Protocol I3Y-MC-JPBO(d)

A Phase 2 Study of Abemaciclib in Patients with Brain Metastasis Secondary to Hormone Receptor Positive Breast Cancer, Non-Small Cell Lung Cancer, or Melanoma

NCT02308020

Approval Date: 08-Feb-2019

1. Protocol I3Y-MC-JPBO(d)

A Phase 2 Study of Abemaciclib in Patients with Brain Metastases Secondary to Hormone Receptor Positive Breast Cancer, Non-Small Cell Lung Cancer, or Melanoma

Confidential Information

Abemaciclib (LY2835219)

This study is a global, multicenter, open-label, Phase 2 trial of abemaciclib in patients with brain metastases secondary to hormone receptor positive breast cancer, non-small cell lung cancer, or melanoma.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly on date provided below.

Initial Protocol Electronically Signed and Approved by Lilly: 11 November 2014
Amendment (a) Electronically Signed and Approved by Lilly: 12 August 2015
Amendment (b) Electronically Signed and Approved by Lilly: 03 August 2016
Amendment (c) Electronically Signed and Approved by Lilly: 25 May 2017
Amendment (d) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 08-Feb-2019 GMT

2. Synopsis

Study Rationale

Brain metastases occur in a significant number of cancer patients, with the incidence being highest in lung cancer, breast cancer, and melanoma. In the United States (US) alone, the incidence of brain metastases is approximately 200,000 cases per year. Although targeted anticancer agents have shown promising results in treating extracranial disease, delivery of these agents to the central nervous system (CNS) has presented challenges.

Abemaciclib (LY2835219) is an oral, selective, and potent small molecule inhibitor of cyclin-dependent kinase (CDK) 4 and 6 (CDK4 and CDK6) with acceptable physical characteristics, pharmacokinetic (PK) properties, and safety profile in nonclinical species. Cell-based studies in breast cancer models indicated that abemaciclib inhibits CDK4 and CDK6 and induces G1 arrest, specifically in retinoblastoma (Rb) cell lines with functional Rb. These studies also showed that sensitivity to CDK4 and CDK6 inhibition was greater in estrogen receptor positive (ER+) lines with luminal histology. In addition, abemaciclib demonstrates antitumor activity in multiple human xenograft models for human cancers, including, but not limited to non-small cell lung cancer (NSCLC) and melanoma. In radiolabeled studies in rats, [^{14}C]LY2835219-derived radioactivity was measurable in CNS tissues (cerebellum, cerebrum, medulla, and spinal cord) protected by the blood-brain barrier (BBB) through 24 hours after a single dose. Abemaciclib has also been shown to inhibit glioblastoma intracranial xenografts, resulting in a statistically significant and dose-dependent improvement in survival.

In the ongoing Phase 1 Study I3Y-MC-JPBA (JPBA), abemaciclib has demonstrated acceptable clinical safety and evidence of single-agent activity in tumor-specific cohorts of patients with hormone receptor positive (HR+) metastatic breast cancer (including a single patient with CNS target disease), NSCLC, and melanoma. Further, cerebrospinal fluid (CSF) samples collected from a subset of these patients demonstrated that concentrations of abemaciclib in CSF were generally consistent with the unbound plasma concentrations. The preclinical results, including those that demonstrate that abemaciclib crosses the BBB, as well as the clinical findings from Study JPBA, support further investigation of abemaciclib in patients with brain metastases secondary to HR+ breast cancer, NSCLC, and melanoma.

Study I3Y-MC-JPBO (JPBO) is a multicenter, open-label, Phase 2 trial of abemaciclib in patients with brain metastases secondary to HR+ breast cancer, NSCLC, or melanoma. This study will evaluate the safety and efficacy of abemaciclib in patients with HR+ metastatic breast cancer, NSCLC, or melanoma and new or not previously irradiated brain lesions as well as previously irradiated progressive brain lesions.

Clinical Protocol Synopsis: Study I3Y-MC-JPBO

Name of Investigational Product: Abemaciclib (LY2835219)

Title of Study: A Phase 2 Study of Abemaciclib in Patients with Brain Metastases Secondary to Hormone Receptor Positive Breast Cancer, Non-Small Cell Lung Cancer, or Melanoma

Number of Planned Patients: 251 Entered: 314 Enrolled/Randomized: 251 Completed: 251	**Phase of Development: 2**

Length of Study: approximately 36 months
Planned first patient visit: April 2015
Planned last patient visit, excluding the continued access period: October 2018
Planned interim analysis: The interim analysis of objective intracranial response rate (OIRR) for each study part (Part A, Part B, Part D, or Part E) will occur approximately 6 months after the 23rd evaluable patient has been enrolled into each respective part.

Objectives: The primary objective of this study is to evaluate abemaciclib with respect to OIRR (complete response [CR] + partial response [PR]) based on tumor assessments and Response Assessment in Neuro-Oncology brain metastases response assessment criteria (RANO-BM):

- in patients with brain metastases secondary to HR+, HER2+ breast cancer.
- in patients with brain metastases secondary to HR+, HER2- breast cancer.
- in patients with brain metastases secondary to NSCLC.
- in patients with brain metastases secondary to melanoma.

The secondary objectives of the study are to evaluate abemaciclib with respect to:

- Intracranial disease per RANO-BM
  - Best overall intracranial response (BOIR)
  - Duration of intracranial response (DOIR) (CR + PR)
  - Intracranial disease control rate (IDCR) (CR + PR + stable disease [SD])
  - Intracranial clinical benefit rate (ICBR) (CR + PR + SD ≥6 months)
- Overall
  - Overall survival (OS)
  - Objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and RANO-BM
  - Disease control rate (DCR) (CR+ PR+ SD) per RECIST v1.1 and RANO-BM
  - Progression-free survival (PFS) per RECIST v1.1 and RANO-BM
- Change in symptoms as assessed by MD Anderson Symptom Inventory – Brain Tumor (MDASI-BT)
- Safety and tolerability
- PK of abemaciclib and its metabolites

The exploratory objectives of the study are:

- To explore change in neurocognitive function as assessed by the Trail Making Tests A and B
- To explore change in neurologic signs as assessed by the Neurologic Assessment in Neuro-Oncology (NANO) scale
- To explore the concentration of abemaciclib and its metabolites in plasma, cerebrospinal fluid (CSF), and brain tumor tissue collected at the time of surgical resection for patients participating in Part C, as well as concentrations in time-matched samples of plasma and CSF for patients participating in Part F
- To explore biomarkers related to the mechanism of action of abemaciclib, the cell cycle, and/or the pathogenesis of HR+ breast cancer, NSCLC, and melanoma
- To assess the effect of abemaciclib on leptomeningeal metastases (LM) in patients with HR+ breast cancer, NSCLC, or melanoma based on proposed RANO-LM response criteria
- To explore the relationship between abemaciclib exposure and response

Study Design: Study JPBO is a multicenter, open-label, Phase 2 trial of abemaciclib in patients with brain metastases secondary to HR+ breast cancer, NSCLC, or melanoma. The study will consist of 6 study parts; 4 of these parts will each accrue as few as 23 evaluable patients or as many as 56 evaluable patients with either metastatic breast cancer, NSCLC, or melanoma and at least 1 new or not previously irradiated brain lesion or at least 1 progressive previously irradiated brain lesion. These 4 parts will include patients with HR+, HER2+ breast cancer (Part A), HR+, HER2- breast cancer (Part B), NSCLC (Part D), and melanoma (Part E). Two study parts are exploratory: Part C will include approximately 8 patients (with the possibility of including up to 4 additional patients in order to evaluate interpatient variability) with HR+ breast cancer, NSCLC, or melanoma with intracranial lesions for which surgical resection is clinically indicated in order to assess concentrations of abemaciclib and its metabolites in plasma, CSF, and brain tumor tissue. These patients may resume abemaciclib dosing at least 15 days but no greater than 21 days postoperatively and continue until 1 of the criteria for discontinuation is met. The second exploratory part (Part F) will include approximately 15 patients with HR+ breast cancer, NSCLC, or melanoma and leptomeningeal metastases.

Diagnosis and Main Criteria for Inclusion and Exclusions: Patients are eligible for inclusion in the study if they meet all of the following criteria: 1) have brain metastases secondary to histologically or cytologically confirmed HR+ breast cancer, NSCLC, or melanoma; For Parts A and B: have confirmed HR+ breast cancer. For Part A: have HR+ breast cancer with confirmed HER2 overexpression (HER2+) status. For Part B: have HR+ breast cancer which does not demonstrate HER2 overexpression (HER2-) by either IHC or ISH.
For Part C: have HR+ breast cancer, NSCLC, or melanoma with brain lesions for which surgical resection is clinically indicated and agree to provide posttreatment (5 to 14 days after initiating abemaciclib) brain tumor tissue. For Part D: have NSCLC of any subtype. For Part E: have melanoma of any subtype. For Part F: have HR+ breast cancer, NSCLC, or melanoma with leptomeningeal metastases by documented positive CSF cytology or by clinical signs and symptoms associated with abnormal magnetic resonance imaging (MRI) features. Concomitant parenchymal brain metastases are allowed (not required), but must be stable for at least 4 weeks following whole brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS). 2) deleted criterion; 3) have either ≥1 new or not previously irradiated measurable (according to RANO-BM criteria) metastatic brain lesion ≥10 mm in the longest diameter (LD) or a progressive previously irradiated metastatic brain lesion (Parts A,B, D, and E) or metastatic brain lesion(s) for which surgical resection is clinically indicated (Part C [surgical]); 4) have completed local therapy (surgical resection or stereotactic radiosurgery [SRS]) ≥14 days prior to initiating abemaciclib and recovered from all acute effects; 5) if receiving concomitant corticosteroids, must be on a stable or decreasing dose for at least 7 days prior to the baseline gadolinium-enhanced magnetic resonance imaging (Gd-MRI); 6) have a Karnofsky performance status of ≥70; 7) have a life expectancy ≥12 weeks; 8) HR+ breast cancer patients in Parts A, B, and F: if currently receiving endocrine therapy, may continue receiving the same endocrine therapy provided that extracranial disease is stable for at least 3 months and CNS disease progression has occurred while on this endocrine therapy. If these conditions are not met, patients must discontinue endocrine therapy prior to initiation of abemaciclib. Part C patients may continue or initiate endocrine therapy concurrently with abemaciclib; HER2+ breast cancer patients in Parts A, C, and F: patients may receive concurrent treatment (ongoing or initiated simultaneously with abemaciclib) with trastuzumab. Concurrent treatment with trastuzumab emtansine (T-DM1) is not allowed; NSCLC patients in Parts D and F: if currently receiving gemcitabine or pemetrexed (single-agent or in combination with another therapy), a patient may continue to receive 1 of these 2 therapies as a single agent provided that extracranial disease is stable for at least 6 weeks and CNS disease progression has occurred while on this therapy. Combination therapies (aside from gemcitabine or pemetrexed) must be discontinued for at least 14 days prior to initiation of abemaciclib.; Part C patients may continue or initiate gemcitabine or pemetrexed concurrently with abemaciclib. 9) have discontinued all previous therapies for cancer for at least 14 days prior to receiving abemaciclib and recovered from the acute effects of therapy (Note: Exceptions for concurrent treatment are outlined in criterion [8]); 10) HER2+ breast cancer patients in Parts A, C, and F: for patients receiving concurrent trastuzumab, must have left ventricular ejection fraction within investigative site's normal range; 11) have adequate organ function; 12) are ≥18 years of age; 13) if a female of childbearing potential, must have a negative serum pregnancy test within 7 days of the first dose of abemaciclib and agree to use a medically approved

contraceptive method during the treatment period and for 3 months following the last dose of abemaciclib; If a male, 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 abemaciclib; 14) are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures; and 15) are able to swallow capsules.

Patients will be excluded from the study if they meet any of the following criteria: 16) require immediate local therapy, including but not limited to WBRT, SRS, or surgical resection, for treatment of brain metastases; 17) require concurrent anticancer treatment at any time during the study treatment period (except therapies outlined in criterion [8], or surgical resection [Part C patients only]); 18) are taking concurrent enzyme-inducing antiepileptic drugs (EIAED); 19) have evidence of significant (ie, symptomatic) intracranial hemorrhage; 20) Parts A, B, C, D, and E: have evidence of leptomeningeal metastases by clinical signs and symptoms associated with abnormal MRI features or by previously documented CSF cytology; 21) have experienced >2 seizures within 4 weeks prior to study entry; 22) have visceral crisis; 23) Parts A, B, D, E, and F: have previously received treatment with any CDK4 and CDK6 inhibitor; Part C patients may have received prior palbociclib or ribociclib, but not abemaciclib, treatment ; 24) have known contraindication to Gd-MRI; 25) deleted criterion; 26) are currently enrolled in a clinical trial involving an investigational product or nonapproved use of a drug or device (other than the study drug 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; 27) have received treatment with a drug that has not received regulatory approval for any indication within 14 days of the initial dose of abemaciclib; 28) have a personal history within the last 12 months of any ventricular arrhythmia (including but not limited to ventricular tachycardia and ventricular fibrillation) or sudden cardiac arrest; 29) have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study; 30) have a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea; 31) have a history of any other cancer (except nonmelanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years; 32) are lactating; 33) have an active systemic fungal and/or known viral infection; 34) have an acute bacterial infection requiring intravenous (IV) antibiotics; 35) have received recent or concurrent yellow fever vaccination.

Test Product, Dosage, and Mode of Administration: Abemaciclib will be supplied as capsules to be administered at doses of 150 mg or 200 mg orally every 12 (± 2) hours on Days 1 through 21 of a 21-day cycle, for a total of 42 doses per cycle.

Planned Duration of Treatment:
Treatment period: until disease progression or other discontinuation criteria are fulfilled.
Short-term follow-up (postdiscontinuation): 30 days
Long-term follow-up (postdiscontinuation): until death or overall study completion.

Criteria for Evaluation:
Efficacy:

- OIRR (CR + PR), as defined by RANO-BM
- BOIR
- DOIR (CR + PR)
- IDCR (CR + PR + stable disease [SD])
- ICBR (CR + PR + SD ≥6 months)
- OS
- ORR per RECIST v1.1 and RANO-BM
- DCR per RECIST v1.1 and RANO-BM
- PFS per RECIST v1.1 and RANO-BM

Safety:

- Adverse events (AEs) and serious adverse events (SAEs) using Medical Dictionary for Regulatory Activities (MedDRA) and National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0

Health Outcomes:

- MDASI-BT to measure patient symptoms

Pharmacokinetics:

- Population PK parameters of abemaciclib and its metabolites

Exploratory:

- Trail Making Tests A and B, to measure neurocognitive function
- NANO scale to measure neurologic response or progression
- Relative concentrations of abemaciclib and its metabolites in plasma, CSF, and tumor tissue
- Exploratory correlative analysis of biomarkers related to the mechanism of action of abemaciclib, the cell cycle, and/or the pathogenesis of HR+ breast cancer, NSCLC, and melanoma.
- Assess the effect of abemaciclib on leptomeningeal metastases in patients with HR+ breast cancer, NSCLC, or melanoma based on RANO-LM

Assess the relationship between abemaciclib exposure and response

Statistical Methods:

Statistical:

The primary objective of this clinical trial is to estimate the antitumor activity, measured by OIRR of abemaciclib in patients with brain metastases secondary to HR+ breast cancer, NSCLC, or melanoma.

Simon 2-stage designs will be employed for this study for the following study parts: Part A (patients with HR+, HER2+ breast cancer), Part B (patients with HR+, HER2- breast cancer), Part D (patients with NSCLC), and Part E (patients with melanoma). Each design assumes a 1-sided type I error of 0.05 and 80% power.

For Part A, up to 56 evaluable patients will be enrolled with the possibility of stopping the study early for either lack of efficacy or unacceptable toxicity. Twenty-three evaluable patients will be enrolled in the first stage. If fewer than 2 of the first 23 evaluable patients respond to abemaciclib, accrual will be stopped, and the conclusion will be drawn that abemaciclib is not worthy of further study in the Part-A population. If at least 2 of the first 23 evaluable patients respond to therapy, accrual will continue until 33 additional evaluable patients have been enrolled. A total of 6 responders out of 56 evaluable patients in Part A would need to be observed to warrant further investigation of abemaciclib in this patient population.

The procedure described above tests the null hypothesis (H_0) that the true OIRR of abemaciclib in Part A is $\leq$5% versus the alternative hypothesis (H_a) that the true OIRR is $\geq$15%. The probability of early termination of the treatment arm under H_0 is 0.68.

Parts B, D, and E will have the identical design as Part A.

Efficacy:

Efficacy analyses will be conducted on the full analysis set (FAS) and in the OIRR evaluable population when appropriate. The FAS includes all data from all enrolled patients receiving at least 1 dose of abemaciclib. The OIRR evaluable population is defined as patients receiving at least 1 dose of abemaciclib who have $\geq$1 measurable brain lesion at the time of enrollment (per RANO-BM) and for whom at least 1 post-baseline overall response assessment for intracranial disease is available. OIRR will be reported along with 95% confidence intervals (CIs) using the normal approximation. Point estimates and 95% CIs (using the normal approximation to the binomial) will be calculated for BOIR, IDCR, ICBR, ORR, and DCR for Parts A B, D, and E. Time-to-event efficacy endpoints (OS, PFS, and DOIR) will be summarized for Parts A, B, D, and E using Kaplan-Meier techniques if there is sufficient data. If performed, Kaplan-Meier curves will be generated, and quartiles and point probabilities will be calculated. Interval estimates will be calculated using 95% CIs.

Safety:

Safety analyses will be conducted on the FAS.

Health Outcomes:

Patients with at least 1 baseline and 1 postbaseline assessment will be included in the analyses.

MDASI-BT data will be summarized by study part and response category (CR/PR, SD, PD); change from baseline and time to worsening will be explored. This summary will include mean, standard deviation, median, minimum, maximum, and change from baseline. The MDASI-BT will be reported as core symptoms, brain tumor symptoms, symptom interference, and symptom groupings (affect, cognition, focal neurologic deficit, treatment-related symptoms, generalized/disease status symptoms, and gastrointestinal symptoms).

Pharmacokinetics:
PK analyses will be conducted on all patients who have received at least 1 dose of abemaciclib and have had samples collected. Mean population PK parameters for abemaciclib in plasma (clearance, exposure, volume of distribution, and half-lives) and interindividual 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.

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

Exploratory:

- Trail Making Tests A and B: Summary statistics will be provided by study parts and each response category (CR/PR, SD, PD); change from baseline and time to worsening will be explored.
- NANO Scale: Clinical response and progression will be explored and summarized for the NANO scale using descriptive statistics.
- Drug Concentrations in Plasma, Cerebrospinal Fluid, and Resected Tumor Tissue: The relative concentrations of abemaciclib and its metabolites in plasma, CSF, and tumor tissue collected at the time of surgical resection for patients participating in Part C will be explored. In addition, the relative concentrations of abemaciclib and its metabolites in time-matched samples of plasma and CSF collected on Cycle 3 Day 1, as well as any other time the collection of CSF is clinically indicated, for patients participating in Part F will be explored.
- Biomarkers: Summary statistics for biomarkers with continuous measures will include means, medians, corresponding standard errors, quartiles, and ranges. Biomarkers with discrete measures will be summarized in frequency tables. Correlative analyses may be performed to investigate associations between biomarkers and clinical endpoints.

3. Table of Contents

A Phase 2 Study of Abemaciclib in Patients with Brain Metastases Secondary to Hormone Receptor Positive Breast Cancer, Non-Small Cell Lung Cancer, or Melanoma

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
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).
BBB	blood-brain barrier
BOIR	best overall intracranial response
CDK4 and CDK6	cyclin-dependent kinases 4 and 6
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
collection database	A computer database where clinical trial data are entered and validated.
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.
continued access period	The period between study completion and end of trial during which patients on study therapy who continue to experience clinical benefit and no undue risks may continue to receive study therapy until 1 of the criteria for discontinuation is met.
CNS	central nervous system
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.
CR	complete response
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DCSI	Development Core Safety Information
DOIR	duration of intracranial response
EIAED	enzyme-inducing antiepileptic drugs
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
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.
ER	estrogen receptor
ER+	estrogen receptor positive
ERB/IRB	ethical review board/institutional 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.
ET	endocrine therapy
FAS	full analysis set
FISH	fluorescence in-situ hybridization
GCP	good clinical practice
Gd-MRI	gadolinium-enhanced magnetic resonance imaging

H_0	null hypothesis
H_a	alternative hypothesis
H&E	hematoxylin and eosin
HER2	human epidermal growth factor receptor 2
HER2+/-	human epidermal growth factor receptor 2 positive or negative
HR+	hormone receptor positive
IB	Investigator's Brochure
ICBR	intracranial clinical benefit rate
ICF	informed consent form
ICH	International Conference on Harmonisation
IDCR	intracranial disease control rate
IHC	immunohistochemistry
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 substance or placebo being tested, or used as a reference, in a clinical trial. Investigational product includes a product with a marketing authorization when: 1. used or assembled (formulated or packaged) in a way different from the authorized form, 2. used for an unauthorized indication, or 3. used to gain further information about the authorized form. In this study, the Investigational Product is abemaciclib.
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.
ISH	in-situ hybridization
IV	intravenous
IWRS	interactive web-response system
LC/MS/MS	liquid chromatography-tandem mass spectrometry

LD	longest diameter
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
LM	leptomeningeal metastases
MDASI-BT	MD Anderson Symptom Inventory – Brain Tumor
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MUGA	multi-gated acquisition
NANO	Neurologic Assessment in Neuro-Oncology
NCI	National Cancer Institute
NONMEM	nonlinear mixed effect modeling
NSCLC	non-small cell lung cancer
OIRR	objective intracranial response rate
ORR	objective response rate
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
PFS	progression-free survival
PgR	progesterone receptor
PK	pharmacokinetic
PR	partial response
PT	Preferred Term
QTc	corrected QT interval
randomize	the process of assigning patients to an experimental group on a random basis

RANO	Response Assessment in Neuro-Oncology
RANO-BM	Response Assessment in Neuro-Oncology brain metastases
RANO-LM	Response Assessment in Neuro-Oncology leptomeningeal metastases
Rb	retinoblastoma
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.
rescreen	to screen a patient who was previously declared a screen failure for the same study
SAE	serious adverse event
screen	The act of determining if an individual meets minimum 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, diagnostic psychological tests, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
screen failure	patient who does not meet 1 or more criteria required for participation in a trial
SD	stable disease
SOC	System Organ Class
SRS	stereotactic radiosurgery
Study completion	This study will be considered complete after the final evaluation of overall survival is performed.
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin
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.
ULN	upper limits of normal
US	United States
VTE	venous thromboembolic event
WBRT	whole brain radiotherapy

A Phase 2 Study of Abemaciclib in Patients with Brain Metastases Secondary to Hormone Receptor Positive Breast Cancer, Non-Small Cell Lung Cancer, or Melanoma

5. Introduction

Brain metastases occur in a significant number of cancer patients, with the incidence being highest in lung cancer (40% to 50%), breast cancer (15% to 25%), and melanoma (5% to 20%). In the United States (US) alone, the incidence of brain metastases is approximately 200,000 cases per year (Eichler and Loeffler 2007). In addition, breast cancer, lung cancer, and melanoma are the most common primary tumors metastasizing to the leptomeninges (Wasserstrom et al. 1982). Current standard-of-care treatment options for parenchymal brain metastases include whole brain radiotherapy (WBRT), surgical resection, and stereotactic radiosurgery (SRS). Though surgery and radiotherapy are effective in palliating neurological symptoms, these therapies are associated with neurocognitive deficits (Lin et al. 2013), and the prognosis for patients remains poor. The median overall survival (OS) of patients with brain metastases secondary to non-small cell lung cancer (NSCLC) and melanoma is approximately 7 months and for breast cancer is 13.8 months (Sperduto et al. 2012). Although targeted anticancer agents have shown promising results in treating extracranial disease, delivery of these agents to the central nervous system (CNS) has presented challenges (Adamo et al. 2011). The blood-brain barrier (BBB) arises from both a structural barrier and drug efflux transporters that may prevent most anticancer drugs from efficiently reaching brain tumors or metastases, though the BBB may be partially compromised at the metastatic site, enabling the delivery of some drugs to the tumor site (Deeken and Loscher 2007).

During the cell cycle, the G1 restriction point controls entry into S phase and is essential for proper regulation of cell proliferation (Sherr 1996; Ortega et al. 2002). Cyclin-dependent kinases 4 and 6 (hereafter referred to as CDK4 and CDK6) participate in a complex with the D type cyclins to initiate progression through the G1 restriction point. The CDK4 and CDK6 – cyclin D1 complex regulates the G1 restriction point through phosphorylation and inactivation of the retinoblastoma (Rb) tumor suppressor protein, thereby promoting S phase entry. Alterations in this pathway occur frequently in human cancers and involve 1) loss of functional CDK inhibitors through deletion or epigenetic silencing, 2) activating mutations and/or overexpression of CDK4 and CDK6 or the D type cyclins, and 3) loss of functional Rb through mutation or deletion. Except for tumors with functional loss of Rb, which functions downstream of the CDK4 and CDK6 – cyclin D1 complex, most cancers are potentially sensitive to pharmacologic inhibition of CDK4 and CDK6. From a therapeutic standpoint, the goal of inhibiting CDK4 and CDK6 with a small molecule is to prevent cell cycle progression through the G1 restriction point, thus arresting tumor growth.

The mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK) pathway are immediately downstream to BRAF and KRAS or NRAS. Cancers that harbor mutations in *KRAS*, *NRAS* and/or *BRAF* lead to the overactivation of this pathway. Patients with metastatic NSCLC that harbor *KRAS* mutations (25%) have a poor prognosis compared to

NSCLC patients who are KRAS wild-type (Guan et al. 2013). 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). The key genetic alterations in melanomas [including *BRAF* mutation (~50%), *NRAS* mutation (~20%), and loss of CDKN2A (~50%)] converge on the CDK4 and CDK6-CyclinD complex to enable malignant proliferation.

Abemaciclib (LY2835219) represents a selective and potent small molecule inhibitor of CDK4 and CDK6 with acceptable physical characteristics, pharmacokinetic (PK) properties, and safety profile in nonclinical species. Cell-based studies in breast cancer models have demonstrated that abemaciclib inhibits CDK4 and CDK6 to induce G1 arrest specifically in cell lines with functional Rb versus lines which lack functional Rb. Additional cell-based studies, which evaluated in vitro growth inhibition across a diverse panel of 46 breast cell lines representing the known molecular subgroups of breast cancer, indicated that sensitivity to CDK4 and CDK6 inhibition was greater in ER+ lines with luminal histology. Abemaciclib demonstrates antitumor activity in multiple human xenograft models for human cancers including, but not limited to, NSCLC and melanoma. Preclinical data indicate that NSCLC models with *KRAS* mutations generally show greater sensitivity to growth inhibition by abemaciclib.

In radiolabeled studies in rats, [^{14}C]LY2835219-derived radioactivity was measurable in CNS tissues (cerebellum, cerebrum, medulla, and spinal cord) protected by the BBB through 24 hours postdose after a single dose. Abemaciclib has also been shown to inhibit glioblastoma intracranial xenografts, resulting in a statistically significant and dose-dependent improvement in survival (Sanchez-Martinez et al. 2011).

In the ongoing Phase 1 Study I3Y-MC-JPBA (JPBA) abemaciclib has demonstrated acceptable safety across 5 tumor-specific cohorts at doses up to 200 mg every 12 hours. The most common treatment-emergent adverse events (TEAEs) possibly related to study drug included diarrhea, nausea, fatigue, vomiting, and neutropenia. Results from Study JPBA suggest that abemaciclib has clinical activity in several distinct cancer populations. In the single agent metastatic breast cancer cohort, abemaciclib demonstrated evidence of clinical activity in 12 patients with hormone receptor positive (HR+) metastatic breast cancer, with either HER2+ or HER2 negative (HER2-) disease, including a single patient with CNS target disease. In the NSCLC cohort, 1 patient with a *KRAS* mutation and 1 patient with KRAS wild-type showed response. The melanoma cohort had 1 patient with a partial response.

In Study JPBA, cerebrospinal fluid (CSF) samples were collected from a limited number of patients with breast cancer, NSCLC, and melanoma with brain metastases present at baseline; samples from 10 patients were analyzed for concentrations of abemaciclib. In general, abemaciclib concentrations in CSF were consistent with unbound plasma concentrations. The clinical results, as well as preclinical findings demonstrating that abemaciclib crosses the BBB, support further investigation of abemaciclib in patients with brain metastases secondary to HR+ breast cancer, NSCLC, and melanoma.

The Phase 2 Study I3Y-MC-JPBO (JPBO) will evaluate the safety and efficacy of abemaciclib in patients with HR+ breast cancer, NSCLC, and melanoma with new or not previously irradiated brain lesions as well as previously irradiated progressive brain lesions.

More information about the known and expected benefits, risks, and reasonably anticipated adverse events (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 [DCSI]) 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.

5.1. Rationale for Amendment (a)

The primary rationale for amendment (a) is to modify eligibility criteria to include additional study parts for patients with brain metastases secondary to NSCLC and melanoma, as well as an exploratory study part for patients with leptomeningeal metastases (LM). Further changes for clarity were provided for study parts with respect to permitted concomitant therapies. Additional changes include modification of language pertaining to supportive care and dose suspensions for patients experiencing diarrhea related to abemaciclib, as well as clarification that the study will use the Response Assessment in Neuro-Oncology Brain Metastases (Lin et al. 2015) criteria to assess intracranial response.

Minor editorial changes have been made to improve clarity and practicability of the protocol and secure alignment with the intended study design.

5.2. Rationale for Amendment (b)

The rationale for amendment (b) is primarily to clarify the abemaciclib dose to be administered in combination with trastuzumab. Additional updates were made to the dosing guidance for cases of hematologic toxicity and on the use of blood cell growth factors. Eli Lilly and Company (Lilly) conducted a review across several clinical trials of abemaciclib and concluded that there were some inconsistencies. This amendment will harmonize the dosing guidance across protocols and clarify that blood cell growth factors are only to be used in a manner consistent with American Society of Clinical Oncology (ASCO) guidelines.

In addition, in order to evaluate interpatient variability for Part C (surgery patients), up to 4 additional patients may be enrolled in this cohort. Finally, the Response Assessment in Neuro-Oncology brain metastases (RANO-BM) and Response Assessment in Neuro-Oncology leptomeningeal metastases (RANO-LM) assessment criteria were added to Attachment 5 rather than referencing a separate manual.

Minor changes have been made to improve clarity and feasibility of the protocol and secure alignment with the intended study design.

5.3. Rationale for Amendment (c)

The rationale for amendment (c) is to update the protocol to define evaluable patients for study Parts A, B, D, and E, and to clarify the number of patients to be enrolled. This is to ensure that an adequate number of evaluable patients are enrolled, since non-evaluable patients reduce the ability to detect a treatment effect in this study.

In addition, re-screening of patients was not previously permitted; however, in this amendment, re-screening is allowed under certain circumstances with prior approval of the Lilly clinical research physician (CRP) or designee.

5.4. Rationale for Amendment (d)

Study JPBO protocol was amended to update the dosing guidance for cases of non-hematologic toxicity, diarrhea, and ALT increase. This amendment will harmonize the dosing guidance across all clinical trials of abemaciclib in the metastatic setting. The amendment updated the safety language regarding hepatic monitoring, assessment of renal function, and venous thromboembolic events (VTEs) for ongoing patients. Minor typographical and formatting edits were made throughout the document for clarity and consistency.

6. Objectives

6.1. Primary Objective

To evaluate abemaciclib with respect to objective intracranial response rate (OIRR; complete response [CR] + partial response [PR]) based on tumor assessments and Response Assessment in Neuro-Oncology brain metastases response assessment criteria (RANO-BM):

- in patients with brain metastases secondary to HR+, HER2+ breast cancer.
- in patients with brain metastases secondary to HR+, HER2- breast cancer.
- in patients with brain metastases secondary to NSCLC.
- in patients with brain metastases secondary to melanoma.

6.2. Secondary Objectives

The secondary objectives of the study are as follows:

To evaluate abemaciclib with respect to:

- Intracranial disease per RANO-BM
  - Best overall intracranial response (BOIR)
  - Duration of intracranial response (DOIR) (CR + PR)
  - Intracranial disease control rate (IDCR) (CR + PR + stable disease [SD])
  - Intracranial clinical benefit rate (ICBR) (CR + PR + SD ≥6 months)
- Overall
  - OS
  - Objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and RANO-BM
  - Disease control rate (DCR) (CR+ PR+ SD) per RECIST v1.1 and RANO-BM
  - Progression-free survival (PFS) per RECIST v1.1 and RANO-BM
- Change in symptoms as assessed by MD Anderson Symptom Inventory – Brain Tumor (MDASI-BT)
- Safety and tolerability
- PK of abemaciclib and its metabolites

6.3. Exploratory Objectives

- To explore change in neurocognitive function as assessed by Trail Making Tests A and B
- To explore change in neurologic signs as assessed by the Neurologic Assessment in Neuro-Oncology (NANO) scale
- To explore the concentration of abemaciclib and its metabolites in plasma, CSF and brain tumor tissue collected at the time of surgical resection for patients participating in Part C, as well as concentrations in time-matched samples of plasma and CSF for patients participating in Part F
- To explore biomarkers related to the mechanism of action of abemaciclib, the cell cycle, and/or the pathogenesis of HR+ breast cancer, NSCLC, and melanoma
- To assess the effect of abemaciclib on LM in patients with HR+ breast cancer, NSCLC, or melanoma based on proposed RANO-LM response criteria

- To explore the relationship between abemaciclib exposure and response

7. Study Population

Rescreening of individuals who do not meet the criteria for participation in this study is permitted only after discussion with and permission from the Lilly CRP or designee.

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 brain metastases secondary to histologically or cytologically confirmed HR+ breast cancer, NSCLC, or melanoma.

For Parts A and B: have confirmed HR+ breast cancer. To fulfill the requirement for HR+ disease, a breast cancer must express, at least 1 of the hormone receptors (ER or progesterone receptor [PgR]). For ER and PgR assays to be considered positive, ≥1% of tumor cell nuclei must be immunoreactive by immunohistochemistry (IHC) (Hammond et al. 2010).

For Part A: have HR+ breast cancer with confirmed HER2 overexpression (HER2+) status. To fulfill the requirement for HER2+ disease, tumor tissue must demonstrate 3+ by IHC or gene amplification by in-situ hybridization (ISH) (Wolff et al. 2013).

For Part B: have HR+ breast cancer which does not demonstrate HER2 overexpression (HER2-) by either IHC or ISH.

For Part C: have HR+ breast cancer, NSCLC, or melanoma with brain lesions for which surgical resection is clinically indicated and agree to provide posttreatment (5 to 14 days after initiating abemaciclib) brain tumor tissue.

For Part D: have NSCLC of any subtype.

For Part E: have melanoma of any subtype

For Part F: have HR+ breast cancer, NSCLC, or melanoma with leptomeningeal metastases by documented positive CSF cytology or by clinical signs and symptoms associated with abnormal magnetic resonance imaging (MRI) features. Concomitant parenchymal brain metastases are allowed (not required), but must be stable for at least 4 weeks following whole brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS).

[2] Deleted criterion.

[3] For Parts A,B, D and E: have ≥1 new or not previously irradiated measurable metastatic brain lesion ≥10 mm in the longest diameter (LD) and ≥5 mm in the perpendicular plane (refer to RANO-BM criteria in Attachment 5) or a progressive previously irradiated metastatic brain lesion on radiographic imaging by gadolinium-enhanced magnetic resonance imaging (Gd-MRI).

Note: for patients with prior WBRT or SRS, previously irradiated lesion(s) must be measurable (≥10 mm in LD and ≥5 mm in the perpendicular plane) and demonstrate unequivocal progression in the opinion of the treating investigator. Otherwise new or not previously irradiated lesions must be present. Previously untreated lesions are preferred target lesions (see Attachment 5).

For Part C (surgical): have metastatic brain lesion(s) for which surgical resection is clinically indicated.

[4] have completed local therapy (surgical resection or SRS) ≥14 days prior to initiating abemaciclib and recovered from all acute effects. Patients are not required to have received prior local therapy for study participation.

[5] if receiving concomitant corticosteroids, must be on a stable or decreasing dose for at least 7 days prior to the baseline Gd-MRI.

[6] have a Karnofsky performance status of ≥70 (see Attachment 4).

[7] have a life expectancy ≥12 weeks.

[8] for HR+ breast cancer patients in Parts A, B, and F: if currently receiving endocrine therapy, a patient may continue to receive the same endocrine therapy provided that extracranial disease is stable for at least 3 months and CNS disease progression has occurred while on this endocrine therapy. If these conditions are not met, patients must discontinue endocrine therapy prior to initiation of abemaciclib. Part C patients may continue or initiate endocrine therapy concurrently with abemaciclib and need not meet the above conditions.

For HER2+ breast cancer patients in Parts A, C, and F: patients may receive concurrent treatment (ongoing or initiated simultaneously with abemaciclib) with trastuzumab. Concurrent treatment with trastuzumab emtansine (T-DM1) is not allowed.

For NSCLC patients in Parts D and F: if currently receiving gemcitabine or pemetrexed (single-agent or in combination with another therapy), a patient may continue to receive 1 of these 2 therapies as a single agent provided that extracranial disease is stable for at least 6 weeks and CNS disease progression has occurred while on this therapy. Combination therapies (aside from gemcitabine or pemetrexed) must be discontinued for at least 14 days prior to initiation of abemaciclib. Part C patients may continue or initiate gemcitabine or pemetrexed (as single agents) concurrently with abemaciclib and need not meet the above conditions.

[9] have discontinued all previous therapies for cancer (including cytotoxic chemotherapy, targeted therapy [including, but not limited to, everolimus], radiotherapy, immunotherapy, and investigational therapy) for at least 14 days prior to receiving abemaciclib and recovered from the acute effects of therapy (treatment-related toxicity resolved to baseline) except for residual alopecia or peripheral neuropathy.

Note: Exceptions for concurrent treatment are outlined in criterion [8].

[10] for HER2+ breast cancer patients in Parts A, C, and F: patients receiving concurrent trastuzumab, must have left ventricular ejection fraction within investigative site's normal range.

[11] have adequate organ function including:

- Hematologic: Absolute neutrophil count (ANC) ≥1.5 x 109/L, platelets ≥100 x 109/L, and hemoglobin ≥8 g/dL. Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator.
- Hepatic: Bilirubin ≤1.5 times upper limits of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0 times ULN (or ALT and AST ≤5.0 times ULN if liver metastases are present).
- Renal: Serum creatinine ≤1.5 times ULN.

[12] are ≥18 years of age.

[13] if a female of childbearing potential, must have a negative serum pregnancy test within 7 days of the first dose of abemaciclib and agree to use a medically approved contraceptive method during the treatment period and for 3 months following the last dose of abemaciclib. If a male, 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 abemaciclib. Contraceptive methods may include an intrauterine device [IUD] or barrier method. If condoms are used as a barrier method, a spermicidal agent should be added as a double barrier protection.

[14] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

[15] are able to swallow capsules.

7.2. Exclusion Criteria

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

[16] require immediate local therapy, including but not limited to WBRT, SRS, or surgical resection, for treatment of brain metastases.

[17] require concurrent anticancer treatment at any time during the study treatment period.

Note: exceptions are therapies outlined in criterion [8] or surgical resection (Part C patients only).

[18] are taking concurrent enzyme-inducing antiepileptic drugs (EIAED).

[19] have evidence of significant (ie, symptomatic) intracranial hemorrhage.

[20] for Parts A, B, C, D, and E: have evidence of leptomeningeal metastases by clinical signs and symptoms associated with abnormal MRI features or by documented CSF cytology.

Note: discrete dural metastases are permitted.

[21] have experienced >2 seizures within 4 weeks prior to study entry.

[22] have visceral crisis. Visceral crisis is not the mere presence of visceral metastases but implies severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of the disease.

[23] for Parts A, B, D, E, and F: have previously received treatment with any CDK4 and CDK6 inhibitor. Part C patients may have received prior palbociclib or ribociclib, but not abemaciclib, treatment.

[24] have known contraindication to Gd-MRI.

[25] deleted criterion.

[26] are currently enrolled in a clinical trial involving an investigational product or nonapproved use of a drug or device (other than the study drug 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.

[27] have received treatment with a drug that has not received regulatory approval for any indication within 14 days of the initial dose of abemaciclib.

[28] have a personal history within the last 12 months of any ventricular arrhythmia (including but not limited to ventricular tachycardia and ventricular fibrillation) or sudden cardiac arrest.

[29] have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study (for example, history of major surgical resection involving the stomach or small bowel).

[30] have a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea.

[31] have a history of any other cancer (except nonmelanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years.

[32] are lactating.

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

[34] have an acute bacterial infection requiring intravenous (IV) antibiotics.

[35] have received recent (within 28 days of initial dose of abemaciclib) or concurrent yellow fever vaccination.

7.3. Discontinuation

The reason for discontinuation and the date of discontinuation will be collected for all patients.

Patients who are discontinued from abemaciclib early will have follow-up procedures performed as shown in the Study Schedule (Attachment 1).

If a patient withdraws informed consent, he or she must not be contacted unless he or she has explicitly provided permission and consent. Lilly may continue to use previously collected medical research data prior to the withdrawal consistent with the original authorization.

7.3.1. Discontinuation of Inadvertently Enrolled 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 CRP and the investigator to determine whether the patient may continue in the study,

with or without abemaciclib. Inadvertently enrolled patients may be maintained in the study and on abemaciclib 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 abemaciclib 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 abemaciclib.

7.3.2. Discontinuation of Investigational Product

Patients will be discontinued from abemaciclib in the following circumstances:

- the patient has intracranial (parenchymal) disease progression according to RANO-BM or extracranial disease progression according to RECIST v1.1. For patients in Part F, evidence of leptomeningeal disease progression based upon radiography, cytology, and/or clinical neurological assessment will also result in discontinuation from abemaciclib. In exceptional circumstances, if discordant disease progression and response (intracranial vs. extracranial or vice versa) occur and the patient has exhausted all other treatment options, the investigator must contact the Lilly CRP to discuss the possibility of continuing the patient on abemaciclib.
- the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication (except those noted as allowable in the inclusion/exclusion criteria and Section 9.6); discontinuation of abemaciclib occurs prior to introduction of the new agent.
- the patient experiences unacceptable toxicity
- the patient is noncompliant with study procedures and/or treatment
- if further dose reduction is required beyond 100 mg every 12 hours.
- the investigator decides that the patient should be discontinued from abemaciclib.
- the patient or the patient's designee (for example, legal guardian) requests that the patient be withdrawn from abemaciclib.
- 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.

7.3.3. Discontinuation from the Study

Patients will be discontinued from the study in the following circumstances:

- the patient or the patient's designee (for example, legal guardian) requests that the patient be withdrawn from the study.
- 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 (GCP).

7.3.4. Patients who are Lost to Follow-Up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make

3 diligent attempts (by telephone and/or email) to contact patients who fail to return for a scheduled visit or who the site is otherwise unable to follow.

7.3.5. 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 discontinuation of study site participation necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

7.3.6. Discontinuation of the Study

The study will be discontinued if Lilly judges discontinuation of the study 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

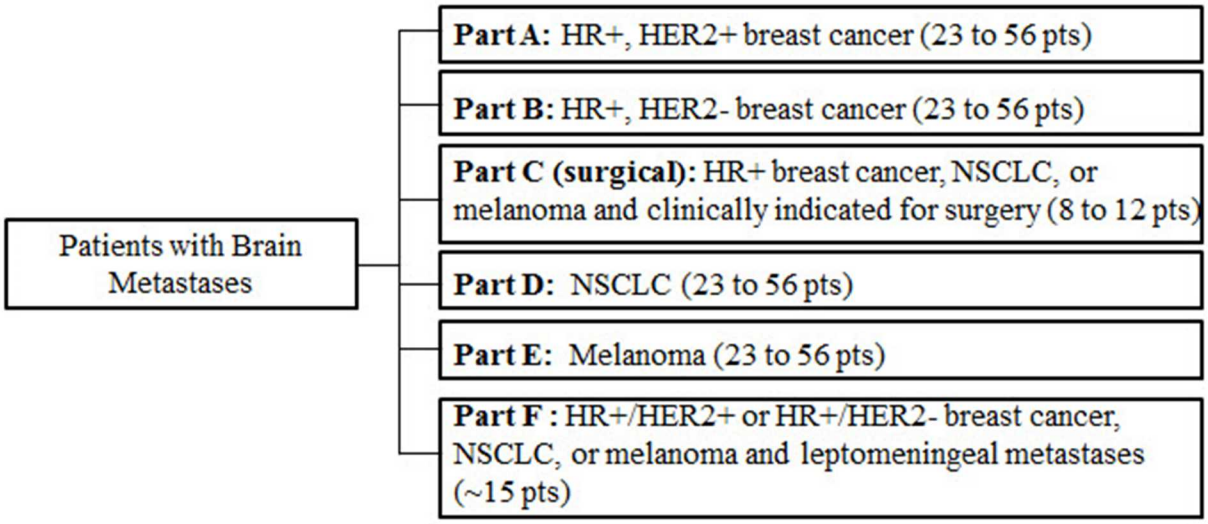
Study JPBO is a multicenter, open-label, Phase 2 trial of abemaciclib in patients with brain metastases secondary to HR+ breast cancer, NSCLC or melanoma.

The study will consist of a total of 6 parts; 4 of these parts will each accrue as few as 23 evaluable patients or as many as 56 evaluable patients with metastatic cancer (breast cancer, NSCLC or melanoma) and at least 1 new or not previously irradiated measurable brain lesion or at least 1 progressive previously irradiated measurable brain lesion. The Part D (NSCLC) and Part E (melanoma) populations will be monitored upon enrollment and may be adjusted to achieve adequate numbers of patients with wild type versus mutant biomarker (*KRAS* for NSCLC and *BRAF* for melanoma) status.

Part C will initially include approximately 8 patients with any of the 3 tumor types (breast cancer, NSCLC, or melanoma) who have intracranial lesions for which surgical resection is clinically indicated in order to assess concentrations of abemaciclib and its metabolites in plasma, CSF, and brain tumor tissue. Up to 4 additional patients may be added to Part C in order to evaluate interpatient variability. Part C patients may resume abemaciclib dosing at least 15 days but no greater than 21 days postoperatively and continue until 1 of the criteria for discontinuation is met (refer to Section 7.3). The day the patient resumes treatment with abemaciclib will be considered as Cycle 2 Day 1 and all pertinent study procedures (Attachment 1) must be completed. In exceptional cases, in consultation with the Lilly CRP, a patient may resume dosing more than 21 days postoperatively. These exceptional cases will not be considered protocol violations.

Part F will include approximately 15 patients with any of the 3 tumor types (breast cancer, NSCLC, or melanoma) and leptomeningeal metastases.

Figure JPBO.1 illustrates the study design.



* All patients in Parts A, B, D, E, and F will receive abemaciclib PO Q12H until PD, unacceptable toxicity, or withdrawal from the study. Patients in Part C will receive abemaciclib PO Q12H for 5 to 14 days prior to surgical resection; dosing may resume after a wound healing period and continue until PD, unacceptable toxicity or withdrawal.
Abbreviations: HER2+ = HER2 positive; HER2-=HER2 negative; HR+ = hormone receptor positive; mg = milligrams; NSCLC = Non-small cell lung cancer; PD = progressive disease; PO = orally; pts = patients; Q12H = every 12 hours.

Figure JPBO.1. Illustration of study design.

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

- **Baseline:** begins when the informed consent form (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 continued access 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 abemaciclib. The date of this agreement is to be reported on the electronic case report form (eCRF) as the Date of Discontinuation from abemaciclib.
    - **Postdiscontinuation Follow-Up**: begins the day after the patient and the investigator agree that the patient will no longer continue abemaciclib.

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

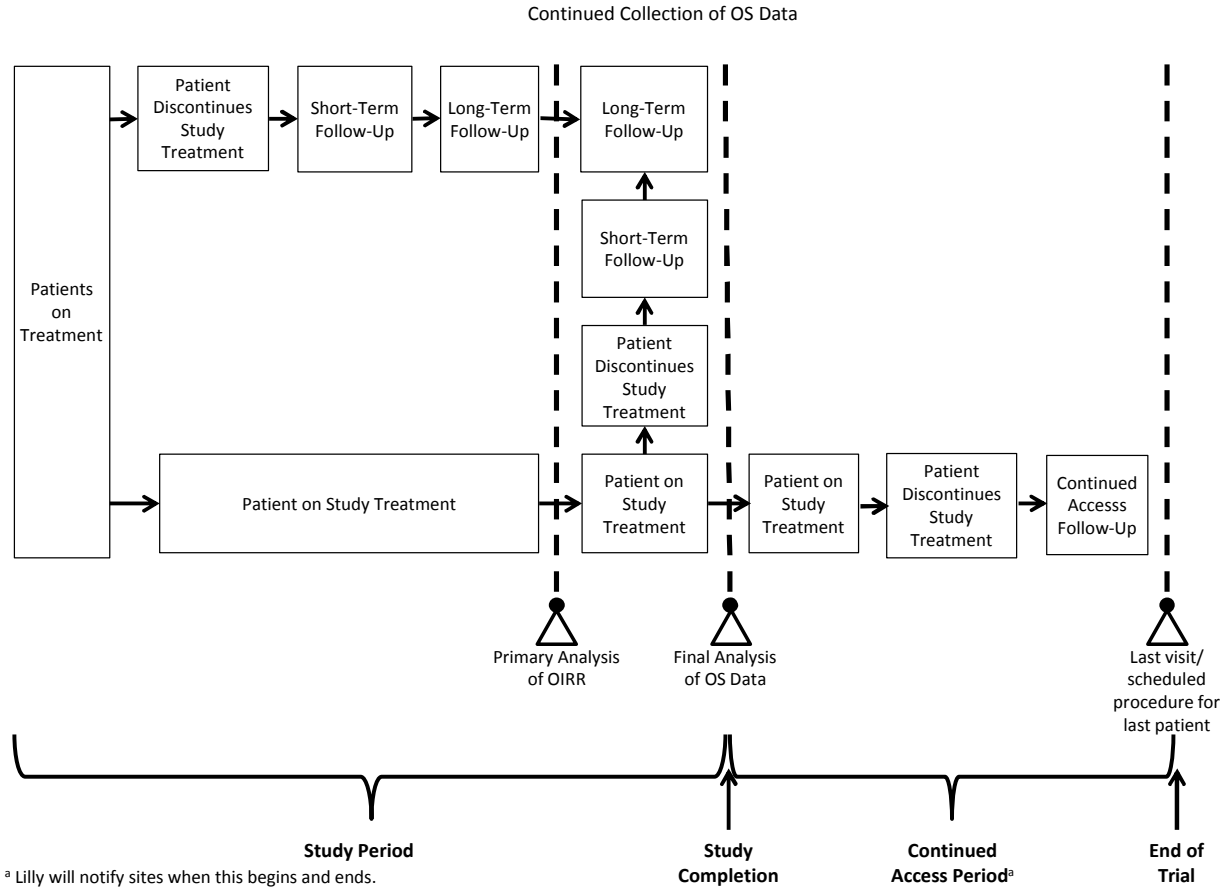
        Long-term follow-up begins the day after short-term follow-up is completed and continues until the patient's death or overall study completion.

- **Continued Access Period:** begins after study completion and ends at the end of trial. During the continued access period, patients on abemaciclib who continue to experience clinical benefit and no undue risks may continue to receive abemaciclib until 1 of the criteria for discontinuation is met. The continued access period includes continued access follow-up.
    - **Continued Access Follow-Up:** begins the day after the patient and the investigator agree that the patient will no longer continue abemaciclib in the continued access period and lasts approximately 30 days.

8.1.1. Study Completion and End of Trial

The primary analysis of OIRR for each study Part (A, B, D, or E) will occur approximately 6 months after up to 56 evaluable patients have been enrolled into each respective part. This is to ensure that adequate durability of response data is available at the time of analysis. 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. The end of trial occurs after study completion and after the last patient has discontinued study treatment and completed any applicable continued access follow-up (Figure JPBO.2).



Abbreviations: OIRR = objective intracranial response rate; OS = overall survival.

Figure JPBO.2. Study period and continued access period diagram.

8.1.2. Continued Access Period

The continued access period will apply to this study only if at least 1 patient is still on abemaciclib when study completion occurs.

Patients receiving abemaciclib and experiencing ongoing clinical benefit and no undue risks may continue to receive abemaciclib in the continued access period until 1 of the criteria for discontinuation is met (Section 7.3). Lilly will notify investigators when the continued access period begins.

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

During the continued access period, all AEs, SAEs, and abemaciclib exposure will be reported on the eCRF. SAEs will also be reported to Lilly Global Patient Safety (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 nonrandomized, uncontrolled design is being used in this study. Although this design has known inferential deficiencies, this design is justified for this study for the following reasons:

1. There is no approved chemotherapeutic option for these patients.
2. The primary endpoint in this study is intracranial tumor response, observation of which is putative evidence of antitumor effect of abemaciclib.

9. Treatment

9.1. Treatments Administered

Abemaciclib 200 mg will be administered orally every 12 (± 2) hours on Days 1 through 21 of a 21-day cycle when administered as a single agent or for breast cancer patients in combination with endocrine therapy. For HER2+ breast cancer patients receiving concurrent trastuzumab or for NSCLC patients receiving concurrent gemcitabine or pemetrexed, abemaciclib will be administered at a starting dose of 150 mg orally every 12 (± 2) hours on Days 1 through 21 of a 21-day cycle.

Table JPBO.1 shows the treatment regimen.

Table JPBO.1. Treatment Regimens/Dosing Schedule

Regimen	Period/Cycle	Dose
Abemaciclib (single agent or in combination with ET)	Treatment/21-day cycle	200 mg Q12H PO on Days 1 – 21 of a 21-day cycle
Abemaciclib (in combination with trastuzumab, gemcitabine, or pemetrexed)	Treatment/21-day cycle	150 mg Q12H PO on Days 1 – 21 of a 21-day cycle

Abbreviations: ET = endocrine therapy; PO = orally; Q12H = once every 12 (± 2) hours.

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

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

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

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

9.2. Materials and Supplies

Abemaciclib will be supplied by Lilly as capsules for oral administration. The capsules should be stored at room temperature according to the range provided on the product label and not opened, crushed, or dissolved. Investigators should instruct patients to store the capsules in the original package and in a location inaccessible to children. Abemaciclib will be labeled according to country regulatory requirements.

9.3. Method of Assignment to Treatment

Upon obtaining informed consent, site personnel should access the interactive web-response system (IWRS) which will assign a patient number. The IWRS will be used to assign abemaciclib to patients who meet all criteria for enrollment in 1 of 6 study parts:

- Part A: patients with HR+, HER2+ breast cancer
- Part B: patients with HR+, HER2- breast cancer
- Part C: patients with HR+ breast cancer, NSCLC or melanoma and intracranial lesions for which surgical resection is clinically indicated.
- Part D: patients with NSCLC
- Part E: patients with melanoma
- Part F: patients with HR+ breast cancer, NSCLC, or melanoma and LM

The period between assignment to abemaciclib in IWRS and the first dose (Cycle 1, Day 1) should not exceed 7 days.

9.4. Selection and Timing of Doses

Abemaciclib will be taken orally every 12 (± 2) hours on Days 1 through 21 of a 21-day cycle according to Table JPBO.1, for a total of 42 doses per 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.

A cycle is defined as an interval of 21 days plus any subsequent delay prior to start of the next cycle. A delay in the start 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. In exceptional cases, for planned delays (including but not limited to vacation or holidays), additional abemaciclib may be dispensed.

A patient may continue to receive abemaciclib until meeting 1 or more of the specified reasons for discontinuation (as described in Section 7.3).

9.4.1. Special Treatment Considerations

9.4.1.1. Dose Adjustments and Delays

Table JPBO.2. Toxicity Dose Adjustments and Delays of Abemaciclib for Study I3Y-MC-JPBO

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity Section 9.4.1.1.3	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 9.4.1.1.3	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 9.4.1.1.3	Grade 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic toxicity: If patient requires administration of blood cell growth factors Sections 9.4.1.1.3 and 9.6.4	Regardless of severity (Use of growth factors 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 led to the use of growth factor.
Nonhematologic Toxicity[a] (except diarrhea and ALT increased) Section 9.4.1.1.4	Persistent or recurrent[b] Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
Nonhematologic Toxicity Section 9.4.1.1.4	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 Sections 9.4.1.1.4.1 and 9.6.5	Grade 2 that does not resolve within 24 hours to at least Grade 1	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose reduction is **NOT** required.
Diarrhea Sections 9.4.1.1.4.1 and 9.6.5	Persistent or recurrent[b] Grade 2 that does not resolve with maximal supportive measures or any Grade of diarrhea that requires hospitalization	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea Sections 9.4.1.1.4.1 and 9.6.5	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.

Toxicity Dose Adjustments and Delays of Abemaciclib for Study I3Y-MC-JPBO

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
ALT Increased (Sections 9.4.1.1.4.2 and 10.3.4.1)	Persistent or recurrent[b] Grade 2 (>3.0-5.0×ULN)[c], or Grade 3 (>5,0-20.0×ULN)[d]	Dose **MUST** be suspended until toxicity resolves to baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
ALT Increased (Sections 9.4.1.1.4.2 and 10.3.4.1)	Grade 4 (>20.0×ULN)	Abemaciclib **MUST** be discontinued.	Abemaciclib **MUST** be discontinued.
ALT Increased with increased total bilirubin, in the absence of cholestasis (Sections 9.4.1.1.4.2 and 10.3.4.1)	Grade 3 increased ALT (>5.0 x ULN) with total bilirubin >2 x ULN	Abemaciclib **MUST** be discontinued	Abemaciclib **MUST** be discontinued

Abbreviations: ALT = alanine transaminase; ASCO = American Society of Clinical Oncology; ULN = upper limit of normal.

Note: MAY = per the investigator's clinical judgment; MUST = mandatory.

a Additional guidance for renal and hepatic monitoring is in Sections 10.3.3.1 and 10.3.3.2.

b Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event). As a general guidance, based on the risk/benefit balance assessment per the investigator, for a patient who experiences a new episode of Grade 3 hematological toxicity after more than 8 weeks following the last episode of same Grade 3 hematological toxicity, the investigator may consider resuming the patient on the same drug dose should the patient satisfy the following conditions:
- shows stable hematological counts (Grade ≤2) during that timeframe
- has absence of any signs or risk of infection
- is benefiting from study treatment

c Note: the patient who presents with no liver metastases at baseline.

d Grade 3 ALT increased is a trigger for additional assessments and possibly hepatic monitoring. See Section 10.3.4.1 for additional guidance for hepatic monitoring

9.4.1.1.1. Dose Adjustments

Abemaciclib dose adjustments, as outlined in Table JPBO.3 are allowed both within a cycle and between cycles. Abemaciclib must be reduced sequentially by 1 dose level.

For patients requiring dose reduction(s), any reescalation to a prior dose level is permitted only after consultation with the Lilly CRP.

Table JPBO.3. Dose Adjustments of Abemaciclib for Study I3Y-MC-JPBO

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

Abemaciclib must be discontinued if further dose reduction is required beyond 100 mg every 12 hours.

9.4.1.1.2. Dose Suspension (within a Cycle) and Cycle Delay

Both abemaciclib dose suspension (within a cycle) and cycle delay are permitted up to 14 days to allow sufficient time for recovery from a toxicity (defined as an AE possibly related to

abemaciclib per the investigator's judgment). Patients not recovering from toxicity within 14 days should be considered for discontinuation of abemaciclib. In exceptional circumstances, a delay >14 days is permitted upon agreement between the investigator and the Lilly CRP, and abemaciclib dose adjustment is to be considered.

In the event of a cycle delay due to logistical reasons (for example, due to patient availability), the patient should continue on abemaciclib if the patient has adequate drug supply. If a patient's treatment is interrupted as a result of not having sufficient drug supply, the cycle may be delayed up to 7 days (and not be considered a protocol violation). In exceptional circumstances, a delay >7 days is permitted upon agreement between the investigator and the Lilly CRP.

An interruption in Cycle 1 dosing or a delay in the initiation of Cycle 2 may occur in order to allow patients participating in Part C to undergo surgical resection. For additional information, refer to Section 9.6.2.

9.4.1.1.3. Hematologic Toxicity

If a patient experiences Grade 4 hematologic toxicity, 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 JPBO.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 JPBO.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 abemaciclib must be reduced by 1 dose level.

Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event). As a general guidance, based on the risk/benefit balance assessment per the investigator, for a patient who experiences a new episode of Grade 3 hematological toxicity after more than 8 weeks following the last episode of same Grade 3 hematological toxicity, the investigator may consider resuming the patient on the same drug dose should the patient satisfy the following conditions:

- The patient showed stable hematological counts (Grade ≤2) during that timeframe
- In the absence of any signs or risk of infection
- The patient is benefiting from study treatment

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 re-initiation of abemaciclib, hematologic toxicity must resolve to either baseline or at least Grade 2.

9.4.1.1.4. Nonhematologic Toxicity

If a patient experiences ≥ Grade 3 nonhematologic toxicity, then dosing must be 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 JPBO.3.

If a patient experiences persistent or recurrent Grade 2 nonhematologic toxicity (except diarrhea, refer to Section 9.4.1.1.4.1 or ALT increased, refer to Section 10.3.4.1) that does not resolve with maximal supportive measures within 7 days to either baseline or Grade 1, then dosing of abemaciclib 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 JPBO.3 at the discretion of the investigator.

Before re-initiation of abemaciclib, nonhematologic toxicity (except alopecia and fatigue) must resolve to either baseline or Grade 1.

9.4.1.1.4.1. Diarrhea

A patient experiencing diarrhea requiring hospitalization (irrespective of grade; that is, requiring IV rehydration) or severe diarrhea (Grade 3 or 4) must have dosing suspended (until the toxicity resolves to at least Grade 1) and must have the abemaciclib dose reduced by 1 dose level as outlined in Table JPBO.3.

If a patient experiences Grade 2 diarrhea that does not resolve with maximal supportive measures (refer to Section 9.6.5) within 24 hours to at least Grade 1, the study drug must be suspended (until the toxicity resolves to at least Grade 1) but abemaciclib dose reduction is not required. However, if a patient experiences persistent or recurrent Grade 2 diarrhea that does not resolve with maximal supportive measures (refer to Section 9.6.5) within 24 hours to at least Grade 1, then dosing must be suspended (until the toxicity resolves to at least Grade 1), and the dose of abemaciclib must be reduced by 1 dose level as outlined in Table JPBO.3.

9.4.1.1.4.2. Hepatic Toxicity

Dose modifications and management for increased ALT are provided in Table JPBO.3. For persistent or recurrent Grade 2 ALT increased that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1, or Grade 3 ALT increased, abemaciclib must be suspended until the toxicity has resolved to at least Grade 1 and the dose must be reduced by 1 dose level. Discontinue abemaciclib for Grade 3 increased ALT (>5.0 x ULN) with total bilirubin (TBL) >2 x ULN, in the absence of cholestasis. For Grade 4 ALT increased, the patient must be discontinued from abemaciclib. Refer to Section 10.3.4.1 for additional hepatic monitoring guidance.

9.5. Blinding

This is an open-label study.

9.6. Concomitant Therapy

Appropriate documentation of all forms of premedications, supportive care, and concomitant medications must be captured at each visit in the eCRF. 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.

With the exceptions listed in the sections below, no other chemotherapy, experimental medications, other anticancer therapy, immunotherapy, radiation, surgery for cancer, or experimental medications will be permitted while patients are on abemaciclib. Use of megestrol acetate as an appetite stimulant is not permitted for patients with breast cancer.

In vivo in humans, abemaciclib is extensively metabolized through oxidation. Additionally, the results from an in vitro human recombinant cytochrome P450 (CYP) phenotyping study indicate that oxidative metabolism of abemaciclib is primarily catalyzed by CYP3A4. Based on these findings, grapefruit juice as well as inducers and strong inhibitors of CYP3A4 should be substituted or avoided if possible (Attachment 10). Concurrent treatment with EIAED is not permitted while on abemaciclib. Patients requiring treatment with antiepileptic drugs should be prescribed a non-EIAED (eg, levetiracetam, lacosamide, lamotrigine, etc). Although dexamethasone is a CYP3A4 inducer, use during the study is allowed. The dose of corticosteroids, including dexamethasone, will be captured throughout the study, with an emphasis on recording changes in dose at the time of intracranial tumor assessments.

In addition, in vitro studies in primary cultures of human hepatocytes indicate that abemaciclib and its significant 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, caution should be exercised when coadministering substrate drugs of the above CYPs with narrow therapeutic margin (see Attachment 10).

9.6.1. Permitted Combination Therapies

Patients with HR+ breast cancer in Parts A, B, and F receiving endocrine therapy prior to study entry may continue to receive the same endocrine therapy throughout the study treatment period per the respective label provided that extracranial disease is stable for at least 3 months and CNS disease progression has occurred while on this endocrine therapy. If these conditions are not met, patients must discontinue endocrine therapy prior to initiation of abemaciclib. These patients may not initiate endocrine therapy immediately prior to study entry or at any time during the study. Part C patients may continue or initiate endocrine therapy concurrently with abemaciclib and need not meet the above conditions. Additionally, patients with HER2+ breast cancer in Parts A, C, and F may receive concurrent trastuzumab per the label throughout the study treatment period provided trastuzumab is initiated prior to or concurrently with the initiation of abemaciclib.

For NSCLC patients in Parts D and F who are receiving gemcitabine or pemetrexed (single-agent or in combination with another therapy) prior to study entry, these patients may continue to receive 1 of these 2 therapies as a single-agent provided that extracranial disease is stable for at least 6 weeks and CNS disease progression has occurred while on this therapy. Combination therapies (aside from gemcitabine or pemetrexed) must be discontinued at least 14 days prior to

initiation of abemaciclib. Part C patients may continue or initiate gemcitabine or pemetrexed (as single agents) concurrently with abemaciclib and need not meet the above conditions.

Changes (i.e., switching from one therapy to another) in concomitant therapy after study entry are not permitted. Patients requiring a change in concomitant therapy should be assessed for PD and be discontinued from abemaciclib. However, in the absence of PD, patients may discontinue concomitant therapy (i.e., in cases of intolerable toxicity) and continue abemaciclib.

9.6.2. Surgery

A patient in Part C with brain lesions for which surgical resection is clinically indicated may undergo surgery following 5 to 14 days of treatment with abemaciclib. Abemaciclib should be taken 6 to 12 hours prior to surgical resection of brain lesions in order to accommodate assessment of drug concentrations in tumor tissue. These patients may resume abemaciclib dosing at least 15 days but no greater than 21 days postoperatively to allow adequate time for wound healing. Patients requiring WBRT or SRS following surgery must be permanently discontinued from abemaciclib.

9.6.3. Supportive Care

Patients should receive full supportive care to maximize quality of life. Patients will receive supportive care as judged by their treating physician. 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 eCRFs.

9.6.4. Growth Factor

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.

9.6.5. Supportive Management for Diarrhea

At enrollment, patients should receive instructions on the management of diarrhea. In the event of diarrhea, 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 (eg, loperamide) and notify the investigator/site for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (eg, 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, then dosing of abemaciclib should be suspended until diarrhea is resolved to at least Grade 1.
- When abemaciclib recommences dosing should be adjusted as outlined in Sections 9.4.1.1.1, 9.4.1.1.2, and 9.4.1.1.4.1.

9.7. Treatment Compliance

Patient compliance with abemaciclib dosing will be assessed by capsule counts at each visit, with the number of capsules taken relative to the number expected to be taken summarized for each cycle. The patient must take ≥75% of the planned doses of abemaciclib in a cycle to be deemed compliant. As outlined in Section 9.4.1.1.2, dose suspensions or delays may occur and will not result in a patient being considered as noncompliant. A patient may be considered noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken ≥125% of the planned doses of abemaciclib in a cycle.

A patient enrolled in Part C who undergoes resection of brain metastases will not be considered noncompliant for doses of abemaciclib withheld in conjunction with surgery and will not incur a protocol deviation. For additional information, refer to Section 9.6.2.

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

Within 28 days before the first dose of abemaciclib, baseline tumor measurements will be performed for each patient. Intracranial tumor assessments will be performed by Gd-MRI according to RANO-BM (Attachment 5). Extracranial tumor assessments will be performed according to RECIST v1.1 (Attachment 6). Computed tomography (CT) scans, including spiral CT scans, and MRI are the preferred methods of measurement of extracranial disease. For melanoma patients with visible lesions, photography will be performed at baseline and each photographic image of the lesion should include a ruler. In addition, for Part F patients only, Gd-MRI of the spine should be performed (see Attachment 1).

For patients with progressive intracranial disease, Gd-MRI acquired prior to study screening must be provided to confirm PD on the baseline intracranial tumor assessment. Additionally, in order to document stable extracranial disease for patients receiving concomitant therapies outlined in Section 9.6.1, CT scan or MRI of extracranial lesions acquired at least 3 months (endocrine therapy) or 6 weeks (gemcitabine or pemetrexed) prior to study screening must be provided.

The method of radiological assessment used at baseline must be used consistently for tumor assessment and will be repeated between Day 14 and Day 21 of every other cycle beginning with Cycle 2 and continuing through Cycle 8; thereafter, tumor assessments will be repeated between Day 14 and Day 21 of every fourth cycle (beginning with Cycle 12). Visible lesions will be assessed on Day 1 of every other cycle beginning with Cycle 3, or more frequently as clinically indicated.

Intracranial and extracranial responses (CR or PR) must be confirmed no less than 28 days from the first evidence of response.

During the continued access period, efficacy assessments (frequency and type of assessments) will be completed at the discretion of the investigator.

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 abemaciclib without objectively measured PD, the investigative sites will continue to monitor patients and periodically evaluate tumor response approximately every 6 weeks for the first 6 months following initiation of abemaciclib and thereafter approximately every 12 weeks by the same method used at baseline and throughout the study until the patient has objective disease progression, or until the final analysis of OS. If a patient's most recent response prior to discontinuation is a PR or CR, an additional radiological assessment should be performed during the 30-day follow-up period to confirm the response, at least 28 days after the previous radiological assessment. Response should be confirmed before the initiation of additional anticancer therapy. However, initiation of new therapy should not be delayed solely to confirm response. After the patient has objective disease progression, radiologic tests are no longer required, and the patient will be followed up approximately every 90 days until the patient's death or overall study completion.

Lilly will continue to collect survival data on all patients but may reduce data collection for other efficacy data. Lilly will notify investigators when this reduced data collection can begin.

10.1.3. Primary Efficacy Measure

The primary efficacy measure is OIRR (CR + PR) as defined by RANO-BM (see Attachment 5). A partial intracranial response is defined as ≥30% decrease in sum of LD of up to 5 target brain lesions sustained for at least 4 weeks in the absence of progression of nonmeasurable brain lesions, new brain lesions, increased corticosteroid dose, or clinical worsening.

Best response is determined from the sequence of responses assessed.

A second assessment must be performed ≥28 days after the first evidence of response. 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 as 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 35 days after the start of abemaciclib.

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.

The date of first documented objective disease progression must be recorded on the eCRF even if it occurs after the patient has started a new therapy.

Lilly or its designee will collect and store tumor assessment images (including photographs of visible lesions), and an independent review of imaging scans may be performed by Lilly or its designee.

The OIRR is estimated as the total number of confirmed CRs and PRs divided by the total number of evaluable patients enrolled. The primary analysis of OIRR for each study Part (A, B, D, or E) will occur approximately 6 months after up to 56 evaluable patients have been enrolled into each respective part. This is to ensure adequate durability of response data is available at the time of analysis. An evaluable patient is defined as a patient who has ≥1 measurable brain lesion at the time of enrollment (per RANO-BM) and for whom at least 1 post-baseline overall response assessment for intracranial disease is available.

10.1.4. Secondary Efficacy Measures

The following secondary efficacy measures (Table JPBO.4) will be collected at the times shown in the Study Schedule (Attachment 1).

Table JPBO.4. Secondary Efficacy Endpoints

Endpoint	Definition
Best overall intracranial response (BOIR)	Derived to encompass all tumor assessments (according to RANO-BM) from baseline until the earliest of objective progression (intracranial or extracranial according to brain metastases response criteria or RECIST v1.1, respectively) or start of new anticancer therapy. Any responses observed after objective progression (intracranial or extracranial) or the start of new anticancer therapy are excluded from the determination of best response. Each patient's BOIR will be categorized as CR, PR, SD, PD, or NE.
Duration of intracranial response (DOIR) (CR + PR)	Defined only for responders (patients with a confirmed CR or PR, as defined in Section 10.1.3). It is measured from the date of first evidence of a confirmed response (CR or PR as defined by brain metastases response criteria) to the date of investigator-determined objective progression (intracranial or extracranial as defined by RANO-BM or RECIST v1.1, respectively) or death from any cause. Patients who have neither progressed nor died will be censored on the day of their last radiographic tumor assessment (if available) or on the date of response (CR or PR as defined by brain metastases response criteria) if no radiographic assessment is available.
Intracranial disease control rate (IDCR)	Defined as the proportion of patients with BOIR of CR, PR, or SD (according to RANO-BM).
Intracranial clinical benefit rate (ICBR)	Defined as the proportion of patients with BOIR of CR, PR, or SD with duration of SD for at least 6 months (according to RANO-BM).
Overall survival (OS)	Measured from the date of enrollment 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, tumor assessment date, visit date, and last known alive date). Patients will be followed for OS for 18 months following the last patient entering treatment in each study part (Parts A or B).
Objective response rate (ORR) per RECIST v1.1 and brain metastases response criteria	The percentage of patients with a best response of CR or PR as defined by RECIST v1.1 and RANO-BM.
Disease control rate (DCR)	Defined as the proportion of patients with best overall response of CR, PR, or SD (according to RECIST v1.1 and RANO-BM).
Progression-free survival (PFS)	Measured from the date of enrollment to the date of investigator-determined objective progression (intracranial or extracranial as defined by RANO-BM or RECIST v1.1, respectively) 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 enrollment if no postinitiation (that is, postbaseline) radiographic assessment is available.

Abbreviations: AE = adverse event; CR = complete response; NE =not evaluable; PD = progressive disease; PR = partial response; RANO-BM = Response Assessment in Neuro-Oncology brain metastases RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

10.1.5. Exploratory Measures

The following exploratory measures (Table JPBO.5) will be collected at the times shown in the Study Schedule (Attachment 1).

Table JPBO.5. Exploratory Endpoints

Endpoint	Definition
Trail Making Test	To assess neurocognitive function using Trail Making Tests A and B. Each test is administered by trained site staff and has a time limit (180 seconds for Test Part A and 300 seconds for Test Part B). The score for each test is determined by either the time in seconds to complete the test or the last number or letter reached at the time limit (Reitan 1992; Wefel et al. 2011).
NANO scale	Clinical assessment of change in neurological signs using the NANO scale, which consists of 9 domains (gait, strength, ataxia, sensation, visual fields, facial strength, language, level of consciousness, and behavior). A modified version of the NANO scale (consisting of 11 domains, including gait, strength, sensation, vision, eye movements, facial strength, hearing, swallowing, level of consciousness, behavior, and other) has been adapted for patients with LM and will be used to assess all Part F patients.
Concentration of abemaciclib and its metabolites	To explore the concentration of abemaciclib and its metabolites in plasma, CSF, and brain tumor tissue collected at the time of surgical resection for patients participating in Part C, as well as patients in Parts A and B with PD and planned surgical resection.
Biomarkers	To explore biomarkers related to the mechanism of action of abemaciclib, the cell cycle, and/or the pathogenesis of breast cancer, NSCLC, and melanoma.
Effect in patients with leptomeningeal metastases	To assess response of patients with LM by applying proposed RANO-LM assessment criteria.

Abbreviations: CSF = cerebrospinal fluid; NANO = Neurologic Assessment in Neuro-Oncology; NSCLC = non-small cell lung cancer; PD = progressive disease, RANO-LM = Response Assessment in Neuro-Oncology leptomeningeal metastases

10.2. Health Outcome/Quality of Life Measures

Patient-reported symptoms will be assessed with the self-administered MDASI-BT on paper. The MDASI-BT assessment will be completed per the Study Schedule (Attachment 1).

The MDASI-BT should be completed at the beginning of office visits, before any extensive contact and consultation with the clinician/study investigator in regards to the tumor assessments. Discussion with the clinician may bias perceptions about symptoms and thus affect assessments.

The MDASI-BT will only be completed by patients for whom there is a valid translation in a language in which the patient is fluent.

10.2.1. Patient-Reported Outcomes

10.2.1.1. MD Anderson Symptom Inventory – Brain Tumor Module

The MDASI-BT is a reliable and valid instrument to assess symptoms in patients with brain metastases (Armstrong et al. 2009; Meyers and Brown 2006). The MDASI-BT consists of

22 symptom items (13 items of the core MDASI plus 9 items specific to brain tumors) plus 6 interference items, all with 11-point rating scales. For the symptom items, 0 equals "not present" and 10 equals "as bad as you can imagine." For the interference items, 0 equals "did not interfere" and 10 equals "interfered completely." The MDASI-BT may be scored by reporting the individual items or by calculating the means of all symptom items and of all interference items. The means of the core and brain tumor items may be reported separately. The 22 symptom items may also be grouped by their underlying constructs: (1) affect; (2) cognition; (3) focal neurologic deficit; (4) treatment-related symptoms; (5) generalized/disease status symptoms; and (6) gastrointestinal symptoms.

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.

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 JPBO.6 presents a summary of AE and SAE reporting guidelines and also shows which database or system is used to store AE and SAE data.

Table JPBO.6. 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 abemaciclib	x	x
Continued access period	All AEs	x	
	All SAEs	x	x
Continued access follow-up	All AEs	x	
	All SAEs	x	x
After the patient is no longer participating in the study (that is, no longer receiving abemaciclib and no longer in follow-up)	All SAEs related to protocol procedures or abemaciclib 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), labs, vital sign measurements, and other study procedures that result in a diagnosis should be reported to Lilly or its designee.

Cases of pregnancy that occur during maternal exposures to abemaciclib should be reported. If a patient is determined to be pregnant following abemaciclib initiation, she must discontinue treatment immediately. 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.

After the 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, the investigator will record all relevant AE/SAE information in the CRF. Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure and 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 study drug or study procedure, the following terminologies are defined:

- **Probably related**: a direct cause and effect relationship between the study drug and the AE is likely
- **Possibly related**: a cause and effect relationship between the study drug 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 drug

The investigator should classify all "probably related," "possibly related," or "does not know" AEs and SAEs as related to study drug or 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) v4.0 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 v4.0 criteria, the investigator will be responsible for selecting the appropriate System Organ Class (SOC) 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 AE from this study that results in 1 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 1 of the outcomes listed in this definition.

SAE collection begins after the patient has signed informed consent and has received abemaciclib. If a patient experiences an SAE after signing informed consent, but prior to receiving abemaciclib, 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 SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If study site personnel contact Lilly or its designee by telephone regarding an SAE, study site personnel must also immediately provide 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 abemaciclib or other protocol-required procedure) should not be considered SAEs.

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

The investigator does not need to actively monitor patients for AEs once the trial has ended, unless provided otherwise in the protocol; however, 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 DCSI in the IB and that the investigator identifies as related to the study drug or study procedure. US 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. Guidance for Monitoring of Renal Function in Patients on Abemaciclib

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting cystatin C calculated glomerular filtration rate (See Section 3.2.4 of the abemaciclib IB for additional background). Increases in serum creatinine occurred within the first 2 weeks of treatment, remained stable through the treatment period, and were reversible upon treatment discontinuation. If deterioration of renal function is suspected, serum creatinine should not be the only measure used to assess a patient's renal function. Dose alterations (omission, reduction, discontinuation) should not solely be based on interpretation of serum creatinine values because these may not reflect renal function.

10.3.3. Other Safety Measures

10.3.3.1. Electrocardiograms

For each patient, a 12-lead digital ECG will be collected according to the Study Schedule (see Attachment 1). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. ECGs may be obtained at additional times, if clinically indicated.

ECGs 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 for immediate patient management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/corrected 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, 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.

10.3.3.2. Echocardiograms or Multi-Gated Acquisition Scans

For only those HER2+ breast cancer patients receiving concurrent IV trastuzumab during the study, an echocardiogram or multi-gated acquisition (MUGA) scan is required within 28 days of initiation of abemaciclib (Attachment 1). Per the trastuzumab prescribing information (Herceptin [trastuzumab] highlights of prescribing information, 2014 and Herceptin [trastuzumab] summary of product characteristics, 2014), continued cardiac function monitoring throughout treatment is recommended but is not required as a protocol procedure.

10.3.4. 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 Global Patient Safety therapeutic area physician or clinical scientist and review:

- trends in safety data
- laboratory analytes
- AEs
- If a patient experiences elevated ALT or AST >5× ULN and elevated total bilirubin >2× ULN, clinical and laboratory monitoring should be initiated by the investigator. For patients entering the study with ALT or AST >3× ULN in the presence of liver metastases, monitoring should be triggered at ALT >2× baseline.
- 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).

10.3.4.1. Special Hepatic Safety Data Collection

If a study patient experiences elevated ALT ≥5×ULN and elevated total bilirubin (TBL)≥2×ULN, or ALT >8x ULN for patients with underlying baseline hepatic metastases, liver tests (Attachment 3), including ALT, AST, TBL, direct bilirubin, gamma glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests (Attachment 3) and in consultation with the Lilly CRP. Monitoring of ALT, AST, and TBL should continue until levels normalize or return to approximate baseline levels. Additional diagnostic testing should be considered to rule out cause of increased liver enzymes per the investigator's discretion.

Hepatic monitoring tests (Attachment 3) should be collected in the event that 1 or more of the following conditions is met for the patient during the course of the study:

- ALT ≥5×ULN and TBL ≥2×ULN
- ALT >8x ULN for patients with underlying hepatic metastasis
- discontinuation from study treatment due to a hepatic event or an abnormality of liver tests

10.3.4.2. Renal Function

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting cystatin C-calculated glomerular filtration rate. Increases in serum creatinine occurred within the first 2 weeks of treatment, remained stable through the treatment period, and were reversible upon treatment discontinuation. If deterioration of renal function is suspected, serum creatinine should not be the only measure used to assess a patient's renal function.

Dose adjustment (omission, reduction, or discontinuation) should not solely be based on interpretation of serum creatinine values because these may not reflect renal function. If deterioration of renal function is suspected per the investigator's clinical assessment, dose alteration should follow the protocol guidance for non-hematological toxicities (Table JPBO.3).

10.3.4.3. Venous Thromboembolic Events (VTEs)

In the randomized Phase 3 studies in breast cancer patients who received abemaciclib in combination with endocrine therapy, there was a greater number of patients who experienced VTEs in the abemaciclib plus endocrine therapy arm than in the placebo plus endocrine therapy arm. The majority of the events were non-serious and were treated with low-molecular-weight heparin. Generally, these events did not result in discontinuation of the study treatment. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known. For suspected or confirmed VTE (e.g., deep vein thrombosis or pulmonary embolism), treatment should occur according to usual clinical practice. In studies with single-agent abemaciclib use in the mBC population or other tumor types, including NSCLC, no increased rates of VTEs were observed as compared to the incidence of VTEs for these particular patient populations who were treated with other anticancer agents.

10.3.5. Complaint Handling

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

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.

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.

Attachment 7 provides a schedule of ECG collection and PK sampling during the study for patients in Parts A and B.

Attachment 8 provides a schedule of ECG collection and PK sampling during the study for patients in Part C.

Attachment 9 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

Investigators must document their review of each laboratory safety report.

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 Biomarkers

Required samples for biomarker research to be collected from all patients enrolled in this study are the following:

- whole blood
- plasma
- archived tumor tissue

Analyses may include, but are not limited to, nucleic acid and protein profiles to better understand the disease process and to develop predictive biomarkers. Similar analyses may be performed with brain tumor tissue and CSF collected from patients undergoing surgical resection (Section 10.4.3.1).

These samples are described in the following sections.

10.4.2.1. 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. Therefore, where local regulations and ERBs allow, a blood sample will be collected for pharmacogenetic analysis.

Samples may be genotyped and analysis may be performed to evaluate a genetic association with response or lack of 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 15 years 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 abemaciclib.

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

10.4.2.2. Plasma Samples for Exploratory Biomarker Evaluations

Ethylenediaminetetraacetic acid (EDTA)-anticoagulated plasma samples will be collected and analysis may be performed on biomarkers that may play a role in the abemaciclib mechanism of action (refer to Attachment 1). The evaluation of these samples may involve analysis of DNA, RNA, and proteins (including any of these components derived from exosomes) to investigate their association with observed clinical outcomes to abemaciclib. The samples will be coded with the patient number and stored for up to 15 years. Details for collecting, processing, and storing the samples are similar those provided in Section 10.4.2.1.

10.4.2.3. Archived Tumor Tissue

For patients in the study, a small amount of archival, preserved tumor tissue is required to be provided by sites upon patient assignment to abemaciclib for biomarker research. However, if this sample is not available for a patient, this should be discussed with the sponsor. A protocol deviation will not be incurred, and the patient is still eligible for the study.

Available formalin-fixed, paraffin-embedded archived primary and/or metastatic tumor tissue should be in a whole block, partial block, or 20 unstained slides, cut at 5 microns, and 1 hematoxylin and eosin (H&E) slide containing tumor specimen will be requested, if available, to be used for exploratory analysis. Due diligence should be used to make sure that a tumor specimen (not normal adjacent or tumor margins) is provided. Pathology notes accompanying archival tissue may also be requested. Tumor blocks or partial blocks will be sectioned and returned to the investigator after completion of analysis.

In tumor tissue samples, the CDK4 and CDK6 pathway components (for example, Rb and its targets) and markers relevant to breast cancer pathogenesis may be evaluated to assess any potential correlation with response to abemaciclib. These studies will be performed in a laboratory designated by the sponsor and may include, but are not limited to, IHC of proteins, fluorescence in-situ hybridization (FISH) for copy number alterations, mRNA gene-expression profiling, and/or genetic analyses of the tumor DNA. Such analyses may employ targeted or high-throughput sequencing approaches. For this purpose, the results of this analysis will be correlated with clinical efficacy data.

10.4.3. Samples for Drug Concentration Measurements Pharmacokinetics

PK samples will be collected for Parts A B, D, E, and F as specified in the Pharmacokinetic Sampling Schedule (Attachment 7). A separate Pharmacokinetic Sampling Schedule (Attachment 8) is provided for patients participating in Part C.

At the visits and times specified in the Pharmacokinetic Sampling Schedules (Attachment 7 and Attachment 8), venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of abemaciclib 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 precautions must be taken to prevent obtaining a

dilute sample when the sample is drawn for PK from a central catheter of any type. 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 samples may be drawn at additional time points during the study if warranted and agreed upon between both the investigator and Lilly.

Supplies required for the collection and shipment of the samples will be provided by the sponsor. Sample handling and shipment to the central laboratory will occur per instructions given to the study site.

These samples will be analyzed at a laboratory designated by the sponsor. Plasma concentrations of abemaciclib and its metabolites will be assayed using a validated liquid chromatography-tandem mass spectrometry (LC/MS/MS) method.

Bioanalytical samples collected to measure abemaciclib 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.

10.4.3.1. Drug Concentrations for Parts C and F Patients

Time-matched blood and CSF samples will be collected for exploratory measurement of abemaciclib and, if deemed necessary, the concentrations of its metabolites. These samples will be collected at the time of surgery for patients participating in Part C, and on Cycle 3 Day 1 and as clinically indicated for patients participating in Part F. In addition, resected brain tumor samples will be collected from patients participating in Part C for exploratory measurement of abemaciclib and, if deemed necessary, the concentrations of its metabolites. Separate samples are not required for the parent and its metabolites. Supplies and instructions for the collection and handling of blood, CSF, and tumor samples will be provided by the sponsor. In cases where collection of CSF is not feasible, a missing sample will not be considered a protocol deviation.

Plasma, CSF, and resected tumor samples will be analyzed at a laboratory designated by the sponsor. Concentrations of abemaciclib and, if deemed necessary, its metabolites will be explored using an LC/MS/MS method. .

Local histopathology results for resected tissue should confirm the presence of tumor tissue. In cases where tumor tissue is not confirmed by histopathology report, the Sponsor must be notified. The remaining submitted tumor tissue and CSF samples after drug concentration measurements may be used for additional analyses including, but not limited to, nucleic acid and protein profiles to better understand the disease process and to develop predictive biomarkers.

10.5. Appropriateness of Measurements

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

Safety measurements by laboratory monitoring are standard, widely used, and 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 eCRFs, 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 eCRF 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.

eCRF data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to Lilly.

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 clinical trial is to estimate the antitumor activity, measured by OIRR of abemaciclib in patients with brain metastases secondary to HR+ breast cancer, NSCLC or melanoma.

Separate Simon 2-stage designs (Simon 1989) will be employed for this study, including; Part A (patients with HR+, HER2+ breast cancer), Part B (patients with HR+, HER2- breast cancer), Part D (patients with NSCLC), and Part E (patients with melanoma). Each design assumes a 1-sided type-I error of 0.05 and 80% power.

For Part A, up to 56 evaluable patients will be enrolled with the possibility of stopping the study early for either lack of efficacy or unacceptable toxicity. Twenty-three evaluable patients will be enrolled in the first stage. If fewer than 2 of the first 23 evaluable patients respond to abemaciclib, accrual will be stopped, and the conclusion will be drawn that abemaciclib is not worthy of further study in the Part-A population. If at least 2 of the first 23 evaluable patients respond to therapy, accrual will continue until 33 additional evaluable patients have been enrolled. A total of 6 responders out of 56 evaluable patients in Part A would need to be observed to warrant further investigation of abemaciclib in this patient population.

The procedure described above tests the null hypothesis (H_0) that the true OIRR of abemaciclib in Part A is $\leq$5% versus the alternative hypothesis (H_a) that the true OIRR is $\geq$15%. The probability of early termination of the treatment arm under H_0 is 0.68.

Parts B, D, and E will have the identical design as Part A.

Assuming approximately 20% screening failure, the study will enter approximately 309 patients.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

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

Safety analyses will be conducted on the full analysis set (FAS). This set includes all data from all enrolled patients receiving at least 1 dose of abemaciclib.

Efficacy analyses will be conducted on the FAS population and in the OIRR evaluable population when appropriate. The FAS includes all data from all enrolled patients receiving at least 1 dose of abemaciclib. The OIRR evaluable population is defined as patients receiving at least 1 dose of abemaciclib who have $\geq$1 measurable brain lesion at the time of enrollment (per RANO-BM) and for whom at least 1 post-baseline overall response assessment for intracranial disease is available.

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

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

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

Unless otherwise stated, all analyses will be conducted on each study part separately. Pooled analyses including patients from all 3 parts will be conducted when applicable.

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

Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report.

The 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.

12.2.2. Patient Disposition

A detailed description of patient disposition will be provided. All patient discontinuations will be documented, and the extent of each patient's participation in the study will be reported. If known, a reason for discontinuation will be given.

A summary of all important protocol deviations will be provided.

12.2.3. Patient Characteristics

Patient demographics including age, sex, screening height and weight, and screening body mass index 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.

Preexisting conditions, historical illnesses, and prior chemotherapy (including both cytotoxic and targeted agents) will be summarized.

Other patient characteristics will be summarized as deemed appropriate.

12.2.4. Concomitant Therapy

Concomitant medication will be summarized 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 anticancer 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, delays, cycles received, and dose intensity will be summarized for all treated patients.

Treatment compliance information for abemaciclib will be collected through pill counts at each 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 will take into account any dose reductions or omissions.

12.2.6. Primary Outcome and Methodology

The primary endpoint of this study is OIRR assessed using RANO-BM (see Attachment 5) in the OIRR evaluable population. The OIRR will be reported along with 95% CIs using the normal approximation.

12.2.7. Secondary Outcome and Methodology

The secondary objectives for this study are stated in Section 6.2; secondary efficacy measures are defined in Section 10.1.4.

Point estimates and 95% CIs (using the normal approximation to the binomial) will be calculated for BOIR, IDCR, ICBR, ORR, and DCR for Parts A, B, D, and E.

Time-to-event efficacy endpoints (OS, PFS, and DOIR) will be summarized for Parts A, B, D, and E using Kaplan-Meier techniques (Kaplan and Meier 1958) if there is sufficient data. If performed, Kaplan-Meier curves will be generated, and quartiles and point probabilities will be calculated. Interval estimates will be calculated using 95% CIs (Brookmeyer and Crowley 1982).

12.2.8. Pharmacokinetic and/or Pharmacodynamic Analyses

PK analyses will be conducted on all patients who have received at least 1 dose of abemaciclib and have had samples collected (see Pharmacokinetic Sampling Schedules in Attachment 7 and Attachment 8).

Mean population PK parameters for abemaciclib in plasma (clearance, exposure, volume of distribution, and half-lives) and interindividual 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.

Finally, pharmacodynamic data (such as neutrophil, lymphocytes, or platelets counts in blood, OIRR, PFS, or OS) 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.

12.2.9. Exploratory Analyses

12.2.9.1. Trail Making Tests A and B

Neurocognitive function will be assessed using Trail Making Tests A and B. Summary statistics will be provided by study part and each response category (CR/PR, SD, and PD). Change from baseline and time to worsening will be explored.

12.2.9.2. Neurologic Assessment in Neuro-Oncology Scale

Clinical response and progression will be explored and summarized for the NANO scale using descriptive statistics. Neurologic response will be defined as an improvement of ≥2 on any single domain in the absence of deterioration in other domains. Neurologic progression will be defined as worsening of ≥2 from baseline on any single domain. These results may be compared with objective tumor assessment results.

12.2.9.3. Drug Concentrations in Samples from Parts C and F Patients

The relative concentrations of abemaciclib and its metabolites in time-matched samples of plasma, CSF, and tumor tissue collected at the time of surgical resection for patients participating in Part C will be explored. In addition, the relative concentrations of abemaciclib and its metabolites in time-matched samples of plasma and CSF collected on Cycle 3 Day 1, as well as any other time the collection of CSF is clinically indicated, for patients participating in Part F will be explored.

12.2.9.4. Biomarker Analyses

The distributions of biomarkers with continuous measures, such as gene or protein expression, will be described. Summary statistics will include means, medians, corresponding standard errors, quartiles, and ranges. Biomarkers with discrete measures, such as genotype locus, will be summarized in frequency tables. Correlative analyses may be performed to investigate associations between biomarkers and clinical endpoints as deemed appropriate.

12.2.10. Health Outcome/Quality of Life Analyses

Patients with at least 1 baseline and at least 1 postbaseline assessment will be included in the analyses. Compliance with completing the questionnaires will be summarized at the group-level at each assessment period (defined as the number of completed

questionnaires/number expected questionnaires given those that are still on study). Reason for missing questionnaires will be assessed.

Relationships among MDASI-BT, Trail Making Tests, and other clinical parameters such as performance status, OS, and disease assessments may be explored.

Data will be summarized by study part and each response category (CR/PR, SD, PD). Change from baseline and time to worsening will be explored. This summary will include mean, standard deviation, median, minimum, maximum, and change from baseline. The MDASI-BT will be reported as core symptoms, brain tumor symptoms, symptom interference, and symptom groupings (affect, cognition, focal neurologic deficit, treatment-related symptoms, generalized/disease status symptoms, and gastrointestinal symptoms). Time to worsening will be described for these categories.

Further analyses will be specified in the statistical analysis plan.

12.2.11. Safety Analyses

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

Overall exposure to abemaciclib, the numbers of patients completing each cycle, and the dose intensity will be summarized using descriptive statistics. The number of patients with any dose adjustment will be presented for entire treatment period as well as for each cycle. 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 v4.0 term reported by the investigator will be mapped to the MedDRA Preferred Term (PT) and 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 AEs that begin prior to the first dose of abemaciclib. A TEAE is defined as an event that first occurred or worsened in severity after baseline. 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 abemaciclib and repeated for events regardless of abemaciclib causality.

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.

12.2.12. Interim Analyses

The Simon 2-stage design has a built-in interim analysis to analyze OIRR and to meet threshold continuation criteria. The interim analysis of OIRR for each study part (A, B, D, or E) will occur approximately 6 months after the 23rd evaluable patient is enrolled into each respective part. This is to ensure adequate durability of response data is available at the time of analysis. This interim analysis for response must be strictly followed to preserve the statistical properties of the Simon 2-stage design. Due to this requirement, objective data will be obtained to document response and to determine if the trial is to continue based on the OIRR. Because of this, no Assessment Committee or Data Monitoring Committee will be convened to oversee this trial.

Additional interim analyses will be planned if deemed necessary.

12.2.13. Subgroup Analyses

Subgroup analyses will be performed for potential prognostic subgroup variables.

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.

The 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.

The investigator is responsible for ensuring that informed consent is given by each patient or, where permitted by local law or regulation, by the patient's 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 and updates during the course of the study
- the 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 (CIOMS) International Ethical Guidelines
- 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 by the investigator 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

Site-specific contact information may be provided in a separate document.

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 coordinating investigator will sign the final clinical study report 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 clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

14. References

Adamo B, Deal AM, Burrows E, Geradts J, Hamilton E, Blackwell KL, Livsay C, Fritchie K, Prat A, Harrell JC, Ewend MG, Carey LA, Miller CR, Anders CK. Phosphatidylinositol 3-kinase pathway activation in breast cancer brain metastases. *Breast Cancer Res*. 2011;13(6):R125.

Armstrong TS, Gning I, Mendoza TR, Weinberg JS, Gilbert MR, Tortorice ML, Cleeland CS. Clinical utility of the MDASI-BT in patients with brain metastases. *J Pain Symptom Manage*. 2009;37(3):331-340.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. *Biometrics*. 1982;38(1):29-41.

Crooks V, Waller S, Smith T, Hahn TJ. The use of the Karnofsky Performance Scale in determining outcomes and risk in geriatric outpatients. *J Gerontol*. 1991;46(4):M139-M144.

Deeken JF, Löscher W. The blood-brain barrier and cancer: transporters, treatment, and Trojan horses. *Clin Cancer Res*. 2007;13(6):1663-1674.

de Haan R, Aaronson A, Limburg M, Hewer RL, van Crevel H. Measuring quality of life in stroke. *Stroke*. 1993;24(2):320-327.

Eichler AF, Loeffler JS. Multidisciplinary Management of Brain Metastases. *Oncologist*. 2007;12(7):884-898.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2) 228-247.

Guan J, Zhong W, An S, Yang J, Su J, Chen Z, Yan H, Chen Z Yan H, Chen Z, Huang Z, Zhang X, Nie Q, Wu Y. KRAS Mutation in Patients with Lung Cancer: A predictor for poor prognosis but not for EGFR-TKIs or chemotherapy. *Ann Surg Onc*. 2013;20(4):1381-1388.

Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, Fitzgibbons PL, Francis G, Goldstein NS, Hayes M, Hicks DG, Lester S, Love R, Mangu PB, McShane L, Miller K, Osborne CK, Paik S, Perlmutter J, Rhodes A, Sasano H, Schwartz JN, Sweep FC, Taube S, Toralakovic EE, Valenstein P, Viale G, Visscher D, Wheeler T, Williams RB, Wittliff JL, Wolff AC . American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol*. 2010;28(16):2784-2795.

Herceptin (trastuzumab) [highlights of prescribing information]. South San Francisco, CA: Genentech, Inc.; 2014.

Herceptin (trastuzumab) [summary of product characteristics]. Welwyn Garden City, United Kingdom: Roche Products Limited; 2014.

Hollen PJ, Gralla RJ, Kris MG, Cox C, Belani CP, Grunberg SM, Crawford J, Neidhart JA. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies. Psychometric assessment of the Lung Cancer Symptom Scale. *Cancer*. 1994;73(8):2087-2098.

Kaplan EL, Meier P. Nonparametric estimation of incomplete observations. *J Amer Stat Assoc*. 1958;53(282):457-481.

Lin NU, Amiri-Kordestani L, Palmieri D, Liewehr DJ, Steeg PS. CNS metastases in breast cancer: old challenge, new frontiers. *Clin Cancer Res*. 2013;19(23):6404-6418.

Lin NU, Lee EQ, Aoyama H, Barani IJ, Barboriak DP, Baumert BG, Bendszus M, Brown PD, Camidge DR, Chang SM, Dancey J, de Vries EG, Gaspar LE, Harris GJ, Hodi FS, Kalkanis SN, Linskey ME, Macdonald DR, Margolin K, Mehta MP, Schiff D, Soffietti R, Suh JH, van den Bent MJ, Vogelbaum MA, Wen PY. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol*. 2015;16(6):e270-e278.

Meyers CA, Brown PD. Role and relevance of neurocognitive assessment in clinical trials of patients with CNS tumors. *J Clin Oncol*. 2006;24(8): 1305-1309.

Ortega S, Malumbres M, Barbacid M. Cyclin-D dependent kinases INK4 inhibitors and cancer. *Biochim Biophys Acta*. 2002;1602(1):73-87.

O'Toole DM, Golden AM. Evaluating cancer patients for rehabilitation potential. *West J Med*. 1991;155(4):384-387.

Oxford textbook of palliative medicine. 1st ed. Oxford University Press;1993:109.

Puyol M, Martín A, Dubus P, Mulero F, Pizcueta P, Khan G, Guerra C, Santamaría D, Barbacid M. A synthetic lethal interaction between K-Ras oncogenes and Cdk4 unveils a therapeutic strategy for non-small cell lung carcinoma. *Cancer Cell*. 2010;18(1):63-73.

Reitan RM. Trail making test. Manual for administration and scoring. Tucson (AZ): Reitan Neuropsychology Laboratory;1992.

Rizzo JD, Somerfield MR, Hagerty KL, Seidenfeld J, Bohlius J, Bennett CL, Cella DF, Djulbegovic B, Goode MJ, Jakubowski AA, Rarick MU, Regan DH, Lichtin AE; American Society of Clinical Oncology; American Society of Hematology. Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update. *J Clin Oncol*. 2008;26(1):132-149. Erratum in: *J Clin Oncol*. 2008;26(7):1192.

Sanchez-Martinez C, Gelbert LM, Shannon H, De Dios A, Staton BA, Ajamie RT, Sawada G, Wishart GN, Raub TJ. LY2835219, a potent oral inhibitor of the cyclin-dependent kinases 4 and 6 (CDK4/6) that crosses the blood-brain barrier and demonstrates in vivo activity against intracranial human brain tumor xenografts [abstract]. *Mol Cancer Ther*. 2011;Meeting Abstract Supplement:B234.

Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. *J Clin Oncology*. 1984;2(3):187-193.

Sherr CJ. Cancer cell cycles. *Science*. 1996;274(5293):1672-1677.

Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials*. 1989;10(1):1-10.

Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, Goldberg JM, Khatcheressian JL, Leighl NB, Perkins CL, Somlo G, Wade JL, Wozniak AJ, Armitage JO. Recommendations for the Use of White Blood Cell Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Onc* 2015, http://jco.ascopubs.org/content/early/2015/07/08/JCO.2015.62.3488.full. Accessed 19 April 2016..

Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, Sneed PK, Chao ST, Weil RJ, Suh J, Bhatt A, Jensen AW, Brown PD, Shih HA, Kirkpatrick J, Gaspar LE, Fiveash JB, Chiang V, Knisely JP, Sperduto CM, Lin N, Mehta M. Summary Report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol*. 2012;30(4)419-425.

Wasserstrom WR, Glass JP, Posner JB. Diagnosis and treatment of leptomeningeal metastases from solid tumors: experience with 90 Patients. *Cancer*. 1982;49(4):759–77.

Wefel JS. Vardy J. Ahles T. Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol*. 2011;12(7):703-708.

Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, Allred DC, Bartlett JM, Bilous M, Fitzgibbons P, Hanna W, Jenkins RB, Mangu PB, Paik S, Perez EA, Press MF, Spears PA, Vance GH, Viale G, Hayes DF; American Society of Clinical Oncology; College of American Pathologists. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol*. 2013;31(31):3997-4013.

Attachment 1. Protocol JPBO Study Schedule

Baseline Assessments

Relative Day Prior to Day 1 of Cycle 1	≤28	≤14	≤7	Comments
Informed consent	X			Informed consent form signed (prior to performance of any protocol-specific tests/procedures).
Pregnancy test			X	Women with childbearing potential must have a negative serum pregnancy test within 7 days of the first dose of abemaciclib.
Medical history		X		Including alcohol/tobacco use and other relevant habits assessments.
Physical exam, vital signs, height, and weight		X		Vital signs include temperature, blood pressure, pulse rate, and respiration rate.
Neurologic assessment using the NANO scale		X		A modified version of NANO scale will be used to assess Part F patients.
Karnofsky Performance Status		X		
Concomitant medications		X		
CTCAE v4.0 grading (preexisting conditions)		X		To be reported only after study eligibility is confirmed.
Brain Gd-MRI assessment according to RANO-BM		X		Required for all patients. Performed locally (Day -28 to Day -1) at baseline.
Radiological tumor assessment according to RECIST v1.1		X		Imaging studies to assess extracranial disease (CT scan or Gd-MRI) are performed locally (Day -28 to Day -1) at baseline. It is recommended that CT imaging of the abdomen and pelvis be performed with IV contrast, whenever possible. For patients with known hypersensitivity to CT contrast material, a CT scan of the chest without contrast and Gd-MRI of the abdomen/pelvis are encouraged. Imaging based evaluation should be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.
Clinical tumor assessment		X		Melanoma patients only: For visible lesions, clinical tumor assessments are performed at baseline and photographs taken (including a ruler).
Gd-MRI of spine		X		Part F only
Echocardiogram or MUGA		X		Parts A, C, or F (HER2+ breast cancer patients only): Echocardiogram or MUGA is required at baseline only for patients receiving concurrent trastuzumab. Per the trastuzumab prescribing information, continued cardiac function monitoring throughout treatment is recommended but is not required as a protocol procedure.

ECG		X		ECGs will be performed locally.
Central hematology		X		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 deviations.
Central chemistry		X		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 local and central laboratory that may have an impact on eligibility or treatment decisions will not be considered protocol deviations.
Cerebrospinal Fluid (CSF) via lumbar puncture		X		Part F only: CSF cytology will be assessed locally at baseline for patients with leptomeningeal metastases. Previously documented CSF cytology results may be used if collected within 28 days prior to initiation of abemaciclib. If patient refuses lumbar puncture, the lack of CSF sample will not be considered a protocol deviation.
MDASI-BT		X		To be completed prior to physical exam and preferably prior to administration of the Trail Making Tests.
Trail Making Tests A and B		X		To be completed prior to physical exam and administered by trained site staff.

Abbreviations: CSF = Cerebrospinal fluid; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; Gd-MRI = gadolinium-enhanced magnetic resonance imaging; IV = intravenous; MDASI-BT = MD Anderson Symptom Inventory – Brain Tumor; MUGA = multi-gated acquisition scan; NANO = Neurologic Assessment in Neuro-Oncology; RECIST = Response Evaluation Criteria in Solid Tumors.

Study Schedule, Protocol I3Y-MC-JPBO
During Treatment Study Schedule

	Study Period	Study Treatment Period [a]						
	Cycle/Visit	1	2		3	4-X		
	Duration	21 ±3 days	21 ±3 days		21 ±3 days	21 ±3 days		A cycle is defined as the planned treatment interval of 21 days plus any subsequent delay prior to the start of the next cycle. A delay of a cycle due to logistical reasons (i.e. holidays, planned vacations) will be permitted up to 7 days and not constituted as a protocol violation. Additionally, a cycle delay up to 14 days to allow sufficient time for recovery from a toxicity is permitted.
	Relative Day within Dosing Cycle	1	1	14-21	1	1	14-21	
Procedure Category	**Procedure**							**Comments**
Physical examination	**Physical exam**	X	X		X	X		
	Neurologic assessment using NANO scale	X	X		X	X		A modified version of NANO scale will be used to assess Part F patients.
	Weight	X	X		X	X		
	Vital signs	X	X		X	X		Includes blood pressure, pulse, respiratory rate, and temperature.
	Karnofsky Performance Status	X	X		X	X		
Archived tumor tissue		X						Formalin-fixed paraffin-embedded archived tumor tissue must be requested after study eligibility is confirmed. The absence of an available specimen of the patient's tumor does not constitute a protocol deviation (see Section 10.4.2.3).
Adverse events collection/CTCAE grading		X	X		X	X		
Concomitant medication notation		X	X		X	X		
Lab/ diagnostic tests	**Central hematology**	X	X		X	X		Central hematology labs may be drawn up to 3 days prior to Day 1 of each cycle. Additional local hematology labs may be drawn for treatment adjustment and patient management purposes. Duplicate central labs should be submitted for assessment.
	Central chemistry	X	X		X	X		Central chemistry labs may be drawn up to 3 days prior to Day 1 of each cycle. Additional local chemistry labs may be drawn for treatment adjustment and patient management purposes. Duplicate central labs should be submitted for assessment.
	CSF via lumbar puncture				X			For Part F only: Additional CSF collection to be performed only as clinically indicated based upon evidence of response by MRI and neurologic assessment. CSF to be assessed locally for cytology, as

	Study Period	Study Treatment Period [a]						
	Cycle/Visit	1	2		3	4-X		
	Duration	21 ±3 days	21 ±3 days		21 ±3 days	21 ±3 days		A cycle is defined as the planned treatment interval of 21 days plus any subsequent delay prior to the start of the next cycle. A delay of a cycle due to logistical reasons (i.e. holidays, planned vacations) will be permitted up to 7 days and not constituted as a protocol violation. Additionally, a cycle delay up to 14 days to allow sufficient time for recovery from a toxicity is permitted.
	Relative Day within Dosing Cycle	1	1	14-21	1	1	14-21	
Procedure Category	**Procedure**							**Comments**
								well as submitting a sample centrally for assessment of drug concentration. If patient refuses lumbar puncture, the lack of CSF sample will not be considered a protocol deviation. CSF will be collected for Part C (surgery) patients at the time of surgical resection (during Cycle 1) and does not require a lumbar puncture.
	PK sampling	X	X		X			See Pharmacokinetic Sampling Schedule (Attachment 7 and Attachment 8)
	Pharmacogenetic blood sample	X						Draw sample before patient is dosed on C1D1.
	Biomarker plasma sample	X	X					Draw sample before patient is dosed on C1D1 and upon arrival at site on C2D1.
	Local ECG	X	X		X	X		ECGs will be performed according to separate schedule (see Attachment 7 and Attachment 8).
Tumor assessment	**Brain Gd-MRI** assessment according to RANO-BM			X			X	Performed locally. Repeat between D14 and D21 of every other cycle beginning with C2 and continuing through C8; thereafter, tumor assessments will be repeated between D14 and D21 of every fourth cycle (beginning with C12).
	Radiologic imaging according to RECIST v1.1			X			X	Performed locally. Imaging studies to assess extracranial disease should be repeated between D14 and D21 of every other cycle beginning with C2 and continuing through C8; thereafter, tumor assessments will be repeated between D14 and D21 of every fourth cycle (beginning with C12). The same method of imaging used at baseline should be used for each subsequent assessment.
	Clinical tumor assessment				X	X		Melanoma patients only: For visible lesions, assessments are performed and photographs taken (including a ruler) on Day 1 of every other cycle beginning with Cycle 3 or as clinically indicated.
	Gd-MRI of spine			X			X	For Part F only: Performed locally. Repeat between D14 and D21 of every other cycle beginning with C2 and continuing through C8; thereafter, tumor assessments will be repeated between D14 and D21 of every fourth cycle (beginning with C12).

	Study Period	Study Treatment Period [a]						
	Cycle/Visit	1	2		3	4-X		
	Duration	21 ±3 days	21 ±3 days		21 ±3 days	21 ±3 days		A cycle is defined as the planned treatment interval of 21 days plus any subsequent delay prior to the start of the next cycle. A delay of a cycle due to logistical reasons (i.e. holidays, planned vacations) will be permitted up to 7 days and not constituted as a protocol violation. Additionally, a cycle delay up to 14 days to allow sufficient time for recovery from a toxicity is permitted.
	Relative Day within Dosing Cycle	1	1	14-21	1	1	14-21	
Procedure Category	**Procedure**							**Comments**
Health outcomes	**MDASI-BT**	X	X		X	X		MDASI-BT will be administered on D1 of each cycle prior to physical exam, administration of the Trail Making Tests, and extensive interaction with site staff. On C1D1, MDASI-BT is to be administered before the first dose of abemaciclib in the clinic.
	Trail Making Tests A and B	X	X		X	X		Tests A and B will be completed on D1 of each cycle prior to physical exam and administered by trained site staff. On C1D1, Tests A and B are to be administered before the first dose of abemaciclib in the clinic.
Investigational product	**Abemaciclib**	Take 200 mg or prescribed dose orally every 12 hours on Days 1 through 21 of every cycle.						The period between assignment to abemaciclib in IWRS and the first dose (C1D1) should not exceed 7 days.

Abbreviations: C = cycle; CSF = Cerebrospinal fluid; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECG = electrocardiogram; IWRS = interactive web-response system; MDASI-BT = MD Anderson Symptom Inventory – Brain Tumor; Gd-MRI = gadolinium-enhanced magnetic resonance imaging; NANO = Neurologic Assessment in Neuro-Oncology; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Study Schedule, Protocol I3Y-MC-JPBO
Post Treatment Discontinuation Study Schedule

		Study Period	Postdiscontinuation Follow-Up	Long-Term Follow-Up	
		Visit	**801**	**802-X**	Posttreatment Discontinuation Follow-Up should begin the day after the last dose of abemaciclib or, if abemaciclib has been omitted for an extended period, the date it is decided that the patient will not restart abemaciclib.
		Duration	30 +/- 5 days	Variable	Long-term follow-up begins the day after the short-term postdiscontinuation follow-up visit (v801) is completed and continues until the patient's death, lost to follow-up, or overall study completion. The variable period depends on whether disease progression has occurred and if tumor assessments are due. Once disease progression has occurred, visits should occur every 90 days.
		Relative Day	**30**		
Procedure Category	**Procedure**				**Comments**
Physical examination	Physical Exam		X		
	Neurologic Assessment using NANO scale		X		
	Weight		X		
	Vital signs		X		Includes blood pressure, pulse, respiratory rate, and temperature.
	Karnofsky Performance Status		X		
Tumor assessment	Brain Gd-MRI (according to RANO-BM)		X	X	Not required if progressive disease is documented while on treatment or if there are clear signs of clinical progression. Reassessment should occur approximately every 6 weeks for the first 6 months following initiation of abemaciclib and thereafter approximately every 12 weeks until disease progression.
	Radiologic imaging according to RECIST 1.1		X	X	Not required if progressive disease is documented while on treatment or if there are clear signs of clinical progression. Reassessment should occur approximately every 6 weeks for the first 6 months following initiation of abemaciclib and thereafter approximately every 12 weeks until disease progression or until the final analysis of OS. If a patient's most recent response prior to discontinuation was a PR or CR, an additional radiological assessment should be performed during the 30-day follow-up period to confirm the response, at least 28 days after the previous radiological assessment. Response should be confirmed before the initiation of additional anticancer therapy. However, initiation of new therapy should not be delayed solely to confirm response.

		Study Period	Postdiscontinuation Follow-Up	Long-Term Follow-Up	
		Visit	**801**	**802-X**	Posttreatment Discontinuation Follow-Up should begin the day after the last dose of abemaciclib or, if abemaciclib has been omitted for an extended period, the date it is decided that the patient will not restart abemaciclib.
		Duration	30 +/- 5 days	Variable	Long-term follow-up begins the day after the short-term postdiscontinuation follow-up visit (v801) is completed and continues until the patient's death, lost to follow-up, or overall study completion. The variable period depends on whether disease progression has occurred and if tumor assessments are due. Once disease progression has occurred, visits should occur every 90 days.
		Relative Day	**30**		
Procedure Category	**Procedure**				**Comments**
Tumor Assessment	**Clinical tumor assessment**		X	X	Melanoma patients only
	Gd-MRI of spine		X	X	Part F patients only
Health outcomes	MDASI-BT		X		Collect MDASI-BT prior to physical exam, administration of the Trail Making Tests, and extensive interaction with site staff.
	Trail Making Tests A and B		X		Tests A and B will be completed prior to physical exam and administered by trained site staff.
Survival information			X	X	Although preferable to collect during a clinic visit, survival information may be collected by contacting the patient or family directly (for example, via telephone) if no procedures are required. This should be collected approximately every 90 days if no other procedures are performed.
Adverse events collection/CTCAE grading			X	X	After Visit 801, only study protocol or drug-related events are reported. If a patient has an ongoing AE or SAE possibly related to abemaciclib (for instance, abnormal electrolytes), the patient should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Any subsequent follow-up(s) for AEs will be no more than 30 days ± 5 days in duration.
Concomitant medication notation			X		
Lab/ diagnostic tests	**Central hematology**		X		
	Central chemistry		X		

		Study Period	Postdiscontinuation Follow-Up	Long-Term Follow-Up	
		Visit	**801**	**802-X**	Posttreatment Discontinuation Follow-Up should begin the day after the last dose of abemaciclib or, if abemaciclib has been omitted for an extended period, the date it is decided that the patient will not restart abemaciclib.
		Duration	30 +/- 5 days	Variable	Long-term follow-up begins the day after the short-term postdiscontinuation follow-up visit (v801) is completed and continues until the patient's death, lost to follow-up, or overall study completion. The variable period depends on whether disease progression has occurred and if tumor assessments are due. Once disease progression has occurred, visits should occur every 90 days.
		Relative Day	**30**		
Procedure Category	**Procedure**				**Comments**
	Biomarker plasma sample		X		Draw sample only for patients discontinuing due to PD.
	Local ECG		X		

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram Gd-MRI = gadolinium-enhanced magnetic resonance imaging; MDASI-BT = MD Anderson Symptom Inventory – Brain Tumor; NANO = Neurologic Assessment in Neuro-Oncology; PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; v = visit.

Study Schedule for the continued access period only, Protocol I3Y-MC-JPBO

Perform procedure as indicated.

		Study Period	Patients on Abemaciclib	Continued Access Period Follow-Up	
		Cycle	X	Follow-Up[a]	
		Visit	501-5XX	901	
		Approximate Visit Duration (days)	21	30	
		Relative day within a cycle	1		
Procedure Category	**Procedure**	**Protocol Reference**			**Comments**
Adverse events collection/CTCAE grading		Section 10.3	X	X	Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.
Investigational product	Abemaciclib	Section 9.1	X		Patients on abemaciclib who are receiving clinical benefit will continue to receive abemaciclib during the continued access period. Abemaciclib is to be administered orally every 12 hours on Days 1 through 21 of each cycle.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; OS = overall survival; SAEs = serious adverse events.

a The continued access period begins after study completion (that is, after final OS analysis) and ends at the end of trial (that is, the last patient visit).

Attachment 2. Protocol JPBO Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry**[a] (except as indicated)
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume (MCV)	Chloride
Mean cell hemoglobin concentration (MCHC)	Calcium
Leukocytes (WBC)	Albumin
Neutrophils (segmented and bands)	Total protein
Lymphocytes	Blood urea nitrogen (BUN)
Monocytes	Creatinine
Eosinophils	Alkaline phosphatase
Basophils	Alanine aminotransferase (ALT)
Platelets	Aspartate aminotransferase (AST)
	Total bilirubin and direct bilirubin
	Serum pregnancy test (women of childbearing potential only)[b]

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

[a] Assayed by Lilly-designated (central) laboratory.

[b] Assayed by investigator-designated (local) laboratory.

Attachment 3. Protocol JPBO 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 and bands	
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	**Antinuclear antibody[a]**
AST	
GGT	**Antismooth 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 JPBO Karnofsky Performance Status

The Karnofsky Performance Scale Index allows patients to be classified as to their functional impairment. This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients. The lower the Karnofsky score, the worse the survival for most serious illnesses.

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Sources: Crooks et al. 1991; de Haan et al. 1993; Oxford 1993; Hollen et al. 1994; O'Toole et al. 1991; Schag et al. 1984.

Attachment 5. Protocol JPBO RANO-BM and RANO-LM Criteria

Section I: Response Assessment in Neuro-Oncology Brain Metastases Criteria

Intracranial response and progression will be evaluated in Study I3Y-MC-JPBO using the international criteria proposed by the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group (Lin et al. 2015).

Measurability of Tumor at Baseline

Tumor lesions will be categorized at baseline as measurable or nonmeasurable. Measurable disease is defined by the presence of at least 1 measurable central nervous system (CNS) lesion.

Measurable

A contrast enhancing lesion at least 10 mm in the longest diameter (LD) that is visible on two or more axial slices that are preferably ≤5 mm apart with 0-mm skip (and ideally ≤1.5 mm apart with 0-mm skip). Additionally, the diameter perpendicular to the longest diameter in the plane of measurement should be at least 5 mm. If the MRI is performed with thicker slices, the lesion must be at least two times the slice thickness. Measurement of tumor around a cyst or surgical cavity represents a challenge, and in general, such lesions should be considered non-measureable unless there is a nodular component measuring ≥10 mm in LD and ≥5 mm in the perpendicular plane.

Nonmeasurable

All other lesions, including small lesions (LD <10 mm) as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include those with borders that cannot be reproducibly measured, dural metastases, bony skull metastases, cystic-only lesions, and leptomeningeal disease.

Specifications by Methods of Measurement

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. It is important to use imaging techniques that are consistent across all imaging time points to ensure interval appearance or disappearance of lesions or change in size is not affected by scan parameters such as slice thickness. Gd-MRI is the most sensitive and reproducible method to measure CNS lesions selected for response assessment. Suggested MRI specifications are included in Appendix A.

Baseline Documentation of Target and Non-Target Lesions

All measurements should be recorded in the eCRF in metric notation. Baseline evaluations should be performed as close as possible to treatment initiation, but no more than 4 weeks prior to treatment. Previously treated lesions should be documented with how each lesion was previously treated (e.g., stereotactic radiosurgery [SRS], whole brain radiotherapy [WBRT], surgical resection).

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of five CNS lesions total should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of size (those with longest diameter) and lend themselves to reproducible repeated measurements. For patients with recurrent disease and multiple lesions, the enlarging lesions should be prioritized as target lesions for evaluation of response. Lesions with prior local treatment (i.e., SRS or surgical resection) can be considered measurable if there has been demonstrated progression since the time of local treatment. However, careful consideration should be given to previously SRS-treated lesions given the possibility of radiation necrosis. If lesions not previously treated with local therapies are present, these are the preferred target lesions. A sum of the diameters for all target lesions will be calculated and reported as the baseline sum of longest diameters (sum LD).

Non-Target Lesions

All other CNS lesions should be identified as non-target lesions and should be recorded as 'present', 'absent', or 'unequivocal progression'.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all CNS target lesions sustained for at least 4 weeks; no new lesions; no corticosteroids; stable or improved clinically.

Partial Response (PR): At least a 30% decrease in the sum LD of CNS target lesions, taking as reference the baseline sum LD sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.

Progressive Disease (PD): At least a 20% increase in the sum LD of CNS target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, at least one lesion must increase by an absolute value of ≥5 mm to be considered progression.

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

Evaluation of Non-Target Lesions

Complete Response (CR): Requires disappearance of all enhancing CNS non-target lesions and no new CNS lesions.

Non-CR/Non-PD: Persistence of one or more non-target CNS lesions.

Progressive Disease (PD): Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s), or unequivocal progression of existing tumor-related non-enhancing (T2/FLAIR) CNS lesions.

Special Considerations for Assessment of CNS Lesions

Target lesions that become too small to measure: While on study, all CNS target lesions should have their actual measurement recorded, even when very small (e.g., 2 mm). If the lesion disappears, the value should be recorded as 0 mm. However, if the lesion is sufficiently small (but still present) that the radiologist does not feel comfortable assigning an exact measure, a default value of 5 mm should be recorded on the eCRF.

*Lesions that coalesce on treatment: A*s lesions coalesce, a plane between them may be maintained that would aid in obtaining maximum LD of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum LD for the 'coalesced' lesion.

Definition of new lesions: The finding of a new CNS lesion should be unequivocal and not due to technique or slice variation. A new lesion is one that was not present on prior scans and visible in axial, coronal, and sagittal reconstructions of ≤1.5 mm projections. If a new lesion is equivocal, for example because of its small size (i.e., ≤5 mm), continued therapy may be considered, and follow up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan showing the new lesion.

Definition of unequivocal progression of non-target lesions: When the patient also has measurable disease, to achieve 'unequivocal progression' on the basis of non-target disease alone, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. When the patient has only non-measurable disease, there must be an overall level of substantial worsening to merit discontinuation of therapy.

Guidance in the case of uncertain attribution of radiographic findings and/or equivocal cases: In the case of patients followed after SRS, there may be radiographic evidence of enlargement of target and non-target lesions which may not necessarily represent tumor progression. If there is evidence of radiographic progression but there is clinical evidence supporting the possibility that the radiological changes are due to treatment effect (and not to progression of cancer), additional evidence is required to distinguish true progression versus treatment effect, as standard MRI alone is not sufficient. Patients may be continued on protocol therapy pending a repeat scan at the next scheduled evaluation or sooner, although the use of an advanced imaging modality such as perfusion MR imaging, magnetic resonance spectroscopy, or ^{18} FLT or ^{18} FDG PET (in the case of SRS) is strongly encouraged. If subsequent testing demonstrates that progression has occurred, the date of progression should be recorded as the date of the scan at which this issue was first raised.

Special Considerations Regarding Corticosteroid Use and Clinical Deterioration

An increase in corticosteroid dose alone, in the absence of clinical deterioration related to tumor, will not be used as a sole determinant of progression. Patients with stable imaging studies whose corticosteroid dose was increased for reasons other than clinical deterioration related to tumor do not qualify for stable disease or progression. They should be observed closely. If their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease; if further clinical deterioration related to tumor becomes apparent, they will be considered to have PD.

The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decline in the Karnofsky Performance Status (KPS) from 100 or 90 to 70 or less, a decline in KPS of at least 20 points from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events, treatment-related toxicity, or changes in corticosteroid dose.

Summary of Response

Table1. Summary of RANO-BM Response Criteria

Criterion	CR	PR	SD	PD
Target lesions	None	≥30% decrease in sum LD relative to baseline	<30% decrease relative to baseline but <20% increase in sum LD relative to nadir	≥20% increase in sum LD relative to nadir. In addition to relative increase of 20%, ≥1 lesion must increase by absolute value of ≥5 mm. *
Nontarget lesions	None	Stable or improved	Stable or improved	Unequivocal PD*
New lesion(s)**	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	NA+
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirement for response	All	All	All	Any+

Abbreviations: CR = Complete Response; LD = Longest Diameter; PD = Progressive Disease; PR = Partial Response; RANO-BM = Response Assessment in Neuro-Oncology for Brain Metastases; SD = Stable Disease.

*Progression occurs when this criterion is met.

**New lesion = new lesion not present on prior scans and visible in at least 2 projections. If a new lesion is equivocal, for example because of its small size, continued therapy may be considered, and follow up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan showing the new lesion.

+Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

Table 2. Bi-Compartmental PFS

CNS (by RANO-BM)	Non-CNS (by RECIST v1.1)	Bi-Compartmental PFS	Note
CR, PR, or SD	PD	Log as PFS event	Log as non-CNS PD
PD	CR, PR, or SD	Log as PFS event	Log as CNS PD
PD	PD	Log as PFS event	Log as both CNS and non-CNS PD

Abbreviations: CNS = Central Nervous System; CR = Complete Response; PD = Progressive Disease; PFS = Progression-Free Survival; PR = Partial Response; RANO-BM = Response Assessment in Neuro-Oncology for Brain Metastases; RECIST = Response Evaluation Criteria in Solid Tumors; SD = Stable Disease.

Appendix A: Recommendations for Minimum Requirements for Brain Imaging

MR Scanners: 1.5T and 3T MR scanners only

- Localizer/Scout
- 3D T1w pre-contrast (MPRAGE, 3D IR SFPGR T1w)
    - minimum TE
    - TI, TR and flip angle according to manufacturer specific / field strength specific recommendations for optimum image quality
    - SENSE / SMASH / GRAPPA / ASSET allowed
    - Slice/3D slab orientation: sagittal or transverse
    - FOV: 256 mm x 256 mm
    - Matrix: 256x256
    - Slice thickness: ≤ 1.5 mm
    - Full brain coverage
- DWI
    - single shot EPI sequence
    - minimum TE
    - TR > 3000 ms
    - Spectral fat suppression
    - b: 0 and 1000 s/mm^2 (3 directions)
    - SENSE / SMASH / GRAPPA / ASSET: optional for 1.5 T, obligatory for 3 T.
    - Slice orientation: transverse
    - Slice thickness: 5mm
    - Slice gap: 0
    - Number of slices: Full brain coverage
    - FOV: 240 mm x 240 mm
    - Matrix: 128 x 128 or higher
    - Postprocessing: Calculation of ADC maps (diffusion trace maps)
- 2D FLAIR, transverse
    - Turbo Spin Echo (TSE) / Fast Spin Echo (FSE) sequence
    - TE: 90-140ms
    - TR: 6000-10000 ms
    - TI: 2000-2500 ms (use TI according to optimized protocol for specific inversion pulses and field strength)
    - SENSE / SMASH / GRAPPA / ASSET allowed
    - Slice orientation: transverse
    - Slice thickness: 5mm
    - Slice gap: 0
    - Number of slices: same as sequence 2
    - FOV: 240 mm x 240 mm
    - Matrix: 256 x 256 or higher
    - Slice positioning as in sequence 2
- 3D FLAIR (OPTIONAL)
    - 3D Turbo Spin Echo (TSE) / Fast Spin Echo (FSE) sequence
    - TE: 90-140ms
    - TR: 6000-10000 ms
    - TI: 2000-2500 ms (use TI according to optimized protocol for specific inversion pulses and field strength)
    - SENSE / SMASH / GRAPPA / ASSET / ARC allowed

    - Slice orientation: sagittal or transverse
    - Slice thickness: ≤ 1.5 mm
    - Number of slices: Full brain coverage
    - FOV: 250 mm x 250 mm
    - Matrix: 224 x 224 or higher
    - Slice positioning as in sequence 1
- Contrast agent injection
    - 0.1 mmol/kg BW of a Gd-based contrast agent
- T2w-TSE
    - Turbo Spin Echo (TSE) / Fast Spin Echo (FSE) sequence
    - TE: 80-120ms
    - TR: ≥ 2500 ms
    - SENSE / SMASH / GRAPPA / ASSET allowed
    - Slice orientation: transverse
    - Slice thickness: 5mm
    - Slice gap: 0
    - Number of slices: same as sequence 2
    - FOV: 240 mm x 240 mm
    - Matrix: 256 x 256 or higher
    - Slice positioning as in sequence 2
- 3D T1w post-contrast (MPRAGE, 3D IR FSPGR T1w)
    - Sequence parameters and slice positioning as in sequence 1

Further sequences can be added to the protocol according to the preferences of the respective center. The order and timing of prescribed sequences after contrast administration should also be respected.

Section II: Response Assessment in Neuro-Oncology Leptomeningeal Metastases Criteria

Leptomeningeal metastases (LM) response and progression will be evaluated in Study I3Y-MC-JPBO using the draft criteria proposed by the Response Assessment in Neuro-Oncology Leptomeningeal Metastases (RANO-LM) working group (Chamberlain et al.; unpublished manuscript).

Assessing Response in Leptomeningeal Metastases

Three basic elements are proposed for assessing response in LM: a standardized neurological examination, CSF cytology, and radiographic evaluation.

Neurological Assessment

The RANO-LM working group in conjunction with the RANO Neurological Assessment working group has created an instrument for assessing the neurological exam in patients with LM in order to standardize response definitions. This assessment is the Neurologic Assessment in Neuro-Oncology (NANO) scale which has been adapted for use in patients with LM. Progressive disease based on neurological assessment is defined by a change of 2 or more levels in a given domain, or alternatively by a change to level 3 (or level 2 in domains defined by only 3 levels) in any one domain. Transient neurological symptoms or deficits often are treatment-related and do not represent progression of LM.

CSF Cytology

CSF cytology is usually a qualitative analysis whereby results are reported ass negative, atypical, suspicious, or positive. The RANO-LM working group endorses the binary outcome measure where results are considered either positive (includes suspicious) or negative (includes atypia). Response based on CSF cytology is considered when CSF converts from positive to negative and in which a confirmatory determination is made from all sites (lumbar or ventricular) previously shown to be positive. Cytological response would be declared in instances where the CSF is cleared of identifiable tumor cells from all sites of identified disease and maintains that status for 4 weeks.

Neuroimaging Assessment

The most challenging element of response assessment in LM is the neuroimaging evaluation. MRI abnormalities of LM include enhancement of the leptomeninges of the brain or spinal cord identified as enhancement of the cranial nerves and spinal nerve roots, brain surface, cerebellar foliae and within cerebral sulci. Pathological enhancement may be nodular, linear or curvilinear as well as focal or diffuse. Because radiographic features typical of LM are generally small in volume and complex in geometry, current MRI technology does not permit quantitative assessment.

The working group recommends contrast MRI of brain and entire spine at baseline and at pre-specified times thereafter. Suggested imaging requirements for MRI are given in Appendix B. The recommendation is to assess 6 regions for pathological contrast enhancement on MRI consistent with LM, with findings for each region documented at baseline as present (abnormality present), absent (no abnormality; normal), or non-evaluable (NE). In follow-up, features in these regions (or new regions of involvement) should be assessed as completely resolved (+3), definitely improved (+2), possibly improved (+1), unchanged (0), possibly worse (-1), definitely worse (-2), or new site of disease (-3) as per Table 3.

Table 3. Radiographic assessment in leptomeningeal metastases

MRI findings	Present (1) or absent (0) or non-evaluable (NE)	Dimensions of measurable nodules defined as >5 x 10mm (orthogonal diameters)	Change from previous MRI (-3 to +3)
BRAIN			
Nodules (subarachnoid or ventricular)			
*Leptomeningeal enhancement			
Cranial nerve enhancement			
Hydrocephalus^			
Parenchymal (brain metastases)^			
SPINE			
Nodules (subarachnoid)			
Leptomeningeal enhancement			
Nerve root enhancement			
Parenchymal(intramedullary metastases)^			
Epidural metastasis ^			
TOTAL SCORE			

Legend:

*Leptomeningeal enhancement may include pia, cerebellar folia, ventricular ependyma or cerebral sulci.

^Both hydrocephalus and parenchymal metastases, either brain or spine, are noted as present or absent but not used for LM response determination.

Column 2: scored as 1 (present) or 0- (absent) or non-evaluable (NE). A maximum of 5 radiographic target lesions are selected from baseline imaging to score on follow-up.

Column 3: scores each measurable lesion (at least 10x5mm) excluding parenchymal as 1 (present with maximum orthogonal diameters) or 0 (absent).

Column 4: change from baseline or prior image scored as same (0), probable improvement (+1), definite improvement (+2), no evidence of disease (+3) or probable worsening (-1), definite worsening (-2), new site(s) of disease (-3). Measurable nodules defined as >5x10mm are scored as same (0), resolved (no evidence of disease, complete response), definitely better (+2; partial response) [decrease by >50% in the summed product of orthogonal diameters], definite worsening (-2; progressive disease) [increase by >25% in the summed product of orthogonal diameters]. A composite score (total score) is calculated and compared to the baseline total score. A 25% worsening in the current score relative to baseline defines radiographic progressive disease. A 50% improvement in the current score defines a radiographic partial response. Resolution of all baseline radiographic abnormalities defines a complete response. All other situations define stable disease.

Response Assessment in Leptomeningeal Metastases

The RANO-LM working group proposes a composite response assessment wherein evaluation of the neurologic examination is performed using the adapted NANO scale, CSF cytology is evaluated, and a composite score of MRI of the neuraxis is applied. Table 4 provides a summary of the response determination.

Table 4. Response determination in leptomeningeal metastases

Assessment		Response		Progressive or refractory disease					Stable disease
				Neurological examination defined progression	CSF defined disease progression	Radiologic defined disease progression	Symptoms^		
Neurological exam		Stable or improved		Worse	Stable	Stable	Stable		Stable
CSF Cytology		Negative		Negative	Positive	Negative	Negative		Negative or positive (solid tumors only)
CNS imaging		Definite Improvement or stable		Stable	Stable	Definite worsening	Stable		Stable or equivocally worsening
Symptom assessment		Stable or improved		Worse or stable	Worse or stable	Worse or stable	Worse		Stable

Legend:

CSF cytology negative	Defined as either true negative or atypical
CSF cytology positive	Defined as true positive or suspicious
Stable	Defined as stable or indeterminate
Symptoms^	Stable; no change (-1 to +1 in symptom inventory Worse; -2 to -3 in symptom inventory Improved; +2 to +3 in symptom inventory

Appendix B: Recommended MRI Parameters in Leptomeningeal Disease

MRI prerequisites
1.5T and 3T MR scanners only
Use of same MRI at baseline and follow-up
MRI to be performed prior to lumbar puncture
Recommended MRI sequences
Brain
Volumetric 3D T1 (MPRAGE or SPGR) post-contrast image with isotropic 1mm voxels to permit reformatting in 3 planes (axial, coronal and sagittal)
Reformatted slice thickness 3mm to obtain good SNR & manageable number of slices for full brain coverage
IV Contrast dose = 0.1mmol/kg of gadolinium-based agent
Spine
Volumetric 3D T1 (MPRAGE or SPGR) post-contrast image in sagittal plane with isotropic 1mm voxels to permit reformatting in 3 planes (axial, coronal and sagittal) with a 2-3mm reformatted slice thickness

Attachment 6. Protocol JPBO RECIST 1.1

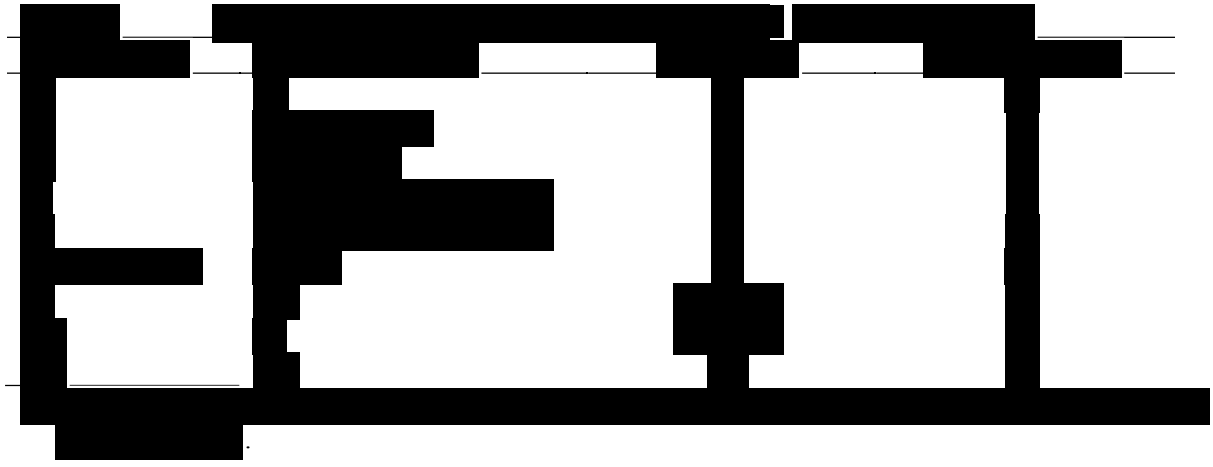
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

Attachment 7. Protocol JPBO Electrocardiogram and Pharmacokinetic Sampling Schedule – Parts A, B, D, E, and F

I3Y-MC-JPBO Electrocardiogram and Pharmacokinetic Sampling Schedule

Cycle (C) and Day (D)	ECG	PK Sample Number	Dosing of Abemaciclib	Sampling Time for ECG and PK from Blood[a]
Baseline (Day -14 to Day -1)	X			Day of visit
C1D1	X	1	X	2-4 hrs after abemaciclib dosed in the clinic
C2D1	X	2	X[b]	Upon arrival at site at least 4 hrs after taking abemaciclib dose at home
C2D1		3		3 ± 0.5 hr after PK sample number 2 (that is, at least 7 ± 0.5 hrs after taking abemaciclib dose at home)
C3D1		4[d]	X[c]	Predose (0 hr)
C3D1		5		3 ± 0.5 hrs after abemaciclib dose
C4D1	X			2 – 4 hrs after abemaciclib dose
30-day follow-up	X			Day of visit

Abbreviations: C = cycle; CSF = cerebrospinal fluid; D = day; ECG = electrocardiogram; hr = hour(s); PD = progressive disease; PK = pharmacokinetic.

[a] Samples of approximately 2 mL of whole blood will be drawn for measurement of abemaciclib and its metabolites.

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

[c] On Cycle 3 Day 1 only, after collection of PK sample number 4, patients should take abemaciclib immediately following the sample collection, prior to conducting other procedures.

[d] For patients participating in Part F, a time-matched sample of CSF should be collected for drug concentration analysis as well as CSF cytology.

Attachment 8. Protocol JPBO Electrocardiogram and Pharmacokinetic Sampling Schedule – Part C

I3Y-MC-JPBO Electrocardiogram and Pharmacokinetic Sampling Schedule - Part C

Cycle (C) and Day (D)	ECG	PK Sample Number	Dosing of Abemaciclib	Sampling Time for ECG and PK from Blood[a]
Baseline (Day -14 to Day -1)	X			Day of visit
C1D1	X	1	X	2-4 hrs after abemaciclib dosed in the clinic
C1 day of surgery[b]		2	X	6-12 hrs after taking abemaciclib dose at home
C1 day of surgery		3		Approximately 6 hours after resection of brain tumor tissue
C3D1	X	4	X[c]	Upon arrival at site at least 4 hrs after taking abemaciclib dose at home
C3D1		5		3 ± 0.5 hr after PK sample number 4 (that is, at least 7 ± 0.5 hrs after taking abemaciclib dose at home)
C4D1		6	X[d]	Predose (0 hr)
C4D1	X	7		3 ± 0.5 hrs after abemaciclib dose
30-day follow-up	X			Day of visit

Abbreviations: C = cycle; CSF = cerebrospinal fluid; D = day; ECG = electrocardiogram; hr = hour(s); PK = pharmacokinetic.

[a] Samples of approximately 2 mL of whole blood will be drawn for measurement of abemaciclib and its metabolites.

[b] Blood, CSF, and brain tumor tissue samples for determination of drug concentration will be collected at the time of surgery, after 5 to 14 days of abemaciclib dosing (during Cycle 1).

[c] On Cycle 3 Day 1 only, patient should take abemaciclib dose at home at least 4 hours before arrival at site. The time of abemaciclib dose intake must be recorded that day.

[d] On Cycle 4 Day 1 only, after the predose PK sample, patients should take abemaciclib immediately following the sample collection, prior to conducting other procedures.

Attachment 9. Protocol JPBO Sampling Summary

This table provides estimates of the maximum number of samples (venipunctures and biopsies), volumes for all sampling, and tests (study qualification, health monitoring, drug concentration, tailoring biomarkers, and exploratory) required for each patient during the study. 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, if the patient discontinues from the study early).

Protocol I3Y-MC-JPBO Sampling Summary[a]

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Study qualification[b]	Blood	4 mL	3	12 mL
Health monitoring/safety monitoring (may be more than 1 tube)[b]	Blood	5 mL/Cycle	2	50 mL
Archived formalin-fixed, paraffin-embedded tumor tissue	Tissue	5 micron	21 slides	105 micron
Drug concentration of abemaciclib for all patients in trial	Blood	2 mL	5	10 mL
Drug concentration of abemaciclib for all patients in Part C	Tissue	50 mg	1	50 mg
Drug concentration of abemaciclib for all patients in Part C	CSF	2 mL	1	2 mL
Drug concentration of abemaciclib for all patients in Part F[c]	CSF	2 mL	2	4 mL
Pharmacogenetic blood sample	Blood	9 mL	1	9 mL
Plasma for exploratory biomarker	Blood	6 mL	3	18 mL
Hepatic monitoring[d]	Blood	3 - 30 mL		-

[a] Covers Cycles 1 through 9 and 1 postdiscontinuation follow up visit.

[b] Additional samples may be drawn if needed for safety purposes.

[c] Additional CSF to be collected for local cytology results.

[d] 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 10. Protocol JPBO Inducers and Strong Inhibitors of CYP3A 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 all these medications (except EIAED as noted below), if clinically indicated. However, these medications should be avoided or substituted, if possible.

Inducers of CYP3A	
Carbamazepine[a]	
Dexamethasone[b]	
Phenobarbital/phenobarbitone[a]	
Phenytoin[a]	
Rifapentine	
Rifampin	
Rifabutin	
St. John's wort	
Strong inhibitors of CYP3A	
Aprepitant	
Ciprofloxacin	
Clarithromycin	
Diltiazem	
Erythromycin	
Fluconazole	
Itraconazole	
Ketoconazole	
Nefazodone	
Verapamil	
Cytochrome P450 Substrates with Narrow Therapeutic Range	
CYP1A2	Theophylline Tizanidine
CYP2C9	Warfarin Phenytoin
CYP2D6	Thioridazine Pimozide

CYP3A	Alfentanil
	Astemizole
	Cisapride
	Cyclosporine
	Dihydroergotamine
	Ergotamine
	Fentanyl
	Pimozide
	Quinidine
	Sirolimus
	Tacrolimus
	Terfenidine

Abbreviations: CYP = cytochrome P450; EIAED = enzyme-inducing antiepileptic drugs; HIV = human immunodeficiency virus.

[a] Patients may not receive concurrent treatment with EIAEDs. Patients requiring treatment with antiepileptic drugs should be prescribed non-EIAED (eg, levetiracetam, lacosamide, lamotrigine, etc).

[b] All patients may receive supportive therapy with dexamethasone.

Attachment 11. Protocol JPBO Amendment(d) Summary A Phase 2 Study of Abemaciclib in Patients with Brain Metastases Secondary to Hormone Receptor Positive Breast Cancer, Non-Small Cell Lung Cancer, or Melanoma

Overview

Study I3Y-MC-JPBO, a Phase 2 Study of Abemaciclib in Patients with Brain Metastases Secondary to Hormone Receptor Positive Breast Cancer, Non-Small Cell Lung Cancer or Melanoma has been amended. The new protocol is indicated by Amendment (d) and will be used to conduct the study in place of any preceding version.

The overall changes and rationale for the changes made to this protocol are as follows:

- Included TBL and VTE in abbreviations (Section 4).
- Section 5.4 incorporated rationale for Amendment (d) to update safety monitoring information for hepatic conditions, renal function, and VTEs.
- Section 9.4.1.1, Table JPBO.2 modified along with Sections 9.4.1.1.3, 9.4.1.1.4, and 9.4.1.1.4.1, and incorporated Section 9.4.1.1.4.2 for alignment with safety updates.
- Updated requirements for AE/SAE reporting in the CRF (Section 10.3.1).
- Sections 10.3.4.1, 10.3.4.2, and 10.3.4.3 incorporated safety monitoring language for hepatic conditions, renal function, and VTEs.
- CYPs text updated to align with abemaciclib program information (Attachment 10).

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.

Section 4. Abbreviations and Definitions

Term	Definition
…	….
TBL	total bilirubin
…	…
VTE	venous thromboembolic event
…	…

Section 5.4. Rationale for Amendment (d)

Study JPBK protocol was amended to update the dosing guidance for cases of non-hematologic toxicity, diarrhea, and ALT increase. This amendment will harmonize the dosing guidance across all clinical trials of abemaciclib in the metastatic setting. The amendment updated the safety language regarding hepatic monitoring, assessment of renal function, and venous thromboembolic events (VTEs) for ongoing patients. Minor typographical and formatting edits were made throughout the document for clarity and consistency.

Section 9.4.1.1. Dose Adjustments and Delays

Table JPBO.2. Toxicity Dose Adjustments and Delays of Abemaciclib for Study I3Y-MC-JPBO

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
…	…	…	…
Hematologic toxicity: If ~~P~~patient requires administration of blood cell growth factors Sections 9.4.1.1.3 and 9.6.4.	Regardless of severity (Use of g~~G~~rowth 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 led to the use of growth factor.
Nonhematologic Toxicity[a] (except diarrhea and ALT increased) Section 9.4.1.1.4	Persistent or recurrent[b] Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose ~~**MAY**~~ **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose ~~**MAY**~~ **MUST** be reduced by 1 dose level~~– investigator's discretion~~.
…	…	…	…
Diarrhea Sections 9.4.1.1.4.1 and 9.6.5	~~Requires hospitalization or Grade 3 or 4~~Grade 2 that does not resolve within 24 hours to at least Grade 1	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose reduction is **NOT** required.~~**MUST be reduced by 1 dose level.**~~
Diarrhea Sections 9.4.1.1.4.1 and 9.6.5	Persistent or recurrent[b] Grade 2 that does not resolve with maximal supportive measures ~~within 24 hours to at least Grade 1~~or any Grade of diarrhea that requires hospitalization	Dose ~~**SHOULD**~~ **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose ~~**MAY**~~ **MUST** be reduced by 1 dose level~~– investigator's discretion~~.
~~Diarrhea Sections 9.4.1.1.4 and 9.6.5~~	~~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.~~
Diarrhea Sections 9.4.1.1.4.1 and 9.6.5	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.

Toxicity Dose Adjustments and Delays of Abemaciclib for Study I3Y-MC-JPBO

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
ALT Increased (Sections 9.4.1.1.4.2 and 10.3.4.1.)	Persistent or recurrent[b] Grade 2 (>3.0-5.0×ULN)[c], or Grade 3 (>5,0-20.0×ULN)[d]	Dose **MUST** be suspended until toxicity resolves to baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
ALT Increased (Sections 9.4.1.1.4.2 and 10.3.4.1.)	Grade 4 (>20.0×ULN)	Abemaciclib **MUST** be discontinued.	Abemaciclib **MUST** be discontinued.
ALT Increased with increased total bilirubin, in the absence of cholestasis (Sections 9.4.1.1.4.2 and 10.3.4.1.)	Grade 3 increased ALT (>5.0 x ULN) with total bilirubin >2 x ULN	Abemaciclib **MUST** be discontinued	Abemaciclib **MUST** be discontinued

Abbreviations: ALT = alanine transaminase; ASCO = American Society of Clinical Oncology; ULN = upper limit of normal.

Note: MAY = per the investigator's clinical judgment; ~~SHOULD = not mandatory but highly recommended;~~ MUST = mandatory.

a Additional guidance for renal and hepatic monitoring is in Sections 10.3.3.1 and 10.3.3.2.

b Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event). As a general guidance, based on the risk/benefit balance assessment per the investigator, for a patient who experiences a new episode of Grade 3 hematological toxicity after more than 8 weeks following the last episode of same Grade 3 hematological toxicity, the investigator may consider resuming the patient on the same drug dose should the patient satisfy the following conditions:

- shows stable hematological counts (Grade ≤2) during that timeframe
- has absence of any signs or risk of infection
- is benefiting from study treatment

c Note: the patient who presents with no liver metastases at baseline.

d Grade 3 ALT increased is a trigger for additional assessments and possibly hepatic monitoring. See Section 10.3.4.1 for additional guidance for hepatic monitoring

Section 9.4.1.1.3. Hematologic Toxicity

…

Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event). As a general guidance, based on the risk/benefit balance assessment per the investigator, for a patient who experiences a new episode of Grade 3 hematological toxicity after more than 8 weeks following the last episode of same Grade 3 hematological toxicity, the investigator may consider resuming the patient on the same drug dose should the patient satisfy the following conditions:

- The patient showed stable hematological counts (Grade ≤2) during that timeframe
- In the absence of any signs or risk of infection
- The patient is benefiting from study treatment

…

Section 9.4.1.1.4. Nonhematologic Toxicity

…

If a patient experiences persistent or recurrent Grade 2 nonhematologic toxicity (except diarrhea~~;~~ , refer to Section 9.4.1.1.4.1 or ALT increased, refer to Section 10.3.4.1) that does not resolve with maximal supportive measures within 7 days to either baseline or Grade 1, then dosing of abemaciclib ~~may~~ must be suspended (until the toxicity resolves to either baseline or Grade 1), and the dose of abemaciclib ~~may~~ must be reduced by 1 dose level as outlined in Table JPBO.3 at the discretion of the investigator.

…

Section 9.4.1.1.4.1. Diarrhea

…

If a patient experiences Grade 2 diarrhea that does not resolve with maximal supportive measures (refer to Section 9.6.5) within 24 hours to at least Grade 1, the study drug must be suspended (until the toxicity resolves to at least Grade 1) but abemaciclib dose reduction is not required. However, ~~If~~ if a patient experiences persistent or recurrent Grade 2 diarrhea that does not resolve with maximal supportive measures (refer to Section 9.6.5) within 24 hours to at least Grade 1, then dosing ~~should~~ must be suspended (until the toxicity resolves to at least Grade 1), and the dose of abemaciclib ~~may~~ must be reduced by 1 dose level as outlined in Table JPBO.3~~ at the discretion of the investigator. If the same dose level was resumed and diarrhea recurred despite maximal supportive measures, the dose must be reduced by 1 dose level as outlined in Table JPBO.3.~~

Section 9.4.1.1.4.2. Hepatic Toxicity

Dose modifications and management for increased ALT are provided in Table JPBO.3. For persistent or recurrent Grade 2 ALT increased that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1, or Grade 3 ALT increased, abemaciclib must be suspended until the toxicity has resolved to at least Grade 1 and the dose must be reduced by 1 dose level. Discontinue abemaciclib for Grade 3 increased ALT (>5.0 x ULN) with total bilirubin (TBL) >2 x ULN, in the absence of cholestasis. For Grade 4 ALT increased, the patient must be discontinued from abemaciclib. Refer to Section 10.3.4.1 for additional hepatic monitoring guidance.

Section 10.3.1. Adverse Events

…

In addition, the investigator will record all relevant AE/SAE information in the CRF~~all AEs occurring after the patient receives the first dose of abemaciclib must be reported to Lilly or its designee via eCRF~~.

…

Section 10.3.4.1. Special Hepatic Safety Data Collection

If a study patient experiences elevated ALT ≥5×ULN and elevated total bilirubin (TBL)≥2×ULN, or ALT >8x ULN for patients with underlying baseline hepatic metastases, liver tests (Attachment 3), including ALT, AST, TBL, direct bilirubin, gamma glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests (Attachment 3) and in consultation with the Lilly CRP. Monitoring of ALT, AST, and TBL should continue until levels normalize or return to approximate baseline levels. Additional diagnostic testing should be considered to rule out cause of increased liver enzymes per the investigator's discretion.

Hepatic monitoring tests (Attachment 3) should be collected in the event that 1 or more of the following conditions is met for the patient during the course of the study:

- ALT ≥5×ULN and TBL ≥2×ULN
- ALT >8x ULN for patients with underlying hepatic metastasis
- discontinuation from study treatment due to a hepatic event or an abnormality of liver tests

Section 10.3.4.2. Renal Function

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting cystatin C-calculated glomerular filtration rate. Increases in serum creatinine occurred within the first 2 weeks of treatment, remained stable through the treatment period, and were reversible upon treatment discontinuation. If deterioration of renal function is suspected, serum creatinine should not be the only measure used to assess a patient's renal function.

Dose adjustment (omission, reduction, or discontinuation) should not solely be based on interpretation of serum creatinine values because these may not reflect renal function. If deterioration of renal function is suspected per the investigator's clinical assessment, dose alteration should follow the protocol guidance for non-hematological toxicities (Table JPBO.3).

Section 10.3.4.3. Venous Thromboembolic Events (VTEs)

In the randomized Phase 3 studies in breast cancer patients who received abemaciclib in combination with endocrine therapy, there was a greater number of patients who experienced VTEs in the abemaciclib plus endocrine therapy arm than in the placebo plus endocrine therapy arm. The majority of the events were non-serious and were treated with low-molecular-weight heparin. Generally, these events did not result in discontinuation of the study treatment. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known. For suspected or confirmed VTE (e.g., deep vein thrombosis or pulmonary embolism), treatment should occur according to usual clinical practice. In studies with single-agent abemaciclib use in the mBC population or other tumor types, including NSCLC, no increased rates of VTEs were observed as compared to the incidence of VTEs for these particular patient populations who were treated with other anticancer agents.

Attachment 10. Protocol JPBO 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 all these medications (except EIAED as noted below), if clinically indicated. However, these medications should be avoided or substituted, if possible.

Inducers of CYP3A4
Carbamazepine[a]
Dexamethasone[b]
Phenobarbital/phenobarbitone[a]
Phenytoin[a]
Rifapentine
Rifampin
Rifabutin
St. John's wort
Strong inhibitors of CYP3A4
~~All HIV protease inhibitors~~
Aprepitant
Ciprofloxacin
Clarithromycin
Diltiazem
Erythromycin
Fluconazole
Itraconazole
Ketoconazole

Nefazodone

Verapamil

Cytochrome P450 Substrates with Narrow Therapeutic Range	
CYP1A2	Theophylline Tizanidine
~~**CYP2C8**~~	~~Paclitaxel~~
…	…