Protocol I3Y-MC-JPBJ(h)

A Phase 1b Study of Abemaciclib in Combination with Multiple Single-Agent Options for Patients with Stage IV NSCLC

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Approval Date: 8-Feb-2019

1. Protocol I3Y-MC-JPBJ(h)

A Phase 1b Study of Abemaciclib in Combination with Multiple Single-Agent Options for Patients with Stage IV NSCLC

Confidential Information

Abemaciclib (LY2835219)

This Phase 1 study is a multicenter, nonrandomized, open-label, dose-escalation study followed by cohort expansion of oral abemaciclib in patients with metastatic non-small cell lung cancer.

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2. Synopsis

Study I3Y-MC-JPBJ (JPBJ) is a Phase 1b trial for patients with non-small cell lung cancer (NSCLC) that will evaluate the safety and tolerability of abemaciclib in combination with multiple single-agent options in approximately 150 patients with metastatic NSCLC.

Clinical Protocol Synopsis: Study I3Y-MC-JPBJ

Name of Investigational Product: Abemaciclib (LY2835219)

Title of Study: A Phase 1b Study of Abemaciclib in Combination with Multiple Single-Agent Options for Patients with Stage IV NSCLC

Number of Planned Patients:	**Phase of Development:** Phase 1b
Entered: 195 Enrolled: 150 Completed (approximate number of patients who will complete the endpoint): 150	

Length of Study: 46 months
Planned first patient visit: March 2014
Planned last patient visit: June 2018

Objectives:
The primary objective of this study is to evaluate the safety and tolerability of abemaciclib when administered orally in combination with multiple single-agent options to patients with Stage IV non-small cell lung cancer (NSCLC) using Common Terminology Criteria for Adverse Events (CTCAE version 4.0, NCI 2009).

The secondary objectives of the study are to determine the pharmacokinetics (PK) of abemaciclib and pemetrexed, gemcitabine, ramucirumab, or LY3023414, when given in combination; and to document the antitumor activity of abemaciclib when given in combination with multiple single-agent options; and to characterize changes in patient-reported pain and disease-related symptoms collected via the MD Anderson Symptom Inventory-Lung Cancer (MDASI-LC).

Study Design:
Multicenter, nonrandomized, open-label, dose-escalation Phase 1b study of abemaciclib in combination with 1) pemetrexed, 2) gemcitabine, 3) ramucirumab, 4) LY3023414 (PI3K/mTOR dual inhibitor) (United States [US] only), and 5) pembrolizumab for approximately 150 patients with Stage IV NSCLC.

Diagnosis and Main Criteria for Inclusion and Exclusions:
Inclusion Criteria

Patients may be included in the study if the following criteria are fulfilled:

[1] For all parts: The patient must have Stage IV NSCLC. Eligibility is not restricted based on molecular features (for example, EGFR mutation or ALK translocation). However, all patients with nonsquamous NSCLC with EGFR activating mutations or ALK alterations should have received and progressed after appropriate tyrosine kinase inhibitor or ALK targeted therapy prior to enrollment.
- For Part A (abemaciclib + pemetrexed): Nonsquamous subtypes only. The patient must have received at least 1 but not more than 3 prior therapies, including 1 platinum-based chemotherapy for advanced/metastatic NSCLC. Patients who have received pemetrexed as first-line or maintenance therapy must be ≥3 months after treatment for determining eligibility.
- For Part B (abemaciclib + gemcitabine): Any subtype. The patient must have received at least 1 but not more than 3 prior therapies for advanced/metastatic NSCLC.
- For Part C (abemaciclib + ramucirumab): Any subtype. The patient must have received at least 2 but not more than 3 prior therapies for advanced/metastatic NSCLC.
- For Part D (abemaciclib + LY3023414 [US only]): Any subtype. The patient must have received at least 2 but not more than 3 prior therapies for advanced/metastatic NSCLC. The patient must not have received prior treatment with any PI3K or mTOR inhibitor.
- For Part E (abemaciclib+pembrolizumab): Any subtype. The patient must have received at least 1 but no more than 3 prior therapies for advanced/metastatic NSCLC.

[2] Have the presence of either measureable or nonmeasurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

[3] Are ≥18 years of age.

[4] Have given written informed consent prior to any study-specific procedures.

[5] 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 transaminase (AST) ≤3.0 times ULN. For patients with tumor involvement of the liver, AST and ALT equaling ≤5.0 times ULN are acceptable. Patients on Part A with tumor involvement of the liver and ALT or AST >3.0 to ≤5.0 times ULN must have Child-Pugh Class A using the Child-Turcotte scoring system.
- Renal: Serum creatinine ≤1.5 times ULN. All patients must have a Creatinine Clearance (CrCl) >45 mL/min using the standard Cockcroft and Gault formula.
- Part E: Thyroid: TSH within normal limits OR Total T3 or free T3 and free T4 within normal limits
- Part E: Coagulation: PTT or aPTT <5 seconds above ULN and INR≤1.5 times ULN or PT <5 seconds above ULN. Patients receiving anticoagulant therapy are permitted if the PTT or aPTT and INR or PT are within therapeutic range of intended use of anticoagulants.

[6] Have a performance status ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale.

[7] Have discontinued all previous therapies for cancer (including chemotherapy, radiotherapy, immunotherapy, and investigational therapy) for at least 21 days for myelosuppressive agents or 14 days for nonmyelosuppressive agents prior to receiving study drug, and recovered from the acute effects of therapy (treatment-related toxicity resolved to baseline) except for residual alopecia.

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

[9] Males and females with reproductive potential must agree to use medically approved contraceptive precautions during the trial and for 3 months following the last dose of study drug.

- Part E patients must agree to use medically approved contraceptive precautions during the trial and for 120 days (4 months) following last dose of study drug.

[10] Females with childbearing potential must have a negative serum pregnancy test within 7 days of the first dose of study drug.

- Part E female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

[11] Have an estimated life expectancy of ≥12 weeks.

[12] Are able to swallow oral medications.

Exclusion Criteria

Patients may not be included in the study if any of the following apply:

[13] Have received treatment within 21 days of the initial dose of study drug with an investigational product or nonapproved use of a drug or device (other than the study drug/device used in this study) for noncancer indications or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[14] Have a personal history of any of the following conditions: syncope of either unexplained or cardiovascular etiology, ventricular arrhythmia (including but not limited to ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. Exception: subjects with controlled atrial fibrillation for >30 days prior to study treatment are eligible.

[15] 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).

[16] Patients on Parts A, B, D, and E only: Have central nervous system (CNS) metastasis with development of associated neurological changes 14 days prior to receiving study drug. Patients may be receiving a stable low dose of corticosteroids. Screening of asymptomatic patients without history of CNS metastasis is not required. Patients with untreated CNS metastases are ineligible.

[17] Have a history of any other cancer (except nonmelanoma skin cancer or carcinoma in-situ of the cervix or breast), unless in complete remission with no therapy for a minimum of 3 years. Patients with history of carcinoma in-situ of the breast must be off tamoxifen for at least 21 days prior to first dose.

[18] Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 3 months after the last dose of

trial treatment

- Part E patients: duration of the trial starts with the pre-screening or screening visit through 120 days (4 months) after the last dose of trial treatment.

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

[20] Parts A, B, C, and E have QTc interval of >470 msec on screening electrocardiogram (ECG). Part D patients have a QTc interval of >450 msec on screening ECG at several consecutive days of assessment, if clinically indicated.

Additional Exclusion Criteria For Part C (Ramucirumab)

Patients may not be included to Part C if any of the following apply:

[21] History or evidence of cardiovascular risk including any of the following

- History of acute coronary syndromes (including myocardial infarction and angina), coronary angioplasty, or stenting within 6 months prior to enrollment.
- History or evidence of current ≥Class II congestive heart failure as defined by New York Heart Association.
- Treatment refractory hypertension defined as a blood pressure of systolic >140 mmHg and/or diastolic >90 mmHg which cannot be controlled by antihypertensive therapy.
- Subjects with intracardiac defibrillators.

[27] History or evidence of CNS metastases. Radiographic screening of all patients without history of CNS metastasis is required.

[28] Radiologically documented evidence of major blood vessel invasion or encasement by cancer. The patient has radiographic evidence of intratumor cavitation, regardless of tumor histology.

[29] Patients with uncontrolled thromboembolic or hemorrhagic disorders.

[30] Patients receiving chronic daily treatment with aspirin ≥325 mg/day or other known inhibitors of platelet function including, but not limited to, clopidogrel.

[31] Patients with a history of gross hemoptysis (defined as bright red blood of ≥½ teaspoon) within 2 months of study entry.

[32] Patients with nonhealing wounds, ulcers, or bone fractures within 28 days prior to study entry.

[33] Patients who have undergone major surgery within 28 days prior to first dose of study medication or have subcutaneous venous access device placement within 7 days prior to first dose.

Additional Exclusion Criteria For Part D (*LY3023414****)***

Patients may not be included to Part D if any of the following apply:

[22] Have insulin-dependent diabetes mellitus or a history of gestational diabetes mellitus: Patients with a type 2 diabetes mellitus are eligible if adequate control of blood glucose level is obtained by oral anti-diabetics as documented by HbA1c <7%.

[23] History or evidence of cardiovascular risk including any of the following:

- History of acute coronary syndromes (including myocardial infarction and angina), coronary angioplasty, or stenting within 6 months prior to enrollment.

Additional Exclusion Criteria For Part E (*Pembrolizumab****)***

[34] Has had a prior anticancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (for example, ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

[35] Active autoimmune disease that has required systemic treatment in past 2 years (for example, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (such as thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

[36] Have received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain a live virus are permitted.

[37] Have hypersensitivity or allergic reactions attributed to compound of similar chemical or biological composition of pembrolizumab.

[38] History of interstitial lung disease.

[39] History of or current pneumonitis.

Test Product, Dosage, and Mode of Administration:
Abemaciclib is administered orally at 100 mg, 150 mg, or 200 mg every 12 (±3) hours on Days 1 through 21 of a 21-day cycle.

Planned Duration of Treatment:
Treatment period: Patients will receive treatment until evidence of disease progression or other discontinuation criteria have been fulfilled.
Follow-up period (postdiscontinuation): approximately 30 ± 7 days.

Criteria for Evaluation:
Safety:
Primary endpoint: Adverse events (AEs), clinical hematology and chemistry, National Cancer Institute (NCI) CTCAE, version 4.0.

Statistical Methods:
Approximately 150 patients will be enrolled in this study. The analyses for this study will be descriptive. Data analyses will be provided by study part, dose group, and for all study patients combined wherever appropriate. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of patients, frequency, and percentages. Missing data will not be imputed.

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 their discontinuation will be given. Analysis of patient characteristics will include a summary of the following: patient demographics, baseline disease characteristics, prior disease-related therapies, concomitant medications. Safety analyses will include summaries of the following: AEs, dose adjustments, laboratory values, vital signs, DLTs, and ECGs. Any antitumor activity will be listed and summarized as appropriate.

Health Outcomes: Change from baseline in MDASI-LC scores will be listed and summarized for each study part at each postbaseline time point specified in the study schedule. Resource utilization will be described as appropriate.
Pharmacokinetic: PK parameters will be summarized for abemaciclib and its metabolites and, whenever possible, for the other anticancer agents used in combination (pemetrexed, gemcitabine, ramucirumab, and LY3023414).

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A Phase 1b Study of Abemaciclib in combination with multiple single-agent options for patients with Stage IV NSCLC

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4. Abbreviations and Definitions

Term	Definition
ACS	American Cancer Society
AE	Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
$AUC_{(0\text{-}tlast)}$	area under the plasma concentration-time curve from time zero to last measurable plasma concentration
$AUC_{(0\text{-}\infty)}$	area under the plasma concentration-time curve from time zero to infinity
audit	A systematic and independent examination of the study-related activities and documents to determine whether the evaluated study-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).
BP	blood pressure
BSC	best supportive care
BUN	blood urea nitrogen
C_{max}	maximum plasma concentration
$C_{min,ss}$	trough plasma levels
CBC	complete blood count
CDK	cyclin-dependent kinase
CL/F (or CL)	apparent systemic clearance
CNS	central nervous system

collection database	A computer database where clinical trial data are entered and validated.
complaint	Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety, effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CR	complete response
CrCl	creatinine clearance
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
CRS	clinical research scientist
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
dFdU	2',2'-difluorodeoxyuridine
DLT	dose-limiting toxicity
DVT	deep vein thrombosis
ECG	electrocardiogram
ECHO	echocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eDC	electronic data capture
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency

EML4	echinoderm microtubule-associated protein-like 4
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	Patients who are enrolled in the trial are those who have been assigned to a treatment and have received at least one dose of study treatment.
enter	Patients who are entered in the trial are those who have signed the informed consent form directly or through their legally acceptable representatives.
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 study are protected.
ERK	extracellular signal-regulated kinase
EU	European Union
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GCP	good clinical practice
HBSAg	hepatitis B surface antigen
HCAb	hepatitis C antibodies
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	International Normalized Ratio
interim analysis	An analysis of clinical study data that is conducted before the final reporting database is authorized for datalock.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.

irRECIST	immune-related Response Evaluation Criteria In Solid Tumors
LC/MS/MS	liquid chromatography-mass spectrometry
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.
LLN	lower limit of normal
mAb	monoclonal antibody
MAPK	mitogen-activated protein kinase
MCV	Mean cell volume
MCHC	Mean cell hemoglobin concentration
MDASI-LC	MD Anderson Symptom Inventory- Lung Cancer
MedDRA	Medical Dictionary for Regulatory Activities
monitor	A person responsible for ensuring the investigator site complies with the monitoring plan, applicable local SOPs (if any), and global Medical SOPs. Monitors are trained on the investigational product(s), the protocol, informed consent document, any other written information provided to subjects, relevant SOPs, International Conference on Harmonisation Good Clinical Practice guidelines (ICH-GCP), and all applicable laws (for example, privacy and data protection) and regulations.
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multi-gated acquisition
NCI	National Cancer Institute
NE	not evaluable
NSAID	nonsteroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participants are aware of the drug therapy received during the study.
ORR	overall response rate

OS	overall survival
patient	A subject with a defined disease.
PD	progressive disease
PE	pulmonary embolism
PET	positron emission tomography
PFS	progression-free survival
PI3K/mTOR	phosphatidylinositol-3-kinase/ mammalian target of rapamycin
PK	pharmacokinetic
PK/PD	pharmacokinetics/pharmacodynamics
PR	partial response
pRb	Rb phosphorylation at serine 780
PS	performance status
PSA	prostate-specific antigen
PT	prothrombin time
Q2W	every 2 weeks
Q3W	every 3 weeks
Q12H	every 12 hours
Rb	retinoblastoma
RECIST	Response Evaluation Criteria in Solid Tumors
rescreen	To screen a patient who was previously declared a screen failure for the same study
RPLS	reversible posterior leukoencephalopathy syndrome
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 trial. In this study, screening involves diagnostic procedures, exams, and blood tests.
screen failure	A patient who does not meet one or more criteria required for participation in a trial
sponsor	The party who takes responsibility for the initiation, management and/or financing of a clinical study.

study completion	This study will be considered complete 6 months after the last patient enters treatment.
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	half-life
TBL	total bilirubin
TED_{70}	threshold effective doses for 70% inhibition
TPO	third-party organization
ULN	upper limit of normal
US	United States
V/F	apparent volume of distribution
VEGF	vascular endothelial growth factor
VTE	venous thromboembolic event
WBC	white blood cell

A Phase 1b Study of Abemaciclib in Combination with Multiple Single-Agent Options for Patients with Stage IV NSCLC

5. Introduction

Lung cancer is the most common cancer worldwide, with an estimated 1.6 million new cases per year, and the leading cause of cancer-related mortality with an estimated 1.4 million cancer-related deaths per year (Bray et al. 2012, Bunn 2012). The incidence of lung cancer for both men and women is highest in North America and the third highest in Europe after breast and colorectal cancers (O'Conner 2011). The American Cancer Society (ACS) estimated in 2012, lung cancer accounted for 226,160 new cancer diagnoses and 160,340 deaths in the United States (US), which corresponded to almost 14% of all new cancer diagnoses and 28% of all cancer-related deaths (ACS 2012).

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. For the purposes of evaluation and treatment, disease stage is important to determine prognosis and the primary consideration for treatment approach. The 1-and 5-year survival rates progressively decline as disease stage increases (Bülzebruck et al. 1992; Goldstraw et al. 2007; Pfannschmidt et al. 2007). The majority of patients with lung cancer are diagnosed with advanced or metastatic disease (ACS 2012). Many patients with locally advanced disease at diagnosis are treated with curative intent but later develop recurrence with advanced stage disease and no prospect of cure and survival outcomes remain poor (Benamore et al. 2007; Bonomi 2010).

Platinum-based chemotherapy has demonstrated significant improvement in overall survival (OS) compared to best supportive care (BSC) and is considered the standard first-line treatment for NSCLC in an unselected patient population (Marino et al. 1994; Non-small Cell Lung Cancer Collaborative Group 1995). Multiple randomized trials combined cisplatin or carboplatin with a "third-generation" drug (eg, gemcitabine, vinorelbine, paclitaxel, docetaxel) and demonstrated similar OS results (Kelly et al. 2001; Scagliotti et al. 2002; Schiller et al. 2002).

In addition, pemetrexed, a third-generation antifolate, has been investigated in the treatment of patients with advanced or metastatic NSCLC as part of a platinum doublet regimen in first-line therapy and was approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2008 for patients with nonsquamous NSCLC (Scagliotti et al. 2008, 2009). To further enhance survival of patients with advanced and metastatic NSCLC, platinum-based doublet regimens have been combined with targeted agents such as bevacizumab (a humanized monoclonal antibody [mAb] against vascular endothelial growth factor [VEGF] ligand) and cetuximab (a chimeric mAb against epidermal growth factor receptor [EGFR]) (Sandler et al. 2006; Pirker et al. 2009; Reck et al. 2009).

A subset of NSCLC patients (17%) with EGFR mutations, mainly composed of adenocarcinoma histology, have significant improvement in progression-free survival (PFS) when treated with an EGFR targeted agent (eg, erlotinib) in the first-line setting (Reguart et al. 2010; Paz-Ares et al. 2010). Similarly, a rarer subset of NSCLC patients (4%) with an echinoderm

microtubule-associated protein-like 4 (EML4) anaplastic lymphoma kinase (ALK) translocation, mainly adenocarcinoma histology and typically younger nonsmokers, have significant improvement in PFS when treated with the targeted agent, crizotinib, which acts as a protein kinase inhibitor (Shaw et al. 2013).

VEGF receptor-2 (VEGFR-2) is normally expressed exclusively on endothelial and hematopoietic cells and is overexpressed in patients with NSCLC (Sanmartin et al. 2009). Overexpression is most responsible for the mitogenic and angiogenic effects of VEGF. The ligand/receptor interactions promote tumor angiogenesis, tumor growth, and metastasis. Targeting tumor-associated endothelial cells is a promising therapeutic approach because endothelial cells have genetic stability and are predisposed to develop less resistance compared to tumor cells. VEGFR-2 signaling and VEGF-induced endothelial cell growth in vitro have produced antiangiogenic, antitumor, and antimetastatic activity in preclinical models (Skobe et al. 1997; Prewett et al. 1999). VEGFR-2 is a promising target for antibody-based inhibition and in combination with a targeted drug that induces inhibition of the cyclin-dependent kinases (CDKs) CDK4 and CDK6, treatment outcomes for patients with advanced and/or metastatic NSCLC may result in improved clinical benefit beyond what is observed with the current agents approved in second- and third-line therapy.

The expression of cyclin D1, a protein that preferentially binds to and activates CDK4 and CDK6, is induced by mitogenic growth factors, acting through various upstream signaling pathways. These multiple signaling pathways, including mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K), converge downstream at the cyclin D1-CDK4 and CDK6 complex, leading to its activation. Frequent activating aberrations of PI3K/mTOR signaling have been reported amongst others for breast cancer, mesothelioma, NSCLC, and endometrial cancers (Opitz et al. 2008; Courtney et al. 2010; Miller et al. 2011; Varghese et al. 2011). The identification of molecular characteristics that promote greater likelihood for tumor response suggests a therapeutic opportunity to provide significant clinical benefit in patients with advanced and/or metastatic NSCLC.

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies (Bremnes et al. 2011; Talmadge 2011; Mei et al. 2014). In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells correlates with improved prognosis and long-term survival (Liu et al. 2011). Cell–based studies with abemaciclib, which evaluated the effect of abemaciclib on immune cell activity and metabolism, indicated moderate, not profound, inhibitory activity in T cells at clinical dose levels. Consequently, combining with a drug targeting the programmed death receptor-1 (PD-1) / programmed death ligand 1 (PD-L1) pathway is attractive for therapeutic intervention in NSCLC.

Unfortunately, not all patients respond to first-line therapy and even patients who initially respond will likely relapse. Irrespective of response to first-line therapy, many patients continue to have a good performance status (PS) and are candidates for second-line therapy. As

monotherapy, docetaxel, pemetrexed, and erlotinib are FDA and EMA approved for second-line therapy after progression of first-line chemotherapy (Gandara et al 2000; Hanna et al. 2004; Shepherd et al. 2005). Most recently, Cyramza (ramucirumab) in combination with docetaxel was FDA approved for second-line metastatic NSCLC with disease progression on or after platinum-based chemotherapy (Garon et al. 2014). Third-line treatment options are limited for patients with advanced and/or metastatic NSCLC. Despite the numerous targeted agents that have been evaluated as third-line therapy or beyond, only erlotinib and crizotinib have received approval in the US (Langer et al. 2013) and European Union as third-line therapy. Erlotinib is approved in all patients, but crizotinib only approved in specific tumors. Available treatment options for second-line therapy and beyond are investigated to not only demonstrate safety and tolerability similar to the overall patient population, but to identify therapeutic options that yield improved clinical benefit for patients with advanced and/or metastatic NSCLC, as this area of investigation continues to represent an unmet medical need and warrants further prospective study.

5.1. Rationale and Justification for the Study

One of the hallmarks of cancer is cell cycle dysregulation, through either over activity of the proliferative machinery (by means of activating mutations in CDKs, gene amplification in regions of the genome that are responsible for encoding, and overexpression of individual proteins related to cell cycle proteins) or inactivation of the proteins that block the cell cycle (eg, p53 or p16, retinoblastoma complex). These alterations render cells less dependent on mitogenic signaling for proliferation and result in tumor growth. Cell cycle dysregulation occurs in >90% of lung cancers, and therefore represents an attractive therapeutic target (Malumbres and Barbacid 2001).

During the cell cycle, the G1 restriction point controls entry into S phase and is essential for maintaining control of cell division (Ortega et al. 2002; Sherr 1996). CDK4 and CDK6 participates in a complex with D-type cyclins to initiate the transition through the G1 restriction point. A broad spectrum of human cancers have alterations in the CDK4 and CDK6-cyclinD-INK4-retinoblastoma (Rb) pathway through either increased CDK4 and CDK6-cyclinD activity or mutations that attenuate function of the INK4 or Rb proteins (Malumbres and Barbacid 2001).

The CDK4 and CDK6-cyclinD complex regulates the G1 restriction point through phosphorylation of the Rb tumor suppressor protein. Alterations in this pathway occur frequently in a broad spectrum of human cancers and involve 1) loss of cyclin-dependent kinase inhibitors (CDKI) by mutation or epigenetic silencing, 2) mutation/overexpression of either CDK4 and CDK6 or cyclin D, or 3) inactivation of Rb. With the possible exception of those tumors with complete inactivation of Rb, which functions downstream of the CDK4 and CDK6-cyclinD complex, all these cancers are potentially sensitive to pharmacologic inhibition of CDK4 and CDK6. From a therapeutic standpoint, the goal of inhibiting CDK4and CDK6 with a small molecule inhibitor is to prevent cell cycle progression through the G1 restriction point, thus arresting tumor growth.

Abemaciclib represents a potent and selective small molecule inhibitor of CDK4 and CDK6. Abemaciclib demonstrates antitumor activity in multiple mouse models of human cancer, physical and pharmacokinetic (PK) properties suitable for drug development, and an acceptable toxicity profile in nonclinical species. Abemaciclib administered orally demonstrates single-agent activity and inhibits tumor growth in human xenograft models of NSCLC. In the Phase 1 study, abemaciclib has shown acceptable safety/tolerability as well as evidence of clinical activity in multiple tumor types (additional information provided in Section 5.3.3). Abemaciclib demonstrated early single-agent clinical activity in NSCLC including 1 patient with confirmed partial response (PR) (Shapiro et al. 2013).

The sponsor, monitor, and investigators will perform this study in compliance with the protocol, good clinical practice (GCP) and International Conference on Harmonisation (ICH) guidelines, and applicable regulatory requirements.

5.1.1. Rationale for Amendment (a)

The protocol was amended prior to study initiation based on FDA feedback to adjust several eligibility criteria, enhance safety evaluation, and clarify monitoring of specific safety events.

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

5.1.2. Rationale for Amendment (b)

The primary rationale for amendment (b) is to further evaluate safety and tolerability in an expansion cohort Part D of Study JPBJ, abemaciclib in combination with LY3023414 in patients with Stage IV NSCLC, as outlined in Section 8.1 of the initial protocol.

LY3023414 demonstrated clinical safety and tolerability benefit in NSCLC patients in Phase 1 Study I6A-MC-CBBA (CBBA), and recent publications indicate that activating aberrations of the PI3K/mTOR pathway have been reported for NSCLC. LY3023414 will replace trametinib as the combination drug in Study Part D.

Ramucirumab exposure has been demonstrated to be related to response. In order to increase the exposures of ramucirumab, a dose escalation has been added to the existing design where the ramucirumab dose was 10 mg/kg. First, a dose of 8 mg/kg on Days 1 and 8 of a 21-day cycle will be evaluated in combination with abemaciclib. If this is safe and tolerable, a dose of 10 mg/kg on Days 1 and 8 of a 21-day cycle will be evaluated in combination with abemaciclib.

If any of the expansion cohorts indicate preliminary efficacy for the combination therapy, then approximately 12 more patients will be enrolled to obtain additional clinical evidence for efficacy.

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

5.1.3. Rationale for Amendment (c)

The rationale for amendment (c) is based on FDA recommendations to adjust the initial dose of abemaciclib for Part D.

Nonclinical murine xenograft models resulted in 15% to 20% body weight loss with the administration of abemaciclib 150-mg dose plus LY3023414 45-mg dose. In addition, abemaciclib is primarily metabolized in vitro by CYP3A4, and LY3023414 is a weak inhibitor of CYP3A4, therefore LY3023414 may lead to increased abemaciclib exposures.

In addition, modifications were performed for supportive management for diarrhea. Minor typographical and formatting edits were made throughout the document for clarity and consistency.

5.1.4. Rationale for Amendment (d)

The primary rationale for amendment (d) is to further evaluate safety and tolerability in expansion cohort of Study JPBJ, abemaciclib in combination with pembrolizumab (Part E) in patients with Stage IV NSCLC.

Additional edits were made to update the dosing guidance for cases of hematologic toxicity and diarrhea and guidance on the use of blood cell growth factors. Lilly conducted a review across several clinical trials of abemaciclib and concluded that there were some inconsistencies in the guidance. This edit will harmonize the dosing guidance across all abemaciclib studies and clarify blood cell growth factors are only to be used in a manner consistent with American Society of Clinical Oncology (ASCO) guidelines.

Minor editorial changes have been made to reflect the new treatment arm, fix typographical and formatting errors, and to improve clarity and consistency throughout the document.

5.1.5. Rationale for Amendment (e)

The rationale for amendment (e) is to update the exclusion criteria regarding pneumonitis for patients participating in study Part E (abemaciclib in combination with pembrolizumab) and to harmonize them with the other clinical trials being conducted with pembrolizumab, as requested by the manufacturer of pembrolizumab.

In addition, results from Study I3Y-MC-JPBA (JPBA) show that abemaciclib inhibited CDK4 and CDK6 as indicated by inhibition of phosphoraylated retinoblastoma (pRb) and TopoIIα, which results in cell cycle inhibition upstream of the G1 restriction point at concentrations achieved by doses of 50 mg to 200 mg twice daily (BID). Sufficient abemaciclib exposures and cell cycle arrest were achieved by doses of 150 mg every 12 hours (Q12H). This inhibition was associated with clinical benefit. Further details on the inhibition of CDK4 and CDK6 by abemaciclib can be found in the Investigator's Brochure (IB). Therefore, to avoid exposing patients to unnecessary potential toxicity, the Study JPBJ protocol was amended to remove escalation of abemaciclib to 200 mg BID in Part E of the study, such that the highest dose of abemaciclib to be evaluated in combination with pembrolizumab will be 150 mg Q12H. Parts A

through D of the study were not modified, as the cohorts including abemaciclib 200 mg BID were ongoing or already completed at the time of this protocol amendment.

Additional updates were made to include information on guidance for renal function monitoring in patients on abemaciclib, supportive care for hyperglycemia for patients in Part D, and immune checkpoint inhibitors delayed toxicity. Minor editorial changes have been made for clarity and consistency throughout the document.

5.1.6. Rationale for Amendment (f)

The primary rationale for amendment (f) is to incorporate additional hematology and chemistry monitoring on Day 8 during cycles 2-8 of study Part E, abemaciclib in combination with pembrolizumab in patients with Stage IV NSCLC. The additional monitoring is based on the clinical data from neoMONARCH (I3Y-MC-JPBY). In the neoMONARCH study, resected breast cancer specimens after 14 weeks of abemaciclib monotherapy revealed increased infiltration with CD3 and CD8 lymphocytes compared to pre-treatment specimens. This observation suggests the theoretical possibility of additive or synergistic interaction between pembrolizumab and abemaciclib in terms of immune related side effects such as hepatitis. More frequent laboratory monitoring allows for early detection should the side effect occur and earlier intervention.

Additionally, ongoing Part D Escalation Cohort 4a (abemaciclib 200mg Q12H in combination LY3023414 150mg Q12H) has been closed prior to completion of enrollment of this cohort. Escalation Cohort 5 (abemaciclib 200mg Q12H in combination LY3023414 200mg Q12H) has been removed. The rationale of this change is the same as described in Section 5.1.5 for the removal of the Study JPBJ Part E escalation of abemaciclib to 200 mg BID.

Furthermore, pembrolizumab background information has been updated to align with the approved label.

Minor editorial changes have been made for clarity and consistency throughout the document.

5.1.7. Rationale for Amendment (g)

The primary rationale for amendment (g) is to incorporate Part D language for LY3023414 dosing and dose adjustments (Section 7.2.4.1.5). Modifications were included to update LY3023414 “capsule” to “capsules/tablets” due to potential formulation change, and to remove the food intake restrictions. For LY3023414 in the relative bioavailability and food-effect Study I6A-EW-CBBB, decreases in exposure observed when a 200-mg dose was administered in a fed state, were not considered to be clinically relevant given the observed inter-subject variability. Therefore, the 1-hour LY3023414 dosing window after food intake has been removed from ongoing studies (Section 7.2).

Additionally, the maximum tolerated dose (MTD) of abemaciclib + LY3023414 has been established, resulting in the revision in number of patients in the Confirmation Cohort D-4 from 12 patients to 6 to 12 patients. Therefore, a maximum of 12 patients will be enrolled to further examine the safety profile of the recommended combination dose of abemaciclib.

The extension period for Study JPBJ is clarified and a schedule of events have been added (see Attachment 1).

Dose modification Table JPBJ.7.13 for pembrolizumab was updated to include dose adjustments in case of myocarditis to be consistent with the current Investigator's Brochure (IB) for pembrolizumab version 15. Formatting changes in the table were also made.

Minor editorial changes have been made for clarity and consistency throughout the document.

5.1.8. Rationale for Amendment (h)

Study JPBJ protocol was amended to update the dosing guidance for cases of nonhematologic toxicity, diarrhea, and ALT increase. This amendment will harmonize the dosing guidance across all clinical trials of abemaciclib in metastatic setting. The amendment updated the safety language regarding hepatic monitoring, assessment of renal function, and venous thromboembolic events (VTEs) for ongoing patients. Updates to Attachment 10 were completed to harmonize the list of CYP inhibitors and inducer, including those with narrow therapeutic range. Minor typographical and formatting edits were made throughout the document for clarity and consistency.

5.2. Objectives

5.2.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of abemaciclib when administered orally in combination with multiple single-agent options to patients with Stage IV NSCLC using Common Terminology Criteria for Adverse Events (CTCAE version 4.0, NCI 2009).

5.2.2. Secondary Objectives

The secondary objectives of this study are:

- To determine the PK of abemaciclib and pemetrexed, gemcitabine, ramucirumab, or LY3023414, when given in combination.
- To document the antitumor activity of abemaciclib when given in combination with multiple single-agent options.
- To characterize changes in patient-reported pain and disease-related symptoms collected via the MD Anderson Symptom Inventory-Lung Cancer (MDASI-LC).

5.2.3. Exploratory Objectives

- To explore biomarkers relevant to abemaciclib and the disease state and to correlate these markers to clinical outcome and to abemaciclib.
- To explore the relationship between pathways and signatures of sensitivity developed in preclinical models based on gene expression and response to therapy using archival tumor specimens (as samples are available).

- To explore the relationship between genetic variants and the role in regulation of the cell cycle and association with observed clinical outcomes to abemaciclib.

5.3. General Introduction to Abemaciclib

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

5.3.1. Mechanism of Action and In Vitro/In Vivo Activity

Abemaciclib mesylate is a potent inhibitor of CDK4 and CDK6 that is selective over other CDKs at the enzyme (3 orders of magnitude more selective for CDK4 compared to CDK1) and cellular level. This is demonstrated in Colo 205 cells by potent cellular inhibition of Rb phosphorylation (pSer780, IC50 = 120 ± 36 nM) and by exclusive G1 cell cycle arrest (indicated by accumulation of cells with 2N DNA content) up to 6 μM concentration. Studies in other cancer cell models have confirmed and demonstrated that abemaciclib mesylate inhibits CDK4 and CDK6 to induce G1 arrest specifically in Rb+ cell lines versus lines which lack functional Rb (Rb-). Using in vitro kinase panel screening, abemaciclib mesylate also demonstrates inhibition (IC50 <0.3 μM) of the human protein kinases hCDK9, hPIM1, hPIM2, hHIPK2, hDYRK2, GSK3β, hCDK5/P35, and CK2; however, the reversible G1 arrest seen in vitro and in vivo indicates that the CDK4 and CDK6 activity of abemaciclib mesylate predominates over these other activities.

The phenotypic selectivity for a G1 arrest is also demonstrated in animal studies. In these studies, in vivo target inhibition was measured in human Colo 205 xenografts with an assay monitoring both biochemical and phenotypic inhibition of CDK4 and CDK6. Rb phosphorylation at serine 780 (pRb) is a specific marker for CDK4 and CDK6 inhibition and also a phenotypic marker for G1 arrest, while TopoIIα is a specific marker for cells in S phase and pHH3 is a marker for cells in M phase. Inhibition of CDK4 and CDK6 associated with reduced pRb and a sustained G1 arrest is indicated by strong inhibition of all markers. The capacity of abemaciclib mesylate to inhibit CDK4 and CDK6 in vivo is illustrated by the sustained pharmacodynamic response in mouse Colo 205 xenograft model, in which a 50 mg/kg oral dose resulted in ≥50% inhibition of Rb phosphorylation for 1 to 24 hours after dosing. This effect also correlated with an inhibition of cell cycle progression as indicated by the potent suppression of pRb, TopoIIα, and pHH3 observed at 24 hours following dosing. A dose response for inhibition was observed in these studies such that the threshold effective doses for 70% inhibition (TED_{70}) for pRb and TopoIIα inhibition 24 hours after oral dosing were 14.1 and 14.3 mg/kg, respectively.

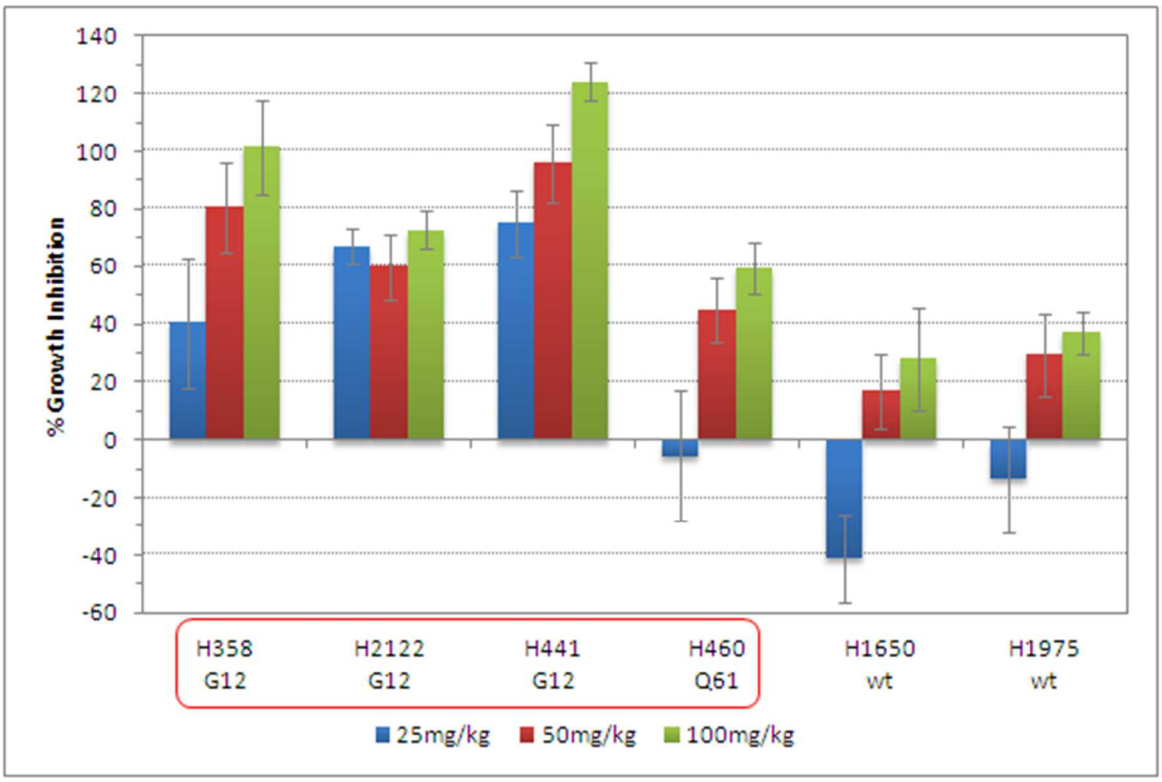
The potential for broad antitumor efficacy by abemaciclib is indicated by the significant inhibition of tumor growth observed in multiple murine xenograft models for human cancer, including models for NSCLC cancer (NCI-H441, NCI-H2122, NCI-H358, NCI-H460); for colorectal cancer (Colo-205); for glioblastoma (U87 MG); for melanoma (A375); and for mantle

cell lymphoma (JeKo-1). Although characterized by a different constellation of genomic mutations, each of these human xenograft models has an intact, functional Rb tumor suppressor protein. Xenograft growth inhibition was, in general, dose dependent from 15 to 100 mg/kg following daily oral administration for 21 days. Consistent with the mechanism of action of abemaciclib, the antitumor activity was correlated with a sustained inhibition of pRb, TopoIIα, and pHH3 in those studies where target inhibition data were collected as additional endpoints with efficacy.

Opportunities to tailor therapy with abemaciclib based on underlying genetic drivers may be possible for NSCLC, whereby genetically engineered mouse models have revealed a possible synthetic lethal relationship between mutational activation of KRAS and inactivation of CDK4 and CDK6 (Puyol et al. 2010). Recent studies with abemaciclib mesylate done in murine models bearing human xenografts provide further support for this relationship for lung adenocarcinomas in that xenograft models such as NCI-H2122, NCI-H358, and NCI-H441, which all express an activated KRAS oncogene, were observed to be the most sensitive to monotherapy with abemaciclib mesylate. Models which express a wild-type KRAS gene such as NCI-H1975 and NCI-H1650 were observed to be among the least sensitive of the lung adenocarcinoma models to growth inhibition by abemaciclib mesylate (Figure JPBJ.5.1).

Combination studies conducted in KRAS-mutant NSCLC models such as NCI-H441 or NCI-H2122 indicated the potential for additivity when agents such as gemcitabine, pemetrexed, DC101 (mouse surrogate of ramucirumab), and everolimus (mTOR inhibitor) were given in combination with abemaciclib mesylate. In these studies the combination therapies as compared to the single-agent treatments resulted in either a greater inhibition of tumor growth during therapy or in a longer duration of growth inhibition following the cessation of treatment (Figure JPBJ.5.2).

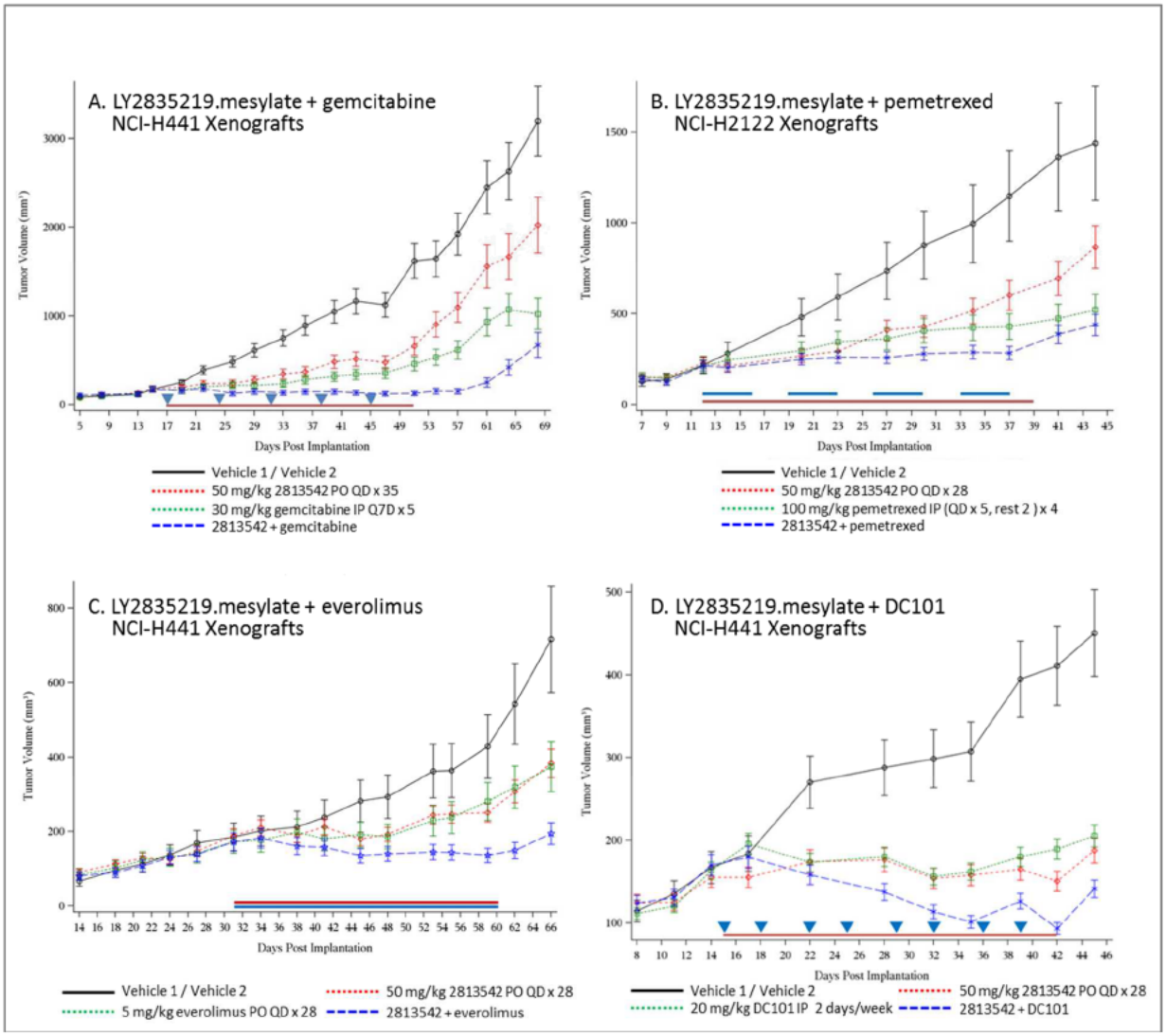
As a result of its brain exposure, treatment with abemaciclib mesylate produces a statistically significant and dose-dependent improvement in survival when assessed in a rat orthotopic brain tumor model whereby tumor cells were implanted intracerebrally. The Kaplan Meier survival analysis following 21 days of treatment at 20, 40, or 80 mg/kg showed a statistically significant improved survival in the 40- and 80-mg/kg groups such that median survival observed for these 2 groups was 33.5 and 36.9 days, respectively, versus 25.1 days for the vehicle control group (Figure JPBJ.5.3).



Athymic nude mice bearing NSCLC xenografts were treated with 25, 50, or 100 mg/kg of abemaciclib mesylate daily for 21 days. The percentage of tumor growth inhibition relative to the vehicle control groups was determined by setting the 21st day of dosing as the reference point for measuring inhibition, while the 100% tumor growth inhibition level was equal to the mean baseline tumor volume measured on the first day of dosing. Values greater than 100% indicate tumor volumes that are less than the baseline on the first day of dosing (regression), whereas negative percent inhibition values indicate tumor volumes that are greater than vehicle controls on the 21st day. The KRAS status of each xenografts model is also provided.

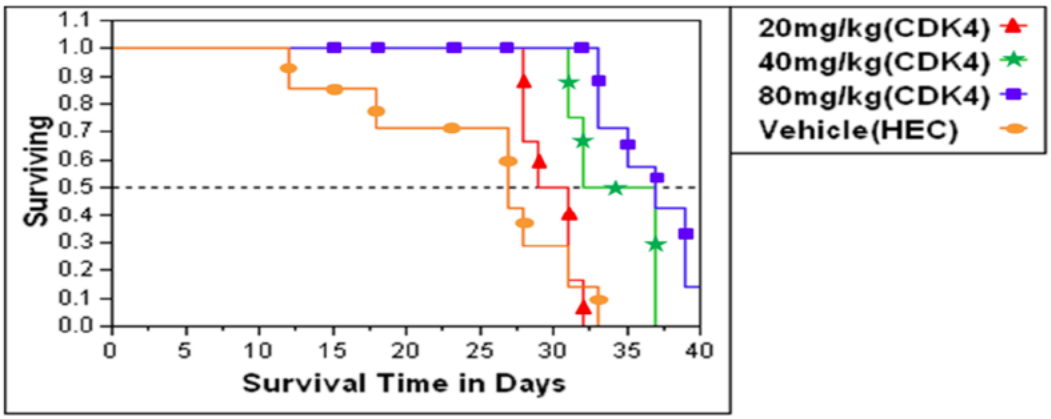
Abbreviations: wt = wild-type KRAS, G12 = activating mutation that replaces the glycine at codon 12, Q61 = activating mutation that replaces the glutamine at codon 61; NSCLC = non-small cell lung cancer.

Figure JPBJ.5.1. The extent of growth inhibition by abemaciclib mesylate in NSCLC xenografts correlates with KRAS status.



Athymic nude mice bearing NCI-H441 or NCI-H2122 NSCLC xenografts were treated with 50 mg/kg of abemaciclib (LY2835219) mesylate (indicated as compound serial # 2813542) either alone or in combination with A) gemcitabine (30 mg/kg), B) pemetrexed (100 mg/kg), C) the mTOR inhibitor everolimus (5 mg/kg), or D) DC101 (20 mg/kg), which is the mouse surrogate of ramucirumab. In each of these studies, abemaciclib mesylate was given once-daily for 28 or 35 days. The exact days of dosing with abemaciclib mesylate in each of the studies are indicated by the red bars just above the X-axes. The blue upside down arrows above the X-axes in panels A and D indicate the days of dosing for gemcitabine and DC101, respectively; whereas the blue bars in panels B and C indicate the days of dosing for pemetrexed and everolimus, respectively.

Figure JPBJ.5.2. Combination efficacy studies with abemaciclib mesylate (AKA 2813524) in mouse xenograft models for human NSCLC.



Group	Median Survival (days)	SE	p value Log-rank	p value Wilcoxon
Vehicle	25.14	2.82	-	-
20mg/kg	29.83	0.70	0.5	0.146
40mg/kg	33,5	1.32	0.0316	0.0333
80mg/kg	36.86	1.28	0.0006	0.0010

Abbreviations: CDK = cyclin dependent kinase; HEC = hydroxyethylcellulose; SE = standard error.
U87MG cells were implanted intracerebrally on Day 1. Once-daily treatments with abemaciclib mesylate began on Day 4 and continued for 21 days (x21). Kaplan-Meier plot for 20, 40, and 80 mg/kg x21 dosing (Days 4 to 24). The statistical significance of compound activity on median survival is shown in the table.

Figure JPBJ.5.3. Abemaciclib mesylate antitumor effects in a rat orthotopic brain xenograft model.

5.3.2. Nonclinical Toxicology

To support the clinical development of abemaciclib, a comprehensive package of nonclinical toxicology studies have been conducted in rats and dogs, including repeat-dose toxicology, safety pharmacology, and genetic toxicology studies. These studies demonstrated an acceptable safety profile consistent with the pharmacologic mechanism of action with effects that are considered to be monitorable and reversible. More detailed information about the characteristics of abemaciclib can be found in the IB (Section 5.2.1).

The primary target organs associated with daily dosing of abemaciclib in rats and dogs are the bone marrow, gastrointestinal tract, lymphoid tissues, and male reproductive tract. Effects in these organs were consistent with antiproliferative effects in rapidly dividing cells, including blood cytopenias and bone marrow hypocellularity; crypt necrosis/hyperplasia and villous atrophy in the intestines; lymphoid depletion; and hypospermatogenesis and atrophy in the testis. The safety profile of abemaciclib in nonclinical toxicology studies is generally consistent with the AEs observed to date in humans.

5.3.3. Overview of Safety for Non-Small Cell Lung Cancer

A total of 51 patients with NSCLC have been treated with abemaciclib in Part B of Study JPBA as of 01 August 2013. Fifty-one patients with NSCLC have experienced at least 1 AE. Treatment-emergent AEs (TEAEs) have been experienced by 48 patients with NSCLC.

A total of 46 patients with NSCLC in Part B experienced TEAEs that were considered possibly related to study drug. The most common (≥10%) possibly drug-related TEAEs reported specifically for patients with NSCLC cancer included diarrhea (31 patients), nausea (23 patients), fatigue (18 patients), vomiting (13 patients), anemia (13 patients), white blood cell (WBC) count decreased (10 patients), anorexia (9 patients), neutrophil count decreased (8 patients), weight loss (8 patients), creatinine increased (8 patients), platelet count decreased (7 patients), dehydration (6 patients), and hyponatremia (6 patients).

SAEs regardless of causality were experienced by 12 patients in Part B with NSCLC; no SAES were possibly related to study drug.

The majority of laboratory AEs that were experienced by patients with NSCLC in Part B postbaseline were Grade 1 or Grade 2 in severity, as determined by the investigator. Grade 3+4 laboratory AEs experienced by ≥5% of patients with NSCLC included WBC count decreased (6 patients), lymphocyte count decreased (5 patients), neutrophil count decreased (4 patients), and hyponatremia (3 patients). Grade 3+4 laboratory AEs possibly related to study drug for patients with NSCLC included WBC count decreased (6 patients), lymphocyte count decreased (5 patients), neutrophil count decreased (4 patients), hyponatremia (2 patients), platelet count decreased (1 patient), and anemia (1 patient).

Among the 51 patients with NSCLC in Part B, 1 patient with NSCLC who received abemaciclib 150 mg Q12H had a dose-limiting toxicity (DLT)-equivalent toxicity of Grade 3 diarrhea that persisted more than 2 days despite maximal supportive intervention during Cycle 1. Two patients with NSCLC who received abemaciclib 200 mg Q12H had DLT-equivalent toxicities, including 1 patient who experienced Grade 3 nausea during Cycle 1 that persisted more than 2 days despite maximal supportive intervention, and 1 patient with Grade 3 fatigue during Cycles 1 and 2.

Three patients with NSCLC who were treated with abemaciclib 150 mg Q12H in Part B of the study died; 2 deaths were due to study disease (1 death during Cycle 1 and 1 death at follow up), and 1 death was due to an overdose of narcotic, not associated with study drug. Eight patients with NSCLC who were treated with abemaciclib 200 mg Q12H died during Part B of Study JPBA due to study disease; 2 patients died during Cycle 1, and the remaining 6 patients died during follow up.

In general, the preliminary safety profile that has been observed for NSCLC patients is similar to the overall patient population analyzed in Study JPBA.

5.3.4. Biomarkers

A formalin-fixed paraffin-embedded (FFPE) archived tumor tissue sample, or precut, unstained slides if the FFPE tumor tissue blocks are not available, from any available archival specimen of

the patient's tumor will be requested for biomarker related studies after study eligibility is confirmed.

Instructions and supplies required for the collection and shipment of the patients' samples will be provided by the sponsor. Sample handling and shipment to the central laboratory will occur per instructions given to the study site. Bioanalytical samples collected to measure for specified biomarker tests will be stored in a sponsor designated facility and retained for a maximum of 5 years following the last patient visit for the study.

Biomarkers will be used to explore the relationship between predictive biomarkers (such as tumor Rb status) and antineoplastic activity. Potential predictive biomarkers will be measured throughout the study in archived tumor tissue (for example, from prior biopsy) for all patients (Parts A, B, C, D, and E).

5.4. General Introduction to LY3023414

Detailed information about LY3023414 characteristics is provided in the IB. The following sections provide a brief summary most relevant to this Phase 1b study.

5.4.1. Mechanism of Action of LY3023414

LY3023414 is a potent selective inhibitor of the Class I PI3K isoforms, mTOR, and DNA-PK, with selectivity in kinase enzyme assays as an ATP competitive inhibitor of PI3Kα (inhibition constant [Ki] 8.5 nM). LY3023414 has inhibitory activity against PI3K/mTOR pathway targets in vitro and in vivo as measured by phosphoprotein levels from cultured cells and tumor xenografts. LY3023414 has antiproliferative and cell-cycle arresting effects in cultured cancer cells, and anti-angiogenesis activity via inhibition of in vitro vascular cord formation.

5.4.2. Clinical Summary of LY3023414

LY3023414 is currently evaluated in the first human dose (FHD) Study CBBA. In this study, a total of 48 patients were enrolled and 47 patients dosed with LY3023414 as of 26 September 2014. There were 25 patients included in the once daily (QD) dosing Part A, ranging from 20 to 450 mg QD and 13 patients in the subsequently opened BID dosing Part A2, ranging from 150 to 250 mg BID. Dose-limiting toxicities (DLTs) for QD were reported only at the 450-mg QD dose level and included 1 case each of hypotension, thrombocytopenia, and hyperkalemia (all Grade 3 according to CTCAE). For BID dosing, DLTs were observed at the 200-mg dose level (n=1 out of 6 patients; CTCAE Grade 2 nausea) and 250-mg BID dose level (n=3 out of 4 patients) and included 1 case each of fatigue, asthenia, mucositis, and hyponatremia (all Grade 3 according to CTCAE), and hypophosphatemia (CTCAE Grade 4). Therefore, the MTD for LY3023414 QD and BID dosing was determined to be 325 mg QD and 200 mg BID.

In the Part B1 cohort, the impact of LY3023414 on the metabolic clearance of drugs that are metabolized through CYP3A4, such as midazolam, was evaluated. As of the data cut-off date of 26 September 2014, Part B1 was completed with 10 patients enrolled, of whom 9 patients received 1 or more doses of 200-mg BID LY3023414.

The most common possibly LY3023414-related AEs reported across the 2 parts in at least 10% of patients include nausea (42.1%), vomiting (34.2%), fatigue (34.2%), diarrhea (15.8%), anemia (13.2%), asthenia (13.2%), and decreased appetite (13.2%). Most of these events were graded as mild or moderate by the investigators. There were only 4 possibly LY3023414-related AEs ≥Grade 3 CTCAE reported in patients treated at a dose level up to the MTD for QD or BID LY3023414 dosing (n=31 patients), including 1 case each of fatigue, hypomagnesaemia, neutropenia, and anemia in a patient entering the study with CTCAE Grade 2 anemia (all CTCAE Grade 3).

Initial clinical pharmacokinetic/pharmacodynamic (PK/PD) data show, that LY3023414 maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC_{∞}) increased approximately dose-proportionally from 20 to 325 mg QD (within the QD dose range determined to be safe). However, the C_{max} and AUC_{∞} increase was greater than dose proportional at 450 mg QD (i.e., exceeding the MTD). PK data following repeated BID LY3023414 (dose range of 150 to 250 mg BID) were consistent with PK data following 20 to 325 mg QD. The oral clearance (CL/F) ranged from approximately 77 to 130 L/hour across the 20-to-325-mg dose range associated with an oral volume of distribution (V/F) ranging from 185 to 315 L in that same dose range. This clearance and volume lead to mean half-life ($t_{1/2}$) of 2.07 hours (coefficient of variation [CV]=45%, n=35), consistent with the prediction. Biomarker assessment demonstrated target inhibition as measured by p4EBP1 inhibition in peripheral mononuclear blood cells (PBMC) at LY3023414 dose levels ≥150 mg QD in a dose related manner. With respect to anti-tumor activity, preliminary clinical benefit was observed in patients treated on both schedules of LY3023414, including 1 patient with a confirmed partial response.

Based on above outlined safety and tolerability, PK/PD, and preliminary activity data, and following discussions between the sponsor and the investigators, the start of the tumor-specific expansion cohorts in Study CBBA justified a recommended dose of 200 mg BID.

5.5. General Introduction to Pembrolizumab

Detailed information about pembrolizumab characteristics is provided in the IB. The following sections provide a brief summary most relevant to this Phase 1b study.

5.5.1. Mechanism of Action of Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

5.5.2. Clinical Summary of Pembrolizumab

An open-label Phase 1 trial (Keynote 001) is being conducted to evaluate the safety and clinical activity of single-agent pembrolizumab. The dose-escalation portion of this trial evaluated 3 dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) and the dose-expansion cohort evaluated 2 mg/kg every 3 weeks (Q3W) and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated and no DLTs were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No MTD has been identified.

In Keynote 001, 2 randomized cohort evaluations (Cohorts B2 and D) of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg Q3W versus 10 mg/kg Q3W have been completed, and one randomized Cohort (Cohort B3) evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg Q3W versus 10 mg/kg Q3W, and the overall response rate (ORR) was 28% (22/79) in the 2-mg/kg Q3W group and 28% (21/76) in the 10-mg/kg Q3W group (per Response Evaluation Criteria In Solid Tumors Version 1.1 [RECIST 1.1] by independent central review). The proportion of subjects with drug-related AEs, Grade 3-5 drug-related AEs, serious drug-related AEs, or death or discontinuation due to an AE was comparable between groups. Cohort D, which compared 2 mg/kg Q3W versus 10 mg/kg Q3W in advanced melanoma subjects naïve to ipilimumab, also demonstrated overall similarity in efficacy and safety profile between the 2 doses. In Cohort B3, advanced melanoma subjects (irrespective of prior ipilimumab therapy) were randomized to receive pembrolizumab at 10 mg/kg Q2W versus 10 mg/kg Q3W. The results demonstrate that the ORR was 35.0% (41/117) in the 10-mg/kg Q2W group and 30.8% (33/107) in the 10-mg/kg Q3W group (per RECIST 1.1 by independent central review) (cut-off date of 18 April 2014). The proportion of subjects with drug-related AEs, Grade 3-5 drug-related AEs, serious drug-related AEs, or death or discontinuation due to an AE was comparable between groups.

An integrated body of evidence suggests that 200 mg Q3W is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with a 2-mg/kg Q3W dose.

A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed using available data from 1139 subjects from PN001, of which the majority (94.6% [N=1077]) were patients with advanced melanoma. The distribution of exposures from the 200-mg fixed dose are predicted to considerably overlap those obtained with the 2-mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. Additionally, this comparison also demonstrates that the 200-mg Q3W regimen provides no

substantive differences in PK variability (range of the distribution of individual exposures) as seen with weight-based dosing.

In translating to other solid tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the antitumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at tested doses among tumor types. Thus, the 200-mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other solid tumor indications as well.

Taken together, the choice of 200 mg Q3W as an appropriate dose is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg Q3W will provide exposures that 1) are optimally consistent with those obtained with a 2-mg/kg dose Q3W, 2) body weight-based dosing does not provide an advantage over fixed dosing and that both dosing strategies should provide adequate and similar control of PK variability, 3) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response, 4) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe, and 5) the dynamics of pembrolizumab target engagement would not vary meaningfully with tumor type.

Based on above outlined safety and tolerability, PK/PD, and preliminary activity data, the dose of pembrolizumab planned to be studied in Study JPBJ is 200 mg Q3W.

5.6. Rationale for Selection of Dose of Abemaciclib

A dose range of 100 to 200 mg of abemaciclib administered orally twice daily was selected based on safety, clinical efficacy, and PK data from the first-in-human dose Study JPBA.

In Study JPBA, during the dose-escalation phase, preliminary analysis of PK data from the initial 4 dose levels (50, 100, 150, and 225 mg every 24 hours) indicated less than dose-proportional increases in exposure. Based on these results, a twice-daily schedule was introduced for the following planned dose levels: 75, 100, 150, 200, 275, 350, and 450 mg Q12H. For the twice-daily schedule, the highest dose of abemaciclib evaluated was 275 mg Q12H. At this dose level, 2 of the 3 patients experienced DLTs of Grade 3 fatigue. At the next lower dose level of 200 mg Q12H, 1 of the 7 patients also experienced a DLT of Grade 3 fatigue. Therefore, the maximum tolerated dose (MTD) was established at 200 mg Q12H and is hereunder referred to as the single-agent MTD.

During the tumor-specific expansion phases, patients initially received abemaciclib at the single-agent MTD of 200 mg Q12H. A preliminary interim safety review with data from 56 patients indicated that 29 patients experienced diarrhea possibly related to study drug: 17 Grade 1 events (30%), 9 Grade 2 events (16%), and 3 Grade 3 events (5%). Based on the frequency of Grade 1/2 diarrhea and the observation of clinical activity at doses below the

single-agent MTD, the initial starting dose was changed to 150 mg Q12H with JPBA amendment(f) to gain additional PK data and clinical experience around safety/tolerability.

An interim PK analysis was conducted on the steady-state PK data obtained in Study JPBA for abemaciclib and its 3 active metabolites from a total of 103 patients dosed repeatedly with abemaciclib at 150 and 200 mg Q12H. This preliminary analysis suggested that the dose of 200 mg dosed Q12H yields slightly higher steady-state plasma concentration levels for abemaciclib and its active metabolites. Moreover, when examining patients' plasma levels throughout the first cycle of treatment, the dose of 200 mg Q12H seems to maintain more consistent trough plasma levels ($C_{min,ss}$) for all active entities in plasma. In particular, the $C_{min,ss}$ for abemaciclib was more consistently maintained at a value of approximately 200 ng/mL, which is associated with a more robust levels of pRb inhibition as measured in patients' skin biopsies and was previously related to cell cycle arrest and tumor growth inhibition in PK/PD analyses performed on mouse xenograft tumor models. Based on the above and the observation that Grade 1/2 diarrhea is manageable with standard antidiarrheal agents (eg, loperamide), the initial starting dose returned to the single-agent MTD of 200 mg Q12H with JPBA amendment(g).

Consistent with this approach, in Study JPBJ, the initial starting dose of abemaciclib during the dose-escalation phase is 150 mg Q12H (Parts A, B, and C) and 100 mg Q12H (Parts D and E) to gain PK data and clinical experience around the safety/tolerability when given in combination with another agent, before escalating to 200 mg Q12H in Parts A, B, C, and D or to 150 mg in Part E.

5.6.1. Rationale for Dose Selection of Abemaciclib and LY3023414 for Combination Therapy (Part D)

Given the potential overlapping toxicities between abemaciclib and LY3023414, the starting dose of both compounds for combination therapy will be below the MTD determined for monotherapy for each compound (see Table JPBJ.7.4). If tolerated, both compounds will be escalated in combination as described in Section 7.2.2.

5.6.2. Rationale for Dose Selection of Abemaciclib and Pembrolizumab for Combination Therapy (Part E)

Given the risk for potential overlapping toxicities between abemaciclib and pembrolizumab, the starting dose of abemaciclib will be below the MTD determined for monotherapy.Pembrolizumab will be administered at the recommended Phase 2 dose determined in the Phase 1 study as described in Section 5.5.2.

6. Investigational Plan

6.1. Study Population

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1.1. Inclusion Criteria

Patients may be included in the study if they meet all of the following criteria during screening prior to first dose of study drug.

[1] For all parts: The patient must have Stage IV NSCLC. Eligibility is not restricted based on molecular features (for example, EGFR mutation or ALK translocation). However, all patients with nonsquamous NSCLC with EGFR activating mutations or ALK alterations should have received and progressed after appropriate tyrosine kinase inhibitor or ALK targeted therapy prior to enrollment.

- For Part A (abemaciclib + pemetrexed): Nonsquamous subtypes only. The patient must have received at least 1 but not more than 3 prior therapies, including 1 platinum-based chemotherapy for advanced/metastatic NSCLC. Patients who have received pemetrexed as first-line or maintenance therapy must be $\geq$3 months after treatment for determining eligibility.
- For Part B (abemaciclib + gemcitabine): Any subtype. The patient must have received at least 1 but not more than 3 prior therapies for advanced/metastatic NSCLC.
- For Part C (abemaciclib + ramucirumab): Any subtype. The patient must have received at least 2 but not more than 3 prior therapies for advanced/metastatic NSCLC.
- For Part D (abemaciclib + LY3023414 [US only]): Any subtype. The patient must have received at least 2 but not more than 3 prior therapies for advanced/metastatic NSCLC. The patient must not have received prior treatment with any PI3K or mTOR inhibitor.
- For Part E (abemaciclib + pembrolizumab): Any subtype. The patient must have received at least 1 but no more than 3 prior therapies for advanced/metastatic NSCLC.

[2] Have the presence of either measureable or nonmeasurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1, Eisenhauer et al. 2009).

[3] Are ≥18 years of age.

[4] Have given written informed consent prior to any study-specific procedures.

[5] Have adequate organ function including:

- Hematologic: Absolute neutrophil count (ANC) ≥1.5 x 10^9/L, platelets ≥100 x 10^9/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 transaminase (AST) ≤3.0 times ULN. For patients with tumor involvement of the liver, AST and ALT equaling ≤5.0 times ULN are acceptable. Patients on Part A with tumor involvement of the liver and ALT or AST ≥3.0 to ≤5.0 times ULN must have Child-Pugh Class A using the Child-Turcotte scoring system (refer to Attachment 11).
- Renal: Serum creatinine ≤1.5 times ULN. All patients must have a Creatinine Clearance (CrCl) >45 mL/min using the standard Cockcroft and Gault formula (refer to Attachment 7).
- For Part E: Thyroid: TSH within normal limits OR Total T3 or free T3 and free T4 within normal limits (refer to Attachment 2).
- For Part E: Coagulation : PTT or aPTT <5 seconds above ULN and INR≤1.5 times ULN or PT <5 seconds above ULN. Patients receiving anticoagulant therapy are permitted if the PTT or aPTT and INR or PT is within therapeutic range of intended use of anticoagulants.

[6] Have a PS ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale (refer to Attachment 6).

[7] Have discontinued all previous therapies for cancer (including chemotherapy, radiotherapy, immunotherapy, and investigational therapy) for at least 21 days for myelosuppressive agents or 14 days for nonmyelosuppressive agents prior to receiving study drug, and recovered from the acute effects of therapy (treatment-related toxicity resolved to baseline) except for residual alopecia.

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

[9] Males and females with reproductive potential must agree to use medically approved contraceptive precautions during the trial and for 3 months following the last dose of study drug (for example, intrauterine device (IUD), birth control pills, or barrier method). If condoms are used as a barrier contraceptive, a spermicidal agent should be added as double barrier protection.

- Part E patients must agree to use medically approved contraceptive precautions during the trial and for 120 days (4 months) following last dose of study drug.

[10] Females with childbearing potential must have a negative serum pregnancy test within 7 days of the first dose of study drug.

- Part E female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

[11] Have an estimated life expectancy of ≥12 weeks.

[12] Are able to swallow oral medications.

6.1.2. Exclusion Criteria

Potential study patients may not be included in the study if any of the following apply during screening.

[13] Have received treatment within 21 days of the initial dose of study drug with an investigational product or nonapproved use of a drug or device (other than the study drug/device used in this study) for noncancer indications or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[14] Have a personal history of any of the following conditions: syncope of either unexplained or cardiovascular etiology, ventricular arrhythmia (including but not limited to ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. Exception: subjects with controlled atrial fibrillation for >30 days prior to study treatment are eligible.

[15] 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).

[16] Patients on Parts A, B, D and E only: Have central nervous system (CNS) metastasis with development of associated neurological changes 14 days prior to receiving study drug. Patients may be receiving a stable low dose of corticosteroids. Screening of asymptomatic patients without history of CNS metastasis is not required. Patients with untreated CNS metastases are ineligible.

[17] Have a history of any other cancer (except nonmelanoma skin cancer or carcinoma in-situ of the cervix or breast), unless in complete remission with no therapy for a minimum of 3 years. Patients with history of carcinoma in-situ of the breast must be off tamoxifen at least 21 days prior to first dose.

[18] Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 3 months after the last dose of trial treatment.

- Part E patients: duration of the trial starts with the pre-screening or screening visit through 120 days (4 months) after the last dose of trial treatment.

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

[20] Parts A, B, C, and E have QTc interval of >470 msec on screening electrocardiogram (ECG).

- Part D patients have QTc interval of >450 msec on screening ECG at several consecutive days of assessment, if clinically indicated.

6.1.2.1. Additional Exclusion Criteria for Part C (Ramucirumab)

Patients may not be included to Part C if any of the following apply:

[21] History or evidence of cardiovascular risk including any of the following:

- History of acute coronary syndromes (including myocardial infarction and angina), coronary angioplasty, or stenting within 6 months prior to enrollment.
- History or evidence of current ≥Class II congestive heart failure as defined by New York Heart Association.
- Treatment refractory hypertension defined as a blood pressure of systolic >140 mmHg and/or diastolic >90 mmHg which cannot be controlled by antihypertensive therapy.
- Subjects with intracardiac defibrillators.

[27] History or evidence of CNS metastases. Radiographic screening of all patients without history of CNS metastasis is required.

[28] Radiologically documented evidence of major blood vessel invasion or encasement by cancer. The patient has radiographic evidence of intratumor cavitation, regardless of tumor histology.

[29] Patients with uncontrolled thromboembolic or hemorrhagic disorders.

[30] Patients receiving chronic daily treatment with aspirin ≥325 mg/day or other known inhibitors of platelet function including, but not limited to, clopidogrel.

[31] Patients with a history of gross hemoptysis (defined as bright red blood of ≥½ teaspoon) within 2 months of study entry.

[32] Patients with nonhealing wounds, ulcers, or bone fractures within 28 days prior to study entry.

[33] Patients who have undergone major surgery within 28 days prior to first dose of study medication or have subcutaneous venous access device placement within 7 days prior to first dose.

6.1.2.2. Additional Exclusion Criteria for Part D (LY3023414)

Patients may not be included to Part D if any of the following apply:

[22] Have insulin-dependent diabetes mellitus or a history of gestational diabetes mellitus:

- Patients with a type 2 diabetes mellitus are eligible if adequate control of blood glucose level is obtained by oral anti-diabetic agents as documented by HbA1c <7%.

[23] History or evidence of cardiovascular risk including the following:

- History of acute coronary syndromes (including myocardial infarction and angina), coronary angioplasty, or stenting within 6 months prior to enrollment.

6.1.2.3. Additional Exclusion Criteria for Part E (Pembrolizumab)

Patients may not be included to Part E if any of the following apply:

[34] Has had a prior anticancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (for example, ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

[35] Active autoimmune disease that has required systemic treatment in past 2 years (for example, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (such as thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

[36] Have received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

[37] Have hypersensitivity or allergic reactions attributed to compound of similar chemical or biological composition of pembrolizumab.

[38] History of interstitial lung disease.

[39] History of or current pneumonitis.

6.2. Summary of Study Design

This study is a multicenter, nonrandomized, open-label, dose-escalation Phase 1b trial in approximately 150 patients with Stage IV NSCLC to receive abemaciclib in combination with 1) pemetrexed (Part A), 2) gemcitabine (Part B), 3) ramucirumab (Part C), 4) LY3023414 (Part D), and 5) pembrolizumab (Part E) as shown in Figure JPBJ.6.1. Patients will be enrolled into 1 of 5 study parts based on prior therapy or histology. During dose escalation, cohorts of at least 3 patients will be enrolled at each of the planned dose levels. Abemaciclib will be

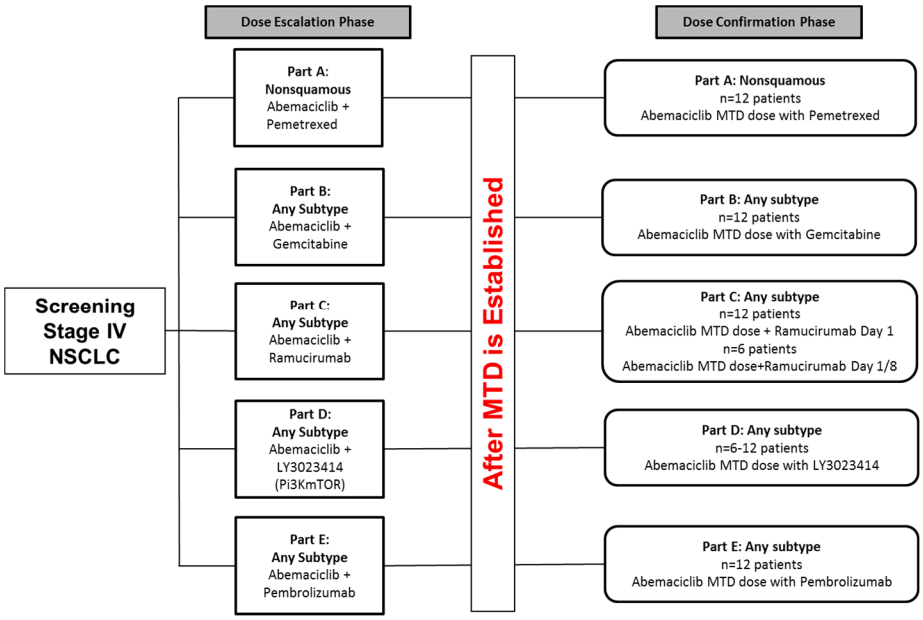
administered orally at 100 mg, 150 mg, or 200 mg every Q12H on Days 1 through 21 of a 21-day cycle. Contingency for de-escalation to abemaciclib at 100 mg orally Q12H on Days 1 through 21 of a 21-day cycle will be permitted. In study Parts A, B, and E, at least 18 and up to 24 patients; in study Part C, at least 30 and up to 42 patients; in study Part D, at least 27 and up to 42 patients will be enrolled. Patients will be treated with abemaciclib no greater than 200 mg Q12H (the established single-agent MTD) for Parts A, B, C, and D or 150 mg Q12H for Part E on Days 1 through 21 of a 21-day cycle.

All patients in the study will continue to receive abemaciclib unless 1 or more of the criteria for discontinuation are fulfilled; the follow-up period for poststudy evaluation is 30 ± 7 days from the date of the last dose of study drug received.

Refer to Attachment 1 for the detailed Study Schedule.

To determine the recommended Phase 2 dose of abemaciclib in combination with pemetrexed, gemcitabine, ramucirumab, LY3023414, or pembrolizumab, an adequate sample size is required. A sufficient sample size will allow for an accurate evaluation of the relationship between exposure and toxicity, as well as an evaluation of the relationship between exposure and pharmacological effects using descriptive statistics and appropriate modeling techniques, if data warrant. This sample size is estimated to be approximately 150 patients.

The planned duration of treatment is not fixed; patients will remain on study until progression or unacceptable toxicity, or they fulfill 1 of the criteria for study discontinuation (Section 6.3). The follow-up period will be 30 ± 7 days after last dose of study drug.



Abbreviations: MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer.

Figure JPBJ.6.1. Illustration of study design for clinical protocol I3Y-MC-JPBJ.

Refer to Attachment 1 for the Study Schedule.

6.2.1. Study Completion and End of Trial

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) 6 months after the last patient has entered treatment (received first dose). "End of trial" refers to the date of the last visit or last scheduled procedure for the last patient.

6.2.2. Extension Period

Treatment may proceed for up to 3 years if the patient experiences a clinical benefit, as determined by the investigator. Patients may continue to receive study treatment beyond 3 years if they continue to benefit from study drug and upon approval of the sponsor. Patients must be discontinued from treatment at any time if they meet the criteria for discontinuation (Section 6.3.1).

Patients who are in follow-up when the extension period begins will continue in follow-up until the final safety assessments are completed 30 days (±7) after last dose of study drug (see Attachment 1).

During the extension period, all AEs, SAEs, study drug dosing, and dose reduction of treatment will be collected on the electronic case report form (eCRF).

SAEs will also be reported to Lilly Global Patient Safety and collected in the pharmacovigilance system (see Section 8.1.2). In the event that an SAE occurs, additional information (such as local laboratory results, concomitant medications, and hospitalizations) may be requested by Lilly in order to evaluate the reported SAE. Lilly will notify investigators when the extension period begins.

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.

6.3. Discontinuations

6.3.1. Discontinuation of Patients

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

In addition, patients will be discontinued from all study treatment (Parts A, B, C, D, and E) and/or from the study in the following circumstances:

- The patient has evidence of progressive disease. In the case of a mixed response, patients who are receiving clinical benefit may remain on study treatment based on investigator discretion and discussion with Lilly CRP.
    - Part E patients may remain on study treatment with repeat imaging > 4 weeks to assess tumor response or confirmed progression per irRECIST to account for unique tumor response seen with immunotherapeutic drugs.
- The patient experiences unacceptable toxicity, including but not limited to the following circumstances (refer to Section 7.2.4).
    - The patient does not meet the criteria for recovery from toxicity within 14 days of the last day of the previous cycle.
- 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.
- Investigator/Physician Decision
    - the investigator or attending physician decides that the patient should be discontinued from the study or study drug(s). If this decision is made because of an SAE or clinically significant laboratory value, then appropriate supportive measures are to be taken. Lilly or its designee is to be alerted immediately (refer to Section 8.1).
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drug(s) occurs prior to introduction of the other agent
- Patient Decision
    - the patient requests to be discontinued from the study or study drug
- Sponsor Decision
    - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP
- The patient is noncompliant with study procedures and/or treatment (Section 7.6).
- For Part E, patients must discontinue pembrolizumab if the patient meets any discontinuation criteria or 24 months of pembrolizumab therapy, whichever occurs first.

The reason for and date of discontinuation will be collected for all patients. The date of discontinuation (for any of the above reasons) from study treatment is to be reported on the

eCRF. Patients who discontinue will have follow-up procedures performed as shown in the Study Schedule (Attachment 1).

For dose escalation, any patient who is discontinued from the study before receiving at least 75% of planned doses of abemaciclib in Cycle 1 will be deemed nonevaluable for assessment of that dose level and may be replaced unless they experience a DLT before withdrawal. Nonevaluable patients may be replaced to ensure that no fewer than 3 patients receive at least 75% of planned doses of abemaciclib in Cycle 1 at each dose level, unless enrollment to that cohort has stopped because more than 1 patient at that dose level has experienced a DLT.

6.3.1.1. Part C Discontinuations

The investigator should withdraw a patient from **abemaciclib and ramucirumab combination therapy** for reasons including but not limited to the following:

- the sponsor or designee or investigator terminates the study
- an unacceptable AE/toxicity (for example, a persistent moderate toxicity that is intolerable to the patient) which in the opinion of the investigator, clearly attributed to ramucirumab

1. a Grade 3 or 4 infusion-related reaction which in the opinion of the investigator is clearly attributed to ramucirumab (for more information, see Section 7.2.4.1.4.1)

- a Grade 3 or 4 arterial thrombotic event or a Grade 3 or 4 venous thrombotic event that is considered by the investigator to be life-threatening, or symptomatic and not adequately treated by anticoagulation therapy (for more information, see Section 7.2.4.1.4.3)
- Grade 3 or 4 bleeding or hemorrhagic event

2. Grade 4 hypertension or persistent/recurrent hypertension (for more information, see Section 7.2.4.1.4.2)

- Grade 4 proteinuria or persistent/recurrent proteinuria >3 g/24 hours (for more information, see Section 7.2.4.1.4.4)

3. any Grade 4 nonhematologic toxicity considered by the investigator to be related to ramucirumab. Any event which would warrant the dose of ramucirumab to be modified by >2 dose reductions, or if ramucirumab will be delayed for more than 5 weeks from the last administered dose (delay of more than 14 days from start of the next cycle; for more information see Section 7.2.4.1.4).

- hemoptysis that exceeds the severity grade present at baseline
- any Grade 3-4 events consistent with congestive heart failure
- new occurrence of hepatic encephalopathy and/or hepatorenal syndrome resulting from liver cirrhosis

6.3.2. Discontinuation of Study Sites

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

6.3.3. Discontinuation of the Study

The study will be discontinued if Lilly, while considering the rights, safety, and well-being of the patient(s), judges it necessary for any scientific, medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

7. Treatment

7.1. Materials and Supplies

Abemaciclib will be supplied as capsules or tablets for oral administration. The capsules/tablets 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/tablets in the original package and in a location inaccessible to children. Clinical study materials will be labeled according to country regulatory requirements.

For Parts A and B (pemetrexed and gemcitabine, respectively), patients should receive standard of care agents as specified in the label. All commercially available drugs should be stored and administered according to the label and will be supplied by the sponsor where required.

For Parts C, D, and E (ramucirumab, LY3023414, and pembrolizumab, respectively), patients should receive investigational agents as specified in the protocol. Ramucirumab (Part C) and pembrolizumab (Part E) should be stored and handled according to the product label and pharmacy manual and will be supplied by the sponsor.

Ramucirumab is a sterile, preservative-free solution for infusion of ramucirumab formulated in an aqueous solution at a concentration of 10 mg/mL (500 mg/50-mL vial). The buffer contains 10 mM histidine, 75 mM sodium chloride, 133 mM glycine, and 0.01% polysorbate 80, pH 6.0. Ramucirumab is supplied in single-use 50-mL nominal volume glass vials.

All excipients used for the manufacture of ramucirumab are of pharmacopeial grade. No animal-derived components are used in the manufacture of ramucirumab excipients.

LY3023414 will be supplied in 25-mg, 100-mg or 200-mg capsules and as 50-, 100-, 150-, or 200-mg tablets for oral administration. LY3023414 capsules/tablets should be stored within the temperature range stated on the label. Investigators should instruct patients to store the capsules/tablets at home in the provided container and to keep out of the reach of children. Capsules/tablets should not be opened, crushed, or dissolved. LY3023414 will be labeled according to local regulatory requirements and supplied by the sponsor.

Pembrolizumab is a lyophilized powder solution for infusion, resconstitued with sterile water for injection prior to use. The buffer contains L-histidine, polysorbate 80 as surfactant, sucrose as stabilizer/tonicity modifier, and hydrochloric acid (HCl) and/or sodium hydroxide (NaOH) for pH adjustment if necessary. Pembrolizumab is supplied in single-use 50-mg/vials.

Clinical study materials will be labeled according to the country's regulatory requirements.

7.2. Study Drug Administration

In Parts A, B, C, and D, patients will receive either 100 mg, 150 mg, or 200 mg of abemaciclib orally Q12H in combination with: pemetrexed (Part A), gemcitabine (Part B), ramucirumab (Part C), or LY3023414 (Part D). In Part E, patients will receive either 100 mg or 150 mg of abemaciclib orally Q12H in combination with pembrolizumab (Part E). In all study parts, de-escalation of abemaciclib at 100 mg orally Q12H on Days 1 through 21 of a 21-day cycle will be

permitted. During Cycle 1 and Cycle 2, when abemaciclib is scheduled to be administered on the same day as the combination treatment and PK samples are drawn, abemaciclib should be given immediately after the combination treatment is administered. Beyond Cycle 2 for Parts A, B, C, and E, abemaciclib may be administered at any time relative to the combination treatment. For Part D, abemaciclib and LY3023414 should be taken at approximately the same time irrespective of cycle time or PK sampling.

Pemetrexed (500 mg/m^2) will be administered as an approximate 10-minute IV infusion on Day 1 of a 21-day cycle. No dose reduction is necessary unless the patient experiences toxicity (see Section 7.2.4.1.2). No dose escalations are permitted. Prior to initiating pemetrexed, initiate supplementation with oral folic acid (folic acid 400 µg to 1000 µg orally once daily beginning 7 days before the first dose) and intramuscular vitamin B12. Continue folic acid during the full course of therapy and for 21 days after the last dose and continue vitamin B12 supplementation throughout treatment. Administer corticosteroids (e.g., dexamethasone 4 mg orally twice daily) the day before, the day of, and the day after pemetrexed administration.

Gemcitabine (1250 mg/m^2) will be administered as an approximate 30-minute IV infusion on Days 1 and 8 of a 21-day cycle. No dose reduction is necessary unless the patient experiences toxicity (see Section 7.2.4.1.3). No dose escalations are permitted.

Ramucirumab (8 mg/kg or 10 mg/kg) will be administered as an approximate 60-minute IV infusion followed by a 1-hour observation period during Cycles 1 and 2. If there is no evidence of an infusion-related reaction during the initial 2 cycles of ramucirumab, then no observation period is required for subsequent treatment cycles. In the event an infusion-related reaction occurs thereafter, then the 1-hour observation should be reinstituted. Premedication is recommended prior to infusion of ramucirumab. Recommended premedication agents include histamine H1 antagonists such as diphenhydramine hydrochloride (or equivalent). Additional premedication may be provided at the investigator's discretion. Premedication must be provided in the setting of a prior Grade 1-2 infusion-related reaction, as detailed in Section 7.2.4.1.4.1. All premedication administered must be adequately documented in the electronic data capture (eDC).

The first dose of ramucirumab is dependent upon the patient's baseline body weight in kilograms. Subsequent doses of ramucirumab must be recalculated if there is a ≥10% change (increase or decrease) in body weight from last dose calculation; subsequent doses may be recalculated if there is a <10% change (increase or decrease) in body weight from last dose calculation.

For Patients in Part D, LY3023414 will be administered orally, Q12H on a 21-day cycle. LY3023414 should be taken approximately at the same time each dosing day with a full glass of water concomitantly with abemaciclib. LY3023414 may be taken *with or without food*. Patients should swallow the capsules/tablets as a whole, and should not chew or crush them.

If the patient misses a dose of LY3023414, the patient should take the dose as soon as possible, but not less than 6 hours before the next dose is due for BID dosing. If the next dose is due in less than 6 hours, the patient should skip the missed dose and take the next dose as scheduled.

If vomiting occurs after taking LY3023414, the patient should be instructed not to retake the dose. Patients should take the next scheduled dose of LY3023414. If vomiting persists, the patient should contact the investigator.

On clinic days with postdose PK sampling associated with blood glucose monitoring (Day 1 of Cycles 1 and 2), patients are permitted to eat a light snack at least 2.5 hours prior to the study drug dosing, but are then asked to fast until after the 4 hour postdose samples are collected. High sugar foods (for example, sugary breakfast cereals, fruit juices, coffee with sugar, etc.) should be avoided as part of this light snack. Missed doses should not be taken within 12 hours (± 2 hours) of the next dose. No dose reduction is necessary unless the patient experiences toxicity (see Section 7.2.4.1.5).

Pembrolizumab 200 mg (fixed dose) will be administered as an approximate 30-minute IV infusion on Day 1 of a 21-day cycle followed by a 1-hour observation period during Cycles 1 and 2. Signs and symptoms of infusion-related reactions usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. All cycles thereafter, no observation period will be required. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (that is, infusion time can be 25 to 40 minutes).

The treatment combinations that will be administered with the assigned dose of abemaciclib in Parts A, B, C, D, and E in this study are listed in Table JPBJ.7.1.

Table JPBJ.7.1. Treatment Combinations for Study I3Y-MC-JPBJ

Study Part	Combination Drug	Dose	Route of Administration	Dose Frequency	Abemaciclib Dose Range
A	pemetrexed	500 mg/m^2	IV	Day 1	100 to 200 mg
B	gemcitabine	1250 mg/m^2	IV	Days 1 and 8	100 to 200 mg
C	ramucirumab	8 mg/kg, 10 mg/kg	IV	Days 1 and 8 or Day 1	100 to 200 mg
D	LY3023414	100 mg, 150 mg, 200 mg	oral	Q12H	100 to 150 mg
E	pembrolizumab	200 mg	IV	Day 1	100 to 150 mg

Abbreviations: IV = intravenous; Q12H = every 12 hours.
Note: Dose frequency is described for each 21-day cycle.

The investigator or designee is responsible for:

- explaining the correct use of the investigational agent(s) and planned duration of each individual's treatment to the patient and, if appropriate, to the patient's designated legal representative,
- verifying that instructions are followed properly,
- maintaining accurate records of study drug dispensation, destruction, and collection, and
- returning or destroying all unused medication to Lilly or its designee at the end of the study.

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

7.2.1. Dosing Schedule

Abemaciclib dosing is administered on a twice-daily schedule. Patients will receive abemaciclib orally Q12H (±3 hours) for Days 1 through 21 of a 21-day cycle. Patients should not consume food beginning 1 hour before and ending 1 hour after taking study drug.

Study drug should be taken at approximately the same time(s) each day. If a patient misses or vomits a dose, that dose should be omitted. Patients must record the time and amount of each dose taken (or alternatively, the time and amount of the dose missed or vomited) in a daily diary.

Patients should receive pemetrexed (Part A), gemcitabine (Part B), ramucirumab (Part C), LY3023414 (Part D), or pembrolizumab (Part E) according to the Study Schedule (Attachment 1).

Patients will receive abemaciclib until progression or unacceptable toxicity, unless 1 or more of the criteria for discontinuation (refer to Section 6.3.1) are fulfilled; the follow-up period for poststudy evaluation will be 30 ± 7 days from the date of the last dose of study drug received (when the final safety assessments are completed).

For Cycle 2 and beyond, a delay of ≤7 days in the start of a cycle (Day 1) for justifiable reasons (for example, inclement weather, holidays, or weekends) other than toxicity will be permitted and does not constitute a protocol violation.

For Cycle 2 and beyond, a delay of ≤14 days in the start of a cycle (Day 1) to allow for recovery from toxicity will be permitted and does not constitute a protocol violation (refer to Section 7.2.4).

7.2.2. Dose-Escalation Phase

Dose escalation follows safety assessments using the standard scoring system, CTCAE version 4.0, established by the National Cancer Institute (NCI). Any AEs possibly related to abemaciclib were considered as toxicities.

For the dose-escalation phase, Table JPBJ.7.2 and Table JPBJ.7.3 summarize the abemaciclib proposed starting dose levels of 150 mg, and 200 mg Q12H on a 21-day cycle for Parts A, B, and C. During the dose-escalation phase, the abemaciclib proposed start dose levels of 100 mg and 150 mg Q12H on a 21-day cycle are summarized for Parts D (Table JPBJ.7.4) and E (Table JPBJ.7.5). Three patients are planned for treatment at each dose level; however, the exact number of patients treated at a specific dose level depends on the number of patients within the cohort who experience a DLT. If a patient in a given cohort experiences a DLT during Cycle 1, then subsequent patients are enrolled sequentially. For Part D, the first patient enrolled in this part will be observed for a DLT (as defined in Section 7.2.2.1) during the first 14 days of Cycle 1 before subsequent patients are treated at that dose level. If the first patient does not experience a DLT during this period, subsequent patients may be concurrently enrolled in the initial cohort. In subsequent cohorts, patients may be enrolled concurrently.

In all cohorts, every patient will be assessed for toxicity (based on CTCAE version 4.0 grading) on Day 21 of Cycle 1.

Table JPBJ.7.2. Dose-Escalation Scheme for Study I3Y-MC-JPBJ

Cohort/Study Part	Patients/Cohort	Abemaciclib Dose
1	3-6	150 mg Q12H
2	3-6	200 mg Q12H
3	12	200 mg or MTD Q12H

Abbreviations: Q12H = every 12 hours; MTD = maximum tolerated dose under the combination treatment.
The scheme is repeated for study Parts A and B (abemaciclib in combination with pemetrexed [Part A], gemcitabine [Part B]).
Note: During dose escalation, de-escalation to 100 mg of abemaciclib Q12H is allowed for study parts.

Table JPBJ.7.3. Dose-Escalation Scheme for Part C

Cohort/Study Part	Patients/Cohort	Abemaciclib Dose	Ramucirumab Dose
C-1 Escalation Cohort 1	3-6	150 mg Q12H	10 mg/kg Day 1
C-2 Escalation Cohort 2	3-6	200 mg Q12H	10 mg/kg Day 1
C-3 Confirmation Cohort	12	200 mg or MTD Q12H	10 mg/kg Day 1
C-4 Escalation Cohort 3	3-6	150 mg Q12H	8 mg/kg Days 1 and 8
C-5 Escalation Cohort 4	3-6	150 mg Q12H	10 mg/kg Days 1 and 8
C-6 Confirmation Cohort 5	6	150 mg Q12H	MTD Days 1 and 8

Abbreviations: Q12H = every 12 hours; MTD = maximum tolerated dose under the combination treatment.
Note: During dose escalation, de-escalation to 100 mg Q12H of abemaciclib is permitted.

Table JPBJ.7.4. Dose-Escalation Scheme for Part D

Cohort/Study Part	Patients/Cohort	Abemaciclib Dose	LY3023414 Dose
D-1 Escalation Cohort 1	3-6	100 mg Q12H	100 mg Q12H
D-2 Escalation Cohort 2	3-6	150 mg Q12H	100 mg Q12H
D-3 Escalation Cohort 3	3-6	150 mg Q12H	150 mg Q12H
D-5* Escalation Cohort 4a	3-6	200 mg Q12H	150 mg Q12H
D-6 Escalation Cohort 4b	3-6	150 mg Q12H	200 mg Q12H
D-4 Confirmation Cohort	6-12	MTD Q12H	MTD Q12H

Abbreviations: MTD = maximum tolerated dose under the combination treatment; Q12H = every 12 hours.
Note: During dose escalation, de-escalation to 100 mg Q12H of abemaciclib is permitted.
* D-5 Cohort 4a enrollment closed before completion of cohort. Reference Section 5.1.6.

The dose-escalation phase is guided by safety assessments from Days 1 through 21 of Cycle 1 for all patients in the cohort and also by the emerging PK data from previous cohorts. If none of the patients in a cohort experienced a DLT, dose escalation could occur to the next prespecified dose level. For all cohorts, if safety assessments and/or the emerging PK data indicate either that dose escalation should occur to a dose level lower than the next prespecified dose level or that dose de-escalation should occur to a dose level lower than the current dose level, then safety assessments and/or the emerging PK data could be used to select an alternate dose level within

these constraints. In Study JPBA, the single-agent MTD was established at 200 mg Q12H for the twice-daily schedule (as discussed in Section 5.6).

Table JPBJ.7.5. Dose-Escalation Scheme for Part E

	Cohort/Study Part	Patients/Cohort	Abemaciclib Dose	Pembrolizumab Dose
E-1	Escalation Cohort 1	3-6	100 mg Q12H	200 mg Day 1
E-2	Escalation Cohort 2	3-6	150 mg Q12H	200 mg Day 1
E-4	Confirmation Cohort	12	MTD Q12H	200 mg Day 1

Abbreviations: MTD = maximum tolerated dose under the combination treatment; Q12H = every 12 hours.

7.2.2.1. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition

A DLT is defined as an AE occurring between Day 1 and Day 21 of Cycle 1 for a patient enrolled in the dose-escalation phase that is possibly related to either abemaciclib or the combination therapy and fulfills any 1 of the following criteria:

- Grade 3 or 4 nonhematological toxicity according to the NCI CTCAE version 4.0 (except for nausea, vomiting, diarrhea, or electrolyte disturbance),
- Grade 3 or 4 nausea, vomiting, diarrhea, or electrolyte disturbance that persists more than 2 days despite maximal supportive intervention.
- Grade 4 hematological toxicity that persists more than 5 days.
- Grade 3 or 4 thrombocytopenia with bleeding.
- Grade 3 or 4 neutropenia with fever.
- For patients in Part D only, the following additional exceptions apply:
  - transient (≤5 days) Grade 3 hyperglycemia (fasting)
  - Grade 3 hypertriglyceridemia or hyperlipidemia without optimal treatment.

Investigators, together with the Lilly CRP, can declare a DLT if a patient is experiencing increasing toxicity during treatment, and it becomes clear that it is not going to be possible to complete the treatment without exposing the patient to excessive risk.

A DLT-equivalent is defined as an AE that would have met the criteria for DLT if it had occurred during Cycle 1 for a patient enrolled in the dose-escalation phase, but that occurs between 1) Day 1 and Day 21 of Cycle 2 and beyond for a patient enrolled in the dose-escalation phase and 2) at any time for a patient in the dose-expansion phase. The MTD will be assessed for each study part and is defined as the highest dose level at which less than 33% of patients experience a DLT during Cycle 1.

7.2.2.2. Dose-Escalation Method

If 1 of 3 patients at any dose level in any study part experiences a DLT, then up to 3 additional patients will be enrolled at that dose level. If a DLT is observed in ≥2 out of a maximum of 6 patients at any given dose, dose escalation will cease and either the previous dose level will be declared the MTD for the combination therapy or, following discussions between the

investigators and the sponsor, additional patients may be treated at intermediate doses between the previous dose level and the level above the MTD for the combination therapy.

For study Parts A, B, and C, if ≥2 of 6 patients experience a DLT at 150 mg Q12H, then the dose of abemaciclib should be de-escalated to 100 mg Q12H and enrollment to the cohort should proceed as noted above. For Parts D and E, if ≥2 of 6 patients experience a DLT at abemaciclib 100 mg Q12H in combination with Part D LY3023414 or Part E pembrolizumab, then enrollment to the cohort should cease and no additional patients will be accrued until this safety review is completed and a decision is made how to proceed. The safety review and decision will be documented in writing.

7.2.3. Dose-Confirmation Phase

After the MTD for each combination therapy has been identified in each study part in the dose-escalation phase, up to approximately 12 patients will be enrolled in each of the 5 confirmation groups: patients receiving pemetrexed (Part A), gemcitabine (Part B), ramucirumab (Part C), LY3023414 (Part D), or pembrolizumab (Part E). In addition, Part C will include a second dose-escalation and confirmation cohort of approximately 12 patients to evaluate alternate dosing schedules for ramucirumab with 8 mg/kg on Days 1 and 8 and if tolerable, dose escalate to 10 mg/kg on Days 1 and 8 of a 21-day cycle. For Part D, enrollment into the dose-confirmation phase will include a minimum of 6 patients and a maximum of 12 patients. The establishment and confirmation of the combination therapy dose for the program will determine the actual number of patients enrolled into the dose-confirmation cohort. For Parts A, B, C, and E following the dose-confirmation phase, if clinical data indicate preliminary efficacy for the combination therapy, then approximately 12 more patients, a total of approximately 24 patients, will be enrolled to the confirmation cohort to obtain clinical evidence for efficacy.

During the dose-confirmation phase, patients may enroll concurrently and will be treated at a dose no greater than the MTD for the specific study part. During the dose-escalation phase, abemaciclib may, at the discretion of the investigator, be de-escalated to 100 mg Q12H. For all patients, dose adjustments are permitted as outlined in Section 7.2.4.

If DLT-equivalents occur in 33% or more of patients within a specific dose-expansion group, then investigators and the Lilly CRP will assess the nature and severity of these toxicities. No additional patients will be accrued until this safety review is completed and a decision is made either to continue at the current dose or to de-escalate the dose and define a new dose for the expansion phase. A decision will be made to explore an intermittent dosing schedule at the current MTD, or a lower dose for each combination therapy. The safety review and decision will be documented in writing.

7.2.4. Dose Adjustments and Delays

7.2.4.1. Dose Adjustments

7.2.4.1.1. Abemaciclib

Table JPBJ.7.6 presents dose adjustments to occur if the event is possibly related to abemaciclib.

Table JPBJ.7.6. Toxicity Dose Adjustments and Delays of Abemaciclib for Study I3Y-MC-JPBJ

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity Section 7.2.4.1.1.1	Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Hematologic Toxicity Section 7.2.4.1.1.1	Recurrent Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic Toxicity Section 7.2.4.1.1.1	Grade 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic toxicity: If patient requires administration of blood cell growth factors Section 7.2.4.1.1.1	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 lead to the use of growth factor.
Nonhematologic Toxicity[a] (except diarrhea and ALT increased) Section 7.2.4.1.1.2	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 7.2.4.1.1.2	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 7.2.4.1.1.3 and 7.5.1.1	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 7.2.4.1.1.3 and 7.5.1.1	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 7.2.4.1.1.3 and 7.5.1.1	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-JPBJ

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
ALT Increased Sections 7.2.4.1.1.4 and 8.1.4.1	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 7.2.4.1.1.4 and 8.1.4.1	Grade 4 (>20.0×ULN)[d]	Abemaciclib **MUST** be discontinued.	Abemaciclib **MUST** be discontinued.
ALT Increased with increased total bilirubin, in the absence of cholestasis Sections 7.2.4.1.1.4 and 8.1.4.1	Grade 3 increased ALT (>5.0 x ULN) with total bilirubin >2 x ULN[d]	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 hepatic and renal monitoring is in Sections 8.1.4.1 and 7.5.1.2.

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).

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 8.1.4.1 for additional guidance for hepatic monitoring

Dose adjustments are allowed both within a cycle and between cycles.

If a patient who, in the judgment of the investigator, is receiving clinical benefit from study therapy requires further dose reduction than is outlined in Table JPBJ.7.7, then the investigator must discuss with the Lilly CRP prior to any further dose reduction. For patients requiring dose reduction(s), re-escalation to a prior dose level is permitted only after consultation with the Lilly CRP.

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

Table JPBJ.7.7. Dose Adjustments of Abemaciclib for Study I3Y-MC-JPBJ

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

7.2.4.1.1.1. Hematologic Toxicity

If a patient experiences a Grade 3 hematologic toxicity possibly related to abemaciclib, then dosing **must** be suspended (until toxicity resolves to either baseline or at least Grade 2) and the dose of abemaciclib **may** be reduced at the investigator's discretion as outlined in Table JPBJ.7.6.

If a patient experiences a recurrent Grade 3 or a Grade 4 hematologic toxicity possibly related to abemaciclib, then dosing **must** be suspended (until the toxicity resolves to either baseline or at least Grade 2) and the dose of abemaciclib **must** be reduced as outlined in Table JPBJ.7.6.

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 (regardless of severity), then dosing **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. The dose of abemaciclib **must** be reduced by 1 dose level (unless already performed for incidence of toxicity that lead to the use of growth factor) as outlined in Table JPBJ.7.6.

7.2.4.1.1.2. Nonhematological Toxicity (except diarrhea and ALT increase)

If a patient experiences ≥Grade 3 nonhematologic toxicity possibly related to abemaciclib, 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 as outlined in Table JPBJ.7.6.

If a patient experiences persistent or recurrent Grade 2 nonhematologic toxicity (except diarrhea; refer to Section 7.2.4.1.1.3 or ALT increased, refer to Section 8.1.4.1) possibly related to abemaciclib that does not resolve with maximal supportive measures within 7 days to either baseline or Grade 1, 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 as outlined in Table JPBJ.7.6.

7.2.4.1.1.3. Diarrhea

If a patient experiences Grade 2 diarrhea that does not resolve with maximal supportive measures (refer to Section 7.5.1.1) 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 or any Grade diarrhea that requires hospitalization (refer to Section 7.5.1.1) study drug must be suspended (until the toxicity resolves to either baseline or at least Grade 1); and a dose reduction is required. For Grade 3 or Grade 4 diarrhea, the dose must be suspended and a dose reduction is required Table JPBJ.7.6.

7.2.4.1.1.4. Hepatic Toxicity

Dose modifications and management for increased ALT are provided in Table JPBJ.7.6. 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 8.1.4.1 for additional hepatic monitoring guidance.

7.2.4.1.2. Pemetrexed

Pemetrexed dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum nonhematologic toxicity from the preceding cycle of therapy. Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients should be re-treated using the guidelines in Table JPBJ.7.8, which are suitable for using pemetrexed as a single-agent or in combination.

Table JPBJ.7.8. Hematologic Dose Reduction for Pemetrexed in Study I3Y-MC-JPBJ

	Dose of Pemetrexed (mg/m2)
Nadir ANC <500/mm^3 and nadir platelets ≥50,000/mm^3	75% of previous dose
Nadir platelets <50,000/mm^3 without bleeding regardless of nadir ANC	75% of previous dose
Nadir platelets <50,000/mm^3 with bleeding[a], regardless of nadir ANC	50% of previous dose

Abbreviations: ANC = absolute neutrophil count; CTCAE = common terminology criteria for adverse events.

[a] These criteria meet the CTCAE version 4.0 definition of ≥CTC Grade 2 bleeding.

If patients develop nonhematologic toxicities (excluding neurotoxicity) ≥Grade 3, treatment should be withheld until resolution to less or equal to the patent's baseline value. Treatment should be resumed according to Table JPBJ.7.9.

Table JPBJ.7.9. Nonhematologic Dose Reduction for Pemetrexed in Study I3Y-MC-JPBJ

	Dose of Pemetrexed (mg/m^2)
Any Grade 3 or 4 toxicities except mucositis	75% of previous dose
Any diarrhea requiring hospitalization (irrespective of Grade) or Grade 3 or 4 diarrhea	75% of previous dose
Grade 3 or 4 mucositis	50% of previous dose

Pemetrexed therapy should be discontinued if a patient experiences any hematologic or nonhematologic Grade 3 or 4 toxicity after 2 dose reductions or immediately if Grade 3 or 4 neurotoxicity is observed. Pemetrexed should not be administered to patients whose creatinine clearance is <45 mL/min using the standard Cockcroft and Gault formula (refer to Attachment 7).

Caution should be exercised when administering pemetrexed concurrently with nonsteroidal anti-inflammatory drugs (NSAIDs) to patients whose creatinine clearance is <80 mL/min.

7.2.4.1.3. Gemcitabine

Patients receiving gemcitabine should be monitored prior to each dose (Day 1 and Day 8 of each cycle) with a complete blood count (CBC), including differential and platelet count. If marrow suppression is detected, therapy should be modified or suspended according to guidelines in Table JPBJ.7.10.

Table JPBJ.7.10. Dose Adjustments of Gemcitabine for Study I3Y-MC-JPBJ

Absolute Granulocyte Count ($\times 10^6$/L)		Platelet Count ($\times 10^6$/L)	% of Full Dose
≥1000	AND	≥100,000	100%
500-999	OR	50,000-99,000	75%
<500	OR	<50,000	HOLD

Dose Modifications for Nonhematologic Adverse Reactions

Permanently discontinue gemcitabine for any of the following:

- Unexplained dyspnea or other evidence of severe pulmonary toxicity
- Severe hepatic toxicity
- Hemolytic-Uremic Syndrome
- Capillary Leak Syndrome

Withhold gemcitabine or reduce dose by 50% for other severe (Grade 3 or 4) nonhematological toxicity until resolved. No dose modifications are recommended for alopecia, nausea, or vomiting.

7.2.4.1.4. Ramucirumab

Dose modifications are permitted for investigational product in the setting of non-life-threatening and reversible Grade 3 clinical AEs (for example, fever) considered to be at least possibly related to investigational product and that resolve to Grade ≤1 or pretreatment baseline within 1 treatment cycle (approximately 3 weeks). If a Grade 4 AE occurs and is deemed at least possibly related to ramucirumab, then treatment should be discontinued except in the specific case of Grade 4 fever or Grade 4 laboratory abnormalities. If Grade 4 fever or laboratory abnormalities resolve to Grade ≤1 or baseline within 1 treatment cycle (approximately 3 weeks), treatment with ramucirumab may be continued at the discretion of the investigator. In these settings, ramucirumab may be readministered. If a second instance of such an event occurs, ramucirumab should be subsequently readministered at a reduced dose level. A second dose reduction is permitted for this level of event (Grade 3 or 4) (refer to Table JPBJ.7.11). If the dose of ramucirumab is reduced because of potentially related AEs, subsequent dose increases are not permitted. Specific guidelines for ramucirumab dose modifications related to infusion reactions and thrombotic events are provided in Section 7.2.4.1.4.1 and Section 7.2.4.1.4.3,

respectively. Criteria for dose reduction in the setting of hypertension and proteinuria are detailed in Section 7.2.4.1.4.2 and Section 7.2.4.1.4.4, respectively.

Table JPBJ.7.11. Dose Adjustments of Ramucirumab for Study I3Y-MC-JPBJ

Dose Adjustment	IV Dose	Dose Frequency
0	10 mg/kg	Days 1 and 8 or Day 1
1	8 mg/kg	Days 1 and 8 or Day 1
2	6 mg/kg	Days 1 and 8 or Day 1
3*	5 mg/kg	Days 1 and 8

Abbreviation: IV = intravenous.

* Ramucirumab 5 mg/kg is only permitted on the alternate dosing schedule on Days 1 and 8 administration. Patients who require >2 dose reductions should be discontinued from ramucirumab.

Patients who enter the study with symptoms or laboratory values equivalent to NCI-CTCAE v. 4.0 Grade 1 or 2 AEs should not have dose reductions related to the persistence or mild worsening of those symptoms or laboratory values; dose reductions may be warranted if worsening of symptoms or laboratory values is clinically significant in the opinion of the investigator.

If the start of the next cycle is delayed due to ramucirumab-related toxicity, abemaciclib should continue as scheduled. If clinically appropriate, both treatments can be delayed up to a maximum of 7 days to maintain synchronized administration. However, if either abemaciclib or ramucirumab dosing is permanently discontinued, dosing should be continued with the remaining compound according to the schedule, if clinically indicated.

Patients receiving ramucirumab should be monitored prior to each dose (Day 1 only or Day 1 and Day 8 of each cycle). In the case of ramucirumab-related toxicity, ramucirumab will be delayed for 1 week and administered on Day 8 of the treatment cycle provided toxicities have resolved to Grade <2 or baseline. If toxicities have not resolved on Day 8, omit ramucirumab for that cycle.

If toxicity related to ramucirumab does not resolve in the same treatment cycle, ramucirumab can be delayed up to 42 days. If the toxicity does not resolve within 42 days, ramucirumab should be discontinued unless the patient is receiving clinical benefit and agreement occurs between the treating investigator and Lilly CRP.

AEs of concern, which may or may not be associated with ramucirumab therapy, may include infusion-related reactions, hypertension, arterial or venous thrombotic events, bleeding (hemorrhagic) events, proteinuria, gastrointestinal perforation, congestive heart failure, surgery and impaired wound healing, liver injury/liver failure, and reversible posterior leukoencephalopathy syndrome (RPLS).

7.2.4.1.4.1. Infusion-Related Reactions

Any treatment-related infusion-related reactions are defined according to the NCI-CTCAE v 4.0 definition (NCI-CTCAE v 4.0 section “General disorders and administration site conditions”).

Symptoms occurring during or following infusion of ramucirumab may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome (NCI-CTCAE v 4.0 section "Immune system disorders"). In the setting of symptoms occurring during or following infusion of ramucirumab, investigators are encouraged to use the AE term "infusion-related reaction" and any additional terms (including those not listed here) that best describe the event.

Consistent with usual medical practice, selected parenteral medications may be utilized for Grade 2 allergic/hypersensitivity reaction as detailed below. The Lilly CRP should be contacted immediately if questions arise concerning the grade of the reaction.

The following are treatment guidelines for infusion-related reactions:

Grade 1:

- Slow the infusion rate by 50%.
- Monitor the patient for worsening of condition.
- For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent); additional premedication may be administered at the investigator's discretion.

Grade 2:

- Stop the infusion.
- Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), acetaminophen 650 mg orally for fever, and oxygen.
- Resume the infusion at 50% of the prior rate once the infusion-related reaction has resolved or decreased to Grade 1; the infusion duration should not exceed 2 hours.
- Monitor for worsening of condition.
- For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent); additional premedication may be administered at the investigator's discretion.

For a second Grade 1 or 2 infusion-related reaction, administer dexamethasone 8 to 10 mg IV (or equivalent); then, for subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent), acetaminophen 650 mg orally, and dexamethasone 8 to 10 mg IV (or equivalent).

Grade 3:

- Stop the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), dexamethasone 8 to 10 mg IV (or equivalent), bronchodilators for bronchospasm, and other medications/treatment as medically indicated.

- Patients who have a Grade 3 infusion-related reaction will not receive further investigational product but will continue to be followed on the protocol.

Grade 4:

- Stop the infusion and disconnect the infusion tubing from the patient.
- Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), dexamethasone 8 to 10 mg IV (or equivalent), and other medications/treatment as medically indicated.
- Give epinephrine or bronchodilators as indicated.
- Hospital admission for observation may be indicated.
- Patients who have a Grade 4 infusion-related reaction will not receive further investigational product, but will continue to be followed on the protocol.

If a patient should have an infusion-related reaction to ramucirumab, all attempts should be made to obtain blood samples for both immunogenicity and PK analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event (see Attachment 1).

7.2.4.1.4.2. Hypertension

The following are treatment guidelines for hypertension (an expected AE in patients receiving ramucirumab) that develops during the study.

Grade <3:

- If the hypertension is not associated with symptoms, continue ramucirumab and initiate antihypertensive therapy.
- If the hypertension is associated with symptoms, hold ramucirumab until symptoms resolve and initiate antihypertensive therapy.
- If ramucirumab is held more than once for hypertension (ie, symptomatic hypertension, markedly elevated blood pressure unresponsive to antihypertensive therapy), the dose of ramucirumab should resume at a reduced dose level. A second dose reduction should be undertaken if an additional postponement of ramucirumab is required.

Grade 3: (systolic blood pressure [BP] ≥160 mm Hg or diastolic BP ≥100 mm Hg; medical intervention indicated; more than 1 drug or more intensive therapy than previously used indicated)

- For Grade 3 hypertension not associated with symptoms, continue investigational product with more intensive antihypertensive therapy. If systolic BP remains ≥160 mm Hg or diastolic BP ≥100 mm Hg >3 weeks after initiation of additional antihypertensive therapy, hold investigational product while continuing appropriate antihypertensive therapy.

- If the hypertension is associated with symptoms, hold ramucirumab until symptoms resolve and initiate antihypertensive therapy.
- If ramucirumab is held more than once for hypertension (that is, symptomatic hypertension, markedly elevated blood pressure unresponsive to antihypertensive therapy), the dose of ramucirumab should resume at a reduced dose level. A second dose reduction should be undertaken if an additional postponement of ramucirumab is required.

Grade 4 or Refractory:

Patients with Grade 4 hypertension (life-threatening consequences; eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis; or urgent intervention indicated) or patients whose hypertension is poorly controlled (>160 mm Hg systolic or >100 mm Hg diastolic for >4 weeks) despite appropriate oral medication (>2 oral agents at MTD) will be discontinued from ramucirumab. Treatment with abemaciclib may be continued, if appropriate in the opinion of the investigator.

7.2.4.1.4.3. Thrombotic Events

Investigators should perform all testing required to fully characterize arterial or venous thrombotic/vascular events. The incidence and type of thrombotic/vascular events will be collected and reported.

Patients who develop ≤Grade 3 venous thrombotic events (deep vein thrombosis [DVT] or pulmonary embolism [PE]) may continue study therapy, with the consent of the Lilly CRP, if the event is not considered to be life-threatening in the opinion of the investigator, the patient is asymptomatic, and/or the event can be adequately treated with low molecular weight heparin-based therapy. The treatment combination (abemaciclib + ramucirumab) should be discontinued in the setting of a DVT or PE that occurs or intensifies while the patient is receiving therapeutic anticoagulation therapy.

7.2.4.1.4.4. Proteinuria

If, while receiving ramucirumab, a patient has proteinuria ≥2+ per a dipstick or routine urinalysis test, ramucirumab will continue as scheduled, and a 24-hour urine collection will be conducted prior to the subsequent scheduled treatment cycle. If the protein level is <2 g/24 hours, the patient will continue on ramucirumab at the same dose without interruption. If the protein level is 2 to 3 g/24 hours, ramucirumab for the subsequent cycle will be held for 3 weeks and a 24-hour urine collection will be repeated. Treatment with ramucirumab will resume at a reduced dose level once the protein level returns to <2 g/24 hours. A second dose reduction is permitted if proteinuria >2 g/24 hours recurs. Ramucirumab will be discontinued if the protein level is >3 g/24 hours, if there is a third occurrence of proteinuria >2 g/24 hours, or if the protein level does not return to <2 g/24 hours within 3 weeks.

7.2.4.1.5. LY3023414

For patients receiving combination treatment with abemaciclib and LY3023414 in Part D, the same guidelines for dose adjustments due to toxicities possibly related to LY3023414 apply as outlined for abemaciclib in Section 7.2.4.1.1.

Dose adjustments of LY3023414 are described in Table JPBJ.7.12.

Table JPBJ.7.12. Dose Adjustments of LY3023414 for Study I3Y-MC-JPBJ

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

For patients in **Part D** (LY3023414 + abemaciclib), the investigator will interpret and document whether or not an AE has a reasonable possibility of being related to each of the study drugs, taking into account the disease, concomitant treatments, or pathologies, in order to individually adjust study drug(s) doses. For a toxicity that due to its nature is possibly related to LY3023414 only, dose adjustments for abemaciclib should be considered only after dose adjustment of LY3023414 (and vice versa for possibly only abemaciclib-related toxicities; see Section 7.2.4.1.1). LY3023414 should be dose-reduced to the next lower dose level (Table JPBJ.7.12) following discussion between the investigator and the sponsor.

Following discussion between the investigator and the sponsor, reductions to intermediate dose levels and splitting the total daily dose of LY3023414 in uneven morning and evening doses (e.g., 100 mg in the morning/200 mg in the evening instead of 150 mg BID) will be allowed, as long as none of the doses (morning/evening) exceed the MTD for QD dosing of 325-mg/d LY3023414 monotherapy. Dosing of either abemaciclib or LY3023414 or both may be dose adjusted due to possibly study drug-related toxicities, as deemed clinically appropriate at the investigator discretion.

7.2.4.1.6. Pembrolizumab

Pembrolizumab must be withheld (dose reductions are not permitted) for drug-related toxicities and severe or life-threatening AEs. See Section 7.2.4.2.6 for pembrolizumab dose adjustment and corticosteroid usage and Section 7.5.1.4 for supportive care guidelines for pembrolizumab.

7.2.4.2. Dose Delays

7.2.4.2.1. Abemaciclib

Before the start of each cycle, hematologic toxicity possibly related to abemaciclib must resolve to either baseline or at least Grade 2.

Before the start of each cycle, nonhematologic toxicity (except alopecia and fatigue) possibly related to abemaciclib must resolve to either baseline or at least Grade 1. Refer to Section 7.5.1 for guidance and supportive measures of diarrhea toxicity possibly related to abemaciclib or Section 8.1.4.1 for additional hepatic monitoring guidance.

The start of a cycle may be delayed to allow sufficient time for recovery from toxicity possibly related to study drug. Patients not recovering from such toxicity within 14 days beyond the last day of the prior cycle should be considered for discontinuation from the study.

7.2.4.2.2. Pemetrexed

To start the next cycle, the following criteria must be fulfilled:

- ANC ≥1.5 x 10^3/μL (≥1.5 x 10^9/L), platelets ≥100 x 10^3/μL (≥100 x 10^9/L)
- Creatinine clearance is ≥45 mL/min

The start of next cycle should be delayed for up to 2 weeks (14 days) to allow for recovery. If a delay of more than 2 weeks (14 days) due to unresolved toxicity is necessary, 1 or both of the drugs should be discontinued (depending on the causality of the drug). The other agent should be continued, with the patient remaining on study, if clinically indicated.

7.2.4.2.3. Gemcitabine

To start the next cycle, the following criteria must be fulfilled:

- ANC ≥1.5 x 10^3/μL (≥1.5 x 10^9/L), platelets ≥100 x 10^3/μL (≥100 x 10^9/L)

The start of next cycle should be delayed for up to 2 weeks (14 days) to allow for recovery. If a delay of more than 2 weeks (14 days) due to unresolved toxicity is necessary, 1 or both of the drugs should be discontinued (depending on the causality of the drug). The other agent should be continued, with the patient remaining on study, if clinically indicated.

7.2.4.2.4. Ramucirumab

To start the next cycle, the following criteria must be fulfilled:

- Total bilirubin less than or equal to ULN
- AST and ALT ≤2.5 x ULN, or ≤5 x ULN if the transaminase elevation is due to liver metastases
- ANC ≥1.5 x 10^3/μL (≥1.5 x 10^9/L), platelets ≥100 x 10^3/μL (≥100 x 10^9/L)
- NCI-CTCAE v 4.0 Grade <2 (except for alopecia; for hypertension, see Section 7.2.4.1.4.2, and for proteinuria, see Section 7.2.4.1.4.4)

When ramucirumab is administered on Day 1 of a 21-day cycle, the start of next cycle should be delayed for up to 2 weeks (14 days) to allow for recovery. If a delay of more than 2 weeks due to unresolved toxicity is necessary, 1 or both of the drugs should be discontinued (depending on the causality of the drug). The other agent should be continued, with the patient remaining on study, if clinically indicated. When ramucirumab is administered on Day 1 and Day 8 of a 21-day cycle, the start of the next cycle can be delayed up to 3 weeks to allow for recover. If a delay of more than 3 weeks due to unresolved toxicity is necessary, 1 or both of the drugs should be discontinued.

Patient should be weighed at the beginning of each cycle and may be dosed based on actual body weight. Applied dosages should be no more than 10% above or below calculated ones. The first dose of ramucirumab is dependent upon the patient's baseline body weight in kilograms. This

dose must be recalculated if there is a ≥10% change (increase or decrease) in body weight from the last dose calculation.

Ramucirumab infusion can be administered on Day 1 (±3 days) of each cycle due to administrative reasons only (for example, weekend) will be considered acceptable and is at the discretion of the treating investigator.

7.2.4.2.5. LY3023414

For patients receiving combination treatment with abemaciclib and LY3023414 in Part D, the same guidelines for dose delays and supportive measures for possibly LY3023414-related toxicities apply as outlined for abemaciclib in Section 7.2.4.2.1.

Dosing of either abemaciclib or LY3023414 or both may be delayed due to possibly study drug-related toxicities as deemed clinically appropriate at the investigator discretion.

7.2.4.2.6. Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Therefore, early recognition and initiation of treatment are critical to reduce complications. Based on existing clinical study data, more AEs were reversible and could be managed with interruptions of study treatment, administration of corticosteroids, and/or other supportive care. Dose modification and toxicity management guidelines for AEs associated with pembrolizumab are provided in Table JPBJ.7.13 below.

Table JPBJ.7.13. Dose Adjustments for Pembrolizumab in Study I3Y-MC-JPBJ

General instructions:
Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.

For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.

For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea /Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If
	Grade 4	Permanently discontinue		

				sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[a]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[a]		
Hypothyroidism	Grade 2-4	Continue	Initiate thyroid replacement hormones	Monitor for signs and symptoms of thyroid disorders.

			(eg, levothyroxine or liothyroinine) per standard of care	
Nephritis and Renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

[a] Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

7.2.4.3. Special Treatment Considerations

7.2.4.3.1. Immune Checkpoint Inhibitors

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

7.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive abemaciclib in this study. Before each patient's enrollment into the study, an eligibility check must be conducted between the investigational site and the Lilly clinical research personnel to confirm that each patient meets all enrollment criteria. Upon confirmation of eligibility, the sponsor will confirm the dose and identification number assignment for each patient. No dose escalations (that is, to the next cohort) can occur without prior discussion and agreement with the responsible Lilly CRP.

7.4. Blinding

This is an open-label study.

7.5. Concomitant Therapy

Pemetrexed, gemcitabine, ramucirumab, LY3023414, and pembrolizumab are permitted in Parts A, B, C, D, and E, respectively.

No other chemotherapy, radiotherapy, immunotherapy, cancer-related hormone therapy, or experimental drugs will be permitted while the patients are on this study. Palliative radiotherapy, unless required due to progressive disease, is permitted during the study. Disease progression requiring specific antitumor therapy will necessitate early discontinuation from the study. Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the case report form.

For Part E, systemic glucocorticoids for any purpose other than to modulate symptoms from an adverse event of suspected immunologic etiology are not permitted while patients are on study therapy. The use of physiologic doses of corticosteroids may be approved after consultation with the Lilly CRP. Inhaled steroids are allowed for management of asthma.

In vivo, abemaciclib is extensively metabolized through oxidation. The results from an in vitro human recombinant cytochrome P450 (CYP) phenotyping study indicate that oxidative metabolism of abemaciclib is primarily catalyzed by CYP3A. Based on these findings, grapefruit juice as well as inducers (for example, phenytoin and carbamazepine) and strong inhibitors of CYP3A should be substituted or avoided if possible (Attachment 10).

In vitro studies in primary cultures of human hepatocytes indicate that abemaciclib and its metabolites LSN2839567 and LSN3106726 down regulate mRNA of CYPs including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, and CYP3A at clinically relevant concentrations. The mechanism of mRNA down regulation and its clinical relevance are not yet understood. Therefore, caution should be exercised when coadministering substrate drugs of the above CYPs with narrow therapeutic margin. For LY3023414, preclinical data suggested potential inhibition of CYP3A4-mediated metabolism and potential secondary QTc interval prolongation by LY3023414. The clinical data from Study CBBA indicates LY3023414 is a weak inhibitor of CYP3A4 as concomitant administration of LY3023414 and midazolam leads to an increased exposure of midazolam (fold increase: mean 1.459 (CV 30.5 %) (90% CI 1.21 – 1.76). LY3023414 may lead to increase in exposure of abemaciclib and other CYP3A4 substrates. Therefore, caution should be exercised when coadministering substrate drugs of CYP3A4 with narrow therapeutic margin.

Patients should receive full supportive care during this study.

WBC growth factors may be used in accordance with the ASCO guideline (Smith et al. 2006) if clinically indicated. However, these agents must be discontinued at least 24 hours before beginning the next cycle of treatment.

Erythropoiesis-stimulating agents (ESAs, including erythropoietin and darbepoetin) may be used in accordance with the ASCO/ASH guideline (Rizzo et al. 2010) if clinically indicated. Transfusion therapy is permitted during this study.

7.5.1. Supportive Care

7.5.1.1. Supportive Management for Diarrhea

At enrollment, patients should receive instructions for diarrhea management. 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 (for example, loperamide) and notify the investigator for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (for example, 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- If diarrhea does not resolve with antidiarrheal therapy within 24 hours to either baseline or Grade 1, then dosing should be suspended until diarrhea is resolved to baseline or Grade 1.

When study drug recommences, dosing should be adjusted as outlined in Table JPBJ.7.6

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

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

Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be carefully monitored and given fluid (IV hydration) and electrolyte replacement.

7.5.1.2. 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.

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, 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 JPBJ.7.6).

7.5.1.3. Supportive Care for Hyperglycemia – Part D Only

Hyperglycemia has been observed in patients treated with LY3023414. Patients who develop hyperglycemia during the study should be treated according to the American Diabetes Association and European Association for the Study of Diabetes consensus guidelines. It is recommended to start treatment with an oral antidiabetic medication, preferably sitagliptin. Additional options may include repaglinide or low-dose sulfonylureas (with due precautions, including standard education of patients regarding the signs of hypoglycemia).

7.5.1.4. Supportive Care Guidelines for Pembrolizumab –Part E only

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined along with the dose modification guidelines in Section 7.2.4.2.6. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary, as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table JPBJ.7.13 for guidelines regarding dose modification.

Management of Infusion Reactions:

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table JPBJ.7.14.

Table JPBJ.7.14. Infusion Reaction Treatment Guidelines in Study I3Y-MC-JPBJ

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

Abbrevations: IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDS = non-steroidal anti-inflammatory drugs.

7.6. Treatment Compliance

Patient compliance with study drug(s) will be assessed at each visit by review of the patient diary, direct questioning, and counting of returned capsules/tablets. Deviation(s) from the prescribed dosage regimen should be recorded on the eCRF.

The patient must take ≥75% of the intended dose to be deemed compliant with study drug administration. Similarly, a patient may be considered noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than 125% of the prescribed amount of medication in a cycle. Dose suspensions or delays may occur and will not result in a patient being considered as noncompliant. Any missed doses during a cycle will be omitted and not replaced. In the event of a missed dose, a patient should resume and continue dosing beginning with the next scheduled dose. Potential discontinuation of a patient due to study drug noncompliance will be discussed between the investigator and the Lilly CRP before making the final determination for discontinuation. If a patient is discontinued due to study drug noncompliance, the patient may be replaced.

Pemetrexed, gemcitabine, ramucirumab, and pembrolizumab will be administered intravenously at the investigational site, under the direction of the investigator. As a result, a patient's compliance with study drug administration is ensured. Patients should attend scheduled clinic visits and must comply with study criteria under their control. Deviation(s) from the prescribed dosage regimen should be recorded on the eCRF.

For Part E, an overdose will be defined as ≥1000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

7.6.1. Evaluable Patients

Patients who withdraw from the study before receiving study drug(s) will be replaced and will not be included in the safety or efficacy assessments. Safety analyses will be conducted on all patients who have received at least 1 dose of study drug, regardless of whether they are deemed evaluable for the assessment of a dose level.

For dose escalation, any patient who is discontinued from the study before receiving at least 75% of planned doses of abemaciclib (and LY3023414 in Part D) in Cycle 1 will be deemed nonevaluable for assessment of that dose level and may be replaced unless they experience a DLT before withdrawal. Nonevaluable patients may be replaced to ensure that no fewer than 3 patients receive at least 75% of planned doses of abemaciclib in Cycle 1 at each dose level, unless enrollment to that cohort has stopped because more than 1 patient at that dose level has experienced a DLT.

Patients evaluable for PK will have received at least 1 dose of the study drug and have sufficient samples collected to allow the estimation of abemaciclib PK parameters. Patients who complete Cycle 1 of therapy but are not evaluable for PK may be replaced upon consultation with the

investigator(s) and the Lilly CRP to ensure adequate PK data collection, unless enrollment to that cohort has stopped because more than 1 patient at that dose level has experienced a DLT.

8. Safety, Pharmacokinetic, Pharmacodynamic, and Efficacy Data Collection

8.1. Safety Evaluations

The safety and tolerability of abemaciclib have been assessed in nonclinical toxicology studies, and the results from these studies are detailed in the IB. This Phase 1 study contains detailed safety monitoring that will permit initial characterization of the safety profile of abemaciclib in patients. Study procedures and their timing, including the collection of blood samples, are described in the Study Schedule (Attachment 1).

Blood samples and ECGs will be collected at the times specified in the Study Schedule (Attachment 1). Standard laboratory tests, including chemistry and hematology panels, will be performed. A serum pregnancy test will be administered if applicable. Attachment 2 lists the specific laboratory tests that will be performed for this study. Enrollment and treatment decisions may be based upon results of tests performed locally. If local laboratory tests are used for this purpose, then a duplicate specimen must be submitted to the central laboratory. Discrepancies between the local and central laboratory that may have an impact on eligibility or treatment decisions will not be considered protocol violations. When both a local and central laboratory result are obtained and there is a discrepancy in these laboratory values, the local laboratory values will be used for determining a DLT, after discussion with the study investigator(s).

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

If a patient's dosage is reduced or treatment 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.

All concomitant medications should be recorded throughout the patient's participation in the study, until conclusion of the study follow-up period.

8.1.1. Safety Data Collection and Review

Investigators are responsible for monitoring the safety of patients who have entered into 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 the patient during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to study treatment or the study, or that caused the patient to discontinue before completing the study. 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. Frequency of AE and SAE 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 JPBJ.8.1 presents a summary of AE and SAE reporting guidelines. Table JPBJ.8.1 also shows which database or system is used to store AE and SAE data.

8.1.2. 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 occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Any clinically significant findings from labs, vital sign measurements, and so on, that occur should also be reported to Lilly or its designee as an AE. Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect. Progression of the cancer under study is not considered an adverse event unless it is considered to be drug-related by the investigator and sponsor.

The investigator, monitor, and sponsor will review the collected data regularly for evidence of AEs. All patients will be assessed routinely for AEs as outlined in the Study Schedule (Attachment 1). All AEs observed will be graded using CTCAE v 4.0.

The NCI-CTCAE v 4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. All AEs observed will be graded using CTCAE v 4.0. Any minor version of CTCAE v 4.0 may be used for this study. Minor CTCAE v 4.0 updates from the NCI will not necessitate a protocol amendment. For AEs without matching terminology within the NCI-CTCAE v 4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event. Note that both CTCAE term (actual or coded) and severity grade must be selected by study site personnel and collected on the eCRF. This collection is in addition to verbatim text used to describe the AE.

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

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported. Upon documentation of pregnancy, the patient must be removed from the study and treatment with study drug must be stopped immediately. Data on fetal outcome and breastfeeding should be collected, if feasible, for regulatory reporting and drug safety evaluation. For patients in Part E, any pregnancy should be reported from the time of treatment allocation through 120 days following cessation of treatment, or 30 days following cessation of treatment if patient initiates new anticancer therapy, whichever is earlier.

For all enrolled patients, 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. While the patient is on study, site personnel will record any change in these preexisting condition(s) and the occurrence and nature of any AEs. In addition all AEs related to protocol procedures are reported to Lilly or designee.

After the informed consent form (ICF) is signed, all AEs possibly related to protocol procedures are reported to Lilly or designee via eCRF. Regardless of relatedness to study drug(s), all AEs occurring while the patient is receiving study drug must be reported to Lilly or its designee via eCRF.

Lilly or its designee will be alerted to AEs occurring from the time of treatment allocation through 30 ± 7 days after a patient is discontinued from the study only if the investigator believes that the event may have been caused by the study drug or protocol procedures.

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 eDC the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to study medication, study procedure, or other concomitant treatment or pathologies via eDC.

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

- **Related**: a direct cause and effect relationship between the study treatment and the AE is likely.
- **Possibly related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible.
- **Unrelated**: without question, the AE is definitely not associated with the study treatment.

As per Lilly's standard operating procedures all "related" and "possibly related" AEs and SAEs will be defined as related to study drug.

8.1.2.1. Serious Adverse Events

SAE collection begins after the patient has signed the informed consent document. During therapy with study drug and for 30 ± 7 days after the last dose of study drug, all SAEs will be collected regardless of relatedness to study drug or protocol procedures. Beyond 30 ± 7 days from the last dose of study drug, only ongoing or new SAEs possibly related to study drug or protocol procedures should be reported. SAE collection prior to administration of study drug(s), see Section 8.1.2.2.1.

Previously planned surgeries (prior to signing the ICF) should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

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

An SAE is any AE during this study that results in 1 of the following outcomes:

- death
- initial or prolonged inpatient hospitalization (except for study drug administration)
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- 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 SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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

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 alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Drug- or procedure-related SAEs should be followed until they resolve, are no longer considered to be drug related, become stable or return to baseline, the patient starts a new therapy, the patient dies, or the patient becomes lost to follow up.

For Part E, SAE collection begins after the patient has signed the informed consent document, during therapy, and for 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier.

If an investigator becomes aware of SAEs 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 SAEs to the sponsor, and the SAEs 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.

8.1.2.1.1. Part E: Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow-up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or procedure.

For the time period beginning at treatment/randomization through 30 days following cessation of treatment, any ECI, or follow-up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor.

An event of clinical interest is defined as: 1) an overdose of pembrolizumab (see Section 7.6) that is not associated with clinical symptoms or abnormal laboratory values or 2) an elevated AST or ALT laboratory value that is great than or equal to 3X the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2X the ULN, and at the same time, an alkaline phosphatase laboratory value that is less than 2X the ULN, as determined by way of protocol-specific laboratory testing or unscheduled laboratory testing.

8.1.2.2. Adverse Event and Serious Adverse Event Reporting

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

8.1.2.2.1. Prior to Administration of Study Drug(s)

During screening, all AEs and SAEs (regardless of relatedness to protocol procedures) are collected after the patient has signed the ICF. For patients who do not enroll in the trial (that is, have not received at least 1 dose of abemaciclib), only AEs and SAEs related to protocol procedures are required to be collected.

8.1.2.2.2. On Therapy

All AEs and SAEs, regardless of relatedness to study drug(s) or protocol procedures, occurring while the patient is receiving study drug must be reported to Lilly or its designee. A patient is considered to be receiving study drug from the time he/she receives the first dose of study drug to when he/she receives the last dose of study drug.

8.1.2.2.3. Follow-Up Visit

All AEs and SAEs, regardless of relatedness to study drug(s) or protocol procedures, occurring during the follow-up visit must be reported to Lilly or its designee. The follow-up visit starts following the last dose of study drug. At the end of the follow-up visit, the patient will be required to have specific safety assessments (Attachment 1). The timing of these safety assessments is 30 ± 7 days from the date of the last dose of study drug received.

Following the safety assessments, which mark the end of the follow-up visit, the patient will be discontinued from the study, unless there is an ongoing AE or SAE that is possibly related to study drug. In this instance, the patient should be followed in subsequent follow-up visits 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.

If it is deemed to be in the best interest of the patient to start a new anticancer treatment prior to the scheduled end of the follow-up visit, the follow-up visit duration may be shortened. In this case, the follow-up assessments should be completed prior to the initiation of the new therapy.

After the follow-up visit, AEs are not required to be reported unless the investigator feels the AEs were related to either study drug, drug delivery system, or a protocol procedure. If an investigator becomes aware of SAEs believed to be related to protocol procedures or study drug, the investigator should report the SAE to the sponsor, and the SAE will be entered in the Lilly Safety System.

8.1.2.3. Suspected Unexpected Serious Adverse Reactions

The US 21 CFR 312.32, the European Union (EU) Clinical Trial Directive 2001/20/EC, and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of suspected unexpected serious adverse reactions (SUSARs). SUSARs are SAEs that are not listed in the Development Core Safety Information in the IB and that the investigator identifies as related to study drug or procedure. The US 21 CFR 312.32, the EU 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 regulatory regulations and the associated detailed guidances.

8.1.2.4. Summary of AE/SAE Reporting Guidelines

The AE and SAE reporting guidelines are summarized in Table JPBJ.8.1.

Table JPBJ.8.1. Adverse Event and Serious Adverse Reporting Guidelines for Study I3Y-MC-JPBJ

Timing	Types of AEs/SAEs Reported	Collection Database	Lilly Safety System
Prestudy (baseline assessments) (starts at the signing of informed consent and ends just before the first dose of study drug)	Preexisting conditions All AEs All SAEs regardless of relatedness	x x x	 x
On therapy (starts at first dose of study drug[s] and ends at last dose of study drug[s])	All AEs All SAEs regardless of relatedness	x x	 x
Follow-up visit (starts following the last dose of study drugs[s] and ends when end of study safety assessments are completed [30 days (±7)[a] after last dose of study drugs(s)]).	All AEs All SAEs regardless of relatedness	x x	 x
Extension period	All AEs All SAEs regardless of relatedness	x x	 x
Extension period follow up	All AEs All SAEs regardless of relatedness	x x	 x
Subsequent follow-up visits, if necessary for patient monitoring	Ongoing AEs possibly related to study drug(s) or protocol procedures All SAEs related to protocol procedures or study drug	x x	 x
Patient no longer on study	All SAEs related to protocol procedures or study drug that the investigator becomes aware of		x

[a] Part E requires SAE collection through 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier

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

8.1.3. Other Safety Measures

8.1.3.1. Electrocardiograms

This study requires ECG monitoring at both baseline and Cycle 1 Day 15 (see Attachment 1). For each subject 12-lead digital ECGs will be obtained as single ECGs according to the Study Schedule (Attachment 1). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine during ECG collection. ECGs may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high quality records.

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, to determine whether any clinically relevant findings are present. The investigator (or qualified designee) must document his/her review of the ECG printed at the time of evaluation.

After enrollment, if a clinically significant increase in the QTcB 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.

8.1.4. Safety Monitoring

The Lilly CRP or CRS will monitor safety data throughout the course of the study. Lilly will review SAEs within time frames mandated by standard operating procedures and will review trends, laboratory analytes, and AEs at periodic intervals. Attachment 5 provides recommendations for reporting SAEs.

To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests (see Attachment 3).

8.1.4.1. 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
- discontinuation from study treatment due to a hepatic event or an abnormality of liver tests

8.1.4.2. 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.

8.1.5. Complaint Handling

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

Complaints related to concomitant drugs are reported directly to the manufacturers of those drugs in accordance with the package insert.

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

- recording a complete description of the complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed 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.

8.2. 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.

Attachment 8 provides a summary of the estimated maximum number and volume of invasive samples, for all sampling, during the study

8.2.1. 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.

8.2.2. Samples for Drug Concentration Measurements Pharmacokinetics/Pharmacodynamics

PK samples will be collected as specified in the Pharmacokinetic Sampling Schedule (Attachment 4).

8.2.2.1. Pharmacokinetic Samples

Venous blood samples from all patients will be collected to measure concentrations of abemaciclib and its metabolites (LSN2839567 [M2], LSN3106729 [M18], and LSN3106726 [M20]). Separate venous blood samples from patients will also be collected to measure concentrations of pemetrexed (Part A), gemcitabine plus its metabolite 2',2'-difluorodeoxyuridine (dFdU) (Part B), ramucirumab (Part C), and LY3023414 (Part D). Instructions for the collection and handling of blood samples will be provided by the sponsor. A maximum of 5 additional PK (blood) samples may be added or removed during the study if warranted and agreed upon by both the investigator and sponsor. For instance, if during Cycle 1 or 2, the patient is in the clinic for management of his/her disease or study-related events, additional PK (blood) samples, not to exceed 5 per patient, may be collected following documented discussions between the investigator and sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

PK plasma or serum samples will be analyzed at a laboratory designated by the sponsor. Plasma concentrations of abemaciclib and its metabolites (LSN2839567 [M2], LSN3106729 [M18], and LSN3106726 [M20]) in all study parts will be assayed using a validated liquid chromatography coupled with tandem mass spectrometry (LC/MS/MS) method. For study Parts A, B, and D,concentrations of the combination agents (pemetrexed, gemcitabine plus its metabolite dFdU, and LY3023414) will be assayed using a validated LC/MS/MS method. For study Part C, concentrations of ramucirumab will be assayed using a validated enzyme-linked immunosorbent assay (ELISA) method. Bioanalytical samples collected to measure investigational product and each combination agent concentration and metabolism, and/or protein binding, will be retained for a maximum of 2 years following last patient visit for the study. The samples will be stored at a facility designated by the sponsor. 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.

8.2.3. Samples for Tailoring Biomarkers

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.

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic biomarker samples may be genotyped and analysis may be performed to evaluate a genetic association with response to study medication. 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.

A FFPE archived tumor tissue sample or 15 unstained slides, cut at 5 microns, and 1 H&E slide containing tumor specimen will be requested if available and used for exploratory analysis. Due diligence should be used to make sure that 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.

For Part E, submission of FFPE tumor tissue sample blocks are preferred. If submitting unstained slides, the slides should be freshly cut and submitted to the testing laboratory within 14 days from site slide sectioning date otherwise a new specimen will be requested.

The samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drug.

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

8.2.4. Samples for Immunogenicity Research

Blood samples for the determination of anti-ramucirumab antibodies are to be collected at the specified time points, including at baseline (-14 days), prior to the ramucirumab infusion on Day 1 in Cycle 3 and Cycle 5, and at the 30-day (±7 days) follow-up visit (Attachment 1). Additionally, blood samples for the determination of ramucirumab concentration are to be collected at the 30-day (±7 days) follow-up visit (Attachment 1).

In the event of an investigational product-related infusion reaction, every effort should be made to collect a blood sample for an anti-ramucirumab antibody determination, as well as a blood sample for ramucirumab serum concentration, as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event.

Anti-ramucirumab antibodies will be determined using a validated immunoassay at a laboratory designated by the sponsor or designee. Bioanalytical samples collected to measure immunogenicity will be retained for a maximum of 5 years following last patient visit for the study.

Samples may be stored for a maximum of 15 years following last patient visit for the trial at a facility selected by the sponsor to enable further analysis of immune responses to ramucirumab. The duration allows the sponsor to respond to regulatory requests related to ramucirumab.

8.3. Efficacy Evaluations

A secondary objective of the study is to document the antitumor activity of abemaciclib when given in combination with multiple therapies. Refer to Attachment 1 for details regarding the timing of specific efficacy measures.

Each patient will be assessed by 1 or more of the following radiologic tests for tumor measurement:

- Computed tomography (CT) scan
- Magnetic resonance imaging (MRI)
- Chest x-ray

Each patient's full extent of disease will also be assessed with:

- Tumor measurement by RECIST 1.1 or irRECIST, refer to Attachment 9 (Eisenhauer et al. 2009)
- Evaluation of tumor markers, if indicated.
- Evaluation of PS (refer to the ECOG scale, Attachment 6).

All lesion assessments, whether by physical exam or radiological methods, should be repeated by the same method at least 4 weeks following the initial observation of an objective response to ensure response confirmation. If a patient is discontinued from the study, repeat radiology may be omitted if there are clear clinical signs of progressive disease.

8.4. Health Outcomes

8.4.1. Patient-Reported Outcomes

The health outcomes research goal is to explore and characterize patient-reported pain ("worst pain"), disease-related symptoms, and interference items as measured by the MDASI-LC. The patient-reported questionnaire should be completed by patients when a language translation is available in which the patient is fluent or literate.

At each time point identified in the Study Schedule (Attachment 1), the MDASI-LC should be administered to the patient prior to extensive interaction with site staff and study drug administration.

Item responses are captured through the use of 11-point numeric rating scales anchored at 0 (*not present* or *does not interfere*) and ranged through 10 (*as bad as you can imagine* or *interfered completely*). The MDASI–LC is a self-reported lung cancer instrument (Mendoza et al. 2011) that consists of 22 items covered by one of the following dimensions:

- Pain scale (1 item)
- Fatigue scale (1 item)
- Core symptom scale (11 total items addressing nausea, disturbed sleep, distress, shortness of breath, remembering things, lack of appetite, drowsy, dry mouth, sad, vomiting, numbness/tingling)
- Lung cancer symptoms (3 items: coughing, constipation, sore throat)
- Interference with mood or functional status (6 items: general activity, mood, work, relations with other people, walking, enjoyment of life)

The MDASI-LC recall period is 24 hours, and typical completion time for this instrument is 5 to 10 minutes.

8.4.2. Resource Utilization

Investigators will be asked to report the use of concomitant medications (in particular, analgesics), radiation therapy, surgery, and hospitalization days. This information should be collected during the study and through the 30-day (±7 days) follow-up visit.

8.5. Procedure/Sampling Compliance

Every attempt will be made to enroll patients who have the ability to understand and comply with instructions. Noncompliant patients may be discontinued from the study.

The collection times of safety assessments, PK samples, and efficacy measurements are given as targets, to be achieved within reasonable limits. The scheduled time points may be subject to minor alterations; however, the actual collection time must be correctly recorded on the eDC.

The scheduled collection times may be modified by the sponsor based on analysis of the safety and PK information obtained during the study. Any major modifications that might affect the conduct of the study, patient safety, and/or data integrity will be detailed in a protocol amendment.

9. Data Management Methods

9.1. 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/or 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 the sponsor, applicable regulatory agencies, and applicable institutional review boards (IRB)/ERBs with direct access to the original source documents.

9.2. Data Capture Systems

9.2.1. Case Report Form

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

Any data for which 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.

For data handled by a data management third-party organization (TPO), eCRF data and some or all data that are related will be managed and stored electronically in the TPO system. Subsequent to the final database lock, validated data will be transferred to Lilly's data warehouse, using standard Lilly file transfer processes.

For data handled by the sponsor internally, eCRF data and some or all data that are related will be managed by the sponsor and stored electronically in the sponsor's system.

9.2.2. Ancillary Data

Data managed by a central vendor will be stored electronically in the central laboratory's database system. Data will subsequently be transferred from the central vendor to the Lilly system and TPO system.

Bioanalytical data will be stored electronically in the bioanalytical laboratory's database. Data will subsequently be transferred from the bioanalytical laboratory to the Lilly system and TPO system.

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

10. Data Analyses

10.1. General Considerations

Approximately 150 patients may be enrolled in this multicenter, open-label, dose-escalation, 5-part, Phase 1b study with dose escalation followed by dose confirmation. Patients will be enrolled into 1 of 5 study parts based on prior therapy or histology. During the dose-escalation portion of study Parts A, B, and C, 6 to 12 patients will be enrolled; Part D, 18 to 36 patients will be enrolled; and Part E, 9 to 18 patients will be enrolled. During the dose-confirmation portion of study Parts A, B, C, D, and E, up to 12 patients will be enrolled. Part C expansion cohort will evaluate alternate dosing schedules in approximately 12 to 18 patients. Additionally, for study Parts A, B, C, and E, following the confirmation phase, if clinical data indicate preliminary efficacy, approximately 12 more patients will be enrolled to obtain clinical evidence for efficacy.

Statistical analysis of this study will be the responsibility of the sponsor. The analyses for this study will be descriptive, except for possible exploratory analysis as deemed appropriate. Data analyses will be provided by study part, dose group, and for all study patients combined wherever appropriate. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of patients, frequency, and percentages. Missing data will not be imputed. Refer to the statistical analysis plan for this study for further detail.

The interpretation of the study results will be the responsibility of the investigator with the Lilly CRP, pharmacokineticist, and statistician. The CRP and statistician will also be responsible for the appropriate conduct of an internal review for both the final study report and any study-related material to be authorized by Lilly for publication.

Exploratory analyses of the data not described below will be conducted as deemed appropriate.

10.2. Patient Disposition

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 their discontinuation will be given.

10.3. Patient Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics will be reported
- Baseline disease characteristics
- Prior disease-related therapies
- Concomitant medications

Other patient characteristics will be summarized as deemed appropriate.

10.4. Safety Analyses

All patients who receive at least 1 dose of abemaciclib will be evaluated for safety and toxicity. AE terms and severity grades will be assigned by the investigator using CTCAE, version 4.0.

Safety analyses will include summaries of the following:

- AEs, including severity and possible relationship to study drug
- dose adjustments
- vital signs
- weight
- DLTs
- laboratory values and ECGs

10.5. Pharmacokinetic Analyses

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

PK parameter estimates will be computed for abemaciclib, its metabolites, and whenever possible, for other anticancer agents used in the combination (pemetrexed, gemcitabine, ramucirumab, and LY3023414). These PK parameters will be computed by standard noncompartmental methods of analysis using WinNonlin Professional Edition on a computer that meets or exceeds the minimum requirements for this program.

The primary parameters for analysis will be maximum concentration (C_{max}) and area under the concentration-time curve ($AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$). Other noncompartmental parameters, such as time of half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (V/F) may be reported.

In addition to a standard noncompartmental assessment, the plasma concentration data of abemaciclib will also be analyzed by means of a compartmental approach using NONMEM. Plasma data from all patients will be pooled for analyses to determine the compartmental PK parameters and between- and within-patient variability. Covariate analysis will be also performed. Once a structural and statistical model has been established, the effect of patient factors will be assessed. Covariate data distributions will be assessed.

Additional exploratory analyses will be performed if warranted by data, and other validated PK software programs (for example, NONMEM) may be used if appropriate and approved by Global Pharmacokinetic management. The version of any software used for the analysis will be documented, and the program will meet the Lilly requirements of software validation.

10.6. Efficacy

The study was not designed to make an efficacy assessment. However, any tumor response data will be tabulated and summarized where appropriate.

10.7. Health Outcomes

Change from baseline in MDASI-LC scores will be listed and summarized for each study part at each postbaseline time point specified in the Study Schedule (Attachment 1). Resource utilization will be described as appropriate.

10.8. Interim Analyses

Since this is a dose-finding study, data will be reviewed on a cohort-by-cohort basis during the study, until the MTDs are determined for each combination therapy. The purpose of these cohort-by-cohort reviews is to evaluate the safety data at each dose level and determine if a DLT has been observed that would suggest MTD for each combination therapy has been met or exceeded. The investigators and the Lilly study team will make the determination regarding dose escalation based upon their review of the safety and tolerability data as described in this protocol.

During the dose-confirmation portion of each study part, interim analyses may be conducted to review available safety, PK, PD, and efficacy data once enrollment to that particular part (A, B, C, D, or E) has completed and all patients in that part have either completed 2 cycles of therapy or discontinued from the treatment.

11. Informed Consent, Ethical Review, and Regulatory Considerations

11.1. 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 study in a timely manner.

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 potential risks and benefits of participating in the study and desires to participate in the study.

The investigator is ultimately responsible for ensuring that informed consent is given by each patient or legal representative before the study is started. 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.

11.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at investigative sites(s). All ICFs must be compliant with the 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 site(s). The ERB(s) will review the protocol as required.

The study site's ERB(s) should be provided with the following:

- the current IB or package labeling (for example, Patient Information Leaflet, Package Insert, or Summary of Product Characteristics) and updates during the course of the study
- ICF
- relevant curricula vitae

11.3. Regulatory Considerations

This study will be conducted in accordance with:

1) 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

2) the International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) Guideline [E6]

3) applicable laws and regulations.

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

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

11.4. Investigator Information

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

11.5. 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.

11.6. Final Report Signature

The final report coordinating investigator or designee will sign the 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.

The investigator with the most enrolled patients will serve as the final report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the final report coordinating investigator.

The sponsor's responsible medical officer and statistician will 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.

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Attachment 1. Protocol JPBJ 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	Serum pregnancy test required for woman of childbearing potential. Females with childbearing potential must have a negative serum pregnancy test within 7 days of the first dose of study drug (ie, Day -7 to Day -1). Part E female patients of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
Medical history		X		Including alcohol/tobacco use and other relevant habits assessments.
Physical exam		X		Each physical exam conducted for patients in Part D should also include discussion with the patient about any vision changes since study entry.
Vital signs and weight		X		Including temperature, blood pressure, pulse rate, respiration rate.
Height		X		
Performance status		X		
Concomitant medications		X		
CTCAE version 4.0 grading (preexisting conditions)		X		To be reported only after study eligibility is confirmed. See Section 8.1.2 for reporting expectations. Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly safety system. Obtain only after study eligibility is confirmed.
Radiological tumor assessment	X			These scans will be performed and reviewed locally.
Tumor measurement (palpable or visible)		X		
Tumor markers		X		
Archived tumor biopsy	X			FFPE tumor tissue requested after study eligibility is confirmed.
Chest x-ray	X			May be omitted in patients having a chest CT for their radiological tumor assessment.
ECG		X		ECGs will be performed locally. This baseline ECG (no replicates required) is required to establish eligibility for this study.
Hematology		X		For central versus local labs, refer to the Clinical Laboratory Tests (Attachment 2).
Serum chemistry		X		For all study parts, baseline CrCl will done based on local lab. See Attachment 2.
HbA1c		X		Part D only
Thyroid Function		X		Part E only. Performed centrally. Thyroid function should be evaluated at baseline (Day -14). See Attachment 2.
Coagulation Parameters		X		Part E only: Performed locally. Coagulation parameters should be evaluated at baseline (Day -14). See Attachment 2.

Relative Day Prior to Day 1 of Cycle 1	≤28	≤14	≤7	Comments
Immunogenicity		X		For Part C only: Immunogenicity samples are to be drawn at baseline (Day -14).
Urinalysis		X		Part C and D only. Performed locally. If urine dipstick or routine analysis indicates proteinuria ≥2+, a 24-hour urine collection (to assess protein) must be obtained.
Brain MRI/CT	X			Part C only: Patients will have a baseline brain MRI or CT to rule out evidence of CNS metastases.
MDASI-LC		X		MDASI-LC should be administered at baseline (Day -14 to Day -1). Patients should complete before interaction with site staff.

Abbreviations: CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; FFPE = formalin-fixed paraffin-embedded; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; Meds = medications; MDASI-LC = MD Anderson Symptom Inventory- Lung Cancer; MRI = magnetic resonance imaging; PK = pharmacokinetic; PD = pharmacodynamic.

During and Poststudy Assessments

Cycle/Visit	Cycle 1			Cycle 2 and Beyond[a] (if Applicable)		Follow-Up[b]
Relative Day within a Cycle	**1**	**8 ± 2**	**15 ± 2**	**1**	**8 ± 2**	
Medical history	X			X		X
Physical exam	X	X		X		X
Vital signs and weight (temperature, pulse rate, blood pressure, respiratory rate)	X	X		X		X
Performance status	X			X		X
CTCAE version 4.0 grading (see Section 8.1.2)	X			X		X[c]
Concomitant medications	X			X		X
Tumor measurement (palpable and visible) (see Section 8.3)	X			X		X
ECG[d]			X			
Abemaciclib therapy[e]	Daily every 12 hours					
Pemetrexed therapy[f]	X			X		
Gemcitabine therapy[g]	X	X		X	X	
Ramucirumab therapy[h]	X	X		X	X	
LY3023414 therapy[i]	Daily every 12 hours					
Pembrolizumab therapy[j]	X			X		
Radiological tumor assessment[k]				X		X[l]
Urinalysis[m]				X		
Hematology[n]	X	X		X	X	X
Serum chemistry[n]	X	X		X	X	X
Thyroid Function[o]	X			X		X
Coagulation Parameters[p]				X		X
Blood PK sampling[q]	X	X	X	X		
Immunogenicity[r]				X		X
DNA genotyping blood sample (stored)	X[s]					
MDASI-LC[t]				X		X

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; LLN = lower limit of normal; PK = pharmacokinetic; PD = pharmacodynamic; PT/INR = prothrombin time / International Normalized Ratio; SAE = serious adverse event.

During and Poststudy Assessments (continued)

[a] Study procedures are to be completed on Day 1 of every cycle starting with Cycle 2 Day 1 (±2 days). Patients may continue to receive study treatment beyond 3 years if they are benefiting from abemaciclib or until they meet the criteria for discontinuation as cited in Section 6.3. Data collected will include: AEs, SAEs, study drug dosing and dose reductions as cited in Section 6.2.2.

[b] Follow-up starts the day after the patient and the investigator agree that the patient will no longer continue study treatment and ends when final safety assessments are completed 30 days (±7) after last dose of study drug.

[c] All drug- or procedure-related AEs and SAEs should be followed until they resolve, are no longer considered to be drug- or procedure-related, become stable or return to baseline, the patient starts a new therapy, the patient dies, or the patient becomes lost to follow up. Frequency of evaluation is left to the judgment of the investigator. Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly safety system.

[d] Local ECGs (no replicates required) should be obtained at baseline (Day -14 to Day -1) and at Cycle 1 Day 15.

[e] Abemaciclib is to be administered every 12 hours on Days 1 through 21 of each cycle. Patients should not consume food beginning 1 hour before and ending 1 hour after taking study drug.

[f] For Part A, pemetrexed is to be administered on Day 1 of a 21-day cycle.

[g] For Part B, gemcitabine is to be administered on Days 1 and 8 of a 21-day cycle.

[h] For Part C, ramucirumab is to be administered on Day 1 of a 21-day cycle. Following dose confirmation, the expansion cohorts will evaluate alternate dosing schedule on Days 1 and 8 of a 21-day cycle.

[i] For Part D, LY3023414 is to be administered every 12 hours on Days 1 through 21 of each cycle. LY3023414 may be taken *with or without food*. On clinic days with postdose PK sampling (Day 1 of Cycle 1 and 2), patients are permitted to eat a light snack at least 2.5 hours prior to the study drug dosing, but are then asked to fast until after the 4 hour postdose samples are collected. Glucose testing will be done via Accu-Chek or equivalent (see Attachment 2 and Attachment 4).

[j] For Part E, pembrolizumab is to be administered on Day 1 of a 21-day cycle.

[k] Imaging studies are performed locally. Radiological assessment is performed at baseline (Day -28 to Day -1), then on Day 1 (or up to 7 days before Day 1) of every other cycle beginning with Cycle 3.

[l] If a patient is discontinued from the study, repeat radiology may be omitted if progressive disease can be documented quantitatively with clinical measurements (see Section 8.3).

[m] Part C and D only. Performed locally. Routine dipstick measurements within 72 hours prior to treatment on Day 1 of every second cycle (screening period, before Cycle 3, Cycle 5, and every 2 cycles thereafter) and, if clinically indicated, microscopic analysis. If urine dipstick or routine analysis indicates proteinuria ≥2+, a 24-hour urine collection (to assess protein) must be obtained.

[n] For central versus local labs, refer to the Clinical Laboratory Tests (see Attachment 2). For Part D only, HbA1c, triglycerides, and cholesterol will be drawn on Day 1 of every third cycle beginning with Cycle 3. For Part E only, Days 1 chemistry and hematology labs will be drawn for all cycles and Day 8 chemistry and hematology will be drawn for the first 8 treatment cycles.

[o] Thyroid studies will performed every other cycle following Cycle 2 (see Attachment 2).

[p] PT/INR and aPTT should be collected at Screening and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory (see Attachment 2).

[q] PK sampling should be performed during Cycle 1 and Cycle 2. For complete details, see PK schedule attachment (Attachment 4).

During and Poststudy Assessments (concluded)

r Part C only: Immunogenicity samples are to be drawn at baseline (Day -14) and preinfusion of ramucirumab (Part C) on Cycle 3 and Cycle 5. Immunogenicity samples will also be drawn at the follow-up visit, 30 days (±7 days) after last dose of study drug. In the event of an infusion-related reaction, blood samples for both PK and immunogenicity analysis will be collected as close to the onset of the reaction as possible, at the resolution of the event, and 30 days following the event.

s Obtain only after study eligibility is confirmed.

t MDASI-LC should be administered at baseline (Day -14 to Day -1), on Day 1 of every cycle beginning with Cycle 2, and at follow up. Patients should complete before interaction with site staff.

Extension Period

Visit	Study Treatment 501-5XX	Follow-Up[a] 901	
Procedure[b]			**Instructions**
AE collection	X	X	CTCAE Version 4.0
Administer study drug	X		

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events.

a Extension Period follow-up begins the day after the patient and the investigator agree that the patient will no longer continue treatment in the Extension Period and lasts approximately 30 days. No follow-up will be performed for a patient who withdraws informed consent.

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

Attachment 2. Protocol JPBJ 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 + bands)	Total protein
Lymphocytes	Blood urea nitrogen (BUN)
Monocytes	Creatinine[a, b, d]
Eosinophils	Alkaline phosphatase
Basophils	Alanine aminotransferase (ALT)
Platelets	Aspartate aminotransferase (AST)
	Total bilirubin and direct bilirubin
Urinalysis (Part C and D only)[b, c]	
Color	Glucose, fasting (Part D only)[b, e]
pH	HBA1c (Part D only)[a]
Specific gravity	Cholesterol (Part D only)[a]
Protein	Triglyceride (Part D only)[a]
Glucose	
Ketones	Serum pregnancy test (females of child bearing
Blood	potential only)[b] (local only)
Urobilinogen	
Bilirubin	Triidothyronine (T3) or Free Triidothyronine (FT3)
	(Part E only) [a,f]
Nitrites	Free thyroxine (FT4) (Part E only) [a,f]
Leukocyte esterase	Thyroid stimulating hormone (TSH) (Part E only) [a,f]
Microscopic evaluation of urine sediment (for	PT/INR (Part E only) [b]
casts and crystals)	aPTT (Part E 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.

c Urine dipstick or routine analysis indicate proteinuria ≥2+ at baseline and/or while receiving study drug a 24 hour urine collection (to assess protein) must be obtained.

d Creatinine clearance (CrCl) requires the use of local creatinine result (see Attachment 7). Creatinine will be assayed by both central and local laboratories when used to calculate CrCl, otherwise only to be drawn centrally.

e Glucose testing will be performed locally via Accu-Chek or equivalent.

f If TSH is not within normal limits at baseline, the subject may still be eligible if total T3 or free T3 and free T4 are within normal limits.

Attachment 3. Protocol JPBJ 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 (CRP).

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	Hepatic Coagulation[a]
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils, segmented + 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	Anti-nuclear antibody[a]
AST	
GGT	Anti-smooth muscle antibody[a]
CPK	

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

a Assayed by Lilly-designated or local laboratory.

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

Attachment 4. Protocol JPBJ Pharmacokinetic Sampling Schedule

Pharmacokinetic Sampling Schedule

Part A – Abemaciclib with Pemetrexed

PK Sample Number	Cycle and Day	Dosing of Study Drugs		Sampling Time for PK from Blood (Study Drugs)[a]
1	C1D1	Abemaciclib	Pemetrexed	Predose (0 h)
2	C1D1			Immediately after abemaciclib dose
3	C1D1			1 h ± 10 min after abemaciclib dose
4	C1D1			2 h ± 10 min after abemaciclib dose
5	C1D1			4h ± 20 min after abemaciclib dose
6	C1D1			6 h ± 20 min after abemaciclib dose
7	C1D1			8 h ± 20 min after abemaciclib dose
8	C1D1			10 h ± 20 min after abemaciclib dose[b]
9	C1D8	Abemaciclib		Predose (0 h)
10	C1D15	Abemaciclib		Predose (0 h)
11	C2D1	Abemaciclib	Pemetrexed	Predose (0 h)
12	C2D1			1 h ± 10 min after abemaciclib dose
13	C2D1			2 h ± 10 min after abemaciclib dose
14	C2D1			4 h ± 20 min after abemaciclib dose
15	C2D1			6 h ± 20 min after abemaciclib dose
16	C2D1			8 h ± 20 min after abemaciclib dose
17	C2D1			10 h ± 20 min after abemaciclib dose[b]

Abbreviations: C = cycle; D = day; h = hour; min = minute; PK = pharmacokinetic.

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

[b] To omit the collection of the 10 hour "postdose" PK sample for that day does not constitute a protocol violation.

Part B – Abemaciclib with Gemcitabine

PK Sample Number	Cycle and Day	Dosing of Study Drugs		Sampling Time for PK from Blood (Study Drugs)[a]
1	C1D1	Abemaciclib	Gemcitabine	Predose (0 h)
2	C1D1			Immediately after abemaciclib dose
3	C1D1			1 h ± 10 min after abemaciclib dose
4	C1D1			2 h ± 10 min after abemaciclib dose
5	C1D1			4h ± 20 min after abemaciclib dose
6	C1D1			6 h ± 20 min after abemaciclib dose
7	C1D1			8 h ± 20 min after abemaciclib dose
8	C1D1			10 h ± 20 min after abemaciclib dose[b]
9	C1D8	Abemaciclib	Gemcitabine	Predose (0 h)
10	C1D15	Abemaciclib		Predose (0 h)
11	C2D1	Abemaciclib	Gemcitabine	Predose (0 h)
12	C2D1			1 h ± 10 min after abemaciclib dose
13	C2D1			2 h ± 10 min after abemaciclib dose
14	C2D1			4 h ± 20 min after abemaciclib dose
15	C2D1			6 h ± 20 min after abemaciclib dose
16	C2D1			8 h ± 20 min after abemaciclib dose
17	C2D1			10 h ± 20 min after abemaciclib dose[b]

Abbreviations: C = cycle; D = day; h = hour; min = minute; PK = pharmacokinetic.

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

[b] To omit the collection of the 10 hour "postdose" PK sample for that day does not constitute a protocol violation.

Part C – Abemaciclib with Ramucirumab

PK Sample Number	Cycle and Day	Dosing of Study Drugs		Sampling Time for PK from Blood (Study Drugs)[a]
1	C1D1	Abemaciclib	Ramucirumab[c]	Predose (0 h)
2	C1D1			Immediately after abemaciclib dose
3	C1D1			1 h ± 10 min after abemaciclib dose
4	C1D1			2 h ± 10 min after abemaciclib dose
5	C1D1			4h ± 20 min after abemaciclib dose
6	C1D1			6 h ± 20 min after abemaciclib dose
7	C1D1			8 h ± 20 min after abemaciclib dose
8	C1D1			10 h ± 20 min after abemaciclib dose[b]
9	C1D8	Abemaciclib	Ramucirumab[c]	Predose (0 h)
10	C1D15	Abemaciclib		Predose (0 h)
11	C2D1	Abemaciclib	Ramucirumab[c]	Predose (0 h)
12	C2D1			1 h ± 10 min after abemaciclib dose
13	C2D1			2 h ± 10 min after abemaciclib dose
14	C2D1			4 h ± 20 min after abemaciclib dose
15	C2D1			6 h ± 20 min after abemaciclib dose
16	C2D1			8 h ± 20 min after abemaciclib dose
17	C2D1			10 h ± 20 min after abemaciclib dose[b]

Abbreviations: C = cycle; D = day; h = hour; min = minute; PK = pharmacokinetic.

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

[b] To omit the collection of the 10 hour "postdose" PK sample for that day does not constitute a protocol violation.

[c] For Part C dose escalation (C1, C2) and dose confirmation (C3), ramucirumab should only be administered on Day 1 of the 21-day cycle. For Part C expansion cohort (C4, C5, and C6), ramucirumab should be administered on Days 1 and 8 of a 21-day cycle. See Table JPBJ.7.3.

Part D – Abemaciclib with LY3023414

PK Sample Number	Cycle and Day	Dosing of Study Drugs		Blood Glucose[c]	Sampling Time for PK from blood (Study Drugs)[a]
1	C1D1	Abemaciclib	LY3023414	X	Predose (0 h)[c]
2	C1D1			X	Immediately after combination[c]
3	C1D1			X	1 h ± 10 min after combination[c]
4	C1D1			X	2 h ± 10 min after combination[c]
5	C1D1			X	4h ± 20 min after combination[c]
6	C1D1			X	6 h ± 20 min after combination[c]
7	C1D1			X	8 h ± 20 min after combination[c]
8	C1D1				10 h ± 20 min after combination[b]
9	C1D8[c]	Abemaciclib	LY3023414	X	Predose (0 h)
10	C1D15[c]	Abemaciclib	LY3023414	X	Predose (0 h)
11	C2D1[c]	Abemaciclib	LY3023414	X	Predose (0 h)
12	C2D1			X	1 h ± 10 min after combination[c]
13	C2D1			X	2 h ± 10 min after combination[c]
14	C2D1			X	4 h ± 20 min after combination[c]
15	C2D1			X	6 h ± 20 min after combination[c]
16	C2D1			X	8 h ± 20 min after combination[c]
17	C2D1				10 h ± 20 min after combination[b]

Abbreviations: C = cycle; D = day; h = hour; min = minute; PK = pharmacokinetic.

a Samples of approximately 2 mL of whole blood will be drawn for measurement of abemaciclib and its metabolites concentrations. Separate samples of approximately 2 mL of whole blood will be drawn for measurement of LY3023414 concentrations. Abemaciclib and LY3023414 will be administered together, approximately at the same time.

b To omit the collection of the 10 hour "postdose" PK sample for that day does not constitute a protocol violation.

c Additional local blood glucose measurements to be performed. Patients are permitted to eat a light snack at least 2.5 hours prior to the morning study drug dosing on these days, but are then asked to fast until after the 4 hour postdose samples are collected. High-sugar foods (for example, sugary breakfast cereals, fruit juices, coffee with sugar, etc.) should be avoided for this light snack until after predose collection.

Part E – Abemaciclib with Pembrolizumab

PK Sample Number	Cycle and Day	Dosing of Study Drugs		Sampling Time for PK from blood (Abemaciclib)[a]
1	C1D1	Abemaciclib	Pembrolizumab	Predose (0 h)[b]
2	C1D1			Immediately after abemaciclib dose
3	C1D1			1 h ± 10 min after abemaciclib dose
4	C1D1			2 h ± 10 min after abemaciclib dose
5	C1D1			4h ± 20 min after abemaciclib dose
6	C1D1			6 h ± 20 min after abemaciclib dose
7	C1D1			8 h ± 20 min after abemaciclib dose
8	C1D1			10 h ± 20 min after abemaciclib dose[c]
9	C1D8	Abemaciclib		Predose (0 h)
10	C1D15	Abemaciclib		Predose (0 h)
11	C2D1	Abemaciclib	Pembrolizumab	Predose (0 h)
12	C2D1			1 h ± 10 min after abemaciclib dose
13	C2D1			2 h ± 10 min after abemaciclib dose
14	C2D1			4 h ± 20 min after abemaciclib dose
15	C2D1			6 h ± 20 min after abemaciclib dose
16	C2D1			8 h ± 20 min after abemaciclib dose
17	C2D1			10 h ± 20 min after abemaciclib dose[c]

Abbreviations: C = cycle; D = day; h = hour; min = minute; PK = pharmacokinetic.

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

b The predose samples should be taken prior to abemaciclib and pembrolizumab dosing. The date and time of abemaciclib dose and pembrolizumab infusion start and stop time should be recorded on the appropriate forms. The date and time of all PK samples should be recorded on the appropriate forms.

c To omit the collection of the 10 hour "postdose" PK sample for that day does not constitute a protocol violation.

Attachment 5. Protocol JPBJ Recommendations for Reporting Serious Adverse Events

Recommendations for Reporting Serious Adverse Events

When contacting Lilly to report a SAE, please have the following information available:

Patient Demographics

- patient identification (number), sex, date of birth, origin, height, and weight

Study Identification

- full trial protocol number, investigator's name, investigator's number

Study Drug

- drug code or drug name, unit dose, total daily dose, frequency, route, start dose, cycle details, start date, and last dose date (if applicable)

Adverse Event

- description, date of onset, severity, treatment (including hospitalization), action taken with respect to study drug, clinical significance, test and procedure results (if applicable)

Relationship to Study Drug and Protocol Procedures

Concomitant Drug Therapy

- indication, total daily dose, duration of treatment, start date, action taken

In Case of Death

- cause, autopsy finding (if available), date, relationship to study drug and protocol procedures.

Attachment 6. Protocol JPBJ ECOG Performance Status

ECOG Performance Status

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

Source: Oken et al. 1982.

Attachment 7. Protocol JPBJ Creatinine Clearance Formula

Note: This formula is to be used for calculating CrCl from **local laboratory results only.**

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age^{a}}) \times (\mathbf{wt}) \times \mathbf{0.85}\ \text{(if female), or} \times \mathbf{1.0}\ \text{(if male)}}{\mathbf{72} \times \mathbf{serum\ creatinine}\ (mg/dL)}$$

For serum creatinine concentration in μmol/L:

$$\text{CrCl (mL/min)} = \frac{(\mathbf{140 - age^{a}}) \times (\mathbf{wt}) \times \mathbf{0.85}\ \text{(if female), or} \times \mathbf{1.0}\ \text{(if male)}}{\mathbf{0.81} \times \mathbf{serum\ creatinine}\ (\mu mol/L)}$$

Abbreviation: CrCl = creatinine clearance

[a] age in years, weight (wt) in kilograms.

Source: Cockcroft and Gault 1976.

Attachment 8. Protocol JPBJ Sampling Summary

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

Protocol I3Y-MC-JPBJ Sampling Summary

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Study qualification[a]	Blood	6 mL	3	18 mL
Health monitoring/Safety monitoring (may be more than 1 tube)[b]	Blood	24 mL/Cycle 1 12mL/Cycle 2-n 5.5mL/ Cycles 2-8, Day 8 12mL/Follow up	6 3 7 3	182.5 mL
Archived formalin-fixed, paraffin-embedded tumor tissue	Tissue	5 micron	15 slides	75 micron
Drug concentration of abemaciclib for all patients in trial	Blood	2 mL	17	34 mL
Drug concentration of pemetrexed for all patients in Part A	Blood	2 mL	17	34 mL
Drug concentration of gemcitabine for all patients in Part B	Blood	2 mL	17	34 mL
Drug concentration of ramucirumab for all patients in Part C	Blood	2 mL	17	34 mL
Drug concentration of LY3023414 for all patients in Part D	Blood	2 mL	17	34 mL
Tailoring biomarkers	Blood	9 mL	1	9 mL
Immunogenicity (Part C patients on ramucirumab only)	Blood	5 mL	4	20 mL
Hepatic monitoring[b]	Blood	3 - 30 mL		-

[a] Additional samples may be drawn if needed for safety purposes.
[b] 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 9. Protocol JPBJ RECIST Criteria 1.1

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

Measurability of Tumor at Baseline

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

Measurable

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

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

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

Nonmeasurable

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

Special Considerations for Lesion Measurability

Bone Lesions:

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

Cystic Lesions:

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

Lesions with Prior Local Treatment:

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

Baseline Documentation of Target and Nontarget Lesion

Target Lesions

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

Nontarget Lesions

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

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

Specifications by Methods of Measurement

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

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

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

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

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

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

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

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

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

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

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

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

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

Response Criteria

Evaluation of Target Lesions

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

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

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

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

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

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

Evaluation of Nontarget Lesions

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

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

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

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

Evaluation of Best Overall Response

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

Time Point Response

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

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

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

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

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

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

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

Abbreviations: CR = complete response; NE = inevaluable.

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

Frequency of Tumor Re-Evaluation

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

Confirmatory Measurement/Duration of Response

Confirmation:
The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in *nonrandomized trials* where response (CR/PR) is the primary end point. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontargets is not required.

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

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

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

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

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

Independent Review of Response and Progression

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

irRECIST Assessment of Disease (Part E only)

As noted above, if tumor imaging shows initial disease progression, the study site may elect to continue treatment, repeat imaging ≥ 4 weeks later and assess tumor response or confirmed progression per irRECIST.

irRECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs. irRECIST will be used by site investigator/local radiology review to assess tumor response and progression, and make treatment decisions. These data will be collected in the clinical database.

Table 3. Imaging and Treatment after First Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD by RECIST 1.1	Repeat imaging at ≥ 4 weeks at site to confirm PD	May continue study treatment at the local site Investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST.	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with sponsor)	No additional imaging required	N/A

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
Repeat tumor imaging shows SD, PR or CR by irRECIST by the local site	Continue regularly scheduled imaging assessments	Continue study treatment at the local site Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the every X week (XX ± 7 days) imaging schedule for the first year and Y weeks (XX ± 7 days) after the first year.

- In determining whether or not the tumor burden has increased or decreased, local study site investigators should consider all target lesions as well as non-target lesions (please refer to irRECIST TIP Sheet). Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation.

- For a **clinically stable** subject with first radiologic evidence of progressive disease by RECIST 1.1 (i.e., **unconfirmed progression of disease**), it is at the discretion of the site investigator to continue treating the subject with the assigned treatment per protocol until progression of disease is confirmed at least 28 days from the date of the scan first suggesting PD. If radiologic progression is confirmed by subsequent scan then the subject will be discontinued from trial treatment. If radiologic progression is not confirmed by irRECIST per the site, then the subjects may continue on treatment and follow the regular imaging schedule intervals until progression is confirmed at a later time point by the site.

    - **NOTE**: If a subject has confirmed radiographic progression (i.e. 2 scans at least 4 weeks apart demonstrating progressive disease) per irRECIST, but the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue treatment may be considered following consultation with the Sponsor. In this case, if treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Table 3.

- Any subject deemed **clinically unstable** should be discontinued from trial treatment at 1st radiologic evidence of PD and is not required to have repeat imaging for PD confirmation.

- In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every Y weeks (XX days ± 7 days), until (1) the start of new anti-cancer treatment, (2) disease progression (3) death, or (4) the end of the study, whichever occurs first.

irRECIST data will be collected in the clinical database.

Attachment 10. Protocol JPBJ Inducers, 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 these medications if clinically indicated.

Inducers of CYP3A
Carbamazepine
Dexamethasone[a]
Phenobarbital/phenobarbitone
Phenytoin
Rifapentine
Rifampin
Rifabutin
St. John's wort

[a] Important note: All patients may receive supportive therapy with dexamethasone, preferably ≤7 days, if clinically indicated.

Strong inhibitors of CYP3A
Aprepitant
Ciprofloxacin
Clarithromycin
Diltiazem
Erythromycin
Fluconazole
Itraconazole
Ketoconazole
Nefazodone
Verapamil

Cytochrome P450 Substrates with Narrow Therapeutic Range

Cytochrome P450	Substrate
CYP1A2	Theophylline Tizanidine
CYP2C9	Warfarin[a] Phenytoin
CYP2D6	Thioridazine Pimozide
CYP3A	Alfentanil Astemizole Cisapride Cyclosporine Dihydroergotamine Ergotamine Fentanyl Pimozide Quinidine Sirolimus Tacrolimus Terfenidine

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

Attachment 11. Protocol JPBJ Child-Pugh Score

Child-Pugh Score

The Child-Pugh score employs 5 clinical measures of liver disease. Each measure is scored 1 through 3, with 3 indicating most severe derangement.

Measure	1 Point	2 Points	3 Points
Total bilirubin, μmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin (g/dL)	>3.5	2.8-3.5	<2.8
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory

Abbreviations: INR = International Normalized Ratio; PT = prothrombin time.
Source: Pugh et al. 1973.

Attachment 12. Protocol JPBJ Protocol Amendment I3Y-MC-JPBJ(g) Summary A Phase 1b Study of Abemaciclib in Combination with Multiple Single-Agent Options for Patients with Stage IV NSCLC

Overview

Protocol I3Y-MC-JPBJ, A Phase 1b Study of Abemaciclib in Combination with Multiple Single-Agent Options for Patients with Stage IV NSCLC, has been amended. The new protocol is indicated by Amendment (h) and will be used to conduct the study in place of any preceding version of the protocol.

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

- Included TBL and VTE in abbreviations (Section 4).
- Section 5.1.8 incorporated rationale for Amendment (h) to update safety monitoring information for hepatic conditions, renal function, and VTEs.
- Included tablets as a formulation that will be supplied (Section 7.1)
- Section 7.2.4.1.1 modified, including addition of Table JPBJ.7.6 along with Sections 7.2.4.1.1.1, 7.2.4.1.1.2, 7.2.4.1.1.3, and 7.2.4.1.1.4 for alignment with safety updates.
- Sections 7.5.1.2, 8.1.4.1, and 8.1.4.2 incorporated additional safety monitoring language for renal function, hepatic conditions, 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 5.1.7. Rationale for Amendment (g)

…

Dose modification ~~Table JPBJ.7.12~~Table JPBJ.13 for pembrolizumab was updated to include dose adjustments in case of myocarditis to be consistent with the current Investigator's Brochure (IB) for pembrolizumab version 15. Formatting changes in the table were also made.

…

Section 5.1.8. Rationale for Amendment (h)

Study JPBJ protocol was amended to update the dosing guidance for cases of nonhematologic toxicity, diarrhea, and ALT increase. This amendment will harmonize the dosing guidance across all clinical trials of abemaciclib in metastatic setting. The amendment updated the safety language regarding hepatic monitoring, assessment of renal function, and venous thromboembolic events (VTEs) for ongoing patients. Updates to Attachment 10 were completed to harmonize the list of CYP inhibitors and inducer, including those with narrow therapeutic range. Minor typographical and formatting edits were made throughout the document for clarity and consistency.

Section 7.1. Materials and Supplies

Abemaciclib will be supplied as capsules or tablets for oral administration. The capsules/tablets 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/tablets in the original package and in a location inaccessible to children. Clinical study materials will be labeled according to country regulatory requirements.

…

Section 7.2.4.1.1. Abemaciclib

Table JPBJ.7.6 presents dose adjustments to occur if the event is possibly related to abemaciclib.

Table JPBJ.7.6. Toxicity Dose Adjustments and Delays of Abemaciclib for Study I3Y-MC-JPBJ

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity Section 7.2.4.1.1.1	Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MAY** be reduced by 1 dose level - investigator's discretion.
Hematologic Toxicity Section 7.2.4.1.1.1	Recurrent Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic Toxicity Section 7.2.4.1.1.1	Grade 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic toxicity: If patient requires administration of blood cell growth factors Section 7.2.4.1.1.1	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 lead to the use of growth factor.
Nonhematologic Toxicity[a] (except diarrhea and ALT increased) Section 7.2.4.1.1.2	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 7.2.4.1.1.2	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 7.2.4.1.1.3 and 7.5.1.1	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 7.2.4.1.1.3 and 7.5.1.1	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.

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

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Diarrhea Sections 7.2.4.1.1.3 and 7.5.1.1	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
ALT Increased Sections 7.2.4.1.1.4 and 8.1.4.1	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 7.2.4.1.1.4 and 8.1.4.1	Grade 4 (>20.0×ULN) [d]	Abemaciclib **MUST** be discontinued.	Abemaciclib **MUST** be discontinued.
ALT Increased with increased total bilirubin, in the absence of cholestasis Sections 7.2.4.1.1.4 and 8.1.4.1	Grade 3 increased ALT (>5.0 x ULN) with total bilirubin >2 x ULN [d]	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 hepatic and renal monitoring is in Sections 8.1.4.1 and 7.5.1.2.

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).

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 8.1.4.1 for additional guidance for hepatic monitoring

Dose adjustments are allowed both within a cycle and between cycles.

~~If a patient experiences a recurrent Grade 3 or a Grade 4 hematologic toxicity possibly related to abemaciclib, then dosing **must** be suspended (until the toxicity resolves to either baseline or at least Grade 2) and the dose of abemaciclib **must** be reduced as outlined in Table JPBJ.7.6.~~

~~If a patient experiences a Grade 3 hematologic toxicity possibly related to abemaciclib, then dosing **must** be suspended (until toxicity resolves to either baseline or at least Grade 2) and the dose of abemaciclib **may** be reduced at the investigator's discretion as outlined in Table JPBJ.7.6.~~

~~If a patient requires administration of blood cell growth factors (regardless of severity), then dosing **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. The dose of abemaciclib **must** be reduced by 1 dose level (unless already performed for incidence of toxicity that lead to the use of growth factor) as outlined in Table JPBJ.7.6.~~

~~If a patient experiences ≥Grade 3 nonhematologic toxicity possibly related to abemaciclib, 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 as outlined in Table JPBJ.7.6.~~

~~If a patient experiences persistent or recurrent Grade 2 nonhematologic toxicity (except diarrhea; refer to Section 7.5.1) possibly related to abemaciclib that does not resolve with maximal supportive measures within 7 days to either baseline or Grade 1, then dosing **may** be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of abemaciclib **may** be reduced as outlined in Table JPBJ.7.6.~~

If a patient who, in the judgment of the investigator, is receiving clinical benefit from study therapy requires further dose reduction than is outlined in Table JPBJ.7.~~6~~7, then the investigator must discuss with the Lilly CRP prior to any further dose reduction. For patients requiring dose reduction(s), re-escalation to a prior dose level is permitted only after consultation with the Lilly CRP.

…

Table JPBJ.7.~~6~~7. Dose Adjustments of Abemaciclib for Study I3Y-MC-JPBJ

…

Section 7.2.4.1.1.1. Hematologic Toxicity

If a patient experiences a Grade 3 hematologic toxicity possibly related to abemaciclib, then dosing **must** be suspended (until toxicity resolves to either baseline or at least Grade 2) and the dose of abemaciclib **may** be reduced at the investigator's discretion as outlined in Table JPBJ.7.6.

If a patient experiences a recurrent Grade 3 or a Grade 4 hematologic toxicity possibly related to abemaciclib, then dosing **must** be suspended (until the toxicity resolves to either baseline or at least Grade 2) and the dose of abemaciclib **must** be reduced as outlined in Table JPBJ.7.6.

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 (regardless of severity), then dosing **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. The dose of abemaciclib **must**

be reduced by 1 dose level (unless already performed for incidence of toxicity that lead to the use of growth factor) as outlined in Table JPBJ.7.6.

Section 7.2.4.1.1.1. Nonhematological Toxicity (except diarrhea and ALT increase)

If a patient experiences >Grade 3 nonhematologic toxicity possibly related to abemaciclib, 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 as outlined in Table JPBJ.7.6.

If a patient experiences persistent or recurrent Grade 2 nonhematologic toxicity (except diarrhea; refer to Section 7.2.4.1.1.3 or ALT increased, refer to Section 8.1.4.1) possibly related to abemaciclib that does not resolve with maximal supportive measures within 7 days to either baseline or Grade 1, 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 as outlined in Table JPBJ.7.6.

Section 7.2.4.1.1.3. Diarrhea

If a patient experiences Grade 2 diarrhea that does not resolve with maximal supportive measures (refer to Section 7.5.1.1) 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 or any grade diarrhea that requires hospitalization (refer to Section 7.5.1.1) study drug must be suspended (until the toxicity resolves to either baseline or at least Grade 1); and a dose reduction is required. For Grade 3 or Grade 4 diarrhea, the dose must be suspended and a dose reduction is required Table JPBJ.7.6.

Section 7.2.4.1.1.4. Hepatic Toxicity

Dose modifications and management for increased ALT are provided in Table JPBJ.7.6. 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 8.1.4.1 for additional hepatic monitoring guidance.

Section 7.2.4.1.2. Pemetrexed

Pemetrexed dose adjustments at the start of a subsequent cycle should be based on nadir hematologic counts or maximum nonhematologic toxicity from the preceding cycle of therapy.

Treatment may be delayed to allow sufficient time for recovery. Upon recovery, patients should be re-treated using the guidelines in ~~Table JPBJ7.7~~Table JPBJ.7.8, which are suitable for using pemetrexed as a single-agent or in combination.

Table JPBJ.7.~~7~~8. Hematologic Dose Reduction for Pemetrexed in Study I3Y-MC-JPBJ

…

If patients develop nonhematologic toxicities (excluding neurotoxicity) ≥Grade 3, treatment should be withheld until resolution to less or equal to the patent's baseline value. Treatment should be resumed according to ~~Table JPBJ.7.8~~Table JPBJ.7.9.

Table JPBJ.7.~~8~~9. Nonhematologic Dose Reduction for Pemetrexed in Study I3Y-MC-JPBJ

…

Section 7.2.4.1.3. Gemcitabine

Patients receiving gemcitabine should be monitored prior to each dose (Day 1 and Day 8 of each cycle) with a complete blood count (CBC), including differential and platelet count. If marrow suppression is detected, therapy should be modified or suspended according to guidelines in ~~Table JPBJ.7.9~~Table JPBJ.7.10.

Table JPBJ.7.~~9~~10. Dose Adjustments of Gemcitabine for Study I3Y-MC-JPBJ

…

Section 7.2.4.1.4. Ramucirumab

Dose modifications are permitted for investigational product in the setting of non-life-threatening and reversible Grade 3 clinical AEs (for example, fever) considered to be at least possibly related to investigational product and that resolve to Grade ≤1 or pretreatment baseline within 1 treatment cycle (approximately 3 weeks). If a Grade 4 AE occurs and is deemed at least possibly related to ramucirumab, then treatment should be discontinued except in the specific case of Grade 4 fever or Grade 4 laboratory abnormalities. If Grade 4 fever or laboratory abnormalities resolve to Grade ≤1 or baseline within 1 treatment cycle (approximately 3 weeks), treatment with ramucirumab may be continued at the discretion of the investigator. In these settings, ramucirumab may be readministered. If a second instance of such an event occurs, ramucirumab should be subsequently readministered at a reduced dose level. A second dose reduction is permitted for this level of event (Grade 3 or 4) (refer to ~~Table JPBJ.7.10~~Table JPBJ.7.11). If the dose of ramucirumab is reduced because of potentially related AEs, subsequent dose increases are not permitted. Specific guidelines for ramucirumab dose modifications related to infusion reactions and thrombotic events are provided in Section

7.2.4.1.4.1 and Section 7.2.4.1.4.3, respectively. Criteria for dose reduction in the setting of hypertension and proteinuria are detailed in Section 7.2.4.1.4.2 and Section 7.2.4.1.4.14 respectively.

Table JPBJ.7.~~10~~11. Dose Adjustments of Ramucirumab for Study I3Y-MC-JPBJ

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Section 7.2.4.1.5. LY3023414

For patients receiving combination treatment with abemaciclib and LY3023414 in Part D, the same guidelines for dose adjustments due to toxicities possibly related to LY3023414 apply as outlined for abemaciclib in Section 7.2.4.1.1.

Dose adjustments of LY3023414 are described in ~~Table JPBJ.7.11~~Table JPBJ.7.12.

Table JPBJ.7.~~11~~12. Dose Adjustments of LY3023414 for Study I3Y-MC-JPBJ

…

For patients in **Part D** (LY3023414 + abemaciclib), the investigator will interpret and document whether or not an AE has a reasonable possibility of being related to each of the study drugs, taking into account the disease, concomitant treatments, or pathologies, in order to individually adjust study drug(s) doses. For a toxicity that due to its nature is possibly related to LY3023414 only, dose adjustments for abemaciclib should be considered only after dose adjustment of LY3023414 (and vice versa for possibly only abemaciclib-related toxicities; see Section 7.2.4.1.1). LY3023414 should be dose-reduced to the next lower dose level (~~Table JPBJ.7.11~~Table JPBJ.7.12) following discussion between the investigator and the sponsor.

…

Section 7.2.4.2.1. Abemaciclib

…

Before the start of each cycle, nonhematologic toxicity (except alopecia and fatigue) possibly related to abemaciclib must resolve to either baseline or at least Grade 1. Refer to Section 7.5.1 for guidance and supportive measures of diarrhea toxicity possibly related to abemaciclib or Section 8.1.4.1 for additional hepatic monitoring guidance.

…

~~**Section 7.2.4.2.1.1. Diarrhea**~~

~~A patient with diarrhea requiring hospitalization (irrespective of grade) or severe diarrhea (Grade 3 or 4) must have study drug suspended (until the toxicity resolves to either baseline or at~~

~~least Grade 1)~~ ~~and~~ ~~must~~ ~~have the study drug dose reduced by 1 dose level as outlined in Table JPBJ.7.6.~~

~~If a patient experiences persistent or recurrent Grade 2 diarrhea that does not resolve with maximal supportive measures (refer to Section 7.5.1)~~ ~~within 24 hours~~ ~~to either baseline or at least Grade 1, then study drug~~ ~~should~~ ~~be suspended (until the toxicity resolves to either baseline or at least Grade 1) and the dose of study drug~~ ~~may~~ ~~be reduced by 1 dose level as outlined in Table JPBJ.7.6 at the discretion of the investigator.~~

Section 7.2.4.2.6. Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Therefore, early recognition and initiation of treatment are critical to reduce complications. Based on existing clinical study data, more AEs were reversible and could be managed with interruptions of study treatment, administration of corticosteroids, and/or other supportive care. Dose modification and toxicity management guidelines for AEs associated with pembrolizumab are provided in ~~Table JPBJ.7.12~~Table JPBJ.7.13 below.

Table JPBJ.7.~~12~~13. Dose Adjustments for Pembrolizumab in Study I3Y-MC-JPBJ

…

Section 7.5.1.2. Guidance for Monitoring of Renal Function in Patients on Abemaciclib

…

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, 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 JPBJ.7.6).

Section 7.5.1.4. Supportive Care Guidelines for Pembrolizumab—Part E only

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Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to ~~Table JPBJ.7.12~~Table JPBJ.7.13 for guidelines regarding dose modification.

Management of Infusion Reactions:

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in ~~Table JPBJ.7.13~~Table JPBJ.7.14.

Table JPBJ.7.~~13~~14. Infusion Reaction Treatment Guidelines in Study I3Y-MC-JPBJ

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Section 8.1.4. Safety Monitoring

The Lilly CRP or CRS will monitor safety data throughout the course of the study. Lilly will review SAEs within time frames mandated by standard operating procedures and will review trends, laboratory analytes, and AEs at periodic intervals. Attachment 5 provides recommendations for reporting SAEs.

- ~~If a study patient experiences elevated ALT >5X ULN and elevated total bilirubin >2X ULN, clinical and laboratory monitoring should be initiated by the investigator.~~
- ~~For patients entering the study with ALT >3X ULN, monitoring should be triggered at ALT >2X 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/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests (see Attachment 3).

Section 8.1.4.1. 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
- discontinuation from study treatment due to a hepatic event or an abnormality of liver tests

Section 8.1.4.2. 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 JPBJ Inducers, Strong Inhibitors of CYP3A or Substrates of VYPs with Narrow Therapeutic Range

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Strong inhibitors of CYP3A
~~All HIV protease inhibitors~~
Aprepitant
Ciprofloxacin
Clarithromycin
Diltiazem
Erythromycin
Fluconazole
Itraconazole
Ketoconazole
Nefazodone
Verapamil

Cytochrome P450 Substrates with Narrow Therapeutic Range

Cytochrome P450	**Substrate**
CYP1A2	Theophylline Tizanidine
~~CYP2C8~~	~~Paclitaxel~~
…	…

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