Protocol I6F-MC-JJCD(a)

A Phase 1b Study of LY3039478 in Combination with Other Anticancer Agents in Patients with Advanced or Metastatic Solid Tumors

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Approval Date: 15-Mar-2016

1. Protocol I6F-MC-JJCD(a)
A Phase 1b Study of LY3039478 in Combination with Other Anticancer Agents in Patients with Advanced or Metastatic Solid Tumors

Confidential Information

LY3039478

Study I6F-MC-JJCD (JJCD) is a multicenter, nonrandomized, open-label, Phase 1b study consisting of 5 separate, parallel dose escalations in patients with advanced/metastatic cancer from a variety of solid tumors followed by a dose-confirmation phase in specified tumor types.

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Protocol Electronically Signed and Approved by Lilly: 17 December 2015.
Amendment (d) Electronically Signed and Approved by Lilly on approval date provided below.

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2. Synopsis

Clinical Protocol Synopsis: Study I6F-MC-JJCD

Name of Investigational Product: LY3039478	
Title of Study: A Phase 1b Study of LY3039478 in Combination with Other Anticancer Agents in Patients with Advanced or Metastatic Solid Tumors.	
Number of Planned Patients: Total study sample size will be approximately 163 patients.	**Phase of Development:** 1b
Length of Study: Planned first patient visit: June 2016 Planned last patient visit: June 2018	

Objectives:

Primary:

The primary objective of this study is to determine the recommended Phase 2 dose of LY3039478 in individual combinations with other anticancer agents.

Secondary:

- to characterize the safety and toxicity profile of LY3039478 in combination with other anticancer agents as assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
- to estimate the pharmacokinetic (PK) parameters of LY3039478 in combination with other anticancer agents
- to estimate the PK parameters of taladegib and its active metabolite LSN3185556, in combination with LY3039478
- to estimate the PK parameters of LY3023414 in combination with LY3039478
- to estimate the PK parameters of abemaciclib and its major active metabolites LSN2839567 and LSN3106726, in combination with LY3039478
- to document any antitumor activity observed with LY3039478 in combination with other anticancer agents
- to assess duration of response and progression free survival (PFS)

Exploratory:

- to explore pharmacodynamic (PD) effects of LY3039478 on biomarkers indicative of Notch activity or other study drugs
- to explore the utility of positron emission tomography (PET) scan to assess treatment effect with LY3039478 in combination with other anticancer agents
- to explore predictive biomarkers related to induction of cytochrome P450 (CYP) enzymes, such as cortisol and 6β-hydroxycortisol
- to evaluate tumor tissue and blood for biomarkers related to the Notch signaling pathway and drug target pathways, immune functioning, mechanism of action of study drug(s) or disease state, and their potential association with the objectives of the study

Study Design: Study I6F-MC-JJCD (JJCD) is a multicenter, nonrandomized, open-label, Phase 1b study consisting of 5 separate, parallel dose escalations in patients with advanced/metastatic cancer from a variety of solid tumors followed by a dose-confirmation phase in specified tumor types.

Part A: In the dose-escalation phase of Part A, eligible patients will receive LY3039478 given orally, 3 times per week (TIW) in combination with a hedgehog/Smoothened (Smo) antagonist (taladegib [LY2940680]) given orally, daily (QD) on a 28-day cycle. A single dose of taladegib will also be given on Day 1 during a 3-day lead-in period (dose-escalation phase only) for PK evaluation. In the dose-confirmation phase of Part A, approximately 10 patients with breast cancer (that have mutations, amplification, or gene expression alterations related to Notch pathway) and 10 patients with soft tissue sarcomas will be treated.

Part B: In the dose-escalation phase of Part B, eligible patients will receive LY3039478 given orally, TIW in combination with a class I phosphatidylinositol 3-kinase (PI3K) and the mammalian target of rapamycin (mTOR)

(PI3K/mTOR) inhibitor (LY3023414) given orally, every 12 hours on a 28-day cycle. A single dose of LY3023414 will also be given on Day 1 during a 3-day lead-in period (dose-escalation phase only) for PK evaluation. In the dose-confirmation phase of Part B, approximately 10 patients each with advanced or metastatic colon cancer or soft tissue sarcoma will be treated. Colon cancer patients have to have mutations, amplification, or gene expression alterations related to Notch pathway.

Part C: In the dose-escalation phase of Part C, eligible patients will receive LY3039478 given orally, TIW in combination with a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor (abemaciclib [LY2835219]) given orally, every 12 hours on a 28-day cycle. A single dose of abemaciclib will also be given on Day 1 during a 3-day lead-in period (dose-escalation phase only) for PK evaluation. In the dose-confirmation phase of Part C, approximately 15 patients with metastatic breast cancer that have mutations, amplification, or gene expression alterations related to Notch pathway will be treated.

Part D: In the dose-escalation phase of Part D, eligible patients will receive LY3039478 given orally, TIW in combination with cisplatin and gemcitabine given as intravenous (IV) infusions on Days 1 and 8 of a 21-day cycle. In the dose-confirmation phase of Part D, approximately 15 patients with cholangiocarcinoma that have mutations, amplification, or gene expression alterations related to Notch pathway will be treated.

Part E: In the dose-escalation phase of Part E, eligible patients will receive LY3039478 given orally, TIW in combination with gemcitabine and carboplatin given as IV infusions on Days 1 and 8 of a 21-day cycle. In the dose-confirmation phase of Part E, approximately 15 patients with triple negative breast cancer (TNBC) (estrogen receptor negative [ER-], progesterone receptor negative [PR-], human epidermal growth factor receptor 2 negative [HER2-]) that have mutations, amplification, or gene expression alterations related to Notch pathway will be treated.

Diagnosis and Main Criteria for Inclusion and Exclusions: Adult patients (≥18 years of age) who are appropriate candidates for experimental treatment with adequate organ function and performance status, have histological or cytological evidence of cancer, either a solid tumor or a lymphoma, which is unresectable or metastatic. In the dose-confirmation phase of the study, all patients must have measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). In Part A dose confirmation: all patients must have histological evidence of unresectable or metastatic soft tissue sarcoma or breast cancer. Breast cancer patients must have prescreened alterations related to Notch pathway. For Part B dose confirmation: all patients must have histological evidence of unresectable or metastatic colon cancer or soft tissue sarcoma. Colon cancer patients must have prescreened alterations related to Notch pathway. For Part C dose confirmation: all patients must have histological evidence of unresectable or metastatic breast cancer and must have prescreened alterations related to Notch pathway. For Part D dose confirmation: all patients must have histological evidence of cholangiocarcinoma, prescreened alterations related to Notch pathway, and must not have received >1 line of prior systemic therapy for metastatic or resectable disease. For Part E dose confirmation: all patients must have histological evidence of locally advanced unresectable or metastatic TNBC, prescreened alterations related to Notch pathway, and not have received >2 lines of prior systemic treatment for unresectable or metastatic TNBC. All patients must have available tumor tissue (archived or newly biopsied). Patients with serious concomitant systemic disorders including malabsorptive syndromes, enteropathies, gastroenteritis (acute or chronic), or diarrhea (acute or chronic), who have received other investigational product within 14 days, have symptomatic central nervous system malignancy or metastases, acute leukemia, active infection including human immunodeficiency virus, cardiac disease, or a second primary malignancy that may affect the interpretation of results will be excluded from treatment. For Part B only; patients with insulin-dependent diabetes mellitus or a history of gestational diabetes mellitus will be excluded from treatment.

Test Product, Dosage, and Mode of Administration: LY3039478, dose range 25-50 mg, given orally as capsules TIW during a 21- or 28-day cycle.

Planned Duration of Treatment:

The planned duration of treatment is not fixed; patients will remain on study drug therapy until they fulfill 1 of the criteria for treatment discontinuation.

Short-term follow-up period (postdiscontinuation): 30 days

Long-term follow-up period (postdiscontinuation): after the short-term follow-up through death or study closure.

Reference Therapy, Dose, and Mode of Administration:

- Taladegib will be supplied as 100-mg tablets in bottles for oral consumption.
- LY3023414 will be supplied as 25-mg, 100-mg, or 200-mg capsules or 100-mg, 150-mg, or 200-mg tablets.
- Abemaciclib will be supplied as 50-mg hypromellose capsules.
- Gemcitabine will be dosed at 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle as an IV infusion.
- Cisplatin will be dosed at 25 mg/m^2 on Days 1 and 8 of each 21-day cycle as an IV infusion.
- Carboplatin will be dosed at area under the plasma concentration-time curve (AUC) 2 on Days 1 and 8 of each 21-day cycle as an IV infusion.

Criteria for Evaluation:

Safety: Safety will be evaluated based on recorded adverse events (AEs), physical examinations, vital sign measurements, electrocardiograms (ECGs), and clinical laboratory assessments. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs and clinical laboratory values will be graded using NCI CTCAE v4.0.

Bioanalytical: Plasma concentrations of LY3039478, taladegib and its active metabolite LSN3185556, abemaciclib and its active metabolites LSN2839567 and LSN3106726, LY3023414, gemcitabine, cisplatin, and carboplatin.

Efficacy: Depending on the histology, efficacy will be assessed using RECIST 1.1 for solid tumors.

Statistical Methods:

Safety: Safety analyses will include listings and/or summaries of the following:

- AEs, treatment-emergent AEs (TEAEs), and dose-limiting toxicities (DLTs)
- drug exposure
- dose adjustments
- laboratory measures
- vital signs
- ECG readings

Efficacy: The study was not designed to make an efficacy assessment. However, any tumor response data will be tabulated. Descriptive analyses of duration of response and PFS will be conducted using the Kaplan-Meier method.

Pharmacokinetics: PK parameters for LY3039478, taladegib and its active metabolite LSN3185556, LY3023414, abemaciclib and its active metabolites LSN3106726 and LY2839567, gemcitabine, cisplatin, and carboplatin will be analyzed by standard noncompartmental methods of analysis.

Pharmacodynamics: Biomarker data from all patients undergoing biomarker assessments will be analyzed using descriptive statistics.

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4. Abbreviations and Definitions

Term	Definition
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.
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APP	amyloid precursor protein
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
assent	Agreement from a minor or other individual who is not legally capable of providing consent, but who can understand the circumstances and potential risks involved in participating in a study.
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{(0\text{-}48hr)}$	area under the plasma concentration-time curve from time zero to 48 hours
$AUC_{(0\text{-}\infty)}$	area under the plasma concentration-time curve from time zero to infinity
$AUC_{(0\text{-}tlast)}$	area under the plasma concentration-time curve from time zero to last measurable plasma concentration
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).
bDNA	branched-chain deoxyribonucleic acid
BID	twice daily
BUN	blood urea nitrogen
CBF-1	C-promoter binding factor-1

CCND1	Cyclin D1
CDK	cyclin-dependent kinase
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL/F	apparent systemic clearance
C_{max}	maximum plasma concentration
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.
CPK	creatine phosphokinase
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
CSC	cancer stem cell
CSF	colony stimulating factor(s)
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
DLET	dose-limiting equivalent toxicity
DLL	Delta-like ligand

DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	Patients who are enrolled in the trial are those who have been assigned to a treatment and have received at least 1 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.
ER-	estrogen receptor negative
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.
FFPE	formalin-fixed paraffin-embedded
GCP	good clinical practice
G-CSF	granulocyte colony stimulating factor(s)
GFR	glomerular filtration rate
GGT	gamma-glutamyl transpeptidase
GI	gastrointestinal
GMP	good manufacturing practice
GnRH	gonadotropin-releasing hormone
GSI	gamma secretase inhibitor
HbA1C	glycosylated hemoglobin
HER2-	human epidermal growth factor receptor 2 negative
HES1	hairy and enhancer of split-1
IB	Investigator's Brochure

IC50	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMS	isotope dilution mass spectrometry
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An analysis of clinical study data that is conducted before the final reporting database is authorized for datalock.
investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial. . Investigational product includes a product with a marketing authorization when: 1. used or assembled (formulated or packaged) in a way different from the authorized form 2. used for an unauthorized indication or 3. used to gain further information about the authorized form
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.
IV	intravenous
K_i	inhibition constant
LC-MS/MS	liquid chromatography-tandem 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.
LSS	Lilly Safety System: Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
MATE1	multidrug and toxin extrusion protein 1
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
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
NCI	National Cancer Institute
NHS	National Health Service (England)
NICD	Notch intracellular domain
NRARP	Notch-Regulated Ankyrin Repeat
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.
patient	a subject with a defined disease
PD	pharmacodynamic(s)
PDX	patient-derived xenograft
PET	positron emission tomography
PFS	progression-free survival
PI3K	phosphatidylinositol 3-kinase
PK	pharmacokinetic(s)
PR-	progesterone receptor negative
PSA	prostate-specific antigen
PT/INR	prothrombin time/international normalized ratio
PTEN	phosphatase and tensin homolog
Q2D	every other day
QD	daily
Rb	retinoblastoma
RBC	red blood cells (erythrocytes)
RBP-Jκ	recombination signal-binding protein-Jκ
RECIST	Response Evaluation Criteria in Solid Tumors

reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	to screen a patient who was previously declared a screen failure for the same study
RP2D	recommended Phase 2 dose
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 invasive or diagnostic procedures and tests (for example, skin biopsy, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
screen failure	A patient who does not meet one or more criteria required for participation in a trial
SE	standard error
Shh-CM	sonic hedgehog conditioned media
Smo	smoothened
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 once it is deemed that sufficient data are obtained to assess the primary and secondary objectives.
Su[H]	Suppressor of Hairless
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	half-life
TACE	tumor necrosis factor-α converting enzyme
T-ALL	T-cell acute lymphoblastic leukemia/lymphoma
TEAE	treatment-emergent adverse event
TIW	3 times per week
T_{max}	time to maximum observed plasma concentration
TNBC	triple negative breast cancer
TPO	third-party organization
TSH	thyroid stimulating hormone

ULN	upper limit of normal
US	United States
WBC	white blood cells (leukocytes)
WHO	World Health Organization

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5. Introduction

5.1. Rationale and Justification for the Study

Notch signaling is an evolutionarily conserved pathway that plays an integral role in development and tissue homeostasis (Artavanis-Tsakonas et al. 1999). There are 4 mammalian Notch receptors (Notch-1, -2, -3, and -4) and 5 ligands (Jagged-1 and Jagged-2 [homologs of Drosophila Serrate-like proteins] and Delta-like ligand [DLL]1, DLL3, and DLL4). The Notch receptors and ligands contain single-pass transmembrane domains that are expressed on the cell surface, and, for that reason, Notch signaling is particularly important in mediating communication between adjacent cells expressing the receptors and ligands (Allenspach et al. 2002). The Notch receptors are heterodimeric proteins composed of extracellular and intracellular domains that are initially synthesized as a single polypeptide. The precursor protein is cleaved at site 1 (S1) by a furin-like convertase in the Golgi before being transported to the cell surface and presented as a heterodimer to form a mature Notch transmembrane receptor. The extracellular domain of both the receptors and ligands consists of several epidermal growth factor (EGF)-like repeats, with the ligands also containing distinct Notch receptor binding domains at the N terminus. The extracellular domain of the Notch receptor is glycosylated by the Fringe proteins which regulate the receptor–ligand interaction. Receptor–ligand interaction triggers a series of proteolytic cleavage of Notch receptor. First, it is processed by the metalloprotease tumor necrosis factor-α converting enzyme (TACE) at S2 cleavage site, which occurs in the ectodomain of the receptor immediately outside of the transmembrane domain, thereby separating the intracellular and extracellular receptor domains and releasing the entire extracellular domain of the receptor. This is followed by an S3 cleavage within the transmembrane domain by γ-secretase which releases the entire Notch intracellular domain (NICD). γ-Secretase is a high molecular weight multiprotein complex possessing protease activity against a number of type I membrane proteins, including amyloid precursor protein (APP), ErbB4 receptor, and Notch receptors. γ-Secretase cleavage of the Notch receptor results in the release of a peptide called the NICD and translocation to the nucleus. The NICD is important in regulating transcriptional activity through interactions with the transcription repressor CSL (C-promoter binding factor-1 [CBF-1] and Suppressor of Hairless [Su[H]], LAG 1), also known as mammalian recombination signal-binding protein-Jκ (RBP-Jκ). NICD binding to the CSL relieves suppressive function by displacing co-repressor and recruiting co-activator to activate the transcription of downstream target genes responsible for various Notch functions including proliferation, differentiation, apoptosis, angiogenesis, migration, and self-renewal. These diverse roles of Notch signaling during the development and maintenance of normal tissues are recapitulated in different forms of cancer. The oncogenic functions of Notch signaling involve the inhibition of apoptosis and the promotion of cell proliferation (Radtke and Raj 2003).

An oncogenic role for Notch was first reported as the result of a chromosomal translocation occurring in a patient with T-cell leukemia (Grabher et al. 2006). Overexpression of NICD in hematopoietic progenitor cells of mice recapitulated this phenomenon, as they developed T-cell leukemia similar to humans. Furthermore, treatment of these cells with the γ-secretase inhibitor prevented their cell growth. Besides T-cell leukemia, there is increasing evidence that Notch signals are oncogenic in other cancers through multiple mechanisms including receptor amplification and overexpression of ligands and/or receptors. Deregulated Notch signaling due to mutation or overexpression of ligands and/or receptors is implicated in a number of malignancies including lymphoid leukemias, melanoma, glioblastoma, and cancers of the breast, ovary, cholangiocarcinoma, lung, pancreas, colon, head and neck, cervix, and kidney (Koch and Radtke 2007; CGARN 2011; Puente et al. 2011). In summary, inhibition of Notch signaling constitutes an attractive strategy to provide therapeutic benefits to cancer patients.

This Phase 1b study will assess the safety of a Notch inhibitor (LY3039478) in combination with different agents in order to determine the recommended Phase 2 dose of LY3039478 in combinations with those different anticancer agents as outlined in Figure JJCD.1.

5.1.1. Rationale for Combination with Taladegib

The presence of small populations of cells with stem-like characteristics (cancer stem cells [CSCs]) is established in most malignancies, although the origin and plasticity of these cells is not fully understood. Experimental models show that CSCs seem to be more resistant to chemotherapy and radiotherapy than "differentiated" tumor cells. CSCs typically demonstrate persistent activation of one or more highly conserved signal transduction pathways involved in development and tissue homeostasis, including the Notch, hedgehog, and Wnt pathways (Takebe et al. 2015).

Results from mainly preclinical models examining combination approaches to overcome the crosstalk among Notch, hedgehog, and Wnt pathways, as well as other signaling pathways, have shown promising results (Takebe et al. 2015). LY3039478 has shown significant antitumor activity when combined with taladegib (LY2940680) – a hedgehog/Smoothened (Smo) inhibitor in a leiomyosarcoma xenograft model (data on file).

Clinically, a previous Notch and hedgehog inhibitors combination showed a good safety profile and clinical activity in patients with advanced sarcoma (Gounder et al. 2012).

In summary, the combination of LY3039478 and taladegib is an attractive regimen to target CSCs.

5.1.2. Rationale for Combination with LY3023414

LY3023414 is an orally available, dual kinase inhibitor of class I phosphatidylinositol 3-kinase (PI3K) and the mammalian target of rapamycin (mTOR). The PI3K/mTOR pathway has been reported as activated in >70% of human cancers and has emerged as a promising target for anticancer therapies. PI3K/mTOR signaling plays a central role in regulating physiological processes such as growth, survival, proliferation, and metabolism, and in the development of malignant disease (Bjornsti and Houghton 2004; Samuels and Ericson 2006).

There are several mechanisms that lead to aberrant activation of this pathway, including mutations of growth factor receptors, PIK3CA, and loss of the tumor suppressor, phosphatase and tensin homolog (PTEN) (Stambolic et al. 1998; Courtney et al. 2010). PTEN loss has been also described as a resistance mechanism to other targeted therapies. For example, T-cell acute lymphoblastic leukemia/lymphoma (T-ALL) loss of PTEN is a common event and is associated with resistance to Notch inhibition (Palomero et al. 2007). Mutational loss of PTEN induces resistance to NOTCH1 inhibition in T-cell leukemia. Furthermore, Notch induces upregulation of the phosphatidylinositol 3-kinase and protein kinase B (PI3K-AKT) pathway via Hairy and enhancer of split-1 (HES1), which negatively controls the PTEN expression. LY302314 has demonstrated activity in preclinical tumor xenograft models with PTEN loss (manuscript submitted). When LY3039478 is administered in combination with LY3023414 (currently in Phase 2 development), a synergistic inhibition of tumor growth in A2780 ovarian carcinoma xenograft model is shown. This suggests that simultaneous inhibition of Notch and PI3K signaling can provide improved therapeutic benefits in solid tumors such as ovarian cancer (data on file).

Based on this, Study I6F-MC-JJCD (JJCD) will evaluate the novel/novel combination of LY3039478 and LY3023414 in patients with advanced cancer.

5.1.3. Rationale for Combination with Abemaciclib

The cell cycle is the process by which mammalian cells replicate their deoxyribonucleic acid (DNA) and undergo cellular division. The mammalian cell cycle has 4 phases: S phase, where DNA replication occurs; G2 phase, where the cell prepares for mitosis; M (mitosis) phase, where the replicated DNA and cellular components are divided to form 2 daughter cells; and G1 phase, where cells commit to another round of DNA and cellular replication. Defects in the pathways that regulate cell proliferation in response to mitogenic signaling and other extracellular stimuli such as cell density and nutrients are a hallmark of cancer cells (Hanahan and Weinberg 2000), and the G1 cell cycle restriction point (R) is believed to be essential to maintaining control of proliferation (Blagosklonny and Pardee 2002; Ortega et al. 2002). A primary mechanism controlling cell cycle progression through the restriction point is the cyclin-dependent kinase 4/6 (CDK4/6) pathway (CDK4/6-cyclinD-INK4-Rb) and the importance of this pathway in regulating cell proliferation is highlighted by inactivation of restriction point control in a majority (>85%) of human tumors including breast cancer (Malumbres and Barbacid 2001).

Notch signaling also plays a role in cell cycle. For instance, in human T-cell malignancies, Notch signaling regulates expression of key cell cycle regulatory proteins such as Cyclin D3, CDK4, and CDK6 for the progression of cells from G1 to S phase (Joshi et al. 2009). Furthermore, gamma secretase inhibitor (GSI)-induced G1 arrest can be partially rescued by ectopic expression of CDK4 or CDK6. Rao et al. (2009) demonstrated that GSI and CDK4 inhibitor produced synergistic growth inhibition of T-ALL cells through induction of CDK inhibitors CDKN2D (p19(INK4d)) and CDKN1B (p27(Kip1)), leading to derepression of retinoblastoma (Rb) tumor suppressor protein and subsequent exit from the cell cycle. Consistent with these reports, we observed that LY3039478 in combination with abemaciclib,

a CDK4/6 inhibitor currently in Phase 3 development, inhibits tumor growth in Colo-205 (human colorectal) and NCI-H2122 (human adenocarcinoma of lung) xenograft models.

In summary, the combination of LY3039478 and abemaciclib is an attractive regimen to target the cell cycle.

5.1.4. Rationale for Combination with Cisplatin and Gemcitabine

A cisplatin and gemcitabine regimen is widely used for the treatment of different cancers.

In cholangiocarcinoma, ABC-02, the first randomized, controlled Phase 3 study for cancers of the biliary tract, established a benefit for the addition of cisplatin to gemcitabine treatment as compared to single agent gemcitabine, with an improved rate of tumor control (81.4% vs 71.8%, p=.049) and a median overall survival of 11.7 months vs 8.1 months (hazard ratio 0.64; 95% confidence interval [CI] 0.52 to 0.80; p<.001) (Valle et al. 2010). These results provided evidence for recent treatment guidelines for advanced cholangiocarcinoma that recommend the use of the gemcitabine and cisplatin (Eckel et al. 2011; NCCN 2015). The gemcitabine and cisplatin dosing regimen used in the ABC-02 trial consisted of repeating cycles of cisplatin (25 mg/m^2) followed by gemcitabine (1000 mg/m^2) with each drug administered on Days 1 and 8 every 3 weeks (Valle et al. 2010).

In a cholangiocarcinoma transgenic mouse model, the expression of the NOTCH1 NICD in mouse livers resulted in the formation of intrahepatic cholangiocarcinomas. Results suggested that intrahepatic cholangiocarcinoma can originate from this cell type as these tumors displayed features of bipotential hepatic progenitor cells. According to Zender et al. (2013), human and mouse cholangiocarcinomas were characterized by high expression of the cyclin E protein. Cyclin E gene was identified as a direct transcriptional target in the pathway for Notch signaling. Inhibiting the γ-secretase activity in human cholangiocarcinoma xenotransplants resulted in downregulation of cyclin E expression, induction of apoptosis, and tumor remission in vivo (El Khatib et al. 2013; Zender et al. 2013).

The demonstrated efficacy of cisplatin and gemcitabine, the nonoverlapping toxicity profile, and role of Notch signaling in cholangiocarcinoma make cisplatin and gemcitabine an attractive regimen to combine with LY3039478.

5.1.5. Rationale for Combination with Gemcitabine and Carboplatin

Triple negative breast cancer (TNBC) is an aggressive histological subclass of breast cancer that is extremely aggressive and accounts for an excessive amount of metastatic disease cases and patient deaths. Given the aggressive nature of TNBC and the need for tumor response in most cases, a multidrug regimen is preferred over a single-drug regimen in this subclass of patient (Andre and Zielinski 2012). A gemcitabine and carboplatin combination is among the proposed regimens for treatment of TNBC (O'Shaughnessy et al. 2011).

Next-generation sequencing has been used to identify Notch mutations in a large collection of diverse solid tumors. Stoeck et al. (2014) reported that NOTCH1 and NOTCH2 rearrangements leading to constitutive receptor activation were confined to TNBC. In addition, the TNBC cell

lines with NOTCH1 alterations associated with high levels of activated NOTCH1were responsive to a γ-secretase inhibitor in vitro and in vivo , whereas cell lines with NOTCH2 alterations were resistant to GSI. Immunohistochemical staining of N1ICD in TNBC xenografts established a connection between responsiveness and expression levels of the direct Notch target gene HES4, which correlated with outcome in patients with TNBC (Stoeck et al. 2014).

An additional study by Robinson et al. (2011) demonstrated that Notch family genes have a meaningful effect on breast epithelial cells. Furthermore, this study showed that various breast cancer cell lines that have Notch gene rearrangements are unique in their sensitivity to the inhibition of Notch signaling (Robinson et al. 2011).

Based on these data, the combination of a Notch inhibitor with standard chemotherapy is an attractive regimen in TNBC.

5.2. Objectives

5.2.1. Primary Objective

The primary objective of this study is to determine the recommended Phase 2 dose of LY3039478 in individual combinations with other anticancer agents.

5.2.2. Secondary Objectives

The secondary objectives of this study are:

- to characterize the safety and toxicity profile of LY3039478 in combination with other anticancer agents as assessed by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
- to estimate the pharmacokinetic (PK) parameters of LY3039478 in combination with other anticancer agents
- to estimate the PK parameters of taladegib and its active metabolite LSN3185556, in combination with LY3039478
- to estimate the PK parameters of LY3023414 in combination with LY3039478
- to estimate the PK parameters of abemaciclib and its major active metabolites LSN2839567 and LSN3106726, in combination with LY3039478
- to document any antitumor activity observed with LY3039478 in combination with other anticancer agents
- to assess duration of response and progression-free survival (PFS)

5.2.3. Exploratory Objectives

The exploratory objectives of this study are:

- to explore pharmacodynamic (PD) effects of LY3039478 on biomarkers indicative of Notch activity or other study drugs
- to explore the utility of positron emission tomography (PET) scan to assess treatment effect with LY3039478 in combination with other anticancer agents

- to explore predictive biomarkers related to induction of cytochrome P450 (CYP) enzymes, such as cortisol and 6β-hydroxycortisol
- to evaluate tumor tissue and blood for biomarkers related to the Notch signaling pathway and drug target pathways, immune functioning, mechanism of action of study drug(s) or disease state, and their potential association with the objectives of the study

5.3. General Introduction to LY3039478

LY3039478 is a potent Notch inhibitor being developed for the treatment of patients with cancer. LY3039478 prevents release of the NICD by inhibiting proteolytic activity of γ-secretase complex and thereby decreasing Notch signaling and its downstream biologic effects. LY3039478 has been shown to inhibit Notch signaling in cell lines representing a number of different solid tumors and leukemia.

In nonclinical studies, the gastrointestinal (GI) tract is the key target organ for toxicity, which is also reflected in the current clinical safety observations.

As of June 2015, the most commonly reported treatment-emergent adverse events (TEAEs), occurring in ≥10% of patients and possibly related to LY3039478 were diarrhea (48 patients, 49.5%); vomiting (38 patients, 39.2%); nausea (34 patients, 35.1%); asthenia (28 patients, 28.9%); decreased appetite (23 patients, 23.7%); hypophosphatemia (18 patients, 18.6%); dry skin (14 patients, 14.4%); dry mouth and mucosal inflammation (13 patients each, 13.4%); weight decreased (12 patients, 12.4%); and alanine aminotransferase (ALT) increased, alopecia, and hair color changes (10 patients each, 10.3%). Most of the TEAEs were mild or moderate in severity. Hypophosphatemia was noted to be the most frequently reported Grade 3 TEAE (8 patients, 8.2%), with only 1 TEAE reported as serious.

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

More detailed information about the known and expected benefits and risks of LY3039478 may be found in the following: Protocol Section 5.1 or in the IB.

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

LY3039478 is a potent Notch inhibitor with a half-maximal inhibitory concentration (IC50) of ≤1 nM in the majority of tumor cell lines tested for its ability to inhibit NOTCH1 cleavage.

LY3039478 potently inhibits Notch cleavage and downstream Notch signaling in lung and skin of Balb/C mice in a dose-dependent manner with a threshold dose concentration of the compound required to inhibit cleavage by 50% (TED50) value for N1ICD inhibition of 0.8 and

0.9 mg/kg, respectively, and threshold plasma concentration of the compound required to inhibit cleavage by 50% (TEC50) value of 6.2 and 6.6 ng/mL, respectively.

Doses of 7 to 10 mg/kg with an intermittent schedule of every other day (Q2D) produced optimal efficacy while balancing on-target GI toxicity. LY3039478 also inhibited NOTCH1 cleavage and downstream signaling as measured by analysis of Notch regulated gene expression within the tumor microenvironment.

LY3039478 inhibited Notch signaling in the tumor and produced antitumor activity in patient-derived human tumor models: EL1986 and EL1989 adenocarcinoma of colon, EL1997 triple negative invasive ductal carcinoma of breast, EL2144 brain metastases from adenocarcinoma of colon, and EL2056 glioblastoma; and cell-line–derived xenograft tumors: A2780 ovarian carcinoma, U-87 MG glioblastoma, HCT-116 and SW480 colon carcinoma, and K562 chronic myelogenous leukemia.

Furthermore, LY3039478 has shown significant antitumor activity when combined with taladegib (LY2940680) in a leiomyosarcoma xenograft model. In a proof-of-concept study using an ovarian cancer patient-derived xenograft (PDX) model (n=1 mouse per model), LY3039478 in combination with carboplatin and paclitaxel was significantly better in 13/26 PDX models compared to single agent LY3039478 or chemotherapy alone (data on file).

5.3.2. Human Pharmacokinetics

As of 06 January 2015, PK data for LY3039478 were available from 52 patients on Day 1 and 35 patients on Day 22 over a dose range of 2.5 to 100 mg in Cycle 1 from the first in human Study I6F-MC-JJCA (JJCA). After oral administration, maximum plasma concentrations (C_{max}) of LY3039478 were reached approximately 1 to 2 hours postdose. The mean half-life ($t_{1/2}$) was approximately 5 to 7 hours, suggesting little to no accumulation upon multiple dosing with a 3-times-per-week (TIW) dosing schedule. The area under the plasma concentration-time curve (AUC) from time zero to 48 hours ($AUC_{[0\text{-}48hr]}$) after multiple dosing was similar to AUC from time zero to infinity ($AUC_{[0\text{-}\infty]}$) after the first dose, indicating that the PK of LY3039478 did not change with time. A preliminary assessment of dose proportionality has been conducted for PK parameters ($AUC_{[0\text{-}48hr]}$ and C_{max}) on Day 22 of dosing in Cycle 1, and no deviations from linearity were observed across the dose range studied (2.5 to 100 mg). The variability in exposures, as assessed by percentage coefficient of variation (CV), ranged from 30% to 90% for both C_{max} and AUC. Preliminary analyses of urine data suggest that renal clearance contributed to approximately 20% of apparent plasma clearance of LY3039478.

In primary cultured hepatocytes using incubation concentrations up to 100 μM, LY3039478 is a mild inducer of CYP3A, with an estimated concentration yielding half the maximum effect (EC50) and maximum induction ratio (E_{max}) of 10 μM and 6.4-fold, respectively. Using a static model, the exposure of midazolam is predicted to be reduced by 20% after a dose of 75 mg LY3039478. In humans, the maximum tested dose was 100 mg and the C_{max} was approximately 2.3 μM.

5.3.3. Pharmacodynamics

γ-Secretase is a multiprotein complex possessing protease activity against a number of type I membrane proteins including Notch receptors and APP. Proteolytic cleavage of Notch receptors and APP by γ-secretase results in production of cleaved proteins NICD and Aβ, respectively. LY3039478 is a potent inhibitor of γ-secretase activity; and therefore, LY3039478 is expected to inhibit production of Aβ in addition to NICD. Quantification of circulating Aβ in plasma was used as a surrogate biomarker to determine PD effect of LY3039478 in patients. The effect of LY3039478 on plasma Aβ concentrations follows an approximate dose related trend, with approximately 80% reductions in plasma Aβ observed from 45 mg to 100 mg.

Additionally, expression of Notch regulated genes was assessed to monitor PD effect of LY3039478 in skin. Skin samples were collected prior to and after approximately 6 hours of LY3039478 treatment. Expressions of HES1, Cyclin D1 (CCND1), and Notch-Regulated Ankyrin Repeat (NRARP) were reduced; trending in a dose proportional manner. Maximum inhibition of HES1 and NRARP occurred between 45 and 100 mg of LY3039478.

5.4. General Introduction to Taladegib

More information about the known and expected benefits, risks, and reasonably anticipated 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 taladegib IB. 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 study, may be found in Section 6 (Effects in Humans) of the IB. The information in the following sections provides a brief summary.

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

Smo, a distant relative of G protein coupled receptors, is a key regulator of Hh signaling. Taladegib binds to the Smo receptor and competitively inhibits binding of ^{3}H-2406189, an agonist to hSmo.

Using an in vitro competitive binding assay, inhibitory concentration and binding constant were calculated based on the competitive displacement of radioligand. LY2940680-Hydrochloride binds to human Smo receptor and inhibits binding of ^{3}H-2406189, a known hSmo agonist, to hSmo with 76.4 ± 75.3 nM inhibition constant (K_i; n=4, geometric mean ± standard error [SE]) and 144 ± 143 nM IC50(n=4, geometric mean ± SE).

To determine biological activity of taladegib in mouse cells, Gli-luciferase activity was quantified in mouse mesenchymal C3H10$T_{1/2}$ cell line stimulated with sonic hedgehog conditioned media (Shh-CM). LY2940680-Hydrochloride inhibited Hh signaling activity in mouse C3H10$T_{1/2}$cells with an IC50 of 11.2 ± 5.33 nM (n=8, geometric mean ± SE).

To determine biological activity of taladegib in human cells, Gli1 transcript levels were quantified in human Daoy tumor cell line stimulated with Shh-CM. LY2940680-Hydrochloride inhibited Hh signaling activity in human Daoy cells, with an IC50 of 2.22 ± 1.14 nM (n=8,

geometric mean ± SE) as determined by measurement of Gli1 messenger ribonucleic acid (mRNA) using branched-chain DNA (bDNA) assay technology.

5.4.2. Clinical Summary

To date, the initial monotherapy study, Study I4J-MC-HHBB, has treated 84 patients at doses ranging from 50 mg to 600 mg daily. The MTD was established at 400 mg as an oral daily dose. The most frequently occurring TEAEs (≥10% of patients) were dysgeusia (47.6%), nausea (46.4%), fatigue (45.2%), muscle spasms (39.3%), decreased appetite (32.1%), vomiting (28.6%), alopecia (27.4%), decreased weight (23.8%), myalgia (16.7%), diarrhea (15.5%), asthenia (10.7%), and constipation (10.7%). Hyponatremia (n=1) was the only Grade 4 TEAE considered possibly related to taladegib treatment by the investigators; this event was also reported as serious. Other Grade 3 TEAEs occurring in at least 2 patients and considered possibly related to taladegib treatment by the investigators were muscle spasms (n=4); fatigue (n=3); and nausea, vomiting, dysgeusia, asthenia, and myalgia (n=2 each).

A monotherapy, dose-escalation study in Japanese patients (Study I4J-MC-HHBH) has treated 15 patients with doses ranging from 100 mg to 400 mg daily. In this study, the most frequently reported TEAEs (≥10% of patients) considered possibly related to taladegib treatment were dysgeusia (n=11); decreased appetite (n=8); fatigue and nausea (n=6 each); vomiting (n=5); alopecia (n=4); pyrexia (n=3); and weight decreased, dehydration, muscular weakness, and insomnia (n=2 each).

After single- and multiple-dose administration, taladegib levels reach C_{max} after approximately 3 hours, with food appearing to have no impact on rate or extent of absorption. The mean value for the apparent clearance is 10 L/hr (75% CV); indicating that taladegib is slowly eliminated from the plasma. The mean value for the apparent volume of distribution is 248 L (47% CV). The mean taladegib $t_{1/2}$ after multiple-dose administration across all doses is estimated to be approximately 22 hours (range: 5 to 55, 61% CV). The accumulation ratio is approximately 2.1 between Day 1 and Day 15 (range: 0.7 to 4.8, 40% CV). A substrate depletion approach using recombinant human CYPs was used to identify the CYPs metabolizing taladegib and LSN3185556, and to predict the relative contributions of these CYPs to microsomal CYP-mediated clearance. For both taladegib and LSN3185556, this approach indicated that CYP3A4 was responsible for 100% of the hepatic CYP-mediated clearance of the respective compounds.

5.5. General Introduction to LY3023414

More detailed information about the known and expected benefits, risks and reasonably anticipated 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 LY3023414 IB. 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 study, may be found in Section 6 (Effects in Humans) of the IB. The information in the following sections provides a brief summary.

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

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 (K_i 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.

5.5.2. Clinical Summary

Study I6A-MC-CBBA (CBBA) is an ongoing dose-escalation study for daily (QD) and twice-daily (BID) dosing of LY3023414 followed by expansion cohorts for different tumor types and LY3023414 combination treatments.

In the dose-escalation phase of Study CBBA, dose-limiting toxicities (DLTs) for BID dosing were observed in 3 out of 4 patients at the 250-mg BID dose level (Grade 4 hypophosphatemia, Grade 3 fatigue, Grade 3 mucositis) and in 1 out of 6 patients at the 200-mg BID dose level (Grade 2 nausea). Therefore, a dose of 200-mg LY3023414 was defined as the maximum tolerated dose (MTD) for BID dosing.

As of 08 June 2015, of the 72 patients who received at least 1 dose of LY3023414, 61 patients (84.7%) had at least 1 possibly study drug-related TEAE (all grades). The most commonly reported TEAEs (that is, occurring in ≥10% of patients) considered as possibly related to study drug(s) across all study parts in Study CBBA were nausea (41.7%), fatigue (31.3%), vomiting (34.7%), diarrhea (18.1%), stomatitis (16.7%), and decreased appetite (16.7%). Most of these TEAEs (58.3%) were mild or moderate in severity.

For patients receiving LY3023414 monotherapy at doses up to and including the MTD (total n=60 patients, including 35 patients who received 200 mg BID monotherapy), 14 possibly related Grade 3 TEAEs have been reported including fatigue (n=3), hyperglycemia (n=2), and maculo-papular rash (n=2).

PK analyses showed a dose-proportional increase in LY3023414 exposures (AUC) at tolerated dose levels with a $t_{1/2}$ of 1.9 hours and a clearance following oral administration of 82 L/hr. Midazolam PK data indicated that LY3023414 is a weak inhibitor of CYP3A4. In vitro metabolism data indicate that LY3023414 is likely primarily metabolized in humans by CYP3A4. Biomarker assessment demonstrated dose-related target inhibition as measured by p4EBP1 inhibition in peripheral mononuclear cells at LY3023414 doses ≥150 mg.

Eleven of 47 patients (23%) had a decrease in their target lesions. A durable partial response, according to Response Evaluation Criteria in Solid Tumors (RECIST), was observed in an endometrial cancer patient harboring PIK3R1 and PTEN mutations. The remaining 10 patients had a decrease in their target lesions by up to 29%.

Considering safety, PK/PD, and preliminary anti-tumor results, a dose of 200-mg LY3023414 BID was determined as the recommended Phase 2 dose for LY3023414 monotherapy.

LY3023414 is currently being evaluated in additional Phase 2 studies for castration-resistant prostate cancer patients in combination with enzalutamide and squamous non-small cell lung cancer (NSCLC) patients in combination with the epidermal growth factor receptor (EGFR) targeting antibody necitumumab.

5.6. General Introduction to Abemaciclib

More information about the known and expected benefits, risks and reasonably anticipated 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 abemaciclib IB. 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 study, may be found in Section 6 (Effects in Humans) of the IB. The information in the following sections provides a brief summary.

5.6.1. 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 CDK4/6 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 CDK4/6 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 CDK4/6. Rb phosphorylation at serine 780 (pRb) is a specific marker for CDK4/6 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 CDK4/6 associated with reduced pRb and a sustained G1 arrest is indicated by strong inhibition of all markers. The capacity of abemaciclib mesylate to inhibit CDK4/6 in vivo is illustrated by the sustained PD 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 (TED70) for pRb and TopoIIα inhibition 24 hours after oral dosing were 14.1 and 14.3 mg/kg, respectively.

5.6.2. Clinical Summary

As of December 2015, 572 patients were treated with abemaciclib across 6 clinical studies. Abemaciclib has been given as monotherapy, in combination with endocrine therapy, and in combination with chemotherapeutic agents. Cumulatively in all of these groups, the most common TEAEs (≥10% of patients) possibly related to study drug included diarrhea (73.3%), fatigue (48.6%), nausea (48.3%), neutropenia (32.9%), vomiting (25.3%), decreased appetite (25.2%), thrombocytopenia (22.9%), anemia (22.4%), leukopenia (20.3%), abdominal pain (18.2%), and blood creatinine increased (14.0%).

Grade 3 TEAEs possibly related to study drug included neutropenia (13.8%); diarrhea (13.6%); leukopenia and fatigue (7.7% each); thrombocytopenia (5.1%); anemia (4.7%); nausea (3.0%); lymphopenia (2.8%); hypokalemia (1.4%); abdominal pain, decreased appetite, and vomiting (1.2% each); ALT increased and blood creatinine increased (0.9% each); dehydration, febrile neutropenia, and stomatitis (0.7% each); AST increased, confusional state, hyponatremia, lung infection, and rash (0.5% each); hypophosphatemia, hypotension, international normalized ratio increased, and pneumonitis (0.3% each); and acute kidney injury, aphasia, arthralgia, chronic kidney disease, colitis, dermatitis acneiform, dyspnea, gait disturbance, gamma-glutamyl transpeptidase (GGT) increased, hematotoxicity, hematuria, hypertension, infection, infusion related reaction, liver function text abnormal, lymphorrhea, malaise, muscular weakness, pain, pancreatitis, pruritus, pyrexia, skin infection, somnolence, syncope, and upper-airway cough syndrome (0.2% each). In addition, Grade 3 scrotal infection was experienced by 1 patient (0.7% by total male population).

Grade 4 TEAEs possibly related to study drug included neutropenia (5.2%); thrombocytopenia (1.4%); leukopenia (0.9%); anemia and GGT increased, (0.3% each); and cardiogenic shock, febrile neutropenia, hypertriglyceridemia, hypokalemia, lymphopenia, sepsis, stress cardiomyopathy (0.2% each).

Grade 5 TEAE of sepsis (0.3%) and sudden death (0.2%) that were possibly related to study drug were reported.

Treatment-emergent CTCAE central laboratory toxicities of increased creatinine were reported in 93% of patients (N=572) who received abemaciclib therapy. Mean serum creatinine rises, to approximately 15% to 40% above baseline, occurred during Cycle 1 in most of the patients exposed to abemaciclib and were maintained during treatment. A decrease in serum creatinine to near baseline was observed following treatment discontinuation, indicating that the serum creatinine increase observed is reversible. Concomitant increases in mean blood urea nitrogen (BUN) were typically not observed in patients exposed to abemaciclib. In vitro studies have indicated that abemaciclib and its major metabolites (LSN2839567 and LSN3106726) inhibit the renal transporter, multidrug and toxin extrusion protein 1 (MATE1), at clinically relevant concentrations. Thus, increases in serum creatinine observed following dosing with abemaciclib, in the absence of simultaneous increases in BUN or development of an abnormal urinalysis, are most likely due to inhibition of its tubular secretion via MATE1 and may not reflect a decline in renal function, making serum creatinine level an unreliable measurement for renal function.

Investigators should be aware that serum creatinine increases may be a consequence of receiving abemaciclib. If deterioration of renal function is suspected, measures other than those relying on assessment of serum creatinine should be used to determine renal function.

PK data for abemaciclib after a single oral dose administration were available from 222 patients dosed over a total dose range of 50 to 275 mg. The exposure of abemaciclib increased in a dose proportional manner; however, statistical significance at the 90% confidence level could not be established. The time course of abemaciclib concentration in plasma is characterized by a slow absorption, with a median time to maximum observed plasma concentration (T_{max}) ranging from 4 to 6 hours postdose. The mean $t_{1/2}$ ranged from 17 to 38 hours across the dose range tested but there was no consistent trend with dose, suggesting no dose-dependent change in CL.
A substrate depletion assay used to identify the CYP enzymes metabolizing abemaciclib and its major active metabolites LSN2839567 and LSN3106726, indicate that CYP3A is primarily involved in the CYP-mediated metabolism and is responsible for over 99% of the CYP-mediated microsomal clearance of abemaciclib, LSN2839567, and LSN3106726. In Study I3Y-MC-JPBF, coadministration of abemaciclib with rifampin, a strong CYP3A inducer, reduced abemaciclib exposure by over 90%.

5.7. Rationale for Selection of Doses for LY3039478 and Other Anticancer Agents

During the dose-escalation phase (Part A) of Phase 1 Study JJCA, 5 of the 55 patients (9.1%) experienced DLTs. DLTs of Grade 4 thrombocytopenia were experienced by 1 patient each in Cohort 4 (20 mg), Cohort 5 (30 mg), and Cohort 7 (60 mg). In 2 out of the 3 patients, the thrombocytopenia was associated with bleeding. DLTs of Grade 3 colitis (1 patient) and Grade 3 nausea (not manageable with medical treatment) associated with Grade 3 fatigue (1 patient) were experienced in Cohort 9 (100 mg). In addition, 1 patient in Cohort 7 (60 mg) experienced a dose-limiting equivalent toxicity (DLET) of Grade 3 colitis during Cycle 2, and 1 patient in Cohort 9 (100 mg) experienced a DLET of Grade 3 fatigue during Cycle 4. The MTD was established at 75 mg TIW.

During Part B of Study JJCA, 2 patients treated with 75 mg experienced DLETs of Grade 3 diarrhea and colitis during Cycle 1 (1 patient) and Grade 3 diarrhea during Cycle 2 (1 patient). Additional review of the safety data from Part B (25 patients) revealed Grades 3 and 4 AEs of diarrhea (5 patients); nausea (3 patients); and vomiting, colitis, and hypophosphatemia (2 patients each) that were assessed as possibly related to study drug by the investigator. In addition, approximately 30% of patients had dose reductions. These developments led to the reduction of the MTD to 50 mg TIW.

At the 50-mg dose level, preliminary safety data show a reduction in all GI toxicities (diarrhea, nausea, and vomiting) in both frequency and severity. In addition, there were no reports of colitis at the 50-mg dose level. There were fewer dose reductions and dose omissions necessary at 50 mg compared with 75 mg. The most frequent (≥10% of patients) TEAEs reported at the 50-mg dose level were: diarrhea (14 patients, 39%); nausea and asthenia (8 patients each, 22%);

and vomiting, fatigue, decreased appetite, and dry skin (4 patients each, 11%). The only Grade 3 events experienced at this dose level were stomatitis (1 report) and asthenia (2 reports).

The starting dose for LY3039478 is 50% of the monotherapy recommended dose (25 mg). LY3039478 will be escalated up to 50 mg.

For Part A, the starting dose for taladegib is 50% of the monotherapy recommended dose (200 mg). Taladegib will be escalated up to 400 mg.

For Part B, the starting dose for LY3023414 is 75% of the monotherapy recommended dose (150 mg BID). LY3023414 will be escalated up to 200 mg.

For Part C, the starting dose for abemaciclib is 50% of the monotherapy recommended dose (100 mg BID). Abemaciclib will be escalated up to 150 mg BID.

For Parts D and E, the dose regimens of cisplatin/gemcitabine and gemcitabine/carboplatin will be the standard regimens used for treatment of cholangiocarcinoma and TNBC, respectively.

5.8. Rationale for Amendment (a)

This study was amended at the request of the Food and Drug Administration (FDA) to clarify inclusion criteria, some criteria for DLTs (Section 7.2.2.1), and the definition for MTD. Minor editorial changes and clarifications have also been made.

6. Investigational Plan

6.1. Study Population

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Individuals may be re-screened up to 3 times. Each time re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

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 be, in the judgment of the investigator, an appropriate candidate for experimental therapy after available standard therapies (per available local guidelines) have failed to provide clinical benefit for their advanced or metastatic cancer.

- For dose escalation for all combinations: The patient must have histological or cytological evidence of cancer, either a solid tumor or a lymphoma, which is unresectable or metastatic.
- For Part A dose confirmation: All patients must have histological evidence of unresectable or metastatic soft tissue sarcoma or breast cancer. Breast cancer patients must have prescreened mutations, amplification, or gene/protein expression alterations related to Notch pathway (Attachment 8).
- For Part B dose confirmation: All patients must have histological evidence of unresectable or metastatic colon cancer or soft tissue sarcoma. Colon cancer patients must have prescreened mutations, amplification, or gene/protein expression alterations related to Notch pathway (Attachment 8).
- For Part C dose confirmation: All patients must have histological evidence of unresectable or metastatic breast cancer and prescreened mutations, amplification, or gene/protein expression alterations related to Notch pathway (Attachment 8).
- For Part D dose confirmation: All patients must have histological evidence of cholangiocarcinoma and prescreened mutations, amplification, or gene/protein expression alterations related to Notch pathway (Attachment 8). Patients must not have received >1 line of prior systemic therapy for metastatic or resectable disease (that is, patients may have received adjuvant gemcitabine and then later gemcitabine/cisplatin for recurrent metastatic disease).

- For Part E dose confirmation: All patients must have histological evidence of locally advanced unresectable or metastatic TNBC and prescreened mutations, amplification, or gene/protein expression alterations related to Notch pathway (Attachment 8). Patients must not have received >2 lines of systemic treatment for unresectable or metastatic TNBC.

[2] For dose confirmation (all parts): Have measurable disease (as defined by the RECIST guideline [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 or >5 mmol/L. Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator; however, initial study drug treatment must not begin earlier than the day after the erythrocyte transfusion.
- Hepatic: Bilirubin ≤1.5 times upper limit of normal (ULN), ALT and aspartate aminotransferase (AST) ≤2.5 times ULN. If the liver has tumor involvement, AST and ALT equaling ≤5 times ULN are acceptable.
- Renal: calculated creatinine clearance >60 mL/min (Attachment 7).
- For Part B only: have fasting glucose ≤140 mg/dL and glycosylated hemoglobin (HbA1c) ≤7 g/dL.

[6] Have a performance status of ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale (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. At the discretion of the investigator, patients with breast or prostate cancers progressing on luteinizing hormone-releasing hormone (LHRH) or gonadotropin-releasing hormone (GnRH) therapies may have that treatment continued while receiving study drug.

[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 highly effective methods of birth control during the study and for 12 weeks following the last dose of the study drugs or country requirements, whichever is longer.

Women of child-bearing potential must test negative for pregnancy within 7 days of enrollment based on a serum pregnancy test and also must not be breastfeeding

[10] Have an estimated life expectancy ≥12 weeks.

[11] Are able to swallow capsules and tablets.

[12] Have available tumor tissue (archived or newly biopsied).

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 14 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 non-cancer 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 serious concomitant systemic disorder (for example, active infection including human immunodeficiency virus, or cardiac disease) that, in the opinion of the investigator, would compromise the patient's ability to adhere to the protocol.

[15] Have symptomatic central nervous system (CNS) malignancy or metastasis (screening not required).

- Patients with treated CNS metastases are eligible for this study if they are not currently receiving corticosteroids and/or anticonvulsants, and their disease is asymptomatic and radiographically stable for at least 60 days.
- Patients with glioblastoma, World Health Organization (WHO) Grade 4, or WHO Grade 2 or 3 glioma are eligible.

[16] Have current acute leukemia.

[17] Have a second primary malignancy that, in the judgment of the Investigator and sponsor, may affect the interpretation of results.

[18] Have current or recent (within 3 months of study drug administration) GI disease with chronic or intermittent diarrhea, or disorders that increase the risk of diarrhea, such as inflammatory bowel disease. Nonchronic conditions (for example, infectious diarrhea) that are completely resolved for at least 1 week prior to starting study treatment are not exclusionary.

[19] **Part B only**: 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 antidiabetics as documented by HbA1c ≤7%.

[20] **Part B only**: Have QTc interval of >470 msec.

[21] **Part B dose expansion only**: Prior treatment with a PI3K/mTOR inhibitor.

6.2. Summary of Study Design

Study JJCD is a multicenter, nonrandomized, open-label, Phase 1b study consisting of 5 separate, parallel dose escalations in patients with advanced/metastatic cancer from a variety of solid tumors followed by a dose-confirmation phase in specified tumor types (Figure JJCD.1). Additional parts exploring other combinations such as ramucirumab combination and/or immuno-oncology agents may be added in the future and will require a protocol amendment.

Part A: A single dose of taladegib will be given on Day 1 during a 3-day lead-in period (dose-escalation phase only) in order to evaluate the effects of LY3039478 on the PK of taladegib and its active metabolite LSN3185556 (see Section 5.3.2). In the dose-escalation phase of Part A, eligible patients will receive LY3039478 given orally TIW in combination with a hedgehog/Smo antagonist (taladegib [LY2940680]) given orally QD on a 28-day cycle. In the dose-confirmation phase of Part A, approximately 10 patients with breast cancer (that have mutations, amplification, or gene/protein expression alterations related to Notch pathway) and 10 patients with soft tissue sarcomas will be treated.

Part B: A single dose of LY3023414 will be given on Day 1 during a 3-day lead-in period (dose-escalation phase only) in order to evaluate the effects of LY3039478 (a mild inducer of CYP3A) on the PK of LY3023414 (see Section 5.3.2). In the dose-escalation phase of Part B, eligible patients will receive LY3039478 given orally TIW in combination with a PI3K/mTOR inhibitor (LY3023414) given orally, every 12 hours on a 28-day cycle. In the dose-confirmation phase of Part B, approximately 10 patients each with advanced or metastatic colon cancer or soft tissue sarcoma will be treated. Colon cancer patients have to have mutations, amplification, or gene/protein expression alterations related to Notch pathway.

Part C: A single dose of abemaciclib will be given on Day 1 during a 3-day lead-in period (dose-escalation phase only) in order to evaluate the effects of LY3039478 on the PK of abemaciclib and its metabolites LSN2839567 and LSN3106726 (see Section 5.3.2). In the dose-escalation phase of Part C, eligible patients will receive LY3039478 given orally TIW in combination with a CDK4/6 inhibitor (abemaciclib [LY2835219]) given orally, every 12 hours on a 28-day cycle. In the dose-confirmation phase of Part C, approximately 15 patients with metastatic breast cancer that have mutations, amplification, or gene/protein expression alterations related to Notch pathway will be treated.

Part D: In the dose-escalation phase of Part D, eligible patients will receive LY3039478 given orally TIW in combination with cisplatin and gemcitabine given as intravenous (IV) infusions on Days 1 and 8 of a 21-day cycle. In the dose-confirmation phase of Part D, approximately 15 patients with cholangiocarcinoma that have mutations, amplification, or gene/protein expression alterations related to Notch pathway will be treated.

Part E: In the dose-escalation phase of Part E, eligible patients will receive LY3039478 given orally TIW in combination with gemcitabine and carboplatin given as IV infusions on Days 1 and 8 of a 21-day cycle. In the dose-confirmation phase of Part E, approximately 15 patients

with TNBC (estrogen receptor negative [ER-], progesterone receptor negative [PR-], human epidermal growth factor receptor 2 negative [HER2-]) that have mutations, amplification, or gene/protein expression alterations related to Notch pathway will be treated.

The total sample size is estimated to be approximately 163 patients. Further details are provided in Section 10.1.

The planned duration of treatment is not fixed; patients will remain on study drug therapy until they fulfill 1 of the criteria for treatment discontinuation. The treatment period will be defined as the time from treatment start until discontinuation from treatment for any reason (Section 6.3.2). The postdiscontinuation follow-up period begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and is defined by the following periods:

- The ***short term follow-up period*** begins 1 day after the patient and investigator agree that the patient will no longer continue treatment and lasts approximately 30 days (Visit 801).
- The ***long-term follow-up period*** begins 1 day after the short-term follow-up period (Visit 801) is completed and continues until death or study closure to collect PFS data (Visit 802-80X).
- After discontinuation, tumor measurements will be performed as indicated in Section 8.3. Other study procedures will be performed as outlined in Attachment 1.

This study will be considered closed once it is deemed that sufficient data are obtained to assess the primary and the secondary objectives, estimated to be approximately 12 months from the date that the last patient was enrolled. This will ensure that the primary objective and the secondary objectives are met for the purpose of the clinical study report. For PFS, in the event that the data are not mature enough to characterize the entire survival curve, a landmark analysis at 12 months will be done for the purpose of the clinical study report. Patients who are benefitting from treatment may continue to receive study drug for long-term durations, even after the study has closed and final database lock has occurred, in the continued access period.

Based on emerging preclinical and clinical data, the protocol may be amended as appropriate to reflect the most current scientific knowledge. Study design may be modified to reflect these data and scientific needs. This includes, and is not limited to, change in the study design, modifications of safety monitoring, addition of cohorts to study, and introduction of new schedules as single agent or in combination with other agents.

Refer to Attachment 1 for the Study Schedule.

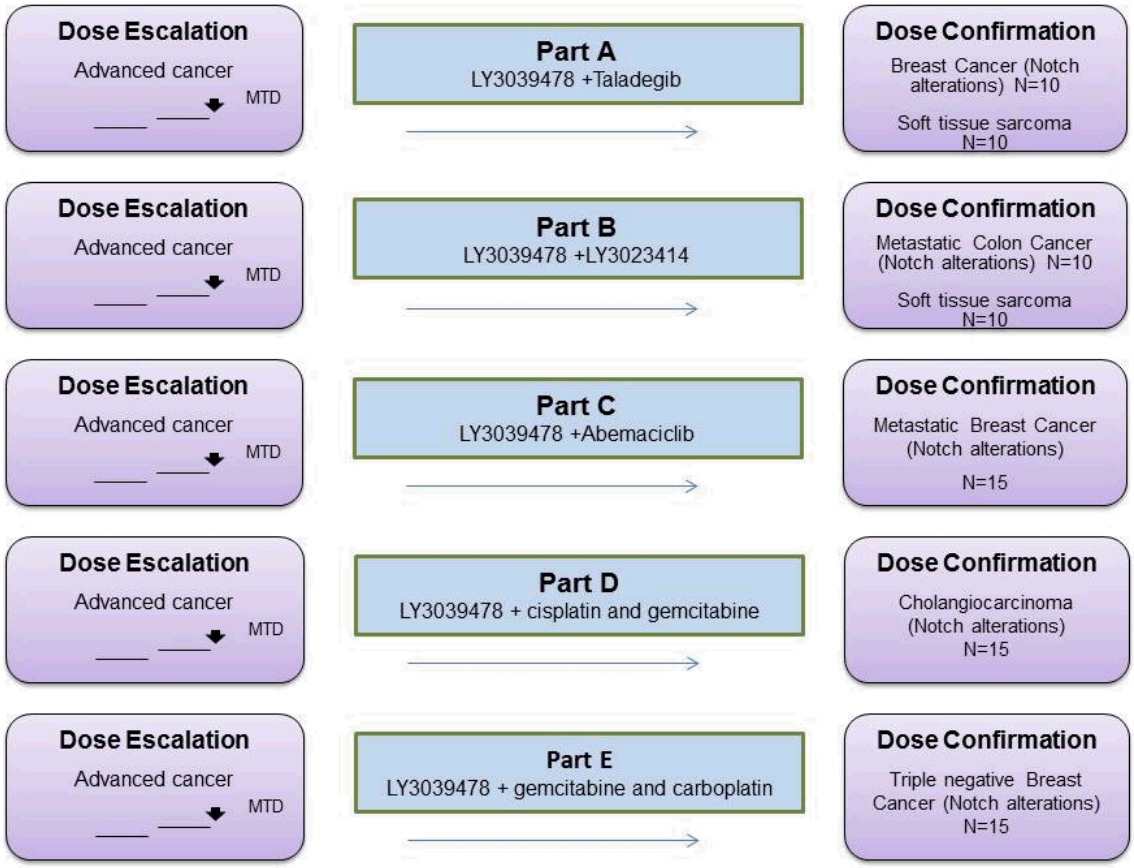

Figure JJCD.1. Illustration of study design for Protocol I6F-MC-JJCD.

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]) following the final analysis. "End of trial" refers to the date of the last visit or last scheduled procedure for the last patient.

The end of trial occurs after study completion and after the last patient has discontinued study treatment and completed any applicable continued access follow-up.

6.2.2. Continued Access Period

All patients remaining on study treatment without disease progression following the final analysis will be able to enter the continued access period of the study. The continued access period begins after study completion and ends at the end of trial. During the continued access period, patients on study treatment who continue to experience clinical benefit may continue to receive study treatment until disease progression, death, unacceptable toxicity, or start of new anticancer treatment. The continued access period includes a follow-up visit. The follow-up visit begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days. 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.

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

SAEs will also be reported to Lilly Global Patient Safety and collected in the Lilly Safety System (LSS). 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.

Investigators may perform other standard procedures and tests needed to treat and evaluate patients; however, Lilly will not routinely collect the results of these assessments.

6.3. Discontinuations

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

6.3.1. Discontinuation of Patients Inadvertently Enrolled

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.

6.3.2. Discontinuation of Patients from Study or Study Drug

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

In addition, patients will be discontinued from the study drug and from the study in the following circumstances:

- 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/physician decides that the patient should be discontinued from the study or study drug(s)
  - 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 good clinical practice (GCP).
- The patient has evidence of progressive disease or confirmed objective progressive disease. The determining factor for whether a patient can continue on study drug should be based on his/her clinical symptoms even if the patient has progressive disease based on radiological evidence. The investigator may also take into consideration biomarker responses (prostate-specific antigen [PSA], alpha-fetoprotein [AFP], etc).
- The patient experiences unacceptable toxicity including, but not limited to, a Grade 4 nonhematological toxicity or a toxicity that does not resolve to baseline within 21 days.
- The patient is noncompliant with study procedures and/or treatment (Section 7.6).

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

6.3.3. Discontinuation of Study Sites

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

6.3.4. Discontinuation of the Study

The study will be discontinued if Lilly, while considering the rights, safety, and well-being of the patient(s), judges discontinuation of the study 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

LY3039478 will be supplied as 25- and 50-mg capsules in bottles for oral consumption. LY3039478 capsules should be stored at room temperature within the temperature range stated on the label. Investigators should instruct patients to store the capsules at home in the original container and to keep out of the reach of children. Capsules should not be opened, crushed, or dissolved.

Taladegib will be supplied as 100-mg tablets in bottles for oral consumption. Taladegib tablets should be stored within the temperature range stated on the label. Investigators should instruct patients to store the tablets at home in the original container and to keep out of the reach of children. Tablets should not be crushed or dissolved.

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

Abemaciclib will be supplied as 50-mg hypromellose capsules and should be stored within the temperature range stated on the label. Investigators should instruct patients to store the capsules at home in the original container and to keep out of the reach of children. Capsules should not be opened, crushed, or dissolved.

Gemcitabine will be supplied in commercially available dosage forms and provided according to the country's regulatory requirements. Gemcitabine should be stored and prepared in accordance with the package insert.

Carboplatin will be supplied in commercially available dosage forms and provided according to the country's regulatory requirements. Carboplatin should be stored and prepared in accordance with the package insert.

Cisplatin will be supplied in commercially available dosage forms and provided according to the country's regulatory requirements. Cisplatin should be stored and prepared in accordance with the package insert.

Clinical trial materials will be labeled according to the country's regulatory requirements, and Lilly will perform the labeling and the final packaging of the study medications under good manufacturing practice (GMP) conditions. All study drugs should be stored within the temperature range stated on the label.

7.2. Study Drug Administration

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/legal representative,
- verifying that instructions are followed properly,
- maintaining accurate records of study drug dispensation 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

LY3039478 will be administered orally TIW in all parts (in both the dose-escalation phases and the dose-confirmation phases) according to the schedule shown below.

- Monday, Wednesday, Friday every week for a 21- or 28-day cycle
- Tuesday, Thursday, Saturday every week for a 21- or 28-day cycle
- Wednesday, Friday, Sunday every week for a 21- or 28-day cycle
- Thursday, Saturday, Monday every week for a 21- or 28-day cycle

Patients will receive LY3039478 orally TIW. LY3039478 will be taken once per day on days of administration prior to a meal (recommendation is within 30 minutes) on an empty stomach.

During all cycles, study drug should be taken at approximately the same time on the dosing days. Any deviations should be documented in the patient diary. If a patient misses or vomits a LY3039478 dose, that dose should be omitted.

In all study parts during Cycles 1 and 2, patients will record the time and amount of each dose of LY3039478 in a patient diary, additionally the amount of each dose of taladegib, LY3023414, and abemaciclib should be recorded by patients in the diary for doses associated with PK sampling days. For Cycle 3 and beyond, the first and last dose dates for each drug in each individual cycle will be documented.

Clinic personnel will instruct patients to pay particularly close attention to and record this information accurately on days of PK assessments (Attachment 4).

The patient or clinic personnel will record this information in the patient diary, and study monitors will cross-reference clinic records at the site to verify accuracy.

For Cycle 2 and beyond, a delay of ≤7 days in the start of a cycle (Dose 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 ≤21 days in the start of a cycle (Dose 1) to allow for recovery from toxicity will be permitted and does not constitute a protocol violation (refer to Section 7.2.4.1.2).

Dose regimens are shown in Table JJCD.7.1.

Table JJCD.7.1. Dose Regimens

Treatment	Regimen
Part A: LY3039478 + taladegib 1 cycle = 28 days	Single dose of taladegib given on Day 1 during a 3-day lead-in period (only for Part A dose escalation) LY3039478 dose-escalation dose TIW, Days 1 to 28 Taladegib dose-escalation dose QD, Days 1 to 28
Part B: LY3039478 + LY3023414 1 cycle = 28 days	Single dose of LY3023414 given on Day 1 during a 3-day lead-in period (only for Part B dose escalation) LY3039478 dose-escalation dose TIW, Days 1 to 28 LY3023414 dose-escalation dose BID, Days 1 to 28
Part C: LY3039478 + abemaciclib 1 cycle = 28 days	Single dose of Abemaciclib given on Day 1 during a 3-day lead-in period (only for Part C dose escalation) LY3039478 dose-escalation dose TIW, Days 1 to 28 Abemaciclib dose-escalation dose BID, Days 1 to 28
Part D: LY3039478 + cisplatin/gemcitabine 1 cycle = 21 days	LY3039478 dose-escalation dose TIW, Days 1 to 21 Cisplatin 25 mg/m^2, Days 1 and 8 of a cycle. Gemcitabine 1000 mg/m^2, Days 1 and 8 of a cycle
Part E: LY3039478 + gemcitabine/carboplatin 1 cycle = 21 days	LY3039478 dose-escalation dose TIW, Days 1 to 21 Gemcitabine 1000 mg/m^2, Days 1 and 8 of a cycle Carboplatin AUC 2, Days 1 and 8 of a cycle

Abbreviations: AUC = area under the plasma concentration-time curve; BID = twice daily; QD = daily; TIW = 3 times per week.

7.2.1.1. LY3039478 in Combination with Taladegib (Part A)

Patients enrolled in Part A for the dose-escalation phase only will receive a single dose of taladegib on Day 1 during a 3-day lead-in period.

LY3039478 will be given orally TIW in combination with taladegib given orally QD. LY3039478 and taladegib should be taken at approximately the same time on the dosing days.

Drugs will be taken as specified above prior to a meal (recommendation is at least 30 minutes prior) on an empty stomach. During all cycles, any study drug deviations should be documented in the patient diary for both drugs. If a patient misses or vomits a dose, that dose should be omitted.

7.2.1.2. LY3039478 in Combination with LY3023414 (Part B)

Patients enrolled in Part B for the dose-escalation phase only will receive a single dose of LY3023414 on Day 1 during a 3-day lead-in period.

LY3039478 will be given orally TIW in combination with LY3023414 given orally BID. LY3039478 and LY3023414 should be taken at approximately the same time on the dosing days when applicable.

LY3023414 will be taken as a chronic/continuous treatment approximately every 12 hours with a full glass of water. Patients should not consume food for approximately 1 hour before taking each dose of LY3023414 (if feasible). Patients should swallow LY3023414 as a whole capsule/tablet 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 scheduled. If the next dose is to be taken in less than 6 hours or the patient vomits a dose, the patient should skip the missed dose and take the next dose as scheduled.

During all cycles, any study drug deviations should be documented in the patient diary for both drugs.

7.2.1.3. LY3039478 in Combination with Abemaciclib (Part C)

Patients enrolled in Part C for the dose-escalation phase only will receive a single dose of abemaciclib on Day 1 during a 3-day lead-in period.

LY3039478 will be given orally TIW in combination with abemaciclib given orally BID. LY3039478 and abemaciclib should be taken at approximately the same time on the dosing days when applicable.

Abemaciclib will be taken as a chronic/continuous treatment every 12 hours. During all cycles, any study drug deviations should be documented in the patient diary for both drugs. If a patient misses or vomits a dose, that dose should be omitted.

7.2.1.4. LY3039478 in Combination with Cisplatin and Gemcitabine (Part D)

Patients will receive LY3039478 orally TIW. On Days 1 and 8 of each 21-day cycle, LY3039478 should be given before the cisplatin and gemcitabine infusions.

Patients enrolled in Part D will receive LY3039478 in combination with cisplatin and gemcitabine. Patients will receive 25 mg/m^2 cisplatin on Days 1 and 8 of each 21-day cycle. Cisplatin should be administered following the institutional-approved protocols for pre- and posthydration together with standard-of-care premedication. All concomitant medications, including premedication, should be recorded on the CRF. Suggested administration is on an outpatient basis as a 1.5-hour IV infusion (1 liter of 0.9% saline including cisplatin, 20 mmol of potassium chloride, and 8 mmol of magnesium sulfate over 1 hour followed by 500 mL of 0.9% saline over 30 minutes). The dose of cisplatin is to remain constant unless dose modification is required (see Section 7.2.4). The dose of cisplatin administered should be rounded to the nearest 1 mg. Treatment should continue on schedule if possible, but a variance of ±2 days may be allowed to accommodate holidays and clinic scheduling conflicts.

Patients will receive 1000 mg/m^2 gemcitabine administered over 30 minutes on Days 1 and 8 of each 21-day treatment cycle. Investigators should consult the approved gemcitabine package insert for complete packaging and labeling information. The gemcitabine infusion should start immediately following the cisplatin dose.

If applicable, after discontinuation of gemcitabine or cisplatin patients may continue to receive treatment with LY3039478 as a single agent if they are deriving clinical benefit.

7.2.1.5. LY3039478 in Combination with Gemcitabine and Carboplatin (Part E)

Patients will receive LY3039478 orally TIW. On Days 1 and 8 of each 21-day cycle, LY3039478 should be given before the gemcitabine and carboplatin infusions.

Patients enrolled in Part E will receive LY3039478 in combination with gemcitabine and carboplatin. Patients will receive 1000 mg/m^2 gemcitabine administered over 30 minutes on Days 1 and 8 of each 21-day treatment cycle. Investigators should consult the approved gemcitabine package insert for complete packaging and labeling information.

Patients will receive carboplatin dosed at AUC 2 IV over 30 minutes on Days 1 and 8 of each 21-day treatment cycle. Investigators should consult the approved carboplatin package insert for complete packaging and labeling information.

At sites where serum creatinine is determined by a method standardized to the isotope dilution mass spectrometry (IDMS) reference material, the estimated glomerular filtration rate (GFR) used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min. All United States (US) and any other outside the US (OUS) site where the IDMS method is available should calculate carboplatin doses based upon serum creatinine values that were measured by the IDMS method. At sites where the IDMS method is not available, for the estimated GFR used to calculate the Calvert formula, all sites should use the method of serum creatinine measurement and carboplatin dosing that is aligned with local practice standard of care.

The site is responsible to consult the local laboratory to determine what method of serum creatinine measurement is used by that laboratory.

If applicable, after discontinuation of gemcitabine or carboplatin patients may continue to receive treatment with LY3039478 as a single agent if they are deriving clinical benefit.

7.2.2. Dose Escalation

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis until the MTD of each combination with LY3039478 is determined.

In this study, dose escalation will be driven by safety using the 3+3 method.

Each new dose level will have a minimum of 3 patients enrolled to it. If 1 patient, at any dose level, experiences a DLT within the first cycle of LY3039478, then up to 3 additional patients will be enrolled at that dose level. If a DLT is observed in 2 or more patients at any dose level, dose escalation will cease and either the previous dose level will be declared the MTD or, following discussions between the sponsor and investigators additional patients may be treated at intermediate doses between the previous and current dose levels.

In addition, if available at the time of dose-escalation decision, PK (C_{max}, AUC, and apparent systemic clearance [CL/F]) results will be used as secondary/supporting data for dose escalation.

Additional patients may therefore be enrolled at a specific dose level to characterize PK/PD, provided the observed DLT rate does not exceed 33%.

No dose escalation can occur without prior discussion and agreement between the investigator and the Lilly CRP; the decision will be documented in writing.

Based on the ongoing safety reviews, modifications to the dose-escalation strategy or other design elements may be made via protocol amendment to ensure patient safety.

During dose escalation, the starting dose LY3039478 will be 25 mg TIW. This dose was defined from Study JJCA, and data will be evaluated on an ongoing basis until the MTD is determined.

Table JJCD.7.2 shows the proposed dose levels for LY3039478 in combination with taladegib for Part A.

Table JJCD.7.3 shows the proposed dose levels for LY3039478 in combination with LY3023414 for Part B.

Table JJCD.7.4 shows the proposed dose levels for LY3039478 in combination with abemaciclib for Part C.

Table JJCD.7.5 shows the proposed dose levels for LY3039478 in combination with cisplatin and gemcitabine for Part D.

Table JJCD.7.6 shows the proposed dose levels for LY3039478 in combination with gemcitabine and carboplatin for Part E.

Intermediate/other dose levels will be explored if deemed necessary after discussion between the sponsor and investigators and taking into account patient safety and PK/PD information.

Table JJCD.7.2. Proposed Dose-Escalation Scheme for Part A

Dose Level	LY3039478 Dose (mg)	Taladegib Dose (mg)
1	25	200
2	50	200
3	50	400

Table JJCD.7.3. Proposed Dose-Escalation Scheme for Part B

Dose Level	LY3039478 Dose (mg)	LY3023414 Dose (mg)
1	25	150 BID
2	50	150 BID
3	50	200 BID

Abbreviation: BID = twice daily.

Table JJCD.7.4. Proposed Dose-Escalation Scheme for Part C

Dose Level	LY3039478 Dose (mg)	Abemaciclib Dose (mg)
1	25	100 BID
2	50	100 BID
3	50	150 BID

Abbreviation: BID = twice daily.

Table JJCD.7.5. Proposed LY3039478 Dose-Escalation Scheme for Part D

Dose Level	LY3039478 Dose (mg)	Gemcitabine Dose (mg/m^2) D1, D8	Cisplatin Dose (mg/m^2) D1, D8
1	25	1000	25
2	50	1000	25

Abbreviation: D = Day.

Table JJCD.7.6. Proposed LY3039478 Dose-Escalation Scheme for Part E

Dose Level	LY3039478 Dose (mg)	Gemcitabine Dose (mg/m^2) D1, D8	Carboplatin Dose (AUC) D1, D8
1	25	1000	2
2	50	1000	2

Abbreviations: AUC = area under the plasma concentration-time curve; D = Day.

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

A DLT is defined as an AE during Cycle 1 that is related to LY3039478, taladegib, LY3023414, or abemaciclib and fulfills any 1 of the following criterion using the NCI CTCAE v 4.0:

- ≥CTCAE Grade 3 nonhematological toxicity. Exceptions will be made for:
  - Grade 3 nausea, vomiting, or constipation that lasts ≤72 hours and that can be controlled with treatment or Grade 4 vomiting or constipation that lasts ≤24 hours and that can be controlled with treatment
  - Grade 3 electrolyte disturbance that can be controlled with treatment. Grade 4 electrolyte disturbance lasting more than 24 hours will be considered a DLT
  - Diarrhea CTCAE Grade 3 for 4 days or less and that can be controlled with standard treatment
  - Transient (<7 days) Grade 3 elevations of ALT and/or AST that are not accompanied by a Grade 2 bilirubin increase are considered an exception to the DLT criteria, unless there is a clear alternative cause for example, worsening

biliary obstruction) if agreed by the study investigator and Lilly CRP/clinical research scientist (CRS)

- CTCAE Grade 4 anemia
- CTCAE Grade 4 neutropenia or leukopenia of >5-days duration
- Any febrile neutropenia
- Grade 3 thrombocytopenia with clinically significant bleeding or Grade 4 thrombocytopenia
- Inability to start Cycle 2 within 3 weeks of the expected date because of persistent toxicity related to LY3039478, taladegib, LY3023414, or abemaciclib
- Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose limiting (for example, any toxicity that is possibly related to the study medication that requires the withdrawal of the patient from the study during Cycle 1)
- Exceptions to the DLT criteria for Part B include:
    - Grade 3 fasting hyperglycemia that resolves to ≤Grade 2 within 7 days
    - Grade 4 hyperglycemia lasting <24 hours
    - Grade 3 mucositis that resolves to ≤Grade 2 within 7 days. Grade 4 mucositis of any duration will be considered a DLT
    - Grade 3 fatigue that resolves to ≤Grade 2 within 5 days
    - 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 DLET is defined as an AE occurring between Day 1 and Day 21/28 of any cycle (other than Cycle 1) for a patient enrolled in the dose-escalation phase of Parts A, B, and C or in any cycle (including Cycle 1) for a patient enrolled in the dose-confirmation phase of Parts A, B, and C that would have met the criteria for DLT if it had occurred during Cycle 1 for a patient enrolled in the dose-escalation phase of Parts A, B, and C.

For the purpose of this study, the MTD is defined as the highest tested dose that has <33% probability of causing a DLT during Cycle 1 in a cohort of at least 6 patients.

Determination of the recommended dose will take into account toxicities beyond Cycle 1, PK, and dose modifications of standard chemotherapy.

7.2.3. Dose-Confirmation Phase

For each combination in the dose-escalation phase, there will be a dose-confirmation phase in specific tumor types. Patients in the dose-confirmation phase will be treated at a dose no greater than the defined MTD from the dose-escalation phase. Should a DLET occur in more than one third of patients at any time during the confirmation phase, Lilly clinical personnel and study investigators will meet and assess the severity and nature of the DLETs. A decision will be made to continue at the current dose or to de-escalate the dose and define a new dose for the expansion phase. This review and decision will be documented in writing.

7.2.4. Dose Adjustments and Delays

7.2.4.1. LY3039478

7.2.4.1.1. Dose Adjustments within a Cycle

Dose adjustments within Cycle 1 should be avoided if possible. If a dose adjustment or delay is required during Cycle 1 of treatment in dose-escalation phase of the study, the patient will be allowed to continue but may be replaced if deemed appropriate by the Lilly CRP and investigator.

If a patient treated at a given dose level experiences a DLT or a DLET (as defined in Section 7.2.2.1), then treatment will be suspended for that patient. Dosing may restart after recovery from toxicity at a lower dose after consultation between the investigator and Lilly CRP. If a toxicity does not meet the criteria for a DLT in Cycle 1 (or a DLET) but nonetheless requires omission of dose(s) for tolerability, then dosing may resume at the same dose or reduced dose after the toxicity resolves to baseline; however, the dose(s) omitted for tolerability during a cycle will not be replaced.

7.2.4.1.2. Dose Adjustments between Cycles

Nonhematologic toxicity must resolve to CTCAE Grade 0, 1, or baseline level before resuming treatment (with the exception of alopecia, fatigue, skin rash, nausea, vomiting, constipation, or diarrhea that can be controlled with treatment). The start of a cycle may be delayed up to 21 days to allow sufficient time for recovery. Patients experiencing Grade 4 nonhematological toxicity or not recovering from toxicity within 21 days should be discontinued from the study.

Hematologic toxicity must resolve to CTCAE Grade 0, 1, or baseline level before resuming treatment.

The dose for a patient should be reduced for all subsequent cycles of therapy, to the dose level administered in the previous cohort, if the investigator determines that it is in the best interest of the patient or if the patient experienced at least 1 of the following events:

- DLT or DLET
- Omission of >7 doses in a single cycle for tolerability.

For such patients requiring a dose reduction, re-escalation to the original dose level is not permitted. If a patient experiences a DLET at the reduced dose level, then the patient will be discontinued from the study. If a patient requires omission of >3 doses for tolerability at the reduced dose level, then treatment may continue if the investigator determines that the patient is receiving clinical benefit. Dose reduction by >1 dose level is not permitted; patients requiring dose reduction by >1 dose level should be discontinued from the treatment.

Diarrhea should be managed by standard treatments as per institutional guidelines. Guidance for diarrhea standard management is provided in Attachment 9.

7.2.4.2. Dose Adjustments with Taladegib

Dose adjustments within Cycle 1 should be avoided if possible. If a dose adjustment or delay is required during Cycle 1 of treatment during the dose-escalation phase, the patient will be allowed to continue but may be replaced if deemed appropriate by the Lilly CRP and investigator. Dose adjustments and delays are allowed after Cycle 1 of treatment, as deemed appropriate by the investigator. See Table JJCD.7.7 for specific dose-reduction guidance relating to nonhematologic toxicities. All dose adjustments and delays are to be documented in the eCRFs.

Patients who do recover within the approximately 14-day time frame may have their dose reduced. Patients in Cohort 1 of Part A who do not recover within this approximately 14-day time frame should discontinue taladegib. Re-escalation to the previous dose is acceptable in the absence of continuing toxicity. If subsequent dose reduction is required after re-escalation, the patient must be maintained at the reduced dose level for all remaining cycles. Patients may have more than 1 dose reduction; however, the lowest dose that may be administered is 100 mg of taladegib.

If a dose is missed, it will not be made up. If a patient has not taken ≥80% of the required doses in the first cycle, the patient will be deemed noncompliant/nonevaluable and will be replaced. The patient, however, will be permitted to continue on study. If the patient experiences a DLT, the cohort will be expanded as described in Section 7.2.2.

If the offending study drug is discontinued because of unacceptable toxicity, the patient may continue single-agent treatment with LY3039478.

Table JJCD.7.7. Dose Adjustments for Taladegib

Toxicity/CTCAE Grade	Percent of Previous Dose (Taladegib)
Grades 0–2	100%
Grade 2 dysgeusia lasting longer than 4 weeks[a]	50%
Grade 2 muscle cramping lasting longer than 4 weeks[a]	50%
Any Grade 3 or 4 nonhematologic toxicities not specified above	50%
Recurrence of any Grade 3 or 4 toxicity after 2 dose reductions	Discontinue[b]

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.

[a] At investigator's discretion; however, the dose may be reduced sooner than 4 weeks if it is determined to be intolerable.

[b] Discontinue patient from study treatment.

7.2.4.3. Dose Adjustments with LY3023414

Dose adjustments for LY3023414 will follow the same principle guidance as outlined for LY3039478 in Section 7.2.4.1.

Dose adjustments in Cycle 1 should be avoided if possible. If a dose adjustment or delay is required during Cycle 1 of treatment in the dose-escalation phase of the study, the patient will be

allowed to continue if an AE has resolved sufficiently but may be replaced if deemed appropriate by the Lilly CRP and investigator.

In Cycle 2 and beyond, dose adjustments and delays are allowed as deemed appropriate by the investigator. If a patient treated at a given dose level experiences a DLT or a DLET (as defined in Section 7.2.2.1), then treatment will be suspended for that patient. Dosing may restart after recovery from toxicity at a lower dose after consultation between the investigator and Lilly CRP. If a toxicity does not meet the criteria for a DLT in Cycle 1 (or a DLET) but nonetheless requires omission of dose(s) for tolerability, then dosing may resume at the same dose or reduced after the toxicity resolves to baseline; however, the dose(s) omitted for tolerability or missed doses during a cycle will not be replaced. Dose omissions within a cycle do not alter the start of the next scheduled cycle.

Doses of LY3023414 may be adjusted according to Table JJCD.7.8. If the patient is receiving the lowest allowable dose and experiences an AE requiring a dose reduction, LY3023414 should be discontinued. Re-escalation of study drug(s) may be considered if clinically warranted, following discussion and approval by the CRP. Re-challenge of patients with dose-reduced study drug(s) following recovery from Grade 4 AEs may be considered on a case-by-case basis in consultation with the CRP. Any patient requiring an AE-related dose delay of more than 21 days after Cycle 1 from the intended day of the next scheduled dose due to a study drug related AE should be discontinued from the study, unless discussed with the Lilly CRP.

Table JJCD.7.8. Dose Adjustments for LY3023414

Dose Level	LY3023414
1	150 mg BID
2	100 mg BID

Abbreviation: BID = twice daily.

If the offending study drug is discontinued because of unacceptable toxicity, the patient may continue single-agent treatment with LY3039478.

If consistent dose omissions of LY3023414 are required because of toxicity during combination therapy, a less frequent dosing schedule of LY3023414 may be instituted. This decision will be made following discussions with the investigators and the Lilly CRP and will be documented in writing.

7.2.4.4. Dose Adjustments with Abemaciclib

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

If a patient experiences 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 JJCD.7.9.

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 JJCD.7.9.

If a patient experiences persistent or recurrent Grade 2 nonhematologic toxicity (except diarrhea) 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 JJCD.7.9.

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 JJCD.7.9, 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.

Patients requiring dose reduction by >2 dose levels should be discontinued from the treatment. Patients may remain on single agent treatment with LY3039478.

Table JJCD.7.9. Dose Adjustments of Abemaciclib

Dose Adjustment levels	Oral Dose	Frequency
1	100 mg	Every 12 hours
2	50 mg	Every 12 hours

7.2.4.5. Dose Adjustments with Cisplatin and Gemcitabine

Initiation of a new cycle with cisplatin requires an ANC of at least 1,000/µL, platelets of at least 75,000/µL, and resolution of nonhematologic toxicities to CTCAE v 4.0 Grade 0, 1, or baseline (except alopecia and fatigue).

Resolution of toxicity is required to occur within 3 weeks of the intended start of the cycle, otherwise cisplatin therapy should be discontinued. Patients discontinuing cisplatin therapy may be allowed to continue LY3039478 and gemcitabine if they are receiving clinical benefit.

Resolution of toxicity is required to occur within 3 weeks of the intended start of the cycle, otherwise gemcitabine therapy should be discontinued. Patients discontinuing gemcitabine therapy may be allowed to continue LY3039478 and cisplatin if they are receiving clinical benefit.

Cisplatin and gemcitabine therapy will not be delayed for LY3039478-related toxicity and the patient will continue to receive regularly scheduled infusions of cisplatin and gemcitabine. If LY3039478 is terminated for LY3039478-related toxicity after a minimum of 4 cycles, cisplatin or gemcitabine may be continued as monotherapy or in combination until progression of disease.

Patients will continue their scheduled evaluation visits according to the Study Schedule (Attachment 1) until progression of disease.

In the case of cisplatin or gemcitabine non-GI-related toxicity, LY3039478 will not be delayed and the planned schedule for administration should be maintained. If cisplatin or gemcitabine is terminated for non-GI-related toxicity, LY3039478 may be continued if clinically indicated (Table JJCD.7.10).

Table JJCD.7.10. Cisplatin and Gemcitabine Dose Adjustment for Toxicity

	Event			**Cisplatin Dose**	**Gemcitabine Dose**
In previous cycle	Febrile neutropenia or Grade 4 ANC ≥7 days			Dose at 75% of prior dose. Prior to treatment toxicity should have recovered to ≤ Grade 2 and ANC ≥1000/µL and platelets ≥75,000/µL. Consider growth factor support per ASCO guidelines.	
Current or prior cycle	Cisplatin or gemcitabine associated Grade 3-4 non-hematologic AE			Treatment with cisplatin and/or gemcitabine should be deferred until recovery, and then continued with an appropriate dose reduction, adjustment of mitigatable factors, or discontinued as clinically indicated.	
	Bilirubin >1.6 mg/dL (>27 µmol/L)				Initiate gemcitabine dose at 800 mg/m^2. May reduce further for hematologic AEs as defined below
	ANC (/µL)		**Platelets (/µL)**		
Day 1	>1000 to <1500	and	≥100,000	Dose at 100% dose.	Dose at 100% dose.
	500 to 1000	or	50,000 to <100,000	Give 100% of dose	Give 75% of prior dose.
	<500	or	<50,000	Postpone until ANC >1000/µL or platelets > 100,000/µL. If longer than 1 week resume dosing in next cycle with a 75% dose reduction.	
Day 8	>1000 to <1500	and	≥100,000	Dose at 100% of prior dose.	Dose at 100% of prior dose.
	500 to 1000	or	50,000 to <100,000	Give 100% of dose.	Administer 75% of prior dose; continue this reduced dose in next cycle.
	<500	or	<50,000	Hold for recovery. At next cycle, restart at 75% of prior dose.	Hold for recovery. At next cycle, restart at 75% of prior dose.

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; ASCO = American Society for Clinical Oncology.

7.2.4.6. Dose Adjustments with Gemcitabine and Carboplatin

A cycle may be delayed up to 21 days to allow a patient sufficient time for recovery from toxicity related to study treatment. Before the start of each cycle, hematologic toxicities must resolve according to the guidelines in Table JJCD.7.11 and Table JJCD.7.12. Nonhematologic toxicities must resolve to the patient's baseline CTCAE grade or lower. A cycle may be delayed by 7 days to accommodate a patient's schedule or for other unforeseen circumstances.

Treatment delays between cycles that fulfill these criteria do not constitute a protocol violation. Patients who require a delay in treatment of more than 21 days for toxicity will be required to discontinue study treatment and enter the postdiscontinuation follow-up period (Section 6.2).

Table JJCD.7.11. Dose Modification Based on Neutrophil and/or Platelet Count on Day of Treatment (Day 1 and Day 8)

Neutrophil Count (/µL)		Platelet Count (/µL)	Dose Modification on Count Recovery	
			Carboplatin Dose	Gemcitabine Dose
≥1000	and	>100,000	100%	100%
500-1000	or	50,000-100,000	100% or delay	75% or delay based on clinical assessment
<500	or	<50,000	Delay	Stop this cycle if Day 8

Table JJCD.7.12. Dose Modification Based on Common Toxicity Criteria

Toxicity	Definition	Dose Adjustment
Febrile neutropenia	ANC <500/µL plus fever requiring IV antibiotics ± hospitalization	Give a 20% reduction for all future doses of carboplatin and gemcitabine
Other toxicities	Grade 3/4 toxicity (except alopecia)	Delay treatment. Resume with 20% dose reduction of carboplatin and/or gemcitabine provided toxicity has resolved to Grade 1 or less. If further toxicity occurs, an additional reduction may be made after discussion with consultant.

Abbreviations: ANC = absolute neutrophil count; IV = intravenous.

Gemcitabine and carboplatin therapy will not be delayed for LY3039478-related toxicity and the patient will continue to receive regularly scheduled infusions of gemcitabine and carboplatin. If the LY3039478 is terminated for LY3039478-related toxicity after a minimum of 4 cycles, gemcitabine (or carboplatin) may be continued as monotherapy or in combination with carboplatin until progression of disease. Patients will continue their scheduled evaluation visits according to the Study Schedule (Attachment 1) until progression of disease.

In the case of gemcitabine or carboplatin non-GI-related toxicity, LY3039478 will not be delayed and the planned schedule for administration should be maintained. If a delay of more than 3 weeks is required for recovery of gemcitabine- or carboplatin-related toxicity, or more than 2 dose reductions of gemcitabine or carboplatin are necessary, the patient should discontinue treatment with gemcitabine and carboplatin. If gemcitabine or carboplatin is terminated for non-GI-related toxicity, LY3039478 may be continued if clinically indicated.

7.3. Method of Assignment to Treatment

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, study part, and cohort for each patient. No dose

escalations (that is, to the next cohort) can occur without prior discussion and agreement with the responsible Lilly CRP or CRS.

If investigators have eligible patients who have consented concurrently, more than 3 patients may be entered at a particular dose level provided that accrual has not ceased due to excessive toxicity. This enrollment procedure is allowed because of the advanced disease state of this patient population and the screening involved in defining eligibility. This event should be approved by the sponsor following discussions with the investigators.

7.4. Blinding

This is an open-label study.

7.5. Concomitant Therapy

No other chemotherapy, immunotherapy, cancer-related hormone therapy, or experimental drugs will be permitted while the patients are on this study. An exception will be made for prostate cancer patients continuing GnRH agonist therapy or breast cancer patients continuing antiestrogen therapy (for example, an aromatase inhibitor). Patients participating in Parts A, B, and C of the study (LY3039478 + taladegib, LY3023414, or abemaciclib, respectively) should not take any concomitant medications that are strong CYP3A4 inhibitors or inducers. In addition, patients receiving LY3023414 (Part B) should avoid concomitant medication known to be sensitive substrates of CYP3A4 (for example, simvastatin, lovastatin, buspirone), cleared by CYP3A4 that have a narrow therapeutic range, or cause QTc interval prolongations (refer to Attachment 10 and Attachment 11 for further details). Palliative radiotherapy is allowed. In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate early discontinuation from the study. Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the CRF.

Patients should receive full supportive care with the exception that the routine use of granulocyte colony stimulating factors (G-CSF) is not permitted during this study. Patients should not receive G-CSF prophylactically in any cycle. G-CSF may be used only for patients who have ANC $<0.5 \times 10^9$, neutropenic fever, or documented infections while neutropenic. Use of G-CSF must be discontinued at least 24 hours before the start of the next cycle of treatment. Should the use of hematopoietic colony-stimulating factors (CSF) be necessary, follow the American Society of Clinical Oncology (ASCO) recommendations for the use of CSFs (Smith et al. 2015). If clinically indicated at any time during the study, erythropoietin and packed red blood cell transfusions may be used according to ASCO guidelines (Rizzo et al. 2008).

Patients should not receive corticosteroids prophylactically with the intent of attenuating GI toxicity. However, corticosteroid therapy initiated before study entry for a preexisting condition may be continued. Corticosteroids may be used for treatment of GI toxicities if deemed necessary after agreement between the investigators and Lilly CRP. As a guidance, standard treatments are provided in Attachment 9.

All concomitant medications should be recorded throughout the patient's participation in the study.

7.6. Treatment Compliance

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

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 the prescribed amount of drug(s). Potential discontinuation of a patient due to study drug noncompliance will be discussed between the investigator and the Lilly CRP or CRS before the final determination is made to discontinue the patient.

Some of the anticancer treatments 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 CRF.

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.

Any patient who is discontinued from the study before completing 1 cycle of LY3039478 treatment will be deemed nonevaluable for assessment of a dose level, unless they experience a DLT prior to withdrawal.

Patients who receive all doses of LY3039478 but discontinue from study treatment before the end of Cycle 1 will be considered evaluable for the assessment of a dose level provided it can be documented whether the patient did or did not experience a DLT within 21 or 28 days of Cycle 1 Day 1.

If the patient is noncompliant during Cycle 1 because of reasons other than drug-related toxicity, he or she will be considered nonevaluable and may be replaced.

Nonevaluable patients may be replaced to ensure that enough patients complete 1 cycle of therapy at each dose level, unless accrual to that cohort has stopped because of a DLT.

Patients who are not evaluable for PK, but who complete 1 cycle of therapy, may be replaced upon consultation with the investigator(s) and the Lilly CRP or CRS to ensure adequate PK data, unless accrual to that cohort has stopped because of a DLT.

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

8.1. Safety Evaluations

The safety and tolerability of LY3039478 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 allow additional characterization of the safety profile of LY3039478 in patients. Study procedures and their timing, including collection of blood and urine samples, are described in the Study Schedule (Attachment 1).

Standard laboratory tests, including chemistry, hematology, coagulation, and urinalysis panels will be performed. A serum pregnancy test will be administered if applicable. Other clinical laboratory tests will also be collected. Attachment 2 lists the specific tests that will be performed for this study.

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 JJCD.8.1 presents a summary of AE and SAE reporting guidelines. Table JJCD.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 laboratory tests, 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.

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. 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 CRF. 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. Data on fetal outcome and breastfeeding should be collected, if feasible, for regulatory reporting and drug safety evaluation.

Upon documentation of pregnancy, the patient must be removed from the study and treatment with study drug(s) must be stopped immediately.

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.

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 designated data transmission methods 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 protocol procedure and study drug via designated data transmission methods.

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

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

Planned hospitalizations or elective procedures for underlying 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 one 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.

If an investigator becomes aware of SAEs occurring after the patient's participation in the trial has ended, and the investigator believes that the SAEs are 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 LSS.

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.

8.1.2.2. 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 LSS.

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 LY3039478, taladegib, LY3023414, abemaciclib, gemcitabine, carboplatin, and/or cisplatin), 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 until the patient and the investigator agree that the patient will no longer continue any study treatment.

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 (Visit 801) must be reported to Lilly or its designee. The follow-up visit starts 1 day after the patient and the investigator agree that the patient will no longer continue any study treatment and lasts approximately 30 days. 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 days ± 3 days after the patient and the investigator agree that the patient will no longer continue any study treatment.

Following the safety assessments, which mark the end of the follow-up visit (Visit 801), 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 (Visit 801), AEs are not required to be reported unless the investigator feels the AEs were related to either study drug or a protocol procedure. If an investigator becomes aware of an SAE 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 LSS.

8.1.2.3. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (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 Code of Federal Regulations (CFR) 312.32, the European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global 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 JJCD.8.1 and Attachment 5.

Table JJCD.8.1. Adverse Event and Serious Adverse Reporting Guidelines for Study JJCD

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 when the patient and the investigator agree that the patient will no longer continue any study treatment)	All AEs All SAEs regardless of relatedness	X X	 X
Follow-up visit (Visit 801) (Starts the day after the patient and the investigator agree that the patient will no longer continue any study treatment and ends when end of study safety assessments are completed in 30 days OR the planned end of the cycle)	All AEs All SAEs regardless of relatedness	X X	 X
Continued access period	All AEs All SAEs regardless of relatedness	X X	 X
Continued access 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 of which the investigator becomes aware		X

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

8.1.3. Other Safety Measures

8.1.3.1. Electrocardiograms

For each patient, a 12-lead digital electrocardiogram (ECG) will be collected according to the Study Schedule (Attachment 1). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Consecutive replicate ECGs (usually triplicates) will be obtained at approximately 1-minute intervals.

ECGs may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs (more replicates) than expected at a particular time point is allowed 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 the patient meets entry criteria at the relevant visit(s) and for immediate patient management, should any clinically relevant findings be identified.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) to determine whether 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 from at least 1 of the replicate ECGs from each time point.

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will then conduct a full overread on 1 of the replicate ECGs (including all intervals). A report based on data from this overread will be issued to the investigative site. For each set of replicates, the RR and QT intervals and heart rate will be determined on the ECGs that were not fully overread. These data are not routinely reported back to the investigative site.

All data from the overreads will be placed in the Lilly database for analytical and study report purposes. Any clinically significant finding that was not present on the fully overread ECG but was present on the partially overread ECG (where only RR, QT, and heart rate is assessed) will be reported to the investigator and to Lilly. If there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the investigator's (or qualified designee's) interpretation will be used for study entry and immediate subject management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes.

The investigator (or qualified designee) must document his/her review of 1 of the replicate ECGs printed at the time of collection, the final overread ECG report issued by the central ECG laboratory, and any alert reports.

8.1.4. Safety Monitoring

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

Representatives from Lilly Global Patient Safety will specifically monitor SAEs. Lilly will review SAEs within time frames mandated by company standard operating procedures. The Lilly CRP/CRS will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or CRS, and periodically review:

- trends in safety data,
- laboratory analytes,

- AEs,
- If a study patient experiences elevated ALT ≥5 times ULN and elevated total bilirubin ≥2 times ULN, clinical and laboratory monitoring should be initiated by the investigator
- For patients entering the study with ALT ≥3 times ULN, monitoring should be triggered at ALT ≥2 times ULN 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).

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 combination 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 and assessments in this study.

Attachment 2 lists the specific tests that will be performed for this study.

Attachment 4 specifies the PK/PD sampling schedule for this study.

8.2.1. Samples for Study Qualification and Health Monitoring

Blood and urine samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health.

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

Pharmacokinetic samples will be collected as specified in Attachment 4.

Additional PK samples may be drawn during the study if warranted and agreed upon by both the investigator and sponsor.

Plasma concentrations of LY3039478, taladegib and its active metabolite (LSN3185556), abemaciclib and its active metabolites (LSN3106726 and LSN2839567), LY3023414, gemcitabine, cisplatin, and carboplatin will be quantified using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. All bioanalytical samples will be stored in a facility chosen by the sponsor. The remaining plasma samples collected for PK evaluation may be used for exploratory studies to assess the metabolism of LY3039478 and/or taladegib, which may involve sample pooling. These samples may be retained for a maximum of 1 year following the last patient visit for the study.

After the first dose in Cycle 1 at all dose levels during dose escalation, total urine output for the first 6 to 8 hours will be collected and pooled for quantification of LY3039478, creatinine, and exploratory metabolite identification. Urine concentrations of LY3039478 will be quantified using validated LC-MS/MS assay. All urine samples will be stored in a facility chosen by the sponsor. The remaining urine from the samples collected for LY3039478 quantification may be used for exploratory metabolism work as deemed appropriate by the sponsor.

Bioanalytical samples collected to measure investigational product concentration and metabolism and/or protein binding will be retained for a maximum of 1 year following last patient visit for the study.

8.2.3. Pharmacogenetic Samples

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 pharmacogenetics analysis. This is a 1-time collection, as noted in the Study Schedule (Attachment 1).

Samples will be stored and exploratory analysis may be performed to identify genetic variants that might play a role in tumor biology or to evaluate their association with observed clinical outcomes to study drugs.

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 drugs. These investigations may be limited to a focused candidate gene study or, if appropriate, genome-wide association studies may be performed to

identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

The samples will be will be coded with the patient number and stored for up to a maximum of 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.

8.2.4. Exploratory Samples

Collection of samples for biomarker research is a component of this study. The following blood and tumor tissue samples will be collected.

Required samples for biomarker research to be collected from all patients in this study:

- blood samples
- skin biopsies
- archived tumor tissue

These samples are described in the following sections.

It is possible that biomarker data has already been generated from samples that were collected and analyzed prior to enrolling in this trial. This may include data generated from genetic analyses. If available, this data may be requested from medical records for use in the research described in the following sections.

8.2.4.1. Blood Samples for Aβ Assays

Blood samples will be collected for exploratory analysis of circulating Aβ peptides (for example, Aβ[1-x] or peptide components thereof) before and after treatment with LY3039478 during the dose-escalation phases of the study (all parts). 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 medically or scientifically appropriate. When medical and scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.2.4.2. Samples for Assessing CYP3A Induction

Blood samples will be collected for the exploratory analysis of cortisol concentrations in plasma. Urine samples collected will also be used for the exploratory analysis of 6β-hydroxy-cortisol excreted in urine. Samples will be retained for a maximum of 1 year following last patient visit for the study.

8.2.4.3. Blood Samples for Biomarker Research

In blood, an evaluation of analytes related to the mechanism of action of study drugs, Notch and signaling pathways of study drugs or downstream effects, and specific tumor cancer pathobiology may be evaluated to assess any potential correlation with response to study drugs. The analyses of these samples may be focused, but not limited to, gene expression panels, proteomics, enzyme-linked immunosorbent assay and/or sequencing approaches .

Samples may be stored for a maximum of 15 years following last patient visit for the trial.

8.2.4.4. Tumor Tissue and Skin Biopsies

Throughout this study, archived tumor tissue obtained previously for diagnostic purposes (for example, at initial diagnosis) will be requested for biomarker research. At baseline, a mandatory pretreatment formalin-fixed paraffin-embedded (FFPE) tumor tissue (paraffin blocks or unstained slides cut from that block) will be collected. Tumor biopsies and skin biopsies (as instructed by the laboratory manual) will be collected pre- and posttreatment for measuring various biomarkers. Table JJCD.8.2 presents tumor and skin biopsy collection time points.

Table JJCD.8.2. Tumor and Skin Biopsy Time Points

Collection Time Point	Dose Escalation Parts A, B, C, D, and E	Dose Confirmation Parts A, B, C, D, and E
Baseline archived tissue collection (FFPE)	Mandatory	Mandatory
Pre-/postdose tumor biopsies	Recommended	Recommended
Pre-/postdose skin biopsies	Mandatory	Mandatory
Disease progression	Recommended	Recommended

Abbreviation: FFPE = formalin-fixed paraffin-embedded.

The archived tissue samples, tumor biopsies, and/or skin biopsies may be analyzed for biomarkers that may include, but are not limited to, mechanism of action of study drugs, Notch signaling pathways or related pathway activation, immune functioning, and specific tumor cancer pathobiology. Mutation profiling, copy number variability, and gene/protein expression profiling may be performed on these samples to assess potential associations with these biomarkers and clinical outcomes.

Additionally, optional skin biopsies and/or optional tumor biopsies at time of disease progression will be collected. Furthermore, skin and/or tumor biopsies may be performed if deemed necessary by the investigator. The samples will be analyzed at laboratories using assays designated by the sponsor. Sample handling and shipment to the central laboratory will occur per instructions given to the study site. Details for the handling and shipping of the tumor tissue will be provided by the sponsor in a separate document. The tissue samples will be obtained using appropriate method. However, cytological or fine-needle aspiration specimens are not acceptable. Due diligence should be used to ensure that tumor specimen (not normal adjacent or tumor margins) is provided. Pathology reports accompanying the tissue may also be requested. Each sample will be labeled with patient number and tissue of origin and be stored for up to

15 years after the last patient visit at a facility selected by the sponsor. Any whole block submitted will be returned to the site.

8.3. Efficacy Evaluations

A secondary objective of the study is to document any antitumor activity. Refer to Attachment 1 for details regarding the timing of specific efficacy measures.

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

- Computed tomography (CT) scan
- Magnetic resonance imaging (MRI)
- PET scan (pre- and postdose [Attachment 1]).

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

- Tumor measurement by RECIST 1.1 (Eisenhauer et al. 2009). For tumor measurement evaluations in patients with soft tissue sarcomas, Choi et al. (2007) response criteria will be used in addition to RECIST 1.1. Response Assessment in Neuro-Oncology (RANO) criteria will be used for glioblastoma patients (Wen et al. 2010)
- Evaluation of tumor markers, if indicated.
- Evaluation of performance status (refer to the ECOG scale, Attachment 6).

To confirm objective responses, all lesions should be radiologically assessed, and the same radiologic method used for the initial response determination should be repeated at least 4 weeks following the initial observation of an objective response, using the sample method that was used at baseline. If a patient is discontinued from the study, repeat radiology assessments may be omitted if clear clinical signs of progressive disease are present.

Table JJCD.8.3 defines the efficacy endpoints assessed during the study.

Table JJCD.8.3. Definition of Efficacy Endpoints

Endpoint	Definition
Progression-free survival (PFS)	The time from the date of study enrollment to the date of first observation of objective progression or death from any cause.
Duration of response	The time from the date of first evidence of a confirmed complete or partial response to the date of objective progression or the date of death from any cause (whichever is earlier).

After patients have discontinued study treatment, they may receive additional anticancer therapy at the discretion of the investigator. For those patients who discontinue study treatment without objectively measured progressive disease, the investigative sites will continue to monitor patients approximately every 60 days (±14 days) to evaluate tumor response by the same method used at

baseline and throughout the study, until objective progression or the patient starts a new anticancer therapy, or study closure.

Lilly or its designee will collect and store all tumor measurement images for patients enrolled in dose-confirmation phases of Parts A, B, C, D, and E. A central review of imaging scans may be performed by Lilly or its designee.

8.4. 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, PD 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 CRF or laboratory requisition form.

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 CRFs, and study procedures
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and/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 (IRBs)/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), CRF 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 using standard Lilly file transfer processes.

For data handled by the sponsor internally, CRF 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, such as laboratory test data or ECG data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Bioanalytical data will be stored electronically in the bioanalytical laboratory's database.

Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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

The total sample size is estimated to be approximately 163 patients. To determine the recommended Phase 2 dose (RP2D) of LY3039478 in combination with other anticancer agents, 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.

A total of 10 (Parts A and B) or 15 (Part C) patients with a given tumor type treated at the RP2D in dose confirmation can provide adequate precision for the estimated incidence rate of the following quantities of interest: (1) patients having a specified AE or (2) patients showing a response (partial response/complete response) to treatment. With a total sample size of N=10-15, the 95% CI is approximately equal to the observed incidence rate ±15% to 35%. Example point estimates of incidence rates and corresponding 2-sided 95% CIs are summarized in Table JJCD.10.1. The values are provided as a reference for estimation rather than a basis of any decision criteria.

Table JJCD.10.1. Estimated Incidence Rate and Its 2-Sided 95% Confidence Interval

N=10				N=15			
Num. of Cases	Est. Rate	95% CI[a]		Num. of Cases	Est. Rate	95% CI[a]	
		Lower Limit	Upper Limit			Lower Limit	Upper Limit
0	0.0	0.0	0.31	0	0.0	0.0	0.22
2	0.20	0.03	0.56	3	0.20	0.04	0.48
3	0.30	0.07	0.65	5	0.33	0.12	0.62
5	0.50	0.19	0.81	8	0.53	0.27	0.79
7	0.70	0.35	0.93	11	0.73	0.45	0.92

Abbreviations: CI = confidence interval; Est = estimated; Num = number.

[a] 95% Clopper-Pearson interval for binomial distribution with sample size of 10 to 15 patients.

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

The interpretation of the study results will be the responsibility of the investigator with the Lilly CRP or CRS, pharmacokineticist, and statistician. The CRP or CRS 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.

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/listing 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. In addition, postdiscontinuation therapies will be recorded and summarized by type of therapy (surgery, radiotherapy, systemic therapy) and by drug name.

10.4. Safety Analyses

All patients who receive at least 1 dose of LY3039478 will be evaluated for safety and toxicity. AE terms and severity grades will be assigned by the investigator using CTCAE, v 4.0.

Safety analyses will include summaries of the following:

- AEs, including severity and possible relationship to study drug
- dose adjustments
- laboratory values
- vital signs
- DLTs at each dose level
- ECG readings.

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 for LY3039478, taladegib and its active metabolite (LSN3185556), LY3023414, abemaciclib and its active metabolites (LSN3106726 and LSN2839567), gemcitabine, carboplatin, and cisplatin will be calculated by standard noncompartmental methods of analyses where data allow.

The primary parameters for analysis will be (C_{max}, AUC from time zero to last measurable plasma concentration ($AUC_{0\text{-}tlast,}$), and AUC from time zero to infinity ($AUC_{0\text{-}\infty}$). Other noncompartmental parameters, such as $t_{1/2}$, CL/F, and apparent volume of distribution (V/F) may be reported. 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.

PK parameter estimates will be evaluated to delineate effects of the following drug interactions: LY3039478 with taladegib compared to taladegib alone, LY3039478 with LY3023414 compared to LY3023414 alone, and LY3039478 with abemaciclib compared to abemaciclib alone.

Log-transformed C_{max} and AUC estimates will be assessed using mixed effect models with random patient effect, to estimate ratios of geometric means and the corresponding 90% CIs.

10.6. Pharmacokinetic/Pharmacodynamic Analyses

The PK data will be combined and analyses may be conducted to determine a relationship between exposure and PD effect (for example, Aβ[1-x]), data permitting. This model may be used to help reassess the dose cohort escalation as the study progresses.

10.7. Efficacy

The study was not designed to make an efficacy assessment. However, any tumor response data will be tabulated. Descriptive analyses of duration of response and PFS will be conducted using the Kaplan-Meier method.

10.8. Tailoring Biomarker Analyses

Efficacy measures may be summarized descriptively within subgroups of patients. Those may be characterized by the types of Notch pathway alterations. Exploratory analyses may be applied to correlate Notch pathway biomarkers with clinical outcome. If applicable, a subset of potential predictive biomarkers associating with interpretable clinical benefit may be further examined with biological evidence.

10.9. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the sponsor will determine if it is necessary to amend the protocol.

Because 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 treatment arm. 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 the MTD 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.

Safety and/or PK data will be reviewed during the study if needed for dose escalation, modifications to the dose-escalation strategy, or other design elements.

After all patients who are deemed evaluable for the assessment of dose levels complete the DLT evaluation period or the MTD is determined, an interim safety and PK analysis may be conducted for planning next studies.

If it is deemed that enough data are obtained to assess the primary objective and the secondary objectives, a clinical study report might be created before the last patient visit. In this case, all data until the data-cutoff date will be used for the analysis of safety, efficacy, PK, and PD biomarkers. All data defined in the protocol will continue to be collected from patients on treatment after the data-cutoff date. These data may be reported separately and the analyses on all patients including these data may not be performed.

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.

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

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 International Conference on Harmonisation (ICH) guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative 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 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 ICH GCP Guideline [E6]

3) applicable laws and regulations.

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

Some of the obligations of the sponsor will be assigned to a TPO.

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

11.3.1. Investigator Information

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

11.3.2. Protocol Signatures

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

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

11.3.3. 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 analyzable 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 JJCD Study Schedule

Baseline Assessments

Relative Day Prior to Day 1 of Cycle 1	≤28	≤14	≤7	Comments
Informed consent	X			Informed consent signed prior to performance of any protocol-specific tests/procedures
Radiological tumor assessment	X			
PET scan		X		Optional
Medical history		X		Including alcohol/tobacco use and other relevant habits assessments
Physical examination		X		
Vital signs		X		Including temperature, blood pressure, pulse rate, respiration rate
Height		X		
ECOG performance status		X		
ECG		X		One set of triplicate ECGs, central
Hematology		X		Local laboratory
Coagulation (PT/INR, aPTT, fibrinogen)		X		Central laboratory
Serum chemistry		X		Central and local laboratory[a]
HbA1c		X		Part B only; central and local laboratory[a]
Cystatin C		X		Part C only
Urinalysis		X		Local laboratory
Tumor measurement (palpable or visible)		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
Concomitant medications		X		
Tumor markers		X		If applicable, local laboratory
Blood PD biomarkers (Aβ[1-x])[b]		X		
Tumor biopsy	X			Predose tumor biopsy is recommended
Screening for alterations of Notch pathway				Screening done locally, any time prior to study drug therapy in all dose-confirmation phases except for soft tissue sarcoma in Part A[c]
Archived tumor sample				Paraffin-embedded tumor tissue (block or unstained slides) will be collected only after study eligibility is confirmed[c]
Pregnancy test			X	Negative results prior to dosing required for women of childbearing potential
Skin biopsy		X		

Abbreviations: aPTT = activated partial thromboplastin time; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HbA1c = glycosylated hemoglobin; PD = pharmacodynamic; PET = positron emission tomography; PT/INR = prothrombin time/international normalized ratio.

[a] Patient eligibility and management is based on local laboratory results only unless the investigator chooses to use the central laboratory for such a purpose.

[b] Only during dose-escalation phase (all parts).

[c] To be performed prior to study drug dosing.

During and Poststudy Assessments - Parts A, B, and C

Study Procedures		Cycle 1			
	3-Day Lead-In	Week 1	Week 2	Week 3	Week 4
	Single dose Taladegib, LY3023414, or Abemaciclib on Day 1[a]	Day 1 of LY3039478 Combination	Day 8 of LY3039478 Combination	Day 15 of LY3039478 Combination	Day 22 of LY3039478 Combination
Physical examination	X	X	X	X	X
Vital signs and weight (temperature, pulse rate, blood pressure, respiratory rate)	X	X	X	X	X
ECOG performance status	X	X	X	X	X
CTCAE version 4.0 grading		X	X	X	X
Concomitant medications	X	X	X	X	X
Central ECG[b]	X	X			
PET scan[c]			X		
Hematology[d]	X	X	X	X	X
Serum chemistry[d]	X	X	X	X	X
Cystatin C (for Part C only)	X	X	X	X	X
HbA1c (for Part B only)		X			
ECG chemistry[b,d]	X	X			
Coagulation (PT/INR, aPTT, fibrinogen)[d]		X	X	X	X
Tumor marker[d]	X	X			
Pharmacogenetics sample (predose)		X			
Blood PK sampling[b]	X	X		X	X
Tumor biopsy, recommended[e]					X
Skin biopsy[b,f]		X			
Blood PD biomarkers (Aβ[1-x]) during dose escalation only)[b,g]		X			X
Blood exploratory circulating biomarkers predose		X			
Urine (8-hour collection)[b,g]	X				X

During and Poststudy Assessments - Parts A, B, and C

Study Procedures	Cycle 2				Cycle 3-n				Visit 801	Follow-Up[i]
	Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4	V801	V802-XX
	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22		
Physical examination	X		X		X				X	
Vital signs and weight (temperature, pulse rate, blood pressure, respiratory rate)	X		X		X				X	
ECOG performance status	X		X		X				X	X
CTCAE version 4.0 grading	X		X		X				X	X[j]
Concomitant medications	X	X	X	X	X	X	X	X	X	X[k]
Tumor measurement (palpable and visible)	X				X					X[l]
ECG[b]	X									
Radiological tumor assessment[h]				X				X		X[l]
PET scan[c]	X				X					
Hematology[d]	X		X		X		X		X	
Cystatin C (for Part C only)	X		X		X		X		X	
HbA1c (for Part B only)	X				X				X	
Serum chemistry[d]	X		X		X		X		X	
ECG chemistry[b,d]	X									
Coagulation (PT/INR, aPTT, fibrinogen)[d]	X			X	X				X	
Tumor marker[d]	X				X				X	
Blood PK sampling[b] predose	X									
Blood PD biomarkers (Aβ[1-x])-during dose escalation only)[b,g] predose	X				X					
Blood exploratory circulating biomarkers predose	X				X				X	

During and Poststudy Assessments - Parts D and E

Study Procedures	Cycle 1			Cycle 2		
	Week 1	Week 2	Week 3	Week 1	Week 2	Week 3
	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15
Physical examination	X	X	X	X		X
Vital signs and weight (temperature, pulse rate, blood pressure, respiratory rate)	X	X	X	X		X
ECOG performance status	X	X	X	X		X
CTCAE version 4.0 grading		X	X	X		X
Concomitant medications	X	X	X	X		X
Tumor measurement (palpable and visible)				X		
Central ECG[b]	X			X		
Radiological tumor assessment[h]						X
PET scan[c]		X		X		
Hematology[d]	X	X	X	X	X	X
Serum chemistry[d]	X	X	X	X	X	X
ECG chemistry[b,d]	X			X		
Coagulation (PT/INR, aPTT, fibrinogen)[d]		X	X	X		
Tumor marker[d]	X			X		
Pharmacogenetics sample (predose)	X					
Blood PK sampling[b]	X		X	X		
Tumor biopsy, recommended[e]			X			
Skin biopsy[b,f]	X					
Blood PD biomarkers (Aβ[1-x]) during dose escalation only)[b,g]	X		X	X		
Blood exploratory circulating biomarkers predose	X			X		
Urine (6- to 8-hour collection)[b,g]	X		X			

During and Poststudy Assessments - Parts D and E

Study Procedures	Cycle 3-n			Visit 801	Follow-Up[i]
	Week 1	Week 2	Week 3	V801	V802-XX
	Day 1	Day 8	Day 15		
Physical examination	X			X	
Vital signs and weight (temperature, pulse rate, blood pressure, respiratory rate)	X			X	
ECOG performance status	X			X	X
CTCAE version 4.0 grading	X			X	X[j]
Concomitant medications	X			X	X[k]
Tumor measurement (palpable and visible)	X				X[l]
Radiological tumor assessment[h]			X		X[l]
PET scan[c]	X				
Hematology[d]	X	X	X	X	
Serum chemistry[d]	X	X	X	X	
Coagulation (PT/INR, aPTT, fibrinogen)[d]	X			X	
Tumor marker[d]	X			X	
Blood PD biomarkers (Aβ[1-x])-during dose escalation only)[b,g] predose	X				
Blood exploratory circulating biomarkers predose	X				

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HbA1c = glycosylated hemoglobin; PD = pharmacodynamic; PK = pharmacokinetic; PET = positron emission tomography; PT/INR = prothrombin time/international normalized ratio; RBM = Rules-Based Medicine; SAE = serious adverse event; V = visit.

[a] Three-day lead-in period only occurs during the dose-escalation phase of Parts A, B, and C.

[b] For complete details, see Attachment 4.

[c] Optional (not limited to Dose 1) repeated at the discretion of the investigator (can be performed ±2 days).

[d] For central versus local laboratories, refer to Attachment 2.

[e] Optional posttreatment tumor biopsy should be obtained (whenever clinically feasible) at Cycle 1, preferably 6 to 8 hours (±1 hour) after Dose 10. Greater flexibility has been provided for the posttreatment tumor biopsy (between Doses 7 and 12, inclusive) compared to other Dose 10 visit assessments (between Doses 9 and 11, inclusive) to enable radiographic guidance and access to appropriate medical specialists. A single PK sample should be obtained as close as possible (for example, ±3 hours) to the time of the biopsy. Additional optional tumor biopsies may be performed at time of disease progression and if deemed necessary by the investigator.

[f] Skin biopsies are mandatory according to the schedule provided in Table JJCD.8.2. Additional optional skin biopsies may be performed at time of disease progression and if deemed necessary by the investigator.

[g] Only in dose-escalation phase for all study parts.

[h] Radiological assessment is performed at baseline (up to 28 days before the first dose), then at the end of Cycle 2 (no more than 10 days prior to Day 1 of Cycle 3), then every other cycle thereafter (no more than 10 days prior to Day 1 of the next cycle). If a patient is discontinued from the study, repeat radiology may be omitted if progressive disease can be documented quantitatively with clinical measurements.

[i] Long-term follow-up for PFS applies to dose-confirmation phase for all study parts.

[j] Collection of AEs and SAEs related to study treatment or study procedures only.

[k] Postdiscontinuation therapies and outcome of treatment will be recorded.

[l] Every 60 (±14) days and applies only to those patients in the dose-confirmation phase for all study parts who discontinue the study without progression or have not started another treatment regimen as outlined in Section 8.3.

Attachment 2. Protocol JJCD Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry[a,b]**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Leukocytes (WBC)	Total bilirubin
Neutrophils	Alkaline phosphatase
Lymphocytes	Alanine aminotransferase (ALT)
Monocytes	Aspartate aminotransferase (AST)
Eosinophils	Gamma-glutamyl transpeptidase (GGT)
Basophils	Blood urea nitrogen (BUN)
Platelets	Creatinine
	Lipase
Coagulation[b]	Lactate dehydrogenase (LDH)
aPTT	Uric acid
PT/INR	Calcium
Fibrinogen	Phosphorus
	Glucose, random (fasted for Part B)
Urinalysis[a]	Albumin
Specific gravity	Total protein
pH	Creatinine clearance
Protein	Serum or urine pregnancy test (females only)[a]
Glucose	
Ketones	**ECG Chemistry[b]**
Blood	
Urine leukocyte esterase	Thyroid-stimulating hormone (TSH)
	Free tri-iodothyronine (T3)
HbA1c (for Part B only)	Free thyroxine (T4)
	Calcium[c]
Cystatin C (for Part C only)	Sodium[c]
	Potassium[c]
Tumor Markers[a]	Phosphorus
	Magnesium
Biomarkers[b]	

Abbreviations: aPTT = activated partial thromboplastin time; ECG = electrocardiogram; HBA1c = glycosylated hemoglobin; PT/INR = international normalized ratio of prothrombin time; RBC = red blood cells; WBC = white blood cells.

[a] Local or investigator-designated laboratory. Local safety laboratory results can be obtained up to 1 day before the scheduled time point.

[b] Assayed by Lilly-designated laboratory.

[c] Test not performed if both chemistry and ECG chemistry required at same time point. See Attachment 4.

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

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

Hepatic Monitoring Tests

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

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

[a] Assayed by Lilly-designated laboratory.

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

Attachment 4. Protocol JJCD Pharmacokinetic, Pharmacodynamic, and Electrocardiogram with Electrocardiogram Chemistry Sampling Schedule

Pharmacokinetic and Pharmacodynamic Sampling Schedule: Part A Dose Escalation – LY3039478 + Taladegib

PK Sample Number	Cycle	Day of LY3039478 Combination	Sampling Time (hr) for LY3039478	Sampling Time (hr) for Taladegib/ LSN3185556	Sampling Time (hr) for Aβ	Sampling Time for Plasma Cortisol	Sampling Time for Urine	PD Sampling Time for Skin Biopsies	ECG with ECG Chemistry
1	Lead in	-3		predose	predose	predose	0-8 hr pooled sample (end time to match with 8 hr PK sample). Record total volume	screening	predose
2	Lead in	-3		0.5					
3	Lead in	-3		1					
4	Lead in	-3		2					
5	Lead in	-3		4					
6	Lead in	-3		6					
7	Lead in	-3		8					
8	Lead in	-2		24-30					
9	1	1		predose	predose				
10	1	22	predose	predose	predose	predose	0-8 hr pooled sample (end time to match with 8 hr PK sample). Record total volume		predose
11	1	22	0.5	0.5	0.5				
12	1	22	1	1	1				
13	1	22	2	2	2				2 hr
14	1	22	4	4	4				
15	1	22	6	6	6			6-8 hr (±1 hr)	
16	1	22	8	8	8				
17	1	22	same time as taladegib predose sample	predose	same time as taladegib predose sample	same time as taladegib predose sample			same time as taladegib predose sample
18	2	1	predose	predose					predose

Abbreviations: ECG = electrocardiogram; hr = hour; PD = pharmacodynamic; PK = pharmacokinetic.

Pharmacokinetic and Pharmacodynamic Sampling Schedule: Part A Dose Confirmation – LY3039478 + Taladegib

PK Sample Number	Cycle	Day	PK Sampling Time (hr) for LY3039478	Sampling Time (hr) for Taladegib/LSN3185556	PD Sampling Time for Skin Biopsies	ECG with ECG Chemistry
1	1	15	predose	predose	screening	predose
2	1	22	predose	predose		
3	1	22	0.5	0.5		
4	1	22	1-2	1-2		2 hr
5	1	22	3-4	3-4	6-8 hr (±1 hour)	
6	2	1	predose	predose		predose

Abbreviations: ECG = electrocardiogram; hr= hour; PD = pharmacodynamic; PK = pharmacokinetic.

Pharmacokinetic and Pharmacodynamic Sampling Schedule: Part B Dose Escalation – LY3039478 + LY3023414

PK Sample Number	Cycle	Day of LY3039478 Combination	Sampling Time (hr) for LY3039478	Sampling Time (hr) for LY3023414	Sampling Time (hr) for Aβ	Sampling Time for Plasma Cortisol	Sampling Time for Urine	PD Sampling Time for Skin Biopsies	ECG with ECG Chemistry
1	Lead in	-3		predose	predose	predose	0-8 hr pooled sample (end time to match with 8 hr PK sample). Record total volume	screening	predose
2	Lead in	-3		0.5					
3	Lead in	-3		1					
4	Lead in	-3		2					
5	Lead in	-3		4					
6	Lead in	-3		6					
7	Lead in	-3		8					
8	Lead in	-2		24-30					
9	1	1		predose	predose				
10	1	22	predose	predose	predose	predose	0-8 hr pooled sample (end time to match with 8 hr PK sample). Record total volume		predose
11	1	22	0.5	0.5	0.5				
12	1	22	1	1	1				
13	1	22	2	2	2				2 hr
14	1	22	4	4	4				
15	1	22	6	6	6			6-8 hr (±1 hr)	
16	1	22	8	8	8				
17	1	22	24-30		24-30	24-30 hr			24-30 hr
18	2	1	predose	predose					predose

Abbreviations: ECG = electrocardiogram; hr= hour; PD = pharmacodynamic; PK = pharmacokinetic.

Pharmacokinetic and Pharmacodynamic Sampling Schedule: Part B Dose Confirmation – LY3039478 + LY3023414

PK Sample Number	Cycle	Day	PK Sampling Time (hr) for LY3039478	Sampling Time (hr) for LY3023414	PD Sampling Time for Skin Biopsies	ECG with ECG Chemistry
1	1	15	predose	predose	screening	predose
2	1	22	predose	predose		
3	1	22	0.5	0.5		
4	1	22	1-2	1-2		2 hr
5	1	22	3-4	3-4	6-8 hr (±1 hr)	
6	2	1	predose	predose		predose

Abbreviations: ECG = electrocardiogram; hr= hour; PD = pharmacodynamic; PK = pharmacokinetic.

Pharmacokinetic and Pharmacodynamic Sampling Schedule: Part C Dose Escalation – LY3039478 + Abemaciclib

PK Sample Number	Cycle	Day of LY3039478 Combination	Sampling Time (hr) for LY3039478	Sampling Time (hr) for Abemaciclib, LSN3106726, LSN2839567	Sampling Time (hr) for Aβ	Sampling Time for Plasma Cortisol	Sampling Time for Urine	PD Sampling Time for Skin Biopsies	ECG with ECG Chemistry
1	Lead in	-3		predose	predose	predose	0-8 hr pooled sample (end time to match with 8 hr PK sample). Record total volume	screening	predose
2	Lead in	-3		0.5					
3	Lead in	-3		1					
4	Lead in	-3		2					
5	Lead in	-3		4					
6	Lead in	-3		6					
7	Lead in	-3		8					
8	Lead in	-2		24-30					
9	1	1		predose	predose				
10	1	22	predose	predose	predose	predose	0-8 hr pooled sample (end time to match with 8 hr PK sample). Record total volume		predose
11	1	22	0.5	0.5	0.5				
12	1	22	1	1	1				
13	1	22	2	2	2				2 hr
14	1	22	4	4	4				
15	1	22	6	6	6			6-8 hr (±1 hr)	
16	1	22	8	8	8				
17	1	22	24-30		24-30	24-30 hr			24-30 hr
18	2	1	predose	predose					Predose

Abbreviations: ECG = electrocardiogram; hr= hour; PD = pharmacodynamic; PK = pharmacokinetic.

Pharmacokinetic and Pharmacodynamic Sampling Schedule: Part C Dose Confirmation – LY3039478 + Abemaciclib

PK Sample Number	Cycle	Day	PK Sampling Time (hr) for LY3039478	Sampling Time (hr) for Abemaciclib, LSN3106726, LSN2839567	PD Sampling Time for Skin Biopsies	ECG with ECG Chemistry
1	1	15	predose	predose	screening	predose
2	1	22	predose	predose		
3	1	22	0.5	0.5		
4	1	22	1-2	1-2		2 hr
5	1	22	3-4	3-4	6-8 hr (±1 hr)	
6	2	1	predose	predose		predose

Abbreviations: ECG = electrocardiogram; hr = hour; PD = pharmacodynamic; PK = pharmacokinetic.

Pharmacokinetic and Pharmacodynamic Sampling Schedule (hours): Part D Dose Escalation – LY3039478 + Cisplatin/Gemcitabine

PK Sample Number	Cycle	Day	Sampling Time for LY3039478	Sampling Time for Cisplatin (Relative to Start of Infusion)	Sampling Time for Gemcitabine (Relative to Start of Infusion)	Sampling Time for Aβ (Relative to LY3039478)	Sampling Time for Plasma Cortisol (Relative to LY3039478)	Sampling Time for Urine (Relative to LY3039478)	PD Sampling Time for Skin Biopsies (Relative to LY3039478)	ECG with ECG Chemistry (Relative to LY3039478)
1						screening			predose	predose
2	1	1	predose	predose	predose	predose	predose	0-8 hr pooled sample (end time to match with 6-8 hr PK sample). Record total volume		
3	1	1	0.5		0.5 (end of infusion)					
4	1	1	1	1.5 (end of infusion)	1					
5	1	1	2	2	2					
6	1	1	4	4	4					4
7	1	1	6-8	6	6				6-8	
8	1	1	24-30							
9	1	15	predose			predose	predose	0-8 hr pooled sample (end time to match with 6-8 hr PK sample). Record total volume		
10	1	15	0.5			0.5				
11	1	15	1			1				
12	1	15	2			2				
13	1	15	4			4				
14	1	15	6-8			6-8				
15	1	15	24-30			24-30				
16	2	1	predose				predose			predose

Abbreviations: ECG = electrocardiogram; hr = hour; PD = pharmacodynamic; PK = pharmacokinetic.

Pharmacokinetic and Pharmacodynamic Sampling Schedule (hours): Part D Dose Confirmation – LY3039478 + Cisplatin/Gemcitabine

PK Sample Number	Cycle	Day	PK Sampling Time for LY3039478	Sampling Time for Cisplatin (Relative to Start of Infusion)	Sampling Time for Gemcitabine (Relative to Start of Infusion)	PD Sampling Time for Skin Biopsies (Relative to LY3039478)	ECG with ECG Chemistry (Relative to LY3039478)
1	1	1	predose	predose	predose	predose	predose
2	1	1	0.5	-	0.5 (end of infusion)		
3	1	1	1-2	1.5 (end of infusion)	1-2		
4	1	1	3-4	3-4	3-4	6-8	4
5	1	15	predose				
6	2	1	predose				predose

Abbreviations: ECG = electrocardiogram; PD = pharmacodynamic; PK = pharmacokinetic.

Pharmacokinetic and Pharmacodynamic Sampling Schedule (hours): Part E Dose Escalation – LY3039478 + Gemcitabine/Carboplatin

PK Sample Number	Cycle	Day	PK Sampling Time for LY3039478	Sampling Time for Gemcitabine (Relative to Start of Infusion)	Sampling Time for Carboplatin (Relative to Start of Infusion)	Sampling Time for Aβ (Relative to LY3039478)	Sampling Time for Plasma Cortisol (Relative to LY3039478)	Sampling Time for Urine (Relative to LY3039478)	PD Sampling Time for Skin Biopsies (Relative to LY3039478)	ECG with ECG Chemistry (Relative to LY3039478)
1	-	-				screening			predose	predose
2	1	1	predose	predose	predose	predose	predose	0-8 hr pooled sample (end time to match with 6-8 hr PK sample). Record total volume		
3	1	1	0.5	0.5 (end of infusion)	0.5 (end of infusion)					
4	1	1	1	1	1					
5	1	1	2	2	2					2
6	1	1	4	4	4					
7	1	1	6-8	6	6				6-8	
8	1	1	24-30							
9	1	15	predose			predose	predose	0-8 hr pooled sample (end time to match with 6-8 hr PK sample). Record total volume		
10	1	15	0.5			0.5				
11	1	15	1			1				
12	1	15	2			2				
13	1	15	4			4				
14	1	15	6-8			6-8				
15	1	15	24-30			24-30				
16	2	1	predose				predose			predose

Abbreviations: ECG = electrocardiogram; PD = pharmacodynamic; PK = pharmacokinetic.

Pharmacokinetic and Pharmacodynamic Sampling Schedule (hours): Part E Dose Confirmation – LY3039478 + Gemcitabine/Carboplatin

PK Sample Number	Cycle	Day	PK Sampling Time for LY3039478	Sampling Time for Gemcitabine (Relative to Start of Infusion)	Sampling Time for Carboplatin (Relative to Start of Infusion)	PD Sampling Time for Skin Biopsies (Relative to LY3039478)	ECG with ECG Chemistry (Relative to LY3039478)
1	1	1	predose	predose	predose	predose	predose
2	1	1	0.5	0.5 (end of infusion)	0.5 (end of infusion)		
3	1	1	1-2	1-2	1-2		2
4	1	1	3-4	3-4	3-4	6	
5	1	15	predose				
6	2	1	predose				predose

Abbreviations: ECG = electrocardiogram; PD = pharmacodynamic; PK = pharmacokinetic.

Attachment 5. Protocol JJCD Recommendations for Reporting Serious Adverse Events

Recommendations for Reporting Serious Adverse Events (SAEs)

When contacting Lilly to report an 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 & 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 JJCD Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Status

Activity Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out performance of a light or sedentary nature, for example, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, 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 MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the eastern cooperative oncology group. *Am J Clin Oncol*. 1982;5(6):649-655.

Attachment 7. Protocol JJCD Creatinine Clearance Formula

Note: This formula is to be used for calculating creatinine clearance (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:

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

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

Source: Cockcroft DW, Gault MD. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16(1):31-41.

-OR-

$$GFR(mL/min/1.73m2) = 170 \times [PCr]^{-0.999} \times [age]^{-0.176}$$

$$\times [0.762 \text{ if patient is female}] \times [1.18 \text{ if patient is black}]$$

$$\times [SUN]^{-0.17} \times [Alb]^{+0.318}$$

Abbreviations: GFR = glomerular filtration rate; PCr = plasma creatinine, mg/dL; SUN = serum urea nitrogen, mg/dL; Alb = serum albumin, g/dL.

Source: Murray PT, Ratain MJ. Estimation of the glomerular filtration rate in cancer patients: a new formula for new drugs. *J Clin Oncol*. 2003;21(14):2633-2635.

Attachment 8. Protocol JJCD Guidance on Alterations Related to Notch Pathway

Mutations

Notch-1

Notch-2

Notch-3

Notch-4

FBXW7

Amplifications

Notch-1

Notch-2

Notch-3

Jagged-1

Jagged-2

Gene and Protein Overexpression

Notch receptors

Notch ligands

Notch intracellular domain (NICD) (by immunohistochemistry [IHC])

Attachment 9. Protocol JJCD Guidance for Diarrhea Management

First report of diarrhea:

- Obtain history of onset and duration of diarrhea to assess drug causality.
- Description of number of stools and stool composition (for example, watery, blood, mucus in stool).
- Assess patient for fever, abdominal pain, cramps, distension, bloating, nausea, vomiting, dizziness, weakness (that is, rule out risk for sepsis, bowel obstruction, dehydration).
- Medication profile (that is, to identify any diarrheogenic agents).
- Dietary profile (that is, to identify diarrhea-enhancing foods).

Management of Diarrhea

General recommendations:

- Stop all lactose-containing products and alcohol.
- Stop laxatives, bulk fiber (Metamucil®), and stool softeners (docusate sodium).
- Drink 8 to 10 large glasses of clear liquids per day (water).
- Eat frequent small meals (bananas, rice, applesauce, Ensure®, toast).
- Stop high-osmolar food supplements (with fiber).

It is recommended that patients be provided loperamide tablets. Patients are instructed on the use of loperamide at Cycle 1 in order to manage signs or symptoms of diarrhea at home. Patients should be instructed to start oral loperamide (initial administration of 4 mg, then 2 mg every 4 hours up to a maximum of 16 mg/day) at the first sign of loose stool or symptoms of abdominal pain. These instructions should be provided at each cycle, and the site should ensure that the patient understood the instruction.

Treatment of Diarrhea Grade 1 or 2

Diarrhea Grade 1 or 2 will be treated with standard loperamide (initial administration 4 mg, then 2 mg every 4 hours [up to a maximum of 16 mg/day] or after each unformed stool).

After 12 to 24 hours:

Diarrhea resolved

- Continue instructions for dietary modification.
- Gradually add solid foods to diet.
- Discontinue loperamide after 12-hours diarrhea-free interval.

Diarrhea unresolved

Persisting diarrhea Grade 1 or 2 will be treated with addition of opium tincture or dihydrocodeine tartrate tablets/injections, with monitoring of patient's condition (to rule out dehydration, sepsis, or ileus) and medical check and selected workup if patient does not need hospitalization. Observe patient for response to antidiarrheal treatment. Persisting diarrhea Grade 3 or 4 may be treated with hospitalization, high dose loperamide (initial 4 mg, then 2 mg every 2 hours) and addition of opium tincture or dihydrocodeine tartrate tablets/injections, start of intravenous (IV) fluids and antibiotics as needed with monitoring of patients condition (to rule out dehydration, sepsis, ileus) medical check and workup (perform appropriate additional testing). Observe patient for response.

After 12 to 24 hours:

Diarrhea resolved

- Continue instructions for dietary modification.
- Gradually add solid foods to diet.
- Discontinue loperamide and/or other treatment after 12-hours diarrhea-free interval.

Diarrhea unresolved

- If diarrhea is still persisting (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Grades 1 and 2) after 2x 24 hours with high-dose loperamide and opiates, then admit to hospital and employ measures as for Grade 3 and 4 until diarrhea is resolved.
- If diarrhea is still persisting and progressed to NCI Grades 3 and 4, employ measures described below.

Treatment of Diarrhea Grade 3 or 4

Severe diarrhea Grade 3 or 4 may be treated with hospitalization, high-dose loperamide (initially 4 mg, then 2 mg every 2 hours) and addition of opium tincture or dihydrocodeine tartrate tablets/injections, start of IV fluids and antibiotics as needed with monitoring of patients condition (to rule out dehydration, sepsis, ileus), medical check, and workup

Diarrhea workup and additional test). Observe patient for response.

After 12 to 24 hours:

- If diarrhea is still persisting, administer subcutaneous (SC) Sandostatin/octreotide (100 to 500 µg 3 times per day [TID]).
- Continue IV fluids and antibiotics as needed.
- If diarrhea Grade 3 or 4 is still persisting, patients should receive opium tincture or dihydrocodeine tartrate injections SC or intramuscular (IM).

- If diarrhea Grade 3 or 4 is still persisting, SC Sandostatin/octreotide (500 to 1000 μg TID) should be administered.
- To control and/or resolve diarrhea, next cycle of treatment should be delayed by 1 or 2 weeks. Treatment should be continued only when diarrhea resolved.

Diarrhea workup

Perform appropriate tests (Fine and Schiller 1999).

Spot stool analysis

- Collect stool, separating it from urine (special containers; analysis immediately; exceptionally, freeze samples).
- Blood.
- Fecal leukocytes (Wright's staining and microscopy).
- *Clostridium difficile* toxin.
- Fecal cultures including Salmonella spp., Campylobacter spp., Giardia, Entamoeba, Cryptosporidium (which can lead to opportunistic infections in immunosuppressed patients), plus Shigella and pathogenic *Escherichia coli* - enterotoxigenic, enterohemorrhagic etc, and possibly Aeromonas, Plesiomonas (if exposure to contaminated water is suspected).

Endoscopic examinations

Endoscopic examinations may be considered only if absolutely necessary. The bowel is likely to be fragile with evidence of colitis, and thus, great care and caution must be exercised in undertaking these invasive procedures.

- Gastroscopy to obtain jejunal fluid (that is, bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis).
- Sigmoidoscopy - reassessment of colitis.

Reference

Fine KD, Schiller LR. AGA Technical review on the evaluation and management of chronic diarrhea. *Gastroenterology.* 1999;116(6):1464-1486.

Attachment 10. CYP3A4 Inhibitors, Inducers, and Substrates for LY3023414 (Part B)

Strong CYP3A4 Inhibitors	Moderate CYP3A4 Inhibitors	Strong CYP3A4 Inducers	Moderate CYP3A4 Inducers	CYP3A4 Substrates with Narrow Therapeutic Range	Sensitive CYP3A4 Substrates	
boceprevir	amprenavir	avasimibe	bosentan	alfentanil	alfentanil	lopinavir
clarithromycin	aprepitant	carbamazepine	efavirenz	astemizole	aprepitant	lovastatin
conivaptan	atazanavir	phenytoin	etravirine	cisapride	budesonide	lurasidone
grapefruit juice	ciprofloxacin	rifampin	modafinil	cyclosporine	buspirone	maraviroc
indinavir	darunavir/ritonavir	St. John's wort	nafcillin	dihydroergotamine	conivaptan	midazolam
itraconazole	diltiazem			ergotamine	darifenacin	nisoldipine
ketoconazole	erythromycin			fentanyl	darunavir	quetiapine
lopinavir/ritonavir	fluconazole			pimozide	dasatinib	saquinavir
mibefradil	fosamprenavir			quinidine	dronedarone	sildenafil
nefazodone	grapefruit juice			sirolimus	eletriptan	simvastatin
nelfinavir	imatinib			tacrolimus	eplerenone	sirolimus
posaconazole	verapamil			terfenadine	everolimus	tolvaptan
ritonavir					felodipine	tipranavir
saquinavir					indinavir	triazolam
telaprevir					fluticasone	vardenafil
telithromycin						
voriconazole						

Source: Food and Drug Administration Drug Development and Drug Interactions page. Table of substrates, inhibitors, and inducers. Food and Drug Administration website. Available at: http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm. Accessed October 13, 2015.

Attachment 11. Drugs Associated with QT Interval Prolongation for LY3023414 (Part B)

Drugs with a Risk of Torsades de Pointes

amiodarone	clarithromycin	halofantrine	pentamidine	terfenadine
arsenic trioxide	cisopyramide	haloperidol	pimozide	thioridazine
astemizole	dofetilide	ibutilide	probucol	vandetanib
bepridil	domperidone	levomethadyl	procainamide	
chlorpromazine	droperidol	mesoridazine	quinidine	
cisapride	erythromycin	methadone	sotalol	
citalopram	flecainide	moxifloxacin	sparfloxacin	

Drugs with a Possible Risk of Torsades de Pointes

alfuzosin	felbamate	lithium	ranolazine	voriconazole
amantadine	fingolimod	moexipril/HCTZ	risperidone	ziprasidone
atazanavir	foscarnet	nicardipine	roxithromycin	
azithromycin	fosphenytoin	nilotinib	sertindole	
chloral hydrate	gatifloxacin	octreotide	sunitinib	
clozapine	gemifloxacin	ofloxacin	tacrolimus	
dolasetron	granisetron	ondansetron	tamoxifen	
dronedarone	indapamide	oxyytocin	telithromycin	
eribulin	isradipine	paliperidone	tizanidine	
escitalopram	lapatinib	perflutren lipid microspheres	vardenafil	
famotidine	levofloxacin	quetiapine	venlafaxine	

Drugs with a Conditional Risk of Torsades de Pointes

amitriptyline	doxepin	itraconazole	ritonavir	trimipramine
ciprofloxacin	fluconazole	ketoconazole	sertraline	
clomipramine	fluoxetine	nortriptyline	solifenacin	
desipramine	galantamine	paroxetine	trazodone	
diphenhydramine	imipramine	protriptyline	trimethoprim-Sulfa	

Reference

Arizona Cert Center for Education and Research on Therapeutics page. QT Drug Lists web site. Available at: http://www.azcert.org/medical-pros/drug-lists/bycategory.cfm#. Accessed October 13, 2015.

Attachment 12. Protocol JJCD Protocol Amendment I6F-MC-JJCD(a) Summary A Phase 1b Study of LY3039478 in Combination with Other Anticancer Agents in Patients with Advanced or Metastatic Solid Tumors

Overview

Protocol I6F-MC-JJCD, A Phase 1b Study of LY3039478 in Combination with Other Anticancer Agents in Patients with Advanced or Metastatic Solid Tumors, has been amended. The new protocol is indicated by Amendment (a) 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:

- Clarification to some inclusion criteria
- Clarification to some dose-limiting toxicity (DLT) criteria
- Clarification to the definition of maximum tolerated dose (MTD)
- Change of wording from extension period to continued access period
- Removal of the provision that patients must sign new informed consent forms (ICFs) to enter the continued access period
- Clarification to the dosage strengths of LY3023414
- Clarification of the dose adjustments between cycles
- Clarification for electrocardiograms

Minor editing and formatting changes were also made.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

2.0. Synopsis

…

Diagnosis and Main Criteria for Inclusion and Exclusions: Adult patients (≥18 years of age) who are appropriate candidates for experimental treatment with adequate organ function and performance status, have histological or cytological evidence of cancer, either a solid tumor or a lymphoma, which is ~~advanced~~ unresectable or metastatic. In the dose-confirmation phase of the study, all patients must have measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). In Part A dose confirmation: all patients must have histological evidence of ~~advanced~~ unresectable or metastatic soft tissue sarcoma or breast cancer. Breast cancer patients must have prescreened alterations related to Notch pathway. For Part B dose confirmation: all patients must have histological evidence of ~~advanced~~ unresectable or metastatic colon cancer or soft tissue sarcoma. Colon cancer patients must have prescreened alterations related to Notch pathway. For Part C dose confirmation: all patients must have histological evidence of ~~advanced~~ unresectable or metastatic breast cancer and must have prescreened alterations related to Notch pathway. For Part D dose confirmation: all patients must have histological evidence of cholangiocarcinoma, prescreened alterations related to Notch pathway, and must not have received >1 line of prior systemic therapy for metastatic or resectable disease. For Part E dose confirmation: all patients must have histological evidence of locally advanced unresectable or metastatic TNBC, prescreened alterations related to Notch pathway, and not have received >2 lines of prior systemic treatment for unresectable or metastatic TNBC. All patients must have available tumor tissue (archived or newly biopsied). Patients with serious concomitant systemic disorders including malabsorptive syndromes, enteropathies, gastroenteritis (acute or chronic), or diarrhea (acute or chronic), who have received other investigational product within 14 days, have symptomatic central nervous system malignancy or metastases, acute leukemia, active infection including human immunodeficiency virus, cardiac disease, or a second primary malignancy that may affect the interpretation of results will be excluded from treatment. For Part B only; patients with insulin-dependent diabetes mellitus or a history of gestational diabetes mellitus will be excluded from treatment.

…

5.8. Rationale for Amendment (a)

This study was amended at the request of the Food and Drug Administration (FDA) to clarify inclusion criteria, some criteria for DLTs (Section 7.2.2.1), and the definition for MTD. Minor editorial changes and clarifications have also been made.

6.1.1. Inclusion Criteria

…

[1] For all parts: The patient must be, in the judgment of the investigator, an appropriate candidate for experimental therapy after available standard therapies (per available local guidelines) have failed to provide clinical benefit for their advanced or metastatic cancer.

- For dose escalation for all combinations: The patient must have histological or cytological evidence of cancer, either a solid tumor or a lymphoma, which is ~~advanced~~ unresectable or metastatic.

- For Part A dose confirmation: All patients must have histological evidence of ~~advanced~~ unresectable or metastatic soft tissue sarcoma or breast cancer. Breast cancer patients must have prescreened mutations, amplification, or gene/protein expression alterations related to Notch pathway (Attachment 8).

- For Part B dose confirmation: All patients must have histological evidence of unresectable ~~advanced~~ or metastatic colon cancer or soft tissue sarcoma. Colon cancer patients must have prescreened mutations, amplification, or gene/protein expression alterations related to Notch pathway (Attachment 8).

- For Part C dose confirmation: All patients must have histological evidence of unresectable ~~advanced~~ or metastatic breast cancer and prescreened mutations, amplification, or gene/protein expression alterations related to Notch pathway (Attachment 8).

- For Part D dose confirmation: All patients must have histological evidence of cholangiocarcinoma and prescreened mutations, amplification, or gene/protein expression alterations related to Notch pathway (Attachment 8). Patients must not have received >1 line of prior systemic therapy for metastatic or resectable disease (that is, patients may have received adjuvant gemcitabine and then later gemcitabine/cisplatin for recurrent metastatic disease).

- For Part E dose confirmation: All patients must have histological evidence of locally advanced unresectable or metastatic TNBC and prescreened mutations, amplification, or gene/protein expression alterations related to Notch pathway (Attachment 8). Patients must not have received >2 lines of systemic treatment for ~~advanced~~ unresectable or metastatic TNBC.

…

[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 or >5 mmol/L. Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator; however, initial study drug treatment must not begin earlier than the day after the erythrocyte transfusion.

- Hepatic: Bilirubin ≤1.5 times upper limit of normal (ULN), ALT and aspartate aminotransferase (AST) ≤2.5 times ULN. If the liver has tumor involvement, AST and ALT equaling ≤5 times ULN are acceptable.

- Renal: calculated creatinine clearance >60 mL/min (Attachment 7).

- For Part B only: have fasting glucose ≤140 mg/dL and glycosylated hemoglobin (HbA1c) ≤7 g/dL.

…

6.1.2. Exclusion Criteria

…

[19] **Part B only**: 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 antidiabetics as documented by ~~glycosylated hemoglobin (~~HbA1c~~)~~ ~~<~~≤7%.

6.2. Summary of Study Design

…

The planned duration of treatment is not fixed; patients will remain on study drug therapy until they fulfill 1 of the criteria for treatment discontinuation. The treatment period will be defined as the time from treatment start until discontinuation from treatment for any reason (Section 6.3.2). The postdiscontinuation follow-up period begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and is defined by the following periods:

- The ***short term follow-up period*** begins 1 day after ~~discontinuation of study treatment~~ the patient and investigator agree that the patient will no longer continue treatment and lasts approximately 30 days (Visit 801).
- The ***long-term follow-up period*** begins 1 day after the short-term follow-up period (Visit 801) is completed and continues until death or study closure to collect PFS data (Visit 802-80X).
- After discontinuation, tumor measurements will be performed as indicated in Section 8.3. Other study procedures will be performed as outlined in Attachment 1.

This study will be considered closed once it is deemed that sufficient data are obtained to assess the primary and the secondary objectives, estimated to be approximately 12 months from the date that the last patient was enrolled. This will ensure that the primary objective and the secondary objectives are met for the purpose of the clinical study report. For PFS, in the event that the data are not mature enough to characterize the entire survival curve, a landmark analysis at 12 months will be done for the purpose of the clinical study report. Patients who are benefitting from treatment may continue to receive study drug for long-term durations, even after the study has closed and final database lock has occurred, in the ~~extension~~ continued access period.

…

6.2.2. ~~Extension~~ Continued Access Period

All patients remaining on study treatment without disease progression following the final analysis will be able to enter the ~~extension~~ continued access period of the study. The ~~extension~~ continued access period begins after study completion and ends at the end of trial. During the ~~extension~~ continued access period, patients on study treatment who continue to experience clinical benefit may continue to receive study treatment until disease progression, death, unacceptable toxicity, or start of new anticancer treatment. The ~~extension~~ continued access period includes a follow-up visit. The follow-up visit begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the ~~extension~~ continued access period and lasts approximately 30 days. 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.

~~Patients must sign a new ICF before entering the extension period. Eli Lilly and Company (Lilly) will notify investigators when the extension period begins.~~

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

SAEs will also be reported to Lilly Global Patient Safety and collected in the Lilly Safety System (LSS). 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.

Investigators may perform other standard procedures and tests needed to treat and evaluate patients; however, Lilly will not routinely collect the results of these assessments.

7.1. Materials and Supplies

…

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

7.2.1.5. LY3039478 in Combination with Gemcitabine and Carboplatin (Part E)

…

The site is responsible to consult the local laboratory to determine what method of serum creatinine measurement is used by that laboratory.

~~**Calvert Formula**~~

~~Total Dose (mg) = (target AUC) × (GFR + 25)~~

~~Maximum carboplatin dose (mg) = target AUC 6 (mg•min/mL) × (125 + 25) = 6 × 150 mL/min = 900 mg~~

...

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

A DLT is defined as an AE during Cycle 1 that is related to LY3039478, taladegib, LY3023414, or abemaciclib and fulfills any 1 of the following criterion using the NCI CTCAE v 4.0:

- CTCAE Grade 3 nonhematological toxicity. Exceptions will be made for:
  - Grade 3 nausea, vomiting, or constipation that lasts ≤72 hours and that can be controlled with treatment or Grade 4 vomiting or constipation that lasts ≤24 hours and that can be controlled with treatment
  - ~~nausea, vomiting, or constipation that lasts <72 hours and that can be controlled with treatment~~
  - Grade 3 electrolyte disturbance that can be controlled with treatment. Grade 4 electrolyte disturbance lasting more than 24 hours will be considered a DLT
    - ~~Electrolyte disturbance that can be controlled with treatment~~
  - Diarrhea CTCAE Grade 3 for 4 days or less and that can be controlled with standard treatment
  - Transient (<7 days) Grade 3 elevations of ALT and/or AST that are not accompanied by a Grade 2 bilirubin increase are considered an exception to the DLT criteria, unless there is a clear alternative cause for example, worsening biliary obstruction) if agreed by the study investigator and Lilly CRP/clinical research scientist (CRS)
- CTCAE Grade 4 anemia
- CTCAE Grade 4 ~~anemia,~~ neutropenia or leukopenia of >5-days duration
- Any febrile neutropenia
- Grade 3 thrombocytopenia with clinically significant bleeding or Grade 4 thrombocytopenia
- Inability to start Cycle 2 within 3 weeks of the expected date because of persistent toxicity related to LY3039478, taladegib, LY3023414, or abemaciclib
- Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose limiting (for example, any toxicity that is possibly related to the study medication that requires the withdrawal of the patient from the study during Cycle 1)
- Exceptions to the DLT criteria for Part B include:
  - Grade 3 fasting hyperglycemia that resolves to ≤Grade 2 within 7 days
  - Grade 4 hyperglycemia lasting <24 hours ~~Grade 4 hyperglycemia of any duration that results in intensive care unit admission will be considered a DLT~~

- Grade 3 mucositis that resolves to ≤Grade 2 within 7 days. Grade 4 mucositis of any duration will be considered a DLT.
- Grade 3 fatigue that resolves to ≤Grade 2 within 5 days
- 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 DLET is defined as an AE occurring between Day 1 and Day 21/28 of any cycle (other than Cycle 1) for a patient enrolled in the dose-escalation phase of Parts A, B, and C or in any cycle (including Cycle 1) for a patient enrolled in the dose-confirmation phase of Parts A, B, and C that would have met the criteria for DLT if it had occurred during Cycle 1 for a patient enrolled in the dose-escalation phase of Parts A, B, and C.

For the purpose of this study, the MTD is defined as the highest tested dose that has <33% probability of causing a DLT during Cycle 1 in a cohort of at least 6 patients.

Determination of the recommended dose will take into account toxicities beyond Cycle 1, PK, and dose modifications of standard chemotherapy.

7.2.4.1.2. Dose Adjustments between Cycles

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Hematologic toxicity must resolve to ~~a level that, in the opinion of the investigator, is reasonable to allow for continuation of treatment~~ CTCAE Grade 0, 1, or baseline level before resuming treatment.

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7.3. Method of Assignment to Treatment

~~Patients who meet all criteria for enrollment will be assigned to receive LY3039478 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, study part, and cohort for each patient. No dose escalations (that is, to the next cohort) can occur without prior discussion and agreement with the responsible Lilly CRP or CRS.

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Table JJCD.8.1. Adverse Events and Serious Adverse Reporting Guidelines for Study JJCD

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 when the patient and the investigator agree that the patient will no longer continue any study treatment)	All AEs All SAEs regardless of relatedness	X X	 X
Follow-up visit (Visit 801) (Starts the day after the patient and the investigator agree that the patient will no longer continue any study treatment and ends when end of study safety assessments are completed in 30 days OR the planned end of the cycle)	All AEs All SAEs regardless of relatedness	X X	 X
~~Extension~~ Continued access period	All AEs All SAEs regardless of relatedness	X X	 X
~~Extension~~ Continued access 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 of which the investigator becomes aware		X

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

8.1.3.1 Electrocardiograms

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~~Digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.~~

~~The machine read ECG intervals and heart rate may be used for data analysis and report writing purposes unless an overread of the ECGs is conducted prior to completion of the final study report (in which case the overread data would be used).~~

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will then conduct a full overread on 1 of the replicate ECGs (including all intervals). A report based on data from this overread will be issued to the investigative site. For each set of replicates, the RR and QT intervals and heart rate will be determined on the ECGs that were not fully overread. These data are not routinely reported back to the investigative site.

All data from the overreads will be placed in the Lilly database for analytical and study report purposes. Any clinically significant finding that was not present on the fully overread ECG but was present on the partially overread ECG (where only RR, QT, and heart rate is assessed)will be reported to the investigator and to Lilly. If there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the investigator's (or qualified designee's) interpretation will be used for study entry and immediate subject management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes.

The investigator (or qualified designee) must document his/her review of 1 of the replicate ECGs printed at the time of collection, the final overread ECG report issued by the central ECG laboratory, and any alert reports.

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Attachment 1. JJCD Study Schedule

During and Poststudy Assessments - Parts A, B, and C

Study Procedures		Cycle 1			
	3-Day Lead-In	Week 1	Week 2	Week 3	Week 4
	Single dose Taladegib, LY3023414, or Abemaciclib on Day 1[a]	~~First Day of the Week 1~~ Day 1 of LY3039478 Combination	~~First Day of the Week 2~~ Day 8 of LY3039478 Combination	~~First Day of the Week 3~~ Day 15 of LY3039478 Combination	~~First Day of the Week 4~~ Day 22 of LY3039478 Combination
Physical examination	X	X	X	X	X
Vital signs and weight (temperature, pulse rate, blood pressure, respiratory rate)	X	X	X	X	X
ECOG performance status	X	X	X	X	X
CTCAE version 4.0 grading		X	X	X	X
Concomitant medications	X	X	X	X	X
Central ECG[b]	X	X			
PET scan[c]			X		
Hematology[d]	X	X	X	X	X
Serum chemistry[d]	X	X	X	X	X
Cystatin C (for Part C only)	X	X	X	X	X
HbA1c (for Part B only)		X			
ECG chemistry[b,d]	X	X			
Coagulation (PT/INR, aPTT, fibrinogen)[d]		X	X	X	X
Tumor marker[d]	X	X			
Pharmacogenetics sample (predose)		X			
Blood PK sampling[b]	X	X		X	X
Tumor biopsy, recommended[e]					X
Skin biopsy[b,f]		X			
Blood PD biomarkers (Aβ[1-x]) during dose escalation only)[b,g]		X			X
Blood exploratory circulating biomarkers predose		X			
Urine (8-hour collection)[b,g]	X				X

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Attachment 2. Protocol JJCD Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry[a,b]**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Leukocytes (WBC)	Total bilirubin
Neutrophils	Alkaline phosphatase
Lymphocytes	Alanine aminotransferase (ALT)
Monocytes	Aspartate aminotransferase (AST)
Eosinophils	Gamma-glutamyl transpeptidase (GGT)
Basophils	Blood urea nitrogen (BUN)
Platelets	Creatinine
	Lipase
Coagulation[b]	Lactate dehydrogenase (LDH)
aPTT	Uric acid
PT/INR	Calcium
Fibrinogen	Phosphorus
	Glucose, random (fasted for Part B)
Urinalysis[a]	Albumin
Specific gravity	Total protein
pH	Creatinine clearance
Protein	Serum or urine pregnancy test (females only)[a]
Glucose	
Ketones	**ECG Chemistry[b]**
Blood	
Urine leukocyte esterase	Thyroid-stimulating hormone (TSH)
	Free ~~T~~tri-iodothyronine (T3)
HbA1c (for Part B only)	Free ~~T~~thyroxine (T4)
	Calcium[c]
Cystatin C (for Part C only)	Sodium[c]
	Potassium[c]
Tumor Markers[a]	Phosphorus
	Magnesium
Biomarkers[b]	

Attachment 4. Protocol JJCD Pharmacokinetic, Pharmacodynamic, and Electrocardiogram with Electrocardiogram Chemistry Sampling Schedule

Pharmacokinetic and Pharmacodynamic Sampling Schedule: Part A Dose Escalation – LY3039478 + Taladegib

PK Sample Number	Cycle	Day of LY3039478 Combination	Sampling Time (hr) for LY3039478	Sampling Time (hr) for Taladegib/ LSN3185556	Sampling Time (hr) for Aβ	Sampling Time for Plasma Cortisol	Sampling Time for Urine	PD Sampling Time for Skin Biopsies	ECG with ECG Chemistry
1	Lead in	-3 ~~1~~		predose	predose	predose	0-8 hr pooled sample (end time to match with 8 hr PK sample). Record total volume	screening	predose
2	Lead in	-3 ~~1~~		0.5					
3	Lead in	-3 ~~1~~		1					
4	Lead in	-3 ~~1~~		2					
5	Lead in	-3 ~~1~~		4					
6	Lead in	-3 ~~1~~		6					
7	Lead in	-3 ~~1~~		8					
8	Lead in	-2 ~~2~~		24-30					
9	1	1		predose	predose				
10	1	22	predose	predose	predose	predose	0-8 hr pooled sample (end time to match with 8 hr PK sample). Record total volume		predose
11	1	22	0.5	0.5	0.5				
12	1	22	1	1	1				
13	1	22	2	2	2				2 hr
14	1	22	4	4	4				
15	1	22	6	6	6			6-8 hr (±1 hr)	
16	1	22	8	8	8				
17	1	22 ~~23~~	same time as taladegib predose sample	predose	same time as taladegib predose sample	same time as taladegib predose sample			same time as taladegib predose sample
18	2	1	predose	predose					predose

Abbreviations: ECG = electrocardiogram; hr = hour; PD = pharmacodynamic; PK = pharmacokinetic.

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Pharmacokinetic and Pharmacodynamic Sampling Schedule: Part B Dose Escalation – LY3039478 + LY3023414

PK Sample Number	Cycle	Day of LY3039478 Combination	Sampling Time (hr) for LY3039478	Sampling Time (hr) for LY3023414	Sampling Time (hr) for Aβ	Sampling Time for Plasma Cortisol	Sampling Time for Urine	PD Sampling Time for Skin Biopsies	ECG with ECG Chemistry
1	Lead in	-3 ~~1~~		predose	predose	predose	0-8 hr pooled sample (end time to match with 8 hr PK sample). Record total volume	screening	predose
2	Lead in	-3 ~~1~~		0.5					
3	Lead in	-3 ~~1~~		1					
4	Lead in	-3 ~~1~~		2					
5	Lead in	-3 ~~1~~		4					
6	Lead in	-3 ~~1~~		6					
7	Lead in	-3 ~~1~~		8					
8	Lead in	-2 ~~2~~		24-30					
9	1	1		predose	predose				
10	1	22	predose	predose	predose	predose	0-8 hr pooled sample (end time to match with 8 hr PK sample). Record total volume		predose
11	1	22	0.5	0.5	0.5				
12	1	22	1	1	1				
13	1	22	2	2	2				2 hr
14	1	22	4	4	4				
15	1	22	6	6	6			6-8 hr (±1 hr)	
16	1	22	8	8	8				
17	1	22 ~~23~~	24-30		24-30	24-30 hr			24-30 hr
18	2	1	predose	predose					predose

Abbreviations: ECG = electrocardiogram; hr= hour; PD = pharmacodynamic; PK = pharmacokinetic.

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Pharmacokinetic and Pharmacodynamic Sampling Schedule: Part C Dose Escalation – LY3039478 + Abemaciclib

PK Sample Number	Cycle	Day of LY3039478 Combination	Sampling Time (hr) for LY3039478	Sampling Time (hr) for Abemaciclib, LSN3106726, LSN2839567	Sampling Time (hr) for Aβ	Sampling Time for Plasma Cortisol	Sampling Time for Urine	PD Sampling Time for Skin Biopsies	ECG with ECG Chemistry
1	Lead in	-3 ~~1~~		predose	predose	predose	0-8 hr pooled sample (end time to match with 8 hr PK sample). Record total volume	screening	predose
2	Lead in	-3 ~~1~~		0.5					
3	Lead in	-3 ~~1~~		1					
4	Lead in	-3 ~~1~~		2					
5	Lead in	-3 ~~1~~		4					
6	Lead in	-3 ~~1~~		6					
7	Lead in	-3 ~~1~~		8					
8	Lead in	-2 ~~2~~		24-30					
9	1	1		predose	predose				
10	1	22	predose	predose	predose	predose	0-8 hr pooled sample (end time to match with 8 hr PK sample). Record total volume		predose
11	1	22	0.5	0.5	0.5				
12	1	22	1	1	1				
13	1	22	2	2	2				2 hr
14	1	22	4	4	4				
15	1	22	6	6	6			6-8 hr (±1 hr)	
16	1	22	8	8	8				
17	1	22 ~~23~~	24-30		24-30	24-30 hr			24-30 hr
18	2	1	predose	predose					Predose

Abbreviations: ECG = electrocardiogram; hr= hour; PD = pharmacodynamic; PK = pharmacokinetic.

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Pharmacokinetic and Pharmacodynamic Sampling Schedule (hours): Part D Dose Escalation – LY3039478 + Cisplatin/Gemcitabine

PK Sample Number	Cycle	Day	Sampling Time for LY3039478	Sampling Time for Cisplatin (Relative to Start of Infusion)	Sampling Time for Gemcitabine (Relative to Start of Infusion)	Sampling Time for Aβ (Relative to LY3039478)	Sampling Time for Plasma Cortisol (Relative to LY3039478)	Sampling Time for Urine (Relative to LY3039478)	PD Sampling Time for Skin Biopsies (Relative to LY3039478)	ECG with ECG Chemistry (Relative to LY3039478)
1						screening			predose	predose
2	1	1	predose	predose	predose	predose	predose	0-8 hr pooled sample (end time to match with 6-8 hr PK sample). Record total volume		
3	1	1	0.5		0.5 (end of infusion)					
4	1	1	1	1.5 (end of infusion)	1					
5	1	1	2	2	2					
6	1	1	4	4	4					4
7	1	1	6-8	6	6				6-8	
8	1	12	24-30							
9	1	15	predose			predose	predose	0-8 hr pooled sample (end time to match with 6-8 hr PK sample). Record total volume		
10	1	15	0.5			0.5				
11	1	15	1			1				
12	1	15	2			2				
13	1	15	4			4				
14	1	15	6-8			6-8				
15	1	15	24-30			24-30				
16	2	1	predose				predose			predose

Abbreviations: ECG = electrocardiogram; hr = hour; PD = pharmacodynamic; PK = pharmacokinetic.

…

Pharmacokinetic and Pharmacodynamic Sampling Schedule (hours): Part E Dose Escalation – LY3039478 + Gemcitabine/Carboplatin

PK Sample Number	Cycle	Day	PK Sampling Time for LY3039478	Sampling Time for Gemcitabine (Relative to Start of Infusion)	Sampling Time for Carboplatin (Relative to Start of Infusion)	Sampling Time for Aβ (Relative to LY3039478)	Sampling Time for Plasma Cortisol (Relative to LY3039478)	Sampling Time for Urine (Relative to LY3039478)	PD Sampling Time for Skin Biopsies (Relative to LY3039478)	ECG with ECG Chemistry (Relative to LY3039478)
1	-	-				screening			predose	predose
2	1	1	predose	predose	predose	predose	predose	0-8 hr pooled sample (end time to match with 6-8 hr PK sample). Record total volume		
3	1	1	0.5	0.5 (end of infusion)	0.5 (end of infusion)					
4	1	1	1	1	1					
5	1	1	2	2	2					2
6	1	1	4	4	4					
7	1	1	6-8	6	6				6-8	
8	1	1~~2~~	24-30							
9	1	15	predose			predose	predose	0-8 hr pooled sample (end time to match with 6-8 hr PK sample). Record total volume		
10	1	15	0.5			0.5				
11	1	15	1			1				
12	1	15	2			2				
13	1	15	4			4				
14	1	15	6-8			6-8				
15	1	15	24-30			24-30				
16	2	1	predose				predose			predose

Abbreviations: ECG = electrocardiogram; PD = pharmacodynamic; PK = pharmacokinetic.

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