Protocol J1F-MC-JZFA (c)

A Phase 1a/1b Study of LY3405105 Administered to Patients with Advanced Solid Tumors

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A Phase 1a/1b Study of LY3405105 Administered to Patients with Advanced Solid Tumors

Confidential Information

LY3405105

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Protocol Electronically Signed and Approved by Lilly on 20 Aug 2018.
Amendment (a) Electronically Signed and Approved by Lilly on 22 Nov 2018.
Amendment (b) Electronically Signed and Approved by Lilly on 02 Jul 2020.
Amendment (c) Electronically Signed and Approved by Lilly on approval date provided below.

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Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (b)	*02-Jul-2020*
Amendment (a)	*22-Nov-2018*
Original Protocol	*20-Aug-2018*

Amendment (c)

This amendment is considered to be substantial based on the criteria set forth in Article 10 (a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
2. Schedule of Activities 9.5 Pharmacokinetics 9.6. Pharmacodynamics 9.8.3. Other Samples for Biomarker Research	Skin biopsies and peripheral blood mononuclear cell collections have been removed from Phase 1a/1b, and urine pharmacokinetics (PK) have been removed from Phase 1a schedule.	There is no further planned analysis for additional samples.
2. Schedule of Activities	Clarification of mandatory versus optional ECG and plasma PK samples in Phase 1a schedule	PK parameters have been characterized; thus, fewer ECG and PK samples are now required, reducing the burden on the sites and patients whilst maintaining safety.
1. Synopsis 2. Schedule of Activities 5.1. Overall Design 5.1.1. Dose Escalation Phase 7.1.1. Dose Escalation Phase (Phase 1a) 7.1.1.2. Dose Escalation Method 7.2.1. Selection and Timing of Doses 10.1. Sample Size Determination 10.3.2. Safety Analyses	The intermittent dosing schedule in Part A2 will no longer be pursued in the study and was removed.	Available safety and human exposure data support continuous daily dosing.
Other minor editorial changes were made to add clarity and correct typos		

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1. Synopsis

Protocol Title:

A Phase 1a/1b Study of LY3405105 Administered to Patients with Advanced Solid Tumors

Rationale:

Study J1F-MC-JZFA (JZFA) is designed to investigate the safety and tolerability of LY3405105 for the treatment of patients with advanced cancers and to evaluate the anti-tumor activity in the defined population in the Phase 1b portion.

Objectives and Endpoints:

Objectives	Endpoints
Phase 1a	
Primary	
• To assess the safety and tolerability of LY3405105 administered as monotherapy, and to determine the RP2D and schedule in patients with solid tumors	• Safety (including but not limited to): incidence and severity of DLTs, TEAEs, SAEs, deaths, and clinical laboratory abnormalities
Secondary	
• To assess the PK of LY3405105 administered as monotherapy to patients with solid tumors	• AUC/C_{max} of LY3405105
• To document any anti-tumor activity observed with LY3405105 when administered as monotherapy to patients with solid tumors	• Per RECIST v1.1: o ORR o DCR o DoR o TTR o PFS • OS
Phase 1b	
Primary	
• To assess the efficacy of LY3405105 when administered as monotherapy in the defined patient population	• ORR (per RECIST v1.1)
Secondary	
• To evaluate the safety and tolerability of LY3405105 when administered as monotherapy to patients with solid tumors	• Safety, including but not limited to incidence and severity of TEAEs, SAEs, deaths, and clinical laboratory abnormalities per CTCAE v.4.0
• To document any anti-tumor activity observed with LY3405105 when administered as monotherapy to patients with solid tumors across the defined cohorts	• Per RECIST v1.1: o DCR o DoR o PFS o TTR • OS
• To assess the PK of LY3405105 administered as monotherapy to patients with solid tumors across the defined cohorts	• Plasma concentration of LY3405105

Abbreviations: AUC = area under the plasma concentration x time curve; C_{max} = maximum concentration; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DLT = dose-limiting toxicity; DoR = duration of response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TTR = time to response.

Overall Design:

Study JZFA is a Phase 1, multicenter, nonrandomized, open-label dose escalation study in patients with advanced solid tumors followed by dose expansion of oral LY3405105 in a defined patient population with advanced solid tumors.

Number of Patients:

Dose Escalation: Phase 1a, approximately 30-64 patients will be enrolled (including up to10 patients in the safety expansion at recommended Phase 2 dose [RP2D]).

Dose Expansion: Phase 1b, approximately 20 patients will be enrolled in each of Cohorts 1-4. In the bladder cancer Cohort 5, approximately 30 patients will be enrolled.

Treatment Arms and Duration:

Patients enrolled in the monotherapy dose escalation will receive LY3405105 orally, on a 28-day cycle. During the escalation, the investigators and Eli Lilly and Company (Lilly) will consider both the Bayesian model-based toxicity band method (N-CRM) recommendation, the observed dose-limiting toxicity rate, and the totality of the data (pharmacokinetics, pharmacodynamics, and overall safety) at each cohort to determine the next dose level, dose schedule, and determine when to stop the escalation.

After the monotherapy RP2D has been determined from Phase 1a, approximately 20 patients will be enrolled in each of the Phase 1b Cohorts 1-4. In the bladder cancer cohort (Cohort 5 in Phase 1b), approximately 30 patients will be enrolled. Patients will receive LY3405105 at the RP2D orally daily on a 28-day cycle.

Study treatment should be continued until evidence of disease progression or discontinuation criteria is met. Patients with documented progressive disease may be allowed to continue LY3405105 if the patient is tolerating treatment and, in the opinion of the investigator, is deriving clinical benefit from continuing study treatment and continuation of treatment is approved by the Sponsor.

30-Day Safety Follow-Up Visit: Occurs 30 ±7 days after the decision is made to discontinue from study treatment.

Long-Term Follow-Up: Begins the day after 30-day follow-up visit is completed and ends with the patient's death, lost to follow-up, or overall study completion, whichever is earlier.

2. Schedule of Activities

Table JZFA.2.1. Baseline, On-Study Treatment, and Post Treatment Schedule of Activities for Phase 1a

Procedure	Baseline	All Remaining Parts on Treatment (Cycle = 28 days)						Post Treatment Follow-Up		Instructions
	Days Prior to C1D1	Cycle 1 (±3 Days)			Cycle 2 (±3 Days)		Cycle 3-n (±3 Days)	Short-Term[a] (30 ± 7 Days)	Long-Term (Every 90 ± 7 Days)	
		Day			Day		Day			
	≤28	1	8	15	1	15	1	Visit 801	Visit 802-8XX	
Informed consent	X									ICF must be signed before any protocol-specific procedures are performed. Baseline/screening labs or imaging, as part of routine patient care, drawn within the indicated window of C1D1 may be used for both screening/baseline and C1D1 labs.
Physical examination*	X	X		X	X	X	X	X		Perform prior to administration/dispensing of study drug.
Vital signs and weight*	X	X		X	X	X	X	X		Perform prior to administration/dispensing of study drug. Include height (only at baseline), weight, and vital signs (temperature, blood pressure, pulse rate)
Medical history	X									
Inclusion/Exclusion evaluation	X									
Concomitant medication	X	X		X	X	X	X			
AE collection	X	X		X	X	X	X	X	X	CTCAE V4.0. During long-term follow-up, only AEs that are related to study treatment will be followed to resolution.
ECOG performance status	X	X		X	X	X	X	X		
Radiologic imaging and measurement of palpable or visible lesions	X	X						X	X	Perform according to RECIST v1.1 criterion, by the same method used at baseline, q 8 wk (±7 days) for the first 6 mo after C1D1 and q 12 wk (±7 days) thereafter until radiographic disease progression, death, or study completion, whichever occurs first.

Procedure	Baseline	All Remaining Parts on Treatment (Cycle = 28 days)						Post Treatment Follow-Up		Instructions
	Days Prior to C1D1	Cycle 1 (±3 Days)			Cycle 2 (±3 Days)		Cycle 3-n (±3 Days)	Short-Term[a] (30 ± 7 Days)	Long-Term (Every 90 ± 7 Days)	
		Day			Day		Day			
	≤28	1	8	15	1	15	1	Visit 801	Visit 802-8XX	
										Perform as scheduled, even if study treatment is delayed or omitted.
ECG	**X**	X		**X**	X	X	X	X		ECG collections that are underlined and in bold are mandatory. All other ECG collections are optional. **Baseline:** Single ECG only **Cycle 1 Day 1:** collect digital ECGs for QT analysis in triplicate at predose, 2 hrs postdose. If possible, a 24 hr reading should be taken. **Day 15:** Predose (triplicate) A corresponding PK sample should be collected after the ECG reading. **Cycle 2:** Single ECGs only (predose on D1 and D15) **Cycle 3-n:** Single ECG on D1 (predose). Perform additional evaluations in the setting of cardiac symptoms and/or at the discretion of the investigator. Perform locally.
Hematology*	X	X		X	X	X	X	X		≤3 days prior to start of each cycle, unless more frequent assessment is clinically indicated.
Coagulation	X									Only collected at baseline, unless more frequent assessment is clinically indicated.
Clinical chemistry*	X	X		X	X	X	X	X		≤3 days prior to start of cycle, unless more frequent assessment is

Procedure	Baseline	All Remaining Parts on Treatment (Cycle = 28 days)						Post Treatment Follow-Up		Instructions
	Days Prior to C1D1	Cycle 1 (±3 Days)			Cycle 2 (±3 Days)		Cycle 3-n (±3 Days)	Short-Term[a] (30 ± 7 Days)	Long-Term (Every 90 ± 7 Days)	
		Day			Day		Day			
	≤28	1	8	15	1	15	1	Visit 801	Visit 802-8XX	
										clinically indicated.
Urinalysis*	X	X			X		X	X		≤3 days prior to start of cycle, unless more frequent assessment is clinically indicated.
Urine pregnancy test	X	X			X		X			**Applies only to women of childbearing potential.** Where required by local law or regulation, perform ≤3 day prior to start of every cycle prior to administration of study treatment.
Patient diary		X		X						Provide patient diary Day 1. Completed daily by patient. Review at each study visit during Cycle 1.
Survival assessment								X	X	Perform q 3 mo (±7 days). If an in-person visit is not possible, confirm survival by contacting the patient directly via phone.
LY3405105		X								Administer orally on Days 1-28 of a 28-day cycle. Patients should be advised to take dose after PK draw on days of PK collection.
Pharmacokinetics – plasma		1. Predose 2. 1hr±5min 3. 2hr±10min 4. 4hr±10min 5. 6hr±15min 6. 8hr±15min 7. 24hr±2hr 8. 48hr±2hr	9. Predose	**10. Predose** 11. 1hr±5min **12. 2hr±10min** **13. 4hr±10min** 14. 6hr±15min 15. 8hr±15min 16. 24hr±2hr 17. 48hr±2hr	**18. Predose**					Sample collection times that are underlined and in bold are mandatory; all other plasma PK samples are optional. 24-hr samples should be drawn prior to next dose. 48-hr samples are not required as Part A2 is no longer being pursued.
Plasma biomarker sample		X			X		X	X		Collect predose on D1 of C1, C2, C3, C5, C7, and then every third cycle (for example, C10).

Procedure	Baseline	All Remaining Parts on Treatment (Cycle = 28 days)						Post Treatment Follow-Up		Instructions
	Days Prior to C1D1	Cycle 1 (±3 Days)			Cycle 2 (±3 Days)		Cycle 3-n (±3 Days)	Short-Term[a] (30 ± 7 Days)	Long-Term (Every 90 ± 7 Days)	
		Day			Day		Day			
	≤28	1	8	15	1	15	1	Visit 801	Visit 802-8XX	
Pharmacogenetics whole blood	X									A pretreatment blood sample is preferred; however, the whole blood sample for pharmacogenetic analysis may be collected at a later time point if necessary.
Archived tumor tissue	X									Sample should be submitted to the central laboratory within 28 days after initiation of study treatment. See Section 9.8.2.
Optional tumor biopsy	X	X								An optional biopsy specimen after treatment with LY3405105 has been initiated or after disease progression may be allowed.

Abbreviations: AE = adverse event; C = cycle; CRP/CRS = clinical research physician/clinical research scientist; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; hr = hour(s); ICF = informed consent form; min = minute(s); mo = month(s); PK = pharmacokinetics; q = every; RECIST v1.1 = Response Criteria in Solid Tumors Version 1.1; wk = week(s).

[a] Short-term follow-up begins the day when the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days (±7 days). No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

* ≤3 days prior to start of cycle, unless more frequent assessment is clinically indicated.

Table JZFA.2.2. Baseline, On-Study Treatment, and Post Treatment Schedule of Activities for Phase 1b

Procedure	Baseline	All Remaining Parts on Treatment (Cycle = 28 days)					Post Treatment Follow-Up		Instructions
	Days Prior to C1D1	Cycle 1 (±3 Days)		Cycle 2 (±3 Days)		Cycle 3-n (±3 Days)	Short-Term[a] (30 ±7 Days)	Long-Term (Every 90 ±7 Days)	
		Day		Day		Day			
	≤28	1	15	1	15	1	Visit 801	Visit 802-8XX	
Informed consent	X								ICF must be signed before any protocol-specific procedures are performed. Baseline/screening labs or imaging, as part of routine patient care, drawn within the indicated window of C1D1 may be used for both screening/baseline and C1D1 labs.
Physical examination*	X	X	X	X	X	X	X		Perform prior to administration/dispensing of study drug.
Vital signs and weight*	X	X	X	X	X	X	X		Perform prior to administration/dispensing of study drug. Include height (only at baseline), weight, and vital signs (temperature, blood pressure, pulse rate).
Medical history	X								
Inclusion/Exclusion evaluation	X								
Concomitant medication	X	X	X	X	X	X			
AE collection	X	X	X	X	X	X	X	X	CTCAE V4.0. During long-term follow-up, only AEs that are related to study treatment will be followed to resolution.
ECOG performance status or LPS	X	X	X	X	X	X	X		
Radiologic imaging and measurement of palpable or visible lesions	X	X					X	X	Perform according to RECIST v1.1 criterion, by the same method used at baseline, q 8 wk (±7 days) for the first 6 mo after C1D1 and q 12 wk (±7 days) thereafter until radiographic disease progression, death, or study completion, whichever occurs first. Perform as scheduled, even if study treatment is delayed or omitted.
ECG	X								**Baseline:** Predose (single). Perform additional evaluations in the setting of cardiac symptoms and/or at the discretion of the investigator. Perform locally.
Hematology*	X	X	X	X	X	X	X		≤3 days prior to start of each cycle, unless more frequent assessment is clinically indicated.

Procedure	Baseline	All Remaining Parts on Treatment (Cycle = 28 days)					Post Treatment Follow-Up		Instructions
	Days Prior to C1D1	Cycle 1 (±3 Days)		Cycle 2 (±3 Days)		Cycle 3-n (±3 Days)	Short-Term[a] (30 ±7 Days)	Long-Term (Every 90 ±7 Days)	
		Day		Day		Day			
	≤28	1	15	1	15	1	Visit 801	Visit 802-8XX	
Coagulation	X								Only collected at baseline, unless more frequent assessment is clinically indicated.
Clinical chemistry*	X	X	X	X	X	X	X		≤3 days prior to start of cycle, unless more frequent assessment is clinically indicated.
Urinalysis*	X	X		X		X	X		≤3 days prior to start of cycle, unless more frequent assessment is clinically indicated.
Urine pregnancy test	X	X		X		X			**Applies only to women of childbearing potential.** Where required by local law or regulation, perform ≤3 day prior to start of every cycle prior to administration of study treatment.
Patient diary		X	X						Provide patient diary Cycle 1, Day 1. Completed daily by patient. Review at each study visit in Cycle 1.
Survival assessment							X	X	Perform q 3 mo (±7 days). If an in-person visit is not possible, confirm survival by contacting the patient directly via phone.
LY3405105		X							Administer orally once a day based on the established RP2D. Patients should be advised to take dose after PK draw on C1D15 and C2D1.
Pharmacokinetics – plasma			1. Predose 2. 1-2hr 3. 3-4hr	4. Predose					
Plasma biomarker sample		X		X		X	X		Collect predose on D1 of C1, C2, C3, C5, C7, and then every third cycle (for example, C10).
Pharmacogenetics whole blood	X								A pretreatment blood sample is preferred; however, the whole blood sample for pharmacogenetic analysis may be collected at a later time point if necessary.
Archived tumor tissue	X								Sample should be submitted to the central laboratory within 28 days after initiation of study treatment. See Section 9.8.2.
Optional tumor biopsy	X	X							An optional biopsy specimen at baseline and/or after treatment with LY3405105 has been initiated or after disease progression may be allowed.

Abbreviations: AE = adverse event; C = cycle; CRP/CRS = clinical research physician/clinical research scientist; CTCAE = Common Terminology Criteria for Adverse Events; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; hr = hour(s); ICF = informed consent form; LPS = Lansky performance status; mo = month(s); PK = pharmacokinetics; q = every; RECIST v1.1 = Response Criteria in Solid Tumors Version 1.1; wk = week(s).

[a] Short-term follow-up begins the day when the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days (±7 days). No follow-up procedures will be performed for a patient who withdraws informed consent unless he or she has explicitly provided permission and consent.

* ≤3 days prior to start of cycle, unless more frequent assessment is clinically indicated.

Table JZFA.2.3. Continued Access Schedule of Activities

Visit	Study Treatment 501-5XX	Follow-Up[a] 901	Instructions
Procedure[b]			
AE collection	**X**	**X**	**CTCAE v4.0**
Administer/dispense study drug(s)	**X**		

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events.

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

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

2.1. Provision for Changes in Study Conduct Due to Emergencies

There may be times due to exceptional circumstances where it may not be feasible for patients to come to investigator sites for study-required visits. To mitigate the risk of patients missing visits to allow patients to safely continue to receive care and maintain the data integrity of the study, the following may be allowed on a case-by-case basis following approval from the Sponsor and if permitted by local regulations:

- Remote/virtual visits or extended visit windows may be used. Medically qualified site personnel may collect study required information (for example, AEs, concomitant medications, ECOG status, and study treatment compliance) via videoconference (preferred) or phone. Visit or cycle windows as defined in the schedule of activities may be extended to facilitate the ability to perform study-specific assessments at the site, which is preferred to remote/virtual visits. Every effort should be made to return to in-clinic visits as soon as reasonably possible and safe for the patient and investigator/site staff.
- Labs, ECGs and/or tumor imaging may be obtained at a local (nonstudy) site. Laboratory results (including reference ranges), ECGs and/or scans obtained at a local lab must be filed and reviewed by the study investigator or qualified designee in a timely manner.
- For patients that meet the protocol criteria to continue or restart dosing, local processes may be leveraged to deliver drug directly to patients.
- A remote informed consent process may be implemented.

Site personnel are responsible for documenting in the source records all changes in study conduct, relevant communications (patient and Sponsor), and dispensing/shipment records of IP and indicating the actions taken as a result of exceptional circumstances mitigation. If mitigations are approved by the Sponsor, additional instructions on the process and documentation will be provided to the site. Additional mitigations may be approved by the Sponsor and will be tracked as protocol deviations as required.

3. Introduction

3.1. Study Rationale

Cyclin-dependent kinases (CDKs) play a critical role in the regulation of cell cycle and global transcription. Within cancer cells, dysregulated transcription enables hallmark capabilities, including resistance to cell death, sustenence of proliferative signaling, and evasion of growth suppressors (Hanahan and Weinberg 2011). The selective advantage that favors cancer cells can thus become dependent upon the aberrant function of deregulated transcription. Thus, selective modulation of CDK7, a key transcriptional regulator, may provide therapeutic benefit to patients with cancer, particularly those with dysregulated transcriptional phenotypes that result in tumor cell survival, growth, and progression.

LY3405105 is an orally bioavailable, covalent inhibitor of CDK7. Nonclinical data have shown that LY3405105 inhibits the proliferation of a variety of cancer cell lines. Cell lines harboring loss-of-function mutation in *ARID1A, KMT2C,* or *KMT2D* demonstrated enhanced sensitivity to LY3405105. LY3405105 also demonstrated robust anti-tumor efficacy, including durable tumor regressions in cell line and patient-derived xenograft tumor models across triple-negative breast cancer (TNBC) irrespective of their molecular profile, *ARID1A*-mutant ovarian histology, and those carrying loss-of-function (LOF) mutations in *ARID1A* or *KMT2C* independent of tumor type.

Study J1F-MC-JZFA (JZFA) is designed to investigate the safety and tolerability of LY3405105, establish the RP2D in patients with solid tumors (Phase 1a), and to assess the anti-tumor activity in patients with defined advanced solid tumors (Phase 1b).

3.2. Background

3.2.1. Role of CDK7

CDK7 is part of the transcription regulating CDKs, which also include CDK9, 12 and 13. CDK7 enacts its function through:

1) phosphorylating RNA polymerase II at the C terminal domain (CTD) to initiate transcription, and
2) regulating CDKs as a CDK activating kinase (CAK) (Fisher 2019; Chou et al.2020).

CDK7 biology has been implicated in transcription regulation and enhancing cancer growth associated with super-enhancer-linked oncogenes (Chipumuro et al. 2014; Zhang et al. 2017; Sharifnia et al. 2019; Zhang et al. 2020). Gene transcription regulation occurs in part by modulating H3K4me3 which impacts epigenetic regulation of gene expression (Ebmeier et al. 2017). This process involves different aspects of chromatin remodeling including histone methyltransferases such as KMT2C and KMT2D, and methyl demethylase (KDM6A) (Valencia and Kadoch 2019). Utilizing pharmacologic approaches in preclinical models demonstrated the ability of targeting CDK7 with small molecule inhibitors to downregulate gene transcription and

induce tumor regression in preclinical models (Christensen et al. 2014; Kwiatkowski et al. 2014; Wang et al. 2015; Zhang et al. 2017; Lu et al. 2019; Rasool et al. 2019; Zhang et al. 2019; Sun et al. 2020).

3.2.2. Targeting the SWItch/Sucrose Non-Fermentable (SWI/SNF) Complex

ARID1A is a tumor suppressor gene that encodes BAF250a and is part of the SWItch/Sucrose Non-Fermentable (SWI/SNF) complex, which is frequently mutated in solid tumors (Reisman et al. 2009). Somatic mutations have been reported in wide range of solid tumors and have been linked to an early event in tumorigenesis of clear cell ovarian cancer and endometriosis associated malignancies (Wiegand et al. 2010). *ARID1A*, as part of the chromatin remodeling machinery, is frequently mutated in bladder cancer along other chromatin regulating genes (*KDM6A/UTX, KMT2C/MLL3,* and *KMT2D/MLL2*) (Gui et al. 2011; Jones et al. 2011; Guo et al. 2013). Our preclinical data suggest that LOF mutation in *ARID1A* leads to activation of super-enhancers, which are DNA sequences that binds to transcription factors and enhance gene transcription. Utilizing LY3405105 in *ARID1A* mutant cell lines inhibits transcription and downregulates MYC and E2F downstream targets.

Mutations in *SMARCB1*, another subunit of the SWI/SNF complex, lead to unopposed activation of polycomb repressive complex 2 (PRC2) (Kim and Roberts 2016), which in turns activates Enhancer of Zeste 2 (EZH2). Epithelioid sarcoma that commonly harbors mutations in *SMARCB1* or loss of protein expression of INI1 due to epigenetic silencing, might be amenable to epigenetic targeted therapy with EZH2 inhibitors (Rothbart and Baylin 2020). While mutations in other subunits of the SWI/SNF complex might have a gene and tissue specific context, systems biology-centered studies indicate that mutations in other SWI/SNF subunits, such as *ARID1A, SMARCE1 or SMARCA4*, may exhibit mechanistic convergence with *SMARCB1* loss, particularly, in generating and maintaining accessibility over enhancer regions (Pan et al. 2018). This hypothesis is also supported by the observation that preclinically, inhibiting EZH2 appears to have a broader effect against models with mutations in the SWI/SNF complex beyond *SMARCB1* (Kim et al. 2015). Preclinical activity of LY3405105 in cell lines and patient-derived xenografts (PDX) models harboring *ARID1A* LOF mutations warrant exploring its role in treating malignancies driven by LOF mutations in other SWI/SNF complex subunits such as *SMARCB1, SMARCA2*, and *SMARCA4*.

In summary, CDK7 regulates gene transcription in malignancies associated with super-enhancer activation. Targeting CDK7 with a covalent bioavailable inhibitor downregulates gene transcription and demonstrates activity in TNBC and several models that harbor mutations in *ARID1A, KMT2C*, and *KMT2D*.

To estimate the prevalence of LOF mutations, data were extracted from the MSK-IMPACT Clinical Sequencing Cohort (Zehir et al. 2017) and analyzed. The following lists the prevalence of LOF mutations for select tumor types:

- *ARID1A*: endometrial cancer (30.9%), bladder cancer (23.2%), ovarian cancer (12.5%), soft tissue sarcoma (0.3%)

- *KMT2C (MLL3)*: bladder cancer (7.3%), endometrial cancer (5.3%), ovarian cancer (1.0%)
- *KMT2D (MLL2)*: bladder cancer (21.0%), endometrial cancer (12.1%), ovarian cancer (1.4%)
- *KDM6A (UTX)*: bladder cancer (29.0%), endometrial cancer (1.0%), ovarian cancer (0%)

The nonclinical toxicity profile of LY3405105 has been characterized in good laboratory practice (GLP) -compliant studies conducted to support first-in-human dosing in patients with advanced cancer, in accordance with International Conference for Harmonization (ICH) S9 guidance. The key studies were oral repeat-dose general toxicology studies in rats and dogs (4 weeks in duration with a 4-week recovery period). These studies evaluated standard toxicological endpoints and assessed safety pharmacology endpoints (cardiovascular, central nervous system [CNS], respiratory) through quantitative and qualitative evaluations of electrocardiograms (ECGs), and detailed clinical observations following dosing. The key nonclinical toxicities were degenerative changes in the gastrointestinal (GI) tract and bone marrow hypocellularity. These findings were expected based on pharmacology, are dose-dependent, are reversible following cessation of dose administration, and are anticipated to translate to humans. All other important toxicities (effects on lymphoid tissues, male reproductive tissues, and skin, and decreased heart rate) are considered to be clinically monitorable and/or manageable in the intended patient population.

Information pertaining to nonclinical efficacy and safety may be found in Section 4.2 of the Investigator's Brochure (IB).

Information pertaining to nonclinical pharmacokinetics (PK) and metabolism may be found in Section 4.1 of the IB.

3.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of LY3405105 are to be found in the IB.

4. Objectives and Endpoints

Table JZFA.4.1 shows the objectives and endpoints of the study.

Table JZFA.4.1. Objectives and Endpoints

Objectives	Endpoints
Phase 1a	
Primary	
• To assess the safety and tolerability of LY3405105, administered as monotherapy to determine the RP2D and schedule in patients with solid tumors	• Safety (including but not limited to): incidence and severity of DLTs, TEAEs, SAEs, deaths, and clinical laboratory abnormalities
Secondary	
• To assess the PK of LY3405105 administered as monotherapy to patients with solid tumors	• AUC/C_{max} of LY3405105

• To document any anti-tumor activity observed with LY3405105 when administered as monotherapy to patients with solid tumors	• Per RECIST v1.1:
	  ○ ORR
	  ○ DCR
	  ○ DoR
	  ○ TTR
	  ○ PFS
	• OS

Exploratory	
• To assess the relationship between biomarkers, LY3405105 exposure, and clinical outcomes	• Results of biomarker analyses • Clinical outcomes data
Phase 1b	
Primary	
• To assess the efficacy of LY3405105	• ORR
Secondary	
• To evaluate the safety and tolerability of LY3405105 when administered as monotherapy to patients with solid tumors	• Safety, including but not limited to incidence and severity of TEAEs, SAEs, deaths, and clinical laboratory abnormalities per CTCAE v4.0
• To document any anti-tumor activity observed with LY3405105 when administered as monotherapy to patients with solid tumors across the defined cohorts	• DCR • DoR • PFS • OS • TTR
• To assess the PK of LY3405105 administered as monotherapy to patients with solid tumors across the defined cohorts	• Plasma concentration of LY3405105
Tertiary/exploratory	
• To correlate the clinical activity with molecular subtypes as defined in the protocol	• ORR in relation to molecular subtypes

Abbreviations: AUC = area under the plasma concentration x time curve; C_{max} = maximum concentration; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DLT = dose-limiting toxicity; DoR = duration of response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TTR = time to response.

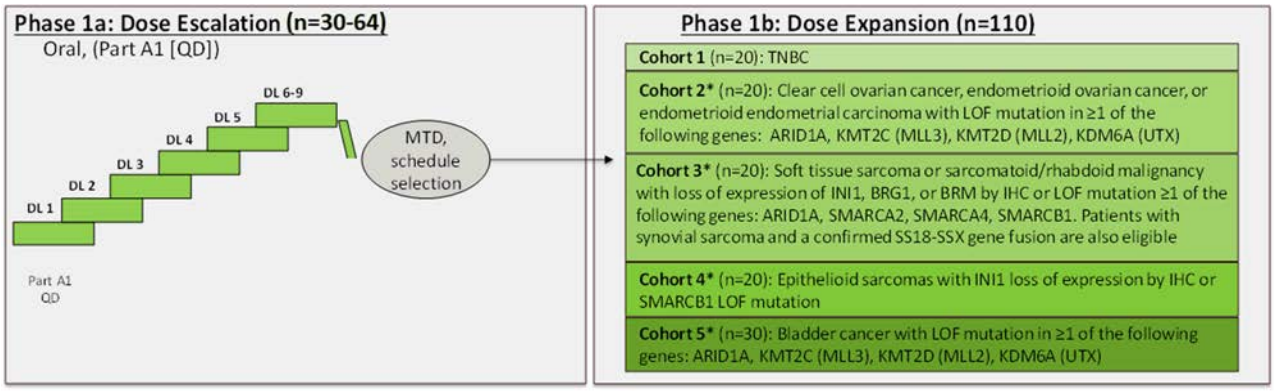
5. Study Design

5.1. Overall Design

Study JZFA is a Phase 1, multicenter, nonrandomized, open-label dose escalation study in patients with advanced solid tumors, followed by dose expansion of oral LY3405105 in patients with advanced selected solid tumors.

This initial Phase 1 study of LY3405105 consists of a once daily (QD) continuous (Phase 1a) dose escalation phase and an expansion phase (Phase 1b) of LY3405105 given as a monotherapy in 5 tumor expansion cohorts (Cohorts 1-5) as shown in Figure JZFA.5.1. The dose escalation will determine the maximum tolerated dose (MTD) as well as the RP2D.

Figure JZFA.5.1 illustrates the overall study design, Section 5.1.1 describes the dose escalation phase and Section 5.1.2 describes the dose expansion phase.



Abbreviations: ARID1A = AT-rich interactive domain-containing protein 1A; BRG1 = Brahma-related gene 1; BRM = Brahma; DL = dose level; DLT = dose-limiting toxicity; ICH = International Conference on Harmonization; INI1 = integrase interactor 1; KDM6A (UTX) = lysine demethylase 6A; KMT2C (MLL3) gene = lysine methyltransferase 2C; KMT2D (MLL2) gene = histone-lysine-methyltransferase 2D; LOF = loss of function; MTD = maximum tolerated dose; n = approximate number of patients per group; pts = patients; QD = once daily; SMARCA2 = SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2; SMARCA4 = SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4; SMARCB1 = SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1; SS18 = SS18 subunit of BAF chromatin remodeling complex; SSX = SSX family member; TNBC = triple-negative breast cancer.

Figure JZFA.5.1. Illustration of study design.

5.1.1. Dose Escalation Phase

Monotherapy dose escalation (Phase 1a) started, with a starting dose of LY3405105 1 mg orally (PO) QD (Part A1) and 2 mg PO intermittently every Monday, Wednesday, and Friday (MWF) or Tuesday, Thursday, and Saturday (TTS) (Part A2) on a 28-day cycle. Based on available human PK exposure data, the intermittent dosing schedule (Part A2) will no longer be pursued in the study. The Bayesian model-based toxicity method called N-CRM will be used to inform the dose levels in each cohort. The dose escalation method is further described in Section 7.1.1.2.

Each dose level will enroll a minimum of 3 patients (but no more than approximately 6 patients per dose level). At the RP2D, up to 10 patients may be enrolled in selected cohorts to further assess the safety and tolerability of the dose selected prior to advancing to the Phase 1b of the study. Subsequent dose levels will enroll patients based on the safety from the previous dose level, any available PK and pharmacodynamic (PD) data, and discussion with investigators without sentinel dosing. This decision is made between the investigators and the Lilly clinical research physician/clinical research scientist (CRP/CRS).

Lilly and the investigators will discuss safety and available PK/PD results after each dose level for Phase 1a of the study, and dose escalation decisions will be made prior to starting enrollment to the next dose level. Lilly will send written notification to the investigator site to specify the dose and dosing schedule before patients may be enrolled in the next dose level. Intermediate and/or higher dose levels, as well as alternative schedules of administration, will be explored if deemed necessary after discussion between Lilly and investigators, taking into account patient safety and PK/PD data.

5.1.2. Dose Expansion Phase

After all patients in the dose escalation phase (Phase 1a) have completed the dose-limiting toxicity (DLT) evaluation period or discontinued, an interim safety and PK/PD analysis will be conducted before opening the dose expansions (Phase 1b). The N-CRM method along with PK/PD analysis will be used to identify a monotherapy RP2D for investigation in the dose expansion phase. The monotherapy RP2D may be below the MTD.

Phase 1b dose expansion will include LY3405105 monotherapy in patients with multiple tumor types and will enroll approximately 20 patients in each of Cohorts 1-4. Cohort 5 will enroll approximately 30 patients. Patients in Cohorts 2-5 will be identified by the treating investigator based on local immunohistochemistry or molecular testing results.

5.1.3. Study Period Definitions

Baseline/Screening: Begins when the informed consent form (ICF) is signed and ends at the first study treatment (defined as receiving any study drug); if no study treatment is given, baseline/screening ends with the decision not to enroll. This period lasts up to 28 days.

Study Period: The overall study period for Study JZFA begins the day of the first patient's first dose of study treatment and ends at overall study completion (as defined in Section 5.3).

- **Study Treatment Period:** Begins with the day of the patient's first study treatment and ends the day the patient and investigator agree that the patient will discontinue study treatment (discontinuation of assigned study drug; Section 8.1). Individual patients who enroll in Study JZFA may continue treatment until they have confirmed progressive disease or discontinue study treatment for any other reason (Section 8).
- **Post Study Treatment Follow-Up Period:** Begins the day the patient and investigator agree that the patient will discontinue study treatment and ends the day of the patient's death, lost to follow-up, or overall study completion, whichever is earlier. It includes one 30-day safety follow-up visit and a long-term follow-up, as follows:
    - **30-Day Safety Follow-Up Visit:** Occurs 30 ±7 days after the decision is made to discontinue from study treatment.
    - **Long-Term Follow-Up:** Begins the day after 30-day follow-up visit is completed and ends with the patient's death, lost to follow-up, or overall study completion, whichever is earlier.

5.2. Number of Patients

Dose Escalation: Phase 1a, approximately 30-64 patients will be enrolled (including up to 10 patients in safety expansion at RP2D).

Dose Expansion: Phase 1b, approximately 20 patients will be enrolled in each of Cohorts 1-4. In the bladder cancer Cohort 5, approximately 30 patients will be enrolled.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient.

5.4. Scientific Rationale for Study Design

The general rationale for the study is described in Section 3 and statistical considerations are described in Section 10.

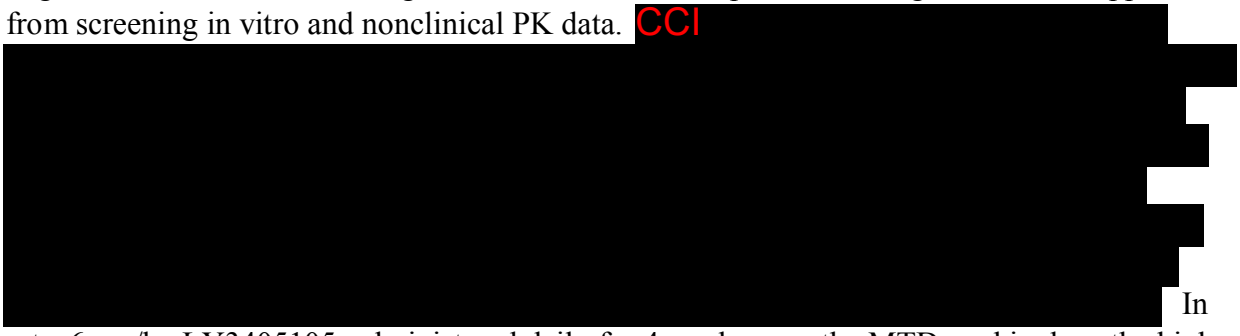
The purpose of the dose escalation is to determine a RP2D and dosing schedule that will be used in the subsequent dose expansion part of the study. The dose escalation method is described in Section 7.1.1.2.

The patient populations in the dose expansion cohorts have been chosen based on preclinical data, in vivo efficacy studies, and tumor histology. TNBC and ovarian tumor histology is broadly addicted to aberrant oncogenic transcription and may demonstrate enhanced sensitivity to selective CDK7 inhibition (Wang et al. 2015; Zhang et al. 2017). Preclinically, TNBC and ovarian tumor models demonstrate broad sensitivity to LY3405105 in vitro and in vivo. Molecular biomarker selection in gynecological malignancies and in bladder cancer were selected based on the internal preclinical data across cell lines and PDX models (LY3405105 Investigator's Brochure 2019, Section 4.2.2.1). Additionally, other molecular alterations in the

SWI/SNF complex may lead to activation of super-enhancer regions where inhibiting CDK7 could yield clinical activity (Chipumuro et al. 2014; Wang et al. 2015).

5.5. Justification for Dose

A starting daily oral dose of 1 mg (Part A1) and 2 mg (Part A2) of LY3405105 was selected based on data from GLP-compliant, 4-week oral, daily repeat-dose toxicity studies in rats and dogs, and PK/PD data modeling. Human clearance was predicted using mechanistic approaches from screening in vitro and nonclinical PK data. CCI



In rats, 6 mg/kg LY3405105, administered daily for 4 weeks, was the MTD, and in dogs the highest non-severely toxic dose (HNSTD) was 2 mg/kg. Key pathology findings in both species were degenerative changes in the GI tract (with correlative clinical chemistry changes and associated abnormal feces) and bone marrow hypocellularity (with correlative hematologic changes). These target organ toxicities in GI and bone marrow were expected based on pharmacology, were dose-dependent, and were reversible following cessation of dose administration. When normalizing mg/kg to body surface area, the rat MTD (6 mg/kg = 36 mg/m^2), when divided by 10 (that is, 3.6 mg/m^2) is lower than the dog HNSTD (2 mg/kg = 40 mg/m^2). Therefore, the rat is the appropriate (more sensitive) species from which to calculate a safe human starting dose. Based on body surface area, 1/10 of 6 mg/kg (that is, 3.6 mg/m^2) in rats is approximately equivalent to a dose of 6 mg daily in humans and would be considered a safe starting dose (DeGeorge et al. 1998). An additional safety factor of 6 was applied to the 6-mg dose to arrive at the human starting dose of 1 mg daily (QD). A safety factor of 3 applied to the 6 mg dose, along with the decrease in frequency of dosing, supports 2 mg QOD, TIW as a safe starting dose regimen.

Additional details may be found in the IB.

Table JZFA.5.1. Dose and Exposure Multiples for Oral Administration of LY3405105 Based on Administered Dose and Predicted Human Exposure

Species Dose Designation	Dose (mg/m^2)	Dose Multiple[a]	Average Plasma Concentration (ng/mL)	Exposure Multiple[b]
Human				
Starting dose (1 mg, QD)	0.6	–	2.4[c,d]	–
Rat				
MTD[e] (6 mg/kg/day)	36	**60**×	22[d]	**9.2**×
Dog				
HNSTD[f] (2 mg/kg/day)	40	**67**×	10[d]	**4.2**×
Human				
Starting dose (2 mg, QOD, TIW)	3.7[g]	–	2.3[c,h]	–
Rat				
MTD[e] (6 mg/kg/day)	252[i]	**68**×	22[d]	**9.6**×
Dog				
HNSTD[f] (2 mg/kg/day)	280[i]	**76**×	10[d]	**4.3**×
Human				
Predicted efficacious dose (7 mg, QD)	4.3	–	17[c,d]	–
Rat				
MTD[e] (6 mg/kg/day)	36	**8.4**×	22[d]	**1.3**×
Dog				
HNSTD[f] (2 mg/kg/day)	40	**9.3**×	10[d]	**0.6**×
Human				
Predicted efficacious dose (15 mg, QOD, TIW)	28[j]	–	17[c,d]	–
Rat				
MTD[e] (6 mg/kg/day)	252[i]	**9.0**×	22[d]	**1.3**×
Dog				
HNSTD[f] (2 mg/kg/day)	280[i]	**10**×	10[d]	**0.6**×

Abbreviations: AUC = area under the plasma concentration × time curve; HNSTD = highest non-severely toxic dose; MTD = maximum tolerated dose; TIW = 3 times per week; QD = once daily; QOD = every other day.

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

b Exposure multiple is the calculated average plasma concentration in animals, divided by the predicted average plasma concentration in humans.

c Plasma pharmacokinetic values shown are steady-state values estimated using mechanistic approaches based on screening in-vitro and in vivo data.

d Value obtained by dividing steady-state AUC (0-24hr) (ng·hr/mL) by 24 hours.

e MTD (and associated exposure at steady state) determined in a 4-week repeat-dose toxicity study (8383678).

f HNSTD (and associated exposure at steady state) determined in a 4-week repeat-dose toxicity study (8383679).

g Value represents mg/m^2 over 1 week of dosing, calculated by multiplying daily value of 1.23 mg/m^2 by 3 days.

h Value obtained by dividing predicted AUC (0-48hr)ss (ng·hr/mL) by 48 hours.

i Value represents mg/m^2 over 1 week of dosing, calculated by multiplying daily mg/m^2 value by 7 days.

j Value represents mg/m^2 over 1 week of dosing, calculated by multiplying daily value of 9.25 mg/m^2 by 3 days.

5.6. Justification for Enrolling Patients ≥12 Years of Age

Soft tissue sarcomas including Epithelioid Sarcoma (ES) and Synovial Sarcoma (SS) are rare tumors that affect adolescents, young adults alongside adults with median age of incidence for ES of 26 years of age (Weiss and Goldblum 2001), and for SS of 34 years of age of which (17% are children or adolescents) (Sultan et al. 2009). Metastatic sarcoma that progressed beyond curative local therapy or standard systemic therapy carry poor prognosis and represent a significant unmet medical need. Based on preliminary data from LY3405105 PK exposure, no significant difference in exposure was observed in relation to body weight over a range of 44 kg to 111 kg. Additionally, we anticipate metabolic organ maturity by 12 years of age; therefore, no weight dose adjustment is necessary.

Besides safety review that is summarized in Section 10.3.2, additionally, the first patient 12-18 years of age enrolled into Phase 1b will be monitored through Cycle 1 prior to enrolling additional patients in the same age group. The safety review committee will review the safety data from the first 3 patients age 12-18 years who are evaluable for safety upon completing the first cycle. Similar reviews will take place after each 5 patients of this age group treated to evaluate for any safety signal in this population.

6. Study Population

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

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria:

[1] have histological or cytological evidence of a diagnosis of a solid tumor (American Joint Committee on Cancer Staging Criteria) (Amin et al. 2017) that is advanced and/or metastatic.

Patients must have received therapies known to confer clinical benefit, must not be a candidate for such therapies in the opinion of the investigator, must have declined such therapy, or have a tumor type for which no standard of care exists.

Patients enrolled to the dose escalation may have any tumor histology. Patients enrolled to the dose expansion must have one of the following:

a) Cohort 1: Triple-negative breast cancer (TNBC).

b) Cohort 2: Clear cell ovarian cancer, endometrioid ovarian cancer, or endometrioid endometrial carcinoma with a LOF mutation in one or more of the following genes: *ARID1A, KMT2C (MLL3), KMT2D (MLL2), or KDM6A (UTX)*.

c) Cohort 3: Soft tissue sarcoma or sarcomatoid/rhabdoid malignancy with loss of expression of INI1, BRG1, or BRM by immunohistochemistry or a LOF mutation in one or more of the following genes: *ARID1A, SMARCA2, SMARCA4, or SMARCB1*. Patients with synovial sarcoma and a confirmed SS18-SSX gene fusion are also eligible.

d) Cohort 4: Epithelioid sarcoma with INI1 loss of expression by immunohistochemistry or *SMARCB1* LOF mutation.

e) Cohort 5: Bladder cancer with a LOF mutation in one or more of the following genes: *ARID1A, KMT2C (MLL3), KMT2D (MLL2), or KDM6A (UTX)*.

For Cohorts 2-5, qualifying genomic alterations as defined in Section 9.8.1 or immunohistochemistry results will be established on the basis of local testing performed as part of routine care at each participating site on a previously collected tumor biopsy or blood sample and established prior to consideration and consent to the study. The result should be generated by a laboratory with CLIA, ISO/IEC, CAP, or other similar certification. The presence of an eligible genomic alteration must be confirmed upon review of the redacted molecular pathology report by the Lilly CRP/CRS prior to enrollment.

[2] must provide archived formalin-fixed paraffin-embedded (FFPE) tumor tissue for exploratory biomarker analysis. If archived tumor tissue is not available, the patient may be eligible with prior Sponsor approval.

Note: Sites should confirm the availability of tumor tissue for exploratory analysis (Section 9.8.2) with the pathology laboratory prior to enrollment.

[3] have the presence of measurable (Phase 1b) or non-measurable but evaluable (Phase 1a) disease as defined by the Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) (Eisenhauer et al. 2009).

[4] are of an acceptable age to provide informed consent according to the local regulations and are at least 18 years of age at the time of screening for Cohorts 1, 2, and 5 or are ≥12 years of age with a body weight of ≥40 kg for Cohorts 3 and 4. Adolescents between 12 and 18 years are not eligible for participation in the Phase 1a dose escalation.

[5] have given written informed consent prior to any study-specific procedures. For minors, consent from the parent or legal guardian and assent from the patient is required.

[6] have adequate organ function as defined in the table below:

System	Laboratory Value
Hematologic	
ANC	≥1.5 × 10^9 cells/L
Platelets	≥100 × 10^9/L
Hemoglobin Note: Transfusions to increase a patient's hemoglobin level or initiation of erythropoietin or G-CSF therapy to meet enrollment criteria are not allowed in the 14 days preceding the first dose of study drug.	≥9 g/dL
Hepatic	
Total bilirubin	≤1.5 × ULN
Serum albumin	≥3 g/dL
ALT and AST	≤2.5 × ULN
Renal	
Serum creatinine *or* Calculated creatinine clearance (see Appendix 6)	≤1.5 × ULN *or* ≥50 mL/min

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; G-CSF = granulocyte colony-stimulating factor; ULN = upper limit of normal.

[7] Eastern Cooperative Oncology Group (ECOG) performance status score of 0-1 (age ≥16 years) or Lansky Performance Score (LPS) ≥40% (age <16 years) with no sudden deterioration 2 weeks prior to the first dose of study treatment (Appendix 8).

[8] have discontinued previous treatments for cancer and recovered from the acute effects of therapy other than alopecia. Patients must have discontinued from previous treatments at least 21 days prior to first dose of study treatment. Patients must have discontinued any other investigational agents ≥4 weeks prior to enrollment or ≥5 half-lives, whichever is shorter, since completion of previous investigational agent.

a) Patients must have discontinued from mitomycin-C or nitrosoureas at least 42 days prior to first dose of study treatment.

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

[10] if a male or female of reproductive potential, must agree to use highly effective methods of birth control during the study and for at least 12 weeks following the last dose of study drug(s), or for the duration specified in country requirements, whichever is longer. Women of childbearing potential must test negative for pregnancy based on a urine pregnancy test within 3 days of enrollment.

[11] have an estimated life expectancy of ≥3 months.

[12] are able to swallow capsules/tablets.

6.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

[13] are currently enrolled in a clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[14] have known symptomatic CNS metastasis (screening not required).

Patients with treated CNS metastases are eligible for this study if they are not currently receiving corticosteroids and/or anticonvulsants, and their disease is asymptomatic and radiographically stable for at least 90 days prior to consent.

[15] have a serious concomitant systemic disorder (for example, active infection, or a GI disorder causing clinically significant symptoms such as nausea, vomiting or diarrhea, or profound immune suppression) that, in the opinion of the investigator, would compromise the patient's ability to adhere to the protocol.

[16] have a symptomatic human immunodeficiency virus infection or symptomatic activated/reactivated hepatitis A, B, or C (screening is not required).

[17] have a serious cardiac condition, such as

- congestive heart failure
- New York Heart Association Class III/IV heart disease

- unstable angina pectoris
- myocardial infarction within the last 3 months
- valvulopathy that is severe or moderate
- or arrhythmias that are symptomatic or require treatment (not including patients with rate-controlled atrial fibrillation)
- cerebrovascular accident (stroke) within the last 3 months
- have a mean QT interval corrected for heart rate of ≥470 msec on screening ECG as calculated using the Bazett's formula at several consecutive days of assessment.

[18] have a second primary malignancy that in the judgment of the investigator and Lilly may affect the interpretation of results (consult with Lilly CRP/CRS).

[19] are currently taking or have taken within 2 weeks prior to start of LY3405105, strong inhibitors and inducers of CYP3A4 as outlined in Appendix 4.

[20] prior treatment with any CDK 7 inhibitor.

[21] are breastfeeding.

[22] are unwilling or unable to participate in, or do not have tissue adequate for participation in, the genetic/biomarker portion of the study.

6.3. Lifestyle Restrictions

Patients should refrain from consuming grapefruit, grapefruit juice, and grapefruit-containing products while on study due to the effect on CYP3A4.

Due to the Phase 1 PK testing and possible unknown interactions, all herbal supplements will not be allowed while on study.

6.4. Screen Failures

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

If laboratory tests are repeated during the screening period, this does not constitute re-screening.

7. Treatment

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the drugs and planned duration of each individual's treatment to the study site personnel
- verifying that instructions are followed properly
- maintaining accurate records of study drug dispensing and collection
- returning all unused medication to Lilly, or its designee, at the end of the study, unless the site is authorized by Lilly to destroy unused medication, as allowed by local law.

7.1. Treatment Administered

7.1.1. Dose Escalation (Phase 1a)

In the monotherapy dose escalation (Phase 1a), approximately 30-64 patients will start with a starting dose of LY3405105 1 mg PO QD (Part A1) on a 28-day cycle. The dose escalation method is described in Section 7.1.1.2.

Safety data, in particular AEs, will be the primary criteria for the dose escalation. In addition, if available at the time of dose escalation decision, PK and PD results will be used for dose escalation. No dose escalation can occur without prior discussion and agreement between Lilly and the investigators.

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

Dose-limiting toxicity is defined as a clinically significant AE during Cycle 1 of the dose escalation phase that is possibly related to LY3405105 during Phase 1a and fulfills any one of the following criteria using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) v4.0:

- ≥CTCAE Grade 3 non-hematological toxicity. Exceptions will be made for:
    - Grade 3 nausea or constipation that lasts for <72 hours and can be controlled with treatment
    - Grade 3 diarrhea, vomiting, or electrolyte disturbance that lasts for <72 hours and can be controlled with treatment
    - fatigue or anorexia. Grade 3 or Grade 4 fatigue should be considered a DLT if persisting >5 days
    - Transient Grade 3 elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), without evidence of other hepatic injury, in the setting of preexisting hepatic metastasis and baseline elevation of these values may not be considered a DLT if agreed by the study investigator and Lilly CRP/CRS.

- Total bilirubin >2 × upper limit of normal (ULN) with ALT/AST >3 × ULN in the absence of cholestasis (alkaline phosphatase <2 × ULN)
- Grade 4 neutropenia >5 days duration
- any febrile neutropenia
- Grade 4 thrombocytopenia of any duration
- Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 3/4 anemia
- any other significant toxicity deemed by the primary investigator and Lilly to be dose limiting (for example, any toxicity that is possibly related to the study medication that requires the withdrawal of the patient from the study during Cycle 1 or certain Grade 2 AEs affecting vital organs)
    - A DLT-equivalent toxicity is defined as an AE occurring after Cycle 1 for a patient enrolled in Phase 1a. It will also apply to patients treated in any cycle in Phase 1b (including Cycle 1) that would have met the criteria for DLT.

Potential DLTs that are AEs which are reasonably anticipated AEs for concomitant medication should be reviewed by the treating investigator and Lilly before final determination as a DLT. Review and discussion may include additional participating investigators. Such review may determine that confounding factors render the case to be not evaluable for the purposes of dose selection. For the purpose of this study, the MTD is defined as the highest tested dose that has less than 33% probability of causing a DLT.

7.1.1.2. Dose Escalation Method

In the dose escalation part of the study, data will be evaluated on an ongoing basis until the MTD is determined. The Bayesian model-based toxicity band method (N-CRM) (Neuenschwander et al. 2008) that incorporates prior expectations about the dose-toxicity relationship will be fitted to the data at the end of each dose level to recommend a dose for the next dose level. The recommendation is based on the model-based posterior probability of a DLT at each dose and the overdose control criteria. Details regarding the toxicity band model and design are provided in Appendix 7.

During the escalation, the investigators and Lilly will consider both the Bayesian model-based toxicity band method (N-CRM) recommendation and the observed DLT rate at each dose level to determine the next dose level and determine when to stop the escalation.

Dose levels will not exceed those recommended by the toxicity band model. Dose escalation will take into account all available PK and PD information. Additional patients may therefore be enrolled at a specific dose level to better characterize PK/PD.

The starting dose of LY3405105 will be 1 mg QD in Part A1. If the starting dose exceeds the MTD, a lower LY3405105 dose level may be explored. The maximum increment of escalation will be no more than 100%. Each dose level will have a minimum of 3 patients enrolled to it.

Subsequent dose levels will enroll patients based on the safety from the previous dose level, any available PK and PD data, and discussion with investigators. This decision is made between the investigators and the Lilly CRP/CRS. Table JZFA.7.1 shows example dose levels for LY3405105. It should be noted that although an example escalation table is shown below, alternate doses may be selected.

Intermediate, alternate, or higher dose levels will be explored if deemed necessary after discussion between Lilly and the investigators. The toxicity band model accommodates such additional dose levels naturally.

Table JZFA.7.1. Example Dose Escalation Scheme for Study J1F-MC-JZFAa

Dose Level	LY3405105 Part A1 Dose
1	1 mg QD
2	2 mg QD
3	4 mg QD
4	8 mg QD
5	15 mg QD
6	30 mg QD
7	45 mg QD

Abbreviations: QD = once daily.

[a] Dose levels will start at 1 mg QD (Part A1) and maximum increase will be no more than 100% from previous level. Table lists example dose levels which may be used.

7.1.2. Dose Expansion (Phase 1b)

After the monotherapy RP2D has been determined from Phase 1a, approximately 20 patients will be enrolled in each of Phase 1b Cohorts 1-4. In Cohort 5, approximately 30 patients will be enrolled. Patients will receive LY3405105 at the RP2D orally daily for a 28-day cycle.

Study treatment should be continued until evidence of disease progression or discontinuation criteria is met. Patients with documented progressive disease may be allowed to continue LY3405105 if the patient is tolerating treatment and, in the opinion of the investigator, is deriving clinical benefit from continuing study treatment and continuation of treatment is approved by the Sponsor.

If DLT-equivalent toxicities occur in 33% or more of patients within a tumor-specific cohort expansion, then investigators and the Lilly CRP/CRS will assess the nature and severity of these toxicities. If a treatment-related death or Grade 4 toxicity not clearly due to underlying disease or extraneous occur, then the investigators and the Lilly CRP/CRS will assess the nature and severity of the toxicities and whether the trial should be stopped due to unacceptable toxicity. No additional patients will be accrued until this safety review is completed and a decision is made either to continue at the current dose or to de-escalate the dose and define a new dose for the expansion phase. The safety review and decision will be documented in writing.

7.1.3. Packaging and Labeling

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

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be assigned to receive LY3405105 in this study. The Sponsor will confirm the dose and identification number assignment and dose level for each patient. No dose escalations (that is, to the next dose level) can occur without prior discussion and agreement with Lilly.

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

7.2.1. Selection and Timing of Doses

The dosing cycle is defined as an interval of 28 days. During the monotherapy dose escalation, patients will receive doses once daily starting on Day 1 through Day 28 of a 28-day cycle. For visits where PK samples will be collected, patients are required to take the morning dose of LY3405105 at the hospital/clinic (not at home) after the predose PK sample collection has occurred.

LY3405105 will be administered on an empty stomach (meals should not be consumed within 1 hour either side of dosing). Doses should be taken approximately the same time each day (±2 hours) as much as possible. 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.

A delay of a cycle due to holiday, weekend, bad weather, or other unforeseen circumstances will be permitted for a maximum of 7 days and not counted as a protocol deviation. The reason for interruption should be documented on the electronic case report form (eCRF).

A patient may continue to receive study treatment until confirmed progressive disease (Section 9.1), unacceptable toxicity, or discontinuation for any other reason (Section 8). Patients with documented progressive disease may be allowed to continue LY3405105 if the patient is tolerating treatment and, in the opinion of the investigator, is deriving clinical benefit from continuing study treatment and continuation of treatment is approved by the Sponsor.

7.3. Blinding

This is an open-label study.

7.4. Dose Modification

Doses of the study drugs may need to be delayed, reduced, or discontinued to manage specific AEs or other toxicities. Investigators should review the relationship of an AE to the study drug to determine if study drug requires dose adjustment or delay (Table JZFA.7.2).

When a study drug is delayed, if possible and appropriate, patients should resume study treatment within 1 treatment cycle and, if not possible, then every effort should be made to start on the first day of the next dosing cycle. In rare circumstances, a delay >28 days may be permitted before permanent treatment discontinuation, as long as the patient has clinical benefit without objective disease progression and is recovering from the toxicity. Such circumstances must be discussed with Lilly. All dose modifications should be documented, including the approach taken, and a clear rationale for the need for modification.

Any patient who requires a dose reduction will continue to receive the reduced dose for the remainder of the study. Any patient who has had 2 dose reductions and who experiences a toxicity that would cause a third dose reduction must be discontinued from study treatment.

If the patient is in Cycle 6 or beyond and is continuing to receive benefit from therapy, additional delays may be acceptable if agreed upon by both the investigator and the Sponsor. If a patient has a non-drug-related AE (for example, pneumonia or prolonged flu) requiring a delay of more than 1 week, the patient may continue on therapy if, in the opinion of the investigator, he/she is showing benefit from therapy and has recovered sufficiently from the AE. Additional procedures may be required for delayed patients before resuming treatment.

Table JZFA.7.2. Dose Modifications in Patients due to Toxicity

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 **MAY** be reduced by 1 dose level at the investigator's discretion.
Hematologic toxicity	Recurrent 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.
Hematologic toxicity: *Patient requires administration of blood cell growth factors*	Regardless of severity. Growth factors use 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 lead to the use of growth factor.
Nonhematologic toxicity (except diarrhea)	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose **MAY** be suspended until toxicity resolves to either baseline or Grade 1.	Dose **MAY** be reduced by 1 dose level – investigator's discretion.
Nonhematologic toxicity	Grade 3 or 4 that does not resolve with maximal supportive measures within 72 hours 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.
Diarrhea	Requires hospitalization for Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
Diarrhea	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 24 hours to at least Grade 1	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MAY** be reduced by 1 dose level – investigator's discretion.
Diarrhea	Persistent or recurrent Grade 1 that does not resolve with maximal supportive measures within 24 hours to baseline	Patient to be followed for 48 hours to ensure grade does not worsen.	Dose **MAY** be maintained during monitoring – investigator's discretion.
Diarrhea	Diarrhea recurs despite maximal supportive measures after resuming same dose level after initial Grade 2 diarrhea	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
Bloody diarrhea	Any grade	Dose **MUST** be suspended until bloody diarrhea resolves and diarrhea resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
Nonhematologic toxicity (laboratory)	Total bilirubin >2 × ULN with ALT/AST >3 × ULN in the absence of cholestasis	Dose **MUST** be permanently suspended.	Dose **MUST** be permanently suspended.
Nonhematologic toxicity (vital organs of clinical concern, for example cardiotoxicity, pneumonitis, neurotoxicity)	Grade 2	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1. If not resolved to Grade 1 within around 14 days, discussion between the investigator and Lilly CRP is recommended.	Dose **MAY** be reduced by 1 dose level – investigator's discretion.

Abbreviation: ALT = alanine aminotransferase; ASCO = American Society of Clinical Oncology; AST = aspartate aminotransferase; MAY = per the investigator's clinical judgment; MUST = mandatory; ULN = upper limit of normal

7.5. Preparation/Handling/Storage/Accountability

LY3405105 capsules/tablets for oral consumption will be supplied by Lilly and labeled according to country regulation requirements. All study treatment should be stored according to their associated product label and taken as directed. Patients should store all study treatment in the original package provided according to the product label and be instructed to keep all medications out of reach from children. Capsules/tablets should not be opened, crushed, or dissolved.

7.6. Treatment Compliance

Patient compliance with study drug will be assessed at each visit. LY3405105 compliance will be assessed by direct questioning, counting returned capsules/tablets/packages, and reviewing patient diaries. Deviations from the prescribed dosage regimen should be recorded on the CRF.

A patient will be considered significantly noncompliant if he/she misses more than 20% cumulative days of study medication (full doses) during each cycle. A patient may be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

7.6.1. Evaluable Patients

Patients who withdraw from the study before receiving study drug(s) will be replaced and will not be included in the safety or efficacy assessments. Safety analyses will be conducted on all patients who have received at least 1 dose of study drug, regardless of whether they are deemed evaluable for the assessment of a dose level.

Any patient who is discontinued from the study before receiving at least 80% of LY3405105 planned doses in Cycle 1 will be deemed non-evaluable for assessment of safety at that dose level and may be replaced unless they experience a DLT or dose omission/reduction due to toxicity prior to withdrawal. A patient may be deemed non-evaluable for assessment of a dose level in the event the patient experiences an AE which would meet DLT criteria, and furthermore has been determined through discussion between investigator and Lilly CRP/CRS to most likely be related to a concomitant medication or a prior line of immune therapy (in the case of immune-related AEs) due to previously established linkage.

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

Non-evaluable patients may be replaced to ensure that at least 3 patients complete 1 cycle of therapy at each dose level, unless accrual to that dose level has stopped due to a DLT.

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

7.7. Concomitant Therapy

The list of excluded medications and procedures is provided in Appendix 4.

No other chemotherapy, radiotherapy, immunotherapy, cancer-related hormone therapy, experimental drugs, or herbal supplements will be permitted while the patients are on this study.

The need for any form of radiotherapy (including palliative) will be cause for early discontinuation from the study.

Patients should refrain from consuming grapefruit, grapefruit juice, and grapefruit-containing products while on study.

In addition, any disease progression requiring other forms of specific anti-tumor therapy will also necessitate early discontinuation from the study. Appropriate documentation for all forms of premedication, supportive care, and concomitant medications must be captured on the case report form. Replacement hormonal therapy initiated before study entry will be allowed.

If clinically indicated at any time during the study, erythropoietin and packed red blood cell transfusions may be used according to American Society of Clinical Oncology (ASCO) guidelines (Rizzo et al. 2008). Prophylactic antibiotic treatment should be consistent with ASCO guidelines (Flowers et al. 2013).

Patients on stable doses of bisphosphonates or denosumab are allowed to continue. These agents should not be initiated within the 2 weeks prior to study enrollment or at any point while on the study.

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

7.7.1. Growth Factors

Growth factors should not be administered to enable a patient to satisfy study inclusion criteria. Granulocyte colony-stimulating factor (G-CSF) or similar agents are not permitted as primary prophylaxis.

The use of G-CSF is permitted at the discretion of the investigator based on ASCO (Smith et al. 2015) and European Society for Medical Oncology (Crawford et al. 2009) guidelines. If the administration of growth factors is clinically indicated, dosing of LY3405105 must be suspended and must not be recommenced within 48 hours of the last dose of growth factors being administered. The dose of LY3405105 must be reduced by 1 dose level following the administration of growth factors.

7.8. Treatment After the End of Study

The end of study definition is defined in Section 5.3. Investigators will continue to follow the schedule of activities provided in Section 2 until notified by Lilly that end of study has occurred.

7.8.1. Treatment After Study Completion

Study completion will occur following the final analysis of primary and secondary objectives, as determined by Lilly. Investigators will continue to follow Schedule of Activities (Section 2) for all patients until notified by Lilly that study completion has occurred.

7.8.1.1. Continued Access

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

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

Patients who are in 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. Long-term follow-up does not apply.

Patients who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

8. Discontinuation Criteria

The reason for discontinuation and the date of discontinuation will be collected for all patients.

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

8.1. Discontinuation from Study Treatment

Patients will be discontinued from study treatment in the following circumstances:

- the patient is enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
- the patient becomes pregnant during the study
- the patient is significantly noncompliant with study procedures and/or treatment as described in Section 7.6
- the patient has confirmed progressive disease

  Exception: Patients with documented progressive disease may be allowed to continue LY3405105 if the patient is tolerating treatment and, in the opinion of the investigator, is deriving clinical benefit from continuing study treatment and continuation of treatment is approved by the Sponsor.
- the patient experiences unacceptable toxicity
- the patient has had 2 dose reductions and experiences an AE that would cause a third dose reduction
- the investigator decides that the patient should be discontinued from study treatment
- the patient requests to be discontinued from study treatment
- the patient's legal representative requests that the patient be discontinued from study treatment.

Patients who are discontinued from study treatment will have follow-up procedures performed as shown in the Schedule of Activities (Section 2).

8.1.1. Discontinuation of Inadvertently Enrolled Patients

If Lilly or the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, a discussion must occur between the Lilly CRP/CRS and the investigator to determine if the patient may continue in the study. If both agree that it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CRP/CRS to allow the inadvertently enrolled patient to continue in the study with or

without study treatment. Safety follow-up is as outlined in the Schedule of Activities (Section 2).

8.2. Discontinuation from the Study

Patients will be discontinued from the study (including follow-up procedures) in the following circumstances:

- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- the patient becomes pregnant during the study. See Section 9.2 regarding regulatory reporting requirements on fetal outcome and breastfeeding
- the investigator decides that the patient should be discontinued from the study
- the patient requests to be discontinued from the study
- the patient's legal representative requests that the patient be discontinued from the study.

Patients who discontinue from the study early will have end-of-study procedures performed as shown in the Schedule of Activities (Section 2).

8.3. Lost to Follow-Up

A patient would be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Study site personnel are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or who the site is otherwise unable to follow-up.

9. Study Assessments and Procedures

Section 2 provides the Schedule of Activities for this study.

Appendix 2 provides a list of the laboratory tests that will be performed for this study.

Section 2 provides the schedule for collection of samples in this study.

Unless otherwise stated in the following subsections, all 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.

9.1. Efficacy Assessments

Tumor assessments will be performed for each patient at the times shown in the Schedule of Activities (Section 2).

The RECIST v1.1 (Eisenhauer et al. 2009) will be applied as the primary criteria for assessment of tumor response and date of disease progression. The method of tumor assessment used at baseline must be used consistently throughout the study. Local tumor imaging (investigator assessment with site radiological reading) will be used.

Computed tomography (CT) scans, including spiral CT, are the preferred methods of measurement (CT scan thickness recommended to be ≤5 mm); however, magnetic resonance imaging is also acceptable in certain situations, such as when body scans are indicated or if there is a concern about radiation exposure associated with CT. Intravenous and oral contrast is required unless medically contraindicated.

The CT portion of a positron emission tomography (PET)-CT scan may be used as a method of response assessment if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (with intravenous and oral contrast). A PET scan alone or as part of a PET-CT may be performed for additional analyses but cannot be used to assess response according to RECIST v1.1.

See Section 10.3.1 for definitions of the efficacy endpoints.

9.2. Adverse Events

The investigator will use CTCAE Version [4.0] (NCI 2009) to assign AE terms and severity grades.

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
- providing appropriate medical care of the patient during the study (including review of laboratory data and examination results)

- following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to study treatment or the study, or that caused the patient to discontinue study treatment before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish safety and toxicity.

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Study site personnel will record via eCRF any change in preexisting conditions and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to study treatment via eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment or a study procedure, taking into account the disease, concomitant treatment, or pathologies. A "reasonable possibility" means that there is a cause and effect relationship between the study treatment and/or study procedure and the AE.

Adverse Event grading of toxicities related to estimated Glomerular Filtration Rate (GFR) should be evaluated based on the Cockcroft-Gault method or measured GFR.

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

Study site personnel must report any dose modifications or treatment discontinuation that results from AEs to Lilly or its designee via eCRF, clarifying, if possible, the circumstances leading to dose modification or discontinuation of treatment.

9.2.1. Serious Adverse Events

An SAE is any AE during this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or require hospitalization, may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above.

Although all AEs after signing the ICF are recorded in the eCRF, SAE reporting to Lilly begins after the patient has signed the ICF and has received study treatment. However, if an SAE occurs after signing the ICF, but prior to receiving study treatment, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

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

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an AE but should be reported. To fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study (the patient summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

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

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

9.2.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to study treatment or study procedure. The United States 21 CFR 312.32, the Regulation (EU) No 536/2014 and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulatory regulations and the associated detailed guidances.

9.2.3. Complaint Handling

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

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

The investigator should notify the Lilly CRP/CRS and a decision on next steps will be determined in consultation with Lilly. Refer to the specific IB Section 7.3.9.

9.4. Safety

9.4.1. Safety Measures

For each patient, ECGs, vital signs, laboratory tests or other tests should be collected as shown in the Schedule of Activities (Section 2). Electrocardiograms should be recorded according to the study-specific recommendations that will be provided separately.

Any clinically significant findings that result in a diagnosis and that occur after the patient receives the first dose of LY3405105 should be reported to Lilly or its designee as an AE via designated data transmission methods.

9.4.2. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

If a study patient experiences elevated alanine aminotransferase (ALT) >5 × ULN and elevated total bilirubin (TBL) >2 × ULN, or ALT ≥8 × ULN, liver tests (Appendix 5) should be repeated within 3 to 5 days including ALT, AST, TBL, direct bilirubin (D.TBL), gamma-glutamyl transferase (GGT) and creatine phosphokinase (CPK) to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on the hepatic monitoring tests (Appendix 5) and in consultation with the Lilly CRP. Monitoring of ALT, AST, and TBL should continue until levels normalize or return to approximate baseline levels.

9.4.2.1. Special Hepatic Safety Data Collection

Hepatic data should be collected in the event that a patient meets one of the following conditions during the course of the study:

- elevation of serum ALT to ≥10 × ULN
- patients without liver tumors or liver metastasis: ALT ≥5 × ULN and TBL ≥2 × ULN
- patients with liver tumors or liver metastasis: ALT ≥8 × ULN and TBL ≥2 × ULN
- discontinuation from treatment due to a hepatic event or abnormality of liver tests
- occurrence of a hepatic event considered to be a SAE.

9.5. Pharmacokinetics

Pharmacokinetic samples will be collected as shown in Section 2.

Plasma samples will be used to determine the concentrations of LY3405105.

A maximum of 5 samples may be added at additional time points or removed during the study if warranted and agreed upon by the investigator and Lilly. Plasma concentrations of LY3405105 will be quantified using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay in a laboratory designated by the Sponsor. All bioanalytical samples will be stored in the United States. The remaining plasma samples collected for PK evaluation may be used for exploratory studies to assess the metabolism of LY3405105, which may involve sample pooling. Results from exploratory metabolism work will not be included in the final integrated study report.

Bioanalytical samples collected to measure LY3405105 concentration and metabolism and/or protein binding will be retained for a maximum of 2 years following last patient visit for the study.

9.6. Pharmacodynamics

Samples collected to measure PD biomarkers will be identified by the patient number (coded) and retained at a facility selected by Lilly for a maximum of 15 years following last patient visit for the study. Plasma samples will be collected as specified in Section 2, where local regulations allow, for biomarker research described in Section 9.8.

9.7. Genetics

9.7.1. Whole Blood Sample for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in Section 2, where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to study treatment and to investigate genetic variants thought to play a role in cancer. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the study site personnel. Samples will be retained at a facility selected by Lilly for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ethical review boards/institutional review boards (ERBs/IRBs) impose shorter time limits. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of LY3405105 or after LY3405105 becomes commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing technologies include whole genome and exome sequencing, genome-wide association studies, multiplex assays, candidate gene studies, and epigenetic analyses. Regardless of the technology utilized, data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

This study will analyze biomarkers relevant to study treatment, the mechanism of action of LY3405105, variable response to study drug(s), immune function, tumor microenvironment, and pathways associated with cancer. These samples may also be used to develop related research methods or to validate diagnostic tools or assays.

Samples for biomarker research will be collected as specified in Section 2, where local regulations allow. It is possible that biomarker data for patients in the study has already been generated from samples that were collected and analyzed prior to enrolling in this study. This may include data generated from genetic analyses. If available, these data may be requested from medical records for use in the research described in Sections 9.7.1 and 9.8.

9.8.1. Biomarkers Required for Eligibility

For patients enrolled to Cohorts 2-5 on the basis of the genomic alterations outlined in Section 6.1, LOF mutations are defined as potentially deleterious frameshift mutations, nonsense mutations, deletions, or splice site alterations. The presence of any such defined genomic alteration identified in tumor or blood will be based on available test results collected outside of Study JZFA as part of prior medical care (local testing).

For patients enrolled to Cohorts 2-5 based on a local laboratory test, the report containing evidence of an eligible genomic alteration or IHC result must be sent to the Sponsor or designee.

9.8.2. Tumor Tissue Samples for Exploratory Biomarker Research

Tissue samples for biomarker research will be collected for the purposes described in Section 9.8.

The following samples for biomarker research will be collected as specified in Section 2, where local regulations allow.

Collection of the following tumor tissue sample is **required** for all patients to participate in this study:

- To meet study eligibility criteria, and therefore, mandatory for study participation, patients must provide archived FFPE tumor tissue for exploratory biomarker analysis. While the tissue can be from either initial diagnosis or later, the sample should be the most recent available specimen containing adequate material. If archived tumor tissue is not available, the patient may be eligible with Sponsor approval.

- Sites should confirm the availability of tumor tissue with the pathology laboratory during screening and prior to enrollment. Tumor tissue should be submitted within 28 days following enrollment, unless this has been discussed with the Lilly CRP/CRS.

Collection of the following tumor tissue sample(s) is **optional** for all patients participating in this study:

- Optional biopsy samples may be requested if warranted and agreed upon by the investigator and Lilly. If these additional samples are requested, they will be used to further investigate biomarkers that may help further characterize treatment response and resistance mechanisms, particularly in patients that have experienced clinical benefit from LY3405105 as a monotherapy or in combination.

Archived FFPE tumor tissue obtained from the primary tumor or metastatic site should be provided as a block (preferred) or unstained slides. Due diligence should be used to make sure that tumor sample (not a normal adjacent or a tumor margin sample) is provided.

The pathology report accompanying tissue will also be requested. The pathology report must be coded with the patient number. Personal identifiers, including the patient's name and initials, must be removed from the institutional pathology report prior to submission. Archived blocks will be sectioned and returned to the study site. Slides and tissue samples collected on study will not be returned.

Samples will be retained at a facility selected by Lilly for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits. This retention period enables the use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of LY3405105 or after LY3405105 becomes commercially available.

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

9.8.3. Other Samples for Biomarker Research

The following samples for biomarker research will be collected as specified in Section 2, where local regulations allow:

- plasma
- a maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon by the investigator and Lilly.

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

Samples will be retained at a facility selected by Lilly for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/IRBs impose shorter time limits. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of LY3405105 or after LY3405105 becomes commercially available.

Technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. Existing approaches, including mutation profiling, copy number variability analysis, and/or gene expression assays may be performed on these samples to assess potential associations between these biomarkers and clinical outcomes.

9.9. Health Economics

Health economics and medical resource utilization parameters will not be evaluated in this study.

10. Statistical Considerations

10.1. Sample Size Determination

For the dose escalation phase, approximately 30-64 patients will be enrolled (including 10 patients in safety expansion at RP2D). The total sample size will be determined by the incidence of DLTs. For the Phase 1b expansion Cohorts 1-4, approximately 20 patients will be enrolled in each cohort. For bladder cancer cohort (Cohort 5) approximately 30 patients will be enrolled. Considering the overlap of different biomarker subgroups among patients with bladder cancer, the main rationale for a larger sample size in Cohort 5 (n=30) is to provide reasonable number of patients per subgroup, thus allowing for descriptive summaries of the bladder cancer patient subpopulations.

To confirm the RP2D of LY3405105 as monotherapy and determine the preliminary efficacy of LY3405105 as monotherapy, an adequate sample size is required. A sufficient sample size will allow for an accurate evaluation of the relationship between exposure and toxicity, as well as an evaluation of the relationship between exposure and pharmacological effects using descriptive statistics and appropriate modeling techniques, if data warrant. A total of 20 patients with a given tumor type treated at the RP2D in dose confirmation can provide adequate precision for the estimated incidence rate of the following quantities of interest: 1) patients having a specified AE, or 2) patients showing a response (partial response/complete response [PR/CR]) to treatment. With a total sample size of n=20, the 95% confidence interval (CI) is approximately equal to the observed incidence rate ±12% to 24%. Example point estimates of incidence rates and corresponding 2-sided 95% CIs are summarized in Table JZFA.10.1, for n=20 and n=30. The values are provided as a reference for estimation rather than a basis of any decision criteria.

Table JZFA.10.1. Estimated Incidence Rate and its 2-Sided 95% CI

Num of Cases	N	Est Rate	95% CI[a]		N	Est Rate	95% CI[b]	
			Lower Limit	Upper Limit			Lower Limit	Upper Limit
0	20	0.0	0.0	0.17	30	0.0	0.0	0.12
3	20	0.15	0.03	0.38	30	0.10	0.02	0.27
5	20	0.25	0.09	0.49	30	0.17	0.06	0.35
10	20	0.50	0.27	0.73	30	0.33	0.17	0.53
15	20	0.75	0.51	0.91	30	0.50	0.31	0.69

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

a 95% Clopper-Pearson interval for binomial distribution with sample size (N) of 20 patients.

b 95% Clopper-Pearson interval for binomial distribution with sample size (N) of 30 patients.

10.2. Populations for Analyses

The following analysis sets will be defined for this study:

Safety population will include all enrolled patients who received any quantity of study treatment, regardless of their eligibility for the study. The safety evaluation will be performed based on the first dose of study treatment a patient actually received. The safety population will be used for all dosing/exposure, safety, and efficacy analyses.

Pharmacokinetic population will include all treated patients who received at least 1 dose of study treatment and have at least 1 postbaseline evaluable PK sample.

Biomarker population will include the subset of patients from the safety population from whom a valid assay result has been obtained.

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Lilly or its designee.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) and the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

The primary analysis of primary and secondary endpoints will be performed no more than 1 year after the last patient is enrolled in the trial. An updated analysis of efficacy may be performed at a later time if deemed appropriate.

10.3.1. Efficacy Analyses

Tumor response data will be tabulated, and further exploratory analyses will be conducted as warranted, grouping patients by tumor type, for the safety population.

Overall response rate (ORR) is the proportion of patients who achieved a CR or PR out of all patients treated. Tumor responses will be measured and recorded using the appropriate guidelines (RECIST v1.1 [Eisenhauer et al. 2009]). To confirm objective responses, all lesions should be radiologically assessed, and the same radiologic method used for the initial response determination should be repeated at least 4 weeks following the initial observation of an objective response, using the same method that was used at baseline.

Disease control rate (DCR) is defined as the proportion of patients who achieved a CR or PR or stable disease (SD) out of all patients treated.

Duration of response (DoR) will be calculated only for responders. It is measured from the date of first evidence of a confirmed response to the date of first progression of disease or the date of death due to any cause, whichever is earlier. For patients who are not known to have died or to have had a progression of disease as of the data-inclusion cutoff date, DoR will be censored at the date of last objective response assessment prior to the date of any subsequent systemic anticancer therapy.

Progression-free survival (PFS) is defined as the time from the date of start of treatment to the first date of radiologically documented progressive disease or the date of death due to any cause, whichever occurs first. For patients who are not known to have died or progressed as of the data-inclusion cutoff date, PFS time will be censored at the date of the last objective progression-free disease assessment prior to the date of any subsequent systemic anticancer therapy.

Time to response (TTR) is defined as the time from the date of start of treatment to the date measurement criteria for confirmed CR or PR (whichever is first recorded) are first met. For patients who are not known to have achieved CR or PR as of the data-inclusion cutoff date, TTR will be censored at the date of the last objective disease assessment prior the date of any subsequent systematic anticancer therapy.

Overall survival (OS) is defined as the time from the date of start of treatment to the date of death due to any cause. For patients who are alive, lost to follow-up, or withdrawn from the study at the time of analysis, OS will be censored at the last date the patient is known to be alive.

10.3.2. Safety Analyses

All patients in the safety analysis set will be evaluated for safety and toxicity.

The Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 (or higher) will be used when reporting AEs by MedDRA terms. The MedDRA Lower Level Term will be used in the treatment-emergent computation. Treatment-emergent adverse events (TEAEs) will be summarized by System Organ Class (SOC) and by decreasing frequency of Preferred Term within SOC.

Safety analyses will include summaries of the following:

- AEs, including severity and possible relationship to study drug
- SAEs, including possible relationship to study drug
- AEs leading to dose adjustments
- DLTs and dose-limiting equivalent toxicities
- discontinuations from study treatment due to AEs or death
- treatment-emergent abnormal changes in laboratory values
- treatment-emergent abnormal changes in vital signs and ECGs.

For dose escalation phase, the model-based recommendation (as detailed in Appendix 7) and the observed DLT rate, will provide guidance on the RP2D. Results will be presented in terms of the posterior probability of under (DLT rate <0.16), target (DLT rate 0.16-0.33), excessive (DLT rate 0.33-0.6), or unacceptable (DLT rate >0.6) dosing for each dose level tested. The final RP2D of LY3405105 will be determined by review of all DLTs, TEAEs, PK, and PD data.

10.3.3. Other Analyses

10.3.3.1. Patient Disposition

A detailed description of patient disposition will be provided, including a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated as well as number and percentage of patients completing the study, as defined in the SAP, or discontinuing (overall and by reason for discontinuation). A summary of all-important protocol deviations will be provided.

10.3.3.2. Patient Characteristics

Demographic data are collected and reported to demonstrate that the study population represents the target patient population considered for regulatory approval.

A summary of baseline patient and disease characteristics, historical diagnoses, preexisting conditions, and prior therapies will be reported using descriptive statistics.

10.3.3.3. Concomitant Therapy

A summary of prior and concomitant medications will be reported.

10.3.3.4. Extent of Exposure/Treatment Compliance

The number of cycles received, dose omissions, dose reductions, dose delays, and dose intensity will be summarized for all treated patients by treatment arm.

Study treatment compliance will be assessed as the proportion of treatment that is actually taken, relative to what is expected, after accounting for protocol-defined dose adjustments. Study treatment taken will be derived from the difference between the total number of pills dispensed and returned over the course of the patient's treatment.

10.3.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic parameter estimates for LY3405105 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be maximum concentration (C_{max}) and area under the concentration-time curve ($AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$). Other noncompartmental parameters, such as half-life ($t_{1/2}$), apparent clearance (CL/F), apparent volume of distribution (V/F), and renal clearance of LY3405105 may be reported. Additional exploratory analyses will be performed if warranted by data and other validated PK software programs (for example, NONMEM) may be used if appropriate. The version of any software used for the analysis will be documented and the program will meet the Lilly requirements of software validation.

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

10.3.3.6. Biomarker Analyses

Biomarkers related to treatment, immune response, mechanism of action, and/or cancer will be measured and analyzed. The association of biomarker and clinical outcome will be assessed via single-marker and/or multi-marker analysis.

10.3.4. Interim Analyses

Because this is a dose-finding study, data will be reviewed on a dose level-by-dose level basis during the dose escalation, until the MTDs are determined. The purpose of these dose level-by-dose level reviews is to evaluate the safety data at each dose level and determine if a DLT has been observed that would suggest MTD has been met or exceeded. The investigators and the Lilly study team will make the determination regarding dose escalation based upon their review of the safety and tolerability data (and PK/PD data were available) as described in this protocol.

For Phase 1a, after all patients who are deemed evaluable for the assessment of dose levels complete DLT evaluation period or MTD is determined, an interim analysis for safety and PK will be conducted.

For Phase 1b, a safety review will be performed after the first 20 patients across all cohorts are enrolled and treated for 1 cycle, and then every 6 months afterward. The purpose of this safety review is to evaluate the safety and tolerability for each expansion cohort and determine if a dose-limiting equivalent toxicity (DLET) has been observed. For the first 20 patients enrolled into Phase 1b, if in 7 patients or more DLETs are observed, accrual may be temporarily paused, and the available data from Phase 1a and Phase 1b will be analyzed to potentially modify the RP2D, or the study. Considerations for stopping recruitment should be given after discussion with the investigator and the Sponsor.

Continued monitoring for safety and efficacy will occur in Phase 1b and if aggregate data suggest that continued enrollment is unlikely to alter the outcome or present an unreasonable risk to patients, enrollment into any one or all Cohorts 1-5 may be stopped.

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

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ARID1A	AT-rich interactive domain-containing protein 1A
AST	aspartate aminotransferase
ASCO	American Society of Clinical Oncology
AUC	area under the plasma concentration × time curve
BOR	best overall response
BRG1	Brahma-related gene 1
BRM	Brahma
CAP	College of American Pathologists
CDK	cyclin-dependent kinases
CI	confidence interval
CL/F	apparent clearance
CLIA	clinical laboratory improvement amendments
C_{max}	maximum concentration
CNS	central nervous system
collection database	A computer database where clinical study data are entered and validated.
CR	complete response
CrCl	creatinine clearance (CrCl)
CrI	credible interval

CRP	Clinical research physician: individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRS	clinical research scientist
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTD	C terminal domain
DCR	disease control rate: the percentage of patients with a best response of CR, PR, or SD.
DL	dose level
DLET	dose-limiting equivalent toxicity
DLT	dose-limiting toxicity
DoR	duration of response: the time from the date measurement criteria for CR or PR (whichever is first recorded) are first met until the first date that disease is recurrent or objective progression is observed, per RECIST v1.1 criteria, or the date of death from any cause in the absence of objectively determined disease progression or recurrence.
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
effective method of contraception	Male condom with spermicide, female condom with spermicide, diaphragm with spermicide, cervical sponge, or cervical cap with spermicide. Also see the definition of highly effective method of contraception.
Enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment and have received at least 1 dose of study treatment.
Enter	Patients entered in the study are those who have signed the ICF directly or through their legally acceptable representatives.
ERB	ethical review board
ES	epithelioid sarcoma
EU	European Union

EZH2	Enhancer of Zeste 2
FFPE	formalin-fixed paraffin-embedded
GCP	good clinical practice
G-CSF	granulocyte colony-stimulating factors
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	good laboratory practice
highly effective method of contraception	Combined oral contraceptive pill and mini-pill, NuvaRing®, implantable contraceptives, injectable contraceptives (such as Depo-Provera®), intrauterine device (such as Mirena® and ParaGard®), contraceptive patch for women <90 kg (<198 pounds), total abstinence, or vasectomy. Also see the definition of effective method of contraception.
HNSTD	highest non-severely toxic dose
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference for Harmonization
Ig	immunoglobulin
INI1	integrase interactor 1
interim analysis	An analysis of clinical study data that is conducted before the final reporting database is authorized for data lock.
Investigational product	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, marketed products used for an unauthorized indication or marketed products used to gain further information about the authorized form.
IRB	institutional review board
ISO/IEC	International Organization for Standardization / International Electrotechnical Commission
KDM6A (UTX)	lysine demethylase 6A
KMT2C (MLL3) gene	lysine methyltransferase 2C
KMT2D (MLL2) gene	histone-lysine-methyltransferase 2D

LC-MS/MS	liquid chromatography-tandem mass spectrometry
Lilly	Eli Lilly and Company
LOF	loss of function
LPS	Lansky performance score
MedDRA	Medical Dictionary for Regulatory Activities
MSK-IMPACT	Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets
MTD	maximum tolerated dose
MWF	Monday, Wednesday, and Friday
NGS	next-generation sequencing
N-CRM	Bayesian model-based toxicity method
open label	A study in which there are no restrictions on knowledge of treatment allocation; therefore, the investigator and the study participants are aware of the drug therapy received during the study.
ORR	overall response rate: the percentage of patients who achieve a BOR of CR or PR
OS	overall survival
PD	pharmacodynamic(s)
PDX	patient-derived xenografts
PET	positron emission tomography
PFS	progression-free survival: the time from the date of start of treatment until the first radiographic documentation of progression or death from any cause in the absence in progressive disease.
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PO	orally
PR	partial response
PRC2	polycomb repressive complex 2
PR/CR	partial response/complete response
QD	once daily
QOD	every other day

RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	To screen a patient who was previously declared a screen failure for the same study.
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirement to become part of a pool of potential candidates for participation in a clinical study.
screen failure	A patient who does not meet one or more criteria required for participation in a study.
SD	stable disease
SMARCA2 (BRM)	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2
SMARCA4 (BRG1)	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 4
SMARCB1 (INI1)	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1
SNF	sucrose non-fermentable
SOC	system organ class
SS	synovial sarcoma
SS18	SS18 subunit of BAF chromatin remodeling complex
SSX	SSX family member
SUSAR	suspected unexpected serious adverse reactions
SWI/SNF	SWItch/Sucrose Non-Fermentable complex
TBL	total bilirubin
TEAE	treatment-emergent adverse event: an untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TIW	3 times per week

TNBC	triple-negative breast cancer
TTR	time to response
TTS	Tuesday, Thursday, and Saturday
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology – Laboratory[a]	Local	Central
Leukocytes (WBC)	X	
Neutrophils[b]	X	
Lymphocytes	X	
Monocytes	X	
Eosinophils	X	
Basophils	X	
Erythrocytes (RBC)	X	
Hemoglobin (HGB)	X	
Hematocrit (HCT)	X	
Mean corpuscular volume (MCV)	X	
Mean corpuscular hemoglobin concentration (MCHC)	X	
Platelets (PLT)	X	
Coagulation – Laboratory		
Activated partial thromboplastin time (aPTT) or partial thromboplastin time (PTT)	X	
International normalized ratio (INR) or prothrombin time (PT)	X	
Clinical Chemistry – Laboratory		
Serum Concentrations of:		
Alanine aminotransferase (ALT)	X	
Albumin	X	
Alkaline phosphatase	X	
Aspartate aminotransferase (AST)	X	
Bilirubin, direct	X	
Bilirubin, total	X	
Blood urea nitrogen (BUN) or blood urea	X	
Calcium	X	
Creatinine	X	
Glucose (random)	X	
Magnesium	X	
Potassium	X	
Protein	X	
Sodium	X	
Urinalysis – Laboratory		
Blood	X	
Glucose	X	
Ketones	X	
pH	X	
Protein	X	
Specific gravity	X	
Urine leukocyte esterase	X	
Pregnancy Test (for Female Patients of Childbearing Potential) –Laboratory		
Urine pregnancy test	X	

Abbreviations: CRF = case report form; Intl = international; RBC = red blood cells; WBC = white blood cells.

[a] Treatment decision will be based on local laboratory results.

[b] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. When a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

Appendix 3. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary
- ensuring that informed consent is given by each patient. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any study protocol procedures and prior to the administration of study treatment.
- 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 the patient's participation in the study.
- providing a copy of the ICF to the patient and retaining a copy of the signed ICF in the site file.

Ethical Review

Documentation of ERB/IRB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve all ICFs, including any changes made by the ERBs/IRBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERB/IRB should be provided with the following:

- The protocol, protocol amendments, relevant protocol addenda, the current IB, and updates during the course of the study
- ICF
- Other relevant documents (for example, curricula vitae, advertisements).

Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- the ICH GCP guideline
- applicable laws and regulations

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

Some of the obligations of Lilly will be assigned to a third-party organization.

Investigator Information

Physicians with a specialty in oncology will participate as investigators in this clinical study.

Protocol Signatures

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

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

Final Report Signature

The CSR coordinating investigator will sign the final CSR 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 participation will serve as the final CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

Lilly's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate
- provide Sponsor start-up training to instruct the investigators and study coordinators. This training 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 verify data reported to detect potential errors.

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

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 Lilly, applicable regulatory agencies, and applicable ERBs with direct access to the original source documents.

Data Capture Systems

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor.

An electronic data capture (EDC) system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the Sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the Sponsor-provided data capture system(s) will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports/electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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

Study and Site Closures

Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB/IRB of the study site judges it necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4. Restricted and Prohibited Concomitant Medications

The table below describes the drug class and associated medications that will be restricted during the study treatment period. Patients who, in the assessment by the investigator, require the use of any of the prohibited treatments for clinical management should be removed from the study.

This is not an all-inclusive list. In general, strong CYP3A4 inhibitors, strong inducers of CYP3A4, or P-gp, are restricted during the study treatment period.

Strong Inhibitors of CYP3A4
All HIV protease inhibitors
Boceprevir
Clarithromycin
Conivaptan
Danoprevir and ritonavir
Diltiazem
Elvitegravir and ritonavir
Idelalisib
Itraconazole
Ketoconazole
Nefazodone
Paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)
Posaconazole
Telaprevir
Troleandomycin
Voriconazole
Strong Inducers of CYP3A4
Aminoglutethimide
Apalutamide
Avasimibe
Carbamazepine
Enzalutamide
Fosphenytoin
Lumacaftor
Mitotane
Phenobarbital
Phenytoin
Rifabutin
Rifampicin (rifampin)
Rifapentine
St. John's wort

Abbreviation: HIV = human immunodeficiency virus.

Appendix 5. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin (HGB)	
Hematocrit (HCT)	**Hepatic Coagulation[a]**
Erythrocytes (RBC)	Prothrombin time (PT)
Leukocytes (WBC)	Prothrombin time, INR
Neutrophils[b]	
Lymphocytes	**Hepatic Serologies[a,c]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets (PLT)	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	
Alanine aminotransferase (ALT)	**Recommended Autoimmune Serology:**
Aspartate aminotransferase (AST)	Anti-nuclear antibody[a]
Gamma-glutamyl transferase (GGT)	Anti-smooth muscle antibody[a]
Creatine phosphokinase (CPK)	Anti-actin antibody[a]

Abbreviations: Ig = immunoglobulin; IgG = immunoglobulin G; IgM = immunoglobulin M; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by local laboratory.

[b] Neutrophils reported by automated differential hematology instruments include both segmented and band forms. Whenever a manual differential is needed to report the neutrophils, the segmented and band forms should be added together and recorded on the CRF, unless the CRF specifically provides an entry field for bands.

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

Appendix 6. Creatinine Clearance Formula

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

For serum creatinine concentration in mg/dL:

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

For serum creatinine concentration in μmol/L:

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

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

Source: Cockcroft and Gault (1976).

Appendix 7. Statistical Details for Dose Escalation

Dose escalation will be driven by safety. A model-based method that incorporates prior expectations about the dose-toxicity curve and controls for over-dosing probability will be applied to the data at the end of each dose level, which will provide quantitative guidance to the investigators and Lilly CRP to help determine the next dose level.

The model to be utilized is a two-parameter logistic model (Neuenschwander et al. 2008). For example, the 2 parameters follow a bivariate normal distribution with minimally informative prior distribution, μ_1=-3.88, μ_2=-0.11, σ_1=2.85, σ_2=0.17, ρ=-0.88 if the prior parameters are set such that the median probability of DLT at the 1 mg dose is 0.01 (95% CrI 0.0 to 0.85), and the median probability of DLT at the 30 mg dose is 0.28 (95% CrI 0.0 to 0.95). In the logistic model, the reference dose is set at dose level 1 (1 mg).

The posterior probability of a DLT at each dose level will be categorized to 4 bands, defined as:

- Under-dosing: the probability of a DLT at a given dose level in (0, 0.20)
- Targeted toxicity: the probability of a DLT at a given dose level in (0.20, 0.33)
- Excessive toxicity: the probability of a DLT at a given dose level in (0.33, 0.60)
- Unacceptable toxicity: the probability of a DLT at a given dose level in (0.60, 1.00)

The model aims to recommend a dose which maximizes the probability of targeted toxicity, while controlling the probability of excessive or unacceptable toxicity to less than 25% and controlling the probability of unacceptable toxicity to less than 5%. The probability of excessive or unacceptable toxicity is changed to 40% after Cohort 8. The maximum increment of escalation will be no more than 100%. The exact increment will be determined by the investigators and Lilly CRP/CRS and may be less than the model prediction or <100%.

Simulations were conducted using FACTs v6.0 to verify the operating characteristics of the model-based dose escalation. Three scenarios were considered with varying DLT rates across the dose range, representing 3 different toxicity profiles, where Scenario 2 is the same as the prior probabilities used to derive the bivariate normal distribution used in the 2-parameter logistic model.

The proportion of simulated trials for which the selected MTD was truly in the target range (DLT rate 0.20-0.33) was approximately 63%, 49%, 32%, for each scenario, respectively. The proportions of simulated trials for which the selected MTD is truly in the excessive and unacceptable range (DLT rate 0.33-1) were 10%, 16%, 13% for each scenario respectively. Overall, the method performs well in selecting the target dose(s) and controlling excessive/unacceptable doses based on the simulation results.

Appendix 8. Performance Scales

Eastern Cooperative Oncology Group (ECOG) Performance Scale

Grade	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.

Lansky Performance Status (<16 years old)

Score	Lansky Description
100%	Fully active, normal
90%	Minor restrictions in strenuous physical activity
80%	Active, but tired more quickly
70%	Greater restriction of play and less time spent in play activity
60%	Up and around, but active play minimal; keeps busy by being involved in quieter activities
50%	Lying around much of the day, but gets dressed; no active playing, participates in all quiet play and activities
40%	Mainly in bed; participates in quiet activities
30%	Bed bound; needing assistance even for quiet play
20%	Sleeping often; play entirely limited to very passive activities
10%	Does not play; does not get out of bed
0%	Unresponsive

Source: Lansky et al. 1987.

Appendix 9. Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment (b): (02 July 2020)
Based on the criteria set forth in Article 10 (a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, Amendment (b) is considered substantial.

Section # and Name	Description of Change	Brief Rationale
1. Synopsis 3.1. Study Rationale 4. Objectives and Endpoints	Objectives for Part 1b were added and updated.	Evaluation of the anti-tumor activity in the defined population in the Phase 1b portion was added.
1. Synopsis 5.1. Overall Design 7.1.1. Dose Escalation Phase (Phase 1a)	The intermittent dosing schedule in Part A2 will no longer be pursued in the study and was deleted.	Available safety and human exposure data support continuous daily dosing.
1. Synopsis 7.1.2. Dose Expansion Phase (Phase 1b)	Cohorts 6 and 7 have been deleted.	Updated study cohorts based on biologic rationale and to evaluate proof of concept in focused cohorts with a smaller number of patients.
1. Synopsis 7.1.2. Dose Expansion Phase (Phase 1b) 7.2.1. Selection and Timing of Doses 8.1. Discontinuation from Study Treatment	Patients with documented progressive disease may be allowed to continue LY3405105.	To allow patients with clinical benefit to remain on study if deemed appropriate by the treating physician.
1. Synopsis and subsequent sections 10.1. Sample Size Determination	Number of patients in Cohorts 1-4 was reduced in Phase 1b.	Study was revised as a focused signal finding study and a smaller number of patients will suffice to establish proof of concept.
1. Synopsis and subsequent sections 10.1. Sample Size Determination	Number of patients in Cohort 5 was increased in Phase 1b.	Due to the marker subgroups among bladder cancer patients, an increase in sample size to 30 in Cohort 5 provides sufficient number of patients in each subgroup.

Section # and Name	Description of Change	Brief Rationale
1. Synopsis 5.2. Number of Patients 10.1. Sample Size Determination	At the recommended Phase 2 dose (RP2D) in Phase 1a, up to 10 backfill patients may be enrolled, which increased the approximate overall number of patients from 54 to 64.	To further assess the safety and tolerability of the dose selected prior to advancing to the Phase 1b part of the study
1. Synopsis 2. Schedule of Activities	Schedule of activities was divided in Phase 1a and Phase 1b and updated to reflect less visits needed.	After establishing safety in Phase 1a, less frequent monitoring is adequate to maintain safety while balancing burden of patients and sites during Phase 1b dose expansion.
2. Schedule of Activities 9.6. Pharmacodynamics 9.8.3. Other Samples for Biomarker Research	Skin biopsies, peripheral blood mononuclear cell (PBMC) and urine pharmacokinetics (PK) have been deleted from Phase 1a schedule	There is no further planned analysis for additional samples.
1. Synopsis 9.8.2. Tumor Tissue Samples for Exploratory Biomarker Research	Archived tumor tissue samples should be sent to central laboratory within 28 instead of 45 days.	To avoid delays and missing samples available, samples will be required to be provided within Cycle 1.
1. Synopsis 6.1. Inclusion Criteria Appendix 8	Lansky Performance Status was added for patients ≤16 years old.	Better functional representation for patients <16 years of age.
6.1. Inclusion Criteria	Biomarker specifics have been updated to reflect reduced number of cohorts in Part 1b.	To align with the study population.
6.1. Inclusion Criteria [4] 5.6. Justification for Enrolling Patients ≥12 Years of Age	The age for patients in Cohorts 3 and 4 was lowered to ≥12 years of age with a body weight of ≥40 kg	Patient age was lowered to expand enrollment to young patients with sarcoma to evaluate LY3405105 efficacy.
6.1. Inclusion Criteria [6]	Calculated creatinine clearance as adequate renal function reduced from ≥60 mL/min to ≥50 mL/min.	Based on renal clearance observed in clinic, a lower cutoff for inclusion criteria is appropriate without impacting the safety of patients.
6.2. Exclusion Criteria [19] Appendix 4	Removed restriction for co-administer with P-glycoprotein (P-gp) inhibitor and strong inhibitors of active renal secretion.	Remove of P-gp inhibitor is based on human exposure variability and the potential saturation of P-gp at the potential RP2D. Remove of active renal secretion inhibitor is based on the observed renal clearance in clinic.

Section # and Name	Description of Change	Brief Rationale
7.1.1.1. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition	Grade 3/4 anemia was added to the DLT determination section.	To clarify the DLT definition in relation to anemia
7.1.1.2. Dose Escalation Method	The dose escalation scheme for Part A1 was modified.	Removing combination therapies throughout dose escalation and expansion.
9.8.1. Biomarkers Required for Eligibility Appendix 2	Central next generation sequencing testing for enrollment is no longer offered. Only local laboratory results will be used.	To avoid enrollment delays for patients or a high rate of screen failures.
10.3.1. Efficacy Analyses	Best overall response (BOR) and change in tumor size have been deleted.	The definition for ORR replaced BOR definition to refine or standardize the definition of endpoints. Change in tumor size is not part of the end point listed in the objective table, so there is no need to define it.
10.3.4. Interim Analyses	Interim analysis for Phase 1b was deleted.	Due to the reduction in sample size, an interim analysis is not expected to allow for appropriate decision making. Instead, safety and clinical response will be monitored on an ongoing basis without formal enrollment hold and interim analysis.
10.3.4. Interim Analyses	Interim analysis plan has been revised according to the revised study design.	Interim analysis plan has been revised to provide more details on monitoring the trial progress (both safety and efficacy).
Other minor editorial changes were made to add clarity and correct typos		

Amendment (a): (22 November 2018)
Based on the criteria set forth in Article 10 (a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, Amendment (a) is considered substantial.

Overall Rationale for the Amendment

Protocol J1F-MC-JZFA (a) Phase 1a/1b Study of LY3405105 Administered to Patients with Advanced Solid Tumors has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

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

- An addition to Section 3.2 adding more background information for ARID1A, KMT2C, KMT2D, and RB1.
- A clarification was made to inclusion Criteria 1, further clarifying that patients should have no available therapies known to confer a clinical benefit for their disease.
- A clarification was made to inclusion Criteria 8 to include patients who have discontinued any other investigational agents ≥4 weeks prior to enrollment or ≥5 half-lives since completion of previous investigational agent.
- A clarification was made to exclusion Criteria 13 further excluding patients recently enrolled in a clinical study involving an investigational product if the half-life of the investigational agent and time since receiving the agent are not medically compatible with the study.
- A correction was made to exclusion Criteria 17, excluding patients with a mean QT interval corrected for heart rate of ≥470 msec on screening ECG.
- An addition to exclusion Criteria 19 and Appendix 4, further excluding patients who have discontinued both strong inhibitors and inducers of CYP3A4 and P-glycoprotein.
- A clarification was made to the lifestyle restrictions restricting patients from all herbal supplements while on study.
- An addition to the DLT and MTD determination Section 7.1.1.1 adding total bilirubin >2 × ULN with ALT/AST >3 × ULN in the absence of cholestasis (alkaline phosphatase <2 × ULN).
- An addition to the DLT and MTD determination Section 7.1.1.1 adding certain Grade 2 AEs affecting vital organs.
- An addition to Table JZFA.7.2 adding further dose modifications in patients due to toxicities.
- A justification for skin biopsies was added to Sections 9.6 and 9.8.3.

- A clarification to Section 9.8.1.2 was added to clarify the anatomical site from which the specimen was collected cannot be specified, as Cohorts 3-7 are tumor agnostic and the archival specimen may be from a primary or metastatic site.
- Other minor editorial changes were made to add clarity.