Protocol (d) I6X-MC-JBDA

A Phase I Study of LY3009120 in Patients with Advanced or Metastatic Cancer

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1. Protocol I6X-MC-JBDA(d)
A Phase 1 Study of LY3009120 in Patients with Advanced or Metastatic Cancer

Confidential Information

LY3009120

This Phase 1 study is a multicenter, nonrandomized, open-label, dose-escalation study followed by dose-confirmation of oral LY3009120 in patients with advanced or metastatic cancer.

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2. Synopsis

This Phase 1 study is a multicenter, nonrandomized, open-label, dose-escalation study followed by dose-confirmation of oral LY3009120 in patients with advanced and/or metastatic cancer.

3. Table of Contents

A Phase 1 Study of LY3009120 in Patients with Advanced or Metastatic Cancer

Section **Page**

1. Protocol I6X-MC-JBDA(d) A Phase 1 Study of LY3009120 in Patients with Advanced or Metastatic Cancer 1
2. Synopsis 2
3. Table of Contents 3
4. Abbreviations and Definitions 9
5. Introduction 13
5.1. Rationale and Justification for the Study 13
5.2. Objectives 14
5.2.1. Primary Objective 14
5.2.2. Secondary Objectives 14
5.2.3. Exploratory Objectives 14
5.3. General Introduction to LY3009120 14
5.3.1. Mechanism of Action and In Vitro/In Vivo Activity 15
5.3.2. Nonclinical Pharmacokinetics/Pharmacodynamics 16
5.3.3. Nonclinical Toxicology 16
5.3.4. Biomarkers 19
5.3.4.1. Pharmacodynamic Biomarkers in Part A 19
5.3.4.2. Archived Sample Biomarkers for Stratification in Part B 20
5.3.4.3. Exploratory Analysis of Predictive Biomarkers 20
5.4. Rationale for Selection of Dose 20
6. Investigational Plan 21
6.1. Study Population 21
6.1.1. Inclusion Criteria 21
6.1.2. Exclusion Criteria 23
6.2. Summary of Study Design 24
6.2.1. Study Completion and End of Trial 26
6.3. Discontinuations 26
6.3.1. Discontinuation of Patients 26
6.3.2. Discontinuation of Study Sites 27
6.3.3. Discontinuation of the Study 27
7. Treatment 28
7.1. Materials and Supplies 28

7.2. Study Drug Administration 28
7.2.1. Dosing Schedule 28
7.2.2. Dose Escalation Phase 29
7.2.2.1. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition 29
7.2.2.2. Dose Escalation Method 30
7.2.3. Dose Confirmation Phase 31
7.2.4. Dose Adjustments and Delays 32
7.2.4.1. Dose Adjustments within a Cycle 32
7.2.4.2. Dose Adjustment between Cycles 32
7.3. Method of Assignment to Treatment 33
7.4. Blinding 33
7.5. Concomitant Therapy 33
7.6. Treatment Compliance 34
7.6.1. Evaluable Patients 34
8. Safety, Pharmacokinetic, Pharmacodynamic, and Efficacy Data Collection 36
8.1. Safety Evaluations 36
8.1.1. Safety Data Collection and Review 36
8.1.2. Adverse Events 36
8.1.2.1. Serious Adverse Events 38
8.1.2.2. Adverse Event and Serious Adverse Event Reporting 38
8.1.2.2.1. Prior to Administration of Study Drug(s) 38
8.1.2.2.2. On Therapy 39
8.1.2.2.3. Follow-Up Visit 39
8.1.2.3. Suspected Unexpected Serious Adverse Reactions 39
8.1.2.4. Summary of AE/SAE Reporting Guidelines 39
8.1.3. Other Safety Measures 40
8.1.3.1. Eye Safety Monitoring 40
8.1.3.2. Dermatological Safety Monitoring 40
8.1.3.3. Electrocardiograms 41
8.1.4. Safety Monitoring 42
8.1.5. Complaint Handling 42
8.2. Sample Collection and Testing 42
8.2.1. Samples for Study Qualification and Health Monitoring 42
8.2.2. Samples for B-Raf Mutational Status Assessment 43
8.2.3. Samples for Drug Concentration Measurements 43
8.2.3.1. Pharmacokinetic Samples 43

8.2.3.1.1. Identification of LY3009120 Metabolites in Urine and Plasma....44
8.2.4. Pharmacodynamic and Tailoring Biomarker Tumor Samples....44
8.2.4.1. Tissue Collection for Pharmacodynamic Studies....45
8.2.4.2. Tissue Collection for Tailoring Biomarker Studies....45
8.2.4.2.1. Collection Procedures of Plasma Samples for Exploratory Biomarkers....46
8.2.5. Pharmacogenetic Samples....46
8.3. Efficacy Evaluations....46
8.4. Procedure/Sampling Compliance....47
9. Data Management Methods....48
9.1. Data Quality Assurance....48
9.2. Data Capture Systems....48
9.2.1. Case Report Form....48
9.2.2. Ancillary Data....49
10. Data Analyses....50
10.1. General Considerations....50
10.2. Patient Disposition....50
10.3. Patient Characteristics....50
10.4. Safety Analyses....50
10.5. Pharmacokinetic Analyses....51
10.6. Pharmacodynamic Analyses....51
10.7. Pharmacokinetic/Pharmacodynamic Analyses....51
10.8. Efficacy....52
10.9. Interim Analyses....52
11. Informed Consent, Ethical Review, and Regulatory Considerations....53
11.1. Informed Consent....53
11.2. Ethical Review....53
11.3. Regulatory Considerations....53
11.3.1. Investigator Information....54
11.3.2. Protocol Signatures....54
11.3.3. Final Report Signature....54
12. References....55

List of Tables

Table **Page**

Table JBDA 5.1. Margin of Safety for Oral Administration of LY3009120 Based on Administered Dose and Predicted Exposure....19

Table JBDA 7.1. Proposed Dose Escalation Scheme....31

Table JBDA 8.1. Adverse Event and Serious Adverse Reporting Guidelines for Study JBDA....40

List of Figures

Figure **Page**

Figure JBDA 6.1.Study Design 25

List of Attachments
List of Protocol Attachments

Attachment **Page**

Attachment 1. Protocol JBDA Study Schedule 58
Attachment 2. Protocol JBDA Clinical Laboratory Tests 68
Attachment 3. Protocol JBDA Hepatic Monitoring Tests for Treatment Emergent Abnormality 69
Attachment 4. Protocol JBDA Pharmacokinetic and Exploratory Blood Plasma Sampling Schedule 70
Attachment 5. Protocol JBDA Recommendations for Reporting Serious Adverse Events 72
Attachment 6. Protocol JBDA ECOG Performance Status 73
Attachment 7. Protocol JBDA Creatinine Clearance Formula 74
Attachment 8. Protocol JBDA Sampling Summary 75
Attachment 9. Protocol JBDA RECIST Criteria 1.1 76
Attachment 10. Protocol JBDA Toxicity Band Design 83
Attachment 11. Protocol JBDA Protocol Amendment I6X-MC-JBDA(d) Summary A Phase 1 Study of LY3009120 in Patients with Advanced or Metastatic Cancer 91

4. Abbreviations and Definitions

Term	Definition
AE	Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ANC	absolute neutrophil count
assent	Agreement from a minor or other individual who is not legally capable of providing consent, but who can understand the circumstances and potential risks involved in participating in a study (required by some Institutional Review Boards [IRBs]/ethical review boards [ERBs]).
AST	aspartate aminotransferase
$AUC_{(0\text{-}tlast)}$	area under the plasma concentration-time curve from time zero to last measurable plasma concentration
$AUC_{(0\text{-}\infty)}$	area under the plasma concentration-time curve from time zero to infinity
audit	A systematic and independent examination of the study-related activities and documents to determine whether the evaluated study-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
C_{max}	maximum plasma concentration
CL/F (or CL)	apparent systemic clearance
CNS	central nervous system
complaint	Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety, effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CR	complete response

CRF/eCRF	case report form/electronic case report form: Sometimes referred to as clinical report form, a printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRC	colorectal cancer
CRM	continual reassessment method
CRP	clinical research physician
CRS	clinical research scientist
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	Patients who are enrolled in the trial are those who have been assigned to a treatment and have received at least one dose of study treatment.
enter	Patients who are entered in the trial are those who have signed the informed consent form directly or through their legally acceptable representatives.
ERB/IRB	ethical review board/institutional review board: /A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
ERK	extracellular signal-regulated kinase
GCP	good clinical practice
G-CSF	granulocyte colony stimulating factors
GLP	good laboratory practices
HBSAg	hepatitis B surface antigen
HCAb	hepatitis C antibodies
HIV	human immunodeficiency virus
IB	Investigator's Brochure

ICF	informed consent form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An analysis of clinical study data that is conducted before the final reporting database is authorized for datalock.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical study.
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
NSCLC	non-small cell lung cancer
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participants are aware of the drug therapy received during the study.
patient	A subject with a defined disease.
PD	pharmacodynamic
PDGFR	platelet-derived growth factor receptor
PK	Pharmacokinetic
PR	partial response
PSA	prostate-specific antigen

RECIST	Response Evaluation Criteria in Solid Tumors
re-screen	To screen a patient who was previously declared a screen failure for the same study
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
screen failure	A patient who does not meet one or more criteria required for participation in a trial
sponsor	The party who takes responsibility for the initiation, management and/or financing of a clinical study.
study completion	This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) after all patients have been discontinued from the treatment and have completed protocol defined follow-up period.
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	half-life
t_{max}	time of maximal plasma concentration
TPO	third-party organization
ULN	upper limit of normal
US	United States
V/F (or V)	apparent volume of distribution

A Phase 1 Study of LY3009120 in Patients with Advanced or Metastatic Cancer

5. Introduction

5.1. Rationale and Justification for the Study

The Raf serine/threonine protein kinase family is comprised of three isoforms, A-Raf, B-Raf and C-Raf. They play a pivotal role in the mitogen-activated protein kinase (MAPK) pathway (Ras/Raf/MEK/ERK) in transducing extracellular signals to the nucleus (Madhunapantula and Robertson 2008; Beeram et al. 2005). As part of the MAPK cascade, Raf protein kinases are involved in tumor cell proliferation, survival, invasion and angiogenesis (Friday and Adjei, 2008). B-Raf point mutations within the kinase domain of the protein occur in several human cancers, including melanoma and thyroid cancer, and to a lesser extent in colon cancer, ovarian cancer, and lung cancer (Flaherty and McArthur, 2010). The majority of B-Raf mutations are substitutions of a single amino acid in the kinase domain (V600E) that results in significant increase in its kinase activity (Davies et al. 2002). In melanoma, B-Raf mutations are found in 40-50% of patients (Sullivan and Flaherty, 2013). Therefore, B-Raf protein kinase is an attractive therapeutic target for improving outcomes of patients with these cancers.

Recently, two B-Raf specific kinase inhibitors, vemurafenib (also called PLX4032) and dabrafenib, were approved by the United States Food and Drug Administration (FDA) for treatment of melanoma patients with B-Raf V600E mutation. Trametinib, a Mek-kinase inhibitor, was also recently approved by the FDA for treatment of melanoma patients with B-Raf V600E and V600K mutations that have not received previous treatment with a B-Raf inhibitor. While vemurafenib has proven its effectiveness in this patient population, most patients eventually develop drug resistance which leads to disease relapse in an average of 7 months (Chapman et al. 2011). It is believed that the drug resistance could be due to reactivation of the MAPK pathway through Ras/Raf dependent mechanisms such as activating mutation in NRas or MEK1 (Nazarian et al. 2010; Wagle et al. 2011), expression of truncated forms of B-Raf or upregulation of C-Raf, or COT1 (Montagut et al. 2008, Corcoran et al. 2010; Johannessen et al. 2010; Poulikakos et al. 2011). Moreover, the persistent expression of the receptor tyrosine kinases platelet-derived growth factor receptor- β (PDGFR-β) and IGF-1R conferred B-Raf inhibitor resistance that may involve enhanced phosphatidylinositol 3-kinase (PI3K)/AKT pathway activation (Nazarian et al. 2010; Villanueva et al. 2010; Shi et al. 2011). Therefore, similar to many other targeted therapies, the acquired resistance to B-Raf inhibition presents a significant therapeutic challenge for long-term survival benefit in this patient population. Additionally, vemurafenib is a B-Raf specific inhibitor, which promotes activation of extracellular signal-regulated kinase (ERK) phosphorylation, in B-Raf wild type cells. Therefore, vemurafenib is not indicated for patients with wild type B-Raf including patients with Ras mutations (Joseph et al. 2010).

LY3009120 is a pan-Raf kinase inhibitor with potent activities against A-, B-, and C-Raf isoforms and B-Raf V600E mutation, and induces minimal paradoxical MAPK pathway

activation due to pan Raf activities. It possesses significant activity against several other receptor tyrosine kinases such as c-Kit and PDGFR-α and β. It is active against vemurafenib resistant cells with different resistance mechanisms including NRas mutation, B-Raf splice variants, C-Raf elevation, and other MAPK reactivation mechanism. More importantly, LY3009120 is active against tumor cells with NRas or KRas mutation such as NRas mutant melanoma and acute myeloid leukemia (AML), and KRas mutant non-small cell lung cancer (NSCLC) and colorectal cancer (CRC). In xenograft models, LY3009120 demonstrates inhibition of phospho-MEK and phospho-ERK, as well as tumor growth inhibition in melanoma or colon tumor models with B-Raf V600E mutation. It also inhibits tumor growth in xenograft models with NRas or KRas mutations. This Phase 1 study (I6X-MC-JBDA [Study JBDA]) will evaluate the safety and tolerability of LY3009120 in patients with advanced cancer and will determine the dose and schedule for Phase 2 studies.

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

5.2. Objectives

5.2.1. Primary Objective

The primary objective of this study is to determine a recommended Phase 2 dose of LY3009120 that may be safely administered to patients with advanced and/or metastatic cancer.

5.2.2. Secondary Objectives

The secondary objectives of this study are:

- to characterize the safety and toxicity profile of LY3009120.
- to estimate the pharmacokinetic (PK) parameters of LY3009120.
- to document any antitumor activity observed with LY3009120.

5.2.3. Exploratory Objectives

- to explore pharmacodynamic (PD) biomarkers.
- to explore biomarkers related to the safety and efficacy of LY3009120.

5.3. General Introduction to LY3009120

More information about the known and expected benefits, risks and reasonably anticipated adverse events (AEs) may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to the investigational product may be found in Section 7 (Development Core Safety Information) of the IB. Information on serious 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

Raf family of protein kinases are activated by Ras proteins in the signal transduction pathway or through *raf* mutations. Mutated Raf protein, particularly B-Raf V600E, is found in many different cancers, with highest percent of this mutation reported in melanoma. LY3009120 is a potent pan-Raf inhibitor with equal affinity in inhibiting A-, B-, and C-Raf, as well as B-Raf V600E. Whole cell assay data show an IC50 of 44, 47 and 42 nM for A-, B- and C-Raf, respectively. In an enzymatic assay, it inhibits wild type B-Raf, wild type C-Raf, and B-Raf V600E with IC50 values of 9.8, 15.47, and 5.77 nM, respectively. In vitro, LY3009120 inhibits cellular phospho-ERK activity in melanoma A375 cells with B-Raf V600E mutation with IC50 of 3 nM. It also inhibits phospho-Mek and phospho-ERK activities in Ras mutant tumor cells with minimal paradoxical pathway activation. It inhibits cell proliferation in vitro and tumor growth in vivo in a broad panel of tumor cells with different genetic background.

- In melanoma B-Raf V600E mutant A375 cells, LY3009120 inhibits cell proliferation with IC50 of 9.2 nM in vitro, and exhibits significant tumor growth inhibition/regression at 5-15 mg/kg in vivo. LY3009120 is predicted to be active for melanoma patients with the B-Raf V600E mutation.
- In preclinical models, LY3009120 was demonstrated to be active against vemurafenib resistant melanoma cells with MAPK reactivation. These resistant mechanisms include NRas mutation, B-Raf splice variants, C-Raf elevation, and FGFR3 activation. Therefore, LY3009120 may have activity in patients failing established B-Raf or MEK-inhibitor treatment.
- In preclinical models of NRas mutant melanoma, LY3009120 inhibits cell proliferation and induces tumor cell apoptosis, whereas vemurafenib is inactive. Similar activities are also observed for other NRas mutant tumor cells including AML cell lines, ie, HL-60 and THP-1cells. Therefore, LY3009120 may have activity in patients with NRas mutations.
- In a panel of KRas mutant tumor cells including CRC, NSCLC, and pancreatic tumor cells, LY3009120 inhibits cell proliferation of many cell lines in vitro and tumor growth in vivo in multiple xenograft models.
- In CRC tumor cells with B-Raf V600E mutation, LY3009120 is active with IC50 of 7.3nM (HT-29) to 27 nM (Colo-205) in vitro, and inhibits tumor growth at 10-30 mg/kg in vivo.
- In in vivo efficacy studies, LY3009120 demonstrated significant tumor growth inhibition and regression at 5-15 mg/kg twice daily dose schedule in melanoma A375 xenograft model. In multiple models with NRas or KRas mutation, LY3009120 showed significant tumor growth inhibition at 10-30 mg/kg twice daily dose schedule. In rat A375 xenograft PD model, LY3009120 demonstrated a dose and time-dependent inhibition of phospho-ERK activities with absolute ED50 and ED80 of 4.36 and 16.37 mg/kg, and EC50 and EC80 of 68.9 and 365.5 ng/mL, respectively. In mouse A375 PD model, LY3009120 inhibited phospho-ERK with absolute ED50 and ED80 of 4.8 and 9.69 mg/kg, and EC50 and EC80 of 127.9 and 428.1 ng/mL, respectively.

- Overall, these preclinical data support testing LY3009120 in unresectable/metastatic melanoma patients with B-Raf mutations, NRas mutations, and in advanced/metastatic non small cell lung cancer patients with KRas or B-Raf mutations.

5.3.2. Nonclinical Pharmacokinetics/Pharmacodynamics

LY3009120 is a poorly soluble but highly permeable molecule with poor oral exposure when dosed in conventional suspension vehicles. LY3009120 has improved oral bioavailability when formulated as a PVP-VA solid dispersion (rat, F = 55%; dog, F = 11% to 19%). Metabolic profiling of rat and dog urine showed multiple oxidative metabolites. These observations indicated that LY3009120 appeared to be cleared by oxidative metabolism. LY3009120 was eliminated with a rapid intravenous $T_{1/2}$ in rats (1.1 hr), dogs (1.8 and 2.1 hr), and monkeys (1.0 hr). The plasma clearance after intravenous administration in rats and dogs was moderate and LY3009120 was well distributed into tissues; $V_{D,SS}$ = 1.08 L/kg (rat), 1.53 and 1.78 L/kg (dog) and 0.84 L/kg (monkey).

A PK/PD model was developed to relate plasma concentrations to the observed level of *in vivo* pERK inhibition in a A375 xenograft model in the rat, with estimated maximal inhibition of 90% and IC_{50} of 63 ng/mL. A PK/PD model linking the pharmacokinetics of LY3009120 with tumor growth rate via pERK inhibition has also been developed. The results indicated that the minimum efficacious dose in rat could be as low as 1.8 mg/kg BID.

5.3.3. Nonclinical Toxicology

The toxicity of LY3009120 was assessed after daily oral administration for one month in rats (0, 10, 75, and 300 mg/kg) with one-month recovery groups (0 and 300 mg/kg) and similarly for one month in dogs (0, 10, 40, and 80 mg/kg) with one-month recovery groups (0, 40, and 80 mg/kg). Safety pharmacology parameters were evaluated in vitro and as part of the repeat dose study in dogs. In dogs, the no-observed adverse-effect level (NOAEL) was 10 mg/kg and the highest non-severely toxic dose (HNSTD) was 40 mg/kg, due to preterminal euthanasia at 80 mg/kg**,** and microscopic changes in lymphoid organs at ≥40 mg/kg/day. Dogs administered 80 mg/kg/day were euthanized early due to clinical signs including fecal changes (soft, watery, mucoid, and discolored), emesis, inappetence, decreased activity, and decreased food consumption and body weight. Similar clinical signs were noted in some dogs at 40 mg/kg but were generally of reduced severity in comparison to the 80 mg/kg group. In the one-month study in rats, no NOAEL was identified, and the HNSTD was 75 mg/kg due to loss of one toxicity animal at 300 mg/kg. There were no clinical signs in rats associated with daily dosing. Common target organs in both species include the gastrointestinal tract, eyes, and lymphoid organs. Additional target organs identified in the rat are liver, kidney, urinary bladder, thyroid, and ovary.

In dogs, important compound-related adverse effects were limited to lymphoid (decreased lymphocytes in lymphoid organs and decreased circulating lymphocytes at the high dose) and gastrointestinal inflammation with ulceration. Clinical pathology changes (decreases in red cell mass, increases in neutrophils, monocytes, and platelets, and decreases in protein and electrolyte levels) correlated with reduced food consumption and inflammation in the GI tract. Lymphoid

and gastrointestinal findings generally resolved or showed evidence of recovery in dogs taken through the one-month recovery period.

In rats, important LY3009120-related adverse findings at a low dose of 10 mg/kg/day included epithelial hyperplasia affecting the intestinal tract (males only), arterial degeneration and subacute portal inflammation in the liver (males only), degeneration/necrosis of tubules in the kidney in males, increased colloid in the thyroid in females, and lymphocyte necrosis in the thymus. Additional adverse findings at the mid- and high-doses of 75 and 300 mg/kg/day included epithelial hyperplasia in the transitional epithelium of the kidney and urinary bladder, portal vein degeneration/proliferation, bile duct hypertrophy/hyperplasia, degeneration/necrosis of tubules in the kidney in males, decreased thickness of the physis in the femur, decreased acidophil granulation in the pituitary in males, increased colloid in the thyroid gland, corpus luteum cysts with hemorrhage and decreased corpora lutea and increased follicles in the ovary and effects secondary to the ovarian findings. All clinical pathology changes reversed during the recovery period. The only anatomic pathological change still present in the recovery group was minimal transitional cell hyperplasia in the bladder in one male.

Ocular effects were identified in both species in the nonclinical toxicology studies. In rats, degeneration/atrophy of the outer retina occurred in all dose groups, including controls (2 control females in the main study and one recovery female). There was an increased incidence (6/10) of retinal degeneration in female rats at the high dose (300 mg/kg). This finding was considered consistent with an exacerbation of light-induced injury. Among the animals in the recovery arm, only one animal demonstrated retinal degeneration, and this rat was in the control group. However, retinal degeneration is not considered reversible due to photoreceptor cell loss.

In LY3009120-treated dogs, ocular effects were identified in the clinical ophthalmology exam at the termination phase. Subtle findings of irregular tapetal hyper-reflectivity, dullness, and occasional thin vasculature were observed in 4/5 of females at 40 mg/kg in ophthalmology exams just prior to terminal sacrifice. In male dogs at 40 mg/kg, similar but more subtle changes were noted. One affected female dog demonstrated a normal ophthalmology exam at the end of recovery period, indicating reversal of the changes. There was no microscopic evidence of retinal degeneration/atrophy in dog eyes by routine histopathology, however, a more detailed histopathology assessment was pursued in an attempt to more fully characterize the test article-related ophthalmic findings and evaluate the potential risk.

A focused histopathology assessment including morphometry was conducted on sections of eyes and optic nerves from terminal and recovery phase vehicle control and 40 mg/kg female dogs. Microscopic findings considered related to administration of LY3009120 were identified in two of three main study females given 40 mg/kg/day, were restricted to the tapetal portion of the retina, and included subtle findings related to vacuolation in the retinal pigmented epithelium (RPE) and minimal changes in the overlying outer segments. These microscopic findings were not observed in the female recovery dogs given 40 mg/kg/day indicating they were likely reversible, consistent with the results of the clinical ophthalmoscopic examinations. Based upon the indication of reversibility, the focal and minimal nature, and the lack of injury to the neuro-retina, the microscopic findings were not considered adverse.

In the dog study, decreases in blood pressure (6 to 34%) and increases in heart rate (16 to 83%) occurred at all doses on day 3 and at the terminal evaluation, with variable decreases in pulse pressure (6 to 18%) primarily observed on day 3. At the terminal evaluation, changes in blood pressure and heart rate were decreased in magnitude, and these cardiovascular parameters returned to normal after the recovery period. In an in vitro hERG (human ether á-go-go-related gene) assay, the half-maximal inhibitory concentration (IC_{50}) was >10 μM. No physiologically significant changes in QT_c were identified in vivo in dogs up to a concentration of 9.8 μM (average C_{max} in male and female dogs administered 80 mg/kg on day 1). The concentration multiple between the IC_{50} in the hERG assay (>10 μM) and cellular efficacy (5.8 nM, see Section 5.3.1) is greater than 1000-fold. Thus the risk for QT_c prolongation in humans is considered low. There were no central nervous system or respiratory safety pharmacology findings. An Ames test, an in vitro chromosomal aberration assay, and an in vivo micronucleus test in SD rats were all negative. In addition, LY3009120 was a nonirritant in the Bovine Corneal Opacity and Permeability (BCOP) and dermal irritation tests.

In conclusion, nonclinical toxicology studies in rats and dogs dosed once daily for 1 month have characterized the target tissues for toxicity that may be clinically relevant. The non-clinical safety findings described above are considered to be clinically monitorable through routine imaging and testing in the advanced cancer patient population. Ophthalmological assessments are also incorporated during clinical testing, due to disparate ocular findings in both species as well as concern for potential target pathway-related ocular toxicity. The planned clinical starting dose (50 mg BID/ 100 mg total) is approximately 7-fold lower than the rat HNSTD of 75 mg/kg and approximately 13-fold lower than the dog HNSTD of 40 mg/kg. The predicted human area under the plasma drug concentration versus time curve (AUC) exposure at the starting dose of 100 mg/day (2640 ng*hr/mL) is 16.9-fold and 4.7-fold lower than AUC at the HNSTD in rats and dogs, respectively. Table JBDA 5.1. shows the dose and exposure multiples to the starting dose and highest anticipated clinical dose.

Table JBDA 5.1. Margin of Safety for Oral Administration of LY3009120 Based on Administered Dose and Predicted Exposure

	Dose (mg/kg/day)	Dose (mg/m^2/day)	Dose Multiple[a] to starting dose (to maximum dose)	AUC (ng*hr/mL)	Exposure Multiple[b] to starting dose (to maximum dose)
Human[c]	1.7	61.7		2640	
Human[d]	16.7	617		7560	
Human[e]	23.3	863.3		7960	
Rat STD_{10}[f]	300	1800	29(2)	145538	55.1(18.3)
Rat HNSTD[f]	75	450	7.3(0.5)	44621	16.9(5.6)
Dog HNSTD[g]	40	800	13(0.9)	12500	4.7(1.6)

Abbreviations: AUC = area under the plasma concentration x time curve; BID = twice daily; HNSTD = highest non-severely toxic dose; STD = severely toxic dose.

a Dose multiple is the dose in animals/dose in humans based on mg/m^2.

b Exposure multiple is the calculated AUC in animals / predicted AUC in humans. (See Table JBDA 7.1)

c Proposed starting clinical dose. Exposure is the median of the predicted AUC range at the starting dose. As no accumulation is expected, AUC has been doubled to estimate daily exposure (BID dosing).

d Predicted clinical efficacious dose. Exposure is the median of the predicted AUC range at the efficacious dose. As no accumulation is expected, AUC has been doubled to estimate daily exposure (BID dosing).

e Highest intended clinical dose. Exposure is the median of the predicted AUC range at the highest intended dose and given that no accumulation is expected, AUC has been doubled to estimate daily exposure (BID dosing).

f STD_{10} and HNSTD determined in a 1-month repeat-dose toxicity study (8271-636). Exposure is the arithmetic mean of male and female exposure on Day 28 except for the exposure for the STD_{10} which is reported as the arithmetic mean of male and female exposure on Day 1 (female TK rats were euthanized on Day 9).

g HNSTD determined in a 1-month repeat-dose toxicity study (130-284). Exposure is the arithmetic mean of male and female exposure on Day 28.

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 LY3009120 treatment, the collection of samples for biomarker research is a mandatory part of this study. Additional details about sampling are summarized in Sections 8.2.4 and 8.2.5, Attachment 1, Attachment 4, and Attachment 8.

It is possible that biomarker data for patients in the study have already been generated from samples that were collected and analyzed before enrolling in this trial. These may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Section 5.3.4.3.

5.3.4.1. Pharmacodynamic Biomarkers in Part A

In Part A, PD biomarkers will be used to assess target engagement for LY3009120 in tumor tissue, and may include, but not be limited to, phospho-ERK, p27, and Ki67 protein expression in tumors.

Tumor tissue for PD evaluation will be collected via core needle or excisional biopsy pre-treatment (≤14 days pre-treatment) and after 4 weeks of treatment (C1 D28 ± 14 days) for patients added to any Part A cohort that will be expanded to determine MTD, and/or for patients added to any cohort expanded to explore a potential Phase 2 dose based on PK, safety, and

possibly early efficacy data. Selection of patients for PD biopsies will be communicated to the sites by the sponsor.

5.3.4.2. Archived Sample Biomarkers for Stratification in Part B

In Part B, patients will be stratified into cohorts based on existing local determination of molecular alterations, or lack thereof, in B-Raf, NRas, or KRas from archived tissue (see Section 6.1.1 for specific alterations).

5.3.4.3. Exploratory Analysis of Predictive Biomarkers

Potential predictive biomarkers of efficacy to LY3009120 will be measured in archived tumor tissue, tumor tissue from core or excisional biopsies, and plasma. Core or excisional biopsies for exploratory biomarker analysis will be performed on patients enrolled in all cohorts in Part B (see Section 6.1.1 Inclusion Criterion [3]) before receiving the first dose of study drug, but this will not delay treatment. Exploratory biomarker analysis may be performed on preexisting archival samples from patients in Part A and Part B. The predictive biomarkers to be studied may include, but not limited to, somatic alterations in cancer-related genes such as B-Raf, NRas, KRas, and cKIT. In plasma, analysis of biomarkers may include, but not limited to, potential nucleic acid predictive profiles to better understand the disease process and to develop predictive biomarkers.

5.4. Rationale for Selection of Dose

A dose range from 100 to 1400 mg/day (50 mg BID to 700 mg BID orally) of LY3009120 administered is planned based on nonclinical toxicology and PK/PD modeling of nonclinical tumor growth and phospho-ERK (pERK) data. Twice daily dosing is recommended due to the predicted human elimination half-life of 6 hours and to maintain maximum pERK inhibition, given the observed direct relationship of PK with pERK inhibition in preclinical species.

A daily dose of 100 mg is predicted to be safe in patients based on nonclinical toxicology data. The planned clinical starting human dose of 100 mg/day (equivalent to 61.7 mg/m^2) is 7-fold and 13.0-fold lower than the MTD/HNSTD dose level of 450 and 800 mg/m^2 in rats and dogs, respectively. Table JBDA 5.1 shows dose multiples based on body surface area and exposure multiples based on predicted human AUC for the proposed clinical doses.

Tumor growth data from experiments with the A375 xenograft models in rats showed that 5 mg/kg BID dosing of LY3009120 was efficacious. The observed total drug exposure in plasma at this dose level was $AUC_{0\text{-}12h}$ = 2200 ng*h/mL, with a range of 1550 to 3200 ng*h/mL. Due to interspecies differences of 1.6 fold in protein binding, the total $AUC_{0\text{-}12h}$ in human will need to be 3520 (2480 to 5120) ng*h/mL to achieve the same unbound concentration in human as that observed in the rat efficacy model. Doses needed to achieve this in clinical conditions were predicted to be approximately 500 mg BID. At this dose, predicted peak pERK inhibition based on PK/PD modeling is predicted to be around 70%.

6. Investigational Plan

6.1. Study Population

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened. Individuals may be re-screened up to 1 time. The interval between re-screenings should be at least 4 weeks (28 days). Each time re-screening is performed, the individual must sign a new ICF and will be assigned a new identification number.

B-Raf mutational status should be documented for all patients enrolled in the study. Results from previous testing or retesting of available archived tissue are acceptable. Patients who do not have results from previous testing or adequate archived tissue available for B-Raf mutation retesting will have to undergo a biopsy prior to study drug administration (although results of B-Raf mutational status are not required before study drug administration).

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] Part A: Have histological or cytological diagnosis of cancer that is advanced and/or metastatic. 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 disease or have a disease for which no proven effective therapy exists.

Part B: All patients must have histological or cytological evidence of cancer that is advanced and/or metastatic and have one of the alterations in the Ras/Raf pathway assessed by previous local somatic mutation testing (from archived tissue) listed below. Patients must have failed or be ineligible for available therapies for their disease, or have a disease for which no proven effective therapy exists.

- Confirmation Cohort A: Advanced unresectable/metastatic melanoma carrying a B-Raf V600X (where X represents any amino acid) mutation that has relapsed after treatment with B-Raf inhibitors, MEK inhibitors, or the combination of B-Raf/MEK inhibitors.

- Confirmation Cohort B: Advanced unresectable/metastatic melanoma carrying a NRas mutation.

- Confirmation Cohort C: Advanced unresectable/metastatic NSCLC carrying a KRas or B-Raf mutation.

[2] Part A: Have the presence of measurable and/or nonmeasurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (Eisenhauer et al. 2009). Tumor lesions located in a previously irradiated area can be considered measurable only if they are new or if have shown unequivocal progression.

Part B: Have the presence of measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (Eisenhauer et al. 2009).

[3] Part A and Part B: Have a tumor that is safely amenable to core needle or excisional biopsies

[4] Are ≥18 years of age.

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

[6] Have adequate organ function, including:

- Hematologic: Absolute neutrophil count (ANC) ≥1.5 x 10^9/L (without use of CSFs within the preceding 14 days), platelets ≥100 x 10^9/L (without platelet transfusion in the preceding 14 days), and hemoglobin ≥8 g/dL (without transfusion in the preceding 14 days).
- Hepatic: Bilirubin ≤1.5 times upper limits of normal (ULN) (If the total bilirubin is >1.5 times ULN, and a subsequent direct bilirubin test is normal, the investigator and the Lilly Clinical Research Physician will determine patient eligibility.), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤2.5 times ULN. If the liver has tumor involvement, AST and ALT equaling ≤5 times ULN are acceptable
- Renal: Serum creatinine ≤1.5 times ULN and calculated creatinine clearance ≥60 mL/min/1.73m^2 (Creatinine Clearance Formula, Protocol Attachment 7)

[7] Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) scale (refer to Attachment 6).

[8] Have discontinued all previous therapies for cancer (including chemotherapy, immunotherapy, corticosteroids, and radiotherapy) and recovered from the acute effects of therapy (treatment related toxicity resolved to Grade 1 or less) for at least 5 half-lives or a minimum of 4 weeks, (at least 42 days for mitomycin-C or nitrosoureas, 14 days for radiotherapy), prior to initiating study treatment.

At the discretion of the investigator, hormone-sensitive prostate cancer patients who are stable on gonadotropin-releasing hormone (GnRH) agonist therapy and breast cancer patients who are stable on anti-estrogen therapy (for example, an aromatase inhibitor) may have that treatment continued while they are enrolled in Study JBDA.

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

[10] Males and females with reproductive potential must agree to use medically approved contraceptive precautions during the trial and for 6 months following the last dose of study drug.

[11] Females with child bearing potential must have a negative serum pregnancy test ≤3 days before the first dose of study drug.

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

[13] Are able to swallow capsules.

6.1.2. Exclusion Criteria

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

[14] Have received treatment within 5 half-lives or a minimum of 28 days of the initial dose of study drug with an investigational product or non-approved use of a drug or device (other than the study drug/device used in this study) for non-cancer indications or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

[15] Have serious preexisting medical conditions that in the opinion of the investigator would preclude participation in the study.

[16] Have active central nervous system (CNS) or leptomeningeal metastasis (brain metastasis) at the time of study entry. Patients with a history of a CNS metastasis previously treated with curative intent (eg, stereotactic radiation or surgery) that have not progressed on follow-up imaging, have been asymptomatic for at least 28 days and are not receiving corticosteroids and or/anticonvulsants, are eligible. Patients with signs or symptoms of neurological compromise should have appropriate radiographic imaging performed before study entry to rule out brain metastasis.

[17] Have current hematologic malignancies.

[18] Have an active fungal, bacterial, and/or known viral infection including human immunodeficiency virus (HIV) or viral (A, B, or C) hepatitis (screening is not required).

[19] Part A: Have a second primary malignancy that in the judgment of the Investigator and of the sponsor may affect the interpretation of results.

Part B: Have a second primary malignancy treated within the previous 5 years

- Exemptions will be permitted on a case-by-case basis after prior approval by the lead Lilly physician or designate, if in the judgment of the investigator the patient's risk of recurrence and death is very low.
- **Exceptions:** The following will be allowed

- Adequately treated nonmelanoma skin cancer or in situ carcinoma of any origin regardless of the time of treatment

[20] Have QTcF (Fridericia corrected) interval of >470 msec on screening electrocardiogram (ECG).

[21] Have significant clinical/instrumental findings of:

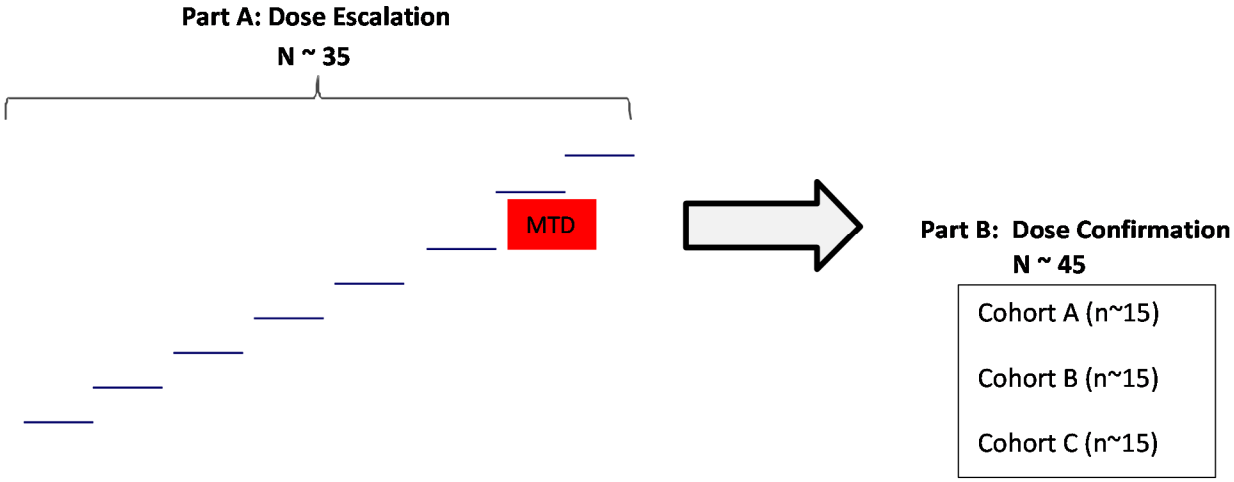
- Advanced dry age-related macular degeneration (AMD) or any wet-AMD.
- Central or branch retinal artery or venous occlusion with significant vision loss
- Moderate or worse non-proliferative diabetic retinopathy that is undergoing active treatment
- Active non-drug related uveitis, or evidence of any drug-related active ocular inflammation, including but not limited to, anterior chamber cell, vitreous cell, and active keratic precipitates
- macular atrophy due to other cause or retinal thinning on Optical Coherence Tomography (OCT) examination.
- Night vision impairment that is of recent onset (in the last year), sudden and progressive
- Other retinal diseases that cause current visual impairment or would likely cause visual impairment over the time period of the study, as assessed by an ophthalmologist

6.2. Summary of Study Design

Study JBDA is a multicenter, nonrandomized, open label, dose-escalation Phase 1 study of oral LY3009120 in patients with advanced or metastatic cancer. Patients will receive LY3009120 administered orally every 12 hours (BID) daily, in a 28-day cycle. LY3009120 will be administered as a flat dose. Study JBDA will consist of a dose-escalation phase in patients with advanced/metastatic cancer (Part A) followed by a dose-confirmation phase in advanced or metastatic melanoma carrying B-Raf or NRas mutations and NSCLC carrying KRas or B-Raf mutation (Part B).

The dose-escalation phase (Part A) (Figure JBDA 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 7.2.2.1) is determined. Patients will be enrolled in cohorts starting with the first dose level at 50 mg BID; dose levels of LY3009120 ranging from 50 to 700 mg BID may be evaluated. Table JBDA 7.1 outlines the proposed dose-escalation scheme. The maximum dose increase that will be allowed is 100%. If the MTD has not yet been reached at the highest prespecified dose level, then additional dose levels may be investigated based on both safety and the available PK data. However, dose increments beyond 700 mg BID will never exceed a maximum increment of 33%. Patients in all cohorts will not be enrolled in the next cohort until safety from the previous cohort has been assessed. In Part A, the sample size is estimated to be approximately 30 to 35 patients depending on the relationship between exposure and toxicity as well as the relationship between exposure and pharmacodynamic effects.

After the last patient on Part A has completed Cycle 1 and the recommended dose for the dose-confirmation phase is determined, Part B will begin following an interim review of the data, as outlined in Section 10.9. The dose-confirmation phase will be opened in 3 cohorts of approximately 15 patients each, treated at a dose no greater than the MTD.



Cohort A: Advanced unresectable/metastatic melanoma carrying a B-Raf V600X (where X represents any amino acid) mutation that has relapsed after treatment with B-Raf inhibitors, MEK inhibitors, or the combination of B-Raf/MEK inhibitors
Cohort B: Advanced unresectable/metastatic melanoma carrying a NRas mutation
Cohort C: Advanced unresectable/metastatic NSCLC carrying a KRas or B-Raf mutation

Figure JBDA 6.1. Study Design

The total sample size for Parts A and B is estimated to be approximately 80 patients. A total of approximately 45 patients has been selected in the dose-confirmation phase to ensure an adequate sample size for assessing the safety, PK, and preliminary efficacy signals. The sample size of approximately 15 for each confirmation cohort provides a reasonable power to explore preliminary signals of efficacy. If we assume that a true overall response (complete response [CR] + partial response [PR]) rate less than 10% indicates inadequate anti-tumor activity, then at a one-sided type 1 error rate of 5%, the sample size of 15 will provide 73% power if the true overall response rate is 30% or higher.

pERK will be investigated as one of the candidate biomarkers. We are looking for 50% or higher pERK inhibition in treated patients. If we assume less than 10% patients reach 50% or higher inhibition, then 100% biopsies in 15 patients will provide 73% power if more than 30% patients reach 50% or higher inhibition, at a one-sided type 1 error rate of 5%.

The planned duration of treatment is 2 cycles. Patients may, however, remain on study for additional cycles if they are receiving clinical benefit (stable disease, partial response [PR], or complete response [CR]) until they fulfill one of the criteria for study discontinuation (Section 6.3). Refer to Attachment 1 for the Study Schedule.

6.2.1. Study Completion and End of Trial

This study will be considered complete (that is, the scientific evaluation will be complete) after all patients have been discontinued from the treatment and have completed protocol defined follow-up period.

"End of trial" refers to the date of the last visit or last scheduled procedure for the last patient.

6.3. Discontinuations

6.3.1. Discontinuation of Patients

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

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

- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Investigator/Physician Decision
    - the investigator/physician decides that the patient should be discontinued from the study.
    - 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 discontinued from the study
- Sponsor Decision
    - Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- The patient has evidence of progressive disease.
- The patient experiences unacceptable toxicity.
- The patient is noncompliant with study procedures and/or treatment (Section 7.6).

- The patient's treatment is delayed for more than 14 days as the result of a drug-related AE (refer to Section 7.2.4) upon discussion with Lilly CRP.

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

LY3009120 will be supplied up to a maximum dose strength of 100 mg capsules for oral consumption. LY3009120 capsules should be stored within the temperature range stated on the label. Investigators should instruct patients to store the capsules at home in the original container and to keep out of the reach of children. Capsules should not be opened, crushed, or dissolved.

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

7.2. Study Drug Administration

The investigator or designee is responsible for:

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

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

7.2.1. Dosing Schedule

During both the dose-escalation phase (Part A) and the dose-confirmation phase (Part B) LY3009120 will be administered orally BID daily in a 28-day cycle. **In Part A only**: on Cycle 1 Day 1, the evening dose should be omitted to enable characterization of a full PK profile. The protocol may be amended to explore alternative schedules as a result of interim PK/PD data collection and analysis. During all cycles, study drug should be taken at approximately the same time. Oral study drug will be taken at least 2 hours after and 2 hours before any food intake.

Patients should take study drug at least 2 hours after their last meal/snack and wait at least 2 hours before eating again. Water consumption will be allowed at any time, while the same guidelines provided for food intake should be followed for any other liquid consumption. Any deviations should be documented in the patient diary. If a patient misses or vomits a dose, that dose should be omitted.

During Cycle 1 and Cycle 2, patients will record the time of dosing and number of capsules taken in a diary. Clinic personnel will instruct patients to pay particularly close attention to record this information accurately on days of PK assessments (Attachment 4).

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. To allow for recovery from toxicity, a delay of

≤14 days in the start of a cycle (Dose 1) will be permitted for Cycle 2 and beyond and does not constitute a protocol violation.

7.2.2. Dose Escalation Phase

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis until the maximum tolerated dose (MTD) is determined.

Safety data, in particular adverse events (AEs), will be the primary criteria for the dose escalation. In addition, if available at the time of dose escalation decision, pharmacokinetics (eg, C_{max}, AUC, and CL) results will be used as secondary/supporting data for dose escalation. No dose escalation can occur without prior discussion and agreement between the investigator and the Lilly study team; the decision will be documented in writing.

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

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

Dose-limiting toxicity (DLT) is defined as an adverse event (AE) during Cycle 1 for a patient enrolled in Part A that is possibly related to the study drug and fulfills any one of the following criterion using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.0:

- ≥CTCAE Grade 3 non-hematological toxicity. Exceptions will be made for:
    - Nausea, vomiting, diarrhea, or constipation that can be controlled with appropriate care. Grade 3 and Grade 4 nausea, vomiting, or diarrhea should be considered DLT if persisting more than 48 hours despite maximum supportive intervention.
    - Grade 3 elevations of ALT and/or AST lasting fewer than 8 days, without evidence of other hepatic injury, in the setting of preexisting hepatic metastasis and baseline elevation of these values, may not be considered a DLT if agreed by the study investigator and Lilly CRP.
    - Grade 3 rash that resolves or improves to a Grade 2 or less within 7 days and remains tolerable may not be considered a DLT if agreed by the study investigator and Lilly CRP/CRS.
- CTCAE Grade 4 hematological toxicity of >5 days duration.
- Grade 4 thrombocytopenia of any duration
- Grade 3 thrombocytopenia with bleeding
- Grade 3 febrile neutropenia
- 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 for a patient enrolled in Part B (including Cycle 1) 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 a safe dose that has the highest probability of DLT in the targeted toxicity interval (20 to 35%). A safe dose means that the probability of DLT larger than 35% is below 25%.

7.2.2.2. Dose Escalation Method

Table JBDA 7.1. outlines the proposed dose-escalation scheme. In this study, the escalation will start from the lowest planned dose, the maximum allowed dose increment is 100%, and each new dose level will have a minimum of 3 patients enrolled to it. The Bayesian model-based toxicity band method (Neuenschwander et al 2008) that incorporates prior expectations about the dose-toxicity curve will be fitted to the data at the end of each cohort to recommend a dose for the next cohort. The toxicity band method is a Bayesian model-based design with built-in escalation with overdose control mechanism. After each cohort, the toxicity band model will utilize data from all available cohorts to make dose recommendation, based on the model based posterior probability of a DLT at each dose, and the overdose control criteria. The toxicity band method will stop if the pre-specified maximum number of subjects is reached or the recommended next dose has been taken by 9 patients.

During the escalation, the investigators and Lilly CRP will consider both the model recommendation and the observed DLT rate at each cohort to determine the next dose level and determine when to stop the escalation. Dose levels for each cohort will not exceed those recommended by the toxicity band model. 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 or higher dose levels will be explored if deemed necessary after discussion between the sponsor and investigators. The JBDA toxicity band model has the ability to accommodate additional dose levels naturally.

Details regarding the JBDA toxicity band design are provided in Attachment 10.

Table JBDA 7.1. Proposed Dose Escalation Scheme

Dose level	LY3009120 Dose (given BID) (mg)	Predicted Median AUC0-τ,ss (ng*h/mL)	Predicted 5th and 95th percentiles AUC0-τ,ss (ng*h/mL)	Predicted Median $C_{max,ss}$ (ng/mL)	Predicted 5th and 95th percentiles $C_{max,ss}$ (ng*h/mL)
1	50	1320	571-2560	139	63-250
2	100	2250	989-4550	232	108-442
3	200	2620	1150-5050	272	125-499
4	300	2770	1220-5310	290	140-528
5	400	3230	1440-6250	339	160-618
6	500	3780	1670-7460	393	187-750
7	600	3840	1630-7690	407	182-773
8	700	3980	1770-7780	419	201-771

Abbreviation: AUC0-τ,ss = area under the plasma concentration versus time curve from time 0 to the end of the dosing interval (where τ=12h); $C_{max,ss}$ = maximum observed drug concentration during a dosing interval at steady state.

If, during dose escalation, a situation presents itself that is not described above, the investigator and Lilly CRP will determine the best method to select the appropriate dose for the patient(s) involved using all available information. This decision will be documented in writing. No dose escalations can occur without prior discussion and agreement between the site-specific investigator and the Lilly CRP. Written notification will be sent to the site specifying the dose to be used for each patient at each dose level.

The first patient enrolled in Part A of the study (Cohort 1) must complete 28 days of dosing before enrolling subsequent patients at that dose level. Once the first patient has completed 28 days of dosing without significant toxicity, the second and third patients may be enrolled concurrently. For cohort 2, the first patient must complete 15 days before enrolling subsequent patients. For cohorts 3 and beyond patients may be enrolled concurrently.

7.2.3. Dose Confirmation Phase

Once the MTD has been defined, the dose-confirmation phase will be opened. Enrollment will be expanded by approximately 45 additional evaluable patients with advanced unresectable/metastatic melanoma and NSCLC. The dose(s) to be studied in Part B will be defined at the end of dose escalation after a safety, PK, and PD review. These dose(s) will not exceed the MTD.

If DLT-equivalent toxicities in the first cycle (that is, toxicities that would meet the DLT criteria in Section 7.2.2.1) occur in 33% or more of patients within this confirmation phase, 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 confirmation portion. If DLT-equivalent toxicity occurs in one third or more of patients during

Cycles 1 or 2 of Part B (with a minimum of 6 patients enrolled), the enrollment of new patients will cease until the Lilly CRP or CRS and study investigators assess the severity and nature of the toxicity.

The safety review and decision will be documented in writing.

7.2.4. Dose Adjustments and Delays

7.2.4.1. Dose Adjustments within a Cycle

Part A: In the event that a patient experiences a DLT, DLT-equivalent or a Grade 3/4 toxicity that is not dose-limiting, treatment will be interrupted. Dosing can be resumed after resolution of the toxicity to baseline levels at the next lower dose level already deemed safe upon discussion with the Lilly CRP.

Part B: In the event that a patient experiences a DLT-equivalent toxicity that resolves with treatment interruption, at the investigator's discretion and with the agreement of the Lilly physician or their designate, treatment may be resumed at a lower dose level than the one that was associated with the DLT event.

Part A and Part B: In the event that a patient experiences visual symptoms**,** or an abnormality is detected during in-treatment eye/vision assessment, treatment will be interrupted and appropriate therapeutic measures will be taken. After resolution of symptoms to baseline and/or normalization of eye tests, dosing can resume at the next lower dose level already deemed safe, after discussion with the Lilly CRP.

7.2.4.2. Dose Adjustment between Cycles

Before the start of each cycle, hematological toxicity except anemia must resolve to baseline and all nonhematological toxicities must resolve to CTCAE v4.0 Grade 0, 1, or baseline (except alopecia and fatigue). The start of a cycle may be delayed up to 2 weeks to allow sufficient time for recovery. Patients who do not recover from toxicity within 2 weeks should be discontinued. If the patient has received granulocyte colony stimulating factors (G-CSFs) (see Section 7.5) and/or if the patient is in Cycle 3 or beyond and is continuing to receiving benefit from therapy, additional delays may be acceptable if agreed upon by both the investigator and sponsor.

The dose should be reduced to the previous dose level for the next cycle of therapy if a patient had at least 1 of the following events or if the investigator thinks it is in the best interest of the patient:

- A DLT-equivalent toxicity (Part A patients in Cohort 2 and above; all patients enrolled in Part B)
- Omission of more than 25% of doses in a single cycle due to toxicity (Part B only).

If a patient experiences a DLT-equivalent toxicity at the reduced dose, then he/she will be discontinued from treatment. If the patient requires a dose reduction or omission in the absence of significant toxicity, then he/she may continue with treatment if the investigator determines that he/she is receiving benefit. Re-escalation to the original dose is acceptable in the absence of

continuing toxicity, provided that this dose is not greater than the declared MTD. If subsequent dose reduction is again required, the patient must be maintained at the reduced dose level for all remaining cycles. If a patient in the first cohort experiences a DLT in the first cycle of treatment, he/she will be discontinued from the study.

7.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive LY3009120 in this study. Before each patient's enrollment into the study, an eligibility check must be conducted between the investigational site and the Lilly clinical research personnel to confirm that each patient meets all enrollment criteria. Upon confirmation of eligibility, the sponsor will confirm the dose, cohort, and identification number assignment for each patient. No dose escalations (that is, to the next cohort) can occur without prior discussion and agreement with the responsible Lilly CRP.

If investigators have eligible patients who have consented concurrently, up to 6 patients may be entered at a particular dose level provided that accrual has not ceased due to excessive toxicity. This enrollment procedure is allowed because of the advanced disease state of this patient population and the screening involved in defining eligibility. This event should be approved by the sponsor following discussions with the investigators.

7.4. Blinding

This is an open-label study.

7.5. Concomitant Therapy

No other chemotherapy, radiotherapy, immunotherapy, cancer-related hormone therapy, or experimental drugs will be permitted while the patients are on this study. An exception will be made for prostate cancer patients continuing GnRH agonist therapy or breast cancer patients continuing antiestrogen therapy (for example, an aromatase inhibitor). The need for any form of radiotherapy (including palliative) will be cause for early discontinuation from the study. In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate early discontinuation from the study. Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the case report form.

Patients should receive full supportive care with the exception that the routine use of G-CSF is not permitted during this study. Patients should not receive G-CSF prophylactically in any cycle. In Part A, no G-CSF use will be allowed in Cycle 1 unless hematological DLT is declared. In Cycle 2 and above and in Part B, patients may receive G-CSF or granulocyte-macrophage colony-stimulating factor therapeutically for neutropenia or fever with neutropenia according to the most recent update of the American Society of Clinical Oncology (ASCO) guidelines for the use of white blood cell growth factors (Smith et al. 2006). During treatment with G-CSFs study drug administration will be discontinued. G-CSFs must be discontinued at least 24 hours before resuming treatment with study drug treatment (pegylated colony-stimulating factors should be discontinued at least 14 days before resuming therapy with study drug). 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).

Based on the available nonclinical data, there is a possible risk of clinical drug-drug interaction when LY3009120 is administered with agents that are metabolized by CYP3A4. In the absence of more data to refine the risk of interaction, caution is warranted in the concomitant use of LY3009120 with CYP3A4 substrates with a narrow therapeutic margin (for example, alfentanil, cyclosporine, diergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus).

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

7.6. Treatment Compliance

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

The patient must take ≥75% of the intended doses 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. Potential discontinuation of a patient due to study drug noncompliance will be discussed between the investigator and the Lilly CRP before making the final determination for discontinuation.

7.6.1. Evaluable Patients

Patients who withdraw from the study before receiving study drug 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.

In Part A, patients who discontinue from the study before receiving at least 75% of planned doses of LY3009120 in Cycle 1 will be deemed non-evaluable for assessment of safety at that dose level and may be replaced unless they experience a DLT or dose omission/reduction due to toxicity prior to withdrawal.

Patients who receive at least 75% of the planned doses of LY3009120 but discontinue from study treatment before the end of Cycle 1 will be considered evaluable for the assessment of a dose level provided it can be documented whether the patient did or did not experience a DLT within 28 days of Day 1 in Cycle 1.

Part A: If the patient is noncompliant during Cycle 1 due to reasons other than drug-related toxicity he or she will be considered non-evaluable and may be replaced.

Part B: If the patient is noncompliant during Cycle 1 or Cycle 2 due to reasons other than drug-related toxicity or disease progression, he or she will be considered non-evaluable and may be replaced for the purpose of response assessment.

In Part A, nonevaluable patients may be replaced to ensure that no fewer than 3 patients receive at least 75% of planned doses of LY3009120 in Cycle 1 at each dose level, unless enrollment to that cohort has stopped due to DLT.

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

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

8.1. Safety Evaluations

The safety and tolerability of LY3009120 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 plan that will permit initial characterization of the safety profile of LY3009120 in patients. Study procedures and their timing (including tolerance limits for timing) are described in the Study Schedule (Attachment 1).

Blood and urine samples will be collected at the times specified in the Study Schedule (Attachment 1). Standard laboratory tests, including chemistry, hematology, ECGs, and urinalysis panels, will be performed. A serum pregnancy test will be administered to females of child bearing potential. Other clinical laboratory tests will also be collected. Attachment 2 lists the specific tests that will be performed for this study.

8.1.1. Safety Data Collection and Review

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

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

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

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 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. Any clinically significant findings from labs, vital sign measurements, and so on, that occur should also be reported to Lilly or its designee as an AE. Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect.

The investigator, monitor, and sponsor will review the collected data regularly for evidence of AEs. All patients will be assessed routinely for AEs as outlined in the study schedule. All AEs observed will be graded using CTCAE v4.0. Any minor version of CTCAE v 4.0 (for example version 4.0X) may be used for this study. Minor CTCAE v 4.0 updates from the NCI will not necessitate a protocol amendment.

CTCAE v4.0 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching terminology within the CTCAE v4.0 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event. Note that both CTCAE term (actual or coded) and severity grade must be selected by study site personnel and collected on the CRF. This collection is in addition to verbatim text used to describe the AE.

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

Cases of pregnancy that occur during maternal or paternal exposures to study drug should be reported. Upon documentation of pregnancy, the patient must be removed from the study and treatment with study drug must be stopped immediately. Data on fetal outcome and breastfeeding should be collected, if feasible, for regulatory reporting and drug safety evaluation.

For all enrolled patients, study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. While the patient is on study, site personnel will record any change in these preexisting condition(s) and the occurrence and nature of any AEs. In addition, all AEs related to protocol procedures are reported to Lilly or designee.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via designated data transmission methods, the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure or study drug, via designated data transmission methods.

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

- **Related**: a direct cause and effect relationship between the study treatment and the AE is likely.
- **Possibly Related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible.

- **Unrelated**: without question, the AE is definitely not associated with the study treatment.

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

8.1.2.1. Serious Adverse Events

Previously planned (prior to signing the ICF) surgeries and non-disease related elective surgeries planned during the course of study, should not be reported as SAEs unless the underlying medical condition has worsened or appeared 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 one of the following outcomes:

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

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

Death due to disease progression should not be reported as an SAE unless the investigator deems it to be related to the use of study drug(s).

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. Refer to Attachment 5 (Recommendations for Reporting Serious Adverse Events) for a list of recommended information to have available when contacting Lilly to report an SAE. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

8.1.2.2. Adverse Event and Serious Adverse Event Reporting

8.1.2.2.1. Prior to Administration of Study Drug(s)

During screening, all AEs and SAEs (regardless of relatedness to protocol procedures) are collected after the patient has signed the informed consent form. For patients who do not enroll

in the trial (that is, receive at least 1 dose of LY3009120), only AEs and SAEs related to protocol procedures are required to be collected.

8.1.2.2.2. On Therapy

All AEs and SAEs, regardless of relatedness to study drug 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 or protocol procedures, occurring during the 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 ± 3 days after the last dose of study drug.

Following the safety assessments, which mark the end of the first follow-up visit (Visit 801), a long-term follow-up will begin for dermatological assessment. Dermatological assessment will be performed every 2 months up to 6 months post-treatment discontinuation (long-term follow-up Visits 802, 803, and 804), after which the patient will be discontinued from the study, unless there is an ongoing AE or SAE that is possibly related to study drug. In this instance, the patient should be followed in subsequent follow-up visits, until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. During the long-term follow-up period (V802 to V804), ongoing or new AEs/SAEs possibly related to study drug(s) or protocol procedures are required to be reported.

After V804, if an additional follow-up period is necessary, new or ongoing AEs and new SAEs are not required to be reported, unless the investigator feels the events were related to either study drug, drug delivery system, or a protocol procedure.

8.1.2.3. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious adverse events that are not listed in the Development Core Safety Information (DCSI) in the Investigator's Brochure (IB) and that the investigator identifies as related to study drug or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulatory regulations and the associated detailed guidances.

8.1.2.4. Summary of AE/SAE Reporting Guidelines

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

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

Timing	Types of AEs/SAEs Reported
Prestudy (baseline assessments) (Starts at the signing of informed consent and ends just before the first dose of study drug)	Preexisting conditions All AEs/SAEs regardless of relatedness
On therapy (Starts at first dose of study drug(s) and ends at last dose of study drug(s))	All AEs/SAEs regardless of relatedness
Follow-up Visit (Visit 801) (Starts just after the last dose of study drugs(s) and ends when end of study safety assessments are completed 30 ± 3 days after last dose of study drugs(s) OR the planned end of the cycle)	All AEs/SAEs regardless of relatedness
Long-term Follow-up Visits (Visits 802, 803, 804) (Dermatological assessment every 2 months while on therapy and continuing up to 6 months after discontinuation of LY3009120)	Ongoing or new AEs/SAEs possibly related to study drug(s) or protocol procedures
Subsequent Follow-up visits, if necessary	Ongoing AEs possibly related to study drugs or protocol procedures All SAEs related to protocol procedures or study drug

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

8.1.3. Other Safety Measures

8.1.3.1. Eye Safety Monitoring

Ophthalmological assessments will be performed as specified in the Study Schedule (Attachment 1) and as clinically indicated. Technical details and sequence of eye assessments will be defined in a study-specific Ophthalmology Manual provided to the sites.

Eye testing will include

- Distance acuity (Visual acuity charts using refraction-based visual acuity measurement)
- Ophthalmoscopy
- Slit lamp exam
- Retinal photography
- OCT with Spectral Domain Optical Coherence Tomography (SD-OCT) scan of the macula
- Fundus autofluorescence imaging

Imaging data and functional visual data from the screening visit will be provided from the local ophthalmologist to the Investigator.

8.1.3.2. Dermatological Safety Monitoring

New primary cutaneous malignancies have been reported with B-Raf inhibitors. Although LY3009120 is a pan-Raf inhibitor, which may mitigate some of the increased risk of cutaneous

malignancies hypothesized to be related to paradoxical Ras activation by B-Raf inhibition, dermatological evaluations will be performed as specified in the Study Schedule (Attachment 1) (at baseline, every 2 cycles while on therapy, and for up to 6 months following discontinuation of LY3009120).

8.1.3.3. Electrocardiograms

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

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

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

On Cycle 1 Day 1 and on Cycle 1 Day 15, a 3-hour post-dose ECG will be collected to coincide the ECG at the anticipated maximal plasma concentrations (C_{max}) with the pharmacokinetic sampling in order to evaluate concentration-QT relationship for LY3009120.

On Cycle 1 Day 15 a baseline ECG will be collected to coincide the ECG at the anticipated steady-state plasma concentration (Css) with PK sampling in order to evaluate concentration-QT relationship for LY3009120.

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

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

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

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

8.1.4. Safety Monitoring

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

Lilly will review SAEs within time frames mandated by standard operating procedures, and will review trends, laboratory analytes, and AEs at periodic intervals.

If a study patient experiences elevated ALT ≥5X upper limit of normal (ULN) and elevated total bilirubin ≥2X ULN, clinical and laboratory monitoring should be initiated by the investigator.

For patients entering the study with ALT ≥3X ULN, monitoring should be triggered at ALT ≥2X baseline.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP regarding collection of specific recommended clinical information and follow-up laboratory tests (see Attachment 3).

8.1.5. Complaint Handling

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

Complaints related to concomitant drugs/drug delivery systems are reported directly to the manufacturers of those drugs/devices 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.

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

Attachment 4 lists the schedule for PK and PD sample collections in this study.

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

8.2.1. Samples for Study Qualification and Health Monitoring

Blood and urine samples will be collected at the times specified in the study schedule (Attachment 1).

Standard laboratory tests, including hematology and urinalysis panels, will be performed and analyzed by a local laboratory. Chemistry panels will be performed and analyzed centrally. Enrollment or dose adjustment decisions may be based upon chemistry results performed at a local laboratory; however, a sample must be sent to the central lab. These central chemistry laboratory results will be used for subsequent safety analyses. In the event of minor discrepancies between local and central laboratory results, the investigator may use the local results for treatment decisions, and the central laboratory results will remain part of the safety database. Discrepancies between local and central results that may have an impact on treatment decisions will not be considered protocol violations. A serum pregnancy test, for females with child-bearing potential, will be performed locally.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.2.2. Samples for B-Raf Mutational Status Assessment

Information on the B-Raf mutational status will be collected for all patients enrolled in the study.

Historical test results: Results from historical tests will be acceptable.

Archived tissue: For patients who do not have historical B-Raf test results available, genetic analysis will be performed on any available adequate archived specimen of the patient's tumor.

Study tumor biopsies: Patients who do not have historical B-Raf testing results or adequate archival tumor tissue will undergo a pre-treatment tumor biopsy before receiving the first dose of study drug. Tumor tissue biopsies will be taken either by core needle or excisional biopsy. The size of the sample will be dependent upon the procedure utilized to obtain the sample. Patients will be able to receive treatment before the results of the biopsy are available.

8.2.3. Samples for Drug Concentration Measurements

8.2.3.1. Pharmacokinetic Samples

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

Blood samples of approximately 3 mL will be drawn into EDTA tubes for measurement of LY3009120. A maximum of 5 additional PK samples per patient (15 mL) may be drawn during the study if warranted and agreed upon by both the investigator and sponsor. Instructions and supplies for the collection, handling, and shipping of blood or tissue samples will be provided by either the sponsor or the central laboratory.

The actual dose and timing (24-hour clock time) of each dose and sampling will be recorded as well as the time of the nearest meal associated to the dose received.

These samples will be analyzed at a laboratory designated by the sponsor. Plasma concentrations of LY3009120 will be assayed using a validated LCMS method.

All bioanalytical samples will be stored in the United States.

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

In Part B, urine samples may be collected for the first 10 hours after dose administration from up to 3 patients for exploratory metabolism work as deemed appropriate. Measure and record total urine volumes collected. Aliquots of the urine (approximately 10 mL) will be frozen and stored until qualitatively analyzed for LY3009120 and other potential metabolites. Because the urinary work is considered exploratory, failure to obtain a urine sample for any reason will not be considered a protocol violation.

Bioanalytical samples collected to measure study-drug concentration and metabolism, and/or protein binding will be retained for a maximum of 2 years following last patient visit for the study.

8.2.3.1.1. Identification of LY3009120 Metabolites in Urine and Plasma

While every effort should be made to collect all urine samples for exploratory work, failure to obtain a sample for any reason will not be considered a protocol violation. Urine will be used for exploratory metabolite identification and quantification of parent concentrations. Total urine output for approximately 10 hours post-dose of LY3009120 will be recorded, pooled and refrigerated. The total urine volume will be recorded, and samples of approximately 10 mL will be stored frozen. The remaining urine will be discarded. Supplies required for the collection and shipment of the patients' stored samples will be supplied by the sponsor. Sample handling and shipment to the central laboratory will occur per instructions given to the study site. All urine samples will be stored in the United States and will be retained for a maximum of 2 years following the last patient visit for the study. Some PK plasma samples may be used to identify the structures of LY3009120 metabolites to determine the concentrations of those metabolites at the discretion of the sponsor. Plasma and urine samples will be analyzed at laboratories designated by the sponsor. LY3009120 metabolite identification and quantification will be conducted by bioanalytical techniques deemed appropriate by the sponsor.

8.2.4. Pharmacodynamic and Tailoring Biomarker Tumor Samples

Pharmacodynamic and tailoring biomarker tumor samples will be collected as specified in the Study Schedule (Attachment 1) and PK, PD and Pharmacokinetic and Exploratory Blood Plasma Sampling Schedule (Attachment 4). Either blocks or precut, unstained slides from any available archival diagnostic specimen of the patient's tumor will be collected for biomarker-related studies.

8.2.4.1. Tissue Collection for Pharmacodynamic Studies

Part A: **Mandatory** tumor biopsies should be collected prior to treatment (following determination of eligibility [≤14 days of C1 D1]) and after 4 weeks of treatment (C1 D28 ± 14 days) for patients added to any cohort that will be expanded to determine MTD and/or for patients added to any cohort expanded to explore potential for Phase 2 dosing on the basis of PK data. Biopsy samples taken within 6 months prior to enrollment will also be permitted as long as patients have not received any recent therapies for the disease prior to starting LY3009120. Sponsor will need to review and approve the timing of in-treatment biopsies performed outside of the allowed 14-day window.

Part B: **Mandatory** tumor biopsies should be collected before treatment (following determination of eligibility [≤14 days of C1 D1]) and after 2 weeks of treatment (C1 D15 ± 5 days). Biopsy samples taken within 6 months before enrollment will also be permitted as long as patients have not received any recent therapies for the disease prior to starting LY3009120.

Tumor tissue biopsies taken either by core needle or excisional biopsy are acceptable provided adequate slides can be obtained. Cytologic samples and fine-needle aspiration specimens are not acceptable. Pathology notes accompanying the archived diagnostic tissue may also be requested.

Details for the handling and shipping of tumor biopsy samples will be provided in a separate document. Instructions and supplies required for the collection, processing, and shipment of the patients' samples will be provided by the sponsor.

The tumor tissue samples will be coded with the patient number and stored for up to a maximum of 15 years after the last patient visit for the study at a facility selected by the sponsor.

8.2.4.2. Tissue Collection for Tailoring Biomarker Studies

Tumor and plasma specimens will be collected throughout the study for the assessment of predictive biomarkers related to the activity of LY3009120, for exploratory research on new biomarkers related, but not limited, to the Raf pathway, and for evaluation of tumor specific biomarkers depending on evolving science.

Archived tissue: Precut, unstained slides from any available archival specimen of the patient's tumor will be requested (but not required) for patients enrolled in Part A.

Study tumor biopsies:

For Part A and Part B: **Mandatory** tumor biopsies will be collected as indicated in Section 8.2.4.1.

Tumor tissue biopsies will be taken either by core needle or excisional biopsy. The size of the sample will be dependent upon the procedure utilized to obtain the sample. These biomarker-related studies will include, but may not be limited to, protein and/or genetic analyses of the tumor specimen.

8.2.4.2.1. Collection Procedures of Plasma Samples for Exploratory Biomarkers

Approximately 10 mL of anticoagulated blood will be collected before treatment in Cycle 1 and again during treatment on C1 D28 (± 3 days) by venipuncture or through a central line into EDTA tubes at times specified in Attachment 4. Plasma samples will then be stored frozen. In Part B, samples will also be collected during treatment on Day 28 (± 3 days) of each cycle starting with Cycle 2 for a maximum of 9 to 12 cycles and during follow-up Visit 801.

8.2.5. Pharmacogenetic Samples

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ethical review boards (ERBs) 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 LY3009120.

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 LY3009120. 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.

8.3. Efficacy Evaluations

A secondary objective of the study is to document any antitumor activity. Refer to Attachment 1 and Attachment 9 for details regarding the timing of specific efficacy measures.

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

- Computed tomography (CT) scan
- Magnetic resonance imaging (MRI)

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

- Tumor measurement of palpable or visible lesions (refer to RECIST 1.1)
- Evaluation of tumor markers, if indicated.

- Evaluation of performance status (refer to the ECOG scale, Attachment 6).

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

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 electronic CRF or lab requisition form.

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

9. Data Management Methods

9.1. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate
- 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 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.

After the study is completed, a copy of the eCRF data and a copy of all the trial components will be sent on CD-ROM to the sponsor. A CD-ROM will also be sent to each investigative site containing only the eCRF data from that site.

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 (PRO) measures (for example, a rating scale), a daily dosing schedule or an event diary.

For data handled by a data management contract research organization (CRO), CRF data and some or all data that are related will be managed and stored electronically in the CRO system. After the final database lock at the CRO, validated data will be transferred to sponsor.

Any diagnostic data collected from a contracted vendor will be stored electronically in that central vendor's database system. Data will subsequently be transferred from the central vendor according to the contract.

Any data for which the electronic CRF will serve as the source document will be identified and documented by each site in that site's study file.

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 80 patients may be enrolled in this multicenter, open-label Phase 1 study with dose escalation followed by dose confirmation. During dose escalation, approximately 30 to 35 patients will be enrolled into cohorts sequentially and without randomization to dose. During dose confirmation, approximately 45 patients will be enrolled.

Statistical analysis of this study will be the responsibility of Eli Lilly and Company. 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 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.

10.2. Patient Disposition

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

10.3. Patient Characteristics

Patient characteristics will include a summary of the following:

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

Other patient characteristics will be summarized as deemed appropriate.

10.4. Safety Analyses

All patients who receive at least 1 dose of LY3009120 will be evaluated for safety and toxicity. Adverse event terms and severity grades will be assigned by the investigator using CTCAE, Version 4.0).

Safety analyses will include summaries of the following:

- adverse events, including severity and possible relationship to study drug
- dose adjustments

- laboratory values
- vital signs
- DLTs at each dose level
- ECG readings.

In addition, after each cohort, the toxicity-band method will be used to summarize the posterior distribution of probability of a DLT.

10.5. Pharmacokinetic Analyses

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

Pharmacokinetic parameter estimates for LY3009120 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be maximum concentration (C_{max}) and area under the concentration-time curve ($AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$ or $AUC_{\tau,ss}$) of LY3009120. Other noncompartmental parameters, such as time of half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (V/F) may be reported. 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.

Pharmacokinetic 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% confidence intervals (CIs).

10.6. Pharmacodynamic Analyses

Pharmacodynamic data from all patients undergoing PD assessments will be analyzed.

Biomarker data from all patients undergoing biomarker assessments will be analyzed by appropriate statistical methods. These data may include, but are not limited to IHC, genetic mutations that are hypothesized to be related to safety, efficacy, drug disposition or pathways associated with the mechanism of action of LY3009120.

10.7. Pharmacokinetic/Pharmacodynamic Analyses

The PK data will be combined, and analyses may be conducted to determine a relationship between exposure and clinical PD effect (eg, phospho-ERK, p27, and/or Ki67 protein expression in tumors), data permitting. This model may be used to help reassess the dose cohort escalation and schedule as the study progresses. If deemed necessary, exploratory PK/PD analysis may be employed to evaluate relationships between LY3009120 exposure and measurements of pharmacologic effects or safety.

10.8. Efficacy

The study was not designed to make an efficacy assessment. However, any tumor response data will be tabulated according to study part and patient cohort. In Part A, blood tumor markers, if applicable, will be drawn at baseline and Day 1 of each cycle.

10.9. 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, available PK/PD profiles of LY3009120 will be reviewed per cohort. Based on these interim results, modifications (eg, reductions in dose increment or changes in dosing schedule) 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.

During Part B, interim analyses may be conducted in each cohort to review available safety, PK, PD, and efficacy data once enrollment to that particular cohort (A, B, or C) has completed and all evaluable patients in that cohort have either completed 3 cycles of therapy or discontinued from the treatment.

11. Informed Consent, Ethical Review, and Regulatory Considerations

11.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study in a timely manner.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study and to document that the patient is satisfied with his or her understanding of the potential risks and benefits of participating in the study and desires to participate in the study.

The investigator is ultimately responsible for ensuring that informed consent is given by each patient or legal representative before the study is started. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study drug.

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

11.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are 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.

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

- the current IB and updates during the course of the study
- ICF
- relevant curricula vitae

11.3. Regulatory Considerations

This study will be conducted in accordance with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2) the International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) Guideline [E6]
3) applicable laws and regulations.

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

All or some of the obligations of the sponsor will be assigned to a CRO.

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

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Attachment 1. Protocol JBDA Study Schedule

Part A: Baseline Assessments

Relative Day Prior to Day 1 of Cycle 1	≤28	≤14	≤3	Comments
Informed Consent				Informed Consent Form signed (prior to performance of any protocol-specific tests/procedures)
Chest X-ray	X			May be omitted in patients having a chest CT scan for their radiological tumor assessment
Radiological Tumor Assessment	X			
Medical History		X		Including any alcohol/tobacco habits
Physical Exam		X		
Vital Signs		X		Including temperature, blood pressure, pulse rate, respiration rate
ECOG Performance Status		X		
ECG (central)		X		Central collection and storage.
Hematology (local)		X		
aPTT, PT, PT/INR (local)		X		
Serum Chemistry		X		
Urinalysis (local)		X		
Tumor Measurement (Palpable or Visible)		X		
CTCAE v 4.0 Grading (Preexisting conditions)		X		To be reported only after study eligibility is confirmed.
Concomitant Meds		X		
Tumor Markers, if applicable (local)		X		If applicable to tumor type of the patient.
Exploratory blood plasma sample		X		EDTA tube baseline collection after eligibility confirmed
Study Tumor Biopsy (designated expansion cohorts)		X		Biopsy should be taken only after study eligibility is confirmed (mandatory). Biopsy samples taken within 6 months prior to enrollment will also be permitted as long as patients have not received any recent therapies for the disease prior to starting LY3009120.
Tumor Biopsy B-Raf Status Assessment (only for patients that do not have historical B-Raf testing results or adequate archived tissue available for B-Raf retesting)	X			Patients will be able to receive treatment before biopsy results are available.
Archived Tumor Sample	X			Paraffin-embedded tumor tissue (optional). Sent after study eligibility is confirmed.
Pregnancy Test (local)			X	Negative results required prior to Cycle 1, Day 1. Only to be performed on women of childbearing potential.
Eye Safety Assessments	X			
Dermatological Evaluation		X		

Abbreviations: aPTT = activated partial thromboplastin time; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; Meds = medications; PD = pharmacodynamic; PT/INR = prothrombin time/international normalized ratio.

Part A: During and Poststudy Assessments

	Cycle 1						Cycle 2					Cycle 3-n		Follow-Up		Comments
Relative Day Within a Cycle	**1**	**2**	**8**	**15**	**22**	**28**	**1**	**8**	**15**	**22**	**28**	**1**	**28**	**Visit 801**	**Visits 802, 803, and 804 (Long-term Follow-up)**	Visit 801 is 30 days (± 3 days) after last dose of study drug; Visits 802, 803, and 804 are each 2 months in duration and will start after Visit 801.
LY3009120	X						X					X				
Physical Exam	X		X	X	X		X					X			X	After C1D1, ± 3 days while on treatment; Will not need to be repeated if performed ≤ 3 days from C1D1.
Eye Assessments						X					X					At baseline, at the end of Cycle 1 and Cycle 2, and every 2 cycles afterwards (end of C4, C6 and so on) up to 7 days before start of next cycle, and at other time points if clinically indicated.
Dermatological Evaluation												X			X	At baseline, every 2 cycles while on therapy, and every 2 months for up to 6 months following discontinuation of LY3009120.
Weight	X						X					X				After C1D1, ± 3 days while on treatment
Vital Signs	X		X	X	X		X	X	X	X		X				Temperature, PR, RR, BP. After C1D1, ± 3 days while on treatment.
ECG	X			X			X					X				In cycle 1 only, on days with PK assessments, ECGs will be performed before patients receive morning dose of study drug at the site and 3 hours post-dosing. After C2D1, ± 3 days while on treatment.

	Cycle 1						Cycle 2					Cycle 3-n		Follow-Up		Comments
Relative Day Within a Cycle	**1**	**2**	**8**	**15**	**22**	**28**	**1**	**8**	**15**	**22**	**28**	**1**	**28**	**Visit 801**	**Visits 802, 803, and 804 (Long-term Follow-up)**	Visit 801 is 30 days (± 3 days) after last dose of study drug; Visits 802, 803, and 804 are each 2 months in duration and will start after Visit 801.
Hematology	X		X	X	X		X	X	X	X		X		X		After C2D1, ± 3 days while on treatment. On days with PK assessment it will be performed before patients receive morning dose of study drug at the site.
Serum Chemistry	X		X	X	X		X	X	X	X		X		X		After C2D1, ± 3 days while on treatment; On days with PK assessment it will be performed before patients receive morning dose of study drug at the site.
Urinalysis	X						X					X				After C1D1, ± 3 days while on treatment; will not need to be performed if completed less than 3 days before Cycle 1 Day 1.
CTCAE v 4.0 Grading	X						X					X		X		Throughout study as needed.
Concomitant Meds	X						X					X		X		Throughout study as needed.
ECOG Performance Status	X						X					X				After C1D1, ± 3 days while on treatment
PK Sampling	X	X		X		X	X									See PK Sampling Attachment 4 for exact timing.
Tumor Measurement (Palpable or Visible)	X						X					X		X		After C1D1, ± 3 days while on treatment
Radiological Tumor Assessment											X		X	X		Approximately every 8 weeks (every other cycle, end of C2, C4, and so on). Up to 7 days before start of next cycle.
Blood Tumor Markers, if applicable	X						X					X				If applicable to tumor type of the patient (± 3 days while on treatment)

	Cycle 1						Cycle 2					Cycle 3-n		Follow-Up		Comments
Relative Day Within a Cycle	**1**	**2**	**8**	**15**	**22**	**28**	**1**	**8**	**15**	**22**	**28**	**1**	**28**	**Visit 801**	**Visits 802, 803, and 804 (Long-term Follow-up)**	Visit 801 is 30 days (± 3 days) after last dose of study drug; Visits 802, 803, and 804 are each 2 months in duration and will start after Visit 801.
Pharmacogenetic blood sample, stored (mandatory)	X															
Study Tumor Biopsy (**Part A, designated expansion cohorts)**						X										± 14 days
Exploratory blood plasma sample						X										

Abbreviations: BP = blood pressure; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PK = pharmacokinetic; PD = pharmacodynamic; PR = pulse rate; RR= respiration rate.

Part B: Baseline Assessments

Relative Day Prior to Day 1 of Cycle 1	≤28	≤14	≤3	Comments
Informed Consent				Informed Consent Form signed (prior to performance of any protocol-specific tests/procedures)
Chest X-ray	X			May be omitted in patients having a chest CT scan for their radiological tumor assessment
Radiological Tumor Assessment	X			
Medical History		X		Including any alcohol/tobacco habits
Physical Exam		X		
Vital Signs		X		Including temperature, blood pressure, pulse rate, respiration rate
ECOG Performance Status		X		
ECG		X		Central collection and storage
Hematology (local)		X		
aPTT, PT, PT/INR (local)		X		
Serum Chemistry		X		
Urinalysis (local)		X		
Tumor Measurement (Palpable or Visible)		X		
CTCAE v 4.0 Grading (Preexisting conditions)		X		To be reported only after study eligibility is confirmed.
Concomitant Meds		X		
Exploratory blood plasma sample		X		EDTA tube collection after eligibility confirmed
Study Tumor Biopsy (Part B, all cohorts)		X		Biopsy should be taken only after study eligibility is confirmed (mandatory).
Pregnancy Test (local)			X	Negative results required prior to Cycle 1, Day 1. Only to be performed on women of childbearing potential.
Eye Safety Assessments	X			
Dermatological Evaluation		X		

Abbreviations: aPTT = activated partial thromboplastin time; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; Meds = medications; PD = pharmacodynamic; PT/INR = prothrombin time/international normalized ratio.

Part B: During and Poststudy Assessments

	Cycle 1					Cycle 2					Cycle 3-n		Follow-Up		Comments
Relative Day Within a Cycle	**1**	**8**	**15**	**22**	**28**	**1**	**8**	**15**	**22**	**28**	**1**	**28**	**Visit 801**	**Visits 802, 803, and 804 (Long-term Follow-up)**	Visit 801 is 30 days (± 3 days) after last dose of study drug; Visits 802, 803, and 804 are each 2 months in duration and will start after Visit 801.
LY3009120	X					X					X				
Physical Exam	X	X	X	X		X					X			X	After C1D1, ± 3 days while on treatment; Will not need to be repeated if performed ≤ 3 days from C1D1.
Eye Assessments					X					X					At baseline, at the end of Cycle 1 and Cycle 2, and every 2 cycles afterwards (end of C4, C6, and so on) up to 7 days before start of next cycle, and at other time points if clinically indicated. Assessment can also be performed on the D1 of the next cycle (predose).
Dermatological Evaluation											X			X	At baseline, every 2 cycles while on therapy, and every 2 months for up to 6 months following discontinuation of LY3009120.
Weight	X					X					X				After C1D1, ± 3 days while on treatment
Vital Signs	X	X	X	X		X					X				Temperature, PR, RR, BP. After C1D1, ± 3 days while on treatment.
ECG	X		X			X					X				In cycle 1 only, on days with PK assessments ECGs will be performed before patients receive morning dose of study drug at the site and 3 hours post-dosing After C2D1, ± 3 days while on treatment.

	Cycle 1					Cycle 2					Cycle 3-n		Follow-Up		Comments
Relative Day Within a Cycle	**1**	**8**	**15**	**22**	**28**	**1**	**8**	**15**	**22**	**28**	**1**	**28**	**Visit 801**	**Visits 802, 803, and 804 (Long-term Follow-up)**	Visit 801 is 30 days (± 3 days) after last dose of study drug; Visits 802, 803, and 804 are each 2 months in duration and will start after Visit 801.
Hematology	X	X	X	X		X	X	X	X		X		X		After C2D1, ± 3 days while on treatment; On days with PK assessment it will be performed before patients receive morning dose of study drug at the site.
Serum Chemistry	X	X	X	X		X	X	X	X		X		X		After C2D1, ± 3 days while on treatment; On days with PK assessment it will be performed before patients receive morning dose of study drug at the site.
Urinalysis	X					X					X				After C1D1, ± 3 days while on treatment; will not need to be performed if completed less than 3 days before Cycle 1 Day 1.
CTCAE v 4.0 Grading	X					X					X		X		Throughout study as needed.
Concomitant Meds	X					X					X		X		Throughout study as needed.
ECOG Performance Status	X					X					X				After C1D1, ± 3 days while on treatment
PK Sampling	X		X	X						X		X			See PK Sampling Attachment 4 for exact timing.
Tumor Measurement (Palpable or Visible)	X					X					X		X		After C1D1, ± 3 days while on treatment
Radiological Tumor Assessment										X		X	X		Approximately every 8 weeks (every other cycle, end of C2, C4, and so on). Up to 7 days before start of next cycle.
Urine Metabolite Collection	X														To be collected from up to 3 patients enrolled in Part B; not a protocol violation if not collected.

	Cycle 1					Cycle 2					Cycle 3-n		Follow-Up		Comments
Relative Day Within a Cycle	**1**	**8**	**15**	**22**	**28**	**1**	**8**	**15**	**22**	**28**	**1**	**28**	**Visit 801**	**Visits 802, 803, and 804 (Long-term Follow-up)**	Visit 801 is 30 days (± 3 days) after last dose of study drug; Visits 802, 803, and 804 are each 2 months in duration and will start after Visit 801.
Pharmacogenetic blood sample, stored (mandatory)	X														
Exploratory blood plasma sample				X						X		X	X		To be collected in all patients in Part B for a maximum of 9 to 12 cycles.
Study Tumor Biopsy			X												Can be ±5 days

Abbreviations: BP = blood pressure; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PK = pharmacokinetic; PD = pharmacodynamic; PR = pulse rate; RR= respiration rate.

Attachment 2. Protocol JBDA Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[b]:	**Clinical Chemistry**[a]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
	Magnesium
Erythrocyte count (RBC)	Potassium
Leukocytes (WBC)	Total bilirubin
Neutrophils	Alkaline phosphatase
Lymphocytes	Alanine aminotransferase
Monocytes	Aspartate aminotransferase
	Gamma-glutamyl transpeptidase
	Lactic dehydrogenase
Eosinophils	Blood urea nitrogen
Basophils	Creatinine
Platelets	Uric acid
	Calcium
aPTT	Glucose, random
PT and PT/INR	Albumin
	Total protein
	Chloride
	Bicarbonate
Urinalysis[b]:	
Specific gravity	Direct bilirubin[b], as needed
pH	Creatinine clearance[b]
Protein	
Glucose	**Serum Pregnancy Test** (females only)[b]
Ketones	
Blood	

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

[a] Assayed by Lilly-designated central laboratory.

[b] Local or investigator-designated laboratory.

Attachment 3. Protocol JBDA Hepatic Monitoring Tests for Treatment Emergent Abnormality

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

Hepatic Monitoring Tests

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

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

[a] Assayed by Lilly-designated or local laboratory.

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

Attachment 4. Protocol JBDA Pharmacokinetic and Exploratory Blood Plasma Sampling Schedule

Pharmacokinetic Sampling Schedule For Part A

Sample Number	Cycle	Day[a]	PK Sampling Time for LY3009120[b]	Exploratory Blood Sample
1	1	1	predose	X[c]
2	1	1	0.5h	
3	1	1	1h	
4	1	1	2h	
5	1	1	4h	
6	1	1	6h	
7	1	1	8h	
8	1	1	10h	
9	1	2	Predose	
10	1	15	Predose	
11	1	15	0.5h	
12	1	15	1h	
13	1	15	2h	
14	1	15	4h	
15	1	15	6h	
16	1	15	8h	
17	1	15	10h	
18	1	28	Predose	X
19	1	28	0.5h	
20	1	28	1h	
21	1	28	2h	
22	1	28	4h	
23	1	28	6h	
24	1	28	8h	
25	1	28	10h	
26	2	1	Predose	

[a] On Cycle 1 Day 1 in Part A only, the evening dose should be omitted to enable characterization of a full PK profile.

[b] Predose PK samples should be collected prior to the morning dose, and all samples collected as close to the scheduled times as possible.

[c] Baseline exploratory blood plasma sample (EDTA tube) can be collected ≤14 days before first dose of LY3009120, after eligibility is confirmed and at Cycle 1 Day 28 predose.

Pharmacokinetic Sampling Schedule For Patients in Part B

Sample Number	Cycle	Day	PK Sampling Time for LY3009120[a]	Exploratory Blood Sample[b]	Urine Sampling (Part B only- up to 3 patients)
1	1	1	Predose	X	0 to 10h pooled samples (end time to coincide with PK blood draw)
2	1	1	0.5		
3	1	1	1		
4	1	1	2		
5	1	1	4		
6	1	1	6		
7	1	1	8		
8	1	15	predose		
9	1	22	predose	X	
10	2	28	predose	X	
11	3-n	28	predose	X	
12	Follow-up (Visit 801)	-	-	X	

[a] Predose PK samples should be collected prior to the morning dose, and all samples collected as close to the scheduled times as possible.

[b] Baseline exploratory blood plasma sample (EDTA tube) will be collected ≤14 days before first dose of LY3009120 after eligibility is confirmed. Samples will also be collected during treatment predose on Day 22 of Cycle 1, and Day28 of each cycle thereafter; and during follow-up Visit 801. During treatment this sample will be collected for a maximum of 9 to 12 cycles.

Attachment 5. Protocol JBDA Recommendations for Reporting Serious Adverse Events

Recommendations for Reporting Serious Adverse Events

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

Patient Demographics

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

Study Identification

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

Study Drug

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

Adverse Event

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

Relationship to Study Drug & Protocol Procedures

Concomitant Drug Therapy

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

In Case of Death

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

Attachment 6. Protocol JBDA ECOG Performance Status

ECOG Performance Status

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

Source: Oken et al. 1982.

Attachment 7. Protocol JBDA 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 and Gault 1976.

-OR-

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

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

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

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

Source: Murray and Ratain 2003

Attachment 8. Protocol JBDA Sampling Summary

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

Protocol I6X-MC-JBDA Sampling Summary

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number of Samples	Maximum Total Amount
Study qualification[a]	Blood	12 mL	1	12 mL
Health Monitoring (may be more than 1 tube)[b]	Blood	9 mL	11	99 mL
Drug concentration[c]	Blood	3 mL	26	78 mL
Pharmacogenetic stored sample	Blood	10 mL	1	10 mL
Tailoring biomarkers	Blood	10 mL	14	140 mL
PD samples[d] (Part A, designated expansion cohorts)	Tumor tissue		2 biopsies	2 biopsies
Other exploratory sample (Part B, all cohorts)	Tumor tissue		2 biopsies	2 biopsies
B-Raf status assessment biopsy[f]	Tumor tissue		1 biopsy	1 biopsy
Hepatic Monitoring[e]	Blood	3 - 30 mL	-	-
Total				Blood: 339 mL Tissue: 2 biopsies

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

[b] Total volume based on average number of 5 cycles.

[c] Part A: 26 PK time points; Part B: 9 PK time points.

[d] Only for patients in designated Part A expansion cohorts as noted in Section 8.2.4.1.

[e] Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with the designated medical monitor.

[f] Only for patients without historical B-Raf mutation test results or adequate archived tumor tissue sample available for genetic testing (Section 8.2.2).

Attachment 9. Protocol JBDA RECIST Criteria 1.1

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

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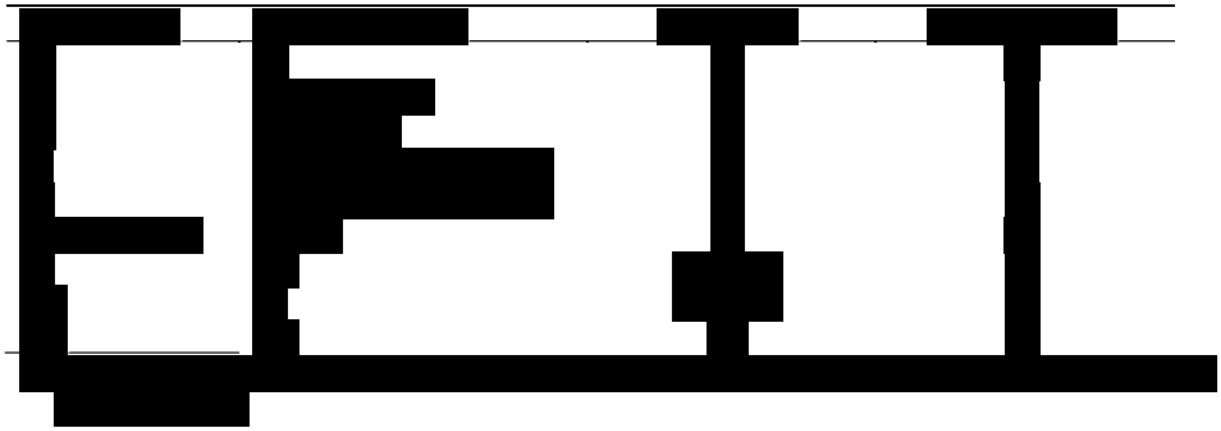

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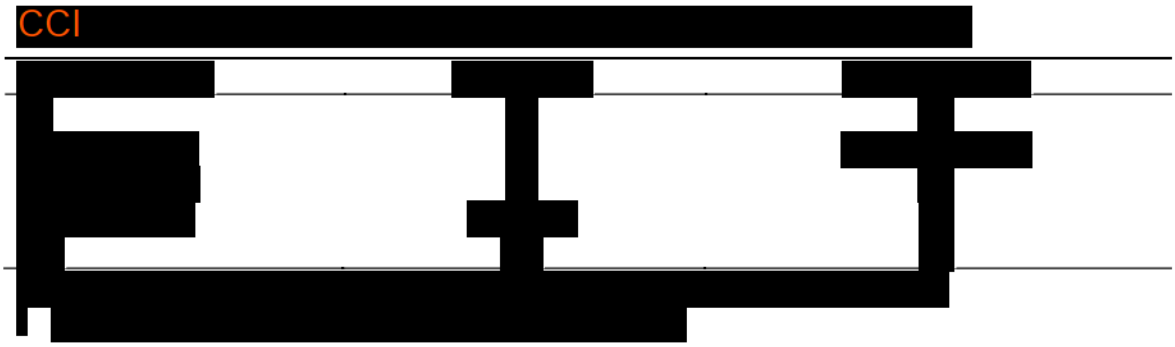

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Attachment 10. Protocol JBDA Toxicity Band Design

This section introduces the background of Toxicity Band design (Neuenschwander et al. 2008) and describes the key elements for this trial. Simulation results from the Toxicity Band design are presented. These results are also compared with those from the simulation of a traditional 3+3 design to demonstrate the benefit of implementing a Toxicity Band design in this trial. Fixed and Adaptive Clinical Trial Simulator (FACTS) software version 3.2 are used for all the simulations.

1.1 Introduction of CRM type approaches

The Continual Reassessment Method, and hereafter, CRM (O'Quigley et al. 1990) is the first Bayesian model-based approach developed for dose escalation studies. Compared to the traditional 3+3 design that only used current dose level DLT data to estimate the MTD, CRM utilizes prior dose toxicity information and all available DLT data to efficiently estimate the MTD. To improve the operating characteristics of CRM, Goodman et al. (1995), among others, have proposed modified- CRM (MCRM) procedures to make the model-based designs more acceptable in practice. The major modifications include:

- Always start at the lowest dose level.
- Limit the escalation increment.
- Escalate by cohorts rather than single patients.

Babb et al. (1998) proposed the Escalation with Overdose Control (EWOC) method that directly controls the probability of overdosing during dose escalation. EWOC is also a CRM-type method. During the escalation, EWOC selects the next dose such that the predicted probability that the new dose exceeds the MTD is equal to a pre-specified feasibility bound $\alpha = 0.25$. The connection between CRM and EWOC is that CRM typically uses the middle (mean, or median) of the MTD's posterior distribution as the next recommended dose, whereas EWOC uses the 25th percentile. Therefore, EWOC is a more conservative method than the original CRM method.

1.2 Toxicity Band design

All the aforementioned approaches use point estimates of the posterior distributions to recommend the next dose. Neuenschwander et al. (2008) extended the concept of EWOC and proposed to consider the uncertainty of the posterior distributions and use interval estimates to make the dose recommendation. We call their approach the Toxicity Band Design.

<u>The Model</u>

A two-parameter logistic model is used to model the relationship between dose and probability of a DLT:

$$\text{logit}\{p(d)\} = \alpha + \beta \log\left(\frac{d}{d^*}\right), \quad \beta > 0. \quad (1.1)$$

In the model, d is the true dose, $p(d)$ is the probability of a DLT at dose d. d^* is the reference dose such that α is interpreted as the log-odds of a DLT at d^*.

Toxicity Band

The probability of a DLT is categorized to four bands:

Under-dosing: $p(d)$ in $(0, 0.20]$

Targeted toxicity: $p(d)$ in $(0.20, 0.35]$

Excessive toxicity: $p(d)$ in $(0.35, 0.60]$

Unacceptable toxicity: $p(d)$ in $(0.60, 1.00]$

The over-dosing means $p(d) > 0.35$.

MTD Definition

The MTD is defined as a safe dose that has the highest probability of DLT in the targeted toxicity interval (20 to 35%). A safe dose means that the probability of DLT larger than 35% is below 25%.

Dose Recommendation

During the escalation, after each cohort of patients, we

1) Calculate the posterior probabilities of the four toxicity bands, for each dose.
2) Exclude the doses such that the posterior probabilities of over-dosing are larger than 0.25 (JBDA over-dosing control criteria). The remaining doses are the ones that satisfy the overdose control criteria.
3) Among the remaining doses, the dose with the highest posterior probability in the targeted toxicity band will be the model recommendation of the next dose.

In this study, the escalation will start from the lowest planned dose; the maximum dose increment is 100%; and each dose cohort will have a minimum of 3 patients enrolled to it. The Bayesian model-based toxicity band method that incorporates prior expectations about toxicity will be fitted to the data at the end of each cohort to recommend a dose for the next cohort. The investigators and Lilly CRP will consider both the model recommendation and the observed DLT rate at each cohort to 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 dose levels will be explored if deemed necessary after discussion between the sponsor and investigators.

1.3 Dose Ranges and Reference Dose

This study has eight pre-specified doses: 50, 100, 200, 300, 400, 500, 600 and 700 mg BID. The reference dose in model (1.1) is chosen as $d^* = 700$, the highest dose. The model typically has satisfactory performance by choosing the highest dose as the reference.

1.4 The Prior Distribution on Model Parameters

A Quantile-based uninformative prior (Neuenschwander et al. 2008) is used to derive a bivariate-normal prior on (α, logβ). This can be achieved by the following two steps: (1) derive a prior distribution of probability of DLT at each dose level (2) derive a bivariate-normal prior on (α, logβ) to match the distributions in the previous step.

Step 1

After discussing with CRP, PK and Toxicology scientists, we selected the median probability of DLT for the lowest dose 50 mg BID and highest dose 700 mg BID as 0.005 and 0.5, respectively, based on preclinical experience. The median probabilities of DLT of the intervening doses are calculated by assuming that the probabilities are linear in log (d/d^*) on the logit scale. We therefore obtain the prior median probability of DLT for each dose.

Table 1. Prior Median Probability of DLT at Each Dose Level

Dose Level	True Dose (mg, BID)	Median Probability of DLT
1	50	0.005
2	100	0.020
3	200	0.075
4	300	0.155
5	400	0.246
6	500	0.337
7	600	0.423
8	700	0.500

For each dose, the minimally informative unimodal Beta (a,b) distribution is derived as the prior distribution for the probability of DLT.

- For median Probability of DLT <0.5, b = 1 and a(<1) is tuned to match the median
- For median Probability of DLT >0.5, a = 1 and b(<1) is tuned to match the median

After obtaining the prior distribution of the probability of DLT, we calculate the 2.5% and 97.5% quantiles for each distribution. Figure 1 shows the three quantiles of each prior distribution.

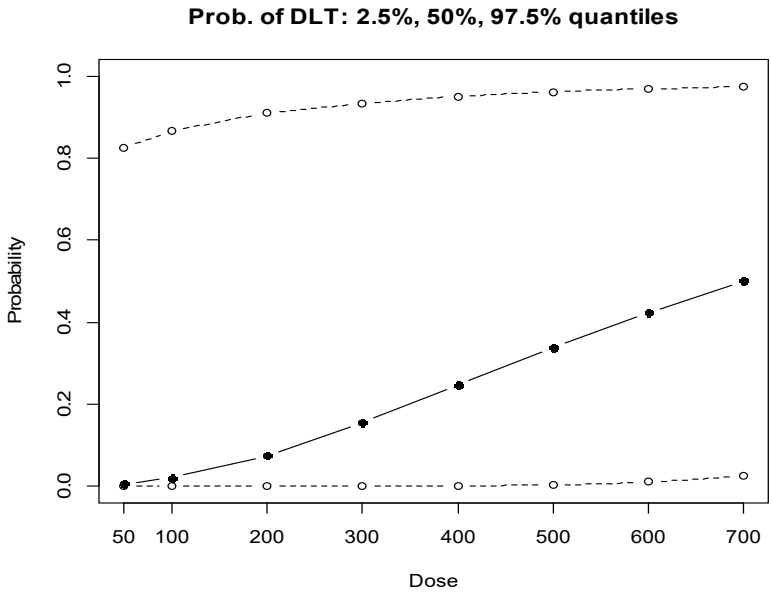

Figure 1. Prior probability of DLT at each dose.

Step 2

Derive a bivariate normal distribution on (α, logβ) that stochastically gives the best fit to the 2.5%, 50%, and 97.5% quantiles of the prior probability of DLT at each dose. Figure 2 is the fitting generated by FACTS. The parameters (α, logβ) has a bivariate normal distribution with Mean = (-0.092, 0.359), SD = (2.507, 0.907), and ρ=.282.

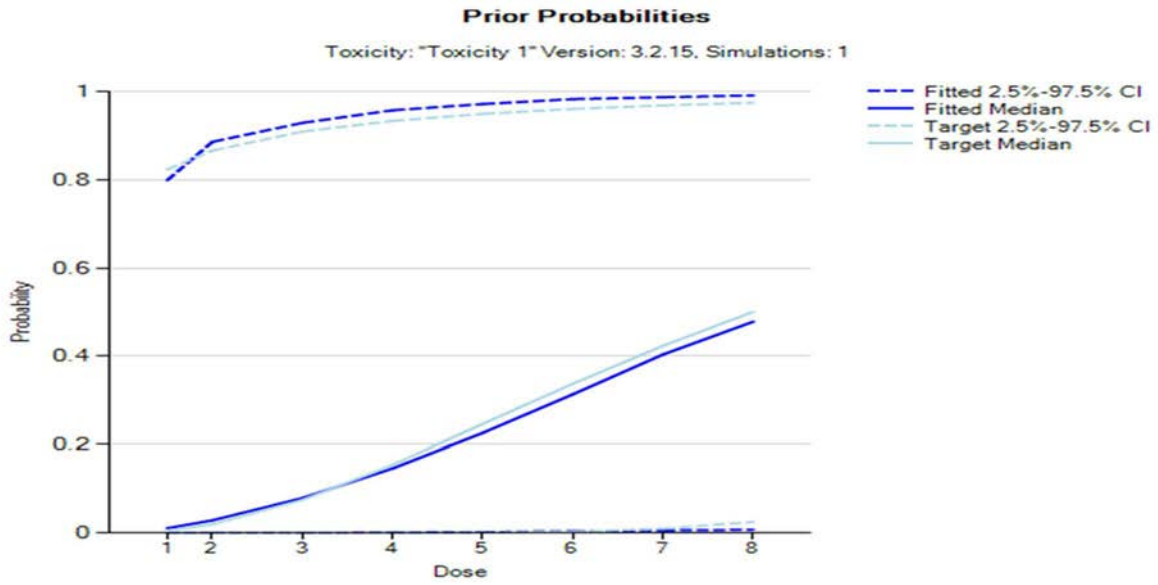

Figure 2. The stochastic fitting for the prior on (, log)

1.5 Simulation Studies

We perform simulations under different scenarios to investigate the operational characteristics: Toxicity band method vs. traditional 3+3.

- 3-patient cohorts starting from the lowest dose. No dose skipping.
- Maximum number of patients: 33
- Stopping rules for Tox-band method: max sample size reached or the recommended next dose has been treated for 9 Patients:

We considered 8 scenarios to represent a wide range of possible curves. The true DLT rate of the MTD is fixed at 25% across scenarios. Scenario 1 and 2 are toxic cases that have MTD at the first and second level. Both scenario 3 and 4 (in blue color) have 300 mg at the MTD with either steep or flat curves. Similarly, we design scenario 5 and 6 to have the same MTD at 400 mg. Scenario 7 has MTD at 500 mg, whereas scenario 8 is a safe case that the MTD is at the last dose.

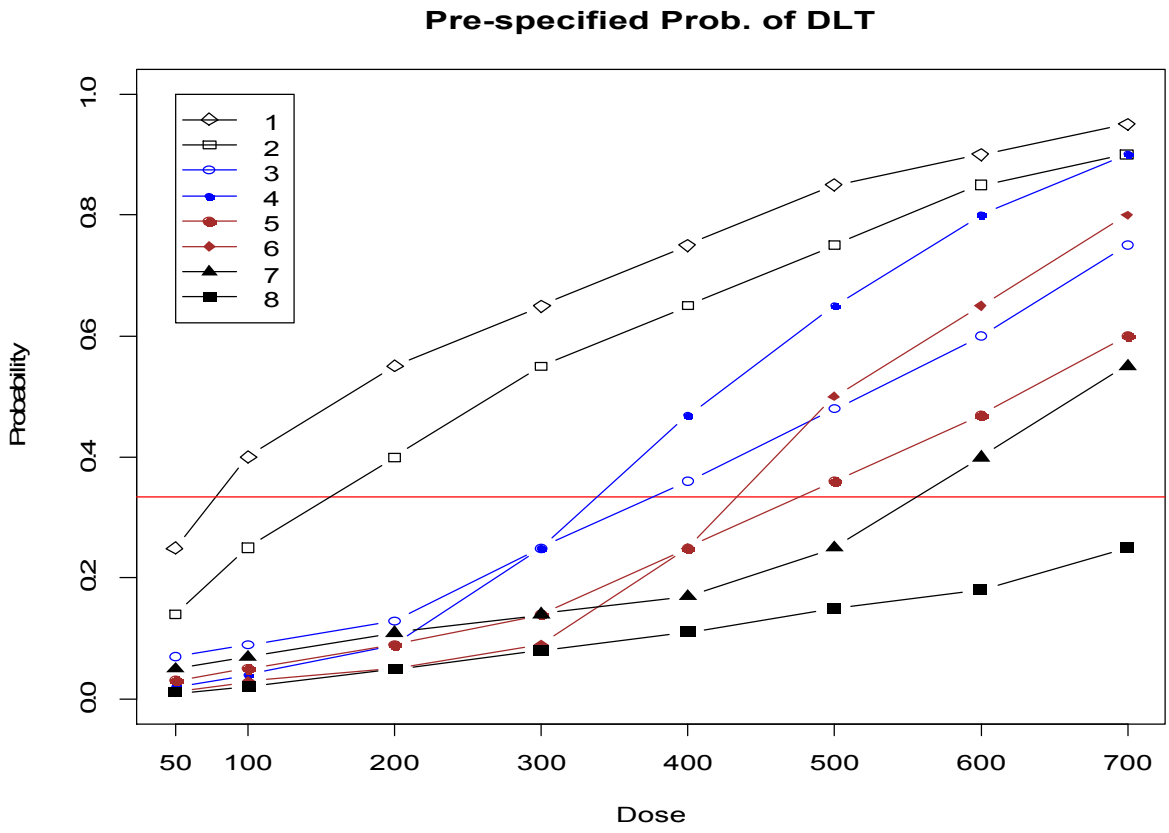

Figure 3. The Pre-specified probability of DLT under each scenario

Table 2. The Pre-specified probability of DLT under each scenario

	Pre-specified Prob. of DLT							
Dose	1	2	3	4	5	6	7	8
50	**0.25**	0.14	0.07	0.02	0.03	0.01	0.05	0.01
100	0.4	**0.25**	0.09	0.04	0.05	0.03	0.07	0.02
200	0.55	0.40	0.13	0.09	0.09	0.05	0.11	0.05
300	0.65	0.55	**0.25**	**0.25**	0.14	0.09	0.14	0.08
400	0.75	0.65	0.36	0.47	**0.25**	**0.25**	0.17	0.11
500	0.85	0.75	0.48	0.65	0.36	0.5	**0.25**	0.15
600	0.90	0.85	0.60	0.80	0.47	0.65	0.40	0.18
700	0.95	0.90	0.75	0.90	0.60	0.80	0.55	**0.25**

We ran 1000 simulations under each scenario to investigate the operating characteristics of the Toxicity Band and 3+3 methods. The results are summarized in Table 3 and 4.

Table 3. Probability of each dose selected as MTD, mean number of subjects, and mean percentages of a DLT under each scenario: Results based on 1000 simulations (Toxicity Band Method)

	Scenarios							
Dose	1	2	3	4	5	6	7	8
50	**0.833**	0.422	0.084	0.008	0.015	0.002	0.031	0
100	0.159	**0.464**	0.159	0.068	0.072	0.019	0.138	0.018
200	0.008	0.109	0.247	0.333	0.105	0.047	0.121	0.038
300	0	0.005	**0.342**	**0.512**	0.274	0.313	0.126	0.093
400	0	0	0.136	0.076	**0.337**	**0.527**	0.204	0.120
500	0	0	0.028	0.003	0.152	0.086	**0.233**	0.138
600	0	0	0.003	0	0.027	0.005	0.095	0.137
700	0	0	0.001	0	0.018	0.001	0.052	**0.456**
Mean # of Subj.	10.035	14.358	21.585	22.479	25.020	25.710	25.266	28.977
Mean % of a DLT	39.20	27.54	19.57	17.62	16.26	15.73	15.93	10.79

Table 4. Probability of each dose selected as MTD, mean number of subjects, and mean percentages of a DLT under each scenario: Results based on 1000 simulations (3+3 Method)

	Scenarios							
Dose	1	2	3	4	5	6	7	8
50	**0.808**	**0.504**	0.133	0.020	0.035	0.008	0.071	0.009
100	0.164	0.344	0.125	0.069	0.080	0.022	0.099	0.023
200	0.028	0.135	**0.302**	0.389	0.167	0.083	0.153	0.057
300	0	0.017	0.282	**0.417**	**0.295**	0.353	0.147	0.090
400	0	0	0.135	0.097	0.269	**0.458**	**0.222**	0.135
500	0	0	0.021	0.008	0.118	0.074	0.213	0.162
600	0	0	0.002	0	0.032	0.002	0.076	0.203
700	0	0	0	0	0.004	0	0.019	**0.321**
Mean # of Subj.	7.605	10.251	16.203	16.554	19.356	19.488	20.331	24.696
Mean % of a DLT	38.76	28.91	19.26	16.95	15.55	14.61	15.93	9.97

From the results, we can see that, in terms of MTD estimation accuracy, the Toxicity band method successfully identified the correct MTD with the highest selection percentages under each scenario, whereas 3+3 failed to identify the correct MTD with the highest selection percentages at half of the scenarios. The MTD determination based on 3+3 algorithm is generally one level lower than the true MTD. Moreover, in general, the Toxicity band method has a higher correct MTD selection percentage than the 3+3 design, under each scenario.

In terms of the mean number of subjects, the Toxicity band typically needed 4 to 6 more patients compared to the traditional 3+3. The mean percentages of a DLT are in general comparable across two methods, which indicates that the Toxicity band method is conservative and safe.

In sum, from the simulation studies, the Toxicity band method has a better MTD estimation accuracy, and a comparable safety profile, compared to the traditional 3+3 design.

1.6 Dose confirmation Phase

The MTD identified in the escalation phase will continue to be evaluated by the model during the dose confirmation. For each confirmation cohort, about 15 patients will be enrolled to ensure adequate safety evaluations.

Attachment 11. Protocol JBDA Protocol Amendment I6X-MC-JBDA(d) Summary A Phase 1 Study of LY3009120 in Patients with Advanced or Metastatic Cancer

Overview

Protocol I6X-MC-JBDA, a Phase 1 Study of LY3009120 in Patients with Advanced or Metastatic Cancer, has been amended. The new protocol is indicated by Amendment (d) and will be used to conduct the study in place of any preceding version of the protocol.

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

- Added statement around previously generated genetic data to Section 5.3.4 such that these data may be requested from medical records for use in the research described in Section 5.3.4.3.
- Section 5.3.4.3. was updated to clarify that exploratory biomarker analysis will be performed on patients enrolled in *all cohorts* in Part B and not just in Cohort A. This was also updated in the inclusion criterion [3] for Part B.
- Section 8.2.4.1: added statement regarding mandatory tumor biopsies before treatment and 2 weeks after treatment for all patients in Part B.
- Requirement of archived tissue for Part B is removed from Section 8.2.4.2 and from the Part B Baseline Assessment schedule.
- Updated Attachment 1, Part B Baseline Assessment schedule to include study tumor biopsy for all cohorts.
- Updated Attachment 1, Part B During and Poststudy Assessments to include tumor biopsy at Day 15, removed PK sampling at Day 28 Cycle 1, and included PK sampling for Day 28 Cycle 2 and beyond to keep it consistent with the information in Attachment 4. Text was also added for eye assessments, such that the Day 28 assessment can also be performed on the Day 1 of the next cycle (predose).
- Updated Attachment 4, Pharmacokinetic Sampling Schedule For Patients in Part B, to remove Cycle 1 Day 1 10 hour PK sampling time, added exploratory blood sampling at Cycle 1 Day 22, and removed all PK samplings at Day 28 for Cycle 1.
- Other minor formatting changes and changes to text were made for consistency and clarity.

Revised Protocol Sections

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

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 LY3009120 treatment, the collection of samples for biomarker research is a mandatory part of this study. Additional details about sampling are summarized in Sections 8.2.4 and 8.2.5, Attachment 1, Attachment 4, and Attachment 8.

It is possible that biomarker data for patients in the study have already been generated from samples that were collected and analyzed before enrolling in this trial. These may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Section 5.3.4.3.

5.3.4.3. Exploratory Analysis of Predictive Biomarkers

Potential predictive biomarkers of efficacy to LY3009120 will be measured in archived tumor tissue, tumor tissue from core or excisional biopsies, and plasma. Core or excisional biopsies for exploratory biomarker analysis will be performed on patients enrolled in all cohorts in Part B ~~Cohort A~~ (see Section 6.1.1 Inclusion ~~Criteria~~ Criterion [3]) before receiving the first dose of study drug, but this will not delay treatment. Exploratory biomarker analysis may be performed on preexisting archival samples from patients in Part A and Part B. The predictive biomarkers to be studied may include, but not limited to, somatic alterations in cancer-related genes such as B-Raf, NRas, KRas, and cKIT. In plasma, analysis of biomarkers may include, but not limited to, potential nucleic acid predictive profiles to better understand the disease process and to develop predictive biomarkers.

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.

…

[3] Part A and Part B ~~Cohort A~~: Have a tumor that is safely amenable to core needle or excisional biopsies

[8] Have discontinued all previous therapies for cancer (including chemotherapy, immunotherapy, corticosteroids, and radiotherapy) and recovered from the acute effects of therapy (treatment related toxicity resolved to Grade 1 or less) for at least 5 half-lives or a ~~maximum~~minimum of 4 weeks, (at least 42 days for mitomycin-C or nitrosoureas, 14 days for radiotherapy), prior to initiating study treatment.

8.2.4.1. Tissue Collection for Pharmacodynamic Studies

Part A: **Mandatory** tumor biopsies should be collected prior to treatment (following determination of eligibility [≤14 days of C1 D1]) and after 4 weeks of treatment (C1 D28 ± 14 days) for patients added to any cohort that will be expanded to determine MTD and/or for patients added to any cohort expanded to explore potential for Phase 2 dosing on the basis of PK data. Biopsy samples taken within 6 months prior to enrollment will also be permitted as long as patients have not received any recent therapies for the disease prior to starting LY3009120. Sponsor will need to review and approve the timing of in-treatment biopsies performed outside of the allowed 14-day window.

Part B: **Mandatory** tumor biopsies should be collected before treatment (following determination of eligibility [≤14 days of C1 D1]) and after 2 weeks of treatment (C1 D15 ± 5 days). Biopsy samples taken within 6 months before enrollment will also be permitted as long as patients have not received any recent therapies for the disease prior to starting LY3009120.

Tumor tissue biopsies taken either by core needle or excisional biopsy are acceptable provided adequate slides can be obtained. Cytologic samples and fine-needle aspiration specimens are not acceptable. Pathology notes accompanying the archived diagnostic tissue may also be requested.

Details for the handling and shipping of tumor biopsy samples will be provided in a separate document. Instructions and supplies required for the collection, processing, and shipment of the patients' samples will be provided by the sponsor.

The tumor tissue samples will be coded with the patient number and stored for up to a maximum of 15 years after the last patient visit for the study at a facility selected by the sponsor.

8.2.4.2. Tissue Collection for Tailoring Biomarker Studies

Tumor and plasma specimens will be collected throughout the study for the assessment of predictive biomarkers related to the activity of LY3009120, for exploratory research on new biomarkers related, but not limited, to the Raf pathway, and for evaluation of tumor specific biomarkers depending on evolving science.

Archived tissue: Precut, unstained slides from any available archival specimen of the patient's tumor will be ~~required from patients enrolled in Part B and will be~~ requested (but not required) for patients enrolled in Part A.

Study tumor biopsies: ~~In addition, patients enrolled in Part B Cohort A (Section 6.1.1 Inclusion Criteria [3]) will undergo a mandatory pre-treatment tumor biopsy before receiving the first dose of study drug.~~

For Part A and Part B: **Mandatory** tumor biopsies will be collected as indicated in Section 8.2.4.1.

Tumor tissue biopsies will be taken either by core needle or excisional biopsy. The size of the sample will be dependent upon the procedure utilized to obtain the sample. These biomarker-related studies will include, but may not be limited to, protein and/or genetic analyses of the tumor specimen.

Attachment 1. Protocol JBDA Study Schedule

Part B: Baseline Assessments

Relative Day Prior to Day 1 of Cycle 1	≤28	≤14	≤3	Comments
Informed Consent				Informed Consent Form signed (prior to performance of any protocol-specific tests/procedures)
Chest X-ray	X			May be omitted in patients having a chest CT scan for their radiological tumor assessment
Radiological Tumor Assessment	X			
Medical History		X		Including any alcohol/tobacco habits
Physical Exam		X		
Vital Signs		X		Including temperature, blood pressure, pulse rate, respiration rate
ECOG Performance Status		X		
ECG		X		Central collection and storage
Hematology (local)		X		
aPTT, PT, PT/INR (local)		X		
Serum Chemistry		X		
Urinalysis (local)		X		
Tumor Measurement (Palpable or Visible)		X		
CTCAE v 4.0 Grading (Preexisting conditions)		X		To be reported only after study eligibility is confirmed.
Concomitant Meds		X		
Exploratory blood plasma sample		X		EDTA tube collection after eligibility confirmed
Study Tumor Biopsy (Part B, ~~Cohort A only~~ all cohorts)		X		Biopsy should be taken only after study eligibility is confirmed (mandatory).
~~Archived Tumor Sample~~	~~X~~			~~Paraffin-embedded tumor tissue (mandatory). Sent after study eligibility is confirmed.~~
Pregnancy Test (local)			X	Negative results required prior to Cycle 1, Day 1. Only to be performed on women of childbearing potential.
Eye Safety Assessments	X			
Dermatological Evaluation		X		

Abbreviations: aPTT = activated partial thromboplastin time; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; Meds = medications; PD = pharmacodynamic; PT/INR = prothrombin time/international normalized ratio.

Part B: During and Poststudy Assessments

	Cycle 1					Cycle 2					Cycle 3-n		Follow-Up		Comments
Relative Day Within a Cycle	**1**	**8**	**15**	**22**	**28**	**1**	**8**	**15**	**22**	**28**	**1**	**28**	**Visit 801**	**Visits 802, 803, and 804 (Long-term Follow-up)**	Visit 801 is 30 days (± 3 days) after last dose of study drug; Visits 802, 803, and 804 are each 2 months in duration and will start after Visit 801.
LY3009120	X					X					X				
Physical Exam	X	X	X	X		X					X			X	After C1D1, ± 3 days while on treatment; Will not need to be repeated if performed ≤ 3 days from C1D1.
Eye Assessments					X					X					At baseline, at the end of Cycle 1 and Cycle 2, and every 2 cycles afterwards (end of C4, C6, and so on) up to 7 days before start of next cycle, and at other time points if clinically indicated. Assessment can also be performed on the D1 of the next cycle (predose).
Dermatological Evaluation											X			X	At baseline, every 2 cycles while on therapy, and every 2 months for up to 6 months following discontinuation of LY3009120.
Weight	X					X					X				After C1D1, ± 3 days while on treatment
Vital Signs	X	X	X	X		X					X				Temperature, PR, RR, BP. After C1D1, ± 3 days while on treatment.
ECG	X		X			X					X				In cycle 1 only, on days with PK assessments ECGs will be performed before patients receive morning dose of study drug at the site and 3 hours post-dosing After C2D1, ± 3 days while on treatment.

	Cycle 1					Cycle 2					Cycle 3-n		Follow-Up		Comments
Relative Day Within a Cycle	**1**	**8**	**15**	**22**	**28**	**1**	**8**	**15**	**22**	**28**	**1**	**28**	**Visit 801**	**Visits 802, 803, and 804 (Long-term Follow-up)**	Visit 801 is 30 days (± 3 days) after last dose of study drug; Visits 802, 803, and 804 are each 2 months in duration and will start after Visit 801.
Hematology	X	X	X	X		X	X	X	X		X		X		After C2D1, ± 3 days while on treatment; On days with PK assessment it will be performed before patients receive morning dose of study drug at the site.
Serum Chemistry	X	X	X	X		X	X	X	X		X		X		After C2D1, ± 3 days while on treatment; On days with PK assessment it will be performed before patients receive morning dose of study drug at the site.
Urinalysis	X					X					X				After C1D1, ± 3 days while on treatment; will not need to be performed if completed less than 3 days before Cycle 1 Day 1.
CTCAE v 4.0 Grading	X					X					X		X		Throughout study as needed.
Concomitant Meds	X					X					X		X		Throughout study as needed.
ECOG Performance Status	X					X					X				After C1D1, ± 3 days while on treatment
PK Sampling	X		X	X	~~X~~					X		X			See PK Sampling Attachment 4 for exact timing.
Tumor Measurement (Palpable or Visible)	X					X					X		X		After C1D1, ± 3 days while on treatment
Radiological Tumor Assessment										X		X	X		Approximately every 8 weeks (every other cycle, end of C2, C4, and so on). Up to 7 days before start of next cycle.
Urine Metabolite Collection	X														To be collected from up to 3 patients enrolled in Part B; not a protocol violation if not collected.

	Cycle 1					Cycle 2					Cycle 3-n		Follow-Up		Comments
Relative Day Within a Cycle	**1**	**8**	**15**	**22**	**28**	**1**	**8**	**15**	**22**	**28**	**1**	**28**	**Visit 801**	**Visits 802, 803, and 804 (Long-term Follow-up)**	Visit 801 is 30 days (± 3 days) after last dose of study drug; Visits 802, 803, and 804 are each 2 months in duration and will start after Visit 801.
Pharmacogenetic blood sample, stored (mandatory)			X												
Exploratory blood plasma sample				X	~~X~~					X		X	X		To be collected in all patients in Part B for a maximum of 9 to 12 cycles.
Study Tumor Biopsy			X												Can be ±5 days

Abbreviations: BP = blood pressure; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PK = pharmacokinetic; PD = pharmacodynamic; PR = pulse rate; RR= respiration rate.

Attachment 4. Protocol JBDA Pharmacokinetic and Exploratory Blood Plasma Sampling Schedule

Pharmacokinetic Sampling Schedule For Patients in Part B

Sample Number	Cycle	Day	PK Sampling Time for LY3009120[a]	Exploratory Blood Sample[b]	Urine Sampling (Part B only- up to 3 patients)
1	1	1	predose	X	0 to 10h pooled samples (end time to coincide with PK blood draw)
2	1	1	0.5		
3	1	1	1		
4	1	1	2		
5	1	1	4		
6	1	1	6		
7	1	1	8		
~~8~~	~~1~~	~~1~~	~~10~~		
~~9~~8	1	15	predose		
~~10~~9	1	22	predose	X	
~~11~~	~~1~~	~~28~~	~~predose~~	~~X~~	
~~12~~	~~1~~	~~28~~	~~0.5~~		
~~13~~	~~1~~	~~28~~	~~1~~		
~~14~~	~~1~~	~~28~~	~~2~~		
~~15~~	~~1~~	~~28~~	~~4~~		
~~16~~	~~1~~	~~28~~	~~6~~		
~~17~~	~~1~~	~~28~~	~~8~~		
~~18~~	~~1~~	~~28~~	~~10~~		
~~19~~10	2	28	predose	X	
~~20~~11	3-n	28	predose	X	
~~21~~12	Follow-up (Visit 801)	-	-	X	

[a] Predose PK samples should be collected prior to the morning dose, and all samples collected as close to the scheduled times as possible.

[b] Baseline exploratory blood plasma sample (EDTA tube) will be collected ≤14 days before first dose of LY3009120 after eligibility is confirmed. Samples will also be collected during treatment predose on Day 22 of Cycle 1, and Day28 of each cycle thereafter; and during follow-up Visit 801. During treatment this sample will be collected for a maximum of 9 to 12 cycles.

Attachment 8. Protocol JBDA Sampling Summary

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

Protocol I6X-MC-JBDA Sampling Summary

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number of Samples	Maximum Total Amount
Study qualification[a]	Blood	12 mL	1	12 mL
Health Monitoring (may be more than 1 tube)[b]	Blood	9 mL	11	99 mL
Drug concentration[c]	Blood	3 mL	26	78 mL
Pharmacogenetic stored sample	Blood	10 mL	1	10 mL
Tailoring biomarkers	Blood	10 mL	14	140 mL
PD samples[d] (Part A, designated expansion cohorts)	Tumor tissue		2 biopsies	2 biopsies
Other exploratory sample (Part B, ~~Cohort A~~all cohorts)	Tumor tissue		~~1 biopsy~~ 2 biopsies	~~1 biopsy~~2 biopsies
B-Raf status assessment biopsy[f]	Tumor tissue		1 biopsy	1 biopsy
Hepatic Monitoring[e]	Blood	3 - 30 mL	-	-
Total				Blood: 339 mL Tissue: 2 biopsies

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

[b] Total volume based on average number of 5 cycles.

[c] Part A: 26 PK time points; Part B: ~~18~~ 9 PK time points.

[d] Only for patients in designated Part A expansion cohorts as noted in Section 8.2.4.1.

[e] Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with the designated medical monitor.

[f] Only for patients without historical B-Raf mutation test results or adequate archived tumor tissue sample available for genetic testing (Section 8.2.2).

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