**Protocol I6F-MC-JJCA (e)**

# A Phase 1 Study of LY3039478 in Patients with Advanced or Metastatic Cancer

**NCT01695005**

**Approval Date: 08-Jul-2016**

# 1. Protocol I6F-MC-JJCA(e)
# A Phase 1 Study of LY3039478 in Patients with Advanced or Metastatic Cancer

## Confidential Information



LY3039478

This Phase 1 study is a multicenter, nonrandomized, open-label, dose-escalation/cohort-expansion study of oral LY3039478 in patients with advanced or metastatic cancer.

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Protocol Electronically Signed and Approved by Lilly: 15 May 2012
Amendment (a) Electronically Signed and Approved by Lilly: 24 April 2013
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Amendment (d) Electronically Signed and Approved by Lilly: 19 November 2015
Amendment (e) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 08-Jul-2016 GMT

# 2. Synopsis

This Phase 1 study is a multicenter, nonrandomized, open-label, dose-escalation study followed by cohort expansion of oral LY3039478 in patients with advanced or metastatic cancer.

**Clinical Protocol Synopsis: Study I6F-MC-JJCA**

**Name of Investigational Product:** LY3039478

**Title of Study:** A Phase 1 Study of LY3039478 in Patients with Advanced or Metastatic Cancer

**Number of Planned Patients:** Total study sample size will be approximately 282 patients, with approximately 55 patients in Part A and approximately 227 patients in Parts B, C, D, E, and F.

**Phase of Development:** 1

**Length of Study:**
Planned first patient visit: September 2012 Planned last patient visit: December 2017

**Objectives:**

**Primary:** Part A: The primary objective of this study is to determine a recommended Phase 2 dose of LY3039478 that may be safely administered to patients with advanced or metastatic cancer.

Parts B, C, D, and E: The primary objectives are to confirm the recommended Phase 2 dose of LY3039478 that may be safely administered to patients with specific tumor types and to document antitumor activity.

Part F: The primary objective is to determine a recommended Phase 2 dose of LY3039478 that may be safely administered to patients according to 2 alternative dosing schedules with co-administration of prednisone and to document antitumor activity.

**Secondary:**

- To characterize the safety and toxicity profile of LY3039478 as assessed by National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.0
- To estimate the pharmacokinetic (PK) parameters of LY3039478
- Part A: To document any antitumor activity observed with LY3039478
- Parts B, C, D, E, and F: To assess duration of response, progression-free survival (PFS), and overall survival (OS)

**Exploratory:**

- To explore renal clearance of LY3039478 and PK of LY3039478 metabolites in plasma and urine
- To explore predictive biomarkers related to LY3039478
- To explore pharmacodynamic (PD) effects of LY3039478 on biomarkers indicative of Notch activity (Notch intracellular domain by immunohistochemistry or an alternative validated method) including cytokeratin 18 or Rules-Based Medicine
- To explore the utility of positron emission tomography scan to assess treatment effect with LY3039478
- To explore the utility of dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) to assess treatment effect with LY3039478

**Study Design:** Phase 1, multicenter, nonrandomized, open-label, dose-escalation study followed by cohort expansion (Parts B, C, D, E, and F) of oral LY3039478 in outpatients with advanced or metastatic cancer.

**Diagnosis and Main Criteria for Inclusion and Exclusions:** Men and women, aged ≥18 years, having advanced or metastatic cancer (solid tumor or lymphoma including chronic lymphocytic leukemia [CLL]) for which available standard therapies have failed. For Part B, patients must have prescreened alterations in the Notch pathway such as mutations, amplification, or gene expressions related to Notch pathway. Part C patients must have histological evidence of advanced or metastatic soft tissue sarcomas. Part D patients must have advanced or metastatic cancer with specific tumor types harboring Notch molecular alterations including triple-negative breast cancer (ER-, PR-, HER2-), cholangiocarcinoma, hepatocellular carcinoma (HCC), CLL, and mature T cell, B cell, or Natural Killer (NK) cell neoplasms. Part E patients must have advanced or metastatic adenoid cystic carcinoma (ACC). Part F patients in the dose confirmation must have histological evidence of nonresectable or metastatic leiomyosarcoma with prescreened alterations in the Notch pathway such as mutations, amplification, or gene expressions related to Notch pathway.

**Test Product, Dosage, and Mode of Administration:** LY3039478, dose range 2.5 to 100 mg, given orally as capsules 3 times per week during a 28-day cycle. In Study Part F, dosing schedules will utilize a loading dose (starting at 75 mg and escalating up to 150 mg) administered 3 times per week for 2 weeks during Cycle 1 (schedule F1) or 2 times per week for 2 weeks during Cycle 1 (schedule F2), followed by 50 mg 3 times per week (TIW) from Week 3 onwards. In Study Parts F1 and F2, prednisone will be co-administered for 2 weeks in Cycle 1.

**Planned Duration of Treatment:** Patients will receive 2 cycles (28 days each) of LY3039478 unless 1 or more of the criteria for discontinuation are fulfilled. In Study Parts F1 and F2, prednisone will be co-administered with LY3039478 for 2 weeks in Cycle 1. A patient may receive >2 cycles of treatment only if: 1) none of the criteria for discontinuation have been fulfilled and 2) the investigator determines that the patient is experiencing clinical benefit from treatment.

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

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

Continued-access period: All patients remaining on study treatment without disease progression following the final analysis will be able to enter the continued-access period of the study, which begins approximately 12 months after the last patient was enrolled and ends after the last patient discontinues study treatment and performs safety follow-up visit.

**Criteria for Evaluation:**

Safety: NCI CTCAE, version 4.0, dose-limiting toxicities (DLT)

Bioanalytical: Plasma concentrations of LY3039478

Efficacy: Depending on the histology, efficacy will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for solid tumors (along with the Choi criteria for soft tissue sarcomas and HCC), the Revised Response Criteria for Malignant Lymphoma, the Guidelines from the National Cancer Institute Working Group for CLL, or the Response Assessment in Neuro-Oncology (RANO) criteria for glioblastoma.

**Statistical Methods:**

Safety: Dose escalation will be driven by safety using the 3+3 method. Model-based analyses that incorporate prior expectations about the dose-toxicity curve will be fitted to the data at the end of each cohort, which will be used by the investigators and the Eli Lilly and Company (Lilly) clinical research physician to determine the next dose level. The maximum tolerated dose is defined as the highest tested dose that has <33% probability of causing a DLT during Cycle 1.

Efficacy: Tumor response data will be tabulated and summarized by study part. For the purposes of statistical analysis, subjects will be grouped by mutation and/or amplification, and by tumor type. Change in tumor size (and/or change in tumor density) will be analyzed by analysis of covariance models with potential covariates including baseline measurements, mutations/amplification group, tumor type, Eastern Cooperative Oncology Group performance status, and other covariates as deemed appropriate. Logistic regression analyses will also be utilized to estimate the overall response rate for each grouping of patients. Descriptive analyses of duration of response, PFS, and OS will be conducted using the Kaplan-Meier method.

Pharmacokinetics: PK parameters for LY3039478 will be analyzed by standard non-compartmental 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 |
|---|---|
| **ACC** | adenoid cystic carcinoma |
| **adverse event (AE)** | 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 adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product. |
| **ALT** | alanine aminotransferase |
| **ANC** | absolute neutrophil count |
| **APP** | amyloid precursor protein |
| **ASCO** | American Society of Clinical Oncology |
| **AST** | aspartate aminotransferase |
| **AUC** | area under the plasma drug concentration versus time curve |
| **AUC(0-∞)** | area under the plasma concentration-time curve from time zero to infinity |
| **AUC(0-$t_{last}$)** | area under the plasma concentration-time curve from time zero to last measurable plasma concentration |
| **$AUC_{T,ss}$** | area under the concentration-time curve over 1 dosing interval at steady state |
| **audit** | A systematic and independent examination of the study-related activities and documents to determine whether the evaluated study-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s). |
| **BID** | twice daily |
| **case report form (CRF) and electronic case report form (eCRF)** | Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol. |
| **CBF-1** | C-promoter binding factor-1 |
| **CI** | confidence interval |
| **CIOMS** | Council for International Organizations of Medical Sciences |
| **CL/F (or CL)** | apparent systemic clearance |

| | |
|---|---|
| **CLL** | chronic lymphocytic leukemia |
| **$C_{max}$** | maximum plasma concentration |
| **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. |
| **confirmation** | A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results. |
| **consent** | The act of obtaining informed consent for participation in a clinical study from patients deemed eligible or potentially eligible to participate in the clinical study. Patients entered into a study are those who sign the informed consent document directly or through their legally acceptable representatives. |
| **CRP** | clinical research physician |
| **CRS** | clinical research scientist |
| **CSF** | colony-stimulating factor |
| **CSL** | C-promoter binding factor-1 (CBF-1) and Suppressor of Hairless (Su[H]), LAG-1 |
| **CT** | computed tomography |
| **CTCAE** | Common Terminology Criteria for Adverse Events |
| **CYP** | cytochrome P450 |
| **DCE-MRI** | dynamic contrast-enhanced magnetic resonance imaging |
| **DCSI** | Development Core Safety Information |
| **DDI** | drug-drug interaction |
| **DLL** | Delta-like |
| **DLT** | dose-limiting toxicity |
| **DLET** | dose-limiting equivalent toxicity |
| **ECG** | electrocardiogram |
| **ECOG** | Eastern Cooperative Oncology Group |

| | |
|---|---|
| **EGF** | epidermal growth factor |
| **end of study** | End of study (trial) is defined as the date of the last visit or last scheduled procedure at the last site shown in the Study Schedule for the last active patient in the study. |
| **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 document 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. |
| **FFPE** | formalin-fixed paraffin-embedded |
| **FISH** | fluorescence in situ hybridization |
| **GALT** | gut-associated lymphoid tissue |
| **GCP** | good clinical practice |
| **G-CSF** | granulocyte colony stimulating factors |
| **GEP** | gene expression profiling |
| **GI** | gastrointestinal |
| **GIST** | gastrointestinal stromal tumors |
| **HBsAg** | hepatitis B surface antigen |
| **HCC** | hepatocellular carcinoma |
| **hERG** | human ether-a-go-go related gene |
| **HIV** | human immunodeficiency virus |
| **IB** | Investigator's Brochure |
| **$IC_{50}$** | half-maximal inhibitory concentration |
| **ICF** | informed consent form |
| **ICH** | International Conference on Harmonisation |
| **IHC** | immunohistochemistry |
| **interim analysis** | An analysis of clinical study data that is conducted before the final reporting database is authorized for datalock. |

| | |
|---|---|
| **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. |
| **IVTI** | in vivo Notch-1 cleavage |
| **LC-MS/MS** | liquid chromatography-tandem mass spectrometry |
| **LDH** | lactate dehydrogenase |
| **LHRH** | luteinizing hormone-releasing hormone |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **monitor** | A person responsible for ensuring the investigator site complies with the monitoring plan, applicable local SOPs (if any), and global Medical SOPs. Monitors are trained on the investigational product(s), the protocol, informed consent document, any other written information provided to subjects, relevant SOPs, International Conference on Harmonisation Good Clinical Practice guidelines (ICH-GCP), and all applicable laws (for example, privacy and data protection) and regulations. |
| **MRI** | magnetic resonance imaging |
| **MTD** | maximum tolerated dose |
| **NCI** | National Cancer Institute |
| **NICD** | Notch intracellular domain |
| **NK cells** | natural killer cells |
| **NOAEL** | no-observed-adverse-effect-level |
| **NOEL** | no-observed-effect level |
| **ORR** | overall response rate |
| **patient** | a subject with a defined disease |
| **PD** | pharmacodynamic |
| **PET** | positron emission tomography |
| **PK** | pharmacokinetic |
| **PSA** | prostate-specific antigen |
| **Q2D** | every other day |
| **QTc** | corrected QT |
| **RANO** | Response Assessment in Neuro-Oncology |

| | |
|---|---|
| **RBM** | Rules-Based Medicine |
| **RBP-Jκ** | recombination signal-binding protein-Jκ |
| **RECIST** | Response Evaluation Criteria in Solid Tumors |
| **S1/S2/S3** | site 1/site 2/site 3 |
| **SAE** | serious adverse event |
| **screen** | The act of determining if an individual meets minimum requirements for participation in a clinical study. |
| **sponsor** | The party who takes responsibility for the initiation, management and/or financing of a clinical study. |
| **Su[H]** | Suppressor of Hairless |
| **SUSAR** | suspected unexpected serious adverse reactions |
| **$t_{1/2}$** | half-life |
| **TACE** | tumor necrosis factor-α converting enzyme |
| **$TEC_{50}$** | threshold plasma concentration of the compound required to inhibit cleavage by 50% |
| **$TED_{50}$** | threshold dose concentration of the compound required to inhibit cleavage by 50% |
| **TID** | 3 times per day |
| **TIW** | 3 times per week |
| **$t_{max}$** | time of maximal plasma concentration |
| **TPO** | third-party organization |
| **ULN** | upper limit of normal |
| **V/F (or V)** | apparent volume of distribution |

# A Phase 1 Study of LY3039478 in Patients with Advanced or Metastatic Cancer

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

An oncogenic role for Notch was first reported as the result of a chromosomal translocation occurring in a patient with T-cell leukemia (Grabher et al. 2006). Overexpression of NICD in hematopoietic progenitor cells of mice recapitulated this phenomenon, as they developed T-cell leukemia similar to humans. Furthermore, treatment of these cells with the γ-secretase inhibitor prevented their cell growth. Besides T-cell leukemia, there is increasing evidence that Notch signals are oncogenic in other cancers through multiple mechanisms including receptor amplification and overexpression of ligands and/or receptors. Deregulated Notch signaling due to mutation or overexpression of ligands and/or receptors is implicated in a number of malignancies including lymphoid leukemias, melanoma, glioblastoma, and cancers of the breast, ovary, lung, pancreas, colon, head and neck, cervix, and kidney (Koch and Radtke 2007; CGARN 2011; Puente et al. 2011; Table JJCA.5.1). In summary, inhibition of Notch signaling constitutes an attractive strategy to provide therapeutic benefits to cancer patients.

**Table JJCA.5.1. Scientific Rationale for LY3039478 Clinical Development**

| Tumors | Frequency of Notch Mutations (% gene) | Frequency of Amplifications (% gene) |
|---|---|---|
| Ovarian | N3[a] | 11% N3[b]; 19.5% N3[c]; 6% N3[d]; 2% J1[b]; 2% J2[b]; 5% J1[d]; 2% J2[d] |
| Lung | 10% N1[e]; 6% N1[f] | 3[d] |
| Colon | 17% N1[f] | <1% N[d]; 5% J1[d] |
| Glioblastoma | 20% N1[f] | 6% N1-4[d] |
| Triple Negative MBC (Breast) | N3[a] | 6% (MBC) N1-4[d]; 2% J1[d]; 2% J2[d] |
| Gastric | 13% N1[f] | 9% N3[d]; 15% N4[d]; 6% J1[d]; 3% J2[d] |
| Pancreatic | | 6.9% N2-4[d] |
| Melanoma | | 35% N2[g]; 6% N2&4[d] |
| T-ALL | 58% N1[h-j] | |
| CLL | 12.2% (N1p2515Rfs*4)[k] | |
| MCL | 12% (N1p2515Rfs*4)[l] | |

Abbreviations: CLL = chronic lymphocytic leukemia; J1 = Jagged-1, J2 = Jagged-2; MBC = metastatic breast cancer; MCL = mantle cell lymphoma; N1 = Notch-1; N2 = Notch-2; N3 = Notch-3; T-ALL = T-cell acute lymphoblastic leukemia.

a Overexpression.
b CGARN 2011.
c Park et al. 2006.
d Mining of public database.
e Westhoff et al. 2009.
f Eli Lilly and Company (Lilly), data on file.
g Gast et al. 2010.
h Grabher et al. 2006.
i Weng et al. 2004.
j Bhanushali et al. 2010.
k Puente et al. 2011.
l Kridel et al. 2012.

Eli Lilly and Company (Lilly) has developed a potent small-molecule inhibitor of Notch, LY3039478, for the treatment of cancer. Study I6F-MC-JJCA (JJCA) is a Phase 1 clinical trial designed to evaluate the safety and tolerability of LY3039478 in humans.

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*

Part A: The primary objective of this study is to determine a recommended Phase 2 dose of LY3039478 that may be safely administered to patients with advanced or metastatic cancer.

Parts B, C, D, and E: The primary objectives are to confirm the recommended Phase 2 dose of LY3039478 that may be safely administered to patients with specific tumor types and to document antitumor activity.

Part F: The primary objective is to determine a recommended Phase 2 dose of LY3039478 that may be safely administered to patients according to 2 alternative dosing schedules with co-administration of prednisone and to document antitumor activity.

### *5.2.2. Secondary Objectives*

The secondary objectives of this study are:

- to characterize the safety and toxicity profile of LY3039478 as assessed by National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.0
- to estimate the pharmacokinetic (PK) parameters of LY3039478
- Part A: to document any antitumor activity observed with LY3039478
- Parts B, C, D, E, and F: to assess duration of response, progression-free survival (PFS) and overall survival (OS)

### *5.2.3. Exploratory Objectives*

The exploratory objectives of this study are:

- to explore renal clearance of LY3039478 and PK of LY3039478 metabolites in plasma and urine
- to explore predictive biomarkers related to LY3039478
- to explore pharmacodynamic (PD) effects of LY3039478 on biomarkers indicative of Notch activity (NICD by immunohistochemistry [IHC] or an alternative validated method) including cytokeratin 18 or Rules-Based Medicine (RBM)
- to explore the utility of positron emission tomography (PET) scan to assess treatment effect with LY3039478
- to explore the utility of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) 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 adverse events (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 ≤1 nM 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% ($TED_{50}$) value for NICD inhibition of 0.8 and 0.9 mg/kg, respectively, and threshold plasma concentration of the compound required to inhibit cleavage by 50% ($TEC_{50}$) 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 (Q2D) produced optimal efficacy while balancing on-target gastrointestinal (GI) toxicity. Furthermore, coadministration of dexamethasone with LY3039478 significantly decreased body-weight loss and GI toxicity without negatively impacting anti-tumor 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 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 3 times per week (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 (eg, 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 (IVTI) in mouse lung, as a surrogate marker for tumor. 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 toxicity. Safety pharmacology parameters were evaluated in vitro and as part of the repeat-dose studies. Based on results from nonclinical studies, the primary target organ is the GI tract. The intestinal toxicity in rat and dog 1-month toxicology studies was characterized by fecal abnormalities and histologic changes described as a mucoid enteropathy (a known target mediated toxicity of Notch inhibitors) with increases in the size and/or number of goblet cells within the mucosal epithelial enterocytes. All sections of the small and large intestine were affected. Although the enteropathy contributed to the mortality in rats at the highest dose, the intestinal toxicity was almost completely reversed following a 3-week reversibility interval in the 1-month rat study.

In the 1-month rat toxicology study, LY3039478 hydrate was given by oral gavage TIW (Monday, Wednesday, and Friday) to rats for up to 1 month and followed by a 3-week reversibility period at dose levels of 0 (vehicle), 1, 3, and 6 mg/kg/dose (equivalent to 0, 6, 18, and 36 mg/$m^2$, respectively). Rats given 0 and 6 mg/kg/dose were also maintained for a 3-week recovery period.

Mortality was observed on Days 20 to 22 in 2 male and 2 female main study rats and in 2 female toxicokinetic rats at 6 mg/kg/dose. Prior to being euthanized or found dead, the early death rats exhibited significant decreases in body weight and food consumption from Days 17 to 21 and clinical observations consistent with poor clinical condition (including decreased activity, few/absent or watery feces, haircoat soiling and unkempt appearance). The intestinal findings described below may have contributed to the declining clinical conditions of these rats found dead or euthanized early. There were no test article-related effects on body weight or food consumption findings for surviving main study rats. A mucoid enteropathy of the small and large intestine characterized by increases in the size and/or number of goblet cells within the mucosal epithelial enterocytes was observed at all doses. This change was sometimes

accompanied by blunting of villi, subacute/chronic inflammation and increased mucus in the intestinal lumen. The mucoid enteropathy was considered to be adverse at ≥3 mg/kg/dose in males and females due to the increased severity (mild to moderate) at these dose levels. Decreased number of ovarian follicles were observed in all female rats (≥1 mg/kg/dose) and were considered adverse to fertility, but not to the overall health of the female rat. Notch inhibition has been previously reported to impact folliculogenesis in rodents. Additional non-adverse histology findings included bone growth plate thickening of the femur and sternum and single cell necrosis of epithelia in the pancreas, exorbital lacrimal glands, and mandibular salivary glands. The mucoid enteropathy, decreased ovarian follicles, and all other toxicities were reversible or partially reversible following a 3-week recovery period in rats. The no-observed-adverse-effect-level (NOAEL) was considered to be 1 mg/kg/dose in males and <1 mg/kg/dose in females based on adverse microscopic findings of mucoid enteropathy at ≥3 mg/kg/dose and decreased ovarian follicles at ≥1 mg/kg/dose, respectively. The MTD was considered to be 3 mg/kg/dose based on mortality observed at the high dose of 6 mg/kg/dose. Additional details and findings from this study are presented in the IB.

In the 1-month dog toxicity study, LY3039478 hydrate was administered to beagle dogs via oral gavage TIW (Monday, Wednesday, Friday) for 1 month at dose levels of 0 (vehicle), 0.1, 0.3, and 1 mg/kg/dose (equivalent to 0, 2, 6, and 20 mg/m$^2$, respectively). No deaths occurred during the conduct of the dog study. Substantial decreases in body weight and food consumption occurred early in the study at 0.3 and 1 mg/kg/dose and resulted in supplemental food being offered to all dogs at these dose levels. Clinical signs were limited to fecal changes including soft, watery, mucoid, and discolored feces in dogs administered 0.3 and 1 mg/kg/dose. Fecal changes at 0.1 mg/kg/dose were less frequent and less severe than at higher doses. These changes were consistent with the dose-dependent mucoid enteropathy that was evident histologically in the small and large intestines at all doses and was considered to be adverse at ≥0.3 mg/kg/dose based on the presence of concurrent mucosal degeneration/necrosis at these mid and high doses. Generalized lymphoid depletion occurred in multiple tissues including the thymus, spleen, mesenteric lymph nodes, and/or gut-associated lymphoid tissue (GALT) and was considered adverse at ≥0.3 mg/kg/dose. Marginal zone lymphoid depletion is a known on-target effect of Notch inhibition. Lymphoid depletion was not considered adverse at 0.1 mg/kg/dose based on occasional overlap with control animals, low magnitude of severity, and lack of impact on peripheral lymphocyte numbers. Hypercellularity of the bone marrow (femur and sternum) at 1 mg/kg/dose correlated with hematology findings including increased total leukocytes, likely associated with inflammation in the large and small intestines. Increased thickness of the hypertrophy zone was also evident in cartilage of the rib and sternum at 1 mg/kg/dose, similar but more subtle than the finding in the rat. The NOAEL was considered to be 0.1 mg/kg/dose based on the combination and severity of the GI changes observed clinically (soft, discolored, watery, mucoid feces) and histologically (mucoid enteropathy with concurrent mucosal degeneration/necrosis) at ≥0.3 mg/kg/dose. The MTD in this dog study was 1 mg/kg/dose, the highest dose tested. Additional details and findings from this study are presented in the IB.

In vitro evaluation of LY3039478 on the human ether-a-go-go related gene (hERG) channel current estimates the $IC_{50}$ to be >281.7 μM. Based on this result, there is no expected risk for

QT prolongation by hERG inhibition as the highest total human plasma concentration of LY3039478 is predicted to be <2.8 μM for the maximum planned clinical dose of 100 mg (maximum plasma concentration [$C_{max}$] at the 90% prediction interval). In vivo cardiovascular endpoints were evaluated in the 1-month repeat-dose dog toxicology study using a jacketed external telemetry system. Dogs were continuously monitored for at least 22 hours for cardiovascular endpoints on Days 3 and 24. 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 [QTc]); therefore the no-observed-effect level (NOEL) for cardiovascular endpoints was 1 mg/kg/dose, the highest dose tested.

No evidence of mutagenicity was observed in a bacterial mutagenicity assay (Ames assay). LY3039478 was classified as a nonirritant based on the results of an in vitro assay that measured effects on corneal opacity and permeability.

In conclusion, nonclinical toxicology studies in rats and dogs dosed TIW for 1 month have characterized the target tissues for toxicity that may be clinically relevant. Data indicate that the gastrointestinal tract is the primary target organ for LY3039478 toxicity. The mucoid enteropathy and all other toxicities were reversible or partially reversible following a 3-week recovery period in rats. The planned clinical starting human dose of 2.5 mg (equivalent to 1.54 mg/m2) is 11.7-fold and 13.0-fold lower than the MTD dose level of 18 and 20 mg/$m^2$ in rats and dogs, respectively. The predicted human area under the plasma drug concentration versus time curve (AUC) exposure at the starting dose of 2.5 mg (112 ng*hr/mL) is 7.0-fold and 23.3-fold lower than AUC at the MTD in rats and dogs, respectively. Although exposure multiples will likely be <1 at higher clinical doses, the dose-limiting enteropathy in nonclinical studies was monitorable and/or reversible. Table JJCA.5.2 shows the dose and exposure multiples to the starting dose and highest anticipated clinical dose.

**Table JJCA.5.2. Dose and Exposure Multiples to the Starting and Maximum Planned Clinical Dose of LY3039478 Based on Administered Dose and Predicted Exposure**

| | Dose (mg/kg) | Dose ($mg/m^2$) | Dose Multiple[a] | AUC (ng*hr/mL) | Exposure Multiple[b] |
|---|---|---|---|---|---|
| **Human**[c] | | | | | |
| Starting dose (2.5 mg) | 0.04 | 1.54 | – | 112 | – |
| Max. planned (100 mg) | 1.67 | 61.7 | – | 4401 | – |
| **Rat MTD**[d] | 3.0 | 18 | | 779 | |
| Starting | | | 11.7x | | 7.0x |
| Max. planned | | | 0.29x | | 0.18x |
| **Dog MTD**[e] | 1.0 | 20 | | 2612 | |
| Starting | | | 13.0x | | 23.3x |
| Max. planned | | | 0.32x | | 0.59x |

Abbreviations: AUC = area under the plasma concentration versus time curve; Max. = maximum; MTD = maximum tolerated dose.

a Dose multiple is the dose in animals/dose in humans based on $mg/m^2$. Doses were converted from mg/kg to $mg/m^2$ using a km conversion factor of 6 for the rat, 20 for the dog, and 37 for a 60-kg human.

b Exposure multiple is the calculated AUC in animals/predicted AUC in humans (see Investigator's Brochure for Predicted Human LY3039478 Steady-State Plasma Exposures).

c Starting and highest proposed clinical dose, assuming a 60-kg human. AUC values in humans are predicted values as presented in the Investigator's Brochure.

d MTD determined in a 1-month repeat-dose rat toxicity study (Study 130-238). AUC based on arithmetic mean of male and female exposure on Days 1, 15, and 29 combined.

e MTD determined in a 1-month repeat-dose dog toxicity study (Study 130-237). AUC based on arithmetic mean of male and female exposure on Days 1, 15, and 29 combined.

### *5.3.4. Biomarkers*

As part of an ongoing effort by Lilly to better understand how to predict which tumors are more likely to respond to LY3039478 treatment, the collection of samples to be stored for possible future biomarker research are a mandatory part of this study.

Biomarkers will be used to assess not only PD response to LY3039478 in plasma, surrogate tissues, and tumors, but also potential predictive markers of efficacy and/or patient tailoring.

In Parts B, D, and the Part F dose confirmation, patients will be entered based on screened molecular alteration related to Notch pathway.

PD 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 during dose escalation and dose confirmation (Parts A, B, C, D, E, and F). Potential predictive biomarkers will be measured (when the assays become available) 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 during dose confirmation.

The following biomarkers will be studied:

- Aβ in plasma (Parts A and B only)
- gene expression profiling in tumors and skin biopsies (pre- and posttreatment)
- NICD = Notch intracellular domain IHC in tumors
- cytokeratin 18 in plasma
- RBM in plasma
- epigenomics in plasma

Additional exploratory biomarkers potentially related to the mechanisms of action of LY3039478 may also be evaluated.

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

## 5.4. Rationale for Selection of Dose

A dose range from 2.5 to 100 mg of LY3039478 administered orally TIW was selected based on nonclinical toxicology and PK/PD data modeling. The dose of 2.5 mg is expected to be safe in patients based on nonclinical toxicology data.

The planned clinical starting human dose of 2.5 mg (equivalent to 1.54 mg/m$^2$) is 11.7-fold and 13.0-fold lower than the MTD dose level of 18 and 20 mg/m$^2$ in rats and dogs, respectively. Table JJCA.5.2 shows dose multiples based on body surface area and exposure multiples based on predicted human AUC for the proposed clinical doses.

Based on the IVTI PK/PD model, simulations for humans suggest that oral doses of 20 to 50 mg LY3039478 TIW are expected to produce ≥85% target inhibition 4 hours after dosing, while doses of 20 to 150 mg LY3039478 TIW are expected to produce the required tumor growth delay. Together, the human simulations with both the IVTI and xenograft efficacy models suggest that the biological efficacious dose is 50 mg (range 20 to 150 mg) LY3039478 TIW.

### *5.4.1. Rationale for Additional Dose-Expansion Cohorts (Amendment C)*

Part A was completed in November 2014, and the MTD has been determined to be 75 mg TIW. The dose-expansion phase of the study was opened at the MTD of 75 mg TIW.

Dose-limiting toxicities (DLTs) observed at dose levels of 20 mg, 30 mg, and 60 mg LY3039478 were Grade 4 thrombocytopenia in 1 patient in each dose group. DLTs at 100 mg included Grade 3 nausea (not manageable by medical treatment) and Grade 3 asthenia, and in addition, 1 patient at 100 mg experienced Grade 3 colitis.

Signs of clinical activity have been observed in patients treated at doses of 75 and 100 mg. Activity was observed in leiomyosarcoma, breast cancer, and adenoid cystic carcinoma.

The safety profile of LY3039478 may be impacted by the tumor type, tumor burden, and underlying conditions.

In addition, in case of major response, patients might present with AEs related to tumor necrosis. Additional cohorts are being added to the dose-expansion part of this study to investigate the safety profile and the potential activity in patients with specific tumor types.

Part C will investigate LY3039478 in sarcoma patients including leiomyosarcoma, rhabdomyosarcoma, angiosarcoma, liposarcoma, pleomorphic sarcoma, and gastrointestinal stromal tumors (GIST). This investigation is based on the reports of Notch pathway activation in these specific sarcoma subtypes and the early signs of activity in Study JJCA.

Part D will investigate LY3039478 in triple-negative breast cancer, chronic lymphocytic leukemia (CLL), hepatocellular carcinoma (HCC), and cholangiocarcinoma. It is important to have a minimum number of patients with specific tumors of interest to confirm the safety profile of LY3039478. An assessment of efficacy in these tumors will be performed to guide LY3039478 clinical development.

Additional changes were made for dose adjustments and efficacy assessments as appropriate.

### *5.4.2. Rationale for Additional Dose-Expansion Cohorts (Amendment D)*

Patients in the dose expansion cohorts were initially treated with a dose of 75 mg TIW. There were a total of 41 patients treated at this dose level in the expansion cohorts. After a review of safety data showed significant dose reductions or omissions related to adverse events, the recommended dose was adjusted to 50 mg TIW.

In order to further explore the 50 mg dose TIW dose level and its potential effects, enrolment in the dose expansions cohorts is being increased and additional cohorts are being added to explore the activity of LY3039478 in patients with specific tumor types including adenoid cystic carcinoma and patients with T, B or natural killer (NK) cell neoplasms.

These tumor types were selected based on emerging published data (Stoeck et al. 2014 and Kluk et al. 2013) and internal data showing activation of Notch pathway in these tumor types.

Given the initial observation of metabolic responses in patients receiving LY3039478, the use of PET scan or PET-CT scan is required to be used systematically for all new patients. Tumor biopsies are required to characterize the changes in the tumor following treatment with LY3039478.

Additional editorial changes are being implemented in the protocol.

### *5.4.3. Rationale for Amendment E*

As of November 2015, approximately 40 patients have been treated at 75 mg TIW and 62 patients have been treated at 50 mg TIW. Review of safety data (treatment emergent adverse events, dose-limiting equivalent toxicities, and dose reductions) confirmed the 50-mg TIW schedule to be adequately tolerated. Initial observations of metabolic responses were observed in patients treated at 100 mg, 75 mg, and 50 mg with exploratory analyses suggestive of a potential relationship to dose.

Study Part F will be added in order to explore 2 alternative dosing schedules allowing a loading dose for 2 weeks in Cycle 1, followed by the current 50-mg TIW schedule. Prednisone will be co-administered with LY3039478 during the loading dose period in order to mitigate potential GI toxicity. Study Part F dose confirmation will enroll patients with histologic evidence of advanced or metastatic leiomyosarcoma with Notch molecular alterations in order to allow a homogeneous population to further characterize the clinical activity of LY3039478.

In addition, a continued-access period was added to the protocol for patients who are benefitting from treatment after final database lock has occurred. Minor editorial changes and clarifications have also been made.

# 6. Investigational Plan

## 6.1. Study Population

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

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

### *6.1.1. Inclusion Criteria*

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

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

For Dose Escalation (Part A): The patient must have histological or cytological evidence of cancer, either a solid tumor or a lymphoma, which is advanced or metastatic.

For Part B: All patients must have histological evidence of their advanced or metastatic cancer and prescreened alterations in the Notch pathway such as mutations, amplification, or gene expressions related to Notch pathway (Attachment 8).

For Part C: All patients must have histological evidence of advanced or metastatic soft tissue sarcoma. Eligible patients must have leiomyosarcoma, angiosarcoma, rhabdomyosarcoma, liposarcoma, pleomorphic sarcoma, or GIST.

For Part D: All patients must have histological evidence of advanced or metastatic cancer and prescreened alterations in the Notch pathway such as mutations, amplification, or gene expressions related to Notch (Attachment 8).

- Cohort 1: Patients must have triple-negative breast cancer (ER-, PR-, HER2-).
- Cohort 2: Patients must have HCC. These patients should have Child-Pugh stage A (Attachment 10).
- Cohort 3: Patients must have cholangiocarcinoma.
- Cohort 4: Patients must have CLL.
- Cohort 5: Patients must have mature T cell, B cell, or Natural Killer (NK) cell neoplasms

For Part E: All patients must have histological evidence of advanced or metastatic adenoid cystic carcinoma (ACC).

For Part F: All patients must have:

Dose Escalation: histological or cytological evidence of cancer, either a solid tumor or a lymphoma, which is advanced or metastatic.

Dose Confirmation: histological evidence of nonresectable or metastatic leiomyosarcoma and prescreened alterations in the Notch pathway such as mutations, amplification, or gene expressions related to Notch pathway (Attachment 8).

[2] As defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1; Eisenhauer et al. 2009), the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007), the Guidelines from the National Cancer Institute Working Group for CLL (Hallek et al. 2008), the Response Assessment in Neuro-Oncology (RANO) criteria for glioblastoma (Wen et al. 2010).

For Dose Escalation (Part A): Have measurable or nonmeasurable disease

For Parts B, C, D, E, and F: Have measurable disease or reliable biomarker measure (for example, prostate-specific antigen [PSA], CA125)

[3] Are ≥18 years of age

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

[5] Have adequate organ function including:

- Hematologic: Absolute neutrophil count (ANC) ≥1.5 x $10^9$/L (for CLL patients ANC ≥1.0 x $10^9$/L), platelets ≥100 x $10^9$/L (for patients with CLL and T cell, B cell, or NK cell neoplasms platelets ≥50 x $10^9$/L), and hemoglobin ≥8 g/dL. Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator; however, initial study drug treatment must not begin earlier than the day after the erythrocyte transfusion.
- Hepatic: Bilirubin ≤1.5 times upper limits of normal (ULN) and alanine aminotransferase (ALT) ≤2.5 times ULN. If the liver has tumor involvement, aspartate aminotransferase (AST) and ALT equaling ≤5 times ULN are acceptable.
- Renal: calculated creatinine clearance >45 mL/min (Attachment 6)

[6] Have a performance status ≤1 on the Eastern Cooperative Oncology Group (ECOG) scale (refer to Attachment 5)

[7] Have discontinued all previous therapies for cancer (including chemotherapy, radiotherapy, immunotherapy, and investigational therapy) for at least 21 days for myelosuppressive agents or 14 days for nonmyelosuppressive agents prior to receiving study drug, and recovered from the acute effects of therapy (treatment-related toxicity resolved to baseline) except for residual alopecia. At the discretion of the investigator, patients with breast or prostate cancers progressing on therapies may have that treatment continued while receiving study drug

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

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

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

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

[12] Are able to swallow capsules

[21] For Parts B, C, D, E, and F: Have available tumor tissue (archival or new biopsy)

### *6.1.2. Exclusion Criteria*

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

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

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

[15] Have central nervous system (CNS) malignancy, except:

a) Patients with treated CNS metastases are eligible for this study if they are not currently receiving corticosteroids and/or anticonvulsants, and their disease is asymptomatic and radiographically stable for at least 60 days (screening not required).

b) Patients with glioblastoma, World Health Organization (WHO) grade IV, or WHO grade II or III glioma are eligible.

[16] Have an acute leukemia.

[17] Have received an autologous or allogeneic stem-cell transplant (for patients with CLL or T cell, B cell, or NK cell neoplasms, autologous stem cell transplant is allowed).

[18] Females who are pregnant or lactating.

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

[20] Have malabsorptive syndromes, enteropathies, gastroenteritis (acute or chronic), or diarrhea (acute or chronic).

[22] Patients with HCC that:

- Have known HCC with fibro-lamellar or mixed histology
- Have presence of clinically relevant ascites
- Have had a liver transplant
- Have active or uncontrolled clinically serious hepatitis B virus or hepatitis C virus infection. Patients with stable and chronic viral hepatitis are eligible.
- Have esophageal or gastric varices that require immediate intervention (eg, banding, sclerotherapy) or represent a high bleeding risk in the opinion of the investigator or consulting gastroenterologist or hepatologist or have experienced any CTCAE Grade 3 or 4 GI bleeding or any variceal bleeding episode in the 3 months prior to enrollment requiring transfusion or endoscopic or operative intervention

## 6.2. Summary of Study Design

Study JJCA is a multicenter, nonrandomized, open-label, dose-escalation Phase 1 study of oral LY3039478 in patients with advanced or metastatic cancer. In Study Parts A, B, C, D, and E, eligible patients will receive LY3039478 administered orally TIW during a 28-day cycle. In Study Part F, eligible patients will receive LY3039478 administered orally during a 28-day cycle, according to 2 alternative dosing schedules, with co-administration of prednisone for 2 weeks in Cycle 1.

Patients will receive 2 cycles of LY3039478 unless 1 or more of the criteria for discontinuation (refer to Section 6.3.1) are fulfilled. A patient may receive >2 cycles of treatment only if: 1) none of the criteria for discontinuation have been fulfilled and 2) the investigator determines that the patient is experiencing clinical benefit from treatment. The follow-up period for poststudy evaluation will be 30 days from the date of the last dose of study drug received.

The study design consists of a dose-escalation phase (Part A), a cohort-expansion phase (Parts B, C, D, and E), and a dose-escalation phase with alternative dosing schedules followed by a cohort-expansion phase (Part F).

The dose-escalation phase (Part A) (Figure JJCA.6.1), described in Section 7.2.2, will be guided primarily by safety assessments from Days 1 through 28 of Cycle 1 for patients in all cohorts. Dose escalation will occur until the maximum tolerated dose (MTD, defined in Section 7.2.2.3) is determined. Patients will be enrolled in cohorts starting with the first dose level at 2.5 mg; dose levels of LY3039478 ranging from 2.5 to 100 mg TIW may be evaluated. Table JJCA.7.1 outlines the proposed dose-escalation scheme. The maximum dose increase that will be allowed is 100%. Dose levels are determined based on the review of the safety, PK, and PD data from the previous doses. Enrolment in Part A is complete with a total of 55 patients.

After the last patient on Part A has completed Cycle 1 and the recommended dose for the expansion phase is determined, the cohort expansion phase (Parts B, C, and D; Figure JJCA.6.1) will begin following an interim review of the data, as outlined in Section 10.3.

In the cohort expansion phase (Parts B, C, D, and E), patients will be treated at a dose no greater than the MTD with LY3039478 administered orally TIW during a 28-day cycle.

Part B focused on approximately 50 patients with tumors that have molecularly defined mutations, amplification, or gene expressions alterations related to Notch pathway or known activated Notch pathways.

Part C focused on approximately 65 patients with soft tissue sarcoma including patients with leiomyosarcoma (approximately 25), angiosarcoma (approximately 10), rhabdomyosarcoma (approximately 5), liposarcoma (approximately 10), pleomorphic sarcoma (approximately 5), and GIST (approximately 10).

Part D focused on approximately 42 patients with specific tumor types harboring Notch molecular alterations, including patients with triple negative breast cancer (ER-, PR-, HER2-) (approximately 8), cholangiocarcinoma (approximately 8), HCC (approximately 8), CLL (approximately 8), and mature T cell, B cell, or NK cell neoplasms (approximately 10).

Part E focused on approximately 15 patients with adenoid cystic carcinoma.

Part F will focus on approximately 55 patients with histologic evidence of advanced or metastatic cancer with expansion cohorts in patients with leiomyosarcoma and prescreened alterations in the Notch pathway. Approximately 10 to 15 patients will be treated in a dose-escalation phase and approximately 15 patients in a cohort-expansion phase at the recommended Phase 2 dose according to the following 2 dosing schedules, to be conducted concurrently.

F1: Dose escalation of a loading dose TIW for 2 weeks in Cycle 1 only followed by 50 mg TIW. Prednisone will be co-administered with LY3039478 for the first 2 weeks in Cycle 1 only.

F2: Dose escalation of a loading dose twice a week for 2 weeks in Cycle 1 only followed by 50 mg TIW. Prednisone will be co-administered with LY3039478 for the first 2 weeks in Cycle 1 only.

The total sample size for Parts A, B, C, D, E, and F is estimated to be approximately 282 patients. Further expansion is possible following the analysis of outcome.

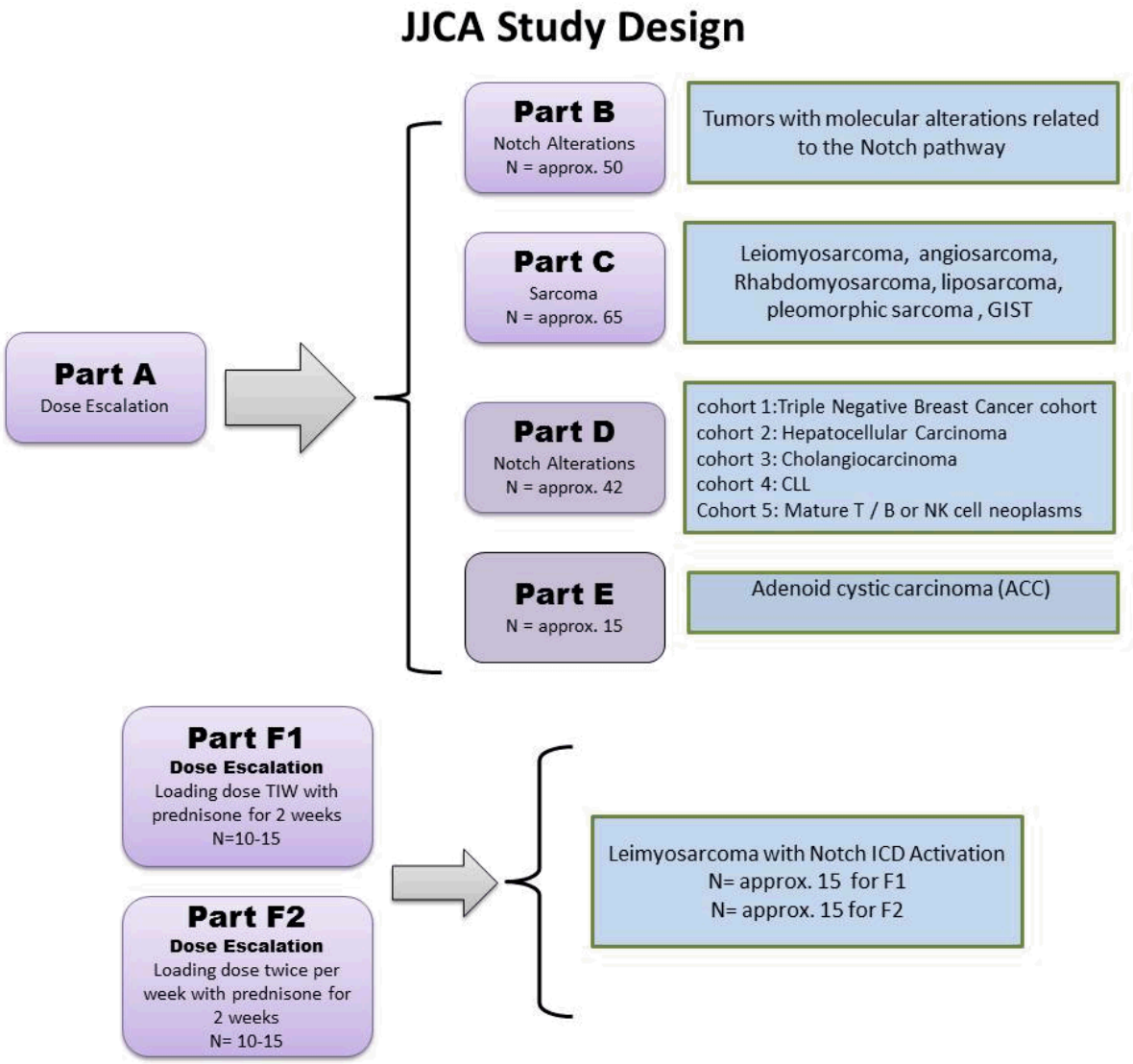
The planned duration of treatment is not fixed; patients will remain on study until they fulfill 1 of the criteria for study discontinuation. The treatment period will be defined as the time from treatment start until discontinuation for any reason (Section 6.3). The postdiscontinuation follow-up period begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and is defined by the following periods:

- **The *short term follow-up period*** begins 1 day after discontinuation of study treatment and lasts approximately 30 days (Visit 801).
- **The *long-term follow-up period*** begins 1 day after the short-term follow-up period (Visit 801) is completed and continues until death or study closure to collect survival data.
- After discontinuation, tumor measurements will be performed as indicated in Section 8.3. Other study procedures will be performed as outlined in Attachment 1.

This study will be considered closed approximately 12 months from the date that the last patient was enrolled. Patients who are benefitting from treatment may continue to receive study drug for long-term durations, even after the study has closed and final database lock has occurred in the continued-access period.

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

Refer to Attachment 1 for the Study Schedule.




Abbreviations: approx = approximately; CLL= Chronic lymphocytic leukemia; GIST = gastrointestinal stromal tumors; ICD = intercellular domain; NK= natural killer; TIW = 3 times per week.

**Figure JJCA.6.1. Study design.**

### *6.2.1. Continued-Access Period*

All patients remaining on study treatment without disease progression following the final analysis will be able to enter the continued-access period of the study, which begins approximately 12 months after the last patient was enrolled and ends after the last patient discontinues study treatment and performs safety follow-up visit. During the continued-access period, patients on study treatment who continue to experience clinical benefit may continue to receive study treatment until they meet discontinuation criteria. The continued-access period includes a follow-up visit. The follow-up visit begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued-access period and lasts

approximately 30 days. If it is deemed to be in the best interest of the patient to start a new anticancer treatment prior to the scheduled end of the follow-up visit, the follow-up visit duration may be shortened. In this case, the follow-up assessments should be completed prior to the initiation of the new therapy.

During the continued-access period, all AEs, SAEs, dose reductions, and study drug exposure will be collected on the case report form/electronic case report form (CRF/eCRF).

SAEs will also be reported to Lilly Global Patient Safety and collected in the Lilly Safety System (LSS). In the event that an SAE occurs, additional information (such as local laboratory results, concomitant medications, and hospitalizations) may be requested by Lilly in order to evaluate the reported SAE.

Investigators may perform other standard procedures and tests needed to treat and evaluate patients; however, Lilly will not routinely collect the results of these assessments. The Study Schedule (Attachment 1) describes all assessments for the continued-access period.

## 6.3. Discontinuations

### *6.3.1. Discontinuation of Patients*

The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is unintentionally enrolled, Lilly or its designee must be contacted. In these rare cases, the investigator must obtain documented approval from Lilly to allow the patient to continue in the study.

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

- Enrollment in any other clinical trial 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
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the other agent
- Patient Decision
    - the patient requests to be withdrawn from the study
- Sponsor Decision
    - the investigator or 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 has evidence of symptomatic progression or confirmed objective progressive disease. The determining factor for whether a patient can continue on study drug should be based on his/her clinical symptoms even if the patient has progressive disease based on radiological evidence. The investigator may also take into consideration biomarker responses (PSA, AFP, etc).
- The patient experiences unacceptable toxicity including, but not limited to, a Grade 4 non-hematological toxicity or a toxicity that does not resolve to baseline within 3 weeks.
- The patient is noncompliant with study procedures and/or treatment (Section 7.6).

The reason and date for discontinuation will be collected for all patients. Patients who discontinue will have follow-up procedures performed as shown in the Study Schedule (Attachment 1).

### 6.3.2. Discontinuation of Study Sites

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

### 6.3.3. Discontinuation of the Study

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

# 7. Treatment

## 7.1. Materials and Supplies

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

Prednisone will either be provided by Lilly or obtained locally as appropriate and required.

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

## 7.2. Study Drug Administration

The investigator or his/her designee is responsible for:

- explaining the correct use of the investigational agent and planned duration of each individual's treatment to the patient/legal representative,
- verifying that instructions are followed properly,
- maintaining accurate records of study drug dispensation, destruction, and collection, and
- returning all unused medication to Lilly or its designee at the end of the study or if appropriate and instructed by Lilly, may be destroyed at the site per local regulations and standard operating procedures.

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 during both the dose-escalation phase (Part A) and the dose-confirmation phase (Part B, C, D, and E) following 1 of these schedules (decision at investigator's discretion):

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

For Study Part F1, LY3039478 will be administered orally TIW following 1 of these schedules (decision at investigator's discretion):

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

For Study Part F2, LY3039478 will be administered orally twice a week for 2 weeks in Cycle 1, followed by TIW dosing, following 1 of these schedules (decision at investigator's discretion):

- For Cycle 1: Monday and Friday for Weeks 1 and 2, followed by Monday, Wednesday, Friday for Weeks 3 and 4. For Cycle 2 and beyond: Monday, Wednesday, and Friday every week for a 28-day cycle.
- For Cycle 1: Tuesday and Saturday for Weeks 1 and 2, followed by Tuesday, Thursday, Saturday for Weeks 3 and 4. For Cycle 2 and beyond: Tuesday, Thursday, Saturday every week for a 28-day cycle.
- For Cycle 1: Wednesday and Sunday for Weeks 1 and 2, followed by Wednesday, Friday, Sunday for Weeks 3 and 4. For Cycle 2 and beyond: Wednesday, Friday, Sunday every week for a 28-day cycle.
- For Cycle 1: Thursday and Monday for Weeks 1 and 2, followed by Thursday, Saturday, Monday for Weeks 3 and 4. For Cycle 2 and beyond: Thursday, Saturday, Monday every week for a 28-day cycle.

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

Twice daily (BID; 12 hours apart) administration of LY3039478 will be explored if deemed necessary.

Prednisone will be administered daily on Days 1 through 14 during Cycle 1 (Part F) at the dosage of 20 mg.

During Cycle 1 and Cycle 2, patients will record the time and amount of each dose in a patient diary. Clinic personnel will instruct patients to pay particularly close attention to record this information accurately on days of PK assessments (Attachment 3).

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

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

For Cycle 2 and beyond, a delay of ≤3 weeks in the start of a cycle (Dose 1) to allow for recovery from toxicity will be permitted and does not constitute a protocol violation (refer to Section 7.2.4.1.2).

## *7.2.2. Dose-Escalation Phase*

### 7.2.2.1. Dose-Escalation Method

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

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

Model-based analyses that incorporate prior expectations about the dose-toxicity curve will also be fitted to the data at the end of each cohort, which may be used by the investigators and Lilly clinical research physician (CRP) to help determine the next dose level. Dose escalation will take into account PK and PD information when available.

Additional patients may therefore be enrolled at a specific dose level to characterize PK/PD.

Intermediate doses levels will be explored if deemed necessary after discussion between the sponsor and investigators.

Further details regarding the model based analyses will be provided in the statistical analysis plan.

#### 7.2.2.2. Criteria for Dose Escalation

Safety data, in particular AEs, will be the primary criteria for the dose escalation. The dose will be escalated following assessment of toxicity using the standard scoring system, CTCAE version 4.0, established by the NCI. Any AEs related to LY3039478 will be considered as toxicities.

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

In the initial cohort only, the first patient will be observed for a dose-limiting toxicity (DLT) (defined in Section 7.2.2.3) during 14 days before subsequent patients are treated at that dose level. If the first patient does not experience a DLT during this period, subsequent patients in the initial cohort may be enrolled concurrently. By contrast, if the first patient experiences a DLT during this period, subsequent patients will be enrolled sequentially after observation for DLT during 14 days of therapy.

In subsequent cohorts, based on the safety and PK results of the previous cohort, enrollment will occur concurrently unless the results of the previous cohort warrant a sequential enrollment. The decision is made between the investigators and the sponsor.

Table JJCA.7.1 shows the proposed dose levels for the Part A dose-escalation portion with the predicted simulated exposure for LY3039478.

Table JJCA.7.1 summarize recommended doses levels. Intermediate dose levels of LY3039478 will be used if deemed appropriate based on agreement between the investigators and the sponsor. LY3039478 will not be increased beyond 100%. Dose doubling between cohorts will cease if 1 patient in a cohort experiences a DLT or 2 patients in a cohort experience Grade 2 adverse events.

**Table JJCA.7.1. Proposed LY3039478 Dose-Escalation Scheme for Study I6F-MC-JJCA and Predicted Human Exposure- Part A**

| Dose Level | LY3039478 Dose (mg) | Predicted Median $AUC_{0-\tau,ss}$ (ng·h/mL) | Predicted 5th and 95th percentiles $AUC_{\tau,ss}$ (ng·h/mL) |
|---|---|---|---|
| -1[a] | 1.25 | 54.9 | 29.2 – 95.9 |
| 1 | 2.5 | 112 | 60.9 – 193 |
| 2 | 5 | 229 | 114 – 393 |
| 3 | 10 | 433 | 233 – 768 |
| 4 | 20 | 882 | 494 – 1600 |
| 5 | 30 | 1320 | 725 – 2290 |
| 6 | 45 | 1990 | 1080 – 3450 |
| 7 | 60 | 2620 | 1440 – 4700 |
| 8 | 80 | 3450 | 1890 – 6260 |
| 9 | 100 | 4400 | 2310 – 7650 |

Abbreviations: $AUC_{0-\tau}$ = area under the plasma concentration versus time curve from time 0 to the end of the dosing interval ($\tau$; where $\tau$ = 48 hours); $AUC_{\tau,ss}$ = area under the plasma concentration versus time curve over 1 dosing interval at steady-state; DLT = dose-limiting toxicity.

[a] Dose Level -1 to be used only in the event of DLTs experienced in Dose Level 1 necessitating a dose de-escalation.

Table JJCA.7.2 shows the proposed dose levels for the Part F dose escalation.

**Table JJCA.7.2. Proposed LY3039478 Dose-Escalation Scheme for Study I6F-MC-JJCA and Predicted Human Exposure- Part F**

| Dose Level | LY3039478 Loading Dose (mg) |
|---|---|
| 1 | 75 |
| 2 | 100 |
| 3 | 125 |
| 4 | 150 |

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis until the MTD is determined, as defined in Section 7.2.2.3. If the MTD has not yet been achieved at the highest prespecified dose level, based on both safety and the available PK data, following discussion with investigators, additional dose levels may be investigated.

In this study, intrapatient dose escalation is not permitted and dose escalation to the next cohort cannot occur without prior discussion and agreement between the investigator and the responsible Lilly CRP. The decision will be documented in writing.

### 7.2.2.3. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition

DLT is defined as an AE during Cycle 1 that is related to LY3039478 and fulfills any 1 of the following criterion using the NCI 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
    - electrolyte disturbance that can be controlled with treatment
    - Diarrhea CTCAE Grade 3 for ≤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 are considered an exception to the DLT criteria, unless there is a clear alternative cause (eg, worsening biliary obstruction) if agreed by the study investigator and Lilly CRP/clinical research scientist (CRS)
- CTCAE Grade 4 hematological toxicity of >5 days duration
- Any febrile neutropenia
- Grade 3 thrombocytopenia with bleeding or Grade 4 thrombocytopenia.
- Any other significant toxicity deemed by the primary investigator and Lilly clinical research personnel to be dose limiting (for example, any toxicity that is possibly related to the study medication that requires the withdrawal of the patient from the study during Cycle 1).

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

A DLT-equivalent toxicity is defined as an AE occurring between Day 1 and Day 28 of any cycle (other than Cycle 1) for a patient enrolled in Part A or in any cycle (including Cycle 1) for a patient enrolled in Part B that would have met the criteria for DLT if it had occurred during Cycle 1 for a patient enrolled in Part A.

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

### *7.2.3. Cohort-Expansion Phase*

Once the MTD has been defined, the cohort-expansion phase (Parts B, C, D, E, and F) will be opened. Part B will consist of up to 50 additional evaluable patients with molecularly defined mutations, amplification, or gene expressions related to Notch pathway. Part C will consist of approximately 65 patients with soft tissue sarcomas. Part D will consist of approximately 42 patients with specific tumor types that have molecularly defined mutations, amplification, or gene expressions related to Notch pathway. Part E will consist of approximately 15 patients with adenoid cystic carcinoma.

The dose studied in Parts B, C, D, and E was defined at the end of dose escalation after a safety, PK, and PD review. The current dose is 50 mg TIW.

Part F will explore 2 alternate dosing schedules, and once an MTD has been defined for each of these alternate schedules, a cohort expansion in approximately 15 leiomyosarcoma patients with alterations in the Notch pathway such as mutations, amplification, or gene expressions related to Notch pathway will be opened for each dosing schedule.

If DLT-equivalent toxicities in the first cycle (ie, toxicities that would meet the DLT criteria described in Section 7.2.2.3) occur in 33% or more of patients within this cohort expansion, then investigators and the Lilly CRP will assess the nature and severity of these toxicities. No additional patients will be accrued until this safety review is completed and a decision is made either to continue at the current dose or to de-escalate the dose and define a new dose for the expansion portion. The safety review and decision will be documented in writing.

## *7.2.4. Dose Adjustments and Delays*

### 7.2.4.1. Part A

#### *7.2.4.1.1. Dose Adjustments within a Cycle*

No dose adjustments will be allowed within a cycle. If a patient treated at a given dose level experiences a DLT or a DLT-equivalent toxicity (DLET) (as defined in Section 7.2.2.3), then treatment will be suspended for that patient for the duration of the current cycle. If a toxicity does not meet the criteria for a DLT in Cycle 1 (or a DLET) but nonetheless requires omission of dose(s) for tolerability, then dosing may resume at the same dose after the toxicity resolves to baseline; however, the dose(s) omitted for tolerability during a cycle will not be replaced.

#### *7.2.4.1.2. Dose Adjustments between Cycles*

Before the start of each cycle, hematological toxicities and nonhematological toxicities (except alopecia and fatigue) must resolve to baseline. The start of a cycle may be delayed up to 14 days to allow sufficient time for recovery. Patients experiencing Grade 4 nonhematological toxicity or not recovering from toxicity within 14 days should be discontinued from the study.

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

- DLT (in Cycle 1 for patients in Part A)
- DLT-equivalent toxicity (in Cycle 2 or beyond for patients in Part A, or in any cycle for patients in Part B)
- Omission of >7 doses in a single cycle for tolerability.

For such patients requiring a dose reduction, re-escalation to the original dose level is not permitted. If a patient experiences a DLT-equivalent toxicity at the reduced dose level, then the patient will be discontinued from the study. If a patient requires omission of >3 doses for tolerability at the reduced dose level, then treatment may continue if the investigator determines that the patient is receiving clinical benefit. Dose reduction by ≥2 dose levels is not permitted, so patients requiring dose reduction by >1 dose level should be discontinued from the study.

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

#### 7.2.4.2. Parts B, C, D, and E

##### *7.2.4.2.1. Dose Adjustments within a Cycle*

If a patient experiences a DLET (as defined in Section 7.2.2.3), then treatment should be suspended for that patient. If a toxicity does not meet the criteria for a DLET but nonetheless requires omission of dose(s) for tolerability, then dosing may resume at the same dose after the toxicity resolves to baseline; however, the dose(s) omitted for tolerability during a cycle will not be replaced.

In either case, depending on the toxicities and whether the patient benefits from the treatment, dosing may resume at the given dose or a reduced dose and with or without allowed concomitant medication after consultation with the Lilly CRP.

##### *7.2.4.2.2. Dose Adjustments between Cycles*

- Nonhematologic toxicity must resolve to CTCAE Grade 0, 1, or baseline level before resuming treatment (with the exception of alopecia, fatigue, skin rash, nausea, vomiting, constipation, or diarrhea that can be controlled with treatment).
- Hematologic toxicity must resolve to a level that, in the opinion of the investigator, is reasonable to allow for continuation of treatment.
- Patients who experience a DLET or do not recover from toxicity within the 3-week time frame may have the dosage reduced to 25 mg TIW.
- Reescalation to the previous dose is acceptable in the absence of continuing toxicities. If subsequent LY3039478 dose reduction is required after reescalation, the patient should be maintained at the reduced dose level.

Adjustments to these dosing guidelines may be permitted following an evaluation of the patient's condition, benefit of treatment, and consultation with the Lilly CRP. All exceptions to these guidelines will be documented.

#### 7.2.4.3. Part F

##### *7.2.4.3.1. Dose Adjustments within a Cycle*

If a patient experiences a DLT or a DLET (as defined in Section 7.2.2.3), then treatment should be suspended for that patient. If a toxicity does not meet the criteria for a DLT or DLET but nonetheless requires omission of dose(s) for tolerability, then dosing may resume at the same dose after the toxicity resolves to baseline; however, the dose(s) omitted for tolerability during a cycle will not be replaced.

In either case, depending on the toxicities and whether the patient benefits from the treatment, dosing may resume at the given dose or a reduced dose and with or without allowed concomitant medication after consultation with the Lilly CRP.

#### *7.2.4.3.2. Dose Adjustments between Cycles*

- Nonhematologic toxicity must resolve to CTCAE Grade 0, 1, or baseline level before resuming treatment (with the exception of alopecia, fatigue, skin rash, nausea, vomiting, constipation, or diarrhea that can be controlled with treatment).
- Hematologic toxicity must resolve to a level that, in the opinion of the investigator, is reasonable to allow for continuation of treatment.
- Patients who experience a DLET or do not recover from toxicity within the 3-week time frame may have the dosage reduced to the previous dose level. Patients in first dose level may be reduced to 50 mg TIW.
- A second dose reduction is allowed.
- Reescalation to the previous dose is acceptable in the absence of continuing toxicities. If subsequent LY3039478 dose reduction is required after reescalation, the patient should be maintained at the reduced dose level.

Adjustments to these dosing guidelines may be permitted following an evaluation of the patient's condition, benefit of treatment, and consultation with the Lilly CRP. All exceptions to these guidelines will be documented.

## 7.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive LY3039478 in this study. For patients participating in Part A and the dose-escalation phase of Part F: 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 or CRS. For patients participating in Study Part F cohort expansion: upon confirmation of eligibility, the sponsor will assign the patient to a dosing schedule (F1 or F2). Further details on the method of assignment are documented in the Statistical Analysis Plan. 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, immunotherapy, cancer-related hormone therapy, or experimental drugs will be permitted while the patients are on this study. An exception will be made for prostate or breast cancer patients continuing gonadotropin-releasing hormone or luteinizing hormone-

releasing hormone agonist therapy. Palliative radiotherapy is allowed. In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate early discontinuation from the study. Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the case report form.

Patients should receive full supportive care with the exception that the routine use of granulocyte colony stimulating factors (G-CSF) is not permitted during this study. Patients should not receive G-CSF prophylactically in any cycle. G-CSFs may only be used for patients who have ANC<$0.5 \times 10^9$, neutropenic fever, or documented infections while neutropenic. G-CSFs 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, erythropoietin and packed red blood cell transfusions may be used according to ASCO guidelines (Rizzo et al. 2008).

For Study Parts A, B, C, D, and E, patients should not receive corticosteroids prophylactically with the intent of attenuating GI toxicity. However, corticosteroid therapy initiated before study entry for a preexisting condition may be continued. Corticosteroids may be used for treatment of GI toxicities if deemed necessary after agreement between the investigators and Lilly CRP. As a guidance, standard treatments are provided in Attachment 9. For Study Part F, prednisone will be co-administered with LY3039478 as detailed in Section 7.2.1.

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

## 7.6. Treatment Compliance

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

The patient must take ≥75% of the intended dose to be deemed compliant with study drug administration. Similarly, a patient may be considered noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication. 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 or 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*

### 7.6.1.1. Parts A, B, C, D, E, and F

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 1 cycle of therapy, may be replaced upon consultation with the investigators and the Lilly CRP or CRS to ensure adequate PK data, unless accrual to that cohort has stopped due to a DLT. Patients who are evaluable for PK are defined as those patients who have a sufficient number of PK samples to evaluate PK parameters after at least 1 dose.

### 7.6.1.2. Dose Escalation Only

Any patient who is discontinued from the study before completing Cycle 1 will be deemed non-evaluable 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 will be replaced to ensure that 3 patients complete 1 cycle of therapy at each dose level, unless accrual to that cohort has stopped due to a DLT.

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

## 8.1. Safety Evaluations

The safety and tolerability of LY3039478 have been assessed in nonclinical toxicology studies and the results from these studies are detailed in the IB. This Phase 1 study contains detailed safety monitoring that will permit initial characterization of the safety profile of LY3039478 in patients. Study procedures and their timing, including collection of blood and urine samples, are described in the Study Schedule (Attachment 1).

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

### *8.1.1. Safety Data Collection and Review*

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

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

The investigator remains responsible for following, through an appropriate health care option, all AEs that are serious or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Frequency of AE and SAE follow-up evaluation is left to the discretion of the investigator.

Investigators or their designees must document their review of each laboratory report.

### *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 using the same guidelines and schedules as those for AEs. 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 4.0) may be used for this study. Minor CTCAE v 4.0 updates from the NCI will not necessitate a protocol amendment. For AEs without matching terminology within the NCI CTCAE v 4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event. Note that both CTCAE term (actual or coded) and severity grade must be selected by study site personnel and collected on the eCRF. This collection is in addition to verbatim text used to describe the AE.

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

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported. 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. 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.

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

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

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

#### 8.1.2.1. Serious Adverse Events

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

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

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

- death
- initial or prolonged inpatient hospitalization (except for study drug administration)
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.

SAEs due to disease progression (including death) should not be reported as an SAE unless the investigator deems it to be related to the use of 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. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

#### 8.1.2.2. Adverse Event and Serious Adverse Event Reporting

##### *8.1.2.2.1. Prior to Administration of Study Drug*

AE 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.

#### *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 initial follow-up visit (Visit 801) must be reported to Lilly or its designee. The follow-up visit starts following the last dose of study drug. At the end of the follow-up visit, the patient will be required to have specific safety assessments (Attachment 1). The timing of these safety assessments is 30 days ± 3 days after the last dose of study drug

Following the safety assessments, which mark the end of the initial follow-up visit (Visit 801), 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 drug- or procedure 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.

After the initial follow-up visit (Visit 801) AEs and SAEs are not required to be reported unless the investigator feels the events were related to either study drug or a protocol procedure. Any subsequent follow-up(s) will be no more than 30 ±3 days in duration.

### 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 (DCSI) 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 Adverse Events and Serious Adverse Event Reporting Guidelines

The AE and SAE reporting guidelines are summarized in Table JJCA.8.1 and Attachment 4.

**Table JJCA.8.1. Adverse Event and Serious Adverse Reporting Guidelines for Study I6F-MC-JJCA**

| Timing | Types of AEs/SAEs Reported |
|---|---|
| Prestudy (baseline assessments), per Section 8.1.2.2.1 | Preexisting conditions<br>Procedure-related AEs/SAEs |
| On therapy, per Section 8.1.2.2.2 | All AEs/SAEs regardless of relatedness |
| Follow-up Visit (Visit 801), per Section 8.1.2.2.3 | All AEs/SAEs regardless of relatedness |
| Continued-access period | All AEs/SAEs regardless of relatedness |
| Continued-access period follow-up | All AEs/SAEs regardless of relatedness |
| Subsequent Follow-up visits, if necessary – no more than 30 ±3 days in duration[a] | Ongoing or new AEs/SAEs related to study drug or protocol procedures |
| Long-term posttreatment discontinuation follow-up[b] | All AE and SAEs related to protocol procedures or study drug |

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

[a] Part A only.

[b] Parts B, C, D, and E only.

## *8.1.3. Other Safety Measures*

### 8.1.3.1. Electrocardiograms

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

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

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

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

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) to determine whether the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control check (for example,

demographics and study details) then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

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

### *8.1.4. Safety Monitoring*

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

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

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

### *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 adverse events 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 sampling schedules for this study.

Attachment 7 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study. Fewer invasive sampling may actually occur, but this will not require a protocol amendment.

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.

A maximum of 5 additional PK (blood) samples may be added or removed during the study if warranted and agreed upon by both the investigator and sponsor. 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. Plasma PK samples (from venous blood) will be analyzed at a laboratory designated by the sponsor. Plasma concentrations of LY3039478 will be quantified using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. All bioanalytical samples will be stored in the United States.

The remaining plasma from the samples collected for PK may be used for exploratory metabolism work as deemed appropriate by the sponsor.

Urine will be collected after Dose 1 of Cycle 1 at all dose levels in Part A. Total urine output for the first 8 to 10 hours post LY3039478 administration will be collected, pooled, and refrigerated. The final urine sample should be collected at the time that Dose 1, 8- to 10-hour PK sample is drawn (Sample #8), and urine collection should cease thereafter. At the end of the 8- to 10-hour collection period, the total urine volume will be recorded, an aliquot sent for creatinine determination, and 2 approximately 10-mL samples will be stored frozen, and the remaining urine will be discarded. Instructions for the collection and handling of urine samples will be provided by the sponsor. Although every attempt should be made to collect urine from patients, failure to do so is not considered a protocol violation.

Urine will be used for exploratory quantification of LY3039478, creatinine, and exploratory metabolite identification at the discretion of the sponsor. Urine concentrations of LY3039478 will be quantified using validated LC-MS/MS assay. Analytes will be quantified using assays deemed appropriate by the sponsor. 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 study drug concentration and metabolism will be retained for a maximum of 2 years following last patient visit for the study.

### *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. Attachment 7 summarizes the blood volumes for all blood and urine sampling (screening, safety laboratories, and bioanalytical assays) during the 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 medically or scientifically appropriate. When medical and 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*

PK samples will be collected as specified in the Pharmacokinetic Sampling 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 validated 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 at all dose levels in Part A, 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 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 study drug concentration and metabolism will be retained for a maximum of 2 years following last patient visit for the study.

### *8.2.3. Pharmacogenetic Samples*

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, where local regulations allow, a blood sample will be collected for pharmacogenetic (PGx) analysis. It is a 1-time collection, as noted in the Study Schedule (Attachment 1).

Samples will be stored and exploratory analysis may be performed to identify genetic variants that might play a role in tumor biology or to evaluate their association with observed clinical outcomes to LY3039478.

In the event of an unexpected AE or the observation of unusual response, the 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. 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.

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

## *8.2.4. Exploratory Samples*

### 8.2.4.1. Blood Samples for Aβ Assays

Blood samples will be collected for exploratory analysis of circulating Aβ peptides (for example, Aβ(1-x) or peptide components thereof) before and after treatment with LY3039478. These samples may be retained for a maximum of 15 years following the last patient visit for the study. 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

Exploratory biomarker studies may be performed on tissues and blood, for cytokeratin 18, RBM and potential epigenomic alterations associated with the host tumor (for example, microRNA expression arrays).

### 8.2.4.3. Tumor and Skin Biopsies

Throughout this study, archived tumor tissue obtained previously for diagnostic purposes (for example, at initial diagnosis) will be requested for biomarker research but is not required for study entry in Part A. At baseline, before the patient received study drug for Parts B, C, D, E, and F, a mandatory pretreatment formalin-fixed paraffin-embedded (FFPE) tumor tissue (paraffin blocks or unstained slides cut from that block) will be collected. For Study Part F, the tumor tissue sample is required to be obtained within 2 years of the date of enrollment if archival. A fresh sample is required if no archival sample meeting that criteria can be located.

Table JJCA.8.2 presents tumor and skin biopsy collection time points.

**Table JJCA.8.2. Tumor and Skin Biopsy Time Points**

| Collection Time Point | Part A | Parts B, C[a], and D[a] | Part E and F |
|---|---|---|---|
| Baseline archived tissue collection | Optional | Mandatory | Mandatory |
| Pre-/Postdose tumor biopsies | Optional | Recommended/optional | Mandatory |
| Pre-/Postdose skin biopsies | Mandatory | Mandatory | Mandatory |

a LMS, GIST, liposarcoma, angiosarcoma, and mature T cell, B cell, or NK cell neoplasm patients enrolled under Amendment d will have mandatory sample collection at each time point.

Pretreatment tumor biopsies and skin biopsies (as instructed by the laboratory manual) will be collected pre- and posttreatment for measuring various biomarkers, potentially including gene-expression profiling (GEP), as well as other exploratory biomarkers. Additionally, optional skin biopsies and/or optional tumor biopsies at time of disease progression will be collected. Furthermore, skin and/or tumor biopsies may be performed if deemed necessary by the investigator. The samples will be analyzed at laboratories using assays designated by the sponsor. Sample handling and shipment to the central laboratory will occur per instructions given to the study site.

Stored tissue samples will retain the patient identifier (for example, trial patient numbers) and therefore will not be stored indefinitely. Archived biopsy specimens submitted as an FFPE tissue block (or sectioned slides) will be returned to the sites by end of study or upon request. Tumor biopsy slides will be stored for a maximum of 15 years after last patient visit for the study; any sample remaining at that time will be destroyed. Samples will be stored at a facility selected by the sponsor.

## 8.3. Efficacy Evaluations

An objective of the study is to document any antitumor activity (secondary in Part A and coprimary for Parts B, C, D, E, and F). Refer to Attachment 1 for details regarding the timing of specific efficacy measures.

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

- computed tomography (CT) scan
- magnetic resonance imaging (MRI)
- chest x-ray
- PET scan – mandatory for Part E and F, Part C patients with sarcoma (leiomyosarcoma, GIST, liposarcoma, and angiosarcoma), and Part D patients with mature T cell, B cell, or NK cell neoplasms enrolled under amendment d.
- DCE-MRI

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

- applicable tumor measurement by RECIST 1.1 (Eisenhauer et al. 2009), Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007), Guidelines from the National Cancer Institute Working Group for CLL (Hallek et al. 2008), or the RANO criteria for glioblastoma (Wen et al. 2010). For tumor measurement evaluations in patients with soft tissue sarcomas or HCC, Choi et al. 2007 will be used in addition to RECIST 1.1.
- evaluation of tumor markers, if indicated
- evaluation of performance status (refer to the ECOG scale, Attachment 5)

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. Responses of CLL patients are confirmed according to the Guidelines from the National Cancer Institute Working Group for CLL (Hallek et al. 2008). Partial metabolic response by PET scan is defined as a minimum of 15±25% in tumour [18F]-FDG SUV after one cycle of therapy, and greater than 25% after more than one treatment cycle and should be confirmed at least 4 weeks later, according to PET response criteria of the European Organization for Research and Treatment of Cancer (Young et al. 1999). If a patient is discontinued from the study, repeat radiology assessments may be omitted if clear clinical signs of progressive disease are present.

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

**Table JJCA.8.3. Definition of Efficacy Endpoints**

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

After patients have discontinued study treatment, they may receive additional anticancer therapy at the discretion of the investigator. For those patients who discontinue study treatment without objectively measured progressive disease, the investigative sites will continue to monitor patients approximately every 60 days (±14 days) to evaluate tumor response by the same method used at baseline and throughout the study, until objective progression or the patient starts a new anticancer therapy, or study closure. Once a patient has objective progression or starts a new anticancer therapy, they will be followed for OS approximately every 60 days (±14 days) until death or study closure.

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

## 8.4. Procedure/Sampling Compliance

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

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

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

# 9. Data Management Methods

## 9.1. Data Quality Assurance

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

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

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

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

## 9.2. Data Capture Systems

### *9.2.1. Case Report Form*

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

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

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

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

### *9.2.2. Ancillary Data*

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

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

ECG data will be stored electronically in the central database system of Lilly's central review organization. Data will subsequently be transferred from the central review organization system to the Lilly generic labs system.

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

# 10. Data Analyses

## 10.1. General Considerations

Approximately 282 patients may be enrolled in this multicenter, open-label Phase 1 study with dose escalation followed by dose confirmation.

During Part A dose escalation, approximately 55 patients will be enrolled into cohorts sequentially and without randomization to dose. The total sample size per cohort will be determined by DLTs.

During the Part B cohort expansion, approximately 50 patients with molecularly defined mutations, amplification, or gene expression alterations related to Notch pathway will be enrolled. This sample size is adequate to explore the PD effects and anti-tumor activity of LY3039478 in patients with molecular alterations related to the Notch pathway. Given that deregulated Notch signaling is implicated in a number of malignancies (refer to Table JJCA.5.1), there was no statistical powering for this part of the study as it is exploratory in nature.

Part C will focus on approximately 65 patients with soft tissue sarcoma including approximately 25 patients with leiomyosarcoma. A sample size of 25 patients is considered sufficient to estimate response rates with adequate precision for this stage of development and to explore antitumor activity in subsets of interest (for example RB1 deletion status) (Table JJCA.10.1).

Part D of the study will include 5 cohorts, for patients with triple-negative breast cancer (approximately 8), cholangiocarcinoma (approximately 8), HCC (approximately 8), CLL (approximately 8), and mature T cell, B cell, or NK cell neoplasms (approximately 10) who have molecularly defined mutations, amplification, or gene expression alterations related to Notch pathway. Part E will focus on approximately 15 patients with adenoid cystic carcinoma. This sample size is adequate to explore PD effects and anti-tumor activity of LY3039478 in within each specific tumor type of interest.

Part F will focus on approximately 55 patients. The total sample size during dose escalation will be determined by DLTs and is estimated to be approximately 10 to 15 patients for each schedule (F1 and F2). The sample size of approximately 15 patients for each schedule (F1 and F2) in the expansion cohorts is adequate to explore anti-tumor activity of LY3039478 in patients with leiomyosarcoma.

For guidance, example point estimates of incidence rates and corresponding 2-sided exact 95% confidence interval (CI) are provided in Table JJCA.10.1 for the proposed sample size of each tumor type in study Parts C, D, E, and F. The values are provided as a reference for estimation rather than a basis of any decision criteria.

**Table JJCA.10.1. Estimated Exact 95% CI for Example Overall Response Rate for Proposed Sample Size**

| Sample Size | Example Number of Responders (%) | Exact 95% CI for ORR (%) |
|---|---|---|
| 5 | 1 (20%) | (1%, 72%) |
| | 3 (60%) | (15%, 95%) |
| 8 | 2 (25%) | (3%, 65%) |
| | 5 (63%) | (24%, 91%) |
| 10 | 2 (20%) | (3%, 56%) |
| | 6 (60%) | (26%, 88%) |
| 15 | 3 (20%) | (4%, 48%) |
| | 9 (60%) | (32%, 84%) |
| 20 | 4 (20%) | (6%, 44%) |
| | 12 (60%) | (36%, 81%) |
| 25 | 5 (20%) | (7%, 41%) |
| | 15 (60%) | (39%, 79%) |

Abbreviations: CI = confidence interval; ORR = overall response rate.

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. Data analyses will be provided by dose groups and study part and for all study patients combined wherever appropriate. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, minimum, and maximum. Categorical endpoints will be summarized using number of patients, frequency, and percentages. Missing data will not be imputed.

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. 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.

### *10.1.2. Patient Characteristics*

Patient characteristics will include a summary and listing of the following:

- Patient demographics
- Baseline disease characteristics
- Prior disease-related therapies
- Concomitant medications.

Other patient characteristics will be summarized as deemed appropriate. In addition, the numbers and percentages of patients reporting post-discontinuation therapies will be provided overall, by type of therapy (surgery, radiotherapy, systemic therapy), and by drug name.

### *10.1.3. Safety Analyses*

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

Safety analyses will include summaries of the following:

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

### *10.1.4. Pharmacokinetic Analyses*

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

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

The primary parameters for analysis will be $C_{max}$, area under the plasma concentration-time curve from time zero to last measurable plasma concentration (AUC[0-$t_{last}$]), and area under the concentration-time curve from time zero to infinity or over 1 dosing interval at steady state (AUC[0-$\infty$] or $AUC_{\tau,ss}$) of LY3039478. Other noncompartmental parameters, such as time of $t_{1/2}$, CL/F, and apparent volume of distribution (V/F) may be reported. Additional exploratory analyses will be performed if warranted by data and other validated PK software programs (for example, NONMEM) may be used if appropriate and approved by Global Pharmacokinetic management. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

PK parameter estimates will be evaluated to delineate effects of dose proportionality. Log-transformed $C_{max}$ and AUC estimates will be assessed to estimate ratios of geometric means and the corresponding 90% CIs.

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.

The PK data will be combined, and analyses may be conducted to determine a relationship between exposure and PD/PGx 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.

### *10.1.5. 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.

## 10.2. Efficacy

The study was not designed to make a formal efficacy assessment. However, any tumor response data will be tabulated and summarized by study part, and further analyses will be conducted as warranted to explore patients grouped by mutation/amplification status and tumor type.

Overall response rate (ORR) is defined as the proportion of patients who achieve a complete response or partial response. Depending on the histology, tumor responses will be measured and recorded using the appropriate guidelines (RECIST 1.1 [Eisenhauer et al. 2009], Revised Response Criteria for Malignant Lymphoma [Cheson et al. 2007], the Guidelines from the National Cancer Institute Working Group for CLL [Hallek et al. 2008], or RANO criteria for glioblastoma [Wen et al. 2010]).

For patients in study Part C, HCC patients from Part D, and leiomyosarcoma patients in Part F, ORR defined using the Choi criteria (Choi et al. 2007) will be considered for response evaluation in addition to RECIST criteria. Modified response criteria incorporating changes in tumor density in addition to tumor size has been demonstrated to be a more sensitive prognostic marker for time to progression and disease specific survival in GIST sarcomas (Benjamin et al. 2007; Choi et al. 2007).

For Part E, Part C, and F patients with sarcoma (leiomyosarcoma, GIST, liposarcoma, and angiosarcoma), and Part D patients with mature T cell, B cell, or NK cell neoplasms enrolled under amendment d, PET maximum standardized uptake values (SUVmax) will also be analyzed, and metabolic responses defined using PET response criteria of the European Organisation for Research and Treatment of Cancer (Young et al. 1999).

For the purposes of statistical analysis, subjects will be grouped by mutation and/or amplification, and by tumor type. Where there are a small number of subjects (<4) with a particular tumor type or mutation/amplification, subjects may be pooled with other small groups for statistical analysis purposes. Change in tumor size (and/or change in tumor density) will be assessed in each patient with measurable disease using radiographic imaging, and is defined as the fold change from the baseline evaluation to the evaluation at the end of Cycle 2. Statistical analyses may be conducted utilizing analysis of covariance models with potential covariates including baseline measurements, mutations/amplification group, tumor type, ECOG status and

other covariates as deemed appropriate. Logistic regression analyses will also be utilized to estimate the ORR for each grouping of patients. Further exploratory analyses may utilize a Bayesian hierarchical model in order to explore response rates across each tumor type. Descriptive analyses of duration of response, PFS, and OS will be conducted using the Kaplan-Meier method.

## 10.3. Interim Analyses

During Part A, patient safety will be assessed prior to each dose escalation to ensure nothing precludes administration of larger doses to future study patients. In addition to reviewing AEs and laboratory measurements, PK/PD profiles of LY3039478 will be reviewed per cohort. Based on these interim results, modifications (eg, reductions in dose increment) to the dose-escalation strategy or other design elements may be made to ensure patient safety. The study investigators and the Lilly CRP will make the determination regarding dose escalation based upon their review of the safety/tolerability data and the PK data from the previous cohorts. In addition, an interim review will be conducted prior to proceeding to Part B including safety, PK, and PD. All relevant data will be reviewed to confirm the estimation of the MTD. The decision to proceed to Part B will be made following discussions between the investigators and Lilly clinical research personnel.

# 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 submitted to the ERB and 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, and
- relevant curricula vitae

## 11.3. Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines

2) the ICH GCP Guideline [E6]

3) applicable laws and regulations

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

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

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

The sponsor's responsible medical officer 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.

# 12. References

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# Attachment 1. Protocol JJCA Study Schedule

### Baseline Assessments

| Relative Day Prior to Day 1 of Cycle 1 | ≤28 | ≤14 | ≤7 | Comments |
|---|---|---|---|---|
| Informed consent | X | | | Informed consent signed prior to performance of any protocol-specific tests/procedures. |
| Radiological tumor assessment | X | | | |
| PET scan | | X | | Optional[a] |
| DCE-MRI | | X | | Optional and not applicable for CLL patients |
| Medical history | | X | | Including alcohol/tobacco use and other relevant habits assessments |
| Physical examination | | X | | |
| Vital signs | | X | | Including temperature, blood pressure, pulse rate, respiration rate |
| Height | | X | | |
| ECOG performance status | | X | | |
| Chest x-ray | X | | | May be omitted in patients having a chest CT for their radiological tumor assessment |
| ECG | | X | | One set of triplicate ECGs, central |
| Hematology | | X | | Local laboratory, for CLL patients includes immunophenotyping (see Attachment 2). |
| Coagulation (PT/INR, aPTT, fibrinogen) | | X | | Local laboratory |
| Serum chemistry | | X | | Central laboratory |
| Urinalysis | | X | | Local laboratory |
| Child-Pugh, BCLC, and CLIP staging | | X | | Only for HCC patients in Part D (see Attachment 10, Attachment 11, and Attachment 12) |
| Tumor measurement (palpable or visible) | | X | | |
| CTCAE v 4.0 grading (preexisting conditions) | | X | | To be reported only after study eligibility is confirmed. See Section 8.1.2.2 for reporting expectations |
| Concomitant medications | | X | | |
| Tumor markers | | X | | If applicable, local laboratory |
| Blood PD biomarkers (A beta) | | X | | For Parts A and B only |
| Tumor biopsy[a] | X | | | |
| Screening for alterations of Notch pathway | X | | | Screening done locally, required only for Part B, D, and F expansion cohort patients. Performed at any time prior to ICF and study drug start. |
| Archived tumor sample | | | X | Paraffin-embedded tumor tissue, only after study eligibility is confirmed. |
| Pregnancy test | | | X | Negative results prior to dosing required for women of childbearing potential |
| Skin biopsy | | X | | |
| Marrow aspirate and biopsy, if clinically indicated | X | | | Only CLL patients, according to institutional guidelines, last results prior dosing |
| Cytogenetic tests (FISH) | X | | | Only CLL patients, if applicable, local laboratory |

Abbreviations: aPTT = activated partial thromboplastin time; BCLC= Barcelona Clinical Liver Classification Table; CLIP = Cancer of the Liver Italian Scoring System; CLL = Chronic Lymphocytic Leukemia; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization; HCC = hepatocellular carcinoma; Meds = medications; PD = pharmacodynamic; PET = positron emission tomography; PT/INR = prothrombin time/international normalized ratio.

a PET scan and tumor biopsy are mandatory for all patients in Part E, Part F, and LMS, GIST, liposarcoma, and angiosarcoma patients in Part C, and mature T cell, B cell, or NK cell neoplasm patients in Part D enrolled under Amendment d.

## During and Poststudy Assessments for Parts A, B, C, D, E, and F1

| Study Procedures | Cycle 1 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 | | | Week 2 | | | Week 3 | | | Week 4 | | |
| | Dose 1 | Dose 2 | Dose 3 | Dose 4 | Dose 5 | Dose 6 | Dose 7 | Dose 8 | Dose 9 | Dose 10 | Dose 11 | Dose 12 |
| LY3039478 therapy[a] | X | X | X | X | X | X | X | X | X | X | X | X |
| Prednisone therapy[p] | X | X | X | X | X | X | | | | | | |
| Physical examination | X | | | X | | | X | | | X | | |
| Vital signs and weight (temperature, pulse rate, blood pressure, respiratory rate) | X | | | X | | | X | | | X | | |
| ECOG performance status | X | | | X | | | X | | | X | | |
| CTCAE version 4.0 grading | | | | X | | | X | | | X | | |
| Concomitant medications | | | | X | | | X | | | X | | |
| Tumor measurement (palpable and visible) | | | | | | | | | | X | | |
| DCE-MRI (optional)[b] | | | | X | | | | | | | | |
| Central ECG[c] | X | | | | | | | | | | | |
| Hematology[d] | X | | | X | | | X | | | X | | |
| Serum chemistry[d] | X | | | X | | | X[e] | | | X | | |
| Serum creatinine[c, d] | X | | | | | | | | | | | |
| ECG chemistry[c, d] | X | | | | | | | | | | | |
| Coagulation (PT/INR, aPTT, fibrinogen)[d] | | | | X | | | X | | | X | | |
| Tumor marker[d] | | | | | | | | | | X | | |
| Pharmacogenetics sample (predose) | X | | | | | | | | | | | |
| Blood PK sampling[c] | X | | | | | | X[q] | | | X | | |
| Tumor biopsy[f] | | | | | | | | | | X | | |
| Skin biopsy[c, g] | X | | | | | | | | | | | |
| Blood PD biomarkers (A beta-Parts A and B only)[c] | X | | | | | | | | | X | | |
| Blood PD biomarkers (RBM, cytokeratin 18, epigenomics) predose | X | | | | | | | | | | | |
| Urine (8- to 10-hour collection)[c,h] | X | | | | | | | | | | | |

## During and Poststudy Assessments for Part F2

| Study Procedures | Cycle 1 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 | | Week 2 | | Week 3 | | | Week 4 | | |
| | Dose 1 | Dose 2 | Dose 3 | Dose 4 | Dose 5 | Dose 6 | Dose 7 | Dose 8 | Dose 9 | Dose 10 |
| LY3039478 therapy | X | X | X | X | X | X | X | X | X | X |
| Prednisone[p] | X | X | X | X | | | | | | |
| Physical examination | X | | X | | X | | | X | | |
| Vital signs and weight (temperature, pulse rate, blood pressure, respiratory rate) | X | | X | | X | | | X | | |
| ECOG performance status | X | | X | | X | | | X | | |
| CTCAE version 4.0 grading | | | X | | X | | | X | | |
| Concomitant medications | | | X | | X | | | X | | |
| Tumor measurement (palpable and visible) | | | | | | | | X | | |
| DCE-MRI (optional)[b] | | | X | | | | | | | |
| Central ECG[c] | X | | | | | | | | | |
| Hematology[d] | X | | X | | X | | | X | | |
| Serum chemistry[d] | X | | X | | X[e] | | | X | | |
| Serum creatinine[c, d] | X | | | | | | | | | |
| ECG chemistry[c, d] | X | | | | | | | | | |
| Coagulation (PT/INR, aPTT, fibrinogen)[d] | | | X | | X | | | X | | |
| Tumor marker[d] | | | | | | | | X | | |
| Pharmacogenetics sample (predose) | X | | | | | | | | | |
| Blood PK sampling[c] | X | | | | X[r] | | | X[s] | | |
| Tumor biopsy[f] | | | | | | | | X | | |
| Skin biopsy[c, g] | X | | | | | | | | | |
| Blood PD biomarkers (RBM, cytokeratin 18, epigenomics) predose | X | | | | | | | | | |

| Study Procedures | Cycle 2 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 | | | Week 2 | | | Week 3 | | | Week 4 | | |
| | Dose 1 | Dose 2 | Dose 3 | Dose 4 | Dose 5 | Dose 6 | Dose 7 | Dose 8 | Dose 9 | Dose 10 | Dose 11 | Dose 12 |
| LY3039478 therapy[a] | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical examination | X | | | | | | X | | | | | |
| Vital signs and weight (temperature, pulse rate, blood pressure, respiratory rate) | X | | | | | | X | | | | | |
| ECOG performance status | X | | | | | | X | | | | | |
| CTCAE version 4.0 grading | X | | | | | | X | | | | | |
| Concomitant medications | X | | | | | | X | | | | | |
| Tumor measurement (palpable and visible) | | | | | | | | | | X | | |
| ECG[c] | X | | | | | | | | | | | |
| Radiological tumor assessment[i] | | | | | | | | | | X | | |
| PET scan[j] | X | | | | | | | | | | | |
| Hematology[d] | X | | | | | | X | | | | | |
| For CLL patients only: Immunophenotyping as per institutional guidelines (at end of every 2 cycles) | | | | | | | | | | X | | |
| Serum chemistry[d] | X | | | | | | X | | | | | |
| ECG chemistry[c,d] predose | X | | | | | | | | | | | |
| Coagulation (PT/INR, aPTT, fibrinogen)[d] | X | | | | | | | | | X | | |
| Tumor marker[d] | | | | | | | | | | X | | |
| Blood PK sampling[c] predose | X | | | | | | | | | | | |
| Blood PD biomarkers (A–beta- Part A and B only)[c] predose | X | | | | | | | | | | | |
| Blood PD biomarkers (RBM, cytokeratin 18, epigenomics) predose | X | | | | | | | | | | | |

| Study Procedures | Cycle 3-n | | | | | | | | | | | | Visit 801 | Follow-up[k] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 | | | Week 2 | | | Week 3 | | | Week 4 | | | V801 | V802-XX |
| | Dose 1 | Dose 2 | Dose 3 | Dose 4 | Dose 5 | Dose 6 | Dose 7 | Dose 8 | Dose 9 | Dose 10 | Dose 11 | Dose 12 | | |
| LY3039478 therapy[a] | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Physical examination | X | | | | | | | | | | | | X | |
| Vital signs and weight (temperature, pulse rate, blood pressure, respiratory rate) | X | | | | | | | | | | | | X | |
| ECOG performance status | X | | | | | | | | | | | | X | X |
| CTCAE version 4.0 grading | X | | | | | | | | | | | | X | X[l] |
| Concomitant medications | X | | | | | | | | | | | | X[m] | X[m] |
| Tumor measurement (palpable and visible) | X | | | | | | | | | | | | | X[n] |
| Radiological tumor assessment | | | | | | | | | | X | | | | X[n] |
| Hematology[d] | X | | | | | | X | | | | | | X | |
| For CLL patients only: immunophenotyping as per institutional guidelines (at end of every 2 cycles) | | | | | | | | | | X | | | X | |
| Serum chemistry[d] | X | | | | | | X | | | | | | X | |
| Coagulation (PT/INR, aPTT, fibrinogen)[d] | X | | | | | | | | | | | | X | |
| Tumor marker[d] | X | | | | | | | | | | | | X | |
| Blood PD biomarkers (A –beta- Parts A and B only) predose | X | | | | | | | | | | | | | |
| Blood PD biomarkers (RBM, cytokeratin 18, epigenomics) predose | X | | | | | | | | | | | | | |
| Marrow aspirate and biopsy, if clinically indicated for CLL patients[o] | | | | | | | | | | | | | X | |

Abbreviations: aPTT = activated partial thromboplastin time; CLL= chronic lymphocytic leukemia; CTCAE = Common Terminology Criteria for Adverse Events; D = day; DCE-MRI= dynamic contrast-enhanced magnetic resonance imaging; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PK = pharmacokinetic; PD = pharmacodynamic; PET = positron emission tomography; PT/INR = prothrombin time/international normalized ratio; RBM = Rules-Based Medicine; V = visit.

a LY3039478 is to be administered 3 times per week through each 28-day cycle. If assessments associated with a dose cannot be performed, the assessments may be performed either with the previous dose (if known in advance) or the next dose. For start of Cycle 2 and beyond, refer to Section 7.2.1 and Section 7.2.4.1.2.

b DCE-MRI should be performed on a day when LY3039478 is given either at Dose 3, 4, or 5 and repeated at the discretion of the investigator. DCE-MRI is not applicable for CLL patients.

c For complete details, see Attachment 3.

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

e Only for patients with ≥Grade 2 nausea, vomiting, or diarrhea.

f Optional posttreatment tumor biopsy should be obtained (whenever clinically feasible) at Cycle 1, preferably 6 to 8 hours (±1 hour) after Dose 10. Greater flexibility has been provided for the posttreatment tumor biopsy (between Doses 7 and 12, inclusive) compared to other Dose 10 visit assessments (between Doses 9 and 11, inclusive) to enable radiographic guidance and access to appropriate medical specialists; however, if this flexibility is exercised and the posttreatment tumor biopsy is obtained on a day other than the 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 are mandatory for all patients in Part E, F, and LMS, GIST, liposarcoma, and angiosarcoma patients in Part C and mature T cell, B cell, or NK cell neoplasm patients in Part D enrolled under Amendment d.

g Skin biopsies are mandatory according to the schedule provided in Attachment 3. Additional optional skin biopsies may be performed at time of disease progression and if deemed necessary by the investigator.

h Part A only.

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

j Optional during Cycle 2 (not limited to Dose 1) repeated at the discretion of the investigator. Mandatory for all patients in Part E and LMS, GIST, liposarcoma, and angiosarcoma patients in Part C, and mature T cell, B cell, or NK cell neoplasm patients in Part D enrolled after Amendment d. Metabolic response by PET scan must be repeated for confirmation at least 4 weeks after initial response see Section 8.3.

k Long-term follow-up for survival applies to Part B, C, D, E, and F only.

l Collection of AEs and SAEs related to study treatment or study procedures only.

m collection of concomitant medication post-study treatment discontinuation must include any subsequent cancer treatment.

n Every 60 ( ±14) days and applies only to those patients who discontinue the study without progression or have not started another treatment regimen as outlined in Section 8.3.

o According to Guidelines from the National Cancer Institute Working Group for CLL, marrow aspirate and biopsy will be performed in CLL patients when a partial remission or complete remission is observed (to obtain bone marrow response information) and also 2 months after the last study drug treatment (to obtain duration of response). Institutional guidelines will be followed.

p Prednisone given during Cycle 1 daily on Days 1-14 in Study Part F only as described in Section 7.2.1.

q For Part C, D, E, and dose-expansion patients in Part F1.

r For Dose 5 in the dose-expansion part of F2 only.

s For Dose 8 in the dose-escalation part of F2 only.

## Continued Access Schedule of Activities

| Study Procedures[b] | Visit 501-n | | | | | | | | | | | | Follow-up[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 | | | Week 2 | | | Week 3 | | | Week 4 | | | 901 |
| | Dose 1 | Dose 2 | Dose 3 | Dose 4 | Dose 5 | Dose 6 | Dose 7 | Dose 8 | Dose 9 | Dose 10 | Dose 11 | Dose 12 | |
| LY3039478 therapy | X | X | X | X | X | X | X | X | X | X | X | X | |
| Hematology | X | | | | | | X | | | | | | |
| Serum chemistry | X | | | | | | X | | | | | | |
| Vital signs and weight (temperature, pulse rate, blood pressure, respiratory rate) | X | | | | | | | | | | | | |
| ECOG performance status | X | | | | | | | | | | | | |
| AE collection (CTCAE version 4.0) | X | | | | | | | | | | | | X |

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group.

[a] Continued access follow-up begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued-access period and lasts approximately 30 days. No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

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

# Attachment 2. Protocol JJCA Clinical Laboratory Tests

## Clinical Laboratory Tests

**Hematology[a]:**
Hemoglobin
Hematocrit
Erythrocyte count (RBC)
Leukocytes (WBC)
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils
Platelets
Reticulocytes[e]
Prolymphocytes[e]
Immunophenotyping, including B-cell lymphocytes and T-cell lymphocytes evaluation or based on institutional guidelines using for examples, CD5, CD19, CD20, CD23 and CD79b[e]

**Coagulation[a]:**
aPTT
PT/INR
Fibrinogen

**Urinalysis[a]:**
Specific gravity
pH
Protein
Glucose
Ketones
Blood
Urine leukocyte esterase

**Tumor markers[a]**

**Serum pregnancy test (females with child-bearing potential only)[a]**

**Biomarkers[b] (research laboratory tests)**

**Marrow aspirate and biopsy[e]**

**Cytogenetics (FISH)[e]**

**Clinical Chemistry[a,b]:**
Serum concentrations of:
Sodium
Potassium
Phosphorus
Total bilirubin
Alkaline phosphatase
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Gamma-glutamyl transpeptidase (GGT)
Blood urea nitrogen (BUN)
Creatinine
Lipase
LDH[e]
Uric acid
Calcium
Glucose random
Albumin
Total protein

**ECG Chemistry[b]:**
Lipase
Thyroid stimulating hormone (TSH)
Tri-iodothyronine (T3)
Thyroxine (T4)
Albumin[c]
Glucose, random[c]
Calcium[c]
Sodium[c]
Potassium[c]
Phosphorus
Magnesium
Serum creatinine[b,d]

Abbreviations: aPTT = activated partial thromboplastin time; ECG = electrocardiogram; FISH = fluorescence in situ hybridization; LDH = lactate dehydrogenase; PT/INR = international normalized ratio of prothrombin time; 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.

[e] Tests performed for CLL patients only and tests performed at local laboratory.

# Attachment 3. Protocol JJCA Pharmacokinetic and Pharmacodynamic Sampling Schedule

**Pharmacokinetic and Pharmacodynamic Sampling Schedule for Part A, 10 Patients in Part B, and Dose-Escalation Patients in Part F1**

| PK Sample Number | Dose Number | Cycle | PK Sampling Time for LY3039478[a] | Urine Sampling Part A Only[a] | Sampling Time for Serum Creatinine Part A Only | PD Sampling Time for Aβ (1-x) (Parts A and B only) | PD Sampling Time for Skin Biopsies | ECG with ECG Chemistry |
|---|---|---|---|---|---|---|---|---|
| 1 | Screening | 1 | | | Screening | Screening | Screening | |
| 2 | 1 | 1 | Predose | 0 to 8-10 hr pooled samples (end time of sample to coincide with PK blood draw) Record total volume | Predose | Predose | | Predose |
| 3 | 1 | 1 | 0.5 hr | | | | | |
| 4 | 1 | 1 | 1 hr | | 1 hr | | | |
| 5 | 1 | 1 | 2 hr | | | 2 hr | | |
| 6 | 1 | 1 | 4 hr | | 4 hr | 4 hr | | 4 hr |
| 7 | 1 | 1 | 6-8 hr | | | 6-8 hr | 6-8 hr (±1 hour) | |
| 8 | 1 | 1 | 8-10 hr | | 8-10 hr | 8-10 hr | | |
| 9 | 1 | 1 | 24-30 hr | | | 24-30 hr | | 24-30 hr |
| 10 | 10 | 1 | Predose | | | Predose | | |
| 11 | 10 | 1 | 0.5 hr | | | | | |
| 12 | 10 | 1 | 1 hr | | | | | |
| 13 | 10 | 1 | 2 hr | | | 2 hr | | |
| 14 | 10 | 1 | 4 hr | | | 4 hr | | |
| 15 | 10 | 1 | 6-8 hr | | | 6-8 hr | | |
| 16 | 10 | 1 | 8-10 hr | | | 8-10 hr | | |
| 17 | 10 | 1 | 24-30 hr | | | 24-30 hr | | |
| 18 | 1 | 2 | Predose | | | Predose | | Predose |

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

[a] All urine needs to 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 8). The collected urine needs to 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. Sample 1 for creatinine should not be frozen, but the two 10-mL samples (Samples 2 and 3) should be frozen at the end of the collection period and should be shipped frozen.

### Pharmacokinetic and Pharmacodynamic Sampling Schedule for Dose-Escalation Patients in Part F2

| PK Sample Number | Dose Number | Cycle | PK Sampling Time for LY3039478 | PD Sampling Time for Skin Biopsies | ECG with ECG Chemistry |
|---|---|---|---|---|---|
| 1 | Screening | 1 | | Screening | |
| 2 | 1 | 1 | Predose | | Predose |
| 3 | 1 | 1 | 0.5 hr | | |
| 4 | 1 | 1 | 1 hr | | |
| 5 | 1 | 1 | 2 hr | | |
| 6 | 1 | 1 | 4 hr | | 4 hr |
| 7 | 1 | 1 | 6-8 hr | 6-8 hr (±1 hour) | |
| 8 | 1 | 1 | 8-10 hr | | |
| 9 | 1 | 1 | 24-30 hr | | 24-30 hr |
| 10 | 8 | 1 | Predose | | |
| 11 | 8 | 1 | 0.5 hr | | |
| 12 | 8 | 1 | 1 hr | | |
| 13 | 8 | 1 | 2 hr | | |
| 14 | 8 | 1 | 4 hr | | |
| 15 | 8 | 1 | 6-8 hr | | |
| 16 | 8 | 1 | 8-10 hr | | |
| 17 | 8 | 1 | 24-30 hr | | |
| 18 | 1 | 2 | Predose | | Predose |

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

### Pharmacokinetic and Pharmacodynamic Sampling Schedule for the Remaining Patients in Part B Who Did Not Complete the Sampling Schedule for Part A

| PK Sample Number | Dose Number | Cycle | PK Sampling Time for LY3039478 | PD Sampling Time for Aβ (1-x) | PD Sampling Time for Skin Biopsies | ECG with ECG Chemistry |
|---|---|---|---|---|---|---|
| 1 | Screening | 1 | | Screening | Screening | |
| 2 | 1 | 1 | Predose | Predose | | Predose |
| 3 | 1 | 1 | 0.5 hr | | | |
| 4 | 1 | 1 | 1 hr | | | |
| 5 | 1 | 1 | 2 hr | 2 hr | | |
| 6 | 1 | 1 | 4 hr | 4 hr | | 4 hr |
| 7 | 1 | 1 | 6-8 hr | 6-8 hr | 6-8 hr (±1 hour) | |
| 8 | 1 | 2 | Predose | Predose | | Predose |

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

### Pharmacokinetic and Pharmacodynamic Sampling Schedule for Parts C, D, E, and Dose-Expansion Patients in Part F1

| Sample Number | Dose Number | Cycle | PK Sampling Time for LY3039478 | PD Sampling Time for Skin Biopsies | ECG with ECG Chemistry |
|---|---|---|---|---|---|
| 1 | Screening | 1 | | Screening | |
| 2 | 1 | 1 | Predose | | Predose |
| 3 | 1 | 1 | 1-3 hr | | 2 hr |
| 4 | 1 | 1 | 4 hr | | |
| 5 | 1 | 1 | 6-8 hr | 6-8 hr (±1 hour) | |
| 6 | 7 | 1 | Predose | | |
| 7 | 1 | 2 | Predose | | Predose |

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

### Pharmacokinetic and Pharmacodynamic Sampling Schedule for Dose-Expansion Patients in Part F2

| Sample Number | Dose Number | Cycle | PK Sampling Time for LY3039478 | PD Sampling Time for Skin Biopsies | ECG with ECG Chemistry |
|---|---|---|---|---|---|
| 1 | Screening | 1 | | Screening | |
| 2 | 1 | 1 | Predose | | Predose |
| 3 | 1 | 1 | 1-3 hr | | 2 hr |
| 4 | 1 | 1 | 4 hr | | |
| 5 | 1 | 1 | 6-8 hr | 6-8 hr (±1 hour) | |
| 6 | 5 | 1 | Predose | | |
| 7 | 1 | 2 | Predose | | Predose |

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

# Attachment 4. Protocol JJCA Recommendations for Reporting Serious Adverse Events

**Recommendations for Reporting Serious Adverse Events**

When contacting Lilly to report a serious adverse event (SAE), please have the following information available:

**Patient Demographics**

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

**Study Identification**

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

**Study Drug**

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

**Adverse Event**

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

**Relationship to Study Drug & Protocol Procedures**

**Concomitant Drug Therapy**

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

**In Case of Death**

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

# Attachment 5. Protocol JJCA Eastern Cooperative Oncology Group Performance Status

### Eastern Cooperative Oncology Group 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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours |
| **3** | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours |
| **4** | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair |
| **5** | Dead |

Reference:

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-655.

# Attachment 6. Protocol JJCA Creatinine Clearance Formula

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

*For serum creatinine concentration in mg/dL:*

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

*For serum creatinine concentration in μmol/L:*

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

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

Reference:

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

**-OR-**

$$GFR(mL/min/1.73m^2) = 170 \times [PCr]^{-0.999} \times [age]^{-0.176}$$

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

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

PCr= Plasma Creatinine, mg/dL; SUN= Serum urea nitrogen, mg/dL; Alb= Serum albumin, g/dL

Reference:

Murray PT, Ratain MJ. Estimation of the glomerular filtration rate in cancer patients: a new formula for new drugs. *Clin Oncol*. 2003 Jul 15;21(14):2633-5.

# Attachment 7. Protocol JJCA Sampling Summary

This table summarizes the maximum number of samples and volumes for all sampling and tests during the study. Fewer samples may actually be taken, but this will not require a protocol amendment.

### Protocol I6F-MC-JJCA Sampling Summary

| Purpose | Sample Type | Average Amount per Sample | Maximum Number Samples | Maximum Total Amount |
|---|---|---|---|---|
| Screening tests[a] | Blood | 4 mL | 5 | 20 mL |
| Screening tests [a] | Urine | 10 mL | 1 | 10 mL |
| Standard tests[a] **V001 Cycle 1** | Blood | 4 mL | 13 | 52 mL |
| Standard tests[a] **V002 Cycle 2** | Blood | 4 mL | 7 | 28 mL |
| Standard tests[a] **V003 Cycle 3-n** | Blood | 4 mL | 5 | 20 mL |
| Standard tests[a] **Follow-Up** | Blood | 4 ml | 4 | 16 mL |
| Cardiac and renal [a] | Blood | 12 mL | 4 | 48 mL |
| Drug concentration | Blood | 2 mL | 35 | 70 mL |
| Drug concentration | Urine | 10 mL | 3 | 30 mL |
| Pharmacogenetic samples | Blood | 10 mL | 1 | 10 mL |
| Nonpharmacogenomic biomarkers | Blood | 4 mL | 6 | 24 mL |
| Skin biopsies | Tissue Biopsy | 5 mm, 0.5 oz, 1 cubic centimeter | 2 | 10 mm 1.0 oz 2 cc |
| Tumor biopsies (optional) | Tissue Biopsy | 5 mm, 0.5 oz, 1 cubic centimeter | 2 | 10 mm 1.0 oz 2 cc |
| Total | **Urine** | | | 40 mL |
| Total | **Tissue** | | | 20 mm 2.0 oz 4 cc |
| Total | **Blood** | | | 288 mL |

Abbreviations: V = visit.

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

# Attachment 8. Protocol JJCA Guidance on Alterations Related to Notch Pathway

**Mutations**

Notch-1

Notch-2

Notch-3

Notch-4

FBXW7

**Amplifications**

Notch-1

Notch-2

Notch-3

Jagged-1

Jagged-2

**Gene and Protein Overexpression**

Notch receptors

Notch ligands

NICD (by IHC)

# Attachment 9. Protocol JJCA 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, 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 will be treated with standard loperamide (initial administration 4 mg, then 2 mg every 4 hours [up to a maximum of 16 mg/day] or after each unformed stool).

**After 12 to 24 hours:**

Diarrhea resolved

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

Diarrhea unresolved

Persisting diarrhea Grade 1 or 2 will be treated with addition of opium tincture or dihydrocodeine tartrate tablets/injections, with monitoring of patient's condition (to rule out dehydration, sepsis, or ileus) and medical check and selected workup if patient does

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

**After 12 to 24 hours:**

Diarrhea resolved

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

Diarrhea unresolved

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

**Treatment of diarrhea Grade 3 or 4**

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

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

**After 12 to 24 hours:**

- If diarrhea is still persisting, administer subcutaneous (SC) Sandostatin/octreotide (100 to 500 μg 3 times per day [TID]).
- Continue IV fluids and antibiotics as needed.
- If diarrhea Grade 3 or 4 is still persisting, patients should receive opium tincture or dihydrocodeine tartrate injections SC or intramuscular (IM).
- If diarrhea Grade 3 or 4 is still persisting, SC Sandostatin/octreotide (500 to 1000 μg 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

**Reference**

Fine KD, Schiller LR. AGA Technical Review on the Evaluation and Management of Chronic Diarrhea. *Gastroenterology.* 1999; 116:1464-1486.

# Attachment 10. Protocol JJCA Child-Pugh Score

## Child-Pugh Score

| Clinical and Biochemical Parameters | Points[a] | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Bilirubin (mg/dL) | <2 | 2-3 | >3 |
| Albumin (g/dL | >3.5 | 2.8-3.5 | <2.8 |
| Ascites | Absent | Moderate | Tense |
| Encephalopathy | Absent | Moderate (Stage I-II) | Severe (Stage III-IV) |
| Prothrombin time | | | |
| Sec prolonged | <4 | 4-6 | >6 |
| % | >60 | 40-60 | <40 |
| INR[b] | <1.7 | 1.7-2.3 | >2.3 |
| In case of primary biliary cirrhosis | | | |
| | 1 | 2 | 3 |
| Bilirubin (mg/dL) | <4 | 4-10 | >10 |

Note: This table applies to hepatocellular carcinoma (HCC) patients only.

Abbreviations: INR = international normalized ratio; Sec = second.

a Total points: 5 to 6: Child-Pugh class A; 7 to 9: Child-Pugh class B; 10 to 15: Child-Pugh class C.

b INR is an expression of prothrombin time, corrected by the sensitivity of the reactiveness to anticoagulants, and should be validated as an alternative to prothrombin time in liver insufficiency.

Source: Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973;60(8):646-649.

# Attachment 11. Protocol JJCA Barcelona Clinic Liver Cancer Classification Table

**Barcelona Clinic Liver Classification Table**

| Stage | Performance Status Test | Tumor Stage | Okuda Stage | Liver Function Status |
|---|---|---|---|---|
| A | 0 | Single | I-II | Child-Pugh A-B |
| B | 0 | Large multinodular | I-II | Child-Pugh A-B |
| C | 1-2 | Vascular invasion/ extrahepatic spread | I-II | Child-Pugh A-B |
| D | 3-4 | Any | III | Child-Pugh C |

Note: This table applies to hepatocellular carcinoma (HCC) patients only. Stage A and B, all criteria should be fulfilled; Stage C and D, at least 1 criterion should be fulfilled.

Source: Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet*. 2003;362(9399):1907-1917.

# Attachment 12. Protocol JJCA Cancer of the Liver Italian Program Scoring System

**CLIP Scoring System**

| Variable | Score |
|---|---|
| Child-Pugh stage | |
| A | 0 |
| B | 1 |
| C | 2 |
| Tumor morphology | |
| Uninodular and extension ≤50% | 0 |
| Multinodular and extension ≤50% | 1 |
| Massive or extension >50% | 2 |
| AFP | |
| <400 | 0 |
| ≥400 | 1 |
| Portal vein thrombosis | |
| No | 0 |
| Yes | 1 |

Note: This table applies to hepatocellular carcinoma (HCC) patients only.
Abbreviations: AFP = alpha-fetoprotein; CLIP = Cancer of the Liver Italian Program.
Source: The Cancer of the Liver Italian Program (CLIP) Investigators. *Hepatology*. 2000;31(4):840-845

# Attachment 13. Protocol JJCA Protocol Amendment I6F-MC-JJCA(e) Summary A Phase 1 Study of LY3039478 in Patients with Advanced or Metastatic Cancer

## Overview

Protocol I6F-MC-JJCA, A Phase 1 Study of LY3039478 in Patients with Advanced or Metastatic Cancer, has been amended. The new protocol is indicated by Amendment (e) and will be used to conduct the study in place of any preceding version of the protocol.

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

- the addition of Study Part F to explore 2 alternative dosing schedules
- the addition of a continued-access period
- Minor editorial changes were made for clarity and consistency.

## Revised Protocol Sections

| | |
|---|---|
| **Note:** | All deletions have been identified by ~~strikethroughs~~.<br>All additions have been identified by the use of underscore. |

**Clinical Protocol Synopsis: Study I6F-MC-JJCA**

| | |
|---|---|
| **Name of Investigational Product:** LY3039478 | |
| **Title of Study:** A Phase 1 Study of LY3039478 in Patients with Advanced or Metastatic Cancer | |
| **Number of Planned Patients:** Total study sample size will be approximately ~~227~~282 patients, with approximately 55 patients in Part A and approximately ~~172~~227 patients in Parts B, C, D, ~~and~~ E, and F. | **Phase of Development:** 1 |
| **Length of Study:**<br>Planned first patient visit: September 2012 Planned last patient visit: December 2017 | |
| **Objectives:**<br>**Primary:** Part A: The primary objective of this study is to determine a recommended Phase 2 dose of LY3039478 that may be safely administered to patients with advanced or metastatic cancer.<br>Parts B, C, D, and E: The primary objectives are to confirm the recommended Phase 2 dose of LY3039478 that may be safely administered to patients with specific tumor types and to document antitumor activity.<br>Part F: The primary objective is to determine a recommended Phase 2 dose of LY3039478 that may be safely administered to patients according to 2 alternative dosing schedules with co-administration of prednisone and to document antitumor activity.<br>**Secondary:**<br>• To characterize the safety and toxicity profile of LY3039478 as assessed by National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.0<br>• To estimate the pharmacokinetic (PK) parameters of LY3039478<br>• Part A: To document any antitumor activity observed with LY3039478<br>• Parts B, C, D, ~~and~~ E, and F: To assess duration of response, progression-free survival (PFS), and overall survival (OS)<br>**Exploratory:**<br>• To explore renal clearance of LY3039478 and PK of LY3039478 metabolites in plasma and urine<br>• To explore predictive biomarkers related to LY3039478<br>• To explore pharmacodynamic (PD) effects of LY3039478 on biomarkers indicative of Notch activity (Notch intracellular domain by immunohistochemistry or an alternative validated method) including cytokeratin 18 or Rules-Based Medicine<br>• To explore the utility of positron emission tomography scan to assess treatment effect with LY3039478<br>• To explore the utility of dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) to assess treatment effect with LY3039478 | |
| **Study Design:** Phase 1, multicenter, nonrandomized, open-label, dose-escalation study followed by cohort expansion (Parts B, C, D, ~~and~~E, and F) of oral LY3039478 in outpatients with advanced or metastatic cancer. | |
| **Diagnosis and Main Criteria for Inclusion and Exclusions:** Men and women, aged ≥18 years, having advanced or metastatic cancer (solid tumor or lymphoma including chronic lymphocytic leukemia [CLL]) for which available standard therapies have failed. For Part B, patients must have prescreened alterations in the Notch pathway such as mutations, amplification, or gene expressions related to Notch pathway. Part C patients must have histological evidence of advanced or metastatic soft tissue sarcomas. Part D patients must have advanced or metastatic cancer with specific tumor types harboring Notch molecular alterations including triple-negative breast cancer (ER-, PR-, HER2-), cholangiocarcinoma, hepatocellular carcinoma (HCC), CLL, and mature T cell, B cell, or Natural Killer (NK) cell neoplasms. Part E patients must have advanced or metastatic adenoid cystic carcinoma (ACC). Part F patients in the dose confirmation must have histological evidence of nonresectable or metastatic leiomyosarcoma with prescreened alterations in the Notch pathway such as mutations, amplification, or gene expressions related to Notch pathway. | |

| |
|---|
| **Test Product, Dosage, and Mode of Administration:** LY3039478, dose range 2.5 to 100 mg, given orally as capsules 3 times per week during a 28-day cycle. In Study Part F, dosing schedules will utilize a loading dose (starting at 75 mg and escalating up to 150 mg) administered 3 times per week for 2 weeks during Cycle 1 (schedule F1) or 2 times per week for 2 weeks during Cycle 1 (schedule F2), followed by 50 mg 3 times per week (TIW) from Week 3 onwards. In Study Parts F1 and F2, prednisone will be co-administered for 2 weeks in Cycle 1. |
| **Planned Duration of Treatment:** Patients will receive 2 cycles (28 days each) of LY3039478 unless 1 or more of the criteria for discontinuation are fulfilled. In Study Parts F1 and F2, prednisone will be co-administered with LY3039478 for 2 weeks in Cycle 1. A patient may receive >2 cycles of treatment only if: 1) none of the criteria for discontinuation have been fulfilled and 2) the investigator determines that the patient is experiencing clinical benefit from treatment.<br>Short-term follow-up period (postdiscontinuation): 30 days<br>Long-term follow-up period (postdiscontinuation): after the short-term follow-up through death or study closure.<br>Continued-access period: All patients remaining on study treatment without disease progression following the final analysis will be able to enter the continued-access period of the study, which begins approximately 12 months after the last patient was enrolled and ends after the last patient discontinues study treatment and performs safety follow-up visit. |
| **Criteria for Evaluation:**<br>Safety: NCI CTCAE, version 4.0, dose-limiting toxicities (DLT)<br>Bioanalytical: Plasma concentrations of LY3039478<br>Efficacy: Depending on the histology, efficacy will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for solid tumors (along with the Choi criteria for soft tissue sarcomas and HCC), the Revised Response Criteria for Malignant Lymphoma, the Guidelines from the National Cancer Institute Working Group for CLL, or the Response Assessment in Neuro-Oncology (RANO) criteria for glioblastoma. |
| **Statistical Methods:**<br>Safety: Dose escalation will be driven by safety using the 3+3 method. Model-based analyses that incorporate prior expectations about the dose-toxicity curve will be fitted to the data at the end of each cohort, which will be used by the investigators and the Eli Lilly and Company (Lilly) clinical research physician to determine the next dose level. The maximum tolerated dose is defined as the highest tested dose that has <33% probability of causing a DLT during Cycle 1.<br>Efficacy: Tumor response data will be tabulated and summarized by study part. For the purposes of statistical analysis, subjects will be grouped by mutation and/or amplification, and by tumor type. Change in tumor size (and/or change in tumor density) will be analyzed by analysis of covariance models with potential covariates including baseline measurements, mutations/amplification group, tumor type, Eastern Cooperative Oncology Group performance status, and other covariates as deemed appropriate. Logistic regression analyses will also be utilized to estimate the overall response rate for each grouping of patients. Descriptive analyses of duration of response, PFS, and OS will be conducted using the Kaplan-Meier method.<br>Pharmacokinetics: PK parameters for LY3039478 will be analyzed by standard non-compartmental methods of analysis.<br>Pharmacodynamics: All PD data will be assessed. Exploratory PK/PD analyses may be conducted to identify the exposure-biomarker response relationship. |

## 4.0 Abbreviations and Definitions

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| | |
|---|---|
| **DLET** | dose-limiting equivalent toxicity |

...

5.2.1. Primary Objective

…

Part F: The primary objective is to determine a recommended Phase 2 dose of LY3039478 that may be safely administered to patients according to 2 alternative dosing schedules with co-administration of prednisone and to document antitumor activity.

5.2.2. Secondary Objectives

The secondary objectives of this study are:

- •to characterize the safety and toxicity profile of LY3039478 as assessed by National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v 4.0
- •to estimate the pharmacokinetic (PK) parameters of LY3039478
- •Part A: to document any antitumor activity observed with LY3039478
- •Parts B, C, D, ~~and~~E, and F: to assess duration of response, progression-free survival (PFS) and overall survival (OS)

…

5.3.4. Biomarkers

As part of an ongoing effort by Lilly to better understand how to predict which tumors are more likely to respond to LY3039478 treatment, the collection of samples to be stored for possible future biomarker research are a mandatory part of this study.

Biomarkers will be used to assess not only PD response to LY3039478 in plasma, surrogate tissues, and tumors, but also potential predictive markers of efficacy and/or patient tailoring.

In Parts B, ~~and~~D, and the Part F dose confirmation, patients will be entered based on screened molecular alteration related to Notch pathway.

PD 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 during dose escalation and dose confirmation (Parts A, B, C, D, ~~and~~E, and F). Potential predictive biomarkers will be measured (when the assays become available) 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 during dose confirmation.

…

5.4.3. Rationale for (Amendment E)

As of November 2015, approximately 40 patients have been treated at 75 mg TIW and 62 patients have been treated at 50 mg TIW. Review of safety data (treatment emergent adverse events, dose-limiting equivalent toxicities, and dose reductions) confirmed the 50-mg TIW schedule to be adequately tolerated. Initial observations of metabolic responses were observed in patients treated at 100 mg, 75 mg, and 50 mg with exploratory analyses suggestive of a potential relationship to dose.

Study Part F will be added in order to explore 2 alternative dosing schedules allowing a loading dose for 2 weeks in Cycle 1, followed by the current 50-mg TIW schedule. Prednisone will be co-administered with LY3039478 during the loading dose period in order to mitigate potential GI toxicity. Study Part F dose confirmation will enroll patients with histologic evidence of advanced or metastatic leiomyosarcoma with Notch molecular alterations in order to allow a homogeneous population to further characterize the clinical activity of LY3039478.

In addition, a continued-access period was added to the protocol for patients who are benefitting from treatment after final database lock has occurred. Minor editorial changes and clarifications have also been made.

6.1.1. Inclusion Criteria

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

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

For Dose Escalation (Part A): The patient must have histological or cytological evidence of cancer, either a solid tumor or a lymphoma, which is advanced or metastatic.

For Part B: All patients must have histological evidence of their advanced or metastatic cancer and prescreened alterations in the Notch pathway such as mutations, amplification, or gene expressions related to Notch pathway (Attachment 8).

For Part C: All patients must have histological evidence of advanced or metastatic soft tissue sarcoma. Eligible patients must have leiomyosarcoma, angiosarcoma, rhabdomyosarcoma, liposarcoma, pleomorphic sarcoma, or GIST.

For Part D: All patients must have histological evidence of advanced or metastatic cancer and prescreened alterations in the Notch pathway such as mutations, amplification, or gene expressions related to Notch (Attachment 8).

- Cohort 1: Patients must have triple-negative breast cancer (ER-, PR-, HER2-).
- Cohort 2: Patients must have HCC. These patients should have Child-Pugh stage A (Attachment 10).
- Cohort 3: Patients must have cholangiocarcinoma.

- Cohort 4: Patients must have CLL.
- Cohort 5: Patients must have mature T cell, B cell, or Natural Killer (NK) cell neoplasms

For Part E: All patients must have histological evidence of advanced or metastatic adenoid cystic carcinoma (ACC).

For Part F: All patients must have:

Dose Escalation: histological or cytological evidence of cancer, either a solid tumor or a lymphoma, which is advanced or metastatic.

Dose Confirmation: histological evidence of nonresectable or metastatic leiomyosarcoma and prescreened alterations in the Notch pathway such as mutations, amplification, or gene expressions related to Notch pathway (Attachment 8).

[2] As defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1; Eisenhauer et al. 2009), the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007), the Guidelines from the National Cancer Institute Working Group for CLL (Hallek et al. 2008), the Response Assessment in Neuro Oncology (RANO) criteria for glioblastoma (Wen et al. 2010).

For Dose Escalation (Part A): Have measurable or nonmeasurable disease

For Parts B, C, D, ~~and~~E, and F: Have measurable disease or reliable biomarker measure (for example, prostate-specific antigen [PSA], CA125)

...

[10] Females with childbearing potential must have a negative serum pregnancy test within 7 days of the first dose of study drug ~~and also must not be breastfeeding.~~

...

[21] For Parts B, C, D, ~~and~~E, and F: Have available tumor tissue (archival or new biopsy)

...

6.2. Summary of Study Design

Study JJCA is a multicenter, nonrandomized, open-label, dose-escalation Phase 1 study of oral LY3039478 in patients with advanced or metastatic cancer. In Study Parts A, B, C, D, and E, ~~E~~eligible patients will receive LY3039478 administered orally TIW during a 28-day cycle. In Study Part F, eligible patients will receive LY3039478 administered orally during a 28-day cycle, according to 2 alternative dosing schedules, with co-administration of prednisone for 2 weeks in Cycle 1.

Patients will receive 2 cycles of LY3039478 unless 1 or more of the criteria for discontinuation (refer to Section 6.3.1) are fulfilled. A patient may receive >2 cycles of treatment only if: 1)

none of the criteria for discontinuation have been fulfilled and 2) the investigator determines that the patient is experiencing clinical benefit from treatment. The follow-up period for poststudy evaluation will be 30 days from the date of the last dose of study drug received.

The study design consists of a dose-escalation phase (Part A), ~~and~~ a cohort-expansion phase (Parts B, C, D, and E), and a dose-escalation phase with alternative dosing schedules followed by a cohort-expansion phase (Part F).

…

Part B ~~will focus~~ focused on approximately 50 patients with tumors that have molecularly defined mutations, amplification, or gene expressions alterations related to Notch pathway or known activated Notch pathways.

Part C ~~will focus~~ focused on approximately 65 patients with soft tissue sarcoma including patients with leiomyosarcoma (approximately 25), angiosarcoma (approximately 10), rhabdomyosarcoma (approximately 5), liposarcoma (approximately 10), pleomorphic sarcoma (approximately 5), and GIST (approximately 10).

Part D ~~will focus~~ focused on approximately 42 patients with specific tumor types harboring Notch molecular alterations, including patients with triple negative breast cancer (ER-, PR-, HER2-) (approximately 8), cholangiocarcinoma (approximately 8), HCC (approximately 8), CLL (approximately 8), and mature T cell, B cell, or NK cell neoplasms (approximately 10).

Part E ~~will focus~~ focused on approximately 15 patients with adenoid cystic carcinoma.

Part F will focus on approximately 55 patients with histologic evidence of advanced or metastatic cancer with expansion cohorts in patients with leiomyosarcoma and prescreened alterations in the Notch pathway. Approximately 10 to 15 patients will be treated in a dose-escalation phase and approximately 15 patients in a cohort-expansion phase at the recommended Phase 2 dose according to the following 2 dosing schedules, to be conducted concurrently.

F1: Dose escalation of a loading dose TIW for 2 weeks in Cycle 1 only followed by 50 mg TIW. Prednisone will be co-administered with LY3039478 for the first 2 weeks in Cycle 1 only.

F2: Dose escalation of a loading dose twice a week for 2 weeks in Cycle 1 only followed by 50 mg TIW. Prednisone will be co-administered with LY3039478 for the first 2 weeks in Cycle 1 only.

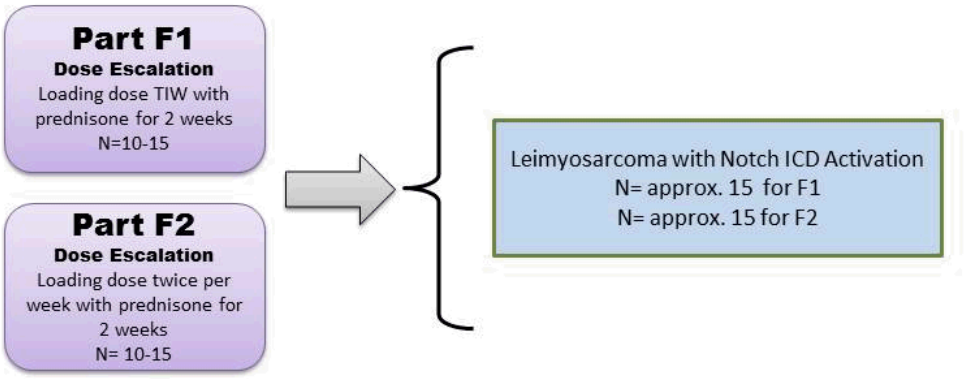
The total sample size for Parts A, B, C, D, ~~and~~E, and F is estimated to be approximately ~~227~~282 patients. Further expansion is possible following the analysis of outcome.

…

This study will be considered closed approximately 12 months from the date that the last patient was enrolled. Patients who are benefitting from treatment may continue to receive study drug for long-term durations, even after the study has closed and final database lock has occurred in the continued-access period. ~~In such cases, the sponsor may amend the protocol to allow for a safety~~

~~extension to follow such patients after the end of the trial or may open a substudy which would be defined in a subsequent amendment.~~

…




Abbreviations: approx = approximately; CLL= Chronic lymphocytic leukemia; GIST = gastrointestinal stromal tumors; ICD = intercellular domain; NK= natural killer; TIW = 3 times per week.

6.2.1. Continued-Access Period

All patients remaining on study treatment without disease progression following the final analysis will be able to enter the continued-access period of the study, which begins approximately 12 months after the last patient was enrolled, and ends after the last patient discontinued study treatment and performs safety follow-up visit. During the continued-access period, patients on study treatment who continue to experience clinical benefit may continue to receive study treatment until they meet discontinuation criteria. The continued-access period includes a follow-up visit. The follow-up visit begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued-access period and lasts approximately 30 days. If it is deemed to be in the best interest of the patient to start a new anticancer treatment prior to the scheduled end of the follow-up visit, the follow-up visit duration may be shortened. In this case, the follow-up assessments should be completed prior to the initiation of the new therapy.

During the continued-access period, all AEs, SAEs, dose reductions, and study drug exposure will be collected on the case report form/electronic case report form (CRF/eCRF).

SAEs will also be reported to Lilly Global Patient Safety and collected in the Lilly Safety System (LSS). In the event that an SAE occurs, additional information (such as local laboratory results, concomitant medications, and hospitalizations) may be requested by Lilly in order to evaluate the reported SAE.

Investigators may perform other standard procedures and tests needed to treat and evaluate patients; however, Lilly will not routinely collect the results of these assessments. The Study Schedule (Attachment 1) describes all assessments for the continued-access period.

7.1. Materials and Supplies

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

Prednisone will either be provided by Lilly or obtained locally as appropriate and required.

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

...

7.2.1. Dosing Schedule

…

For Study Part F1, LY3039478 will be administered orally TIW following 1 of these schedules (decision at investigator's discretion):

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

For Study Part F2, LY3039478 will be administered orally twice a week for 2 weeks in Cycle 1, followed by TIW dosing, following 1 of these schedules (decision at investigator's discretion):

- For Cycle 1: Monday and Friday for Weeks 1 and 2, followed by Monday, Wednesday, Friday for Weeks 3 and 4. For Cycle 2 and beyond: Monday, Wednesday, and Friday every week for a 28-day cycle.
- For Cycle 1: Tuesday and Saturday for Weeks 1 and 2, followed by Tuesday, Thursday, Saturday for Weeks 3 and 4. For Cycle 2 and beyond: Tuesday, Thursday, Saturday every week for a 28-day cycle.
- For Cycle 1: Wednesday and Sunday for Weeks 1 and 2, followed by Wednesday, Friday, Sunday for Weeks 3 and 4. For Cycle 2 and beyond: Wednesday, Friday, Sunday every week for a 28-day cycle.
- For Cycle 1: Thursday and Monday for Weeks 1 and 2, followed by Thursday, Saturday, Monday for Weeks 3 and 4. For Cycle 2 and beyond: Thursday, Saturday, Monday every week for a 28-day cycle.

…

Prednisone will be administered daily on Days 1 through 14 during Cycle 1 (Part F) at the dosage of 20 mg.

…

7.2.2.2. Criteria for Dose Escalation

…

Table JJCA.7.1 shows the proposed dose levels for the Part A dose-escalation portion with the predicted simulated exposure for LY3039478.

**Table JJCA.7.1. Proposed LY3039478 Dose-Escalation Scheme for Study I6F MC JJCA and Predicted Human Exposure- Part A**

| Dose Level | LY3039478 Dose (mg) | Predicted Median $AUC_{0-\tau,ss}$ (ng·h/mL) | Predicted 5th and 95th percentiles $AUC_{\tau,ss}$ (ng·h/mL) |
|---|---|---|---|
| -1[a] | 1.25 | 54.9 | 29.2 – 95.9 |
| 1 | 2.5 | 112 | 60.9 – 193 |
| 2 | 5 | 229 | 114 – 393 |
| 3 | 10 | 433 | 233 – 768 |
| 4 | 20 | 882 | 494 – 1600 |
| 5 | 30 | 1320 | 725 – 2290 |
| 6 | 45 | 1990 | 1080 – 3450 |
| 7 | 60 | 2620 | 1440 – 4700 |
| 8 | 80 | 3450 | 1890 – 6260 |
| 9 | 100 | 4400 | 2310 – 7650 |

…

Table JJCA.7.2 shows the proposed dose levels for the Part F dose escalation.

**Table JJCA.7.2. Proposed LY3039478 Dose-Escalation Scheme for Study I6F MC JJCA and Predicted Human Exposure- Part F**

| Dose Level | LY3039478 Loading Dose (mg) |
|---|---|
| 1 | 75 |
| 2 | 100 |
| 3 | 125 |
| 4 | 150 |

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis until the MTD is determined, as defined in Section 7.2.2.3. If the MTD has not yet been achieved at the highest prespecified dose level ~~(100 mg),~~ based on both safety and the available PK data, following discussion with investigators, ~~the following additional dose levels may be investigated: 120 mg, 140 mg, and 160 mg (Intermediate doses may be explored as previously described in the protocol)~~additional dose levels may be investigated.

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

DLT is defined as an AE during Cycle 1 that is related to ~~the study drugs~~ LY3039478 and fulfills any 1 of the following criterion using the NCI CTCAE v 4.0:

…

7.2.3. Cohort-Expansion Phase

Once the MTD has been defined, the cohort-expansion phase (Parts B, C, D, ~~and~~ E, and F) will be opened. Part B will consist of up to 50 additional evaluable patients with molecularly defined mutations, amplification, or gene expressions related to Notch pathway. Part C will consist of approximately 65 patients with soft tissue sarcomas. Part D will consist of approximately 42 patients with specific tumor types that have molecularly defined mutations, amplification, or gene expressions related to Notch pathway. Part E will consist of approximately 15 patients with adenoid cystic carcinoma.

The dose studied in Parts B, C, D, and E was defined at the end of dose escalation after a safety, PK, and PD review. The current dose is 50 mg TIW.

Part F will explore 2 alternate dosing schedules, and once an MTD has been defined for each of these alternate schedules, a cohort expansion in approximately 15 leiomyosarcoma patients with alterations in the Notch pathway such as mutations, amplification, or gene expressions related to Notch pathway will be opened for each dosing schedule.

…

7.2.4.1.1. Dose Adjustments within a Cycle

No dose adjustments will be allowed within a cycle. If a patient treated at a given dose level experiences a DLT or a DLT-equivalent toxicity (DLET) (as defined in Section 7.2.2.3), then treatment will be suspended for that patient for the duration of the current cycle. If a toxicity does not meet the criteria for a DLT in Cycle 1 (or a ~~DLT-equivalent toxicity~~ DLET) but nonetheless requires omission of dose(s) for tolerability, then dosing may resume at the same dose after the toxicity resolves to baseline; however, the dose(s) omitted for tolerability during a cycle will not be replaced.

7.2.4.1.2. Dose Adjustments between Cycles

…

For such patients requiring a dose reduction, re-escalation to the original dose level is not permitted. If a patient experiences a DLT-equivalent toxicity at the reduced dose level, then the patient will be discontinued from the study. If a patient requires omission of >3 doses for tolerability at the reduced dose level, then treatment may continue if the investigator determines that the patient is receiving clinical benefit. Dose reduction by ~~>~~≥2 dose levels is not permitted, so patients requiring dose reduction by >1 dose level should be discontinued from the study.

…

7.2.4.2.2 Dose Adjustments between Cycles

…

- ~~If dosing is delayed for >3 weeks for treatment-related AEs, the patient should be withdrawn from the study treatment.~~

…

7.2.4.3. Part F

7.2.4.3.1. Dose Adjustments within a Cycle

If a patient experiences a DLT or a DLET (as defined in Section 7.2.2.3), then treatment should be suspended for that patient. If a toxicity does not meet the criteria for a DLT or DLET but nonetheless requires omission of dose(s) for tolerability, then dosing may resume at the same dose after the toxicity resolves to baseline; however, the dose(s) omitted for tolerability during a cycle will not be replaced.

In either case, depending on the toxicities and whether the patient benefits from the treatment, dosing may resume at the given dose or a reduced dose and with or without allowed concomitant medication after consultation with the Lilly CRP.

7.2.4.3.2. Dose Adjustments between Cycles

- Nonhematologic toxicity must resolve to CTCAE Grade 0, 1, or baseline level before resuming treatment (with the exception of alopecia, fatigue, skin rash, nausea, vomiting, constipation, or diarrhea that can be controlled with treatment).
- Hematologic toxicity must resolve to a level that, in the opinion of the investigator, is reasonable to allow for continuation of treatment.
- Patients who experience a DLET or do not recover from toxicity within the 3-week time frame may have the dosage reduced to the previous dose level. Patients in first dose level may be reduced to 50 mg TIW.
- A second dose reduction is allowed.
- Reescalation to the previous dose is acceptable in the absence of continuing toxicities. If subsequent LY3039478 dose reduction is required after reescalation, the patient should be maintained at the reduced dose level.

Adjustments to these dosing guidelines may be permitted following an evaluation of the patient's condition, benefit of treatment, and consultation with the Lilly CRP. All exceptions to these guidelines will be documented.

7.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive LY3039478 in this study. For patients participating in Part A and the cohort-escalation phase of Part F: 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 or

CRS. For patients participating in Study Part F cohort expansion: upon confirmation of eligibility, the sponsor will assign the patient to a dosing schedule (F1 or F2). Further details on the method of assignment are documented in the Statistical Analysis Plan. 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.

…

7.5. Concomitant Therapy

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For study Parts A, B, C, D, and E, p~~P~~atients should not receive corticosteroids prophylactically with the intent of attenuating ~~gastrointestinal~~ GI toxicity. However, corticosteroid therapy initiated before study entry for a preexisting condition may be continued. Corticosteroids may be used for treatment of GI toxicities if deemed necessary after agreement between the investigators and Lilly CRP. As a guidance, standard treatments are provided in Attachment 9. For Study Part F, prednisone will be co-administered with LY3039478 as detailed in Section 7.2.1.

…

7.6.1. Evaluable Patients

7.6.1.1. Parts A, B, C, D, ~~and~~E, and F

…

7.6.1.2. ~~Part A~~ Dose Escalation Only

…

**Table JJCA.8.1. Adverse Event and Serious Adverse Reporting Guidelines for Study I6F-MC-JJCA**

| Timing | Types of AEs/SAEs Reported |
|---|---|
| Prestudy (baseline assessments), per Section 8.1.2.2.1 | Preexisting conditions<br>Procedure-related AEs/SAEs |
| On therapy, per Section 8.1.2.2.2 | All AEs/SAEs regardless of relatedness |
| Follow-up Visit (Visit 801), per Section 8.1.2.2.3 | All AEs/SAEs regardless of relatedness |
| Continued-access period | All AEs/SAEs regardless of relatedness |
| Continued-access period follow-up | All AEs/SAEs regardless of relatedness |
| Subsequent Follow-up visits, if necessary – no more than 30 ±3 days in duration[a] | Ongoing or new AEs/SAEs related to study drug or protocol procedures |
| Long-term posttreatment discontinuation follow-up[b] | All AE and SAEs related to protocol procedures or study drug |

…

8.1.4. Safety Monitoring

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

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

…

8.2.4.3. Tumor and Skin Biopsies

Throughout this study, archived tumor tissue obtained previously for diagnostic purposes (for example, at initial diagnosis) will be requested for biomarker research but is not required for study entry in Part A. At baseline, before the patient received study drug for Parts B, C, D, ~~and~~E, and F, a mandatory pretreatment formalin-fixed paraffin-embedded (FFPE) tumor tissue (paraffin blocks or unstained slides cut from that block) will be collected. For Study Part F, the tumor tissue sample is required to be obtained within 2 years of the date of enrollment if archival. A fresh sample is required if no archival sample meeting that criteria can be located.

Table JJCA.8.2 presents tumor and skin biopsy collection time points.

**Table JJCA.12.1. Tumor and Skin Biopsy Time Points**

| Collection Time Point | Part A | Parts B, C[a], and D[a] | Part E and F |
|---|---|---|---|
| Baseline archived tissue collection | Optional | Mandatory | Mandatory |
| Pre-/Postdose tumor biopsies | Optional | Recommended/optional | Mandatory |
| Pre-/Postdose skin biopsies | Mandatory | Mandatory | Mandatory |

…

8.3. Efficacy Evaluations

An objective of the study is to document any antitumor activity (secondary in Part A and coprimary for Parts B, C, D, ~~and~~E, and F). Refer to Attachment 1 for details regarding the timing of specific efficacy measures.

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

- computed tomography (CT) scan
- magnetic resonance imaging (MRI)
- chest x-ray
- PET scan – mandatory for Part E and F, Part C patients with sarcoma (leiomyosarcoma, GIST, liposarcoma, and angiosarcoma), and Part D patients with mature T cell, B cell, or NK cell neoplasms enrolled under amendment d.

…

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

…

10.1. General Considerations

Approximately ~~182~~282 patients may be enrolled in this multicenter, open-label Phase 1 study with dose escalation followed by dose confirmation.

…

Part F will focus on approximately 55 patients. The total sample size during dose escalation will be determined by DLTs and is estimated to be approximately 10 to 15 patients for each schedule (F1 and F2). The sample size of approximately 15 patients for each schedule (F1 and F2) in the expansion cohorts is adequate to explore anti-tumor activity of LY3039478 in patients with leiomyosarcoma.

For guidance, example point estimates of incidence rates and corresponding 2-sided exact 95% confidence interval (CI) are provided in Table JJCA.10.1 for the proposed sample size of each tumor type in study Parts C, D, ~~and~~E, and F. The values are provided as a reference for estimation rather than a basis of any decision criteria.

…

10.2. Efficacy

…

For patients in study Part C ~~and~~, HCC patients from Part D, and leiomyosarcoma patients in Part F, ORR defined using the Choi criteria (Choi et al. 2007) will be considered for response evaluation in addition to RECIST criteria. Modified response criteria incorporating changes in tumor density in addition to tumor size has been demonstrated to be a more sensitive prognostic marker for time to progression and disease specific survival in GIST sarcomas (Benjamin et al. 2007; Choi et al. 2007).

For Part E, Part C, and F patients with sarcoma (leiomyosarcoma, GIST, liposarcoma, and angiosarcoma), and Part D patients with mature T cell, B cell, or NK cell neoplasms enrolled under amendment d, PET maximum standardized uptake values (SUVmax) will also be analyzed, and metabolic responses defined using PET response criteria of the European Organisation for Research and Treatment of Cancer (Young et al. 1999).

…

## Baseline Assessments

| Relative Day Prior to Day 1 of Cycle 1 | ≤28 | ≤14 | ≤7 | Comments |
|---|---|---|---|---|
| Informed consent | X | | | Informed consent signed prior to performance of any protocol-specific tests/procedures. |
| Radiological tumor assessment | X | | | |
| PET scan | | X | | Optional[a] |
| DCE-MRI | | X | | Optional and not applicable for CLL patients |
| Medical history | | X | | Including alcohol/tobacco use and other relevant habits assessments |
| Physical examination | | X | | |
| Vital signs | | X | | Including temperature, blood pressure, pulse rate, respiration rate |
| Height | | X | | |
| ECOG performance status | | X | | |
| Chest x-ray | X | | | May be omitted in patients having a chest CT for their radiological tumor assessment |
| ECG | | X | | One set of triplicate ECGs, central |
| Hematology | | X | | Local laboratory, for CLL patients includes immunophenotyping (see Attachment 2). |
| Coagulation (PT/INR, aPTT, fibrinogen) | | X | | Local laboratory |
| Serum chemistry | | X | | Central laboratory |
| Urinalysis | | X | | Local laboratory |
| Child-Pugh, BCLC, and CLIP staging | | X | | Only for HCC patients in Part D (see Attachment 10, Attachment 11, and Attachment 12) |
| Tumor measurement (palpable or visible) | | X | | |
| CTCAE v 4.0 grading (preexisting conditions) | | X | | To be reported only after study eligibility is confirmed. See Section 8.1.2.2 for reporting expectations |
| Concomitant medications | | X | | |
| Tumor markers | | X | | If applicable, local laboratory |
| Blood PD biomarkers (A beta) | | X | | For Parts A and B only |
| Tumor biopsy[a] | X | | | |
| Screening for alterations of Notch pathway | X | | | Screening done locally, required only for Part B~~,and~~ D, and F expansion cohort patients. Performed at any time prior to ICF and study drug start. |
| Archived tumor sample | | | X | Paraffin-embedded tumor tissue, only after study eligibility is confirmed. |
| Pregnancy test | | | X | Negative results prior to dosing required for women of childbearing potential |
| Skin biopsy | | X | | |
| Marrow aspirate and biopsy, if clinically indicated | X | | | Only CLL patients, according to institutional guidelines, last results prior dosing |
| Cytogenetic tests (FISH) | X | | | Only CLL patients, if applicable, local laboratory |

Abbreviations: aPTT = activated partial thromboplastin time; BCLC= Barcelona Clinical Liver Classification Table; CLIP = Cancer of the Liver Italian Scoring System; CLL = Chronic Lymphocytic Leukemia; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization; HCC = hepatocellular carcinoma; Meds = medications; PD = pharmacodynamic; PET = positron emission tomography; PT/INR = prothrombin time/international normalized ratio.

a PET scan and tumor biopsy are mandatory for all patients in Part E, Part F, and LMS, GIST, liposarcoma, and angiosarcoma patients in Part C, and mature T cell, B cell, or NK cell neoplasm patients in Part D enrolled under Amendment d.

## During and Poststudy Assessments for Parts A, B, C, D, E, and F1

| Study Procedures | Cycle 1 | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 | | | Week 2 | | | Week 3 | | | Week 4 | | |
| | Dose 1 | Dose 2 | Dose 3 | Dose 4 | Dose 5 | Dose 6 | Dose 7 | Dose 8 | Dose 9 | Dose 10 | Dose 11 | Dose 12 |
| LY3039478 therapy[a] | X | X | X | X | X | X | X | X | X | X | X | X |
| Prednisone therapy[p] | X | X | X | X | X | X | | | | | | |
| Physical examination | X | | | X | | | X | | | X | | |
| Vital signs and weight (temperature, pulse rate, blood pressure, respiratory rate) | X | | | X | | | X | | | X | | |
| ECOG performance status | X | | | X | | | X | | | X | | |
| CTCAE version 4.0 grading | | | | X | | | X | | | X | | |
| Concomitant medications | | | | X | | | X | | | X | | |
| Tumor measurement (palpable and visible) | | | | | | | | | | X | | |
| DCE-MRI (optional)[b] | | | | X | | | | | | | | |
| Central ECG[c] | X | | | | | | | | | | | |
| Hematology[d] | X | | | X | | | X | | | X | | |
| Serum chemistry[d] | X | | | X | | | X[e] | | | X | | |
| Serum creatinine[c, d] | X | | | | | | | | | | | |
| ECG chemistry[c, d] | X | | | | | | | | | | | |
| Coagulation (PT/INR, aPTT, fibrinogen)[d] | | | | X | | | X | | | X | | |
| Tumor marker[d] | | | | | | | | | | X | | |
| Pharmacogenetics sample (predose) | X | | | | | | | | | | | |
| Blood PK sampling[c] | X | | | | | | X[q] | | | X | | |
| Tumor biopsy[f] | | | | | | | | | | X | | |
| Skin biopsy[c, g] | X | | | | | | | | | | | |
| Blood PD biomarkers (A beta-Parts A and B only)[c] | X | | | | | | | | | X | | |
| Blood PD biomarkers (RBM, cytokeratin 18, epigenomics) predose | X | | | | | | | | | | | |
| Urine (8- to 10-hour collection)[c,h] | X | | | | | | | | | | | |

**During and Poststudy Assessments for Part F2**

| Study Procedures | Cycle 1 | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 | | Week 2 | | Week 3 | | | Week 4 | | |
| | Dose 1 | Dose 2 | Dose 3 | Dose 4 | Dose 5 | Dose 6 | Dose 7 | Dose 8 | Dose 9 | Dose 10 |
| LY3039478 therapy | X | X | X | X | X | X | X | X | X | X |
| Prednisone[p] | X | X | X | X | | | | | | |
| Physical examination | X | | X | | X | | | X | | |
| Vital signs and weight (temperature, pulse rate, blood pressure, respiratory rate) | X | | X | | X | | | X | | |
| ECOG performance status | X | | X | | X | | | X | | |
| CTCAE version 4.0 grading | | | X | | X | | | X | | |
| Concomitant medications | | | X | | X | | | X | | |
| Tumor measurement (palpable and visible) | | | | | | | | X | | |
| DCE-MRI (optional)[b] | | | X | | | | | | | |
| Central ECG[c] | X | | | | | | | | | |
| Hematology[d] | X | | X | | X | | | X | | |
| Serum chemistry[d] | X | | X | | X[e] | | | X | | |
| Serum creatinine[c, d] | X | | | | | | | | | |
| ECG chemistry[c, d] | X | | | | | | | | | |
| Coagulation (PT/INR, aPTT, fibrinogen)[d] | | | X | | X | | | X | | |
| Tumor marker[d] | | | | | | | | X | | |
| Pharmacogenetics sample (predose) | X | | | | | | | | | |
| Blood PK sampling[c] | X | | | | X[r] | | | X[s] | | |
| Tumor biopsy[f] | | | | | | | | X | | |
| Skin biopsy[c, g] | X | | | | | | | | | |
| Blood PD biomarkers (RBM, cytokeratin 18, epigenomics) predose | X | | | | | | | | | |

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f Optional posttreatment tumor biopsy should be obtained (whenever clinically feasible) at Cycle 1, preferably 6 to 8 hours (±1 hour) after Dose 10. Greater flexibility has been provided for the posttreatment tumor biopsy (between Doses 7 and 12, inclusive) compared to other Dose 10 visit assessments (between Doses 9 and 11, inclusive) to enable radiographic guidance and access to appropriate medical specialists; however, if this flexibility is exercised and the posttreatment tumor biopsy is obtained on a day other than the 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 are mandatory for all patients in Part E, F, and LMS, GIST, liposarcoma, and angiosarcoma patients in Part C and mature T cell, B cell, or NK cell neoplasm patients in Part D enrolled under Amendment d.

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k Long-term follow-up for survival applies to Part B, C, D, ~~and~~E, and F only.
l Collection of AEs and SAEs related to study treatment or study procedures only.
m collection of concomitant medication post-study treatment discontinuation must include any subsequent cancer treatment.
n Every 60 ( ±14) days and applies only to those patients who discontinue the study without progression or have not started another treatment regimen as outlined in Section 8.3.
o According to Guidelines from the National Cancer Institute Working Group for CLL, marrow aspirate and biopsy will be performed in CLL patients when a partial remission or complete remission is observed (to obtain bone marrow response information) and also 2 months after the last study drug treatment (to obtain duration of response). Institutional guidelines will be followed.
p Prednisone given during Cycle 1 daily on Days 1-14 in Study Part F only as described in Section 7.2.1.
q For Part C, D, E, and dose-expansion patients in Part F1.
r For Dose 5 in the dose-expansion part of F2 only.
s For Dose 8 in the dose-escalation part of F2 only.

## Continued Access Schedule of Activities

| Study Procedures[b] | Visit 501-n | | | | | | | | | | | | Follow-up[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Week 1 | | | Week 2 | | | Week 3 | | | Week 4 | | | 901 |
| | Dose 1 | Dose 2 | Dose 3 | Dose 4 | Dose 5 | Dose 6 | Dose 7 | Dose 8 | Dose 9 | Dose 10 | Dose 11 | Dose 12 | |
| LY3039478 therapy | X | X | X | X | X | X | X | X | X | X | X | X | |
| Hematology | X | | | | | | X | | | | | | |
| Serum chemistry | X | | | | | | X | | | | | | |
| Vital signs and weight (temperature, pulse rate, blood pressure, respiratory rate) | X | | | | | | | | | | | | |
| ECOG performance status | X | | | | | | | | | | | | |
| AE collection (CTCAE version 4.0) | X | | | | | | | | | | | | X |

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group.

[a] Continued access follow-up begins 1 day after the patient and the investigator agree that the patient will no longer continue treatment in the continued-access period and lasts approximately 30 days. No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

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

## Attachment 3. Protocol JJCA Pharmacokinetic and Pharmacodynamic Sampling Schedule

**Pharmacokinetic and Pharmacodynamic Sampling Schedule for Part A ~~and for,~~ 10 Patients in Part B, and Dose-Escalation Patients in Part F1**

| PK Sample Number | Dose Number | Cycle | PK Sampling Time for LY3039478[a] | Urine Sampling Part A Only[a] | Sampling Time for Serum Creatinine Part A Only | PD Sampling Time for Aβ (1-x) (Parts A and B only) | PD Sampling Time for Skin Biopsies | ECG with ECG Chemistry |
|---|---|---|---|---|---|---|---|---|
| 1 | Screening | 1 | | | Screening | Screening | Screening | |
| 2 | 1 | 1 | Predose | 0 to 8-10 hr pooled samples (end time of sample to coincide with PK blood draw) Record total volume | Predose | Predose | | Predose |
| 3 | 1 | 1 | 0.5 hr | | | | | |
| 4 | 1 | 1 | 1 hr | | 1 hr | | | |
| 5 | 1 | 1 | 2 hr | | | 2 hr | | |
| 6 | 1 | 1 | 4 hr | | 4 hr | 4 hr | | 4 hr |
| 7 | 1 | 1 | 6-8 hr | | | 6-8 hr | 6-8 hr (±1 hour) | |
| 8 | 1 | 1 | 8-10 hr | | 8-10 hr | 8-10 hr | | |
| 9 | 1 | 1 | 24-30 hr | | | 24-30 hr | | 24-30 hr |
| 10 | 10 | 1 | Predose | | | Predose | | |
| 11 | 10 | 1 | 0.5 hr | | | | | |
| 12 | 10 | 1 | 1 hr | | | | | |
| 13 | 10 | 1 | 2 hr | | | 2 hr | | |
| 14 | 10 | 1 | 4 hr | | | 4 hr | | |
| 15 | 10 | 1 | 6-8 hr | | | 6-8 hr | | |
| 16 | 10 | 1 | 8-10 hr | | | 8-10 hr | | |
| 17 | 10 | 1 | 24-30 hr | | | 24-30 hr | | |
| 18 | 1 | 2 | Predose | | | Predose | | Predose |

**Pharmacokinetic and Pharmacodynamic Sampling Schedule for Dose-Escalation Patients in Part F2**

| PK Sample Number | Dose Number | Cycle | PK Sampling Time for LY3039478 | PD Sampling Time for Skin Biopsies | ECG with ECG Chemistry |
|---|---|---|---|---|---|
| 1 | Screening | 1 | | Screening | |
| 2 | 1 | 1 | Predose | | Predose |
| 3 | 1 | 1 | 0.5 hr | | |
| 4 | 1 | 1 | 1 hr | | |
| 5 | 1 | 1 | 2 hr | | |
| 6 | 1 | 1 | 4 hr | | 4 hr |
| 7 | 1 | 1 | 6-8 hr | 6-8 hr (±1 hour) | |
| 8 | 1 | 1 | 8-10 hr | | |
| 9 | 1 | 1 | 24-30 hr | | 24-30 hr |
| 10 | 8 | 1 | Predose | | |
| 11 | 8 | 1 | 0.5 hr | | |
| 12 | 8 | 1 | 1 hr | | |
| 13 | 8 | 1 | 2 hr | | |
| 14 | 8 | 1 | 4 hr | | |
| 15 | 8 | 1 | 6-8 hr | | |
| 16 | 8 | 1 | 8-10 hr | | |
| 17 | 8 | 1 | 24-30 hr | | |
| 18 | 1 | 2 | Predose | | Predose |

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

Pharmacokinetic and Pharmacodynamic Sampling Schedule for Parts C, D, ~~and~~E, and Dose-Expansion Patients in Part F1

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Pharmacokinetic and Pharmacodynamic Sampling Schedule for Dose-Expansion Patients in Part F2

| Sample Number | Dose Number | Cycle | PK Sampling Time for LY3039478 | PD Sampling Time for Skin Biopsies | ECG with ECG Chemistry |
|---|---|---|---|---|---|
| 1 | Screening | 1 | | Screening | |
| 2 | 1 | 1 | Predose | | Predose |
| 3 | 1 | 1 | 1-3 hr | | 2 hr |
| 4 | 1 | 1 | 4 hr | | |
| 5 | 1 | 1 | 6-8 hr | 6-8 hr (±1 hour) | |
| 6 | 5 | 1 | Predose | | |
| 7 | 1 | 2 | Predose | | Predose |

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

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