Protocol Addendum I6F-JE-JJCC(b)

A Phase 1 Study of LY3039478 in Japanese Patients with Advanced Solid Tumors

NCT02836600

Approval Date: 12-Apr-2019

1. Protocol I6F-JE-JJCC(b)
A Phase 1 Study of LY3039478 in Japanese Patients with Advanced Solid Tumors

Confidential Information

LY3039478

This Phase 1 study is a single center, nonrandomized, open-label, dose-escalation study of oral LY3039478 in Japanese patients with advanced and/or metastatic solid tumors.

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Protocol Electronically Signed and Approved by Lilly: 20-Apr-2016
Amendment (a) Electronically Signed and Approved by Lilly: 30-May-2016
Amendment (b) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 12-Apr-2019 GMT

2. Synopsis

This Phase 1 study is a single center, nonrandomized, single arm, open-label, dose-escalation study of LY3039478 in Japanese patients with advanced solid tumors.

Clinical Protocol Synopsis: Study I6F-JE-JJCC

Name of Investigational Product: LY3039478	
Title of Study: A Phase 1 Study of LY3039478 in Japanese Patients with Advanced Solid Tumors	
Number of Planned Patients: 9 to 12	**Phase of Development:** 1

Objectives:

The primary objective of this study is to evaluate the tolerability of LY3039478 up to the global recommended dose in Japanese patients with advanced solid tumors.

The secondary objectives of this study are:

- to characterize the safety and toxicity profile of LY3039478
- to evaluate the pharmacokinetic (PK) parameters of LY3039478.
- to document any antitumor activity observed with LY3039478.

The exploratory objectives of this study are:

- to explore pharmacodynamic (PD) effects of LY3039478 on biomarkers indicative of Notch activity.
- to evaluate tumor tissue and blood for biomarkers related to solid tumors, the Notch signaling pathway and drug target pathways, immune functioning, and mechanism of action of study drug, and their potential association with the study objectives.
- to explore the utility of positron emission tomography scan to assess treatment effect with LY3039478.

Study Design:

Study I6F-JE-JJCC (JJCC) is a Phase 1, single center, nonrandomized, single-arm, open-label, dose-escalation study of LY3039478 in Japanese patients with advanced solid tumors. Study JJCC will consist of 2 dose levels, 25 and 50 mg LY3039478 3 times per week (TIW; 3 or 6 patients per dose level). Transition of dose level (from 25 to 50 mg) will proceed if the frequency of dose-limiting toxicity (DLT) observed in Cycle 1 (28 days) is <33% of patients in the first dose level (25 mg). Eligible patients will be treated with LY3039478 at the assigned dose. Treatment will continue until disease progression, development of unacceptable toxicity, or any other discontinuation criteria are met.

Diagnosis and Main Criteria for Inclusion and Exclusions:

Patients must be ≥20 years of age and have histological or cytological evidence of a diagnosis of solid tumor that is advanced and/or metastatic. In the judgment of the investigator, patients must be appropriate candidates for experimental therapy after available standard therapies have failed or for whom standard therapy is not appropriate. Patients must have a performance status of ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale. Patients also must have adequate organ function, including hematologic, hepatic, and renal, and an estimated life expectancy of ≥12 weeks.

Patients may be excluded if they have received previous therapy for cancer within 14 or 21 days of the initial dose of study drug for a nonmyelosuppressive or myelosuppressive agents, respectively; have serious preexisting medical conditions; have current or recent (within 3 months of study drug administration) gastrointestinal disease with chronic or intermittent diarrhea; have an active bacterial, fungal, and/or known viral infection; or have known acute or chronic leukemia or current hematologic malignancies that may affect the interpretation of results.

Investigational Product, Dosage, and Mode of Administration:

LY3039478 25 and 50 mg, administered orally as capsules 3 times per week during a 28-day cycle.

Planned Duration of Treatment:

The planned duration of treatment is not fixed. A cycle is defined as 28 days, and treatment will continue until disease progression, development of unacceptable toxicity, or any other discontinuation criteria are met. Follow-up: 30 days ±3 days after the patient and the investigator agree that the patient will no longer continue study treatment.

Criteria for Evaluation:

Safety: National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.0 will be used for classifying or grading events and severity. Medical Dictionary for Regulatory Activities will be used for coding

and summarizing reporting event terms. Safety measurements will include DLTs, serious adverse events (AEs), dose adjustments, laboratory tests, electrocardiograms (ECGs), and vital signs.

Bioanalytical: Plasma and urine concentrations of LY3039478.

Efficacy: Response Evaluation Criteria in Solid Tumors version 1.1 for solid tumors; Response Assessment in Neuro-Oncology criteria for glioblastoma.

Pharmacokinetics/Pharmacodynamics: Maximum plasma concentration and area under the plasma concentration versus time curve. In addition, half-life, apparent clearance, and apparent volume of distribution may be reported. The PK data will be combined, and analyses may be conducted to determine a relationship between exposure and PD/pharmacogenetic effect data.

Statistical Methods:

Safety: Safety analyses will include summaries of the following:

- DLTs at each dose level (using the DLT analysis set)
- AEs, including severity, possible relationship to study drug and outcome
- dose adjustments
- laboratory values
- vital signs and physical examination
- ECG readings.

Efficacy: The study was not designed to make an efficacy assessment. However, any tumor response data will be tabulated.

Pharmacokinetics: The PK parameters for LY3039478 will be calculated by standard noncompartmental methods of analysis.

Pharmacodynamics: All PD data will be assessed. Exploratory PK/PD analyses may be conducted to identify the exposure-biomarker response relationship.

3. Table of Contents

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4. Abbreviations and Definitions

Term	Definition
Aβ	Amyloid-β
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 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.
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
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, good clinical practice, and the applicable regulatory requirement(s).
ChE	cholinesterase
C_{max}	maximum plasma concentration
CL/F	apparent systemic clearance
CNS	central nervous system
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.
eCRF	electronic case report form: Sometimes referred to as clinical report form, an electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	clinical research physician
CRS	clinical research scientist

CSF	colony-stimulating factor
CSL	C-promoter binding factor-1 (CBF-1), Suppressor of Hairless (Su[H]), and lin-12 and glp-1 (LAG-1)
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
DLET	dose-limiting equivalent toxicity
DLL	Delta-like
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
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.
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.
F	oral absorption/bioavailability
FDP	fibrin/fibrinogen degradation products
GCP	good clinical practice
G-CSF	granulocyte colony stimulating factor
GI	gastrointestinal
hERG	human ether-a-go-go-related gene
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form

ICH	International Conference on Harmonisation
ILD	interstitial lung disease
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 data lock.
investigational product	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial. Investigational product includes a product with a marketing authorization when: 1. used or assembled (formulated or packaged) in a way different from the authorized form 2. used for an unauthorized indication or 3. used to gain further information about the authorized form.
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.
LC-MS/MS	liquid chromatography-tandem mass spectrometry
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
LDH	lactate dehydrogenase
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 standard operating procedures, International Conference on Harmonisation Good Clinical Practice guidelines, and all applicable laws (for example, privacy and data protection) and regulations.
MTD	maximum tolerated dose
NCI	National Cancer Institute
NICD	Notch intracellular domain
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)

PD	progressive disease
PET	positron emission tomography
PK	pharmacokinetic(s)
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.
SAC	Safety Assessment Committee
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/or tests (for example, 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.
sponsor	The party who takes responsibility for the initiation, management and/or financing of a clinical study.
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TIW	3 times per week
t_{max}	time of maximal plasma concentration
TPO	third-party organization
ULN	upper limit of normal
V/F	apparent volume of distribution
WHO	World Health Organization

A Phase 1 Study of LY3039478 in Japanese Patients with Advanced Solid Tumors

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 [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 these 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 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. γ-Secretase is a high molecular weight multiprotein complex possessing protease activity against a number of type I membrane proteins, including amyloid precursor protein, ErbB4 receptor, and Notch receptors. γ-Secretase cleavage of the Notch receptor results in the release of a peptide called the Notch intracellular domain (NICD) and translocation to the nucleus. The NICD is important in regulating transcriptional activity through interactions with the transcription repressor C-promoter binding factor-1, Suppressor of Hairless, and lin-12 and glp-1 (CSL), also known as mammalian recombination signal-binding protein-Jκ. Notch intracellular domain binding to the CSL relieves suppressive function by displacing co-repressors and recruiting co-activators 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, 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.

Eli Lilly and Company (Lilly) has developed a potent small-molecule inhibitor of Notch, LY3039478, for the treatment of cancer. The Phase 1 first-in-human Study I6F-MC-JJCA (JJCA) established a maximum tolerated dose (MTD) of 75 mg 3 times per week (TIW) on Days 1 through 28 of a 28-day cycle. However, a review of safety data showed significant dose reductions or omissions related to adverse events (AEs); therefore, the recommended dose was adjusted to 50 mg TIW. This study in Japanese patients with advanced cancers, Study I6F-JE-JJCC (JJCC), is a Phase 1 trial designed to confirm the safety and tolerability of LY3039478 up to the recommended dose, 50 mg TIW, which was established in Study JJCA.

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

5.2. Objectives

5.2.1. Primary Objective

The primary objective of this study is to evaluate the tolerability of LY3039478 up to the global recommended dose in Japanese patients with advanced solid tumors.

5.2.2. Secondary Objectives

The secondary objectives of this study are:

- to characterize the safety and toxicity profile of LY3039478.
- to evaluate the pharmacokinetic (PK) parameters of LY3039478.
- to document any antitumor activity observed with LY3039478.

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.
- to evaluate tumor tissue and blood for biomarkers related to solid tumors, the Notch signaling pathway and drug target pathways, immune functioning, and mechanism of action of study drug, and their potential association with the study objectives.
- to explore the utility of positron emission tomography (PET) scan to assess treatment effect with LY3039478.

5.3. General Introduction to LY3039478

Detailed information about LY3039478 is provided in the Investigator's Brochure (IB). This section provides a summary of the information most relevant for this initial Phase 1 study.

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 study drug may be found in Section 7 (Development Core Safety Information) of the IB. Information on serious adverse events (SAEs) expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

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

LY3039478 is a potent Notch inhibitor with a half-maximal inhibitory concentration (IC_{50}) of ≤1nM in the majority of tumor cell lines tested for its ability to inhibit Notch-1 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% value for Notch-1 intracellular domain inhibition of 0.8 and 0.9 mg/kg, respectively, and threshold plasma concentration of the compound required to inhibit cleavage by 50% 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 produced optimal efficacy while balancing on-target gastrointestinal (GI) toxicity. Furthermore, coadministration of dexamethasone with LY3039478 significantly improved body weight loss and GI toxicity without negatively impacting antitumor activity of LY3039478. LY3039478 also inhibited Notch-1 cleavage and down-stream 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: EL1989 adenocarcinoma of colon, EL1986 adenocarcinoma of colon, EL1997 triple-negative invasive ductal carcinoma of breast, and EL2056 glioblastoma; and cell line-derived xenograft tumors: A2780 ovarian carcinoma, U-87 MG glioblastoma, HCT-116 colon carcinoma, SW480 colon carcinoma, and K562 chronic myelogenous leukemia.

5.3.2. Nonclinical Pharmacokinetics/Pharmacodynamics

Preliminary nonclinical PK of LY3039478 was characterized in mice, rats, and dogs. Oral absorption (F) was extensive and rapid (F = 65% to 67%; time of maximal plasma concentration [t_{max}] = 0.25 to 0.4 hour). Elimination half-life ($t_{1/2}$) of 2 to 6 hours was consistent with desired washout between TIW doses. LY3039478 was well distributed into tissues (volume of distribution = 1.4 to 4.9 L/kg), with preferential tumor partitioning (tumor/plasma = 3.4 to 33) and unbound brain concentrations 22- to 118-fold in excess of the Notch IC_{50}. In 1-month rat and dog toxicokinetic studies (TIW dosing), LY3039478 exposure increased in proportion to dose, with no apparent sex differences or time-dependent changes in exposure (for example, accumulation). LY3039478 was extensively cleared by urinary excretion of parent compound, and by hydrolysis of the amide bond connecting the azepine ring to the aliphatic side chain. No drug-drug interaction (DDI) perpetrator potential was identified: LY3039478 was not an inhibitor or inducer of key cytochrome P450s (CYPs) or transporters. LY3039478 clearance

mechanisms (urinary excretion of parent and amide hydrolysis) are consistent with low DDI potential.

A PK/PD model was developed to relate the LY3039478 plasma concentration to the level of in vivo Notch-1 cleavage in mouse lung, as a surrogate tumor marker. A precursor-dependent indirect-response model with a rebound was used to describe the relationship between plasma concentrations and Notch-1 cleavage. The model identified a maximal inhibition of the Notch-1 signal of 98% and the estimated IC_{50} was 1.8 ng/mL. The model adequately characterized the observed rebound above baseline levels in Notch-1 that occurred between 12 and 24 hours with a recovery to baseline by 36 to 48 hours. A tumor growth kinetics model was also developed based on tumor sizes in mice bearing A2780 xenografts. This model supported an understanding of the relationship between LY3039478 exposure and tumor growth delay.

5.3.3. Nonclinical Toxicology

LY3039478 was evaluated in nonclinical toxicology studies up to 1 month in duration using TIW oral dosing in rats and dogs to characterize the target tissues for toxicity that may be clinically relevant. Based on results from the repeat-dose toxicity studies, the primary target organ for LY3039478 toxicity is the GI tract. The mucoid enteropathy and all other toxicities were reversible or partially reversible following a 3-week recovery period in rats. Details and findings from the rat and dog studies are presented in the IB.

The intestinal toxicity in the toxicology studies was characterized by fecal abnormalities such as few/absent or watery feces in rats and soft, watery, mucoid, and discolored feces in dogs, and histologic changes described as a mucoid enteropathy. Mucoid enteropathy is a known target-mediated toxicity of Notch inhibitors (Milano et al. 2004). Based on in vitro human ether-a-go-go-related gene (hERG) results, there is no expected risk for QT prolongation by hERG inhibition. In the 1-month dog study, no test article-related effects were observed in any of the electrocardiogram (ECG) parameters (heart rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT interval). No evidence of mutagenicity or clastogenicity was observed in a bacterial mutagenicity (Ames) or in vitro chromosomal aberration assay, respectively. In additional in vitro assays, LY3039478 was classified as a nonirritant and demonstrated no phototoxic potential.

5.3.4. Prior Clinical Experience

5.3.4.1. Clinical Adverse Events with LY3039478

During the dose-escalation phase (Part A) of Phase 1 Study JJCA, 5 of the 55 patients (9.1%) experienced dose-limiting toxicities (DLTs). Dose-limiting toxicities 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. Dose-limiting toxicities 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. 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 Grade 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. 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) treatment-emergent adverse events 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).

5.3.4.2. Clinical Pharmacokinetics with LY3039478

As of 06 January 2015, PK data for LY3039478 were available from 52 patients after a single dose and from 35 patients after multiple dosing, over a dose range of 2.5 to 100 mg in Cycle 1 from Study JJCA. After oral administration, t_{max} of LY3039478 was reached approximately 1 to 2 hours postdose and the mean $t_{1/2}$ was approximately 5 to 7 hours. The PK of LY3039478 did not change upon multiple dosing, and there was little to no accumulation with the TIW dosing schedule. A preliminary assessment of dose proportionality has been conducted for PK parameters (area under the plasma concentration versus time curve (AUC) from time zero to 48 hours and maximum plasma concentration [C_{max}]) after multiple dosing, and no deviations from linearity were observed across the dose range studied (2.5 to 100 mg). The variability in exposures, assessed by percentage coefficient of variation, ranged from 30% to 90% for C_{max} and AUC. Preliminary analyses of urine data suggest that renal clearance contributed to approximately 20% of apparent plasma clearance of LY3039478.

5.3.4.3. Clinical Absorption, Distribution, Metabolism, and Excretion

Preliminary human plasma and urine profiling indicated that LY3039478 is cleared by glucuronidation, by hydrolysis of the amide bond connecting the azepine ring to the aliphatic side chain, and by urinary excretion. LY3039478 does not inhibit key CYPs or drug transporters in vitro. LY3039478 is a weak inducer of CYP3A4 in vitro and is predicted to decrease the AUC of midazolam (a sensitive substrate of this enzyme) by 20%. LY3039478 clearance mechanisms (urinary excretion of parent, glucuronidation, and amide hydrolysis) indicate low DDI potential.

5.3.5. Biomarkers

As part of an ongoing effort by Lilly to better understand the relationship between cancer, genetics, and response to therapy, this study will analyze biomarkers relevant to solid tumors, the

Notch signaling pathway and drug target pathways, immune functioning, mechanism of action of study drug, and their potential association with the objectives of the study.

Pharmacodynamic biomarkers will be measured before and after administration of study drug in plasma and skin throughout the study. Whenever clinically feasible, biomarkers will be measured before and after administration of study drug in tumors. Potential predictive biomarkers will be measured throughout the study in archived tumor tissue (for example, from prior biopsy), as well as before and after administration of study drug in both tumors and blood.

Additional details about sampling are provided in Section 8.2.4, Attachment 1, and Attachment 3.

5.4. Rationale for Selection of Dose

A dose range from 25 to 50 mg of LY3039478 administered orally TIW was selected based on the safety and PK data of Study JJCA.

During the dose escalation phase (Part A) of Study JJCA, doses between 2.5 and 100 mg TIW were investigated. As described in Section 5.3.4.1, the MTD was determined to be 75 mg initially, but a review of safety data showed significant dose reductions or omissions related to AEs; therefore, the recommended dose was adjusted to 50 mg.

The objective of Study JJCC is to confirm tolerability in patients up to the recommended dose, 50 mg in TIW, as determined in Study JJCA. The maximum dose level in Study JJCC is also 50 mg. To ensure the patients' safety, the initial dose is 25 mg, which is 50% of the recommended dose in non-Japanese patients (50 mg).

6. Investigational Plan

6.1. Study Population

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened; however, individuals who failed screening due to a minor deviation from the range of eligibility may be rescreened by agreement between the investigator and the sponsor.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is 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] Have histological or cytological evidence of a diagnosis of solid tumor that is advanced and/or metastatic and must be, in the judgment of the investigator, an appropriate candidate for experimental therapy after available standard therapies have failed or for whom standard therapy would not be appropriate.

[2] Have measurable and/or nonmeasurable disease as defined by the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) (Eisenhauer et al. 2009; refer to Attachment 9).

[3] Are ≥20 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 × 10^9/L, platelets ≥100 × 10^9/L, and hemoglobin ≥8 g/dL.
- Hepatic: bilirubin ≤1.5 × upper limit of normal (ULN), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤3.0 × ULN. If the liver has tumor metastatic involvement, ALT and AST equaling ≤5.0 × ULN are acceptable.
- Renal: calculated creatinine clearance ≥45 mL/min (refer to Attachment 7).

[6] Have a performance status of ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale (Oken et al. 1982; refer to Attachment 6).

[7] Have discontinued all previous therapies for cancer (including chemotherapy, radiotherapy, immunotherapy, and investigational therapy) for at least 21 days for myelosuppressive agents or 14 days for nonmyelosuppressive agents prior to receiving study drug, and recovered from the acute effects of therapy (treatment-related toxicity resolved to baseline or Grade ≤1, except alopecia). At the discretion of the investigator, patients with breast or prostate cancers progressing on hormone 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 must agree to use medically approved barrier contraceptive precautions during the study and for 3 months following the last dose of study drug. This precaution should also be followed by vasectomized males.

Females of childbearing potential: must agree to use medically approved contraceptive precautions during the study and for 3 months following the last dose of study drug, and must have had a negative serum or urine pregnancy test ≤7 days before the first dose of study drug, and must also not be breastfeeding. If a female patient stops breastfeeding for the study entry, breastfeeding must cease from the day of the first study drug administration until at least 3 months after the last administration.

Acceptable methods of contraception include bilateral tubal ligation, condoms with spermicide, intrauterine device that has been in place for at least 3 months before the first dose of study drug, or the oral contraceptive pill taken for at least 3 months before the first dose of study drug.

A woman of childbearing potential is defined as a premenopausal female. The postmenopausal condition or post-menopause is defined as:

1) at least 6 weeks after surgical bilateral oophorectomy that can be confirmed via medical history records

or

2) spontaneous amenorrhea for at least 12 months, not induced by a medical condition such as anorexia nervosa nor induced by medication.

[10] Have an estimated life expectancy of ≥12 weeks, in the judgment of the investigator.

[11] Are able to swallow capsules.

6.1.2. Exclusion Criteria

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

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

[13] Have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study.

[14] Have central nervous system (CNS) malignancy with the following exceptions:

- 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 28 days prior to initial dosing (screening not required). Patients with brain edema should be excluded despite conditions.
- Patients with glioblastoma; World Health Organization (WHO) Grade IV, or WHO Grade II or III glioma, are eligible.

[15] Have known acute or chronic leukemia or current hematologic malignancies that, in the judgment of the investigator and sponsor, may affect the interpretation of results.

[16] Have received an autologous or allogeneic stem cell transplant.

[17] Are pregnant or lactating.

[18] Have an active bacterial, fungal, and/or known viral infection (for example, human immunodeficiency virus antibodies, active uncontrolled clinically serious hepatitis B virus or hepatitis C virus infection). Screening is not required for enrollment.

[19] 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.

[20] Have received prior treatment with a Notch inhibitor.

[21] Have hepatocellular carcinoma.

[22] Have persistent bleeding.

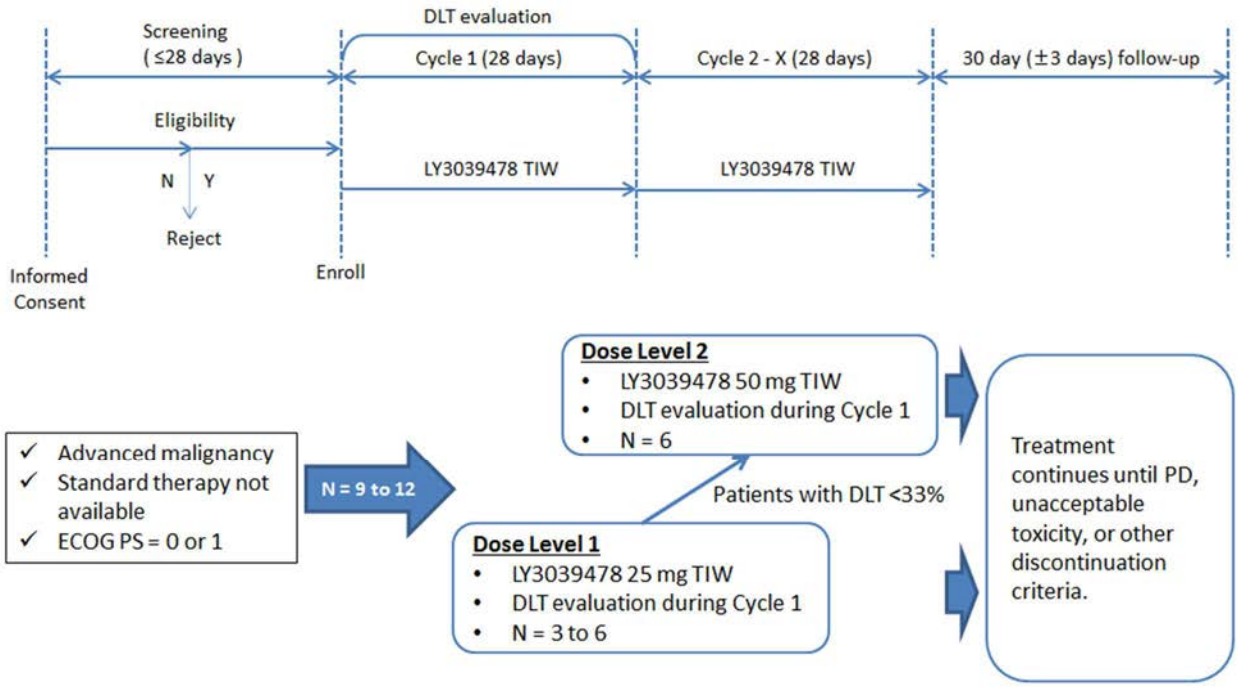
[23] Have undergone major surgery within 28 days prior to first dose. If the procedure is minimally invasive (for example, tumor biopsy), the treatment should be initiated after the investigator confirms the hemostasis and does not anticipate any significant bleeding.

6.2. Summary of Study Design

Study JJCC is a Phase 1, single center, nonrandomized, single-arm, open-label, dose-escalation study of LY3039478 in Japanese patients with advanced solid tumors.

Study JJCC will consist of 2 dose levels, 25 and 50 mg LY3039478 TIW (3 or 6 patients per dose level). Transition of dose level (from 25 to 50 mg) will proceed if the frequency of DLT observed in Cycle 1 (28 days) is <33% of patients in the first dose level (25 mg). Figure JJCC.1 illustrates the study design.

Eligible patients will be treated with LY3039478 at the assigned dose. The planned duration of treatment is not fixed. Treatment will continue until disease progression, development of unacceptable toxicity, or any other discontinuation criteria are met (Figure JJCC.1).



Abbreviations: DLT = dose-limiting toxicity; ECOG = Eastern Cooperative Oncology Group; N = number of patients or no; PD = progressive disease; PS = performance status; TIW = 3 times per week; Y = yes.

Figure JJCC.1. Illustration of study design.

Refer to Attachment 1 for the Study Schedule.

6.2.1. Study Completion and End of Trial

Study completion will occur following the data cutoff date for the primary analysis of primary and secondary objectives. The data cutoff date will be the time of when it is deemed that enough data is obtained for the analysis as determined by Lilly. Investigators will continue to follow Study Schedule for each cycle (Attachment 1) for all patients until notified by Lilly that study completion has occurred. The "end of trial" refers to the date of the last visit or last scheduled procedure for the last patient. "End of trial" occurs after study completion and after the last patient has discontinued study treatment and completed the final follow-up visit (including the final follow-up visit for the continued access period, if applicable) or has been declared lost to follow-up.

6.3. Discontinuation

The reason for and date of discontinuation will be collected for all patients. The Date of Discontinuation from study treatment is to be reported on the case report form (CRF). Patients

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

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

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)/clinical research scientist (CRS) 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 sponsor CRP/CRS 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 sponsor CRP/CRS 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 sponsor CRP/CRS 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 will have follow-up procedures performed as shown in the Study Schedule (Attachment 1).

Patients will be discontinued from the study drug 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 withdrawn from the study or study drug(s).
    - the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study drug(s) occurs prior to introduction of the other agent.
- Patient Decision
    - the patient requests to be discontinued from the study or study drug.
- Sponsor Decision

  - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

- The patient becomes pregnant.
- The patient has evidence of progressive disease by radiological assessments (RECIST v1.1). However, the patient may continue the study drug if, in the opinion of the investigator, the patient will clinically benefit from continuation of study drug, following discussion and approval by the sponsor. The patient will re-sign the informed consent form (ICF) for the continuation of study treatment.
- The patient has evidence of deteriorating clinical symptoms of progressive disease.
- The patient experiences unacceptable toxicity including, but not limited to, a Grade 4 nonhematological toxicity or a toxicity that does not resolve to baseline or Grade 1 within 3 weeks.
- The patient, treated at 25 mg TIW, experiences a toxicity requiring dose reduction. However, the patient may continue after the toxicity has recovered to baseline or Grade 1 if, in the opinion of the investigator, the patient will clinically benefit from continuation of study drug. The dosing schedule for resuming study treatment at 25 mg can be modified after agreement with the sponsor, while safety assessment will be maintained as Attachment 1. The patient will re-sign the ICF for the continuation of study treatment.
- The patient is noncompliant with study procedures and/or treatment (Section 7.6).

An exception to these discontinuation criteria may be granted in rare circumstances where the patient has a serious or life-threatening condition for which there is no effective alternative therapy and, in the opinion of the investigator, is receiving benefit from study drug. In these rare cases, the investigator must obtain documented approval from sponsor to allow the patient to continue study treatment and the patient will re-sign the ICF for the continuation of study treatment.

6.3.3. Patients Lost to Follow-Up

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

6.3.4. 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.

6.3.5. 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- or 50-mg capsules in bottles for oral consumption. LY3039478 capsules should be stored at room temperature as 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.

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

7.2. Study Drug Administration

The investigator or designee is responsible for:

- explaining the correct use of the investigational agents and planned duration of each individual's treatment to the site personnel.
- 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 so that the situation can be assessed.

7.2.1. Dosing Schedule

LY3039478 will be administered orally TIW as stated in Attachment 1. A cycle is defined as 28 days. In principle, the patients will be admitted to the investigational site for 4 weeks through the entire Cycle 1. However, if the investigator judges that the patient can be managed on an outpatient basis based on the safety evaluation results, the patient may be discharged on or after Day 15.

The following are examples; the schedule will be determined at the investigator's discretion.

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

LY3039478 will be taken once per day on days of administration prior to a meal (recommendation is 30 minutes prior) on an empty stomach. During all cycles, study drug should be taken at approximately the same time on the dosing days. If a patient misses or vomits a dose, that dose should be omitted.

The patient will be instructed to record time and amount of each dose in the patient diary through entire study and study monitors will cross-reference clinic records at the site to verify accuracy.

7.2.2. Dose Escalation

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis until the tolerability of LY3039478 for 50 mg TIW is confirmed.

Safety data, in particular AEs, will be the primary criteria for the dose escalation. In addition, if available at the time of dose escalation decision, PK results (for example, C_{max} and AUC) may be used as secondary/supporting data for dose escalation. If there are patients who are considered nonevaluable for DLT, safety data from such patients should also be reviewed for the dose escalation decision.

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.

7.2.2.1. Dose-Limiting Toxicity Determination

Dose-limiting toxicity is defined as an AE during Cycle 1 (first 28 days) that is related to study drug and fulfills any one of the following criteria using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.0:

- CTCAE Grade ≥3 non-hematological toxicity. Exceptions will be made for:
  - nausea, vomiting, or constipation that lasts <72 hours and that can be controlled with treatment
  - asymptomatic electrolyte disturbance that can be controlled with treatment
  - Grade 3 diarrhea, stomatitis, or mucositis that lasts ≤5 days 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, unless there is a clear alternative cause (for example, worsening biliary obstruction) if agreed by the study investigator and Lilly CRP/CRS
  - tumor lysis/necrosis syndrome
- CTCAE Grade 4 hematological toxicity of >5 days duration
- CTCAE Grade ≥3 anemia which requires a transfusion of packed red blood cells
- Any febrile neutropenia
- Neutropenia that requires treatment with granulocyte-colony stimulating factors (G-CSFs). However, the investigators and Lilly clinical research personnel will comprehensively determine the dose-limiting toxicity based on the clinical course of the patient, including laboratory test results.

- CTCAE Grade 3 thrombocytopenia with bleeding, Grade 3 thrombocytopenia which requires platelet transfusion, or Grade 4 thrombocytopenia
- Any other significant toxicity deemed by the investigators 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)

Dose-limiting toxicity will be confirmed based on the agreement between the primary investigator and the sponsor, with a consultation with the Safety Assessment Committee (SAC) as needed.

7.2.2.2. Dose Escalation Method

In this study, dose escalation will be driven by safety using the 3+3 method. Dose escalation will proceed as follows:

Dose Level 1 (25 mg):

- 3 patients will be enrolled. If 1 out of 3 evaluable patients for DLT experience a DLT, 3 additional patients will be enrolled in the same dose level.
- If 0 out of 3, or 1 out of 6 evaluable patients for DLT experience a DLT, the dose will be escalated to Dose Level 2.
- If dose escalation is made based on 3 evaluable patients in Dose Level 1 and Dose Level 2 is judged as intolerable, an additional 3 patients will be enrolled in Dose Level 1 and tolerability of Dose Level 1 will be evaluated based on a total of 6 patients' data.

Dose Level 2 (50 mg):

- 6 patients will be enrolled. If ≤1 out of 6 evaluable patients for DLT experience a DLT, the dose will be judged as tolerable.

All dose levels:

- If 2 patients experience DLTs at any given dose, the sponsor will examine the safety data and consult with the SAC as needed. With the consultation, the sponsor and the primary investigator will decide if the dose is intolerable or additional patients will be enrolled to the same dose level.
- If ≥3 patients experience DLTs at any given dose, it will be judged that the dose is not tolerable for Japanese patients.

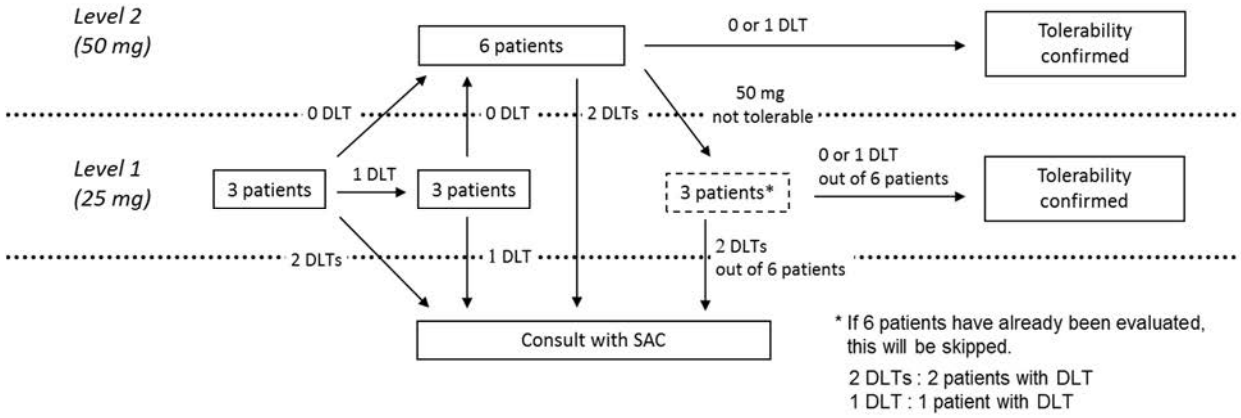
An evaluable patient for DLT is defined as a patient who takes ≥75% of the planned dose in Cycle 1 (first 28 days) or a patient who experiences DLT in Cycle 1 (first 28 days). A patient who takes <75% in Cycle 1 due to reasons other than drug-related toxicity (for example, early discontinuation due to progressive disease) will be considered nonevaluable for DLT and replaced by a new patient. If a patient takes <75% in Cycle 1 due to drug-related toxicities, the investigators and Lilly clinical research personnel will discuss whether the toxicities could be

deemed to be dose-limiting, and will consult with the SAC if needed. If it is not considered DLT, the patient is deemed to be nonevaluable for DLT and will be replaced by a new patient.

The reason for taking <75% of the planned dose needs to be documented appropriately and may be confirmed by the sponsor.

Dose escalation decisions will be made by agreement between the primary investigator and the sponsor, with a consultation with the SAC as needed. Additional patients may be enrolled at a specific dose level to characterize PK/PD or safety profile.

Figure JJCC.2 illustrates the dose level transition method and tolerability confirmation.



Abbreviations: DLT = dose-limiting toxicity; SAC = Safety Assessment Committee.

Figure JJCC.2. Schema of dose level transition.

7.2.3. Dose Adjustments and Delays

7.2.3.1. Dose Adjustments within Cycle 1

If a patient experiences a DLT, the patient should be discontinued from study treatment, unless, in the opinion of the investigator, the patient can clinically benefit from continuation of LY3039478 at a reduced dose level after the toxicity has recovered to baseline or Grade 1. For patients receiving Dose Level 1 (25 mg TIW), study treatment at 25 mg can be resumed and the dosing schedule may be modified, while safety assessment will be maintained as described in the Study Schedule (Attachment 1). For these situations, agreement between the investigator and the sponsor is required and the patient will re-sign the ICF for the continuation of study treatment.

If a patient experiences a toxicity which does not meet the criteria for a DLT, but requires dose omission in the opinion of investigator, the dose can be omitted. Dosing may resume at the same dose after the toxicity resolves to baseline or Grade 1; however, the dose(s) omitted for tolerability during a cycle will not be replaced.

7.2.3.2. Dose Adjustments within Cycle 2 and Beyond

If a patient treated at a given dose level experiences a DLET, the treatment will be discontinued for that patient. The dose may be resumed at a reduced dose level after the toxicity resolves to

baseline or Grade 1 if the investigator determines that it is in the best interest of the patient. For patients receiving 25 mg, the dosing schedule for resuming study treatment can be modified, while safety assessment will be maintained as described in the Study Schedule (Attachment 1). For these situations, agreement between the investigator and the sponsor is required and the patient will re-sign the ICF for the continuation of study treatment.

If a patient experiences a toxicity which does not meet the criteria for a DLET, but requires dose omission in the opinion of the investigator, the dose can be omitted. Dosing may resume at the same dose level after the toxicity resolves to baseline or Grade 1; however, the dose(s) omitted for tolerability during a cycle will not be replaced. A DLET is defined as an AE occurring in any cycle (other than Cycle 1) that would have met the criteria for DLT if it had occurred during Cycle 1.

7.2.3.3. Dose Adjustments Between Cycles

Before the start of each cycle, hematological and nonhematological toxicities (except alopecia and fatigue) must resolve to baseline or Grade 1. The start of a cycle may be delayed up to 3 weeks to allow sufficient time for recovery. Patients not recovering from toxicity to baseline or Grade 1 within 3 weeks after development should be discontinued from study treatment.

The dose for a patient in Dose Level 2 should be reduced for all subsequent cycles of therapy to Dose Level 1 in the cases below:

1. if the investigator determines that it is in the best interest of the patient, or
2. if the patient experiences dose omission of >7 doses in a single cycle due to toxicities which are not considered DLTs/DLETs.

If a patient requires omission of >3 doses for tolerability at the reduced dose level in a single cycle, the patient should be discontinued from study treatment.

Study treatment should be discontinued for patients started at 25 mg TIW who experience a toxicity requiring dose reduction. For such patients who experience toxicities that may cause discontinuation from study treatment as noted above, the dosing may be resumed at a reduced dose level after the toxicities have recovered to baseline or Grade 1 if, in the opinion of the investigator, those patients can clinically benefit from continuation of study drug. For patients at 25 mg, the dosing schedule for resuming study treatment can be modified while safety assessment will be maintained as described in the Study Schedule (Attachment 1). For the exceptions noted above, agreement between the investigator and the sponsor are required and the patient will re-sign the ICF for the continuation of study treatment.

For patients requiring a dose reduction, re-escalation to the original dose level is not permitted.

A delay in the start of a cycle due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 3 working days.

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, identification number assignment, 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/CRS.

If investigators have eligible patients who have consented concurrently, >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, radiotherapy, immunotherapy, cancer-related hormone therapy, or experimental drugs will be permitted while patients are on this study. An exception will be made for prostate or breast cancer patients continuing gonadotropin-releasing hormone or luteinizing hormone-releasing hormone agonist therapy. The need for any form of radiotherapy (except palliative) will be cause for early discontinuation from the study. 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-CSFs) is not permitted during this study. Patients should not receive G-CSFs prophylactically in any cycle. Granulocyte-colony stimulating factors may only be used for patients who have ANC$<0.5 \times 10^9$/L, neutropenic fever, or documented infections while neutropenic and must be discontinued at least 24 hours before the start of the next cycle of treatment. Should the use of hematopoietic colony-stimulating factors (CSFs) be necessary, follow the American Society of Clinical Oncology (ASCO) recommendations for the use of CSFs (Smith et al. 2006). If clinically indicated at any time during the study, transfusions may be used according to ASCO guidelines (Schiffer et al. 2001; Rizzo et al. 2008).

Diarrhea should be managed by standard treatments as per institutional guidelines. Guidance for diarrhea standard management is provided in Attachment 8.

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

7.6. Treatment Compliance

Patient compliance with study drug will be assessed at Day 1 of each cycle (other than Cycle 1) by direct questioning or counting returned capsules, and reviewing patient diary. More frequent

assessment may be performed if necessary. Deviation(s) from the planned dosage regimen should be recorded on the CRF.

The patient must take ≥75% of the intended dose in a single cycle 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 planned amount of study drug. Any missed doses during a cycle will be omitted and not replaced. In the event of a missed dose, a patient should resume and continue dosing, beginning with the next scheduled dose.

Potential discontinuation of a patient due to study drug noncompliance will be discussed between the investigator and the Lilly CRP/CRS before the final determination is made to discontinue the patient. If a patient is discontinued due to study drug noncompliance, the patient may be replaced.

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.

Patients who are not evaluable for PK, but who complete Cycle 1, may be replaced upon consultation with the investigator and the Lilly CRP/CRS to ensure adequate PK data, unless accrual to that cohort has stopped due to a DLT.

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

If the patient is noncompliant during Cycle 1 due to 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 the required number of patients complete Cycle 1, unless accrual to that cohort has stopped due to a DLT.

7.7. Continued Access

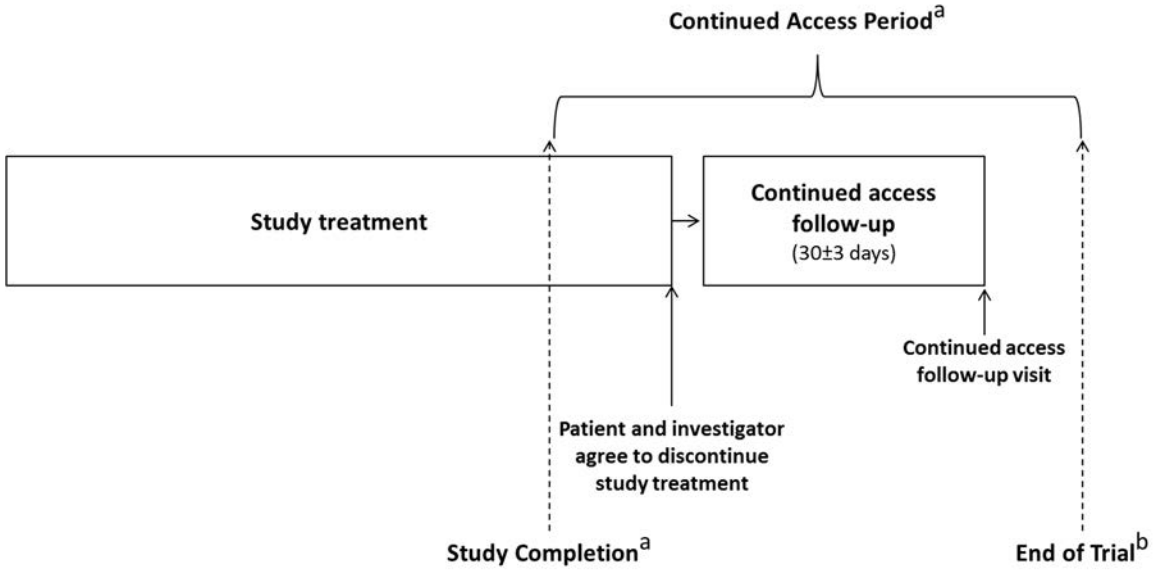
Patients who are still on study treatment at the time of study completion may continue to receive study treatment if they are experiencing clinical benefit and no undue risks.

The continued access period will apply to this study only if at least 1 patient is still on study treatment when study completion occurs. Lilly will notify investigators when the continued access period begins.

Patients who are in 30-day follow-up when the continued access period begins will continue in 30-day follow-up until the 30-day follow-up visit is completed.

The patient's continued access will end when a criterion for discontinuation is met (Section 6.3). Continued access follow-up will begin the day after the patient and the investigator agree to discontinue study treatment and lasts 30 (±3) days.

Study procedures during continued access period are described in the Study Schedule (Continued Access) (Attachment 1).



[a] Lilly will notify sites when the study completion occurs and the continued access period begins.
[b] End of trial occurs at the last visit or last scheduled procedure for the last patient.

Figure JJCC.3. Continued access diagram.

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 completed dose-escalation phase (Part A) of Phase 1 Study JJCA; the results from these studies are detailed in the IB. This Phase 1 study contains detailed safety monitoring that will permit initial characterization of the safety profile of LY3039478 in Japanese 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 or urine 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 study 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.

For interstitial lung disease (ILD) and suspected ILD cases being diagnosed after starting the study drug, external specialists may evaluate related examination results, such as image data. The investigator will provide the test results, including imaging examination and pathological examination, upon request of the sponsor.

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1). Table JJCC.1 presents a summary of AE and SAE reporting guidelines.

8.1.2. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or

disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Any clinically significant findings from labs, vital sign measurements, and so on that occur should also be reported to Lilly or its designee as an AE. Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect.

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. Any minor version of CTCAE v 4.0 (for example, version 4.03) 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 dictionary.

Cases of pregnancy that occur following maternal or paternal exposures to study drug during the study and for 3 months following the last administration of the investigational product 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 study drug via designated data transmission methods.

The investigator decides whether he or she interprets the observed AEs as either related to disease, 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.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria.

8.1.2.1. Serious Adverse Events

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

Planned hospitalizations or procedures for 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 treatment 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.

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

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/electronic case report form (eCRF). 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 study has ended, and the investigator believes that the SAE is related to a protocol procedure or study drug, the investigator should report the SAEs to the sponsor and the SAEs will be entered in the Lilly Safety System.

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

8.1.2.2. Adverse Event and Serious Adverse Event Reporting

Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System. Recommendations for reporting SAEs are provided in Attachment 5.

8.1.2.2.1. Prior to Administration of Study Drug(s)

Adverse event and SAE collection begins after the patient has signed the ICF and has received study drug. If a patient experiences an AE or SAE after signing informed consent, but prior to receiving study drug, the event will NOT be collected unless the investigator believes the event may have been caused by a protocol procedure.

8.1.2.2.2. On Study

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

This applies to the continued access period.

8.1.2.2.3. Follow-Up Visit

All AEs and SAEs, regardless of relatedness to study drug(s) or protocol procedures, occurring during the follow-up visit must be reported to Lilly or its designee. The follow-up visit starts following the day after the patient and investigator agree to discontinue the study drug. At the end of the follow-up visit, the patient will be required to have specific safety assessments (Attachment 1). The timing of these safety assessments is 30 days ±3 days after the patient and the investigator agree that the patient will no longer continue study treatment.

Following the safety assessments, which mark the end of the 30-day follow-up visit, the patient will be discontinued from the study, unless there is an ongoing AE or SAE that is related to study drug or protocol procedure. 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 related to

study drug or protocol procedure, 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.

After 30-day follow-up visit, AEs and SAEs are not required to be reported unless the investigator judges whether the events have been related to either study drug or a protocol procedure.

This applies to the continued access follow-up in the continued access period.

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 or in the IB and that the investigator identifies as related to study drug or procedure. 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 JJCC.1.

Table JJCC.1. Adverse Event and Serious Adverse Reporting Guidelines for Study JJCC

Timing	Types of AEs/SAEs Reported
Prestudy (baseline assessments), per Section 8.1.2.2.1	Preexisting conditions Procedure-related AEs/SAEs
On study, per Section 8.1.2.2.2	All AEs/SAEs regardless of relatedness
30-day follow-up visit, per Section 8.1.2.2.3	All AEs/SAEs regardless of relatedness
Subsequent follow-up visits, if necessary	Ongoing or new AEs/SAEs related to study drug, or protocol procedures

Abbreviations: AE = adverse event; SAE = serious adverse event.

8.1.3. Vital Signs and Laboratory Measurements

8.1.3.1. Electrocardiograms

For each patient, a 12-lead digital ECG will be collected according to the Study Schedule (Attachment 1) and the Pharmacokinetic, Pharmacodynamic, and Pharmacogenetic Sampling and Electrocardiogram Schedule (Attachment 3). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Consecutive replicate ECGs (triplicates) will be obtained at approximately 1-minute intervals. It is highly recommended that ECGs are recorded before collecting any blood for safety or PK tests.

Electrocardiograms 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.

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

All digital ECGs designated for central evaluation and over-read will be electronically transmitted to a central ECG laboratory designated by Lilly. For central ECGs, a cardiologist at the central ECG laboratory will conduct a full over-read on 1 of the replicates (including all intervals). A report based on data from this over-read will be issued to the investigative site. For each set of replicates, the cardiologist will determine the RR and QT intervals and heart rate on the ECGs that were not fully over-read. These data are not routinely reported back to the investigative site. All data from the over-reads will be placed in the Lilly database for analytical and study report purposes. However, any clinically significant finding that was not present on the fully over-read ECG will be reported to the investigator and to Lilly. It is recognized that ECG interpretations by the investigator (or qualified designee) and by the cardiologist at the central ECG laboratory may be different. When 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 patient 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 the final over-read ECG report issued by the central ECG laboratory, and any alert reports.

8.1.4. Safety Monitoring

The Lilly CRP/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 clinical research scientist, and periodically review:

- trends in safety data
- laboratory analytes including any analytes of special interest
- AEs, including monitoring of any AEs of special interest

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

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP/CRS regarding collection of specific recommended clinical information and follow-up laboratory tests (see Attachment 4).

8.1.5. Complaint Handling

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

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

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

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

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

8.2. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study and assessments.

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

Attachment 3 specifies the PK, PD, pharmacogenetic, ECG, and blood plasma biomarker sampling schedule for this study.

Venous blood samples will be drawn for measurement of relevant analytes in plasma; in addition, creatinine in serum will be measured after the first dose in Cycle 1 at all dose levels. Blood samples will be collected throughout the study.

Instructions for the collection and handling of blood samples will be provided by the sponsor. Supplies required for the collection and shipment of the samples will be provided by the sponsor.

Sample handling and shipment to the central laboratory will occur per instructions given to the study site.

8.2.1. Samples for Standard Laboratory Testing

Blood and urine samples will be collected at the times specified in the Study Schedule (Attachment 1). Routine clinical laboratory tests will be analyzed by a central laboratory selected by Lilly or local laboratory, depending on the tests. Attachment 2 lists the specific tests that will be performed for this study.

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. Pharmacokinetic Samples

Pharmacokinetic samples will be collected as specified in the Pharmacokinetic, Pharmacodynamic, and Pharmacogenetic Sampling and Electrocardiogram Schedule (Attachment 3).

A maximum of 5 additional PK samples may be drawn during the study if warranted and agreed upon by both the investigator and sponsor.

Plasma concentrations of LY3039478 will be quantified using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. All bioanalytical samples will be stored in the United States. The remaining plasma samples collected for PK evaluation may be used for exploratory studies to assess the metabolism of LY3039478, which may involve sample pooling. These samples may be retained for a maximum of 2 years following the last patient visit for the study.

After the first dose in Cycle 1, total urine output for the first 8 to 10 hours will be collected and pooled for quantification of LY3039478, creatinine, and exploratory metabolite identification. Urine concentrations of LY3039478 will be quantified using a validated LC-MS/MS assay. All urine samples will be stored in the United States.

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 will be retained for a maximum of 2 years following last patient visit for the study.

8.2.3. Pharmacogenomic 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 pharmacogenetic analysis. This will be a 1-time collection, as noted in the Study Schedule (Attachment 1 and Attachment 3).

Pharmacogenetic biomarker samples of 10 mL will be collected in this study. 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 LY3039478.

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 LY3039478. 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. These results may not be disclosed to patients, because this research is exploratory and the outcome based on the research may not be sufficiently validated to disclose to the patients. When a patient withdraws his/her consent and requests to discard these samples (for example, blood or deoxyribonucleic acid), the samples will be destroyed. Analysis results which are available before the consent withdrawal may be published in articles or other disclosures without an identifiable individual patient.

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

8.2.4. Exploratory Samples

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

- blood samples (see Sections 8.2.4.1 and 8.2.4.2)
- tumor tissue (archived or newly biopsied) and skin biopsies (see Section 8.2.4.3)

Samples for biomarker research will be collected as specified in Attachment 3, where local regulations allow. These samples are also described in the following subsections.

It is possible that biomarker data for patients in the study 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, these data may be requested from medical records for use in the research described in Sections 8.2.4.1 through 8.2.4.3.

8.2.4.1. Blood Samples for Amyloid Beta Assays

Blood samples will be collected for exploratory analysis of circulating Amyloid-β (Aβ) peptides (for example, Aβ[1-x] or peptide components thereof) before and after treatment with LY3039478. These samples may be retained for a maximum of 60 days after the testing lab has released the 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. Blood Samples

Blood samples for nonpharmacogenetic biomarker research will be collected as specified in Attachment 1 and Attachment 3, where local regulations allow.

Blood samples will be examined for biomarkers related to solid tumors, the Notch signaling pathway and drug target pathways, immune functioning, variable response to LY3039478, mechanism of action of study drug, and/or for research-related methods, or validating diagnostic tools or assays.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/institutional review boards (IRBs) impose shorter time limits, at a facility selected by Lilly. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of LY3039478 or after LY3039478 becomes commercially available.

8.2.4.3. Tumor and Skin Biopsies

Samples will be examined for biomarkers related to the Notch signaling pathway and drug target pathways, immune functioning, variable response to LY3039478, and mechanism of action of study drug or disease state, and to correlate these markers to clinical outcome and/or for research-related methods, or validating diagnostic tools or assays.

Throughout this study, archived tumor tissue obtained previously for diagnostic purposes (for example, at initial diagnosis) will be requested for biomarker research, but is not required for study entry. Skin biopsy is mandatory and collected as specified in Attachment 1 and Attachment 3. Collection of tumor biopsies collected pre- and posttreatment is optional. Table JJCC.2 presents tumor and skin biopsy collection times. Tumor biopsy must be collected only if the investigator does not anticipate any significant bleeding post-treatment. If the investigator considers a high risk of significant bleeding, the procedure should be omitted.

Table JJCC.2. Tumor and Skin Biopsy Time Points

Collection Time Point	Requirement
Baseline archived tumor tissue collection	Optional
Pre-/postdose tumor biopsies	Optional
Pre-/postdose skin biopsies	Mandatory

In addition to the required and optional biopsies and biomarker sample collections, patients may be asked to undergo collection of an additional biopsy specimen and blood sample after treatment with the study drug has been initiated, including potentially after disease progression. Such additional biopsies are optional and should be performed only if clinically feasible. If these additional samples are requested, they will be used to further investigate biomarkers that may explain treatment response and resistance mechanisms.

Formalin-fixed paraffin-embedded tumor tissue should be provided as a block or unstained slides. Due diligence should be used to make sure that tumor sample (not a normal adjacent or a tumor margin sample) is provided. Pathology reports accompanying archival tissue may also be requested. The report must be coded with the patient number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology report prior to submission. Archival blocks will be sectioned and returned to the study site. Slides and tissue samples collected on-study will not be returned.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by Lilly. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of LY3039478 or after LY3039478 becomes commercially available.

Technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing technologies, including mutation profiling, copy number variability, gene expression, multiplex assays, and/or immunohistochemistry may be performed on these tissue samples to assess potential associations with these biomarkers and clinical outcomes.

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 1 or more of the following radiologic tests for tumor measurement (computed tomography [CT] scan or magnetic resonance imaging is mandatory):

- CT scan
- magnetic resonance imaging
- chest x-ray (may be omitted in patients having a chest CT for their radiological tumor assessment)

- PET scan (optional).

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

- applicable tumor measurement, including overall response rate by RECIST v1.1 (Eisenhauer et al. 2009; Attachment 9) or the Response Assessment in Neuro-Oncology criteria for glioblastoma (Wen et al. 2010)
- applicable tumor measurement by PET response criteria of the European Organization for Research and Treatment of Cancer (Young et al. 1999) if performed
- 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.

Endpoint	Definition
Overall response rate	Solid tumor measurement by RECIST v1.1 (Eisenhauer et al. 2009)
Evaluation of tumor markers	

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 lab 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
- provide 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 ERBs/IRBs 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 a daily dosing schedule or an event diary.

For data handled by a data management third-party organization (TPO), CRF data will be managed and stored in the electronic data capture system. Subsequent to the final database lock, validated data will be transferred using standard Lilly file transfer processes.

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.

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

Statistical analysis of this study will be the responsibility of Lilly. The analyses for this study will be descriptive, except for possible exploratory analysis as deemed appropriate.

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.

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

10.1.1. Analysis Populations

Each analysis is done on a specific analysis population. The analysis populations are defined as follows:

- Efficacy Analyses Set: All patients who have received at least 1 dose of study drug and who are evaluable for the assessment of a dose level will form the efficacy analysis set. This population will be used in all efficacy reporting and analyses.
- Safety Analyses Set: 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, will form the safety analysis set. This population will be used in all safety reporting and analyses.
- DLT Analyses Set: All patients in safety analysis set who are deemed evaluable for the assessment of DLT will form the DLT analyses set. The following patients will not be considered as evaluable for DLT:
    - Any patients who are 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.
    - If a patient is noncompliant during Cycle 1 due to reasons other than drug-related toxicity, he or she will be considered nonevaluable and may be replaced.
- PK/PD Analyses Set: All patients who have received at least 1 dose of the study drug and have had sufficient postdose samples collected to allow estimation of PK parameters will form the PK/PD analyses set. This population will be used in all PK/PD reporting and analyses.

10.2. Patient Disposition

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

10.3. Patient Characteristics

Patient characteristics will include a summary of the following:

- patient demographics (including age, sex, screening height and weight, and screening body mass index)
- baseline disease characteristics
- prior disease-related therapies
- concomitant medications.

Other patient characteristics will be summarized as deemed appropriate.

10.4. Safety Analyses

All patients who receive at least 1 dose of LY3039478 will be evaluated for safety and toxicity. Adverse event terms and severity grades will be assigned by the investigator using CTCAE v 4.0. Note that any minor version of CTCAE v 4.0 (for example, CTCAE v 4.03) may be used for this study.

Safety analyses will include summaries of the following:

- DLTs at each dose level (using the DLT analysis set; see Section 10.1.1)
- AEs, including severity and possible relationship to study drug
- dose adjustments
- laboratory values
- vital signs and physical examination
- ECG readings.

10.5. Pharmacokinetic Analyses

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

Pharmacokinetic parameter estimates for LY3039478 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be C_{max} and AUC from time zero to infinity or over 1 dosing interval at steady state ($AUC_{\tau,ss}$) of LY3039478. Other noncompartmental parameters, such as time of $t_{1/2}$, apparent systemic clearance, and apparent volume of distribution 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.

Exploratory renal clearance of LY3039478, as well as the accompanying creatinine clearance, will be calculated as the ratio of amount excreted/AUC, and will be compared to unbound glomerular filtration rate, estimated using creatinine renal clearance.

10.6. Pharmacokinetic/Pharmacodynamic Analyses

The PK data will be combined, and analyses may be conducted to determine a relationship between exposure and PD/pharmacogenetic effect, data permitting. This model may be used to help reassess the dose cohort escalation as the study progresses. If deemed necessary, PK/PD modeling may be employed to evaluate variability in exposure, pharmacologic effects, and safety parameters.

10.7. Efficacy

The study was not designed to make a formal efficacy assessment. However, any tumor response data will be tabulated.

10.8. Exploratory Biomarker Analyses

Biomarker data from all patients undergoing biomarker assessments will be analyzed using descriptive statistics. These data may include, but are not limited to, circulating Aβ peptides that are hypothesized to be related to safety, efficacy, drug disposition, or pathways associated with the mechanism of action of LY3039478.

10.9. Interim Analyses

Interim access to safety data, including DLTs, will be performed during the study. In order to assess DLTs, which is key to proceed with dose escalation or to determine a tolerable dose, a DLT evaluation form at Dose Level 1 and Dose Level 2 will be prepared. Therefore, no database lock activities on safety CRF pages are mandatory.

Interim analyses for safety and PK may be conducted after all patients receiving Dose Level 2 complete Cycle 1 (DLT evaluation period).

Additional interim analyses may be conducted when deemed necessary (for example, in case of a safety concern).

If it is deemed that enough data is 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.

11.2. Ethical Review

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

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). The ERB(s) will review the protocol as required.

Any member of the ERB who is directly affiliated with this study as an investigator or as site personnel must abstain from the ERB's vote on the approval of the protocol.

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

- the current IB or package labeling 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 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).

All or 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 investigator or designee will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

If multiple sites participate in the study, the investigator with the most qualified patients will serve as the final report coordinating investigator and will sign the clinical study report for this study. 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 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 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 JJCC Study Schedule

Study Entry (Screening and Baseline) to Cycle 1 Assessments

Cycle/Visit	Screening/Baseline			Cycle 1											
Day Relative to Day 1 in Each Cycle	≤28	≤14	≤7	Week 1			Week 2			Week 3			Week 4		
				1	3	5	8	10	12	15	17	19	22	24	26
LY3039478 therapy (dose)[a]				1	2	3	4	5	6	7	8	9	10[c]	11	12
Informed consent	X														
Medical history		X													
Physical examination		X		X	X	X	X	X	X	X			X(±3)		
Vital signs and weight		X		X	X	X	X	X	X	X			X(±3)		
Height		X													
ECOG performance status		X		X	X	X	X	X	X	X			X(±3)		
ECG		X		X									X		
Hematology/serum chemistry		X		X	X	X	X	X	X	X			X(±3)		
Coagulation		X		X	X	X	X	X	X	X			X(±3)		
Urinalysis		X		X	X	X	X	X	X	X			X(±3)		
Pregnancy test (if applicable)			X												
Serum creatinine		X		X											
ECG chemistry				X									X		
Blood PD biomarkers (Aβ)		X		X									X		
Blood for exploratory biomarker research (predose)				X											
Urine collection (0 to 8-10 hours)				X											
Blood PK sampling				X									X		
Pharmacogenetic sampling				X											
Radiological tumor assessment (CT/MRI)	X														
Tumor biopsy (optional)	X												X		
Tumor marker (if applicable)		X											X(±3)		
Tumor measurement (palpable or visible if applicable)		X													
Archival tumor tissue sample (optional)			X												
Skin biopsy (mandatory)		X		X											
Chest X-ray	X														
PET scan (optional)	X														
CTCAE grading		X													
Concomitant medications		X													
Dispense/return LY3039478, diary/drug accountability				X											

Cycle 2 Assessments

Cycle/Visit	Cycle 2											
Day Relative to Day 1 in Each Cycle	Week 1			Week 2			Week 3			Week 4		
	1[b]	3	5	8	10	12	15	17	19	22	24	26
LY3039478 therapy (dose)[a]	1	2	3	4	5	6	7[c]	8	9	10[c]	11	12
Physical examination	X						X(±3)					
Vital signs and weight	X						X(±3)					
ECOG performance status	X						X(±3)					
ECG	X											
Hematology/serum chemistry	X						X(±3)					
Coagulation	X						X(±3)					
Urinalysis	X						X(±3)					
ECG chemistry	X											
Blood PD biomarkers (Aβ) (predose)	X											
Blood PD biomarkers for exploratory biomarker research (predose)	X											
Blood PK sampling (predose)	X											
Tumor marker (if applicable)							X(±3)					
Radiological tumor assessment (CT/MRI)										X No more than 10 days prior to Day 1 of Cycle 3		
Tumor measurement (palpable or visible if applicable)												
Chest X-ray												
PET scan (optional)	X											
CTCAE grading	X											
Concomitant medications	X											
Dispense/return LY3039478, diary/drug accountability	X											

Cycle 3 to Follow-up Assessments

Cycle/Visit	Cycle 3-n												30-day Follow-up Visit[d]
Day Relative to Day 1 in Each Cycle	Week 1			Week 2			Week 3			Week 4			
	1[b]	3	5	8	10	12	15	17	19	22	24	26	
LY3039478 therapy (dose)[a]	1	2	3	4	5	6	7[c]	8	9	10	11	12	
Physical examination	X												X
Vital signs and weight	X												X
ECOG performance status	X												X
Hematology/serum chemistry	X						X(±3)						X
Coagulation	X						X(±3)						X
Urinalysis	X						X(±3)						X
Blood PD biomarkers (Aβ) (predose)	X												X
Blood PD biomarkers for exploratory biomarker research (predose)	X												X
Tumor marker (if applicable)							X(±3)						X
Radiological tumor assessment (CT/MRI)							X(±3)						X[e]
Tumor measurement (palpable or visible if applicable)							X(±3)						X[e]
Chest X-ray							X(±3)						X[e]
CTCAE grading	X												X
Concomitant medications	X												X
Dispense/return LY3039478, diary/drug accountability	X												

Abbreviations: Aβ = Amyloid-β; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; PD = pharmacodynamic; PET = positron emission tomography; PK = pharmacokinetic

a LY3039478 is to be administered 3 times per week through each 28-day cycle.

b A delay in the start of a cycle due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 3 working days.

c The doses need to be done on the planned date.

d 30-day follow-up visit to occur 30 days (±3) after the patient and the investigator agree that the patient will no longer continue study treatment.

e For patients who discontinue study treatment without objectively measured progressive disease, subsequent assessments are not required. Refer to comments for those assessments in the table below for details.

Assessment	Comments
Informed consent	Informed consent form must be signed before performing any protocol procedure.
Medical history	Including alcohol/tobacco use and other relevant habits assessments. Also, any preexisting and pretreatment toxicity (treatment- or disease-related) should be documented and recorded as part of the pretreatment (baseline) medical history.
Physical examination	Physical exam per local practice needs to be performed prior to drug administration at each scheduled time point.
Vital signs and weight	Including temperature, blood pressure, pulse rate, respiration rate.
Height	Height measurements to be performed at baseline only.
ECOG performance status	Assessment needs to be completed prior to drug administration at each scheduled time point.
ECG	For Screening/ Baseline: One set of triplicate ECGs, central. For Cycle 1: Perform central triplicate ECGs at 1, 2, 4, and 24 to 30 hours postdose for Dose 1 (Day 1). Perform central triplicate ECG at 1, 2, 4, and 24 to 30 hours postdose for Dose 10 (Day 22). For Cycle 2: Perform central triplicate ECG prior to start of treatment. Refer to Attachment 3 for detailed time points.
Hematology/serum chemistry	Conducted at local laboratory. Refer to Attachment 2 for details. It is acceptable to use the test results of the hematology/chemistry laboratory values obtained during screening if the tests have been performed within 3 days before Day 1 of Cycle 1. It is also acceptable to use the test results if the tests have been performed within 3 days before Day 1 of each cycle.
Coagulation	aPTT, PT/INR, fibrinogen, fibrin/fibrinogen degradation products (FDP), and D-dimer. Conducted at local laboratory. It is acceptable to use the test results of the coagulation values obtained during screening if the tests have been performed within 3 days before Day 1 of Cycle 1. It is also acceptable to use the test results if the tests have been performed within 3 days before Day 1 of each cycle.
Serum creatinine	Conducted at local laboratory. Performed at screening/baseline, predose, 1, 4, and 8 to 10 hours postdose.
ECG chemistry	Conducted at local laboratory. Refer to Attachment 2 and Attachment 3 for details.
Pregnancy test (if applicable)	Serum or urine pregnancy test will be conducted at local laboratory at screening/baseline. Negative results prior to dosing required for women of childbearing potential.
Urinalysis	Conducted at local laboratory. Refer to Attachment 2 for details. It is acceptable to use the test results obtained during screening if the tests have been performed within 3 days before Day 1 of Cycle 1. It is also acceptable to use the test results if the tests have been performed within 3 days before Day 1 of each cycle.

Assessment	Comments
Urine collection	All urine will be collected between 0 and 8 to 10 hours. The urine collection should cease at the time that the Dose 1, 8- to 10-hour PK sample is drawn (Sample number 8; refer to Attachment 3). The collected urine will be pooled and the total volume recorded. From the pooled urine, 3 aliquots will be collected: 1) creatinine measurement, 2) approximately 10 mL to measure LY3039478 concentrations, and 3) approximately 10 mL to measure LY3039478 metabolites. The rest of the urine will then be discarded. During the 0- and 8- to 10-hour urine collection/pooling, the urine should not be frozen. Urine sample number 1 for creatinine should not be frozen, but the two 10-mL samples (urine sample number 2 and 3) should be frozen at the end of the collection period and should be shipped frozen.
Blood PD biomarkers (Aβ)	Assayed by Lilly-designated laboratory. Refer to Attachment 3 for detailed time points.
Blood PD biomarkers for exploratory biomarker research	Collected predose at Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, and 30-day follow-up visit, and assayed by Lilly-designated laboratory. Refer to Attachment 3 for detailed time points.
PK sampling	Assayed by Lilly-designated laboratory. Refer to Attachment 3 for detailed time points.
Pharmacogenetic sampling	Assayed by Lilly-designated laboratory. This is a 1-time sample which may be taken prior to start of treatment (Cycle 1 predose).
Skin biopsy	Mandatory. Collected at baseline/screening and postdose (6 to 8 hours after Dose 1). Additional optional skin biopsies may be performed at time of disease progression and if deemed necessary by the investigator. The samples will be analyzed at laboratories using assays designated by Lilly.
Archival tumor tissue sample (optional)	Optional. Request archived paraffin-embedded tumor tissue, but only after study eligibility is confirmed. The archived tumor samples can be shipped anytime during the study. Availability of archived tissue is optional for participation in this study but is highly encouraged. If archived tumor is not available, it will not constitute a protocol deviation.
Tumor biopsy (optional)	Optional. Collected at baseline/screening and posttreatment tumor biopsy should be obtained (whenever clinically feasible) at Cycle 1, preferably 6 to 8 hours after Dose 10 (Day 22). Greater flexibility has been provided for the posttreatment tumor biopsy (between Doses 7 and 12, inclusive) compared to other Dose 10 visit assessments (±3 days of planned visit) to enable radiographic guidance and access to appropriate medical specialists; however, if this flexibility is exercised and the posttreatment tumor biopsy is obtained on a day other than Cycle 1 Day 22 (Dose 10) visit, then 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. Tumor biopsy must be collected only if the investigator does not anticipate any significant bleeding post-treatment. If the investigator considers a high risk of significant bleeding, the procedure should be omitted.
Tumor marker (if applicable)	Optional. Conducted at local laboratory, if applicable.

Assessment	Comments
Radiological tumor assessment (CT/MRI)	Radiological assessment is performed at baseline (up to 28 days before the first dose but the assessment obtained prior to informed consent may be used as the baseline assessment provided they were performed within 28 days of Cycle 1 Day 1), then at the end of Cycle 2 (no more than 10 days prior to Day 1 of Cycle 3[inclusive]). If the start of Cycle 3 is delayed, then it is not necessary to perform the assessment again in the time window of 10 days prior to Day 1 of Cycle 3. After Cycle 4 (inclusive), radiological assessment is performed at Day 15 of every other cycle. Radiological assessment performed out of time window (±3 days of planned date) due to logistical reasons or patient safety concerns may not be considered as a deviation but the investigator should make every effort to conduct as close to the time window as possible. For patients who discontinue study treatment without objectively measured progressive disease, the radiological tumor assessment is not required. If the result of assessment is available by 30- day follow-up visit, it should be reported.
Tumor measurement (palpable or visible)	Performed at the same timing as radiological tumor assessment. Visible tumor (such as skin lesions) should be documented by photography and each photographic image of the tumor should include a ruler.
PET scan	Optional. Performed locally at baseline/screening and during Cycle 2 (not limited to Dose 1) repeated at the discretion of the investigator.
Chest X-ray	The chest X-ray will be measured on the same date as radiological tumor assessment. May be omitted in patients having a chest CT scan for their radiological tumor assessment
CTCAE grading	Refer to Section 8.1.2 for reporting guidelines.
Concomitant medications	Performed throughout study. Collection of concomitant medication post-study treatment discontinuation, including subsequent cancer treatment, will last until the end of 30-day follow-up visit.
Dispense/return LY3039478, diary/drug accountability	Performed at the end of each cycle or the start of each cycle, and the end of study treatment.

Abbreviations: Aβ = Amyloid-β; aPTT = activated partial thromboplastin time; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; PD = pharmacodynamic; PET = positron emission tomography; PK = pharmacokinetic; PT/INR = prothrombin time/international normalized ratio.

Continued Access

Cycle/Visit	Cycle n												30-day Follow-up Visit[c]
Day Relative to Day 1 in Each Cycle	Week 1			Week 2			Week 3			Week 4			
	1[b]	3	5	8	10	12	15	17	19	22	24	26	
LY3039478 therapy (dose)[a]	1	2	3	4	5	6	7	8	9	10	11	12	
CTCAE grading	X												X
Dispense/return LY3039478, diary/drug accountability	X												

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events

[a] LY3039478 is to be administered 3 times per week through each 28-day cycle.

[b] A delay in the start of a cycle due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 3 working days.

[c] 30-day follow-up visit to occur 30 days (±3) after the patient and the investigator agree that the patient will no longer continue study treatment.

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

Assessment	Comments
CTCAE grading	Refer to Section 8.1.2 for reporting guidelines.
Dispense/return LY3039478, diary/drug accountability	Performed at the end of each cycle or the start of each cycle, and the end of study treatment.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

Attachment 2. Protocol JJCC Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry**[a]
Hemoglobin	**Serum concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Leukocytes (WBC)	Phosphorus
Neutrophils	Total bilirubin
Lymphocytes	Alkaline phosphatase
Monocytes	ALT
Eosinophils	AST
Basophils	GGT
Platelets	BUN
Reticulocytes	Creatinine
	Lipase
Coagulation[a]	Uric acid
aPTT	Calcium
PT/INR	Glucose, random
Fibrinogen	Albumin
D-dimer	Total protein
Fibrin/fibrinogen degradation products (FDP)	Lactate dehydrogenase (LDH)
	Cholinesterase (ChE)
Urinalysis[a]	**ECG Chemistry**[a]
Specific gravity	Lipase[c]
pH	Thyroid stimulating hormone (TSH)
Protein	Free tri-iodothyronine (fT3)
Glucose	Free thyroxine (fT4)
Ketones	Albumin[c]
Blood	Glucose, random[c]
	Calcium[c]
Serum or urine pregnancy test (females with child-bearing potential only) [a]	Sodium[c]
	Potassium[c]
	Phosphorus[c]
Tumor markers[a]	Magnesium
Biomarkers[b] **(research laboratory tests)**	Serum creatinine[a,d]
Pharmacogenomic[b]	
Pharmacokinetic[b]	

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ECG = electrocardiogram; GGT = gamma glutamyl transferase; PT/INR = prothrombin time/international normalized ratio; RBC = red blood cells; WBC = white blood cells.

a Local or investigator-designated laboratory.

b Assayed by Lilly-designated laboratory.

c Test not performed if both chemistry and ECG chemistry required at same time point. See Attachment 3.

d Test not performed if both chemistry and creatinine required at same time point. See Attachment 3.

Attachment 3. Protocol JJCC Pharmacokinetic, Pharmacodynamic, and Pharmacogenetic Sampling and Electrocardiogram Schedule

Cycle	Dose Number (Day)	Sample Number	PK Sampling Time[a]	Urine Sampling[a]	Serum Creatinine Sampling Time	PD Aβ (1-x) Sampling Time	PD biomarkers for exploratory biomarker research	PD Skin Biopsies Sampling Time	Pharmaco-genetic Sampling Time	ECG with ECG Chemistry
Screening	Screening	1			Screening	Screening		Screening		Screening
1	1 (Day 1)	2	Predose	0 to 8-10-hr pooled samples (end time of sample to coincide with PK blood draw).	Predose	Predose	Predose		Predose	Predose
		3	0.5 hr							
		4	1 hr		1 hr					1 hr
		5	2 hr			2 hr				2 hr
		6	4 hr		4 hr	4 hr				4 hr
		7	6-8 hr			6-8 hr		6-8 hr		
		8	8-10 hr		8-10 hr	8-10 hr				
		9	24-30 hr			24-30 hr				24-30 hr
	10 (Day 22)	10	Predose			Predose				Predose
		11	0.5 hr							
		12	1 hr							1 hr
		13	2 hr			2 hr				2 hr
		14	4 hr			4 hr				4 hr
		15	6-8 hr			6-8 hr				
		16	8-10 hr			8-10 hr				
		17	24-30 hr			24-30 hr				24-30 hr
2	1 (Day 1)	18	Predose			Predose	Predose			Predose
3	1 (Day 1)	19				Predose	Predose			
30-day Follow-up visit		20				Same time as other safety assessment	Same time as other safety assessment			

Abbreviations: Aβ = Amyloid-β; ECG = electrocardiogram; hr = hour; PD = pharmacodynamic; PK = pharmacokinetic;.

a All urine will be collected between 0 and 8-10 hours. The urine collection should cease at the time that the Dose 1, 8- to 10-hour PK sample is drawn (Sample number 8). The collected urine will be pooled and the total volume recorded. From the pooled urine, 3 aliquots will be collected: 1) creatinine measurement, 2) approximately 10 mL to measure LY3039478 concentrations, and 3) approximately 10 mL to measure LY3039478 metabolites. The rest of the urine will then be discarded. During the 0- and 8- to 10-hour urine collection/pooling, the urine should not be frozen. Urine sample number 1 for creatinine should not be frozen, but the two 10-mL samples (urine sample number 2 and 3) should be frozen at the end of the collection period and should be shipped frozen.

Attachment 4. Protocol JJCC 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	**Recommended Autoimmune Serology[a]**
AST	Anti-nuclear antibody
GGT	Anti-smooth muscle antibody
CPK	Anti actin antibody

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

[a] Assayed by central laboratory or local/investigator-designated laboratory.

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

Attachment 5. Protocol JJCC Recommendations for Reporting Serious Adverse Events

Recommendations for Reporting Serious Adverse Events

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

Patient Demographics

- patient identification (number), sex, year 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 JJCC 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 self-care. Totally confined to bed or chair
5	Dead

Reference: Oken et al. 1982.

Attachment 7. Protocol JJCC Creatinine Clearance Formula

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

For serum creatinine concentration in mg/dL:

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

For serum creatinine concentration in μmol/L:

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

[a] age in years.

Abbreviations: CrCl = creatinine clearance; wt = weight (in kilograms).

Reference: Cockcroft and Gault 1976.

-OR-

$$GFR(mL/min/1.73m^2) = 170 \times [PCr]^{-0.999} \times [age]^{-0.176}$$
$$\times [0.762 \text{ if patient is female}] \times [1.18 \text{ if patient is black}]$$
$$\times [SUN]^{-0.17} \times [Alb]^{+0.318}$$

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

Reference: Murray and Ratain 2003.

Attachment 8. Protocol JJCC Guidance for Diarrhea Management

Diarrhea should be managed by standard treatments as per institutional guidelines. Guidance used in the phase 1 study (JJCA) for diarrhea standard management is provided as below.

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 (eg, watery, blood, mucus in stool).
- Assess patient for fever, abdominal pain, cramps, distension, bloating, nausea, vomiting, dizziness, weakness (ie, rule out risk for sepsis, bowel obstruction, and dehydration).
- Medication profile (ie, to identify any diarrheogenic agents).
- Dietary profile (ie, 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 should 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 should 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.

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 (NCI CTCAE Grades 1 and 2) after 48 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 intravenous (IV) fluids and antibiotics as needed with monitoring of patients condition (to rule out dehydration, sepsis, ileus) medical check and workup. 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 3 times daily [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 (ie, bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis).
- Sigmoidoscopy - reassessment of colitis.

Attachment 9. Protocol JJCC RECIST Criteria 1.1

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

Measurability of Tumor at Baseline

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

Measurable

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

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

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

Nonmeasurable

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

Special Considerations for Lesion Measurability

Bone lesions:

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

Cystic lesions:

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

Lesions with Prior Local Treatment:

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

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

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

Nontarget Lesions

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

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

Specifications by Methods of Measurement

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

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

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

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

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

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

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

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

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

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

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

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

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

Response Criteria

Evaluation of Target Lesions

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

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

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

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

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

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

Evaluation of Nontarget Lesions

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

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

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

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

Evaluation of Best Overall Response

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

Time Point Response

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

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

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

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

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

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

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

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

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

Frequency of Tumor Re-Evaluation

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

Confirmatory Measurement/Duration of Response

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

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

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

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

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

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

Independent Review of Response and Progression

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

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 (ie, bacterial overgrowth for cultures and biopsy of proximal jejunum to assess extent of inflammatory jejunitis)
- Sigmoidoscopy - reassessment of colitis.

Attachment 10. Protocol I6F-JE-JJCC(b) Amendment Summary [A Phase 1 Study of LY3039478 in Japanese Patients with Advanced Solid Tumors]

Overview

Protocol I6F-JE-JJCC [A Phase 1 Study of LY3039478 in Japanese Patients with Advanced Solid Tumors] has been amended. The new protocol is indicated by Amendment (b) 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:

- Section 2: Deleted the Length of the Study since it is defined in the protocol separate brochure separately.
- Section 6.2.1.: Clarified the definition of the study completion and the end of the trial.
- Sections 7.7.: Added new section for the continued access.
- Section 8.1.2.2.2. and Section 8.1.2.2.3.: Added the Adverse Event and Serious Adverse Event Reporting during the continued access.
- Attachment 1.: Added new table for the continued access.
- Minor editorial changes were made for clarity.

Revised Protocol Sections

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

2. Synopsis

[…]

~~**Length of Study:**~~
~~Planned first patient visit: July 2016~~

~~Planned last patient visit: April 2017 (End of study is defined as the last visit or last scheduled procedure shown in the Study Schedule for the last active patient in the study.)~~

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]) after all patients have completed treatment and their safety summary visit.~~ Study completion will occur following the data cutoff date for the primary analysis of primary and secondary objectives. The data cutoff date will be the time of when it is deemed that enough data is obtained for the analysis as determined by Lilly. Investigators will continue to follow Study Schedule for each cycle (Attachment 1) for all patients until notified by Lilly that study completion has occurred. The "end of trial" refers to the date of the last visit or last scheduled procedure for the last patient. "End of trial" occurs after study completion and after the last patient has discontinued study treatment and completed the final follow-up visit (including the final follow-up visit for the continued access period, if applicable) or has been declared lost to follow-up.

7.7 Continued Access

Patients who are still on study treatment at the time of study completion may continue to receive study treatment if they are experiencing clinical benefit and no undue risks.

The continued access period will apply to this study only if at least 1 patient is still on study treatment when study completion occurs. Lilly will notify investigators when the continued access period begins.

Patients who are in 30-day follow-up when the continued access period begins will continue in 30-day follow-up until the 30-day follow-up visit is completed.

The patient's continued access will end when a criterion for discontinuation is met (Section 6.3). Continued access follow-up will begin the day after the patient and the investigator agree to discontinue study treatment and lasts 30 (±3) days.

Study procedures during continued access period are described in the Study Schedule (Continued Access) (Attachment 1).

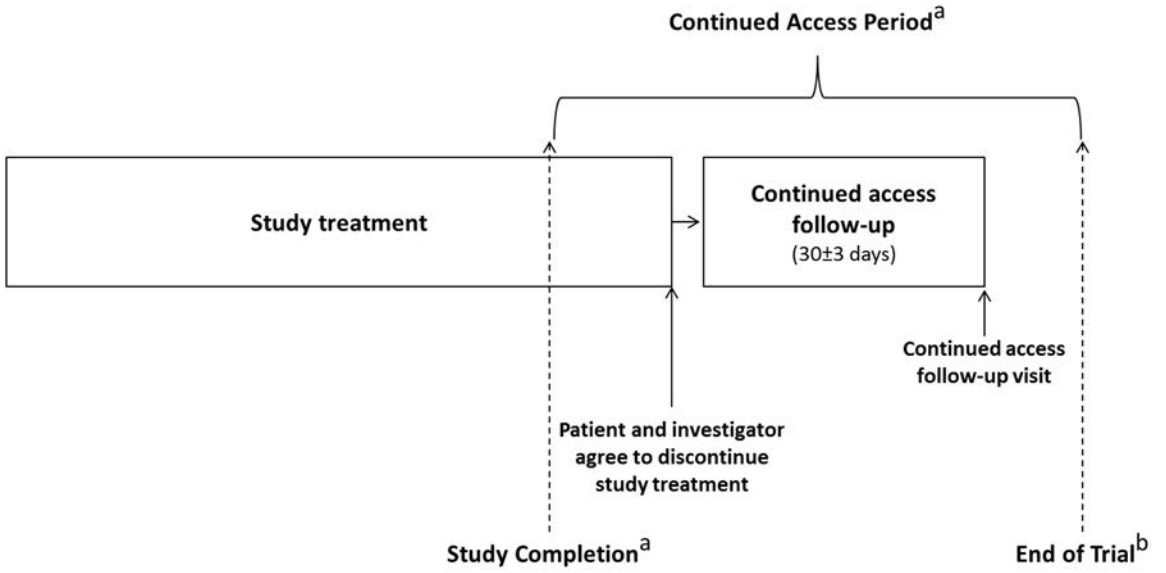

Figure JJCC.3. Continued access diagram.

8.1.2 Adverse Events

[…]
All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria.

8.1.2.2.2 On Study

[…]
This applies to the continued access period.

8.1.2.2.3 Follow-Up Visit

[…]
This applies to the continued access follow-up in the continued access period.

Attachment 1. Protocol JJCC Study Schedule

[…]

Continued Access

Cycle/Visit	Cycle n												30-day Follow-up Visit[c]
Day Relative to Day 1 in Each Cycle	Week 1			Week 2			Week 3			Week 4			
	1[b]	3	5	8	10	12	15	17	19	22	24	26	
LY3039478 therapy (dose)[a]	1	2	3	4	5	6	7	8	9	10	11	12	
CTCAE grading	X												X
Dispense/return LY3039478, diary/drug accountability	X												

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events

[a] LY3039478 is to be administered 3 times per week through each 28-day cycle.

[b] A delay in the start of a cycle due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 3 working days.

[c] 30-day follow-up visit to occur 30 days (±3) after the patient and the investigator agree that the patient will no longer continue study treatment.

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

Assessment	Comments
CTCAE grading	Refer to Section 8.1.2 for reporting guidelines.
Dispense/return LY3039478, diary/drug accountability	Performed at the end of each cycle or the start of each cycle, and the end of study treatment.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

Attachment 4. Protocol JJCC Clinical Laboratory Tests

[…]

[a] Assayed by central laboratory or local/investigator-designated laboratory.

[…]

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