within 14 days of treatment start), on Day 1 of every cycle beginning with Cycle 2, and at the 30-day follow up visit (V801). The preferred order of collection is MDASI-LC and then EQ-5D 5L. Patients should complete before interaction with site staff.

[x] Abemaciclib is to be administered every 12 hours (± approximately 2 hours) on Days 1 through 28 of each cycle. On Cycle 1 Day 1 only, patients should take 1 single dose of abemaciclib at clinic and initiate subsequent Q12H dosing from Cycle 1 Day 2 moving forward.

[y] Erlotinib is to be administered every 24 hours (± approximately 2 hours) on Days 1 through 28 of each cycle.

[z] The medical history and physical examination will be performed by a qualified healthcare provider with assessments that include general appearance, skin, head and neck, respiratory, cardiovascular, abdomen, lymph nodes, thyroid, and musculoskeletal and neurological systems.

[aa] Pharmacogenetic whole blood sample should be collected. This may be collected either predose or postdose.

[ab] The study ICF must be signed at baseline before any study screening procedures are performed, but this does not have to be within 28 days of treatment start (Cycle 1 Day 1). No window is defined; however, the patient will have to re-sign the study ICF in case it has been updated/revised. The study ICF needs to be signed prior to requesting approval by the sponsor for study entry for those with a local KRAS result.

Study Schedule for the extension period only, Protocol I3Y-MC-JPBK]

Patients experiencing ongoing clinical benefit may continue to receive abemaciclib or erlotinib in the extension period. There is no cross-over between the 2 study treatment arms.

Perform procedure as indicated.

			Patients on Study Treatment	Extension Period Follow-Up
		Cycle	2 – n	Follow-Up[a]
		Visit	501-5XX	901
		Duration (days)	28	30
		Relative day within a cycle	1	
Procedure Category	**Procedure**	**Protocol Reference**		
Adverse Events Collection/CTCAE Grading[b]		**Section 10.3.1**	X	X
Study Drug	Abemaciclib or Erlotinib [c]	**Section 9.1**	X	

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; PK = pharmacokinetics; SAEs = serious adverse events.

[a] The extension period begins after study completion and ends at the end of trial.

[b] Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly safety system.

[c] Abemaciclib is to be administered every 12 hours (± approximately 2 hours) on Days 1 through 28 of each cycle. Erlotinib is to be administered every 24 hours (± approximately 2 hours) on Days 1 through 28 of each cycle.

Note: Efficacy assessments will be done at the investigator's discretion based on the standard of care.

Attachment 2. Protocol JPBK Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry**[a]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume (MCV)	Chloride
Mean cell hemoglobin concentration (MCHC)	Total bilirubin
Leukocytes (WBC)	Direct bilirubin
Neutrophils	Alkaline phosphatase
Lymphocytes	Alanine aminotransferase (ALT)
Monocytes	Aspartate aminotransferase (AST)
Eosinophils	Blood urea nitrogen (BUN)
Basophils	Creatinine
Platelets	Calcium
	Albumin
	Total Protein
	Pregnancy Test (females only)[b]
	Serum

Abbreviations: RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated laboratory.

[b] Local or investigator-designated laboratory.

Other Laboratory Tests

KRAS[a]
Sanger Sequencing[b]

[a] Assayed by Lilly-designated central laboratory or with sponsor approval by local or investigator-designated laboratory.

[b] To be performed on the same samples used for *KRAS* central laboratory testing.

Attachment 3. Protocol JPBK Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow up with patients in consultation with the Lilly clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Anti-smooth muscle antibody[a]**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Attachment 4. Protocol JPBK ECOG Performance Status

ECOG Performance Status

Activity Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead.

Source: Oken et al. 1982.

Attachment 5. Protocol JPBK RECIST Criteria 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the New Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1; Eisenhauer et al. 2009).

Measurability of Tumor at Baseline

Tumor lesions/lymph nodes will be categorized at baseline as measurable or nonmeasurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

Measurable

Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness ≤5 mm)
- 10 mm caliper measurement by clinical exam (non-measurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

Nonmeasurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measureable by reproducible imaging techniques.

Special Considerations for Lesion Measurability

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable)
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If noncystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are non-measurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Non-nodal Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and can be reproduced in repeated measurements.. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the case record form (CRF) in millimeters (or decimal fractions of centimeters [cm]).

Nontarget Lesions

All other lesions (or sites of disease) are identified as nontarget lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as 'present,' 'absent,' or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the CRF (for example, multiple liver metastases recorded as 1 liver lesion).

Lymph nodes with short axis ≥10 mm but <15 mm should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and are not recorded or followed.

Specifications by Methods of Measurement

All measurements should be recorded in metric notation, using a ruler or calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is

should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical exam.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. If prior to enrollment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the patient at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray when progression is an important endpoint. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI: CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scan have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Ultrasound: Ultrasound should not be used to measure lesion size. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response (CR). Specific guidelines for both prostate-specific antigen (PSA) response (in recurrent prostate cancer) and CA-125 response (in recurrent ovarian cancer) have been published.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete response (CR) in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and progressive disease (PD).

Pet Scan (FDG-PET, PET CT): PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

Bone Scan: If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a complete response (CR) or partial response (PR) in target disease or when progression in bone is suspected.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. Tumor marker results must have normalized.

Partial Response (PR): At least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

For equivocal findings of progression (for example, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Not Evaluable: When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

Evaluation of Nontarget Lesions

Complete Response: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be non-pathological or normal in size (<10mm short axis).

Non-CR/ non-PD: Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing nontarget lesions. The appearance of 1 or more new lesions is also considered progression.

Not Evaluable: When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

Evaluation of Best Overall Response

The best overall response (BOR) is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. The BOR will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.) Table 1 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

Table 1. Time Point Response: Patients with Target (± Nontarget) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

Table 2 is to be used when patients have *nonmeasurable* disease only.

Table 2. Time Point Response: Patients with Nontarget Disease Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; PD = progressive disease ; NE = inevaluable.

[a] non-CR/non-PD is preferred over SD for nontarget disease.

Frequency of Tumor Re-Evaluation

A baseline tumor evaluation must be performed within 4 weeks before patient begins study treatment. Frequency of tumor re-evaluation while on and adapted to treatment should be protocol-specific and adapted to the type and schedule of treatment. In the context of Phase 2 studies where the beneficial effect therapy is not known, follow-up every 6-8 weeks is reasonable. Normally, all target and non-target sites are evaluated at each assessment using the same method. However, bone scans may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Confirmatory Measurement/Duration of Response

Confirmation:
The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in *nonrandomized trials* where response (CR/PR) is the primary end point. In this setting, to be assigned a status of PR/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. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontargets is not required.

However, in *randomized trial* (Phase 2 or 3) or studies where SD or progression is the primary endpoints, confirmation of response is not required. But, elimination of the requirement may increase the importance of central review to protect against bias, in particular of studies which are not blinded.

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 6 weeks measured from first dose.

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease
Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of PD).

Independent Review of Response and Progression

When objective response (CR + PR) is the primary end point, and when key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment.

Attachment 6. Protocol JPBK Sampling Summary

This table summarizes the maximum number of samples (venipunctures, biopsies), volumes for all sampling, and tests (study qualification, health monitoring, drug concentration, pharmacodynamics/tailoring biomarkers) during the study. The summary below provides estimates. More samples could be required in the case of retests, additional health monitoring (if needed), or for patients continuing treatment beyond the protocol-specified number of cycles in the study. Fewer samples may actually be taken (for example, patients who discontinue from the study).

Protocol I3Y-MC-JPBK Sampling Summary[a]

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Study qualification[b]	Blood	6 mL	1	6 mL
KRAS mutant status[b]	FFPE tumor tissue slides or block	FFPE tumor tissue slides OR FFPE tumor tissue block	8 slides OR 1 tumor tissue block	FFPE tumor tissue slides or block
Tissue for biomarker research	FFPE tumor tissue slides or block	FFPE tumor tissue slides OR FFPE tumor tissue block	20 slides 5 micron thickness OR 1 tumor tissue block	FFPE tumor tissue slides or block
Health monitoring[a]	Blood for chemistry	3 mL	15	45 mL
	Blood for Hematology	3 mL	15	45 mL
Drug concentration	Blood	2 mL	5	10 mL
Pharmacodynamics and/or circulating biomarkers	Plasma	6 mL	3	18 mL
Pharmacogenetic evaluations	Whole blood	10 mL	1	10 mL
Hepatic monitoring[c]	Blood	3 - 30 mL	-	-
Total: Blood				**134 mL**

Abbreviation: FFPE = formalin-fixed paraffin-embedded.

a Covers 12 cycles and Visit 801.

b This sample is required for initial qualification unless sponsor approves enrollment per local *KRAS* mutation result. The remaining samples are for those patients enrolled in the study.

c Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with the designated medical monitor.

Attachment 7. Protocol JPBK Pharmacokinetic Sampling Schedule

Pharmacokinetic Sampling Schedule

PK Sample Number	Cycle (C) and Day (D)	Dosing of Abemaciclib	Sampling Time for PK from Blood[a]
1	C1D1	X[b]	4-6 hrs after abemaciclib dose
2	C2D1	X[c]	At least 4 hrs after taking abemaciclib dose at home (that is, upon arrival at site)
3	C2D1		At least 7 ± 0.5 hrs after taking abemaciclib dose at home (that is, 3 ± 0.5 hrs after arrival at site)
4	C3D1	X	Prior to abemaciclib dose
5	C3D1		3 ± 0.5 hrs after abemaciclib dose

Abbreviations: C = Cycle; D = Day; hr = hour; PK = pharmacokinetic; Q12H = every 12 hours.

a Samples of approximately 2 mL of whole blood will be drawn, for measurement of abemaciclib and its metabolites concentrations in plasma.

b On Cycle 1 Day 1 only, patients should take 1 single dose of abemaciclib and initiate chronic Q12H dosing on Cycle 1 Day 2.

c On Cycle 2 Day 1 only, patient should take abemaciclib dose at home at approximately 4 hours before arrival at site. The time of abemaciclib dose intake must be recorded that day.

Attachment 8. Protocol JPBK Inducers and Strong Inhibitors of CYP3A4 or Substrates of CYPs with Narrow Therapeutic Range

The information in this attachment is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated.

Inducers of CYP3A4

Carbamazepine
Dexamethasone[a]
Phenobarbital/phenobarbitone
Phenytoin
Rifapentine
Rifampin
Rifabutin
St. John's wort

Strong inhibitors of CYP3A4

All HIV protease inhibitors
Clarithromycin
Itraconazole
Ketoconazole
Nefazodone

[a] Important note: All patients may receive supportive therapy with dexamethasone, preferably ≤7 days, if clinically indicated. A patient who develops brain metastases may receive acute or chronic therapy with dexamethasone if clinically indicated. Development of brain metastases is considered progressive disease and the patient should discontinue study treatment.

Cytochrome P450 Substrates with Narrow Therapeutic Range

CYP1A2	Theophylline
	Tizanidine
CYP2C8	Paclitaxel
CYP2C9	Warfarin[a]
	Phenytoin
CYP2D6	Thioridazine
	Pimozide
CYP3A	Alfentanil
	Astemizole
	Cisapride
	Cyclosporine
	Dihydroergotamine
	Ergotamine
	Fentanyl
	Pimozide
	Quinidine
	Sirolimus
	Tacrolimus
	Terfenidine

[a] Important note: For patients who receive concomitant warfarin, appropriate monitoring of the International Normalized Ratio (INR) must be performed.

Attachment 9. Protocol JPBK CTCAE 4.03 Diarrhea Definition

Diarrhea will be evaluated in this study using the criteria proposed by Common Terminology Criteria for Adverse Events (CTCAE) v4.0 revised: CTCAE 4.03-June 14, 2010: Gastrointestinal disorders.

Gastrointestinal Disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline.	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase >= 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: a disorder characterized by frequent and watery bowel movements					

Abbreviation: ADL = Activities of Daily Living.

Attachment 10. Protocol JPBK Amendment(e) Summary JUNIPER: 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

Study I3Y-MC-JPBK(d), 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, has been amended. The new protocol is indicated by Amendment (e) and will be used to conduct the study in place of any preceding version.

The overall changes made to this protocol are as follows:

- Synopsis updated the following: number of planned patients and interim analysis, length of study, PFS as a secondary objective and statistical method information
- Section 5 updated erlotinib background information to align with erlotinib label
- Section 5.5 incorporated amendment (e) rationale
- Sections 6.1 and 6.2 deleted co-primary objective of PFS and added it as a secondary objective
- Section 8.1 updated study design illustration number of patients
- Section 9.5 removed DMC information for OS interim analysis
- Sections 10.1.3 and 10.1.4 moved PFS efficacy measure information from primary to secondary efficacy measure
- Section 12.1 updated study enrollment patient numbers; OS number of events, HR and median OS information; and removed PFS information.
- Section 12.2.1 clarified assumptions for statistical methods
- Section 12.2.6 and 12.2.7 moved PFS outcome and methodology analysis and endpoint information from primary to secondary outcome
- Section 12.2.8 provided clarity for sensitivity analyses for efficacy endpoints
- Section 12.2.12 clarified TEAE definition as an event
- Section 12.2.13 clarified subgroup analyses
- Section 12.2.14.2 updated interim efficacy analysis and reference to DMC plan

Minor typographical and formatting edits were made throughout the document for clarity and consistency.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

1. Protocol I3Y-MC-JPBK(~~d~~e)

JUNIPER: 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

2. Synopsis

Clinical Protocol Synopsis: Study I3Y-MC-JPBK

<table>
<tr><td colspan="2">Name of Investigational Product: Abemaciclib</td></tr>
<tr><td colspan="2">Title of Study: JUNIPER: 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.</td></tr>
<tr><td>Number of Planned Patients:
Entered: 2500
Enrolled/Randomized: approximately 450~~550~~
Completed: ~~550~~approximately 450</td><td>Phase of Development: 3</td></tr>
<tr><td colspan="2">Length of Study: Approximately 47 months
Planned first patient visit: September 2014
Planned last patient visit: excluding the extension period: ~~August 2018~~November 2017
Planned interim analysis: Analysis for safety will occur every 6 months. One futility analysis will occur after approximately 100 progression-free survival (PFS) events have been observed. ~~One efficacy analysis will occur after approximately 338 PFS events have been observed, or approximately 1 month after study enrollment completion, whichever comes later.~~</td></tr>
<tr><td colspan="2">Objectives: The ~~co~~ primary objective~~s~~ of this study is~~are~~ to compare abemaciclib plus BSC versus erlotinib plus BSC in patients with Stage IV NSCLC whose tumors have detectable KRAS mutations and who have progressed after prior platinum-based therapy and 1 other prior therapy or are not eligible for further chemotherapy with respect to:
~~• PFS~~
• overall survival (OS)
The secondary objectives of the study are to compare abemaciclib plus BSC to erlotinib plus BSC with respect to:
• overall response rate (complete response + partial response)
• progression-free survival (PFS)
• 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)
An additional secondary objective is to examine the pharmacokinetic (PK)/pharmacodynamic (PD) properties of abemaciclib.
Statistical Methods:
Statistical: The study will enroll approximately ~~550~~ 450 patients in 3:2 randomization (~~330~~ approximately 270 patients in the abemaciclib arm and ~~220~~ 180 patients in the erlotinib arm). ~~The primary PFS analysis will be performed after approximately 338 PFS events have occurred or approximately 1 month after the last patient is</td></tr>
</table>

~~enrolled, whichever is later. An interim OS analysis will be conducted at the time of primary PFS analysis.~~ The final ~~OS~~ analysis will occur when approximately 304~~407~~ OS events have been observed. ~~The study-wise alpha of .05 will be split between the endpoints: .005 for PFS and .045 for OS. The test on PFS will occur first; if the test on PFS is significant, the alpha used for this test will be added to the .045 originally allocated to OS for a total of .05. If the primary PFS analysis is significant, two-sided alpha=0.0112 will be spent in the interim OS analysis and alpha=0.0466 will be used in the final OS analysis based on O'Brien and Fleming alpha-spending approach using East® 6.3 (Lan and DeMets 1983). If the primary PFS is not significant, two-sided alpha=0.0096 will be spent in the interim OS analysis and alpha= 0.0420 will be used in the final OS analysis. A fallback procedure (Wiens 2003) will be used to maintain a study-wise alpha level of .05.~~

~~Assuming a PFS hazard ratio (HR) of 0.67, 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 .005. If the true median PFS for the erlotinib arm is 2 months, then the HR of 0.67 amounts to an approximately 1-month improvement in median PFS for the abemaciclib arm under an additional assumption of exponential survival distribution.~~ Assuming an OS HR of 0.72~~5~~, 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 .045. If the true median OS for the erlotinib arm is 6.5 months, then the HR of 0.72~~5~~ amounts to an approximately 2.5~~2~~-month improvement in median OS for the abemaciclib arm under an additional assumption of exponential survival distribution.

Efficacy: Efficacy analyses will be based on the intention-to-treat (ITT) analysis set. This population is defined as all patients randomized to study treatment. For ~~the co-primary endpoints of PFS~~ and OS and PFS, the comparison of the survival curves between treatment groups will be conducted by 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 (GLY12CYS [G12C] vs. all others). In addition, the Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the survival curves as well as survival rates at 3, 6, 9, and 12 months for each treatment group. As supportive analysis of OS and PFS, the Cox proportional hazard model will be used to estimate treatment HR and corresponding 95% confidence interval (CI) ~~with Wald's test p-value~~ after adjusting for the same randomization variables specified for the primary analysis. All randomized patients, according to the ITT principle, will be included in the analysis of this endpoint.

5. Introduction

Erlotinib is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen (Tarceva United States [US] package insert [USPI], 2010). Until recently, u~~U~~nlike the use of erlotinib for first-line treatment of patients with NSCLC, second- and third-line treatment has no limitation with regard to epidermal growth factor receptor (*EGFR*) or *KRAS* mutation status. In October 2016 the FDA modified the erlotinib label to include only those patients with tumors with common *EGFR* mutations, del 19 and exon 21 L858R substitutions. Before this action, there ~~has~~ had been some concern regarding the activity of erlotinib in treating NSCLC with *KRAS* mutations due to results from 3 studies. First, in the original BR-21 study, a subgroup evaluation of 30 patients with *KRAS* mutant tumors randomized between placebo and erlotinib demonstrated a nonsignificant better survival outcome in the placebo group (Zhu et al. 2008). Second, in TITAN, a second-line study of erlotinib versus chemotherapy, 35 patients with *KRAS* mutant tumors had inferior outcome on erlotinib compared to chemotherapy (Ciuleanu et al. 2012). Lastly, a meta-analysis of response

rate showed numerically inferior response rate in patients with *KRAS* mutant tumors treated with EGFR tyrosine kinase inhibitors (TKIs, such as erlotinib and gefitinib) (Linardou et al. 2008). In the TAILOR study comparing docetaxel to erlotinib as second-line therapy, overall survival (OS) favored docetaxel treatment in patients with both *KRAS* wild-type and *KRAS* mutant tumors (hazard ratio [HR] = 0.79 and 0.81, respectively); similarly, progression-free survival (PFS) favored docetaxel (HR = 0.68 and 0.89) for *KRAS* wild-type and *KRAS* mutant, respectively (Garassino et al. 2013). There was not a significant treatment interaction based on *KRAS* status. However, the SATURN study of erlotinib maintenance therapy demonstrated that improved PFS was preserved in a subset of 90 patients with *KRAS* mutant tumors (HR = 0.77 erlotinib compared to placebo) (Brugger et al. 2011). Overall, the data remain conflicting and after extensive review of the literature, Langer stated, "*KRAS* mutation cannot be used at this time to preclude NSCLC patients from receiving anti-EGFR TKI's" (Langer 2011). A more recent evaluation of pooled results from four Phase 3 studies of erlotinib showed that *KRAS* mutation was not predictive of treatment outcome with tyrosine kinase inhibitors (Zer et al. 2015). The selection of treatment depends on the overall benefit/risk for the patient. Given the differences in toxicity profile for available treatments, and the limited treatment options for patients, erlotinib is an acceptable control arm as the only oral drug available for patients with lung cancer, and only approved drug for treatment of third-line patients in selected geographies.

5.5. Rationale for Amendment (e)

Due to recent changes in the FDA ertlotinib label and National Comprehensive Cancer Network (NCCN) Guidelines, the Sponsor amended the protocol to address the impact on study enrollment completion, and the need for a larger improvement in OS than that historically targeted for NSCLC patients. The amendment updates include the followings:

- PFS is removed as a co-primary endpoint and changed to a secondary endpoint. With this change OS becomes the sole primary endpoint.
- The final OS analysis will occur when approximately 304 OS events have been observed, a reduction from the current protocol requirement of 407 OS events. With this change, the study will provide 80% statistical power for a new targeted hazard ratio of 0.72.
- 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 (note that current protocol requires 550 patients).

While amending the protocol, the Lilly study team remains blinded to aggregate data and will not be unblinded until the final OS analysis.

Previously, erlotinib was indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen (Tarceva® United States [US] package insert [USPI], 2010) based upon the BR-21 study. In addition, NCCN Guidelines (April 2015) supported erlotinib use as an option for subsequent second line or third line treatment in NSCLC patients (all histologies) for PS 0-3.

On 18 October 2016, the FDA modified the indication for erlotinib (Tarceva®) for treatment of NSCLC, limiting the use to patients whose tumors have specific *EGFR* mutations (exon 19 deletions or exon 21 L858R substitutions). This labeling supplement occurred based on study results of the IUNO Study (a randomize, double-blind, placebo controlled, trial of erlotnib administered as maintenance therapy in advanced NSCLC patients who had not experienced disease progression or unacceptable toxicity during four cycles of platinum-based first-line chemotherapy). The results showed no observed benefits in PFS, ORR, DCR or OS (median OS was 9.7 and 9.5 months with 'early' and 'late erlotinib', respectively (HR, 1.02, 95% CI: 0.85−1.22; log-rank p = 0.82) in patients receiving erlotinib as maintenance therapy ("early erlotinib") compared to second-line treatment ("late erlotinib") in patients whose tumor did not harbor an *EGFR*-activating mutation. However, safety results were consistent with the established safety profile of erlotinib. Furthermore, in lieu of the FDA labeling supplement, the NCCN Guidelines removed erlotinib from recommended therapies in patients who progress on platinum therapy and who do not have *EGFR* mutations (NCCN Guidelines October 2016).

Minor typographical and formatting edits were made throughout the document for clarity and consistency.

6.1. Primary Objective

The ~~co-~~primary objective~~s~~ of this study is~~are~~ to compare abemaciclib plus BSC versus erlotinib plus BSC in patients with Stage IV NSCLC whose tumors have detectable *KRAS* mutations 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 treatment; or are not eligible for further chemotherapy with respect to:~~progression-free survival (PFS)~~

- overall survival (OS)

6.2. Secondary Objectives

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

- overall response rate (complete response [CR] + partial response [PR])
- progression-free survival (PFS)
- 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)

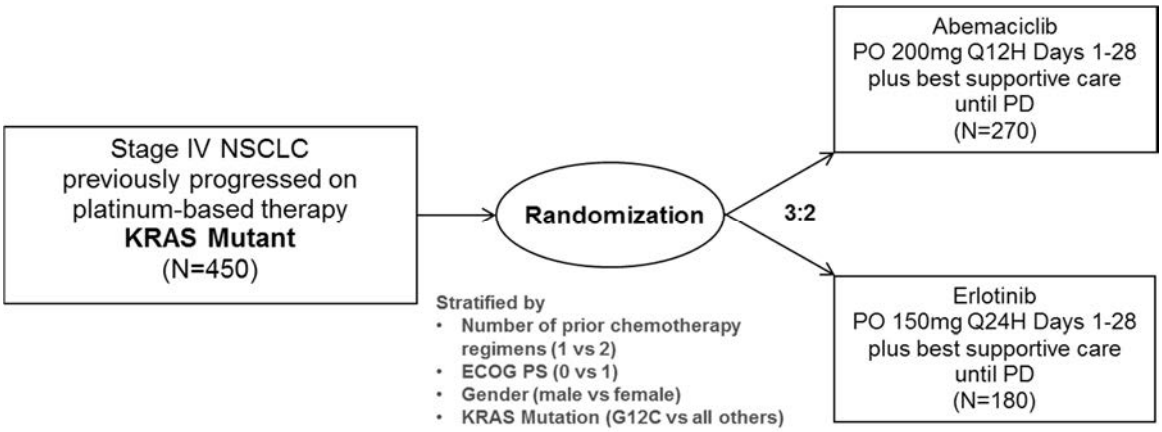
7. Study Population

If a *KRAS* mutation positive result was obtained for an individual under their first patient number, this result can be linked to their new number in an effort to preserve patient tissue. If a *KRAS* mutation result was not successfully obtained for an individual under their first patient

number, then the investigator can submit a new sample for this individual (as well as one repeat if needed) ~~can be submitted~~ to the central lab with the new patient number.

8.1. Summary of Study Design

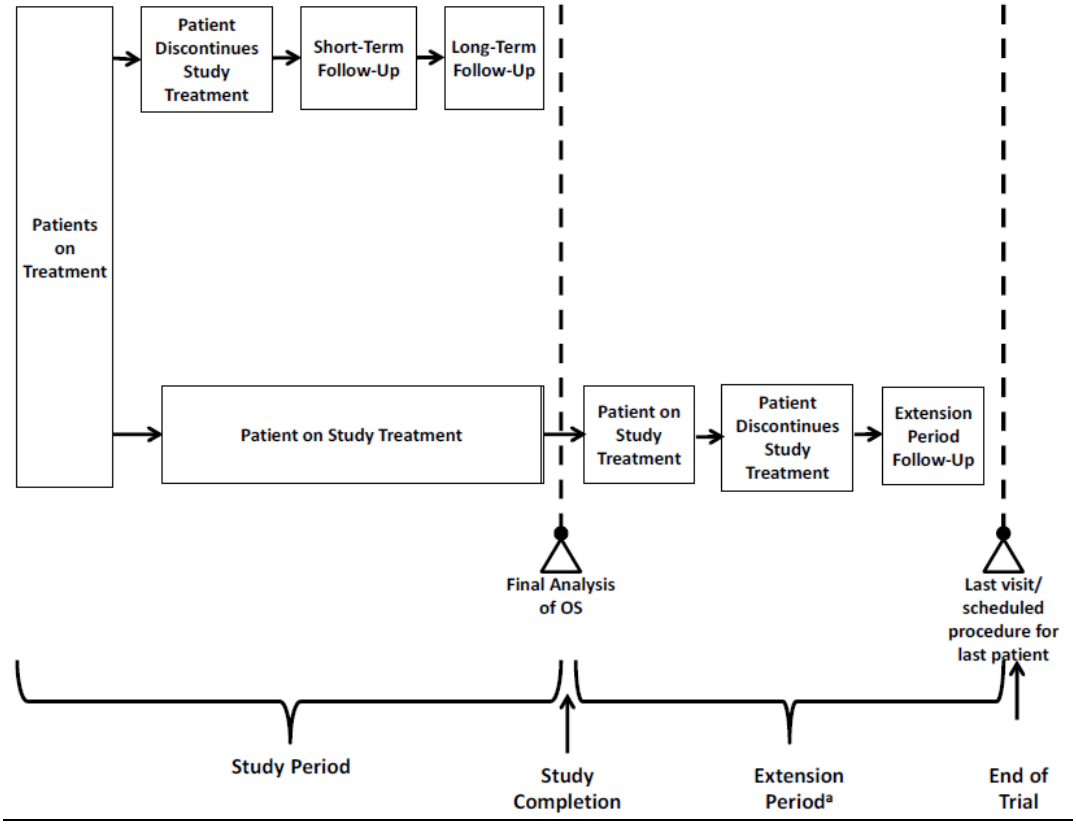
Figure JPBK.8.1 illustrates the study design.



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

Figure JPBK.8.1. Illustration of study design.

8.1.1. Study Completion and End of Trial



Abbreviations: OS = overall survival~~; PFS = progression-free survival~~.

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

Figure JPBK.8.2. Study period and extension period diagram.

8.2. Discussion of Design and Control

A randomized, controlled design is being used in this study. Randomization minimizes systematic bias in the selection and assignment of patients to study therapy and provides justification for inferential statistical methods to be used on data from this study. It is expected that abemaciclib will produce better efficacy outcomes than the control; therefore, this study uses a 3:2 randomization~~ has been used in this study~~. Using an appropriate concurrent control arm enables direct statistical estimation of benefits and harms due to study therapy and minimizes bias in the assessment and interpretation of observed treatment effects. Patients will be stratified for differences in factors thought to be associated with clinical outcomes to further reduce the potential for bias and improve the power of the analyses.

9.5. Blinding

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. Scrambled treatment assignments will be used in the reporting database for Lilly trial-level safety review until the final database lock. 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 the Statistical Analysis Center (SAC), which is also external to Lilly, will carry out analyses for the DMC. Until the primary analyses, only the SAC and the DMC will be unblinded to the summary statistics and reports. ~~If the DMC recommends to stop the trial based on positive outcome of OS interim analysis, in light of the critical importance of obtaining unbiased results of final OS analysis in the study, the unblinded database will be accessible to a limited number of individuals who need to have such access to perform analyses and make critical decisions (for example, regulatory submission). This group of individuals will be identified and documented prior to the database lock for the final analysis.~~

10.1.3. Primary Efficacy Measure

This ~~study has co-~~primary efficacy measures of the study is ~~PFS and~~ OS.

~~Progression-free survival will be defined as the time from randomization until the first evidence of objective progression as defined by RECIST v1.1 (Eisenhauer et al. 2009), or death from any cause, whichever is earlier. Patients who are not known to have either progressed or died at the time of analysis will be censored at the day of their last radiographic tumor assessment, if available, or the date of randomization if no postbaseline radiographic assessment is available. The detailed censoring rules are described in Table JPBK.12.2.~~

The primary PFS analysis will be based on the local investigator's tumor assessments.

~~Lilly or its designee will collect and store all tumor measurement images on all enrolled patients throughout the study. A central review of imaging scans may be performed by Lilly or its designee.~~

10.1.4. Secondary Efficacy Measures

~~The secondary efficacy measure is~~Tumor response is~~as~~ defined by RECIST v1.1 (Eisenhauer et al. 2009) provided in Attachment 5. ~~A~~To derive the overall response rate, a responder is defined as any patient who exhibits a confirmed CR or PR. Best response is determined from the sequence of responses assessed.

Progression-free survival will be defined as the time from randomization until the first evidence of objective progression as defined by RECIST v1.1 (Eisenhauer et al. 2009), or death from any cause, whichever is earlier. Patients who are not known to have either progressed or died at the time of analysis will be censored at the day of their last radiographic tumor assessment, if available, or the date of randomization if no postbaseline radiographic assessment is available. The detailed censoring rules are described in Table JPBK.12.2.

The PFS analysis will be based on the local investigator's tumor assessments.

The date of first documented objective disease progression must be recorded on the CRF even if it occurs after the patient has started a new therapy. Lilly or its designee will collect and store all tumor measurement images on all enrolled patients throughout the study. A central review of imaging scans may be performed by Lilly or its designee.

12.1. Determination of Sample Size

The ~~co-~~primary objective~~s~~ of this study is~~are~~ to compare abemaciclib versus erlotinib with respect to ~~PFS and~~ 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 other prior therapy or are not eligible for further chemotherapy.

The study will enroll approximately ~~550~~ 450 patients in 3:2 randomization (approximately 270~~330~~ patients in the abemaciclib arm and 180~~220~~ patients in the erlotinib arm). ~~The primary PFS analysis will be performed after 338 PFS events have occurred.~~ The final ~~OS~~ analysis will occur when approximately 304~~407~~ OS events have been observed.

Assuming an OS HR of 0.72~~5~~, 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 .045.

If the true median OS for the erlotinib arm is 6.5 months, then the HR of 0.72~~5~~ amounts to an approximately 2.5~~2~~-month improvement in median OS for the abemaciclib arm under an additional assumption of exponential survival distribution.

12.2.1. General Considerations

Before unblinding of the aggregate database, minor modifications or clarifications to the data analysis methods may be described and justified in the SAP. The assumptions for each statistical method will be evaluated. If there is violation of assumptions, alternative statistical methods may be used. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the CSR.

~~The assumptions for each statistical method will be evaluated. If there is violation of assumptions, alternative statistical methods may be used.~~

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

12.2.6. Primary Outcome and Methodology

The ~~co-~~primary endpoint~~s~~ of this study is~~are PFS and~~ OS.~~The study-wise alpha of .05 will be split between the endpoints: .005 for PFS and .045 for OS. There is 1 planned interim analysis and 1 primary analysis for the PFS endpoint. The interim PFS analysis will occur after approximately 100 PFS events have been observed and will be for futility only. The primary PFS analysis will be performed after approximately 338 PFS events have occurred, or approximately 1 month after study enrollment completion, whichever comes later. There is 1 interim analysis and 1 final analysis planned for the OS endpoint. The interim OS analysis will be conducted at the time of primary PFS analysis. The final OS analysis will be conducted after at least approximately 407 OS events have been observed. Two-sided alpha of 0.0112 (if PFS analysis is significant) or 0.0096 (if PFS analysis is not significant) will be spent in the interim OS analysis based on O'Brien and Fleming alpha-spending approach using East® 6.3 (Lan and DeMets 1983). A fallback procedure (Wiens 2003) will be used to maintain a study-wise alpha level of .05. Specifically:~~

~~If the primary PFS analysis is significant, the final OS analysis will be conducted at 2-sided alpha level of .0466.~~

~~If the primary PFS analysis is not significant, the final OS analysis will be conducted at 2-sided alpha level of 0.0420.~~

~~The alpha level used for each test at each analysis is described in Table JPBK.12.1. The alpha levels for OS analyses are approximate based on projected 266 OS events at interim; the actual levels will depend on the exact accrued OS events at the time of interim OS analysis.~~

~~Table JPBK.12.1. Alpha Allocation (2-Sided) for Progression-Free Survival and Overall Survival~~

~~**Endpoint**~~	~~**Alpha at PFS Analysis (338 PFS events)**~~	~~**Alpha at OS Analysis (407 OS events)**~~
~~PFS~~	~~0.005~~	~~---~~
~~OS (If PFS is significant)~~	~~0.0112~~	~~0.0466~~

~~OS (If PFS is not significant) 0.0096 0.0420~~

~~Abbreviations: OS = overall survival; PFS = progression-free survival.PFS time is measured from the date of randomization to the date of investigator-determined objective progression as defined by RECIST v1.1, or death from any cause. 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 (that is, postbaseline) radiographic assessment is available. All randomized patients, according to the ITT principle, will be included in the analysis of both endpoints. The detailed censoring rules for PFS are described in Table JPBK.12.2.~~

~~Table JPBK.12.2. 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: Progression-free survival and associated outcome is determined by the earliest of the dates above, if more than 1 situation applies.~~

Overall survival duration is measured from the date of randomization 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 (contacts considered in the determination of last contact date include AE date, lesion assessment date, visit date, and last known alive date).

The comparison of each of the ~~PFS and~~ 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 Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the ~~PFS and~~ 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.

12.2.7. Secondary Outcome and Methodology

The secondary objectives for this study are stated in Section 6.2.

Progression-free survival time is measured from the date of randomization to the date of investigator-determined objective progression as defined by RECIST v1.1, or death from any cause. 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 (that is, postbaseline) radiographic assessment is available. The detailed censoring rules for PFS are described in Table JPBK.12.2.

Table JPBK.12.2. 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: Progression-free survival and associated outcome is determined by the earliest of the dates above, if more than 1 situation applies.

The statistical comparison of PFS between treatment groups will be conducted using the same methods for OS as described in Section 12.2.6.

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

Details of the statistical methods for analyzing efficacy outcomes are described in the SAP.

12.2.8. Sensitivity Analysis

Sensitivity analyses maywill be undertaken for calculation of the primary endpointthe efficacy endpoints in order to evaluate the robustness of the analysis. The following sensitivity analyses maywill be performed for PFS:

12.2.12. Safety Analysis

Preexisting conditions are defined as adverse events that begin prior to the first dose of study drug. A TEAE is defined as an event that first occurred or worsened in severity between the day of first dose and 30 days after treatment discontinuation (or up to any time if serious and related to study treatment)after baseline. Comparisons of preexisting conditions to on-treatment events at the LLT level will be used in the treatment-emergent computation.

12.2.13. Subgroup Analyses

Subgroup analyses of PFS and OS will be performed for potential prognostic and predictive subgroup variables (for example, patients with or without prior immunotherapy).

12.2.14.2. Efficacy Interim Analyses

OneTwo interim efficacy analysies isare planned based on the PFS endpointco-primary endpoints, as described in Section 12.2.6. BothThis interim analysies is for futility only and will be conducted by the DMC. There is no plan for interim efficacy analysis based on the OS endpoint. The DMC may also call for additional, unplanned, interim efficacy analyses. Details of the DMC communication plan can be found in the DMC charter.

The first interim efficacy analysis will be conducted after approximately 100 PFS events have occurred. This analysis will be based on the PFS endpoint and will be for futility only. The DMC will be instructed to recommend the study be stopped for futility if the observed hazard ratio for PFS (as calculated using a stratified Cox proportional hazards model) is greater than 0.95.The second interim efficacy analysis will be conducted after at least 338 PFS events have occurred, or approximately 1 month after study enrollment completion, whichever comes later. This analysis will include both the primary PFS and an interim OS analyses. For both the PFS and OS endpoints, a stratified log-rank test will be conducted to compare the survival distribution between treatment groups. The DMC will review unblinded efficacy and safety data. If the efficacy result meets the prespecified threshold and is supported by safety data, the DMC will be instructed to engage the Senior Management Designee, who may subsequently convene an Internal Review Committee to propose actions based upon the DMC's recommendation. Details of the DMC communication plan can be found in the DMC charter.

14. References

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