Protocol I3Y-MC-JPBA(j)

Phase 1 Study of a CDK4/6 Dual Inhibitor in Patients with Advanced Cancer

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1. Protocol I3Y-MC-JPBA(j) Phase 1 Study of a CDK4/6 Dual Inhibitor in Patients with Advanced Cancer

Confidential Information

CDK4/6 Inhibitor (LY2835219)

This Phase 1 study is a single-arm, dose-escalation trial of a CDK4/6 dual inhibitor in patients with advanced cancer.

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2. Table of Contents

Section **Page**

CCI

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Attachments

Attachment **Page**

3. Abbreviations and Definitions

Term	Definition
adverse event (AE)	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society for Clinical Oncology
AST	Aspartate aminotransferase
Assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study (required by some Institutional Review Boards [IRBs]).
AUC	Area under the concentration-time curve
Audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-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).
BED	Biologically efficacious dose
Blinding/Masking	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the patient(s) being unaware, and double-blinding usually refers to the patient(s), investigator(s), monitor(s), and in some cases select sponsor personnel, being unaware of the treatment assignment(s).
C_{max}	Maximal concentration
CDKI	Cyclin-dependent kinase inhibitors
CI	Confidence interval
CL	Clearance
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
Compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

Confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
consent	The act of obtaining informed consent for participation in a clinical study from patients deemed eligible or potentially eligible to participate in the clinical study. Patients entered into a study are those who sign the informed consent document directly or through their legally acceptable representatives.
CRF	Case report form (sometimes referred to as clinical report form): a printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	Clinical research physician
CSF	Cerebrospinal fluid
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form (sometimes referred to as an electronic clinical report form): an electronic form for recording study participants' data during a clinical study, as required by the protocol.
End of Study (Trial)	End of study (trial) is defined as the date of the last visit or last scheduled procedure at the last site shown in the Study Schedule for the last active patient in the study.
enroll	Patients who are enrolled in the trial are those who have 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 document directly or through their legally acceptable representatives.
ESA	Erythroid-stimulating agents
FFPE	Formalin-fixed paraffin-embedded
FNA	Fine needle aspirate
GBM	Glioblastoma multiforme, including its variants

GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factors
GFR	Glomerular filtration rate
GLP	Good Laboratory Practices
GM-CSF	Granulocyte-macrophage colony stimulating factors
HBSAg	Hepatitis B surface antigen
HR+	Hormone receptor positive
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICD	Informed consent document
ILD	Interstitial lung disease
IND	Investigational New Drug
Interim Analysis	An analysis of clinical trial data that is conducted before the final reporting database is authorized for datalock. In a single arm trial, any aggregate summary is considered an interim analysis.
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
IRB/ERB	Institutional review board/ethical 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 trial are protected.
IV	Intravenous
LC/MS/MS	Liquid chromatography/mass spectrometry/mass spectrometry
Legal Representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient, to the patient's participation in the clinical trial.
MATE	multidrug and toxin extrusion protein
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 Harmonization Good Clinical Practice guidelines (ICH-GCP), and all applicable laws (e.g., privacy and data protection) and regulations.

MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
CCI	
Patient	A subject with a defined disease.
PD	Pharmacodynamic
PK	Pharmacokinetic
Q12H	Every 12 hours
Q24H	Every 24 hours
Rb	retinoblastoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
screen	The act of determining if an individual meets minimum requirements for participation in a clinical study.
Sponsor	The party who takes responsibility for the initiation, management and/or financing of a clinical trial.
Study Entry Terms	**Screen** The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, x-rays, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study. **Enter/Consent** The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the informed consent document directly or through their legally acceptable representatives. **Enroll** The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
TBL	Total bilirubin level
TED_{70}	Threshold effective dose, 70% inhibition
TPO	Third party organization
t_{max}	Time of maximum concentration

ULN	Upper limits of normal
US	United States
V_d	Volume of distribution
VTE	Venous thromboembolic event

Phase 1 Study of a CDK4/6 Dual Inhibitor in Patients with Advanced Cancer

4. Introduction

4.1. Rationale and Justification for the Study

During the cell cycle, the G1 restriction point controls entry into S phase and is essential for maintaining control of cell division (Ortega et al. 2002; Sherr 1996). The cyclin-dependent kinases, CDK4 and CDK6 (hereafter designated CDK4/6), participate in a complex with D-type cyclins to initiate the transition through the G1 restriction point. A broad spectrum of human cancers have alterations in the CDK4/6-cyclinD-INK4-Rb pathway through either increased CDK4/6-cyclinD activity or mutations that attenuate function of the INK4 or Rb proteins (Malumbres and Barbacid 2001). These alterations render cells less dependent on mitogenic signaling for proliferation, one of the hallmarks of cancer cells.

The CDK4/6-cyclinD complex regulates the G1 restriction point through phosphorylation of the retinoblastoma (Rb) tumor suppressor protein. Alterations in this pathway occur frequently in a broad spectrum of human cancers and involve 1) loss of cyclin-dependent kinase inhibitors (CDKI) by mutation or epigenetic silencing, 2) mutation/overexpression of either CDK4/6 or cyclin D, or 3) inactivation of Rb. With the possible exception of those tumors with complete inactivation of Rb, which functions downstream of the CDK4/6-cyclinD complex, all these cancers are potentially sensitive to pharmacologic inhibition of CDK4/6. From a therapeutic standpoint, the goal of inhibiting CDK4/6 with a small molecule inhibitor is to prevent cell cycle progression through the G1 restriction point, thus arresting tumor growth.

LY2835219* represents a selective and potent small molecule CDK4/6 dual inhibitor with broad antitumor activity in preclinical pharmacology models, favorable physical and pharmacokinetic (PK) properties, and an acceptable toxicity profile in nonclinical species. This compound demonstrates significant inhibition of tumor growth in 4 human xenograft models: 1) colorectal cancer, 2) glioblastoma multiforme, 3) acute myeloid leukemia, and 4) non–small cell lung cancer. Although characterized by a different constellation of genomic mutations, each of these 4 human xenografts has an intact, functional Rb protein. Xenograft growth inhibition is generally dose dependent from 25 to 100 mg/kg following daily oral administration for 21 days.

LY2835219 distributes extensively to the brain (refer to Section 4.6.3 and Investigator's Brochure [IB]) and therefore provides a unique opportunity to treat human cancers that have metastasized to the brain. Currently, these patients have short survival and no treatment options upon relapse in the brain after receiving radiotherapy. As a result of its brain exposure, treatment with this compound in a rat orthotopic brain tumor model produces statistically significant and dose-dependent improvement in survival.

Study I3Y-MC-JPBA (Study JPBA) is a Phase 1 trial designed to evaluate the safety and tolerability of LY2835219 in humans. The sponsor, monitor, and investigators will perform this

study in compliance with the protocol, GCP and ICH guidelines, and applicable regulatory requirements.

*Formally, LY2835219 refers to the free base whereas LSN2813542 refers to LY2835219 mesylate; however, LY2835219 has been used for uniformity throughout this protocol, except when important for experimental clarity.

4.2. Rationale for Amendment (h)

Study JPBA protocol was amended to update the safety language regarding hepatic monitoring, assessment of renal function, venous thromboembolic events (VTEs), and interstitial lung disease (ILD)/pneumonitis to align with updated guidance for LY2835219. Table JPBA.6.2 was added to clarify dose-modification and dose-delay criteria. Section 6.3.1 was added and the Study Schedule (Attachment 1) was updated to incorporate a continued access period to allow patients experiencing clinical benefit the option to continue study therapy until 1 of the criteria for discontinuation is met. The list of Inducers and Strong Inhibitors of cytochrome P450 (CYP) 3A (Attachment 8) and Concomitant Therapy (Section 6.5) were also modified to reflect updated guidance.

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

4.3. Rationale for Amendment (i)

Study JPBA protocol was amended to update safety language regarding ILD/pneumonitis. Changes to the dose adjustments and delays in Table JPBA.6.2 were done to specify dose modifications in response to ILD/pneumonitis events. These updates are in alignment with changes made in the development core safety information of the IB.

The protocol was updated to bring references to LY2835219 into alignment with the sponsor's standard language.

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

4.4. Rationale for Amendment (j)

This amendment to the Study JPBA protocol updates the dose adjustment guidance related to nonhematologic toxicity and ALT/AST increased to ensure alignment with the current IB. Specifically, protocol updates were made to the dose adjustment Table JPBA.6.2. Additionally, the Concomitant Therapy (Section 6.5) information was updated for CYP3A modulators and transporter substrates. The safety monitoring language in Hepatic Monitoring (Section 7.1.3.1) and Venous Thromboembolic Events (Section 7.1.3.3) was updated to align with current guidance and the IB, respectively. Finally, Section 7.1.3.4 was edited slightly for clarity to include specific ILD/pneumonitis CTCAE grades requiring LY2835219 discontinuation.

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

4.5. Objectives

4.5.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of LY2835219 when administered orally to patients with advanced cancer.

4.5.2. Secondary Objective(s)

The secondary objectives of this study are to:

- Determine the pharmacokinetics (PK) of LY2835219
- Evaluate pharmacodynamic (PD) and predictive biomarkers
- Document the antitumor activity of LY2835219
- Establish a recommended dose range for Phase 2 studies.

4.6. General Introduction to LY2835219

Detailed information about LY2835219 is provided in the IB. This section provides a summary of the information most relevant for this initial Phase 1 study.

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

LY2835219 represents a novel class of potent ATP competitive and reversible CDK4/6 kinase inhibitor (IC50 for CDK4 = 0.00196 μM and IC50 for CDK6 = 0.0099 μM). This molecule displays a high level of selectivity over other related cyclin-dependent kinases at the enzyme and cellular level; for example, LY2835219 is approximately 3 orders of magnitude more selective for CDK4 compared to CDK1. In colo-205 cells, the compound induces potent cellular inhibition of Rb phosphorylation (pSer780, IC50 = 0.121 μM). Other data has demonstrated that LY2835219 inhibits CDK4/6 to induce G1 arrest specifically in Rb+ tumors and is selective for G1 arrest at concentrations as high as 2.5 to 6 μM.

This phenotypic selectivity is also demonstrated *in vivo*, where LSN2813542 (that is, LY2835219 mesylate) suppresses Rb phosphorylation and induces a G1 arrest as indicated by inhibition of toposiomerase II alpha and phospho-histone H3 (topoIIα and pHH3 markers respectively, for cells in S phase and M phase), in a concerted fashion only consistent with arrest at the G1 restriction point *in vivo*. Additionally, LSN2813542 showed excellent, sustained PD response in a mouse colo-205 xenograft model (in vivo pRb inhibition ≥50% from 1 to 36 hours post oral dose of 50 mg/kg and potent suppression of topoIIα and pHH3 at 24 hours post oral dose of the same 50-mg/kg dose). Dose response TED_{70} (threshold effective dose for 70% inhibition) values for pRb and topoIIα inhibition (24 hours post oral dose time point) were 14.1 and 14.3 mg/kg, respectively. This prolonged, robust target inhibition and G1 arrest has resulted in the demonstration of statistically significant, dose-dependent antitumor activities (measured by tumor volume reduction) of LSN2813542 in 4 human subcutaneous xenograft models: colo-205 colorectal, H460 lung, U87 MG glioblastoma multiforme and MV4-11 acute myeloid

leukemia. For example, LSN2813542 can achieve statistically significant tumor growth inhibition when dosed orally at 25, 50 and 100 mg/kg for 21 days in the colo-205 xenograft model. Consistent with the mechanism of action of LSN2813542, the antitumor activity in colo-205 was associated with a sustained inhibition of pRb, topoIIα and pHH3 (30% to 50% inhibition of each marker on days 14 and 21 of dosing at 100 mg/kg).

As a result of its brain exposure, treatment with this compound produces a statistically significant and dose dependent improvement in survival in a rat orthotopic brain tumor model. Median survival was improved 8 and 12 days compared to vehicle following daily oral treatment at 40 mg/kg and 80 mg/kg for 21 days, respectively.

4.6.2. Biomarkers

Biomarkers will be used for 2 key purposes: 1) to assess PD response to LY2835219 in both surrogate tissues and tumors and 2) to explore the relationship between predictive biomarkers (such as tumor Rb status) and antineoplastic activity. Table JPBA.4.1 provides an overview of the biomarker strategy for this study. PD biomarkers will be measured in proliferating cell populations before and after administration of LY2835219 and will include both pRb (with total Rb as a control) and topoisomerase IIα (topoIIα). PD biomarkers will be measured in hair follicles and skin throughout the study (Parts A, B, C, D, E, F, and G) and, whenever clinically feasible, in tumors during dose confirmation (Parts B, C, D, E, F, and G). Potential predictive biomarkers will be measured throughout the study in archived tumor tissue (for example, from prior biopsy) during dose confirmation (Parts B, C, D, E, F, and G).

Table JPBA.4.1. Overview of Biomarker Strategy

Tissue	Biomarkers	Purpose
Hair follicles	pRb, total Rb, topoIIα	PD
Skin	pRb, total Rb, topoIIα	PD
Tumors (pre- and post-LY2835219)	pRb, total Rb, topoIIα	PD / Predictive
Archived tumors	pRb, total Rb	Predictive

Abbreviations: PD = pharmacodynamic; pRb = phosphorylated retinoblastoma protein; topoIIα = topoisomerase IIα protein; total Rb = total retinoblastoma protein.

4.6.3. Nonclinical Pharmacokinetics

Preliminary PK parameters of LY2835219 were estimated in mouse, rat, and dog following a single intravenous (IV) or oral dose of LY2835219 as the mesylate salt. When administered orally, the absorption was relatively slow in rat (time of maximum concentration [T_{max}] 3 hours) and dog (T_{max} 9 hours) but rapid in mouse (T_{max} 0.5 hour) at a comparable dose (1 or 3 mg/kg). Overall, the oral bioavailability was moderate to high in these species. Following IV administration, plasma clearance was moderate and volume of distribution was high in all 3 species with elimination half-lives ranging from approximately 6 to 17 hours. After oral dosing, LY2835219 was distributed well into brain tissues in rat and to a relatively lesser extent in mouse.

The plasma toxicokinetics of LY2835219 were evaluated in rats and dogs following daily oral doses for 28 days. In rats, exposures increased slightly less than proportionally to the increase in dose from 10 to 50 mg/kg/day. A slight accumulation (approximately up to 2-fold) was observed with repeated daily dosing of LY2835219 for 14 days; however, exposure on Day 28 was generally similar to that observed on Day 14, indicating that steady state might have been achieved between Day 14 and Day 28. In dogs, exposures generally increased proportionally to the increase in dose from 1 to 10 mg/kg/day. A slight accumulation (approximately 1.5- to 3-fold) of LY2835219 was observed with repeated daily dosing for 12 or 14 days. Again, exposure on Day 28 was generally similar to that observed on Day 14, suggesting that steady state might have been achieved between Day 14 and Day 28. In both species, there were no notable gender differences in exposure.

4.6.4. Nonclinical Pharmacokinetic/Pharmacodynamic Modeling

The primary objective of PK/PD modeling in preparation for the Phase 1 study was to estimate a pharmacologically effective and safe dose range in humans, based on preclinical data.

The nonclinical PK/PD analysis was conducted using data generated using a colo-205 xenograft model developed in the mouse.

A PK/PD model was developed to relate the predicted plasma concentrations to the observed level of in vivo CDK4/6 inhibition in the colo-205 xenograft tumor model (measured by the extent of pRb, topoIIα and pHH3 inhibition). A series of transit compartments connected to a precursor compartment was used to relate the predicted plasma concentrations with the observed level of these biomarkers by means of an indirect response model (Sharma et al. 1998; Sun and Jusko 1998; Hazra et al. 2006; Mager and Jusko 2001). In order to establish a connection between CDK4/6 inhibition and *in vivo* efficacy (measured by the tumor growth delay) following drug administration, a fully-integrated PK/PD/IVE model was developed by connecting the PK/PD model described above to a model describing the kinetics of tumor growth by means of a modified Gompertz model (Simeoni et al. 2004). This preclinical PK/PD modeling indicated that the minimum level of CDK4/6 inhibition associated with *in vivo* tumor growth delay after repeated administration is 30% to 50% maintained throughout the whole duration of the treatment. A projected human PK model, obtained from allometric scaling, was linked to this PK/PD model generated from the mouse efficacy data to simulate the human PD profiles. These simulations suggest that a minimum daily dose of 150 to 300 mg is expected to produce the minimum level of CDK4/6 inhibition that has been associated with tumor growth delay in the preclinical studies.

Finally, the range of area under the concentration-time curve (AUC) levels required to produce *in vivo* efficacy in colo-205 tumor-bearing mice was approximately 3600 to 9500 ng·hr/mL. Simulations using the projected human PK model obtained by allometric scaling were used to determine the dose range in human that should produce a similar exposure range. The prediction intervals obtained from these simulations suggest that such exposures should be reached at a daily dose level of approximately 300 to 700 mg.

4.6.5. Nonclinical Toxicology

To support human clinical studies, the toxicity profile of LY2835219 has been effectively characterized in rat and dog through a package of repeat-dose toxicology, safety pharmacology, and genetic toxicology studies. These studies demonstrate an acceptable safety profile with toxicities that are generally considered to be monitorable and reversible.

For Study JPBA, a clinical starting dose of 50 mg administered daily for 28 days on a 28-day cycle was selected based on the highest doses of LY2835219 in nonclinical toxicology studies that did not produce any toxicities considered to be irreversible and/or nonmonitorable. Based on the effects of LY2835219 observed in rats and dogs, the dose-limiting toxicity (DLT) in humans is expected to be reversible myelosuppression and/or gastrointestinal toxicity. Mortality associated with administration of LY2835219 was limited to the highest doses investigated of 50 mg/kg (300 mg/m^2) in rats and 10 mg/kg (200 mg/m^2) in dogs. In rats, mortality occurred in 2 of 30 rats given 50 mg/kg and was associated with clinical signs of dehydration, reduced food consumption, body weight loss, decreased activity, and soft stools and/or reduced feces. In dogs, declining clinical condition of animals given 10 mg/kg started on Day 9, leading to euthanasia of 2 dogs on Days 12 and 15 and early termination of the dose group on Day 18. The dogs exhibited clinical signs including but not limited to: decreased activity and food consumption, dehydration, thinness, hypothermia, red and/or liquid and/or soft feces, and paleness. These animals also exhibited marked pancytopenia characterized by decreases in reticulocytes, leukocytes (neutrophils, monocytes, and lymphocytes), and platelets. The cause of the mortality in dogs was attributed to gastrointestinal lesions in conjunction with marked myelosuppression.

The nonclinical toxicology studies consisted of 28-day repeat-dose studies in rats at doses of 10, 30, and 50 mg/kg/day (60, 180, and 300 mg/m^2, respectively) and in dogs at doses of 1, 3, and 10 mg/kg/day (20, 60, and 200 mg/m^2, respectively). The dosing schedule was designed to reflect the most dose-intense regimen in the Phase 1 clinical dosing study. Dose-responsive hematotoxicity (as indicated by cytopenias and bone marrow hypocellularity) and gastrointestinal injury were the most prominent adverse effects observed in both rats and dogs. Changes in hematology parameters exhibited partial or complete reversibility within the 28-day recovery period in both species.

Besides the clinical signs and hematologic effects described above, morphologic changes were observed in several tissues. Important findings that were considered adverse consisted of bone marrow hypocellularity in rat and dog; intestinal crypt hyperplasia and villous atrophy in rat and dog, associated with minimal neutrophilic inflammation in rat; lymphoid depletion in the thymic cortex and lymph nodes in rat and dog; macrophage accumulation in the lungs and bronchoalveolar inflammation in rat; and changes in the male reproductive tract (germ cell degeneration and depletion; atrophy of the seminal vesicle, seminiferous tubule epithelium, and prostate) in rat and dog. These changes demonstrated complete or partial reversibility within the 28-day recovery period.

Other morphologic changes seen in either rat or dog were generally considered minor and not considered to be toxicologically important. In rats, microscopic changes at higher doses

included tubular vacuolar degeneration in the kidneys without evidence of renal functional impairment; diffuse vacuolation of acinar cells in the pancreas without evidence of cellular degeneration or functional impairment; macrophage vacuolation in the spleen; myofiber degeneration/necrosis; and hypercellularity of the thymic medulla. In dogs, cytoplasmic eosinophilia/decreased vacuolation and mononuclear cell infiltration were seen in the adrenal gland, which were not accompanied by a notable change in cell size or evidence of degeneration or necrosis.

LY2835219 was also investigated in a standard battery of safety pharmacology and genetic toxicology studies. No adverse findings associated with respiratory and central nervous system function were observed in rats. LY2835219 was negative in a standard battery of genotoxicity tests (Ames, chromosomal aberration, and rat micronucleus) and is thus not considered to be a genotoxicant.

In the cardiovascular safety pharmacology study, ventricular tachycardia occurred in 1 of 8 dogs given 10 mg/kg, the highest dose administered. This arrhythmia occurred intermittently between 22 and 48 hours postdose. Although parent drug is detectable during this period following oral administration in dogs, occurrence of ventricular tachycardia did not correlate with the maximum plasma level of LY2835219. No blood pressure changes were associated with this arrhythmia, and no QTc prolongation was observed in dogs at doses up to 10 mg/kg. Based upon the incidence in only a single animal and the delayed onset, the arrhythmia was likely caused by ventricular irritation originating from the insertion site of the left ventricular pressure transducer and/or positive ECG electrode. However, as ventricular tachycardia was noted only following the high dose, a compound-related effect is possible.

In conclusion, results from the nonclinical toxicology, safety pharmacology, and genetic toxicology studies for LY2835219 demonstrate an acceptable safety profile with toxicities that are generally considered to be monitorable and reversible. Based on the repeat-dose toxicity studies, a starting dose of 50 mg (31 mg/m^2) given daily for 28 days was selected for Study JPBA. Table JPBA.4.2 shows the calculated exposure multiples for doses from 50 mg (31 mg/m^2) to 900 mg (562 mg/m^2).

More detailed information about the characteristics of LY2835219 can be found in the IB.

Table JPBA.4.2. Exposure Multiples for Oral Administration of LY2835219 Based on Administered Dose and Predicted Exposure

	Dose (mg/kg)	Dose (mg/m^2)	Dose Multiple[a]	$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	Exposure Multiple[b]
Human[c]					
Starting Dose	0.8	31	Rat: 10 Dog: 2	450	Rat: 52 Dog: 1.8
Planned Highest Dose	15	562	Rat: 0.5 Dog: 0.1	7,800	Rat: 3 Dog: 0.1
Rat NSTD[d]	50	300	-	23,800	-
Dog MinTD[e]	3	60	-	800	-

Abbreviations: NSTD = highest Not Severely Toxic Dose; MinTD = highest Minimally Toxic Dose; $AUC_{0\text{-}24\ hr}$ = area under the concentration versus time curve from time 0-24 hours.

a Dose multiple is the dose in animals / dose in humans based on body surface area (mg/m^2).

b Exposure multiple is the mean calculated $AUC_{0\text{-}24\ hr}$ (males and females) on Day 1 in animals / predicted $AUC_{0\text{-}24\ hr}$, in humans at steady state. The $AUC_{0\text{-}24\ hr}$ on Day 1 in animals are summarized in Section 5.1.3 of the Investigator's Brochure (Tables 5.2 and 5.3).

c Assumes body weight of 60 kg and body surface area of 1.6 m^2.

d NSTD based on 28-day repeat-dose toxicity study in rats (803871).

e MinTD based on 28-day repeat-dose toxicity study in dogs (803872).

4.7. Rationale for Selection of Dose and Dose Range

For the once daily schedule, an initial dose range of 50 to 900 mg of LY2835219 administered orally once daily for 28 days was selected based on nonclinical toxicology and PK/PD data. For dose escalation on this schedule, there were 9 planned dose levels: 50, 100, 150, 225, 300, 400, 525, 700, and 900 mg administered orally every 24 hours for 28 days.

Table JPBA.4.3 summarizes the predicted median steady-state AUC and 90% prediction interval for the initially planned dose levels to be tested in Study JPBA. Exposure levels ($AUC_{0\text{-}24\ hr}$) on Day 1 and at steady state in rats and dogs are summarized in the IB. Based on a starting dose of 50 mg given once daily and the *exposures on Day 1* at the Not Severely Toxic Dose in rats and highest Minimally Toxic Dose in dogs, the median predicted exposure multiples were approximately 52 and 1.8, respectively. Based on the *steady-state exposures* observed at these doses in rats and dogs, the exposure multiples predicted for this starting dose of 50 mg were approximately 106 and 4.2, respectively.

Preclinical efficacy associated with administration of LY2835219 was evaluated by 2 endpoints: 1) CDK4/6 inhibition (measured by the extent of phosphorylated Rb, topoIIα and pHH3 inhibition) in xenograft tumors implanted in mice; and 2) exposure levels associated with xenograft tumor growth delay in mice. These efficacy parameters were integrated into a nonclinical PK/PD model.

Modeling the level of CDK4/6 inhibition associated with tumor growth delay in mice suggested that a clinical dose of 150 to 300 mg, administered once daily, should produce exposure levels demonstrated to produce the minimum level of CDK4/6 inhibition associated with efficacy in preclinical studies. Based on the *steady-state exposures* at the Not Severely Toxic Dose in rats

and the highest Minimally Toxic Dose in dogs, the median exposure multiples predicted at steady state for this clinical dose range were approximately 18 to 33 and 0.7 to 1.3 respectively.

In addition, PK/PD modeling suggested that AUC levels associated with tumor growth delay in preclinical *in vivo* efficacy studies (approximately 3600 to 9500 ng·hr/mL) should be reached in patients within a dose range of 300 to 700 mg administered once daily (Table JPBA.4.3). Based on the *steady-state exposures* observed at the Not Severely Toxic Dose in rats and the highest Minimally Toxic Dose in dogs, the median exposure multiples predicted at steady state for this clinical dose range were approximately 8 to 18 and 0.3 to 0.7, respectively.

During the dose escalation phase, preliminary analysis of PK data from the initial 4 dose levels (50, 100, 150, and 225 mg every 24 hours) indicated less than dose-proportional increases in exposure. Based on these results, a twice daily schedule was introduced in Part A with LY2835219 administered orally at the following planned dose levels: 75, 100, 150, 200, 275, 350, and 450 mg every 12 hours for 28 days. Importantly, the first planned dose level (75 mg every 12 hours) corresponded to a daily dose of 150 mg, which was 1 dose level lower than that of the highest previously explored dose level (225 mg every 24 hours). For the twice daily schedule, the highest dose of LY2835219 evaluated was 275 mg every 12 hours. At this dose level, 2 of the 3 patients experienced DLT of Grade 3 fatigue. At the next lower dose level of 200 mg every 12 hours, 1 of the 7 patients also experienced DLT of Grade 3 fatigue. Therefore, the maximum tolerated dose (MTD) was established at 200 mg every 12 hours.

During the tumor-specific expansion phases, patients initially received LY2835219 at the MTD of 200 mg every 12 hours. A preliminary interim safety review with data from 56 patients indicated that 29 patients experienced diarrhea possibly related to study drug: 17 Grade 1 (30%), 9 Grade 2 (16%), 3 Grade 3 (5%), none Grade 4 (0%), and none Grade 5 (0%). Based on the frequency of Grade 1/2 diarrhea and the observation of clinical activity at doses below the MTD, the initial starting dose was changed to 150 mg every 12 hours with JPBA amendment (f) to gain additional PK data and clinical experience around safety/tolerability. Importantly, diarrhea experienced by patients is manageable with standard anti-diarrheal agents. Therefore, early treatment with anti-diarrheal agents (e.g., loperamide) is recommended and the initial starting dose will return to the MTD of 200 mg every 12 hours with JPBA amendment (g).

Table JPBA.4.3. Predicted Steady-State Plasma Exposure Levels of LY2835219 in Humans Based on Daily Dosage Level

Daily dose (mg)	Predicted $AUC_{0\text{-}24\ hr,\ ss}$ in Humans (ng·hr/mL)	
	Median	90% Prediction Interval
50	450	(200 – 1,000)
100	900	(400 – 1,900)
150	1,450	(550 – 3,000)
225	2,000	(900 – 4,600)
300	2,700	(1,200 – 5,800)
400	3,650	(1,600 – 8,100)
525	4,700	(2,100 – 10,400)
700	6,250	(2,700 – 13,800)
900	7,800	(3,500 – 17,200)

Abbreviation: $AUC_{0\text{-}24\ hr,\ ss}$ = area under the concentration versus time curve from time 0-24 hours at steady state.

5. Investigational Plan

5.1. Study Population

5.1.1. Inclusion Criteria

Patients may be included in the study if they meet all of the following criteria:

[1] For all Parts: The patient must be, in the judgment of the investigator, an appropriate candidate for experimental therapy, either after available standard therapies have ceased to provide clinical benefit (Parts A, B, C, D, E, and F) or in combination with fulvestrant (Part G only).

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

For Dose Confirmation (Parts B, C, D, E, F, and G): The patient must have histological or cytological evidence of one of the following cancers:

- Part B: Non-small cell lung cancer of any subtype that is advanced and/or metastatic.
- Part C: Glioblastoma multiforme (GBM) that has progressed or recurred after radiotherapy and/or chemotherapy.
- Part D: Breast cancer that is advanced and/or metastatic.
- Part E: Melanoma that is advanced and/or metastatic.
- Part F: Colorectal cancer that is advanced and/or metastatic.
- Part G: Breast cancer that is not only advanced and/or metastatic but also hormone receptor positive (HR+). The patient must be a postmenopausal woman with disease progression following anti-estrogen therapy and may be currently receiving fulvestrant at the time of study entry.

[2] Have the presence of measurable or non-measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1, Eisenhauer et al. 2009) or the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007),

For Parts A and G: Have measurable or nonmeasurable disease.

For Parts B, C, D, E, and F: Have measurable disease.

[3] Are ≥18 years of age.

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

[5] Have adequate organ function including:

- Hematologic: Absolute neutrophil count (ANC) ≥1.5 x 10^9/L platelets ≥100 x 10^9/L, and hemoglobin ≥8 g/dL. Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator; however, initial study drug treatment must not begin earlier than the day after the erythrocyte transfusion.
- Hepatic: Bilirubin ≤1.5 times upper limits of normal (ULN) and alanine aminotransferase (ALT) ≤3.0 times ULN.
- Renal: Serum creatinine ≤ ULN.

[6] Have a performance status ≤1 for Dose Escalation (Part A) and ≤2 for Dose Confirmation (Parts B, C, D, E, F, and G) on the Eastern Cooperative Oncology Group (ECOG) scale (refer to Attachment 6).

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

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

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

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

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

[12] Are able to swallow capsules.

5.1.2. Exclusion Criteria

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

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

[14] Have a personal history of any of the following conditions: presyncope or syncope of either unexplained or cardiovascular etiology, ventricular arrhythmia (including but not limited to ventricular tachycardia and ventricular fibrillation), sudden cardiac death, or sudden cardiac arrest.

[15] Exclusion Criterion [15] has been deleted.

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

[17] For Dose Escalation (Part A): Have CNS malignancy or metastasis. Screening of asymptomatic patients without history of CNS metastases is not required for enrollment.

For Dose Confirmation (Parts B, D, E, F, and G): Have CNS metastasis that is radiographically or clinically unstable less than 14 days prior to receiving study drug, regardless of whether they are receiving corticosteroids.

For Dose Confirmation (Part C): Have GBM that is radiographically or clinically unstable less than 14 days prior to receiving study drug, regardless of whether they are receiving corticosteroids.

[18] Have an acute leukemia.

[19] Have received an autologous or allogeneic stem-cell transplant within 75 days of the initial dose of study drug. In addition, recipients of an allogenic stem-cell transplant must have discontinued immunosuppressive therapy at least 11 days before study drug administration with no more than Grade 1 acute graft-versus-host disease (refer to Attachment 7 for grading and staging of graft-versus host disease) on Day-3.

[20] Females who are pregnant or lactating.

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

5.2. Summary of Study Design

This study is a multicenter, nonrandomized, open-label, dose-escalation Phase 1 trial of LY2835219 in approximately 300 patients with advanced cancer. During dose escalation (Part A), 33 patients were treated across 2 schedules. For the once daily schedule, patients received LY2835219 orally every 24 hours. For the twice daily schedule, patients received LY2835219 orally every 12 hours for Days 1 through 28 of a 28-day cycle (refer to Figure JPBA.5.1), with modifications during Cycle 1 to enable PK sampling following a single dose and repeated doses. During dose escalation, cohorts of at least 3 patients were enrolled at each of the planned dose levels.

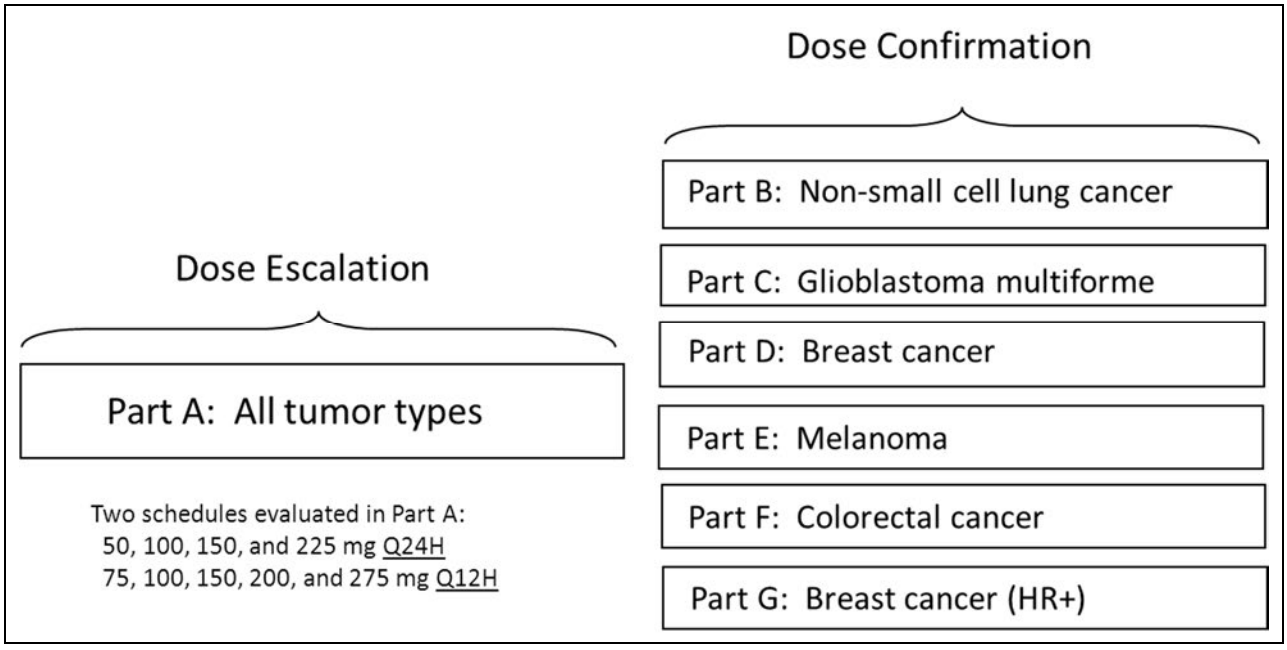
During dose escalation (Part A), 33 patients were treated across 2 schedules. For the once daily schedule, patients were treated at 50, 100, 150, and 225 mg every 24 hours (Q24H). For the twice daily schedule, patients were treated at 75, 100, 150, 200, and 275 mg every 12 hours (Q12H). An MTD for the once daily schedule was not reached, whereas the MTD for the twice daily schedule was tentatively established (pending dose confirmation) at 200 mg Q12H. As depicted in Figure JPBA.5.1, the study design consists of a *dose escalation phase (Part A)* and *6 tumor-specific expansion phases (Parts B, C, D, E, F, and G)*. The dose escalation phase

(Part A), described in Section 6.2.2, was guided by safety assessments from Days 1 through 28 of Cycle 1 for all patients in the cohort and also by the emerging PK data. Dose escalation occurred until the MTD (defined in Section 6.2.2.1) was determined for at least 1 schedule.

After the last patient enrolled in the dose escalation phase (Part A) completes Cycle 1, then the 6 tumor-specific expansion phases (Parts B, C, D, E, F, and G) may begin. In each tumor-specific expansion phase, at least 15 and up to 45-60 patients will be treated on the twice daily schedule at a dose no greater than the MTD (200 mg every 12 hours) with administration of LY2835219 on Days 1 through 28 of a 28-day cycle, with modifications during Cycle 1 to enable PK sampling following a single dose and repeated doses. Patients enrolled in Part G should receive fulvestrant according to the study schedule.

All patients in the study receive 2 cycles of LY2835219 unless one or more of the criteria for discontinuation (refer to Section 5.3.1) are fulfilled; the follow-up period for poststudy evaluation is 30 ±7 days from the date of the last dose of study drug received. A patient may receive more than 2 cycles of treatment only if 1) none of the criteria for discontinuation have been fulfilled, and 2) the investigator, in consultation with the Lilly clinical research physician (CRP), determines that the patient is experiencing clinical benefit from treatment.

Refer to Attachment 1 for the detailed study schedule.



Abbreviations: HR+ = hormone receptor positive; Q12H = every 12 hours; Q24H = every 24 hours.

Figure JPBA.5.1. Study design for I3Y-MC-JPBA.

5.3. Discontinuations

5.3.1. Discontinuation of Patients

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

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

- The investigator or attending physician decides the patient should be withdrawn. If this decision is made because of a serious adverse event or a clinically significant laboratory value, then appropriate supportive measures are to be taken. Lilly or its designee is to be alerted immediately. (Refer to Section 7.1).
- The patient requests to be withdrawn from the study.
- The patient, for any reason, requires treatment with another therapeutic agent that has proven efficacious in the treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.
- The investigator or Lilly, for any ethical, medical, or scientific reason, while considering the rights, safety, and well-being of the patient(s), stops the study or stops the patient's participation in the study.
- The patient experiences unacceptable toxicity, including but not limited to the following circumstance (refer to Section 6.2.4.2):
  - The patient does not meet the criteria for recovery from toxicity within 14 days of the last day of the previous cycle.
- The patient is noncompliant with study procedures and/or treatment.(refer to Section 6.6).
- The patient has evidence of progressive disease.

Patients who discontinue the study drug and/or study early will have end-of-study and follow-up procedures performed as shown in the Study Schedule (Attachment 1).

For dose escalation (Part A), any patient who is discontinued from the study before receiving at least 75% of planned doses of LY2835219 in Cycle 1 will be deemed nonevaluable for assessment of that dose level and may be replaced unless they experience a DLT before withdrawal. Nonevaluable patients may be replaced to ensure that no fewer than 3 patients receive at least 75% of planned doses of LY2835219 in Cycle 1 at each dose level, unless enrollment to that cohort has stopped because more than 1 patient at that dose level has experienced a DLT. Patients who complete Cycle 1 of therapy but are not evaluable for PK may be replaced upon consultation with the investigator(s) and the Lilly CRP to ensure adequate PK

data collection, unless enrollment to that cohort has stopped because more than 1 patient at that dose level has experienced a DLT.

For Part G, any patient who is discontinued from the study for a reason other than progressive disease and before receiving a post-treatment radiological tumor assessment will be deemed nonevaluable for assessment of response. Additional patients may be enrolled to replace nonevaluable patients.

5.3.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, the institutional review board (IRB)/ethical review board (ERB) or the regulatory authority deems it necessary for any scientific, medical, or ethical reason.

5.3.3. Discontinuation of the Study

The study will be discontinued if Lilly, while considering the rights, safety, and well-being of the patient(s), deems it necessary for any scientific, medical, or ethical reason.

6. Treatment

6.1. Materials and Supplies

LY2835219 will be supplied by the sponsor for oral administration. LY2835219 should be stored at room temperature according to the label, and not opened, crushed, or dissolved. Investigators should instruct patients to store LY2835219 in the original package and in a location inaccessible to children. Clinical study materials will be labeled according to US regulatory requirements.

For Part G, patients with HR+ breast cancer should receive fulvestrant as specified in the label. Fulvestrant (50 mg/mL) is available commercially, should be stored and administered according to the label, and will not be supplied.

6.2. Treatments Administered

The investigator or his/her designee is responsible for:

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

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

6.2.1. Dosing Schedule

For the once daily schedule, patients will continue to receive LY2835219 orally every 24 hours (±3 hours) for Days 1 through 28 of a 28-day cycle. For the twice daily schedule, patients will receive LY2835219 orally every 12 hours (±3 hours) for Days 1 through 28 of a 28-day cycle. For both schedules, there are modifications during Cycle 1 to enable PK sampling following a single dose and repeated doses.

During Cycle 1 on the twice daily schedule, the initial dose of study drug will be taken on Day -3 to enable PK sampling over 72 hours following a single dose; the remaining 55 doses will be taken every 12 hours on Days 1 to 28, with PK sampling on Day 1 and Day 15 and over 24 hours following the single dose taken on Day 28. For Cycle 1, patients should be specifically instructed not to take a second dose of study drug on Day 28; if such a dose is inadvertently taken on Day 28, it constitutes a protocol violation. Patients should not consume food beginning 1 hour before and ending 1 hour after taking study drug.

During Cycle 2 and beyond on the twice daily schedule, study drug is taken orally every 12 hours on Days 1 through 28 of a 28-day cycle.

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

For Part G, patients should receive fulvestrant according to the study schedule. For patients already receiving fulvestrant at time of study entry, the fulvestrant dose on Cycle 1 Day 1 should correspond approximately to the expected date for its monthly administration and fulvestrant should not be administered on Cycle 1 Day 15.

For Part G, fulvestrant 500 mg should be administered intramuscularly into the buttocks slowly (1 to 2 minutes per injection) as two 250-mg injections, one in each buttock; however, for patients with moderate hepatic impairment (defined as Child-Pugh Class B), fulvestrant 250 mg should be administered intramuscularly into the buttock slowly (1 to 2 minutes) as one 250-mg injection.

Patients will receive 2 cycles of LY2835219 unless one or more of the criteria for discontinuation (refer to Section 5.3.1) are fulfilled; the follow-up period for poststudy evaluation will be 30 ±7 days from the date of the last dose of study drug received. A patient may receive more than 2 cycles of treatment only if 1) none of the criteria for discontinuation have been fulfilled, and 2) the investigator, in consultation with the Lilly CRP, determines that the patient is experiencing clinical benefit from treatment.

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

For Cycle 2 and beyond, a delay of ≤14 days in the start of a cycle (Day 1) to allow for recovery from toxicity will be permitted and does not constitute a protocol violation (refer to Section 6.2.4.2).

6.2.2. Dose-Escalation Phase

The dose was escalated following assessment of toxicity using the standard scoring system, Common Terminology Criteria for Adverse Events (CTCAE [redacted] established by the National Cancer Institute (NCI). Any AEs possibly related to LY2835219 were considered as toxicities.

For the dose-escalation phase, Table JPBA.6.1 summarizes the dose levels completed for the once daily schedule (50 to 225 mg every 24 hours) and the proposed dose levels for the twice daily schedule (75 to 450 mg every 12 hours). Three patients were planned for treatment at each dose level; however, the exact number of patients treated at a specific dose level depended, as discussed below, on the number of patients within the cohort who experienced a DLT. If a patient in a given cohort experienced a DLT during Cycle 1, then subsequent patients were enrolled sequentially.

In all cohorts (including the first cohort), every patient was assessed for toxicity (based on CTCAE CCI grading) on Days 15 and 29 of Cycle 1. Except for the initial cohort, patients in all subsequent cohorts were enrolled concurrently.

Table JPBA.6.1. Dose-Escalation Scheme for Study I3Y-MC-JPBA

Cohort	Patients/Cohort	LY2835219 Dose
1	3	50 mg Q24H
2	3	100 mg Q24H
3	3	150 mg Q24H
4	3	225 mg Q24H
5	3	75 mg Q12H
6	3	100 mg Q12H
7	3	150 mg Q12H
8	3	200 mg Q12H
9	3	275 mg Q12H
10	3	350 mg Q12H
11	3	450 mg Q12H

Abbreviations: Q24H = every 24 hours, Q12H = every 12 hours.
Note: Cohorts 1-4 received study drug Q24H on the once daily schedule.

The dose-escalation phase was guided by safety assessments from Days -3 through 29 of Cycle 1 for all patients in the cohort and also by the emerging PK data from previous cohorts. If none of the patients in a cohort experienced a DLT, dose escalation could occur to the next prespecified dose level. For all cohorts, if safety assessments and/or the emerging PK data indicated either that dose escalation should occur to a dose level lower than the next prespecified dose level or that dose de-escalation should occur to a dose level lower than the current dose level, then safety assessments and/or the emerging PK data could be used to select an alternate dose level within these constraints. Dose escalation occurred until the MTD (defined in Section 6.2.2.1) was established at 200 mg every 12 hours for the twice daily schedule.

Dose escalation, unless guided by the emerging PK data as described above, proceeded as indicated in Table JPBA.6.1 until 1 patient experienced a DLT; thereafter, all subsequent patients in that cohort were enrolled sequentially. If a DLT occurred in only 1 of 3 patients at a given dose level, up to 6 patients could be treated at that dose level; however, a total of 6 patients had to be treated at that dose level without further occurrences of a DLT before dose escalation could resume. If a DLT occurred in more than 1 patient at a given dose level, then the MTD had been exceeded and both dose escalation and enrollment to the cohort ceased. However, following discussion and agreement with investigators, additional patients could be treated at intermediate doses between the previous dose level and the dose level that exceeded the MTD to define the MTD more precisely.

In this study, intrapatient dose escalation was not permitted and dose escalation to the next cohort could not occur without prior discussion and agreement between the investigator and the responsible Lilly CRP.

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

Dose-limiting toxicity (DLT) is defined as an AE occurring between Day -3 and Day 29 of Cycle 1 for a patient enrolled in Part A that is possibly related to the study drug and fulfills any one of the following criteria:

- Grade 3 or 4 nonhematological toxicity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE CCI except for nausea, vomiting, diarrhea, or electrolyte disturbance.
- Grade 3 or 4 nausea, vomiting, diarrhea, or electrolyte disturbance that persists more than 2 days despite maximal supportive intervention.
- Grade 4 hematological toxicity that persists more than 5 days.
- Grade 3 or 4 thrombocytopenia with bleeding.
- Grade 3 or 4 neutropenia with fever.

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 that would have met the criteria for DLT if it had occurred during Cycle 1 for a patient enrolled in Part A but that occurs between 1) Day 1 and Day 28 of Cycle 2 and beyond for a patient enrolled in Part A; 2) Day 1 and Day 29 of Cycle 1 for a patient enrolled in Parts B, C, D, E, F, or G; or 3) Day 1 and Day 28 of Cycle 2 and beyond for a patient enrolled in Parts B, C, D, E, F, or G.

Maximum tolerated dose (MTD) is defined as the highest dose level at which less than 33% of patients experience a DLT during Cycle 1.

6.2.2.2. Biologically Effective Dose

Pharmacokinetic (PK) and PD data will be used for estimating the biologically effective dose (BED). For the purpose of this study, the BED is defined as the lowest dose that achieves a minimum of 30 to 50% inhibition of CDK4/6 (measured by pRb and topoIIα) in surrogate tissues (hair follicles or skin) at steady state. This level of CDK4/6 inhibition corresponds to that observed in mouse preclinical experiments at the lowest dose achieving tumor growth delay. Nonclinical PK/PD modeling predicts that a dose of 150-300 mg of LY2835219 administered every 24 hours will produce the minimum level of CDK4/6 inhibition that has been associated with tumor growth delay in preclinical efficacy studies.

6.2.3. Dose Confirmation Phase (Parts B, C, D, E, F, and G)

After the MTD has been identified in Part A, at least 15 and up to 45-60 patients will be enrolled in each of the 6 tumor-specific expansions: Part B (non–small cell lung cancer), Part C

(glioblastoma multiforme), Part D (breast cancer), Part E (melanoma), Part F (colorectal cancer), and Part G (HR+ breast cancer).

During the dose confirmation phase, patients may enroll concurrently and will be treated at a dose no greater than the MTD (200 mg every 12 hours). Patients enrolled under JPBA amendment (f) who are still receiving LY2835219 at a dose of 150 mg every 12 hours may, at the discretion of the investigator, be escalated to 200 mg every 12 hours. Patients enrolled under JPBA amendment (g) or subsequent amendment should initially receive LY2835219 at a dose of 200 mg every 12 hours. For all patients, dose adjustments are permitted as outlined in Section 6.2.4.1.

If DLT-equivalent toxicities occur in 33% or more of patients within a tumor-specific cohort expansion, then investigators and the Lilly CRP will assess the nature and severity of these toxicities. No additional patients will be accrued until this safety review is completed and a decision is made either to continue at the current dose or to deescalate the dose and define a new dose for the expansion phase. The safety review and decision will be documented in writing.

During the dose confirmation phase, paired tumor biopsies should be obtained, whenever clinically feasible, before (Day -14 to Day -4) and after (Day 8 to Day 22) administration of study drug in Cycle 1.

6.2.4. Dose Adjustments

6.2.4.1. Dose Adjustments

Table JPBA.6.2 is a guidance for management of treatment-emergent, related, and clinically significant toxicities of LY2835219.

Table JPBA.6.2. Toxicity Dose Adjustments and Delays of LY2835219

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity	Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose reduction is **NOT** required.
Hematologic Toxicity	Recurrent[a] Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.
Hematologic Toxicity	Grade 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level.

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity: **If patient requires administration of blood cell growth factors**	Regardless of severity (Use of growth factors according to ASCO Guidelines)	Dose **MUST** be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2.	Dose **MUST** be reduced by 1 dose level unless already performed for incidence of toxicity that led to the use of growth factor.
Non-hematologic Toxicity[b] (except diarrhea, ALT/AST increased, and ILD/Pneumonitis)	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
Non-hematologic Toxicity[b] (except diarrhea, ALT/AST increased, and ILD/Pneumonitis)	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea	Grade 2 that does not resolve within 24 hours to at least Grade 1	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose reduction is **NOT** required.
Diarrhea	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea	Requires hospitalization or Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
ALT/AST Increased	Persistent or recurrent[a] Grade 2 (>3.0-5.0×ULN), or Grade 3 (>5.0-20.0×ULN)[c]	Dose **MUST** be suspended until toxicity resolves to baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
ALT/AST Increased	Grade 4 (>20.0×ULN)	LY2835219 therapy **MUST** be discontinued.	LY2835219 therapy **MUST** be discontinued.
ALT/AST Increased with increased total bilirubin, in the absence of cholestasis	≥Grade 2 increased ALT/AST (>3.0×ULN) with total bilirubin >2×ULN	LY2835219 therapy **MUST** be discontinued.	LY2835219 therapy **MUST** be discontinued.
ILD/Pneumonitis[d]	Grade 2 that persists or recurs despite maximal supportive measures and does not return to baseline or Grade 1 within 7 days	Dose **MUST** be suspended until toxicity resolves to baseline or Grade ≤1.	Dose **MUST** be reduced by 1 dose level.
ILD/Pneumonitis[d]	Grade 3 or 4	LY2835219 therapy **MUST** be discontinued.	LY2835219 therapy **MUST** be discontinued.

Abbreviations: ALT = alanine aminotransferase; ASCO = American Society of Clinical Oncology; AST = aspartate aminotransferase; ILD = interstitial lung disease; ULN = upper limit of normal.

Note: MUST = mandatory.

[a] Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 8 weeks (as measured from the stop date of the preceding event). As a general guidance, based on the benefit/risk balance assessment per the investigator, for a patient who experiences a new episode of Grade 3 hematologic toxicity after more than 8 weeks following the last episode of same Grade 3 hematologic toxicity, the investigator may consider resuming the patient on the same drug dose should the patient satisfy the following conditions:

- shows stable hematologic counts (Grade ≤2) during that timeframe
- has absence of any signs or risk of infection
- is benefiting from study treatment

[b] Additional guidance for renal and hepatic monitoring is provided in Sections 7.1.3.2 and 7.1.3.1.

[c] Grade 3 ALT/AST increased is a trigger for additional assessments and possibly hepatic monitoring. See Section 7.1.3.1 for additional guidance for hepatic monitoring.

[d] Additional guidance for ILD/pneumonitis monitoring is provided in Section 7.1.3.4.

Dose adjustments as outlined in Table JPBA.6.3 are allowed both within a cycle and between cycles. LY2835219 dose alterations (omission, reduction, and discontinuation) should not be based solely on the presentation of serum creatinine values, because these may not reflect actual renal function. Further information can be found in the Section 3.2.4 of the LY2835219 IB.

If a patient who, in the judgment of the investigator, is receiving clinical benefit from study therapy requires further dose reduction than is outlined in Table JPBA.6.3, then the investigator must discuss with the Lilly CRP prior to any further dose reduction.

For patients requiring dose reduction(s), re-escalation to a prior dose level is permitted only after consultation with the Lilly CRP.

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

Table JPBA.6.3. Dose Adjustments of LY2835219 for Study I3Y-MC-JPBA

Dose Adjustment	Oral Dose	Frequency
0	200 mg	Every 12 hours
1	150 mg	Every 12 hours
2	100 mg	Every 12 hours
3	75 mg	Every 12 hours

For patients in Part G with moderate hepatic impairment (defined as Child-Pugh Class B), fulvestrant 250 mg should be administered intramuscularly into the buttock slowly (1 to 2 minutes) as one 250-mg injection, according to the study schedule. In the event that fulvestrant must be discontinued, a patient may continue to receive LY2835219.

6.2.4.2. Dose Delays

Before the start of each cycle, hematologic toxicity possibly related to LY2835219 must resolve to either baseline or at least Grade 2.

Before the start of each cycle, non-hematologic toxicity (except alopecia and fatigue) possibly related to LY2835219 must resolve to either baseline or at least Grade 1.

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

6.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be assigned to receive LY2835219 in this study. Prior to enrollment into the study, an eligibility check must be conducted (for every patient) between the investigational site and the Lilly clinical research personnel, to confirm that the patient meets all enrollment criteria. Upon confirmation of eligibility, the sponsor will confirm the dose, cohort, and identification number assignment for each patient. No patients can be enrolled into the next cohort without prior discussion and agreement with the responsible Lilly CRP.

6.3.1. Continued Access

Participants who are still on study drug may continue to receive study drug during the continued access period if they are experiencing clinical benefit and no undue risks. Lilly will notify investigators when the continued access period begins. Lilly may allow participants to enroll in a "rollover" protocol to provide long-term continued access for participants enrolled in this study.

Patients are not required to sign a new informed consent form (ICF) before treatment is provided during the continued access period.

During the continued access period, all adverse events (AEs), serious adverse events (SAEs), and study drug exposure will be reported on the case report form (CRF). Serious adverse events will also be reported to Lilly Global Patient Safety (see Section 7.1.2). In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE.

Investigators will perform any other standard procedures and tests (locally) needed to treat and evaluate patients; however, the choice and timing of the tests will be at the investigator's discretion. Lilly will not routinely collect the results of these assessments.

The patient's continued access to study drug will end when a criterion for discontinuation is met (Section 5.3). Continued access follow-up will begin the day after the patient and investigator agree to discontinue study drug and last approximately 30 days.

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

In all cases, no follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

6.4. Blinding

This is an open-label study.

6.5. Concomitant Therapy

For Part G, concomitant therapy with fulvestrant is permitted.

No other chemotherapy, immunotherapy, or experimental medications are permitted while the patients are on this study. Hormone replacement therapy initiated before study entry may be continued but should be considered for discontinuation. Palliative radiotherapy, unless required due to progressive disease, is permitted during the study. Disease progression requiring specific antitumor therapy will necessitate early discontinuation from the study. Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured for each cycle on the case report form.

Patients should receive full supportive care during this study.

Growth factors may be administered in accordance with American Society of Clinical Oncology (ASCO) guidelines, if clinically indicated (Smith et al. 2015; Rizzo et al. 2010). See Table JPBA.6.2 for dose adjustments and delays related to administration of growth factors.

Transfusion therapy is permitted during this study.

Modulators of CYP3A

LY2835219 is extensively metabolized through oxidation by CYP3A. In clinical drug interaction studies,

- coadministration of clarithromycin, a strong CYP3A inhibitor, increased exposure (AUC) of LY2835219 by 3.4-fold (Study I3Y-MC-JPBE), and
- coadministration of rifampin, a strong CYP3A inducer, decreased exposure of LY2835219 by 95% (Study I3Y-MC-JPBF).

Strong inhibitors of CYP3A (given via non-topical routes of administration) should be substituted or avoided if possible (Attachment 8). This includes grapefruit or grapefruit juice. In particular, avoid oral administration of the very strong CYP3A inhibitor, ketoconazole.

If coadministration with a strong CYP3A inhibitor is unavoidable, investigators should reduce the dose of LY2835219 by 50 mg at the start of CYP3A inhibitor treatment. That is, for patients receiving 150 mg twice daily, reduce the dose to 100 mg twice daily. For patients who have already dose reduced to 100 mg twice daily for tolerability, reduce the dose further to 50 mg twice daily. Alternatively, the investigator may consider suspending LY2835219 for the duration of the CYP3A inhibitor medication. Dose suspensions ≥28 days must be discussed with Lilly CRP/CRS.

Upon discontinuation of the strong CYP3A inhibitor, the dose of LY2835219 may be re-escalated to the dose that was used before starting the strong inhibitor after a sufficient washout period (3-5 half-lives of the strong inhibitor). Re-escalation of the LY2835219 dose requires review and approval from Lilly CRP/CRS.

Inducers of CYP3A should be substituted or avoided if possible (Attachment 8). Coadministration with a CYP3A inducer ≥28 days must be discussed with Lilly CRP/CRS.

Transporter Substrates

At clinically relevant concentrations, LY2835219 inhibits the transporters P-glycoprotein, breast cancer resistance protein, organic cation transporter 2 (OCT2), multidrug and toxin extrusion protein 1 (MATE1), and MATE2-K. The observed serum creatinine increase in clinical studies with LY2835219 is likely due to inhibition of tubular secretion of creatinine via OCT2, MATE1, and MATE2-K. In vivo interactions of LY2835219 with narrow therapeutic index substrates of these transporters, such as digoxin and dabigatran, may occur.

6.5.1. Supportive Management for Diarrhea

In the event of diarrhea while a patient is receiving LY2835219, supportive measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the patient should initiate anti-diarrheal therapy (for example, loperamide), and notify the investigator for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (for example, 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- If diarrhea does not resolve with anti-diarrheal therapy within 24 hours to at least Grade 1, then dosing should be suspended until diarrhea is resolved to at least Grade 1.
- When LY2835219 recommences, dosing should be adjusted as outlined in Table JPBA.6.2.

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

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

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

6.6. Treatment Compliance

Patient compliance with study medication will be assessed at each visit by review of the patient diary, direct questioning, and counting of returned solid oral dosage units. Deviation(s) from the prescribed dosage regimen should be recorded on the Case Report Form (CRF).

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

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

7.1. Safety Evaluations

The safety and tolerability of LY2835219 have been assessed in nonclinical toxicology studies and the results from these studies are detailed in the IB. This Phase 1 study contains a detailed safety monitoring plan that will permit initial characterization of the safety profile of LY2835219 in patients. Study procedures and their timing, including tolerance limits for timing, are described in the Study Schedule (Attachment 1).

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

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

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

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

7.1.1. 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, 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 on study will be graded using the Common Terminology Criteria for Adverse Events (CTCAE [redacted]

The investigator remains responsible for following, through an appropriate health care option, all AEs that are SAEs or that caused the patient to discontinue before completing the study. The

patient should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Frequency of AE and SAE follow-up evaluation is left to the discretion of the investigator.

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

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

ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present, to determine whether any clinically relevant findings are present.

After enrollment, if a clinically significant increase in the QTcB interval from baseline, or other clinically significant quantitative or qualitative change from baseline, is present, the investigator will assess the subject for symptoms (for example, palpitations, near syncope, syncope) and to determine if the subject can continue in the study. The investigator or qualified designee is responsible for determining if any change in subject management is needed and must document his/her review of the ECG printed at the time of evaluation.

All digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. A cardiologist at the central ECG laboratory will then conduct a full overread on the ECG (including all intervals); a report based on data from this analysis will be issued to the investigative site.

It is recognized that ECG interpretations by the investigator (or qualified designee) and by the cardiologist at the central ECG laboratory may be different. When there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the interpretation of the investigator (or qualified designee) will be used for study entry and immediate subject management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes.

The investigator (or qualified designee) must document his/her review of the ECG printed at the time of evaluation, the final over-read ECG report issued by the central ECG laboratory, and any alert reports.

7.1.2. 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 trial AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any

unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product. Any clinically significant findings from labs, vital sign measurements, and so on that occur should be reported to Lilly or its designee as an AE using the same guidelines and schedules as those for AEs. Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect.

The investigator, monitor, and sponsor will review the collected data regularly for evidence of AEs. All patients will be assessed routinely for AEs as outlined in the study schedule. All AEs observed will be graded using CTCAE CCI

The National Cancer Institute (NCI)-CTCAE CCI 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 NCI-CTCAE CCI 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 pre-existing 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 pre-existing condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to Lilly or its designee.

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

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

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

The investigator decides whether he/she interprets the observed safety signals 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:

- **Probably 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.
- **Does not know:** the investigator cannot determine
- **Not related:** without question, the AE is definitely not associated with the study treatment.

As per Lilly's standard operating procedures all "probably related," "possibly related," "does not know" AEs and SAEs will be defined as related to study drug.

Any clinically significant findings (including but not limited to vital signs, physical findings, laboratories, and ECGs) that occur should be reported to Lilly or its designee on the eCRF.

7.1.2.1. Serious Adverse Events

Serious adverse event collection begins after the patient has signed the informed consent document. If a patient experiences an SAE after signing informed consent, but prior to receiving study drug, the event will NOT be collected unless the investigator feels the event may have been caused by a protocol procedure. During therapy with study drug and for 30 ±7 days after the last dose of study drug, all SAEs will be collected regardless of relatedness to study drug or protocol procedures. Beyond 30 ±7 days from the last dose of study drug, only ongoing or new SAEs possibly related to study drug or protocol procedures should be reported.

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

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

An SAE is any AE during this study that results in 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 upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms. The 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Drug- or procedure-related SAEs should be followed until they resolve, are no longer considered to be drug related, become stable or return to baseline, the patient starts a new therapy, the patient dies, or the patient becomes lost to follow-up.

7.1.2.2. Adverse Event and Serious Adverse Event Reporting

7.1.2.2.1. Prior to Administration of Study Drug

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

7.1.2.2.2. On Study Drug

All AEs and SAEs, regardless of relatedness to study drugs 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.

7.1.2.2.3. Follow-Up Visit

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

Following the safety assessment, which marks the end of the follow-up visit, the patient will be discontinued from the study, unless there is an ongoing AE or SAE that is possibly related to study drug. In this instance, the patient should be followed in subsequent follow-up visits until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up.

After the follow-up visit, only new AEs or SAEs that are considered possibly related to study drug or protocol procedures should be reported to Lilly or its designee.

7.1.2.2.4. Summary of Adverse Event/Serious Adverse Event Reporting Guidelines

The AE and SAE reporting guidelines are summarized in Table JPBA.7.1. Refer to Attachment 5 for specific recommendations about reporting SAEs.

Table JPBA.7.1. Adverse Event and Serious Adverse Reporting Guidelines for Study I3Y-MC-JPBA

Timing	Types of AEs and SAEs Reported
Prestudy (baseline assessments) (Starts at the signing of informed consent and ends just before the first dose of study drug)	Preexisting conditions Only AEs and SAEs possibly related to protocol procedures
On therapy (Starts at first dose of study drug and ends at last dose of study drug)	All AEs and SAEs regardless of relatedness
Follow-up Visit (Visit 801) (Starts just after the last dose of study drug and ends when final safety assessments are completed [30 ±7 days after last dose of study drug])	All AEs and SAEs regardless of relatedness
Beyond 30 ±7 days after last dose of LY2835219	Only ongoing or new AEs and SAEs possibly related to study drug or protocol procedures

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

Any SAE due to progressive disease (including death) should not be reported unless the investigator also determines there is a possible contribution related to the study drug.

7.1.3. Safety Monitoring

The Lilly clinical research physician or clinical research scientist 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.

7.1.3.1. Hepatic Monitoring

Liver testing (Attachment 3), including ALT, AST, alkaline phosphatase (ALP), total bilirubin (TBL), direct bilirubin (D. Bil), gamma-glutamyl transferase (GGT), and creatine kinase (CK), should be repeated within 2 to 4 days to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a participant with baseline results of…	develops the following elevations:
ALT or AST <1.5× ULN	ALT or AST ≥5× ULN or ALT or AST ≥3× ULN concurrent with TBL ≥2× ULN
ALT or AST ≥1.5×ULN	ALT or AST ≥3× baseline or ALT or AST ≥2× baseline concurrent with TBL ≥2× ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), history of concomitant medications (including over-the-counter, herbal and dietary supplements, history of alcohol drinking, and other substance abuse). In addition, the evaluation should include a blood test for prothrombin time international normalized ratio (PT-INR); serological tests for viral hepatitis A, B, C, E, autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Additional Hepatic Safety Collection

Additional safety data should be collected via the case report form (CRF) if 1 or more of the following conditions occur:

In participants enrolled with baseline ALT or AST <1.5× ULN

- Elevation of serum ALT or AST to ≥5× ULN on 2 or more consecutive blood tests
- The combination of elevated ALT or AST ≥3× ULN and elevated TBL ≥2× ULN

In participants enrolled with baseline ALT or AST ≥1.5× ULN

- Elevated ALT or AST ≥3× baseline on 2 or more consecutive tests
- The combination of elevated ALT or AST ≥2× baseline and elevated TBL ≥2× ULN

In all study participants

- Discontinuation from study treatment due to a hepatic event or abnormality of liver tests
- Occurrence of a hepatic event considered to be an SAE

7.1.3.2. Renal Function

LY2835219 has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting cystatin C-calculated glomerular filtration rate (GFR). Increases in serum creatinine occurred within the first 2 weeks of treatment, remained stable through the treatment period, and were reversible upon treatment discontinuation. If deterioration of renal function is suspected, serum creatinine should not be the only measure used to assess a patient's renal function. Local testing of cystatin C for calculation of GFR can be considered for a more thorough assessment of renal function.

Dose adjustment (omission, reduction, or discontinuation) should not solely be based on interpretation of serum creatinine values because these may not reflect renal function. If deterioration of renal function is suspected per the investigator's clinical assessment, dose alteration should follow the protocol guidance for non-hematological toxicities (Table JPBA.6.2).

7.1.3.3. Venous Thromboembolic Events

VTE has been identified as an adverse drug reaction for LY2835219 in combination with endocrine therapy. In the randomized Phase 3 studies in patients with breast cancer treated with LY2835219 in combination with endocrine therapy (ET), a greater number of patients experienced VTEs in the LY2835219 plus ET arm than in the placebo plus ET arm or ET alone arm. The majority of patients who experienced VTEs were treated with anticoagulants.

In studies with single-agent abemaciclib use in the metastatic breast cancer (mBC) population or other tumor types, including non-small cell lung cancer (NSCLC), no increased rates of VTEs were observed as compared to the incidence of VTEs for these particular patient populations who were treated with other anticancer agents. At this time, the mechanism underlying the association between LY2835219 and the occurrence of VTEs is not known. Monitor patients for signs and symptoms of deep vein thrombosis and pulmonary embolism and treat as medically appropriate.

7.1.3.4. Interstitial Lung Disease/Pneumonitis

Interstitial lung disease/pneumonitis has been identified as an adverse drug reaction for LY2835219. Additional information is available in the IB.

Ask your patients to report any new or worsening pulmonary symptoms such as dyspnea, cough, and fever; and investigate and treat as per your local clinical practice (including corticosteroids as appropriate). If ILD/pneumonitis is suspected, investigations may include imaging such as high-resolution computed tomography, bronchoalveolar lavage, and biopsy as clinically indicated.

Refer to Table JPBA.6.2 for guidance on dose adjustments of LY2835219 for patients with ILD/pneumonitis. Discontinue LY2835219 in cases of severe (Grade 3 or 4) ILD/pneumonitis.

7.1.4. Complaint Handling

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

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

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

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

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

7.2. Sample Collection and Testing

7.2.1. Pharmacokinetic Evaluations

Pharmacokinetic (PK) samples will be collected as specified in the Study Schedule (Attachment 1) and PK and PD Sampling Schedule (Attachment 4)

Venous blood samples from all patients will be analyzed to measure concentrations of LY2835219 and its metabolites (LSN2839567 [M2], LSN3106729 [M18], and LSN3106726 [M20]). For Part G only, venous blood samples from patients will also be analyzed to measure concentrations of fulvestrant. Blood samples will be collected throughout the study (Parts A, B, C, D, E, F, and G). Separate samples are not required for the parent, its metabolites, and fulvestrant. Instructions for the collection and handling of blood samples will be provided by the sponsor.

A maximum of 5 additional PK (blood) samples may be added or removed during the study if warranted and agreed upon by both the investigator and sponsor. For instance, if during Cycle 1 or 2, the patient is in the clinic for management of his/her disease or study-related events, additional PK (blood) samples, not to exceed 5 per patient, may be collected following documented discussions between the investigator and sponsor.

Plasma PK samples (from venous blood) will be analyzed at a laboratory designated by the sponsor. Concentrations of LY2835219 and its metabolites (LSN2839567 [M2], LSN3106729 [M18], and LSN3106726 [M20]) will be assayed using a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) method. For Part G, concentrations of fulvestrant will be assayed using a validated LC/MS/MS method. 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.

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7.2.2. Pharmacodynamic Evaluations

Pharmacodynamic (PD) samples will be collected as specified in the Study Schedule (Attachment 1) and PK and PD Sampling Schedule (Attachment 4). Refer to these attachments (including footnotes) for important information about these samples and their collection.

Hair follicles will be collected for the measurement of the following cell cycle biomarkers: total retinoblastoma protein (Rb), phosphorylated retinoblastoma protein (p-Rb) and topoisomerase II alpha (topoIIα).

In addition, skin and tumor biopsies will be collected pre- and post-treatment as supplemental tissue for measuring these biomarkers. Due to the absence of fixed timing for tumor biopsies, which should be obtained (whenever clinically feasible) only during dose confirmation (Parts B, C, D, E, F, and G), these are not indicated in the PK and PD Sampling Schedule (Attachment 4).

Precut, unstained slides from any available archival specimen of the patient's tumor will be requested for biomarker related studies. In addition, tumor biopsy samples will be obtained from patients enrolled in Parts B, C, D, E, F, and G when feasible and safe. Although it is preferred that tumor tissue biopsies be taken by either core needle or excisional biopsy, fine needle aspirate (FNA) biopsies will be acceptable. The size of the sample will be dependent upon the procedure utilized to obtain the sample. These biomarker-related studies will include, but not be limited to, IHC, protein, and/or genetic analyses of the tumor specimens.

For purpose of comparison, in the event a patient participating in this clinical trial elects to have a surgical procedure that involves removing some part of their tumor, a formalin-fixed paraffin-embedded (FFPE) tumor tissue sample, or duplicate paraffin block, will be requested.

The goal of obtaining these samples will be to obtain a better understanding of molecular tumor markers that might help predict which cancer patients are more likely to respond to treatment with LY2835219.

Instructions and supplies required for the collection and shipment of the patients' samples will be provided by the sponsor. Sample handling and shipment to the central laboratory will occur per instructions given to the study site.

Bioanalytical samples collected to measure for specified PD tests will be stored in a sponsor designated facility and retained for a maximum of 5 years following the last patient visit for the study.

7.2.3. Samples for Standard Laboratory Testing

Blood and serum samples (Attachment 2) will be collected at the times specified in the Study Schedule (Attachment 1).

Investigators must document their review of each laboratory safety report.

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

7.3. Efficacy Evaluations

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

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

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

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).

All lesion assessments, whether by physical exam or radiological methods, should be repeated by the same method at least 4 weeks following the initial observation of an objective response to

ensure response confirmation. If a patient is discontinued from the study, repeat radiology may be omitted if there are clear clinical signs of progressive disease. CT scans and MRIs may be requested to be sent to an off-site storage facility, and potentially independently reviewed and/or read by Lilly or its designee.

7.4. 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 eCRF.

The scheduled collection times may be modified by the sponsor based upon 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.

8. Data Management Methods

8.1. 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 eCRF data and/or use standard computer edits to detect errors in data collection.
- Conduct a periodic review of the database.

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

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable IRB/ERBs with direct access to the original source documents.

8.2. Data Capture Systems

8.2.1. Case Report Form

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

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

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

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

8.2.2. Ancillary Data

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

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

Electrocardiogram 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 system and TPO system.

9. Data Analyses

9.1. General Considerations

Patients will be enrolled in this multicenter, open-label, Phase 1 study with dose escalation CCI [redacted] design followed by dose confirmation in 6 tumor-specific expansions. During dose escalation, patients were enrolled CCI [redacted] the total number of patients in a specific cohort was determined based on the occurrence of DLTs at that dose level (refer to Section 6.2.2), CCI [redacted] During dose confirmation, at least 15 and up to 45-60 patients will be enrolled in each of 6 tumor-specific cohort expansions (refer to Section 6.2.3).

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

The analyses for this study will be descriptive. Data analyses will be provided CCI [redacted] for all study patients combined wherever appropriate. For continuous variables, summary statistics will include number of patients, mean, median, standard deviation, standard error, minimum, and maximum. Categorical endpoints will be summarized using number of patients, frequency, percentages, and their standard errors. For time to event endpoints, the Kaplan-Meier curves (Kaplan and Meier 1958) will be estimated. Quartiles and rates at various time points, together with the 95% CIs, will be provided. Missing data will not be imputed.

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

CCI [redacted]

9.1.1. Determination of Sample Size (Parts B, C, D, E, F, and G)

Although at least CCI [redacted] patients will be enrolled in each of the 6 tumor-specific expansions, up to 45-60 patients may be enrolled in each tumor-specific expansion if approved by the sponsor. The sample size of up to 45-60 patients for each of the 6 tumor-specific expansions is based on differentiating 34.5% to 40% from 5% (uninteresting) overall response rate (ORR) in tumors with (marker present) and without (marker absent) a tumor-relevant exploratory marker, respectively (that is, $ORR_{marker\ present}$=34.5% to 40% and $ORR_{marker\ absent}$=5%). Examples of tumor-relevant exploratory markers include KRAS (non-small cell lung cancer, colorectal cancer), CDKN2A (glioblastoma multiforme, melanoma), and estrogen receptor (ER; breast cancer). Assuming an equal number of patients having tumors with and without the exploratory marker, 45 or 60 patients provide approximately 85% power to differentiate 40% or 34.5% from 5% ORR, respectively (refer to Table JPBA.9.1). To maximize the power to detect the ORR difference between the marker groups, enrollment to a tumor-specific expansion may be adjusted to achieve an equal number of patients having tumors with and without the exploratory marker.

CCI

9.1.2. Patient Disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

9.1.3. 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.

9.1.4. Safety Analyses

Safety analyses will be conducted on all patients who have received at least 1 dose of the study drug.

All patients who receive at least 1 dose of LY2835219 will be evaluated for safety and toxicity. Adverse events will be classified using the CTCAE CCI

Safety analyses will include summaries of the following:

- AEs, including severity and possible relationship to study drug
- Dose adjustments
- DLTs
- Laboratory measures and electrocardiograms.

9.1.5. Pharmacokinetic Analyses

Pharmacokinetic (PK) analyses will be conducted on patients who have received at least 1 dose of the study drug and have sufficient samples collected to allow the estimation of LY2835219 PK parameters.

Pharmacokinetic (PK) parameter estimates for LY2835219 will be computed by standard noncompartmental methods of analysis using CCI Professional Edition on a computer that meets or exceeds the minimum requirements for this program. The maximum concentration (C_{max}), area under the concentration-time curve (AUC), half-life ($T_{1/2}$), volume of distribution (V_d), clearance (CL), and other relevant parameters that can be calculated from the data will be reported from the noncompartmental analyses.

Providing that the data allow, the PK parameter estimates (C_{max} and AUC) for LY2835219 will be evaluated statistically to delineate the effects of dose proportionality using the methods described previously (Smith et al. 2000). Least-squares estimates of geometric means and their corresponding 90% confidence intervals (CI) will be provided by dose, together with the dose-normalized ratio of geometric means and CI.

In addition, the plasma PK data of LY2835219 will also be analyzed using nonlinear mixed effect modeling CCI (Section 9.1.7). The version of any software used for the analysis will be documented and the program will meet Lilly requirements of software validation. It is possible that other validated equivalent PK software programs may be utilized if appropriate, warranted, and approved by Lilly Global PK management.

Finally, in Part G, the plasma concentration data of fulvestrant will also be analyzed by standard noncompartmental methods of analysis, and any relevant PK parameter that can be calculated from the data will be reported.

CCI

9.1.7. Pharmacokinetic/Pharmacodynamic Analyses

In addition to a standard noncompartmental assessment, the plasma concentration data of LY2835219 will also be analyzed by means of a compartmental approach using CCI Plasma data from all patients will be pooled for analyses to determine the compartmental PK parameters and between- and within-patient variability. Covariates analysis will be also performed. Once a structural and statistical model has been established, the effect of patient factors will be assessed. Covariate data distributions will be assessed.

This population PK model will then be used to develop a PK/PD model where the levels of Rb, pRb and topoIIα in hair follicles are the primary PD measure. Additional PK/PD models may be developed using other PD measures.

Since a secondary objective of this clinical trial is to determine a recommended dose range of LY2835219 that may be safely administered to patients with advanced cancer, the results from these analyses may be used to support dose selection for Phase 2 studies.

The PK/PD data will be analyzed using validated software programs (for example, CCI [redacted]). The version of the software used for the analysis will be documented and will meet the Lilly requirements of software validation.

9.2. Efficacy

Response and progression for tumors will be evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Eisenhauer et al. 2009), with the notable exception that response and progression for lymphomas will be evaluated using the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007).

Tumor response and time-to-event data will be tabulated. For each expansion cohort, the time-to-event data analysis will include calculation of 6-month progression-free survival probability. Any patient that discontinues due to a reason other than progressive disease or death (for example, AE, patient/investigator decision) will have their time-to-event data either censored at Visit 801 if no progressive disease is found during this visit, or censored at the date of the last objective progression-free disease assessment if progressive disease is found at Visit 801.

For Part G, patients may have already received 1 or more cycles of fulvestrant prior to study enrollment. This prior therapy confounds the interpretation of response and progression. As a result, tabulations of tumor response and time-to-event data will be considered descriptive only.

9.3. Interim Analyses

Although an external safety review committee will not be formed, safety data for all patients will be reviewed continuously throughout this study by Investigators, the Lilly CRP, and Lilly Global Patient Safety.

Only the assessment committee is authorized to review complete interim analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients or for dose escalation. The assessment committee may consist of the members of the study team.

9.3.1. Analysis by Cohort during Dose Escalation (Part A)

Safety and PK data will be transferred to Lilly at the end of each completed cohort. A summary of safety and PK data will be provided.

9.3.2. Interim Analyses

CCI [redacted]

Safety, PK, and PD data will be transferred to Lilly at the completion of dose escalation (Part A).

Safety, efficacy, PK, and PD data will be transferred to Lilly approximately every 3 months and/or at the completion of each tumor-specific expansion (Parts B, C, D, E, F, and G).

10. Informed Consent, Ethical Review, and Regulatory Considerations

10.1. 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 informed consent document 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 informed consent document 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.

10.2. Ethical Review

Lilly must agree with all informed consent documents before they are submitted to the IRB/ERB and are used at investigative sites(s). All informed consent documents must be compliant with the International Conference on Harmonisation guideline on Good Clinical Practice (GCP). Informed consent obtained under special circumstances may occur only if allowed by local laws and regulations, and performed in accordance with a written process approved by Lilly.

The investigator will provide Lilly with documentation of IRB/ERB approval of the protocol and the informed consent document *before* the study may begin at the investigative site(s). Any member of the IRB/ERB who is directly affiliated with this study as an investigator or as site personnel must abstain from the review board's vote on the approval of the protocol. The IRB/ERB(s) will review the protocol as required.

The investigator will supply the following to the investigative site's IRB/ERB(s):

- the current IB and updates during the course of the study
- informed consent document
- relevant curricula vitae.

10.3. 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 of 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/IRB(s).

LY2835219 is being studied in the United States (US) under a US Investigational New Drug (IND) application. The US IND number is 106100.

Some of the obligations of the sponsor will be assigned to a contract research organization (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 trial-related data.

10.3.1. Investigator Information

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

10.3.2. Protocol Signatures

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.

10.3.3. Final Report Signature

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

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

The sponsor's responsible medical officer will sign 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.

11. References

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Attachment 1. Protocol JPBA Study Schedule

Schedule 1: Assessments for Parts A, B, C, D, E, F, and G

Cycle/Visit	Pre-study/ Visit 0		Cycle 1									Cycle 2 and Beyond		Follow-Up[o]
Relative Day Prior to Day 1 of Cycle 1	**-28 to -4**	**-14 to -4**	**-3***	**-2**	**-1**	**1**	**8 ±2**	**15 ±2**	**22 ±2**	**28**	**29**	**1 to 27**	**28 ±2[p]**	
Informed Consent	X													
Medical History		X									X		X	X
Pregnancy Test (if applicable)		X[a]												
Physical Exam		X						X			X		X	X
Vital Signs and Weight (Temperature, Pulse Rate, Blood Pressure, Respiratory Rate)		X					X	X	X		X		X	X
Height		X												
Chest X-ray[b]	X												X[h]	
Performance Status		X									X		X	X
CTCAE CCI Grading		X[c]						X			X		X	X[d]
Concomitant Medications		X									X		X	X
Tumor Measurement (Palpable and Visible)		X									X		X	X
ECG[e]		X	X	X	X			X						
LY2835219 Therapy[f]			X			X	X	X	X	X		X	X	
Fulvestrant Therapy (Part G only)						X[q]		X[r]			X		X	
Radiological Tumor Assessment[g]	X												X[h]	
Archived Tumor Samples[i]		X												
Tumor Biopsy		X[j]						X[j]						
Hematology[k]		X	X				X	X	X		X		X	X
Serum Chemistry[k]		X	X				X	X	X		X		X	X
Serum Cortisol (random)		X									X		X	
Lymphocyte Subset Analysis (CD3, 4, 8, and 19)		X									X		X	

Study Schedule 1: Assessments for Parts A, B, C, D, E, F, and G (Continued)

Cycle/Visit	Pre-study/ Visit 0		Cycle 1									Cycle 2 and Beyond		Follow-Up[o]
Relative Day Prior to Day 1 of Cycle 1	**-28 to -4**	**-14 to -4**	**-3***	**-2**	**-1**	**1**	**8 ±2**	**15 ±2**	**22 ±2**	**28**	**29**	**1 to 27**	**28 ±2[p]**	
Blood PK Sampling[l]			X	X	X	X		X	X	X	X			
CSF PK Sampling[l,m]			X					X						
Hair Follicle (PD sample)[l]			X	X				X		X				
Skin Biopsy (PD sample)[l]		X[c]						X						
DNA Genotyping Blood Sample (stored)		X[c]												
Record results for any tumor markers in clinical database, if applicable	X										X		X	

Abbreviations: CSF = cerebrospinal fluid; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; PK = pharmacokinetic; PD = pharmacodynamic.

*= Day -3 in Cycle 1 has to be either on Monday or Tuesday only.

[a] Females with child bearing potential must have a negative serum pregnancy test within 3 days of the first dose of study drug (i.e., Day-6 to Day-4).

[b] Chest X-ray may be omitted in patients having a chest CT as part of their radiological tumor assessment. Radiological tumor assessment, including Chest X-ray, is performed at baseline (Day -28 to Day-4), then between Day 21 and Day 28 of every other cycle beginning with Cycle 2.

[c] Obtain only after study eligibility is confirmed.

[d] All drug- or procedure-related adverse events and serious adverse events should be followed until they resolve, are no longer considered to be drug- or procedure-related, become stable or return to baseline, the patient starts a new therapy, the patient dies, or the patient becomes lost to follow-up. Frequency of evaluation is left to the judgment of the investigator.

[e] A central ECGs (no replicates required) should be obtained at baseline (Day-14 to Day-4) and at the following time points during Cycle 1 only: pre-dose, 2 and 4 hrs post-dose on Day-3; both Day-2 and Day-1 (as close to PK sample collection as possible); predose, 2 and 4 hrs postdose on Day 15.

[f] For the once daily schedule, LY2835219 is to be administered every 24 hours on Days 1 through 28 of each cycle except in Cycle 1, when study drug will be administered as a single (morning) dose on Day -3 and then every 24 hours on Days 1 to 27. For the twice daily schedule, LY2835219 is to be administered every 12 hours on Days 1 through 28 of each cycle except in Cycle 1, when LY2835219 will be administered as a single (morning) dose on Day -3, every 12 hours on Days 1 to 27, and as a single (morning) dose on Day 28. Patients should not consume food beginning 1 hour before and ending 1 hour after taking study drug.

Study Schedule 1: Assessments for Parts A, B, C, D, E, F, and G (Concluded)

g Imaging studies are performed locally. Radiological tumor assessment is performed at baseline (Day -28 to Day-4), then between Day 21 and Day 28 (inclusive) of every other cycle beginning with Cycle 2; if necessary, radiological tumor assessment between Day 21 and Day 28 may be extended to Day 29 or Day 30 if the Day 28 procedures occur on Day 29 or Day 30, respectively (refer to footnote p for additional information). For patients with glioblastoma multiforme who are receiving corticosteroids (for example, dexamethasone), the baseline imaging study should be performed on a stable dose of corticosteroids. For patients with glioblastoma multiforme or brain metastases, radiological tumor assessment should also include MRI scan (preferred) or CT scan of the brain.

h If a patient is discontinued from the study, repeat radiology may be omitted if progressive disease can be documented quantitatively with clinical measurements.

i Request archived paraffin-embedded tumor tissue (to be used for assessment of tumor Rb and p-Rb status), but only after study eligibility is confirmed.

j Only for patients in Parts B, C, D, E, F, and G. Pre-treatment biopsy should be obtained (whenever clinically feasible) between Day -14 and Day -4, but only after study eligibility is confirmed. Posttreatment biopsy should be obtained (whenever clinically feasible) between Day 8 and Day 22. Greater flexibility has been provided for the post-treatment tumor biopsy (15±7) compared to other Day 15 assessments (15±2) to enable radiographic guidance and access to appropriate medical specialists.

k For central versus local labs, refer to Attachment 2.

[redacted]

o Follow-up starts just after the last dose of study drug and ends when final safety assessments are completed (30 ±7 days after last dose of study drug).

p If Day 28 procedures occur on Day 29 or 30, then these procedures are included in the current cycle and initiation of the next cycle is delayed until the following day.

q For patients already receiving fulvestrant at time of study entry, fulvestrant dose on Cycle 1 Day 1 should correspond approximately to the date of its expected monthly administration.

r For patients already receiving fulvestrant at time of study entry, fulvestrant should not be administered on Cycle 1 Day 15.

Continued Access Assessments

Cycle/Visit	Cycles 501-5XX		Continued Access Follow-up (901)	Comments
Relative Day Within Cycle	**1 to 27**	**28 ±2**		
Adverse Events Collection/CTCAE Grading		X	X	All AEs and SAEs will be reported on the CRF.
LY2835219 Therapy	X	X		LY2835219 is to be administered according to Section 6.2.1. Study drug exposure will be reported on the CRF.
Fulvestrant Therapy (Part G only)		X		Fulvestrant (Part G) is to be administered according to Section 6.2.1. Study drug exposure will be reported on the CRF.

Abbreviations: AE = adverse event; CRF = case report form; CTCAE = Common Terminology Criteria for Adverse Event; SAE = serious adverse event.
Note: Efficacy and laboratory assessments will be done at the investigator's discretion based on the standard of care.

Attachment 2. Protocol JPBA Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology [a]	**Clinical Chemistry**[a] (except as indicated)
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume (MCV)	Bicarbonate[b] (local only)
Mean cell hemoglobin concentration (MCHC)	Chloride
Leukocytes (WBC)	Glucose (random)
Neutrophils (segmented + bands)	
Lymphocytes	Calcium
Monocytes	Albumin
Eosinophils	Total Protein
Basophils	Blood Urea Nitrogen (BUN)
Platelets	Creatinine
Reticulocyte count[a] (central only)	Alkaline Phosphatase
	Alanine Aminotransferase (ALT)
	Aspartate Aminotransferase (AST)
	Total Bilirubin and Direct Bilirubin
	Creatine Kinase (CK) Total
	Lactate Dehydrogenase (LDH)
	Uric Acid
	Serum Pregnancy Test (females only)[b] (local only)
	Special Blood Tests[a] (central only)
	Serum Cortisol (random)
	Lymphocyte Subset Analysis (CD3, 4, 8, and 19)

Abbreviations: RBC = red blood cells; WBC = white blood cells; INR = International Normalized Ratio.

[a] Assayed by Lilly-designated (central) laboratory.

[b] Assayed by investigator-designated (local) laboratory.

Attachment 3. Protocol JPBA Recommended Hepatic Monitoring Tests for Treatment Emergent Abnormality

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 local laboratory.

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

Attachment 4. Protocol JPBA
Pharmacokinetic and Pharmacodynamic Sampling Schedule

PK Sample Number	Day in Cycle 1	LY 2835219 Dosing	Sampling Time for PK from blood (LY2835219)[a]	Sampling Time for PK from CSF (LY2835219)[a] (Parts B, C, D, E, F only)	CCI
	-14 to -4				
1	-3	X	Pre-dose (0 h)	Pre-dose (0 h)[d]	
2	-3		1 h ± 10 min post-dose		
3	-3		2 h ± 10 min post-dose		
4	-3		4h ± 20 min post-dose		
5	-3		6 h ± 20 min post-dose		
6	-3		8 h ± 20 min post-dose		
7	-3		10 h ± 20 min post-dose[e]		
8	-2	No dose	24 ± 2 h post-dose		
9	-1	No dose	48 ± 2 h post-dose		
10	1	X	Pre-dose		
11	15	X	Pre-dose (0 h)		
12	15		1 h ± 10 min post-dose		
13	15		2 h ± 10 min post-dose		
14	15		4 h ± 20 min post-dose	4 h post-dose[d]	
15	22	X	Pre-dose (0 h)		
16	28	X	Pre-dose (0 h)		
17	28		1 h ± 10 min post-dose		
18	28		2 h ± 10 min post-dose		
19	28		4 h ± 20 min post-dose		
20	28		6 h ± 20 min post-dose		
21	28		8 h ± 20 min post-dose		
22	28		10 h ± 20 min post-dose[e]		
23	29	No dose	24 ± 2 h post-dose		

Pharmacokinetic and Pharmacodynamic Sampling Schedule (Concluded)

Abbreviations: CSF = cerebrospinal fluid; h or hrs = hours; min = minutes; PD = pharmacodynamic; PK = pharmacokinetic.

[a] Samples of approximately 2 mL of whole blood will be drawn to measure concentrations of fulvestrant (Part G only), LY2835219, and its metabolites. concentrations. For Part G, the pre-dose PK samples on Days 1, 15, 22, and 28 will also be used to measure concentrations of fulvestrant. Samples of approximately 2 mL of cerebrospinal fluid will be drawn for measurement of LY2835219 and its metabolites. If a patient does not take the LY2835219 dose on a day with PK sampling, then it does not constitute a protocol violation to omit collection of the "post-dose" PK samples for that day.

CCI

For dose confirmation (Parts B, C, D, E, F and G) only, patients with glioblastoma multiforme or brain metastases should have lumbar puncture at these time points (whenever clinically feasible) with collection of approximately 2ml of cerebrospinal fluid for measurement of LY2835219. To provide flexibility for patients and study personnel, the baseline (pre-dose) sample on Day -3 may be obtained before the first dose of study drug from Day -14 through Day -3; the sample (4 h post-dose) on Day 15, though preferably obtained at approximately the same time as a corresponding plasma PK sample, may be obtained 2 to 8 hours post-dose. In no instance should the timing of other PD or blood PK samples be compromised due to constraints associated with collection of the CSF sample. Omission of CSF samples (for example, not clinically feasible) will not constitute a protocol violation.

[e] If patient constraints preclude collection of this 10-hour PK sample, omission of this sample will not constitute a protocol violation.

Attachment 5. Protocol JPBA
Recommendations for Reporting Serious Adverse Events

Recommendations for Reporting Serious Adverse Events

When telephoning the Lilly office to report a serious adverse event, please have the following information available:

Patient Demographics

- patient identification (number)
- sex
- date of birth
- race
- height & 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 & last dose date (if applicable)

(continued)

Adverse Event

- description
- date of onset
- severity
- treatment (including hospitalization)
- action taken with respect to study drug
- clinical significance
- test & 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 & protocol procedures.

Attachment 6. Protocol JPBA ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Status

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

Source: Oken et al. 1982.

Attachment 7. Protocol JPBA
Staging and Grading of Acute Graft-versus-Host Disease

Table 1. Criteria for Organ Staging

Stage	Skin	Liver	Intestine
1	Rash on <25% of skin	Bilirubin ≥2 and <3 mg/dL	Diarrhea >500 ml/day
2	Rash on 25%-50% of skin	Bilirubin ≥3 and <6 mg/dL	Diarrhea >1000 ml/day
3	Rash on >50% of skin or generalized erythroderma	Bilirubin ≥6 and <15 mg/dL	Diarrhea >1500 ml/day
4	Generalized erythroderma with bullous formation	Bilirubin ≥15 mg/dL	Severe abdominal pain with or without ileus

Table 2. Overall Clinical Grading

Grade	Skin	Liver	Intestine
I	1	0	0
I	2	0	0
II	0-2	0-1	1
II	0-2	1	0-1
II	3	0-1	1
II	3	1	0-1
II	3	0	0
III	0-2	0-2	2
III	0-2	2	0-2
III	0-3	2-3	0-3
III	3	0-3	2-3
III	0-3	4	0-3
IV	0-3	0-4	4
IV	4	0-4	0-4

References

Cahn J-Y, Klein JP, Lee SJ, Milpied N, Blaise D, Antin JH, Leblond V, Ifrah N, Jouet J-P, Loberiza F, Ringden O, Barrett AJ, Horowitz MM, Socie G. 2005. Prospective evaluation of 2 acute graft-versus-host (GVHD) grading systems: a joint Societe Francaise de Greffe de Moelle et Therapie Cellulaire (SFGM-TC), Dana Farber Cancer Institute (DFCI), and International Bone Marrow Transplant Registry (IBMTR) prospective study. *Blood* 106(4):1495-1500.

Glucksberg H, Storb R, Fefer A, Buckner CD, Neiman PE, Clift RA, Lerner KG, Thomas ED. 1974. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HLA-matched sibling donors. *Transplantation* 18:295-304.

Przepiorka D, Weisdorf D, Martin P, Klingemann H-G, Beatty P, Hows J, Thomas ED. 1995. Consensus conference on acute GVHD grading. *Bone Marrow Transplantation* 15:825-828.

Thomas ED, Strob R, Clift RA, Fefer A, Johnson FL, Neiman PE, Lerner KG, Glucksberg H, Buckner CD. 1975. Bone-marrow transplantation. *New England Journal of Medicine* 292:895-902.

Attachment 8. Protocol JPBA Inducers and Strong Inhibitors of CYP3A

The information in this Attachment is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated.

Strong Inducers of CYP3A
Carbamazepine
Dexamethasone*
Phenobarbital/phenobarbitone
Phenytoin
Rifapentine
Rifampin
Rifabutin
St. John's wort

Moderate Inducers of CYP3A
Bosentan
Lesinurad
Modafinil
Primidone
Telotristat ethyl

Strong Inhibitors of CYP3A
Aprepitant
Ciprofloxacin
Clarithromycin
Conivaptan
Diltiazem
Erythromycin
Fluconazole
Itraconazole
Ketoconazole
Nefazodone
Posaconazole
Troleandomycin
Verapamil

*Important note: Patients with glioblastoma multiforme or brain metastases may receive acute or chronic therapy with dexamethasone, if clinically indicated. All patients may receive supportive therapy with dexamethasone, preferably ≤7 days, if clinically indicated.

Attachment 9. Protocol JPBA Protocol Amendment I3Y-MC-JPBA(j) Summary Phase 1 Study of a CDK4/6 Dual Inhibitor in Patients with Advanced Cancer

Overview

Protocol I3Y-MC-JPBA, a Phase 1 Study of a CDK4/6 Dual Inhibitor in Patients with Advanced Cancer has been amended. The new protocol is indicated by amendment (j) and will be used to conduct the study in place of any preceding version of the protocol.

Modifications to the study protocol introduced in amendment (j) involve the following:

- The Rationale for Amendment (j) was added as Section 4.4.
- Table JPBA.6.2 was updated with dose adjustment criteria for nonhematologic toxicity and ALT/AST increased.
- Information for modulators of CYP3A and transporter substrates was updated in the section for Concomitant Therapy (Section 6.5).
- The Hepatic Monitoring guidance in Section 7.1.3.1 was updated based on current information.
- The safety monitoring language for VTEs in Section 7.1.3.3 was updated.
- Section 7.1.3.4 was edited slightly for clarity to include specific ILD/pneumonitis Grades requiring LY2835219 discontinuation.

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

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