MELVIN AND BREN SIMON CANCER CENTER
INDIANA UNIVERSITY

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A Phase 2 basket trial of an ERK1/2 inhibitor (LY3214996) in combination with abemaciclib for patients whose tumors harbor pathogenic alterations in BRAF, RAF1, MEK1/2, ERK1/2, and NF1

Principal Investigator: Anita Turk, MD
Division of Hematology/Oncology
Indiana Cancer Pavilion
535 Barnhill Dr., Suite RT130C
Indianapolis, IN 46202
Phone: 317-948-7576
aaturk@iu.edu

Collaborating Investigator: Bryan Schneider, MD
Division of Hematology/Oncology
Indiana University Simon Cancer Center
1030 W. Michigan St., Suite 3307
Indianapolis, IN 46202

Phone: 317-948-9510
bpschnei@iu.edu

Biostatistician: Yong Zang, PhD
Department of Biostatistics and Health Data Sciences
Indiana University School of Medicine
410 West 10th Street, Suite 3000
Indianapolis, IN 46202
Phone: 317-278-2108
zangy@iu.edu

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PROTOCOL SIGNATURE PAGE

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I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to Indiana University Simon Cancer Center and keep a record for your files.

_____ _____

Signature of Investigator Date

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Investigator Name (printed)

_____

Investigator Title

_____

Name of Facility

_____

Location of Facility (City and State)

_____ ☐ Not Submitting to IRB

Expected IRB Submission Date

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1 Synopsis

TITLE	A Phase 2 basket trial of an ERK1/2 inhibitor (LY3214996) in combination with abemaciclib for patients whose tumors harbor pathogenic alterations in BRAF, RAF1, MEK1/2, ERK1/2, and NF1.
PHASE	2
OBJECTIVES	**Primary Objective:** • To evaluate the proportion of patients with objective response to an ERK1/2 inhibitor (LY3214996) in combination with abemaciclib for patients whose tumors harbor pathogenic alterations in BRAF, RAF1, MEK1/2, ERK1/2, and NF1 **Secondary Objective:** • To evaluate the safety and tolerability of LY3214996 + abemaciclib as defined by CTCAE v5 criteria. • To evaluate the median progression-free survival (PFS). • To evaluate the duration of response (DOR). **Correlative Objectives:** • To identify potential predictive biomarkers beyond the genomic alteration by which treatment is assigned and/or resistance mechanisms. • To evaluate pharmacokinetic parameters of LY3214996 and abemaciclib.
STUDY DESIGN	Single arm, non-randomized, open-label
TOTAL NUMBER OF SUBJECTS	35
KEY INCLUSION CRITERIA	1. Patients must have histologically confirmed, metastatic/advanced cancer with tumors that harbor the following alterations as defined below using a CLIA-certified next-generation sequencing: a. Point mutations in BRAF, RAF1, MEK1/2, or ERK1/2 that have been previously characterized to be gain-of-function mutations. These mutations have to be specified as gain-of-function as listed in the OncoKB and/or JAX-CKB databases. i. Patients with NSCLC that harbor BRAF V600E treated with prior RAF and/or MEK inhibition therapy will be excluded ii. Patients with tumor types other than NSCLC that harbor BRAF V600E mutations who have been treated and progressed on prior BRAF and/or MEK inhibition will be included iii. Patients with NSCLC that harbor BRAF V600E will only be enrolled if they are not a candidate for FDA approved therapy b. Amplification of RAF1 defined as > 6 copies of the respective gene. c. Gene fusions in which BRAF, RAF1, MEK1/2 or ERK1/2 is a fusion partner; in which the fusion is determined to be in-frame; and the kinase domain of BRAF, RAF1, MEK1/2, or ERK1/2 is retained. d. Point mutations, frameshift insertions/deletions, splice site mutations, or stop gain mutations that results in loss-of-function of NF1.

	2. Measurable, metastatic disease amenable to biopsy. If biopsy is deemed unsafe at time of procedure, patients will remain eligible for study. 3. ECOG performance status 0 or 1. 4. Laboratory evidence of adequate organ function and hematologic function. 5. Patients with untreated brain metastases are excluded. However, patients with metastatic CNS tumors may participate in this trial, if the patient is > 4 weeks from therapy completion (incl. radiation and/or surgery), is clinically stable at the time of study entry and is receiving a stable or decreasing dose of corticosteroid therapy. Brain MRI or head CT is required at screening for patients with known brain metastases. 6. Patients who have received prior treatment with an ERK kinase inhibitor are excluded
TREATMENT PLAN	Abemaciclib 150 mg orally twice daily with LY3214996 200 mg orally daily until disease progression, unacceptable toxicity, or patient preference to withdraw from study.
STATISTICAL CONSIDERATIONS	The primary end point is overall response rate (ORR), where overall response is defined as the complete or partial response per RECIST v1.1 criteria. We will use the one stage design for the phase II trial. We will specify the null hypothesis that the true ORR is 5% versus the alternative hypothesis that that the true ORR is 19% using a one-sided test with the designing parameters type-I error=0.05 and type II error=0.2 (power=80%). A total sample size of 28 evaluable patients will be accrued. Of note, an evaluable patient is defined as a patient who receives at least one dose of trial drug. Assuming a 20% drop-out rate, it is anticipated that the total accrual would be 35 patients. An additional early stopping rule for futility will be used to monitor the following subgroups of patients with pathogenic alterations in 1) BRAFV600E 2) BRAF nonV600E, RAF1 3) MEK1/2, ERK1/2 and 4) NF1 based on the Bayesian posterior probability.
ESTIMATED ENROLLMENT PERIOD	12 months
ESTIMATED STUDY DURATION	18 months

2 Schedule of Activities

Table 2.1 presents the schedule of activities for patients receiving LY3214996 in combination with abemaciclib.

Table 2.1 Schedule of Activities

Study Evaluation Cycle = 28 days	Screening	Cycle 1		Cycle 2		Cycle 3 and beyond	Safety follow up visit
	-21 ± 7 days	Day 1	Day 15 ± 3 days	Day 1 ± 3 days	Day 15 ± 3 days	Day 1 ± 7 days	30 days (±7) post last dose
REQUIRED ASSESSMENTS							
Informed Consent	X						
Demographics	X						
Medical History[A]	X						
Concomitant Medications	X	X		X		X	X
Physical Exam	X	X	X	X	X	X	X
Vital signs and ECOG Performance Status	X	X	X	X	X	X	X
Height	X						
Weight	X	X	X	X	X	X	X
Adverse Event Evaluation[B]	X	X	X	X	X	X	X
LABORATORY ASSESSMENTS							
Complete Blood Cell Count with differential (CBC)[J]	X	X	X	X	X	X	X
Comprehensive Metabolic Profile (CMP)[C]	X	X	X	X	X	X	X
Pregnancy test (serum or urine) (WOCBP)[D]	X	X		X		X	X
DISEASE ASSESSMENT							
CT of chest[E]	X					X	
CT or MRI of abdomen and pelvis[E]	X					X	
TREATMENT EXPOSURE							

Study Evaluation Cycle = 28 days	Screening	Cycle 1		Cycle 2		Cycle 3 and beyond	Safety follow up visit
	-21 ± 7 days	Day 1	Day 15 ± 3 days	Day 1 ± 3 days	Day 15 ± 3 days	Day 1 ± 7 days	30 days (±7) post last dose
LY3214996 and abemaciclib[F]		X	X	X	X	X	
SPECIMEN COLLECTION							
Tissue biopsies at screening and at progression[G]	X						X
Blood sample for plasma ctDNA		X		X		X	X
Blood for germline mutations	X						
Pharmacokinetics (PK)[H]			X	X			

A: Medical history to include prior treatments, radiation and surgical history. Diagnosis and staging to include pathology report and Tumor Node Metastasis (TNM) staging 8th edition.
B: CTCAE Version [5.0] Adverse Events will be colleted from the time informed consent is signed through 30 days after the last dose of study treatment.
C: To include albumin, alkaline phosphatase, ALT, AST, bicarbonate, BUN, calcium, chloride, creatinine, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total bilirubin, and total protein.
D: All females of childbearing potential must have a negative blood or urine pregnancy test within 14 days prior to enrollment and prior to treatment on day 1
E: CT or MRI scans of chest and abdomen will be done at baseline to assess the response per RECIST v1.1 criteria. CTs or MRIs of the abdomen with IV contrast are encouraged but will be done at the investigator's discretion. Disease assessments should be completed every odd cycle (i.e. cycle 3, cycle 5, etc.).
F: Antiemetic prophylaxis will be required in cycle 1 in an effort to improve patient safety and reduce the incidence of nausea and vomiting. Refer to Section 8.6.1.3 for details.
G: Biopsy at screening is mandatory if deemed safe by the treating physician and should be completed following determination of eligibility, ≤14 (+/- 7) days before start of treatment. Patients unable to undergo the screening biopsy may donate archived tissue if available. See Section 10.5.2 for details. Biopsy at time of progression is not mandatory.
H: Plasma samples for pharmacokinetics will be collected on cycle 1 day 15 and cycle 2 day 1 prior to dosing of abemaciclib and LY3214996. Please refer to Section 10.3.
I: Vital signs to be performed per standard of care and should include heart rate, blood pressure, respiratory and oxygen saturation
J: To include WBC, ANC, platelets, and Hgb

3 Introduction

3.1 Study Rationale

3.1.1 Rationale for Investigation of LY3214996, an ERK1/2 Inhibitor

The mitogen-activated protein kinase (MAPK) pathway is a key regulator of cellular proliferation and survival. Abnormalities of the MAPK pathway including alterations in BRAF, RAS, Neurofibromin-1 (NF1), and MEK are common in many cancers including melanoma, colorectal cancer (CRC), non-small cell lung cancer (NSCLC), pancreatic ductal adenocarcinoma (PDAC), ovarian cancer, and many others. Extracellular signal regulated kinase (ERK) is a downstream member of this pathway and plays a central role in transmitting extracellular signals from activated receptor tyrosine kinases (RTKs) such as epidermal growth factor receptor (EGFR), FGFR, PDGFR, VEGFR, and others. When activated, ERK1/2 phosphorylates RSK1, and regulates several additional downstream cytoplasmic and nuclear targets involved in cell cycle, cell proliferation, cell growth, and cell survival.

The feasibility of pharmacologic inhibition of the MAPK pathway in cancer has been shown through the success of BRAF and MEK inhibitors in the treatment of various cancer subtypes especially patients who harbor *BRAF* mutations. Two BRAF kinase inhibitors, vemurafenib and dabrafenib, are approved in the United States (US), Australia and several European countries for the treatment of melanoma patients with $BRAF^{V600E}$ mutation. Two MEK kinase inhibitors – trametinib alone, and in combination with a BRAF inhibitor, dabrafenib, and cobimetinib, in combination with a BRAF inhibitor, vemurafenib – are approved by the Food and Drug Administration (FDA) for the treatment of unresectable or metastatic melanoma patients with $BRAF^{V600E/K}$ mutations that have not received previous treatment with a BRAF inhibitor. However, while BRAF and MEK inhibitors have proven effective in these patient populations, most patients eventually develop drug resistance, which leads to disease relapse (Samatar et al. 2014). Most resistance mechanisms to RAF and MEK inhibitors result in reactivation of ERK1/2; therefore, blockade of ERK1/2 directly is postulated to overcome many of the current limitations of RAF and MEK inhibitors. In addition, RAF and MEK inhibitors remain ineffective in RAS-mutant cancers. Neurofibromin-1, a tumor suppressor gene, is a negative regulator of RAS. Loss of function of NF1 has been linked to the development of tumors in mice (Jacks et al. 1994). Neurofibromin-1 deletions and mutations are common in cancers and may recapitulate RAS mutations and represent an attractive target in the MAPK pathway (Jacks et al. 1994; Yap et al. 2014). LY3214996 is a potent inhibitor of ERK1/2 kinases that can potentially obviate resistance mechanisms in cancers that harbor BRAF, RAS, NF1, MEK, and other MAPK alterations. A general introduction of LY3214996 is provided in Section 3.2.1. Detailed information about LY3214996 is provided in the Investigator's Brochure (IB).

3.1.2 Rationale for Combination Therapy

Activating mutations in *BRAF* and *KRAS*, key signaling components of the MAPK pathway, are among the most common oncogenic mutations in human cancers, occurring in ~7% and ~20% of all cancers. The frequency in common cancer histologies such as NSCLC, PDAC, CRC and melanoma (Oikonomou et al. 2014.). Genome and transcriptome wide analysis in various cancers demonstrated a diversity of altered pathway targets and feedback mechanisms that

contribute to disease pathogenesis and resistance. In MAPK driven cancers, this may explain the lack of success in *RAS* mutant tumors, limited efficacy of cancer agents in many *BRAF* mutant tumors and toxicities experienced by patients due to paradoxical signaling when these agents are given as a single agent. The feasibility and usefulness of combining agents that affect targets within the MAPK pathway has been clearly demonstrated by the success of combining BRAF and MEK inhibitors (vemurafenib and cobimetinib or dabrafenib with trametinib) in $BRAF^{V600E/K}$ mutant melanoma patients, improving not just response rates and duration of response but in reducing the rates of certain therapy related toxicities. This underscores the importance of combination therapy in MAPK driven tumors.

3.1.2.1 Rationale for Exploring Combination Therapy with Abemaciclib in Tumors with Gain-of-Function Alterations in BRAF, RAF1, MEK1/2, and ERK1/2

3.1.2.1.1 ***Abemaciclib Background/Rationale***

Abemaciclib is an orally bioavailable selective cyclin-dependent kinase (CDK) 4 and 6 inhibitor currently FDA approved as monotherapy and in combination with endocrine therapy in hormone-receptor positive breast cancer. It causes cell cycle arrest in Rb-proficient cells and has significant in vivo antitumor activity in several human cancer xenograft models (Spring et al. 2016). Abemaciclib crosses the blood brain barrier and has been shown to inhibit the growth of intracranial tumors both as a single agent and in combination with temozolomide (Raub et al. 2015). In a $KRAS^{G12V}$ mouse model, a synthetic lethal interaction between the $KRAS^{G12V}$ mutation and ablation of CDK4 was observed (Puyol M et al. 2010). Ablation of CDK4 leads to immediate senescence response in the lung tumors of $KRAS^{G12V}$ animals. Increased sensitivity to abemaciclib has been observed preclinically both in in vitro and in vivo models of *KRAS* mutant NSCLC.

Abemaciclib has been or is currently being investigated in clinical trials

- Phase 1 study of abemaciclib for advanced NSCLC, breast cancer, and other solid tumors
- Phase 1 study of abemaciclib for Japanese patients with advanced cancer
- Phase 1b study of abemaciclib in combination with endocrine or targeted therapies for patients with advanced breast cancer
- Phase 1b study of abemaciclib in combination with another anti-cancer drugs for patients with NSCLC
- Phase 2 study of abemaciclib in relapsed or refractory mantle cell lymphoma
- Phase 2 Study of abemaciclib for patients with previously treated hormone receptor positive (HR+), HER2 negative metastatic breast cancer
- Phase 2 study for patients with brain metastasis secondary to HR+ breast cancer, NSCLC, or melanoma
- Phase 2 neoadjuvant study of abemaciclib for postmenopausal women with HR+, HER2 negative breast cancer (neoMONARCH)
- Phase 2 study of abemaciclib versus docetaxel for patients with stage intravenous (IV) squamous NSCLC previously treated with platinum-based chemotherapy
- Phase 3 study of fulvestrant with or without abemaciclib for patients with HR+, HER2 negative locally advanced or metastatic breast cancer (MONARCH 2)
- Phase 3 study of nonsteroidal aromatase inhibitors with or without abemaciclib in patients with HR+, HER2 negative locally advanced or metastatic breast cancer (MONARCH 3)

- Phase 3 study of abemaciclib plus best supportive care (BSC) versus erlotinib plus BSC for patients with stage IV NSCLC with a detectable KRAS mutation who have progressed after platinum-based chemotherapy (JUNIPER)

The safety profile of abemaciclib has been manageable when given as monotherapy or in the combinations investigated to date.

The Phase 2 MONARCH 1 study treated patients with endocrine resistant, hormone-receptor positive breast cancer with single-agent abemaciclib dosed at 200mg twice a day (N=132). Safety data from this study showed the most common treatment-emergent adverse events (TEAEs) (≥20%) that occurred in patients included diarrhea (90.2%), fatigue (65.2%), nausea (64.4%), decreased appetite (45.5), abdominal pain (38.6%), vomiting (34.8%), neutropenia (37.1%), anemia (25.0%), headache (20.5%) and thrombocytopenia (20.5%) (IB; Lilly 2019). More information about the known and expected benefits, risks and reasonably anticipated adverse events (AEs) may be found in the abemaciclib IB (IB; Lilly 2019).

3.1.2.1.2 *Rationale for Exploring Combination Therapy with Abemaciclib*

The importance of combination therapy to target various aspects of cancer pathogenesis has become more evident in an attempt to facilitate anti-tumor activity or to overcome acquired resistance in cancer. The RAF/MEK/ERK pathway is commonly mutated in a variety of solid tumors. While mutations in *BRAF* are the most common, particularly codon 600, a variety of additional mutations in the pathway have been identified that lead to pathway activation. Many of these mutations are uncommon but may lead to sensitivity to ERK inhibition. A recently published example of a patient with gallbladder cancer that harbored a rare gain-of-function *BRAF* L485W achieved a complete response with the ERK inhibitor, Ulixertinib (Sullivan et al. Cancer Discovery 2018). Unpublished preclinical data from Eli Lilly has demonstrated that gain-of-function mutations in MEK1/2 rendered cell lines sensitive to ERK inhibition. Open questions include ERK inhibitor sensitivity to other classes of mutations including *BRAF* fusions and *RAF1* amplification. Further, it is not known whether ERK inhibition may play a role in patients with *BRAF* mutations who have become resistant to BRAF inhibition.

Mitogens that stimulate the RAS-MAPK pathway are known to induce expression of D-type cyclins via the activation of downstream transcription factors in the AP1 or ETS family, which in turn activate CDK4 and CDK6, promoting cell cycle progression (Sherr 1996; Klein and Assoian 2008). Therefore, concomitant inhibition of the MAPK pathway exemplified by ERK inhibitors may augment the antitumor activity of CDK4 and 6 inhibitors like abemaciclib. Previous published data has also demonstrated that CDK4/6 inhibition is synergistic with inhibition of the MEK/ERK pathway (de Leeuw et al. Clin Can Res. 2018, Hart LS et al. Clin Can Res. 2016). To this end, Lilly has an ongoing phase I trial combining LY3214996 with Abemaciclib (CDK4/6 inhibitor) for which an RP2D of the combination is established at LY3214996 200 mg orally daily with abemaciclib 150 mg orally twice daily.

The manageable clinical safety profile of abemaciclib and preclinical safety data for LY3214996, coupled with the additive effects of the combination pre-clinical data provide the rationale for clinically evaluating the combination of LY3214996 and abemaciclib in the clinical setting in

tumors with overactivated MAPK pathyway identified via pathogenic alterations in *BRAF*, *RAF1*, *MEK1/2*, *ERK1/2*, and *NF1*.

Expected overlapping toxicities of the combination include nausea, vomiting, fatigue, diarrhea, decreased appetite, blood creatinine increase, and alanine aminotransferase increased. Though rash is not considered an overlapping toxicitiy, an increased incidence of maculo-papular rash and dermatitis acneiform was observed in the combination during dose escalation of the phase 1 JUAB study.

3.2 Background

3.2.1 General Introduction to LY3214996

LY3214996 is an adenosine triphosphate (ATP) competitive inhibitor of ERK2 with a Ki of 0.064 nM and ERK1 with a Ki of 0.65 nM. LY3214996 has solubility (FasSIF) of 0.113, high free fraction (0.39) and D_{ABS} (742-1570 mg) above the projected human efficacious dose (50-350 mg, QD). LY3214996 has acceptable ADME properties and a manageable toxicology profile. LY3214996 has a >40-fold selectivity compared to the nearest most potent kinase when tested against 464 kinases in a kinome profile.

3.2.1.1 Mechanism of Action and In Vitro/In Vivo Activity

LY3214996 is an ATP competitive, selective inhibitor of ERK1 and ERK2 with comparable biochemical IC_{50} values of 5 nM for each. Ki for ERK1-2P is 650 pM and Ki for ERK2-2P is 64 pM. It inhibits cellular phospho-RSK1 (T359/S363) in *RAF* and *RAS* mutant cancer cell lines. In Cancer Cell Sensitivity Profiling (CCSP) of 535 cell lines, LY3214996 showed higher sensitivity in a majority of cell lines with MAPK pathway mutations compared to cells lines that do not harbor MAPK pathway mutations. It inhibits cell proliferation and leads to significant tumor growth inhibition/regression in preclinical models of CRC (*KRAS* G13D mutant HCT116, *BRAF*^{V600E} mutant Colo205, *MEK1* Q56P mutant SW48), melanoma (*NRAS* Q61K mutant SK-MEL-30, vemurafenib-resistant *BRAF*^{V600E} mutant A375), NSCLC (*KRAS* Q61K mutant Calu-6), PDAC (*KRAS* G12C mutant MiaPaCa-2, *BRAF*^{V600E} mutant PDX PAXF2196) and AML (*KRAS* Q61L mutant HL-60).

In addition, combination with various agents showed preclinical activity across a range of tumor types: gemcitabine in PDAC (*KRAS* G12V mutant Capan-2), abemaciclib in PDAC (*KRAS* G12V mutant Capan-2, *KRAS* G12D mutant HPAF-II) and NSCLC (*KRAS* G12C mutant H2122, *KRAS* G12S mutant A549, *KRAS* G12V mutant H441) and CRC (*KRAS* G13D mutant HCT116) and CHK1 inhibitor in PDAC (*KRAS* G12V mutant Capan-2).

3.2.1.2 Nonclinical Pharmacokinetics/Pharmacodynamics

Nonclinical pharmacokinetics (PK) of LY3214996 were characterized in rats and dogs following IV and oral doses. Following oral administration, absorption was rapid in the rat and moderate in the dog, with mean oral bioavailability ranging from 25.9% to 72.7%. Following IV administration, clearance was less than hepatic blood flow in both rat and dog. The volume of distribution ranged between 1.32 and 2.03 L/kg. Half-life ($t_{½}$) ranged from 0.51 to 1.63 hours. Toxicokinetics of LY3214996 were determined in male and female rats and dogs following LY3214996 oral administration for up to 28 days. Exposure of LY3214996 increased with dose level, with no evidence of accumulation upon multiple dosing.

Preliminary studies evaluated the in vitro metabolism of LY3214996 in mouse, rat, dog and human liver microsomes and cryopreserved hepatocytes, as well as in rat and dog plasma and urine following a single oral dose. The in vitro results were generally predictive of the significant metabolic pathways observed in vivo. Metabolism of LY3214996 appeared to be primarily oxidative in nature, with some minor subsequent glucuronide conjugation observed. A direct response relationship adequately described the PK-pRSK inhibition in mouse Colo205 and rat and mouse HCT116 tumor models. The predicted IC_{50} values in human were 73 nM, 459 nM and 760 nM, respectively, after correction for species differences in protein binding. Assuming a desired level of target inhibition of greater than 50% for at least 6-8 hours per day, human PK simulations suggest that doses of 50 mg (90% prediction interval 20-105 mg) to 350 mg (90% prediction interval 140-740 mg) and above are expected to fulfill these conditions.

3.2.1.3 Nonclinical Toxicology

LY3214996 was evaluated in 1-month daily oral dosing toxicity studies in Sprague-Dawley rats and Beagle dogs (with 1 month reversibility in mid-dose animals) at tolerated dose levels as well as at dose levels that exceeded the maximum tolerated dose (MTD). Safety pharmacology parameters were evaluated in vitro and as part of the repeat-dose toxicity study in dogs. Genetic toxicity was evaluated in a bacterial mutation (Ames) assay. Results from these studies have identified a starting dose that is anticipated to be safe in patients. Based on nonclinical study findings, potential toxicities include: Gastrointestinal (GI) inflammation, fecal changes, emesis, dehydration, sores on gums, scabs on skin, and clinical pathology changes including increased neutrophils and monocytes, decreased lymphocytes, decreases in red cell mass, decreased albumin, increased globulin and/or increases in serum phosphorus. Injury to the long bones (femur and tibia) and female reproductive tract (ovary) and effects in the skin were also observed in rats only. With the exception of effects on skin, bone and ovaries, all findings either recovered or showed evidence of recovery after a 1 month reversal period.

The toxicity of LY3214996 was assessed after daily administration for 1 month in rats (5, 15 and 30 mg/kg) and dogs (3, 10 and 20 mg/kg). In rats, the MTD was 15 mg/kg due to all females in the 30-mg/kg/day group being either found dead or euthanized due to clinical signs from Days 17-20. One male rat (in the Toxicokinetic subgroup) given 30 mg/kg was euthanized on Day 28 (the day before scheduled sacrifice).

In dogs, the MTD was 10 mg/kg, due to preterminal euthanasia at 20 mg/kg. Three dogs given 20 mg/kg (2 males and 1 female) were euthanized on Day 13 due to compound-related clinical observations including hunched posture, thin appearance, emesis, hypoactivity, excessive salivation, vomitus, liquid and mucoid feces, entire body cold to the touch, and visible sores on the gums. The remaining animals given 20 mg/kg (1 male and 2 female) were euthanized on Day 14 with clinical observations that were similar to those euthanized on Day 13. One female dog given 10 mg/kg was put on a dosing holiday on Days 15 and 16 due to clinical observations of emesis, excessive salivation, vomitus, red/nonformed feces and 0.7 kg loss in body weight (8.8% decrease) from Days 11 to 15. The animal's body condition and appetite rebounded quickly and by Day 17 it had regained nearly all of the lost weight (0.6 kg). The animal resumed dosing at 10 mg/kg on Day 17 and remained on study to its scheduled sacrifice. Other clinically monitorable changes occurring in dogs given ≥10 mg/kg and rats given ≥15 mg/kg included

increases in increased neutrophils and monocytes, decreased lymphocytes, decreases in red cell mass, decreased albumin, increased globulin and/or increases in serum phosphorus.
The dose limiting toxicity (DLT) in dogs at 20 mg/kg/day was identified microscopically as GI toxicity (including acute inflammation, necrosis, erosion/ulcer and crypt dilatation). There were no similar findings in the GI tract in rats. At 10 mg/kg in dogs, increased incidence of crypt dilatation in the duodenum was noted at 10 mg/kg in dogs; however this finding was of a lesser severity and incidence than in animals given 20 mg/kg and resolved during the recovery phase.
In rats, the dose limiting toxicity at 30 mg/kg in female rats was identified microscopically as soft tissue mineralization. Mineralization was observed in female rats given 30 mg/kg, correlating with mildly to moderately higher serum phosphorous concentrations noted in animals given ≥15 mg/kg. Mineralization of multiple tissues was considered the primary cause of morbidity. Soft tissue mineralization is considered to be the result of calcium:phosphorus imbalance due to inhibition of the FGF23 pathway. MEK inhibitors have shown this effect nonclinically through FGF-23 signal blockade in the kidneys of rats, which leads to transcriptional upregulation of 25-hydroxyvitamin D(3) 1-alpha-hydroxylase, the rate-limiting enzyme in vitamin D activation. Blocking FGF-23 signaling also leads to down regulation of 1,25-dihydroxyvitamin D(3) 24-hydroxylase, the enzyme responsible for starting degradation of the active form of vitamin D leading to hyperphosphatemia but this has not appeared to translate at clinical doses (Diaz et al. 2012; Carvajal et al. 2014; Larkin et al. 2014; Long et al. 2016). Clinical monitoring for increased serum phosphorus will help mitigate the concern for tissue mineralization.

In female rats, microscopic findings of decreased numbers of the corpora lutea and the presence of retained follicles were observed in the ovary of females given ≥5 mg/kg, correlating with decreased ovary weight parameters in females given 15 mg/kg. While the effect on ovarian weights reversed during the recovery period, microscopic effects in the ovary were still present in recovery female rats given 15 mg/kg. These effects of decreased corpora lutea and retained follicles were considered adverse to fertility, but not to the overall health of the female rat. Non-clinical findings indicate that LY3214996 may adversely influence human female fertility.
In rats, microscopic findings were observed in the skin of rats given ≥15 mg/kg (including epidermal hyperplasia and inflammation). Effects observed in the skin did not show evidence of recovery after a 1 month reversal period.

In rats, microscopic findings of physeal hypertrophy and increased primary spongiosa were observed in the femur and tibia of males given ≥15 mg/kg and in females given ≥5 mg/kg. The finding of physeal hypertrophy was not present in recovery sacrifice rats whereas increased primary spongiosa was still evident after a 1 month reversal period. These effects on bone are only expected to occur in growing bone (for example, in juveniles) and are not relevant for an adult population.

In an in vitro hERG (human ether á-go-go-related gene) assay, the half-maximal inhibitory concentration (IC50) was 28.1 μM. This IC50 is at least 10x greater than the highest projected C_{max} required for efficacy. Cardiovascular endpoints were evaluated in the 1-month repeat-dose dog toxicology study using a jacketed external telemetry system. No test article-related effects were observed in any of the electrocardiogram (ECG) parameters (heart rate, PR interval, QRS duration, QT interval, and corrected QT [QTc] interval); therefore the no-observed-effect level (NOEL) for cardiovascular endpoints was 20 mg/kg/dose, the highest dose tested.

An Ames test for mutagenicity was negative. Two additional genetic toxicity assays (in vitro micronucleus [MN] and in vivo rat MN) demonstrated increases in micronuclei. The in vitro MN assay established a no-observed-effect-level (NOEL) concentration of 5 μg/mL. In the in vivo rat MN assay, LY3214996 showed weak evidence of inducing micronuclei in the polychromatic erythrocytes of the bone marrow of male rats at doses of 50 and 100 mg/kg. The NOEL was 25 mg/kg based on effects at 50 and 100 mg/kg in male rats. Subsequent mechanistic analysis in the in vitro assay, with the use of fluorescence in situ hybridization with pan centromeric DNA probes, demonstrated that the causal basis for the MN was consistent with an aneugenic mechanism. Micronuclei induction by aneugens is generally recognized as being a threshold effect (Guérard et al. 2015). Any clinical trial in healthy subjects should be designed to maintain exposures that do not exceed the threshold required for micronuclei induction (AUC and C_{max} exposures in male rats at the MN NOEL of 25 mg/kg were 13417 ng·hr/mL and 1225 ng/mL, respectively). In advanced cancer patients, the potential benefit of treatment likely outweighs the risk; even in cases where the threshold for MN induction is exceeded. LY3214996 was a nonirritant in the Bovine Corneal Opacity and Permeability (BCOP) and non-toxic with minimal potential irritation (sporadic erythema) at 2000 mg/kg in the acute dermal toxicity study in rats.

Combination toxicology studies with LY3214996 and abemaciclib or LY3214996 and gemcitabine plus nab-paclitaxel have not been conducted, as these studies are not warranted to support combination clinical trials intended to treat patients with advanced cancer (Nonclinical Evaluation for Anticancer Pharmaceuticals, ICH S9). The toxicity profiles of abemaciclib, gemcitabine, and nab-paclitaxel have been characterized individually in both clinical and nonclinical studies and they have a clinically manageable safety profile. The clinical assessment of safety and tolerability for LY3214996 and abemaciclib do not indicate a significant or unreasonable risk from overlapping toxicity (e.g. GI toxicity).

Please refer to the IB for additional details on nonclinical toxicology information.

3.2.1.4 Clinical Pharmacokinetics

In an ongoing phase I JUAB study of LY3214996, the pharmacokinetics (PK), pharmacodynamics (PD), safety, and anti-tumor activity of LY3214996 are being evaluated. This initial Phase 1 study of LY3214996 consists of a once daily (QD) dose escalation phase (Part A), a twice a day (BID) dose escalation phase (Part A2), a drug-drug interaction (DDI) study to evaluate potential CYP3A4 drug-drug interaction of LY3214996 with midazolam (Part B1), and a tumor expansion phase of LY3214996 given as a monotherapy in 5 tumor expansion cohorts (Parts B2-6). LY3214996 was also given in combination with other agents including abemaciclib, gemcitabine/nab-paclitaxel, and encorafenib/cetuximab (Parts C, D, and E respectively).

After oral administration, maximum plasma concentrations of LY3214996 were reached approximately 1 to 2 hours post dose. The mean $t_{1/2}$ was approximately 3 to 5 hours, suggesting little to no accumulation upon multiple QD and BID dosing. Exposures increased with dose from 25 to 800 mg, and AUCτ at steady state on Day 15 was similar to AUC0-∞ on Day 1, suggesting that the PK of LY3214996 did not change with time at these doses. Early exposures (AUC0-6) in the sparse sampling patients in Parts B2 to B6, C and D did not appear to differ from the

intensive sampling patients in Parts A, A2, and B1. Therefore, the PK of LY3214996 did not appear to be affected by the presence of abemaciclib, gemcitabine, or paclitaxel.

The variability in exposures, assessed by percentage coefficient of variation, ranged from 3% to 126% for both Cmax and AUC and did not display any apparent trend with dose. These variabilities are most likely associated with a typical Phase 1 patient population that is heavily pre-treated with varying metabolic functions and small numbers of patients per dose level.

3.2.1.5 Clinical Safety

In Part A daily dosing of LY3214996 of the phase 1 study, the maximum tolerated single agent dose was deemed to be 400 mg. Within part A (N = 54), the most common adverse event leading to dose limiting toxicity (DLT) as blood creatinine increase, acute kidney injury, and dehydration. Treatment related adverse events occurring ≥ 10% included nausea (53.7%), vomiting (35.2%), maculo-papular rash (27.8%), diarrhea (27.8%), dermatitis acneiform (22.2%), fatigue (18.5%), pruritis (16.7%), blurred vision (14.8%), and rash (11.1%).

In Part C combinging LY3214996 and abemaciclib, one DLT was experienced at the 200 mg LY3214996 dose. A summary of DLTs is provided in Table 3.1.

Table 3.1 Summary of Phase I DLTs

Dose (ERK + Abema)	Enrolled	Evaluable	# DLT	Reason for DLT
200mg QD + 150mg BID	9	6	1	Increased ALT/AST (G3)
400mg QD + 150mg BID	15	7	2	Pt #1: Diarrhoea (G3) Pt #2: Rash (G3) Fatigue
600mg QD + 150mg BID	8	4	3	Pt #1: Hypophosphatemia (G3) Pt #2: Vomiting (G3) Pt #3: Nausea/Diarrhoea (G3)
200mg BID + 150mg BID	5	3	3	Pt #1: Anemia/Thrombocytopenia (G3) Pt #2: Nausea, Dehydration (G3) Pt #3: Diarrhoea (G2↑)
400mg QD + 100mg BID	12	4	0	N/A

Of the 108 patients in all parts, 105 (97.2%) experienced at least 1 treatment-emergent adverse event (TEAE); 62 patients (57.4%) had Grade 3 or higher TEAE. Of the total TEAEs, the most commonly reported TEAEs included nausea, vomiting, fatigue, diarrhea, anemia, rash maculo-papular, decreased appetite, and dermatitis acneiform. Table 3.2 summarizes TEAEs that occurred in > 10% of patients.

Table 3.2. Summary of Related TEAEs in ≥10% of the patients (total)

Preferred Term	Part A N = 36 n (%)		Part A2 N = 18 n (%)		Part B N = 27 n (%)		Part C N = 20 n (%)		Part D N = 6 n (%)		Part JP N = 1 n (%)		Total N =108 n (%)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Subjects with ≥1 TEAE	32 (88.9)	7 (19.4)	18 (100)	6 (33.3)	24 (88.9)	9 (33.3)	17 (85.0)	7 (35.0)	4 (80.0)	4 (80.0)	1 (100.0)	1 (100.0)	98 (90.7)	36 (33.3)
Nausea	19 (52.8)	2 (5.6)	6 (33.3)	0	11 (40.7)	2 (7.4)	8 (40.0)	1 (5.0)	0	0	1 (100.0)	0	45 (41.7)	5 (4.6)
Diarrhoea	11 (30.6)	1 (2.8)	4 (22.2)	0	12 (44.4)	1 (3.7)	8 (40.0)	3 (15.0)	2 (33.3)	0	0	0	37 (34.3)	5 (4.6)
Vomiting	16 (44.4)	3 (8.3)	4 (22.2)	0	5 (18.5)	2 (7.4)	7 (35.0)	0	2 (33.3)	0	0	0	34 (31.5)	5 (4.6)
Fatigue	7 (19.4)	2 (5.6)	3 (16.7)	0	10 (37.0)	0	5 (25.0)	1 (5.0)	1 (16.7)	0	0	0	26 (24.1)	3 (2.8)
Rash maculo-papular	7 (19.4)	1 (2.80	8 (44.4)	3 (16.7)	3 (11.1)	0	2 (10.0)	0	1 (16.7)	0	0	0	21 (19.4)	4 (3.7)
Dermatitis acneiform	7 (19.4)	0	5 (27.8)	0	6 (22.2)	2 (7.4)	3 (15.0)	0	0	0	0	0	21 (19.4)	2 (1.9)
Pruritus	4 (11.1)	0	5 (27.8)	1 (5.6)	1 (3.7)	0	2 (10.0)	0	0	0	0	0	12 (11.1)	1 (0.9)
Rash	4 (11.1)	0	2 (11.1)	1 (5.6)	5 (18.5)	0	4 (20.0)	0	1 (16.7)	0	1 (100.0)	0	17 (15.7)	1 (0.9)
Vision blurred	5 (13.9)	0	3 (16.7)	0	3 (11.1)	1 (3.7)	3 (15.0)	0	0	0	1 (100.0)	0	15 (13.9)	1 (0.9)
Alanine aminotransferase increased	3 (8.3)	0	2 (11.1)	1 (5.6)	2 (7.4)	0	3 (15.0)	1 (5.0)	2 (33.3)	0	1 (100.0)	1 (100.0)	13 (12.0)	3 (2.8)
Anaemia	3 (8.3)	1 (2.8)	2 (11.1)	0	2 (7.4)	0	5 (25.0)	0	2 (33.3)	1 (16.7)	0	0	14 (13.0)	2 (1.9)

Abbreviations: N = total number of enrolled patients in each cohort; n = number of patients with that event; TEAE = treatment-emergent adverse event.

3.2.1.6 Single-Agent Clinical Activity

Part A (N = 54) included patients with CRC (44.4%), NSCLC (5.6%), breast cancer (1.9%), ovarian (3.7%), PDAC (14.8%), and other (29.6%). Of these, 23 had *KRAS* mutations, 10 *NRAS* mutations, and 18 with *BRAF* mutations. At time data presentation, 41 patients have evaluable disease. No partial responses were seen. 13 patients had stable disease and 28 with progressive disease. Notably, some patients with *BRAF* or *NRAS* mutations treated at higher doses of LY3214996 (400 mg and 600 mg daily) stayed on treatment longer with stable disease for ≥4 months. Further efficacy studies are ongoing as part of the phase 1 JUAB study.

4 Objectives and Endpoints

Table 4.1 shows the objectives of the study.

Table 4.1 Objectives

Objectives
Primary
• To evaluate the proportion of patients with objective response to an ERK1/2 inhibitor (LY3214996) in combination with abemaciclib for patients whose tumors harbor pathogenic alterations in BRAF, RAF1, MEK1/2, ERK1/2, and NF1

Secondary
• To evaluate the safety and tolerability of LY3214996 + abemaciclib as defined by CTCAE v5 criteria. • To evaluate the median progression-free survival (PFS). • To evaluate the duration of overall response.
Correlative
• To identify potential predictive biomarkers beyond the genomic alteration by which treatment is assigned and/or resistance mechanisms. • To evaluate pharmacokinetic parameters of LY3214996 and abemaciclib.

NOTE: For a more complete description of terms and abbreviations, see Appendix 1.
Abbreviations: ORR = overall response rate; PFS = progression-free survival

5 Study Design

5.1 Overall Design

The purpose of CTO-IUSCC-0730 is to assess the clinical efficacy of LY3214996 in combination with abemaciclib at the recommended phase 2 dose of LY3214996 200 mg orally daily and abemaciclib 150 mg orally twice daily. Patients will be treated until evidence of disease progression, non-compliance with study protocol, unacceptable major toxicity, at subject's own request for withdrawal, or if the study closes for any reason.

5.1.1 Study Period and Subject Status Definitions

5.1.2 Subject Status 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. Lasts up to 28 days.
- **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(s); Section 9). Individual patients who enroll in Study CTO-IUSCC-0730 may continue treatment until they have confirmed progressive disease, or discontinued study treatment for any other reason (Section 9).
- **30-Day Safety Follow-Up Visit:** Once decision is made to discontinue study treatment, this visit occurs approximately 30 days (+/- 7) after last dose of study drug.

5.1.3 Study Period Definitions

- **Study Period:** The overall study period for CTO-IUSCC-0730 begins the day of the first patient's first dose of study treatment and ends at overall study completion (as defined in a bullet below).

- **Study Completion:** occurs after the last patient's last's visit.

- **End of Trial**: occurs when the clinical trial database is locked and the final analysis and evaluation of the study endpoints have been performed.

5.2 Number of Patients

It is anticipated that approximately 35 patients will be enrolled.
For sample size calculations, see Section 14.1.

5.3 End of Study Definition

Study Completion and End of Trial are defined in Section 5.1.1.

5.4 Scientific Rationale for Study Design

The general rationale for the study design is described in the Study Rationale of the Introduction (Section 3.1), and the Statistical Considerations Section 14.

6 Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is 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 a histological or cytological diagnosis of advanced unresectable or metastatic cancer (American Joint Committee on Cancer Staging Criteria) (Edge et al. 2009).
2. The patient must be, in the judgement of the investigator, an appropriate candidate for experimental therapy, either after available standard therapies (per available local guidelines) have failed to provide clinical benefit for their disease or after the patient has refused standard treatments.
3. Have one of the following alterations as defined below using a CLIA-certified next-generation sequencing test:
    a. Point mutation in *BRAF*, *RAF1*, *MEK1/2*, or *ERK1/2* that have been previously characterized to be gain-of-function mutations. These mutations have to be specified as gain-of-function as listed in the OncoKB and/or JAX-CKB databases.
        i. Patients with NSCLC that harbor BRAF V600E treated with prior RAF and/or MEK inhibition therapy will be excluded.
        ii. Patients with tumor types other than NSCLC that harbor BRAF V600E mutations who have been treated and progressed on prior BRAF and/or MEK inhibition will be included.
        iii. Patients with NSCLC that harbor BRAF V600E will only be enrolled if they are not a candidate for FDA approved therapy
    a. Amplification of *RAF1* defined as >6 copies of the respective gene.
    b. Gene fusion in which *BRAF*, *RAF1*, *MEK1/2*, or *ERK1/2*, is a fusion partner; in which the fusion is determined to be in-frame; and the kinase domain of *BRAF*, *RAF1*, *MEK1/2*, or *ERK1/2* is retained.

c. Point mutations, frameshift insertions/deletions, splice site mutations, or stop gain mutations that results in loss-of-function of *NF1*.

4. Have measurable disease amenable to biopsy. If biopsy is deemed unsafe at time of procedure, patients will remain eligible for study.
5. Must be able to provide written informed consent and HIPAA authorization for release of personal health information.
6. Have a performance status (PS) of 0 or 1 on the Eastern Cooperative Oncology (Group (ECOG) scale (Oken et al. 1982) within 21 (+/-7) days prior to registration for protocol therapy.
7. Have discontinued previous systemic treatments > 3 weeks for cancer prior to first dose of investigational therapy. Patient must have resolution, except for alopecia, of all clinically significant toxic effects of prior chemotherapy, surgery, or radiotherapy to Grade ≤1 by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.
8. Have adequate organ function, as defined below:

System	Laboratory Value
Hematologic	
ANC	≥1.5 × 10^9/L
Platelets	≥100 × 10^9/L
Hemoglobin	≥9.0 g/dL
	Transfusions to increase the patient's hemoglobin level to 9 g/dL are not permitted within 1 week prior to the baseline hematology profile
Hepatic	
Total bilirubin	≤1.5 × ULN **OR** ≤2.0 mg/dL in patients with Gilbert's disease
ALT and AST	≤2.5 × ULN **OR** ≤5 × ULN if the liver has tumor involvement
Renal	
Serum creatinine **OR** Calculated creatinine clearance (see Appendix 3)	≤1.5 × ULN **OR** ≥50 mL/min

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ANC = absolute neutrophil count; ULN = upper limit of normal.

9. Are at least 18 years old at the time of screening.
10. Are male patients who are sterile (including vasectomy confirmed by post vasectomy semen analysis), or agree to use an effective method of contraception and not to donate sperm, or who practice total abstinence from heterosexual activity, starting with the first dose of study treatment, during the study, and for at least 6 months following the last dose of study treatment.

11. Are female patients of non-childbearing potential (surgically sterile after having a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy or postmenopausal), or are female patients of child-bearing potential who are not pregnant, as confirmed by a serum pregnancy test within 14 (+/-7) days prior to receiving first dose of study treatment and who agree to use 2 methods of birth control (hormonal or intrauterine plus a barrier method) or practice total abstinence from heterosexual activity during the study for at least 6 months following the last dose of the study treatment.
12. Are able to swallow capsules or tablets
13. Have an estimated life expectancy of ≥12 weeks, in the judgment of the investigator.

6.2 Exclusion Criteria

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

1. Have a serious concomitant systemic disorder (for example, active infection or a gastrointestinal 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.
2. Have or known activated/reactivated hepatitis A, B, or C (screening is not required).
3. Uncontrolled human immunodeficiency virus (HIV) infection are considered ineligible. HIV- infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial. Known HIV positive patients who meet the following criteria will be considered eligible:
    a. CD4 count ≥ 350 cells/mm3
    b. Undetectable viral load
    c. Maintained on modern therapeutic regimens utilizing non-CYP interactive agents (i.e. excluding ritonavir)
    d. No history of AIDS-defining opportunistic infections
4. Have symptomatic and untreated central nervous system (CNS) malignancy or metastasis (screening is not required).
    a. Patients with treated CNS metastases are eligible for this study if they are not currently receiving corticosteroids for their CNS metastasis and/or anticonvulsants. Patient must be > 4 weeks from therapy completion (including radiation and/or surgery) and clinically stable at time of study entry. Brain MRI or head CT is required at screening for patients with known brain metastases.
5. Have current hematologic malignancies, acute or chronic leukemia
6. Have a second primary malignancy that in the judgment of the principle investigator may affect the interpretation of results
7. Have prior malignancies within the last 3 years prior to study enrollment. Patients with carcinoma in situ of any origin and patients with prior malignancies who completed curative intent-treatment and whose likelihood of recurrence is very low, as judged by the principal investigator, will remain eligible for this study. The principal investigator will approve enrollment of patients with prior malignancies in remission before these patients are enrolled.

8. Are currently enrolled in a clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
9. Have participated, within the last 28 days in a clinical trial involving an investigational product.
10. Have previously completed or withdrawn from this study or any other study investigating an ERK1/2 inhibitor.
11. Had prior therapy with an ERK1/2 inhibitor.
12. Had prior chemotherapy within 3 weeks of study registration.
13. Had prior non-CNS radiation within 2 weeks of study registration. Please refer to exclusion criteria #4 for patients who have required radiation for CNS disease.
14. If female, is pregnant, breastfeeding, or planning to become pregnant.
15. Currently using concomitant medications that are strong inhibitors or inducers of CYP3A4.
16. Have serious and/or uncontrolled preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study.
    a. This includes cardiogenic syncope, ventricular arrhythmias, history of sudden cardiac arrest, or severe dyspnea at rest or requiring oxygen therapy.
    b. This includes patients with any evidence of interstitial lung disease (ILD) (not just serious and/or uncontrolled ILD) and any history of severe ILD.

6.3 Lifestyle Restrictions

Patients must meet the study entry criteria. There are no additional lifestyle restrictions for participation in Study CTO-IUSCC-0730.

6.4 Screen Failures

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

Repeating of laboratory tests during the 21-day screening period does not constitute re-screening.

7 Patient Registration

All patients will be registered with the Indiana University Simon Cancer Center (IUSCC) Clinical Trials Office (CTO). Regulatory files will be maintained by the IUSCC CTO. Applicable regulatory documents must be completed and on file prior to registration of any patients. Potential patients will be identified in the Oncology outpatient clinics or by referrals from outside physicians. Patients who appear to be eligible for this trial will undergo the Informed Consent Process and be screened for eligibility utilizing the Eligibility Criteria. The original signed IRB approved Informed Consent Document and completed Eligibility Checklist will be forwarded to the CTO designee for eligibility verification and registration in the

OnCore® database. Notification will be sent to the principal investigator, treating physician and research nurse when registration is complete to confirm registration and inform them of patient ID number.

8 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 patients and study site personnel.
- verifying that instructions are followed properly
- maintaining accurate records of study treatment dispensing and collection
- timely reporting of adverse events and product complaints to Lilly
- at the end of the study returning all unused medication to Lilly, or its designee, unless Lilly and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law.

8.1 Treatments Administered

8.1.1 Treatment Plan

8.1.1.1 LY3214996

LY3214996 will be administered at a dose of 200 mg orally once daily on Days 1 through 28 of a 28-day cycle. LY3214996 can be taken with or without food. 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. Treatment will be continued until progressive disease, unacceptable toxicity or patient desire to discontinue study therapy.

8.1.1.2 Abemaciclib

Abemaciclib will be administered at a dose of 150 mg orally Q12 hours (± approximately 2 hours) on Days 1 through 28 of a 28-day cycle. During all cycles, abemaciclib should be taken at approximately the same times each day. If a patient misses or vomits a dose, that dose should be omitted. LY3214996 should be taken at the same time as either the a.m. or p.m. dose of abemaciclib.

8.1.2 Packaging and Labelling

LY3214996 and abemaciclib will be provided by Lilly in the United States and will be labeled according regulatory requirements. Lilly will perform the labeling and the final packaging of these study medications under good manufacturing practice (GMP) conditions. All capsules/tablets should be stored according to their associated product label and taken as indicated. Patients should store these agents in the original package provided and according to the product label (where applicable) and be instructed to keep all medications out of reach of children.

8.1.3 Selection and Timing of Doses

A cycle is defined as an interval of 28 days. 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 the treatment interruption should be documented

on the CRF. A cycle begins when study treatment is dispensed for the cycle and administered. Thus, if an expected cycle start is delayed, the number of days in the current cycle is increased beyond 28 days.

A patient may continue to receive study treatment until confirmed progressive disease (Section 10.1), unacceptable toxicity, or discontinuation for any other reason (Section 9).

8.2 Blinding

This is an open-label study.

8.3 Dosage Modification

Please refer to Appendix 4 for dose adjustment guidelines.

Study therapy may be held up to 3 weeks to allow sufficient time for recovery. Patients who do not recover from drug-related toxicity to ≤ grade 1 within 3 weeks will be discontinued (except alopecia, fatigue, skin rash, elevated creatinine, nausea, vomiting, constipation or diarrhea that can be controlled with treatment). If a dose adjustment is made, the patient must be maintained at the reduced dose level for all remaining cycles.

For the purposes of dose modification, the investigator must first assess if the toxicity is considered at least possibly due to one of the study drugs, and must then apply the study drug-specific dose-modification guidelines accordingly. If the toxicity is not clearly attributable to either individual study drug, then the causality should be attributed to both study drugs. Dosing interruptions of any study drug are permitted for reasons not related to study treatment (for example, minor surgery, unrelated medical events, patient vacation, and/or holidays). The reason for interruption should be documented on the CRF.

8.4 Treatment Compliance

Patient compliance with study medication will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned tablets/capsules. Deviations from the prescribed dosage regimen should be recorded in the CRF. A patient dosing diary will be used to capture dose information for LY3214996 and abemaciclib.

The patient must take ≥80% of the intended doses in each cycle to be deemed compliant with study drug administration. Similarly, a patient may be considered noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of drug(s). Potential discontinuation of a patient due to study drug noncompliance will be discussed between the treating physician and the principal investigator before the final determination is made to discontinue the patient.

8.4.1 Evaluable Patients

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

Patients evaluable for anti-tumor activity will comprise all patients who receive at least one dose of trial drugPatients who have clinical progression prior to first disease evaluation will discontinue therapy due to progressive disease and not be replaced. Patients who are not evaluable for anti-tumor activity (e.g., study discontinuation due to patient decision before first scan) may be replaced upon consultation with the principal investigator to ensure adequate tumor response data.

8.5 Preparation/Handling/Storage/Accountability

LY3214996 will be supplied as 100-mg capsules for oral consumption. LY3214996 should be stored within the temperature range stated on the label. Investigators should instruct patients to store the capsules at home in the original container and to keep out of the reach of children. Capsules should not be opened, crushed, or dissolved.

Abemaciclib will be supplied as 50-mg tablets and should be stored within the temperature range stated on the label. Investigators should instruct patients to store the capsules at home in the original container and to keep out of the reach of children. Tablets should not be opened, crushed, or dissolved.

8.6 Concomitant Therapy

No other chemotherapy, radiotherapy immunotherapy, cancer related hormone therapy, or experimental drugs, or herbal supplements intended to treat cancer will be permitted while the patients are on this study. An exception will be made for the following circumstances:

- Prostate cancer patients continuing GnRH agonist therapy or breast cancer patients continuing antiestrogen therapy (for example, an aromatase inhibitor).
- 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

In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate early discontinuation from the study. Replacement hormone therapy initiated before study entry will be allowed.

In vitro data suggests potential inhibition of CYP3A4-mediated metabolism by LY3214996, therefore use of concomitant therapy with sensitive substrates of CYP3A4, particularly those that also have a narrow therapeutic range, should be used with caution for all patients in Study CTO-IUSCC-0730. Concomitant therapy with sensitive substrates of CYP3A4 must be avoided (Appendix 5).

In vitro, LY3214996 was an inducer of CYP2D6 and CYP3A5 messenger ribonucleic acid. The clinical relevance of the in vitro induction of CYP2D6 and CYP3A5 by LY3214996 is currently unknown. Caution should be used when using concomitant therapy with CYP2D6 and CYP3A5 substrates as the metabolism of such drugs may be induced.

In vitro data indicates that the major cytochrome P450 involved in the clearance of LY3214996 is CYP3A (~88%). Clinical studies have demonstrated that the major route of abemaciclib clearance is through CYP3A metabolism. Therefore, patients are not allowed to have any concomitant medications that are moderate or strong inhibitors (that is, grapefruit juice,

ketoconazole, etc.) or inducers of CYP3A4. Please refer to Appendix 5 for a list of contraindicated medications. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference for a list of drugs to avoid.

Abemaciclib and its major metabolites inhibit the efflux transporters P-glycoprotein and breast cancer-resistant protein and the renal transporters organic cation transporter 2, multidrug and toxin extrusion protein 1 (MATE 1), and MATE2-K at clinically relevant concentrations. Therefore, substrates of these transporters such as metformin and those with a narrow therapeutic index such as digoxin and dofetilide should be substituted or avoided if possible.

All premedication, supportive care and concomitant medication must be reported on the electronic case report form (eCRF) at each visit.

8.6.1 Supportive Care

Patients should receive full supportive care. Patients are instructed to maintain adequate oral hydration at home, in order to prevent dehydration secondary to vomiting and diarrhea. During visits, patients should be evaluated for signs and symptoms of dehydration and, if necessary, intravenous hydration should be implemented at the discretion of the investigator. American Society of Clinical Oncology (ASCO) guidelines (Smith et al. 2015) should be followed for patients requiring support with granulocyte-colony stimulating factor (G-CSF). If G-CSF is required, study therapy should be held. Patients should not receive G-CSF prophylactically in the first cycle of therapy.

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

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

8.6.1.1 Supportive Management Recommendations for Rash

LY3214996 may cause rash. To help mitigate the rash, the following recommendations are provided. These recommendations are intended to be a guideline for the investigator and should not replace the investigator's best judgment.

Once a patient starts treatment on the study, patients will be instructed to initiate the use of a moisturizer with no scents added. In addition, patients will be directed to limit sun exposure or to apply sunscreen protection before going outdoors (PABA-free, SPF 15 or higher) if appropriate. A prescription for topical antimicrobials and steroidal agents based on institutional practice or guidelines will be provided by the investigator(s)/nurse(s) to the patient. The patient will be instructed to immediately fill the prescription for the topical agents and to start it immediately at the first onset of a Grade 1 rash. If the rash escalates further, then the patient will be instructed to call the study investigator(s)/nurse(s) and additional interventions per institutional practice or guidelines for oral steroids, oral antimicrobials, or dose reductions per investigator discretion may be implemented. Rash management recommendations are listed in Table 8.1.

Table 8.1 Management Recommendations for Skin Reactions

Toxicity Grade	Management Recommendations
Grade 1	• Administer topical clindamycin 1% or topical hydrocortisone 1% in lotion base twice daily to affected areas until resolution of reaction.
Grade 2	• Administer topical clindamycin 2% and topical hydrocortisone 1% in lotion base twice daily to affected areas until resolution of reaction. • If clinically appropriate in the opinion of the investigator, administer oral minocycline or doxycycline 100 mg twice daily (or equivalent), for a minimum of 4 weeks and continue using for as long as rash is symptomatic.
Grade 3	• Temporarily withhold LY3214996 and abemaciclib until symptoms resolve to Grade ≤2 or pre-treatment baseline. Treatment may be held for up to 21 days • Continue ongoing rash treatment. • Following improvement to Grade ≤2, re-administer LY3214996 with a dose reduction of 1 dose level. Abemaciclib does not require a dose reduction • If symptoms do not recur for another treatment cycle, the LY3214996 dose may be re-escalated to the previous dose level.
Grade 4	• Immediately and permanently discontinue treatment with LY3214996 and abemaciclib. • Continue ongoing rash management treatment. • Provide intravenous hydration or electrolyte replacement if needed. • Request dermatologist advice if needed.

8.6.1.2 Supportive Management for Diarrhea

Patients should receive instructions on the management of diarrhea. In the event of diarrhea (Appendix 4), supportive measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the patient should initiate anti-diarrheal therapy (for example, loperamide) and notify the investigator/site for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (for example, 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.

- If diarrhea does not resolve with anti-diarrheal therapy within 24 hours to either baseline or Grade 1, abemaciclib should be suspended until diarrhea is resolved to either baseline or at least Grade 1.
- When abemaciclib resumes, dosing should be adjusted as outlined in Appendix 4.

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

If diarrhea is severe (requiring IV rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones must be prescribed. Patients with severe diarrhea or any grade of diarrhea associated with severe nausea or vomiting should be carefully monitored and given intravenous fluid (IV hydration) and electrolyte replacement.

8.6.1.2.1 *Loperamide*

Based on the toxicities observed with abemaciclib loperamide, 2 mg orally, may be administered with the first dose of abemaciclib daily. If the daily dose of loperamide is not taken with the first dose of abemaciclib, it should be taken after the first loose stool. Patients may take an additional 2-mg-dose (1 capsule/tablet) of loperamide after each loose stool up to a maximum of 16 mg (8 capsules/tablets) per day (including doses taken with abemaciclib). In the event a patient experiences Grade 2 diarrhea (4 to 6 loose stools per day above baseline) despite loperamide, a dose reduction (−1 level) of abemaciclib can be considered before additional doses of loperamide are taken. If diarrhea recurs within 24 hours despite a dose reduction, additional doses (2 mg each) of loperamide may be taken at the investigator's discretion. Loperamide may be discontinued 28 days after initiation of abemaciclib therapy at the investigator's discretion. Loperamide dose can be omitted if the abemaciclib dose is omitted for a reason other than diarrhea. Loperamide administration, including dose adjustments (increases and/or decreases) and changes for indicated use, will be captured on the electronic case report form (eCRF). If a patient experiences constipation or other symptoms related to loperamide dosing (for example, abdominal cramping), the investigator may reduce/stop the patient's dosing of loperamide. If a patient does not have a bowel movement for ≥36 hours, loperamide is to be suspended until bowel movements resume. If loperamide administration resumes, the dose may be adjusted (e.g., once every other day) at the investigator's discretion. Investigators should take into account the patient's history and/or risk of constipation when considering increases in loperamide dosing.

8.6.1.3 Supportive Management Recommendations for Nausea and Vomiting

Approximately 90% of patients have experienced nausea and/or vomiting due to LY3214996, which in a limited number of cases has led to more severe adverse events (i.e., dehydration, acute kidney injury). Therefore, patients will be required to receive antiemetic prophylaxis in cycle 1, in an effort to improve patient safety and reduce the incidence of these events. Recommended antiemetic treatment should follow current guidelines for high/moderate emetic risk agents, such as consensus-based guidelines from the National Comprehensive Cancer Network, but is left to investigator's discretion based on patient characteristics and local medical practices.

Current recommendation for antiemetic treatment consists of a 5-HT3 receptor antagonist and should be given prior to starting study drug (continue daily, choose 1):

- Ondansetron 8-16 mg (total dose) PO daily
- Dolasetron 100 mg PO daily, as needed

Breakthrough treatment can be given by adding 1 agent from a different drug class to the current regimen (i.e., olanzapine 5-10 mg PO daily, dexamethasone 12 mg PO/IV daily).

In the event that the investigator believes concomitant antiemetic medication is not necessary in cycles 2+, the antiemetic regimen may be discontinued.

Caution should be taken when administering medications that are metabolized by CYP3A4 when given with LY3214996 due to the potential inhibition of CYP3A4 metabolism by LY3214996 that could result in increased exposures of the co-medications. If possible, alternate medications that are not reliant on CYP3A4 metabolism for elimination should be utilized whenever possible.

8.6.1.4 Growth Factor Therapy

Growth factors should not be administered to a patient to satisfy study inclusion criteria. Growth factors may be administered in accordance with ASCO guidelines (Smith et al. 2015). Dosing of abemaciclib and LY3214996 must be suspended if the administration of growth factors is required and must not be recommenced within 48 hours of the last dose of growth factors having been administered. Following the administration of growth factors, the dose of abemaciclib must be reduced by 1 dose level on recommencement, if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred.

8.7 Treatment after the End of the Study

Study completion occurs after the last patient's last visit (Section 5.1.1). End of Trial occurs when the clinical trial database is locked and the final analysis and evaluation of the study endpoints has been performed (Section 5.1.1). Investigators will continue to follow Schedule of Activities (Section 2) for all patients until study completion has occurred.

9 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. Medical research data collected prior to the withdrawal consistent with the original authorization may continue to be used.

9.1 Discontinuation from Study Treatment

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

- the patient is enrolled in any other clinical trial 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
- disease progression

  - If a patient is clinically stable at the first radiologic progressive disease by RECIST v1.1 (Eisenhauer et al. 2009), the patient may be considered for continuation on the study until progression is confirmed. For patients to be considered for continuation the following criteria must all be met, and after consultation with the Principal Investigator:
    - Absence of symptoms and signs indicating clinically significant progression of disease
    - No decline in ECOG performance status
    - Absence of symptomatic rapid disease progression requiring urgent medical intervention (e.g. symptomatic pleural effusion, spinal cord compression).
  - Treatment beyond progression must not delay an imminent intervention to prevent serious complications of disease progression (e.g., central nervous system metastases).
  - Subjects' clinical data must be available for CRF source verification. Copies of tumor images must be made available for review by the sponsor or its designee upon request.
- unacceptable toxicity
- the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. Discontinuation from study treatment will occur prior to introduction of the new agent.
- the investigator decides that the patient should be discontinued from study treatment
- the patient requests to be discontinued from study treatment
- the patient's designee (for example, parents, legal guardian, or caregiver) requests that the patient be discontinued from study treatment

Patients are considered to have discontinued from study treatment when all study treatments are no longer administered. Based on investigator discretion and/or patient preference, patients may continue on study treatment while taking either LY3214996 or abemaciclib alone.
Patients who are discontinued from study treatment will have follow-up procedures performed as shown in the Schedule of Activities (Section 2).

9.2 Discontinuation of Inadvertently Enrolled Patients

If a patient who did not meet enrollment criteria was inadvertently enrolled, a discussion must occur between the Lilly CRP, the principal investigator, and the treating physician to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without study treatment.

9.3 Discontinuation from the Study

Patients will be discontinued from the study 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 12 regarding regulatory reporting requirements on fetal outcome and breast-feeding
- the investigator decides that the patient should be discontinued from the study

- the patient requests to be discontinued from the study
- the patient's designee (for example, parents, legal guardian, or caregiver) 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 and Section 9.4).

9.4 Follow Up

Patients will be followed until the day 30 safety follow up visit (Table 2.1) after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Post study-treatment anticancer therapies will be collected and will include type of therapy (surgery, radiotherapy, or systemic therapy), drug class and/or name, overall and by line of therapy.

9.5 Lost to Follow-Up

A patient will 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.

10 Study Assessments and Procedures

Study procedures, assessments, and related timing are described in the sections below and shown in the Schedule of Activities (Section 2).

10.1 Efficacy Assessments

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

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 (MRI) 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 v.1.1 (Eisenhauer et al. 2009).

The method of tumor assessment used at baseline must be used consistently throughout the study. Each patient's full extent of disease will be assessed using RECIST v1.1 (Eisenhauer et al. 2009).

See Section 14.3.2 for definitions of the efficacy endpoints.

10.2 Safety

10.2.1 Other Safety Measures

For each patient, vital signs, laboratory tests, or other tests should be collected as shown in the Schedule of Activities (Section 2).

10.2.2 Safety Monitoring

Aggregate safety data will periodically be reviewed within the study by appropriate methods.

Interstitial lung disease (ILD) or pneumonitis has been identified as an adverse drug reaction for abemaciclib. The majority of events observed in clinical trials were Grade 1 or Grade 2 with serious cases and fatal events reported. Additional information is available in the IB.

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

Refer to Appendix 4 for guidance on dose adjustments of abemaciclib.

10.3 Pharmacokinetics

The plasma pharmacokinetics of abemaciclib, metabolites of abemaciclib (M2 and M20), and LY3214996 will be evaluated on all patients who have received at least 1 dose of study treatment and have had samples collected. On each day with a PK collection time point, abemaciclib and LY 3214996 will be dosed in clinic. Plasma samples will be collected prior to dosing of abemaciclib and LY3214996 on cycle 1 day 15 and cycle 2 day 1.

PK Sample Time points		
Cycle, Day	**PK Sample[a]**	**Comments**
Cycle 1 Day 15	3	Prior to study drug dosing
Cycle 2 Day 1	3	Prior to study drug dosing

[a] PK sampling will include abemaciclib and metabolites of abemaciclib (M2 and M20), and LY3214996.

It is essential that exact dosing times are recorded. Also, it is recommended that the exact time of collection of each venous blood sample be based on the clock used to record dosing times. Adherence to the time points listed in the sampling schedule as closely as possible is requested. Aberrations to specified sampling times will not be considered protocol deviations as long as the samples are taken and the actual sampling time is recorded.

10.3.1 Processing

Whole blood is drawn into K2EDTA Vacutainer tubes and is gently mixed by inversion (~8-10 times) and is kept on wet ice.

- The samples must be processed by centrifugation within ~60 minutes after the sample is drawn.
- The samples are spun to plasma at ~1500 to 2000 x g for 15-20 minutes.
- Plasma is transferred, ensuring no RBC contamination.
- Plasma samples must be frozen at -20ºC +/- 10ºC (or colder) as soon as possible. Samples can be placed on dry-ice for short-term storage; however, must be placed in the appropriate freezer within 24 hours of the draw-time.

Pharmacokinetic analyses will be conducted on all patients who have received at least 1 dose of study treatment and have had samples collected. Plasma concentrations of study drugs (LY3214996, abemaciclib and its metabolites) will be summarized using descriptive statistics. Additional analyses utilizing the population PK approach may also be conducted if deemed appropriate. Relationships between exposure, toxicity, and measures of efficacy and safety may be explored.

Detailed sample collection, shipping, and storage instructions are included the Laboratory Manual.

10.4 Genomics

10.4.1 Whole Blood and Tumor Samples for Genomic Biomarker Research

A whole blood sample will be collected for germline genomic analysis as specified in Section 2.

Using DNA from the tumor biopsy at screening and progression (along with the aforementioned blood germline control), we plan to perform next-generation whole-exome sequencing. The results will serve two purposes: 1) to compare the mutational profile of a tumor biopsy at progression compared to the baseline tumor mutational profile to identify potential acquired mutations driving resistance and 2) to provide mutational data to help identify potential novel biomarkers of response in the form of genomic aberrations either within the RAS/REF/MEK/ERK pathways and/or potentially other cancer pathways. Sequencing will be performed at Indiana University using the Illumina NovaSeq 6000 at our Center for Genomics

and Bioinformatics. Samples will not be used to conduct unspecified disease or population genetic research either now or in the future.

All samples will be coded with the patient ID and sample ID. These samples and any data generated can be linked back to the patient only by the study site personnel. Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ethical review boards (ERBs) impose shorter time limits, at a facility selected by Lilly. This retention period enables use of new technologies, response to questions from regulatory agencies, and investigation of variable response that may not be observed until later in the development of LY3214996 or after LY3214996 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.

Detailed sample collection, shipping, and storage instructions are included the Laboratory Manual.

10.5 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 (including circulating tumor DNA, ctDNA), ribonucleic acid (RNA), proteins, lipids, and other cellular elements.

As part of Indiana University's ongoing efforts to understand the relationship between cancer, genetics, and response to therapy, this study will analyze biomarkers relevant to LY3214996 and abemaciclib, immune functioning, and the disease state, and to correlate these markers to clinical outcome, and/or for related research methods or validation of diagnostic tools or assays.

Samples for biomarker research will be collected as specified in Section 2.

It is possible that biomarker data for patients in the study has already been generated from samples that were collected and analyzed prior to enrolling in this trial. This may include data generated from genetic analyses. If available, these data may be requested from medical records for pre-screening for enrollment eligibility in the molecularly defined cohorts, or used in the research described in Sections 10.5.1 and 10.5.2.

Detailed sample collection, shipping, and storage instructions are included the Laboratory Manual.

10.5.1 Samples for Non-pharmacogenomic Biomarker Research

Plasma and whole blood samples for non-pharmacogenomic biomarker research will be collected as specified in Section 2.

Samples will be examined for biomarkers related to the disease state, variable response to, and the mechanism of action of, LY3214996, abemaciclib, immune functioning, and/or for research-related methods, or validating diagnostic tools or assays.

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

Samples will be retained for a maximum of 15 years after the last patient visit for the study at a facility selected by Indiana University. 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 LY3214996 or after LY3214996 become commercially available.

10.5.2 Tissue Samples for Research

Tumor tissue will be examined for biomarkers related to the disease state, LY3214996 in combination with abemaciclib, and immune functioning.

Collection of the following tumor tissue sample is required for all patients in order to participate in this study via newly obtained biopsy specimens, following determination of eligibility, ≤14 (+/- 7) days before start of treatment. If biopsy of tumor tissue is not deemed safe by the investigator, the patient may still enroll on study and archived tumor tissue will be requested if available. Archived tissue may be from a primary or metastatic site.

In addition to the required biopsies and biomarker samples discussed in Sections 10.5.1 and 10.5.2, patients will undergo collection of an additional biopsy specimen and blood sample after treatment with LY3214996 has been initiated, including after disease progression. Such additional biopsies should be performed only if clinically feasible. If these additional samples are requested, they will be used to further investigate biomarkers that may explain treatment response and resistance mechanisms.

Ex vivo models that mimic the tumor microenvironment are valuable resources to drive translational research into understanding sensitivity and resistance to targeted agents. From this trial we will collect fresh biopsy material at screening and progression for the establishment of ex vivo organoid models. This will enable us to have matched tissues prior to exposure to LY3214996 and abemaciclib to give us matched models of both intrinsic and acquired resistance.

10.5.2.1 Specimen preparation, handling and shipment:

The fresh tumor tissue will be placed and delivered in supplemented advanced DMEM/F12 medium (Gibco, cat. no. 12634-028) in 50-ml Falcon tubes. The supplements are defined as: 1% (vol/vol) Penicillin–streptomycin (Gibco, cat. no. 15070063), 1% (vol/vol) HEPES (Gibco, cat. no. 15630-056), 1% (vol/vol) Ultraglutamine type I (Lonza, cat. no. BE17-605E) and 1x Primocin

(Invivogen, cat. no. PML-40-60) at 4°C. Supplemented advanced DMEM/F12 medium can be stored at 4°C for up to 6 months.

In order to arrange the courier collections, the following information will be provided: number of samples to be delivered, the name and telephone number of the main contact at Indiana University Simon Cancer Center to liaise with the courier company, the exact address of where the samples are to be collected from. The courier company will liaise with the main contact at Indiana University Simon Cancer Center directly to arrange pick-up of samples.

The packaging must consist of three components to meet the following conditions:
1. a leak-proof primary receptacle(s)
2. a leak-proof secondary packaging
3. An outer packaging of adequate strength for its capacity, mass and intended use, and with at least one surface having minimum dimensions of 100mm x 100mm (4in X 4in).

The following procedure will be used:

A large polystyrene box will be prepared containing ice packages for same-day shipment. All samples will be placed into the leak-proof primary receptacle. The primary receptacle will be labeled with the de-identified sample ID and date of sample collection. The de-identified sample ID will be shared by e-mail at the day of sample collection and shipment. As much air as possible will be removed from the secondary packaging before sealing to make it as compact as possible. Absorbent material (e.g. tissue paper) must be placed between the primary and secondary containers to absorb all potential leakage and entire contents so that no liquid release will reach the outer packaging. The polystyrene box lid will be sealed with tape and labeled with the delivery details listed below. The outer package must be marked as “Exempt human specimen”. The courier will be contacted as soon as the samples are ready for collection.

Delivery Details:
Karsten Boehnke
Eli Lilly and Company
Alexandria Center for Life Science
East Tower, 12th Floor
450 East 29th Street
New York
NY 10016
boehnke_karsten@lilly.com
Phone: +1 646 784 6993

Due diligence will be used and personal identifiers, including the patient’s name and initials, must be removed from the institutional pathology report. De-identification and anonymization of individual patient data will be applied to meet transparency and disclosure commitments while safeguarding the privacy of individuals.

All tumor biopsy tissue samples will be used for research purposes only per IRB approval. The preclinical research conducted at Lilly will be at an early stage being exploratory, and such data may not be used for any medical decisions. All samples will be registered at Lilly as anonymized data in order to sufficiently devoid of personal information to protect personal privacy and meet the requirements of data protection and privacy laws. Upon organoid culture establishment, cryovials with organoids will be placed in liquid nitrogen at a dedicated space for human samples for long-term storage and detailed logs will generated electronically and manually of all specimens stored.

10.6 Health Economics

Not applicable.

11 Data Forms and Submission Schedule

This study will utilize electronic Case Report Form (eCRF) completion in the OnCore® database. A calendar of events and required forms are available in OnCore®. The OnCore® database is a comprehensive, web-based, Clinical Trial Management System (CTMS) which utilizes an Oracle database. OnCore® was developed by Forte Research Systems, Inc. and is used by the IUSCC Clinical Trials Office and supported by the Indiana Clinical and Translational Sciences Institute (CTSI). OnCore® properly used is compliant with Title 21 CFR Part 11. The system is supported and managed by Forte Research Systems who have developed a security program that is compliant with HIPAA and HITECH requirements. Applications and databases are housed off-site at Rackspace, Inc. which is SSAE16 SOC2, ISO 27001, PCI, and HITRUST certified. OnCore provides users secure access with unique IDs/passwords and restricts access by assigned roles, from any location, to record, manage, and report on data associated with the operation and conduct of clinical trials.

12 Reporting Adverse Events

The investigator will use Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 or above (NCI 2009) to assign AE terms and severity grades.

Investigators are responsible for:

- Monitoring the safety of patients in this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient
- The appropriate medical care of patients during the study
- Documenting their review of each laboratory safety report
- 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 drug 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.

The investigator will record all relevant AE and SAE information in the eCRF. 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. In addition, study site personnel will record via eCRF any change in the preexisting conditions and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to study procedure or 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 treatments, 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.

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

12.1 Adverse Events

An **adverse event** is defined as untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event can be **ANY** unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite'). Adverse events will be graded according to the NCI Common Toxicity Criteria, Version 5.0.

12.2 Serious Adverse Events

An SAE is any AE from 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
- considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment.

12.3 Adverse Event and Serious Adverse Event Reporting

All AEs after signing the ICF through 30 days from the last dose of study treatment will be recorded in the eCRF. All AEs considered related to trial medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

SAE reporting begins after the patient has signed the ICF and has received study treatment and for at least 30 days after treatment discontinuation. 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. 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.

12.3.1 Reporting to the IRB

Unanticipated problems involving risks to subjects or others will be reported **promptly** to the IRB if they:

- are unexpected;
- are related or possibly related to participation in the research; **and**
- suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the serious adverse event does not meet all three (3) criteria listed above, the event does not have to be promptly reported to the Indiana University IRB. However, it should be reported at the time of continuing review. **Prompt** reporting of unanticipated problems to the IRB is defined as within 5 days from becoming aware of the event.

12.3.2 Reporting to the FDA

Per CFR 312.32 (c), the investigator-sponsor of the IND must notify the Food and Drug Administration (FDA) and all participating investigators in a written IND safety report of any adverse experience. There are two types of reports to the FDA: 7-day and 15-day reports.

12.3.2.1 15-Day IND Reports

The investigator-sponsor of the IND must notify the Food and Drug Administration (FDA) and all participating investigators in a written IND safety report of any:

- **suspected adverse reaction** that is ***both***
- **serious *and***
- **unexpected**

Each written notification shall be made as soon as possible, and no later than **15 calendar** days after the investigator-sponsor's initial receipt of the information.

12.3.2.2 7-Day Reports

The investigator-sponsor must notify FDA and all participating investigators in a written IND safety report of any adverse experience:

- **fatal or life-threatening experience** that is ***both***
- **associated with use of the drug *and***
- **unexpected**

The FDA will be notified as soon as possible but no later than **7 calendar** days after initial receipt of the information.

12.3.2.3 Report Content

Each written notification may be submitted on FDA Form 3500A or in a narrative format and must bear prominent identification of its contents, i.e., "IND Safety Report". For purposes of this protocol, the **MedWatch Report Form (FDA 3500A mandatory reporting), along with FDA Form 1571, and a cover letter** submitted to the appropriate FDA division, will serve as the written IND safety report. Follow-up information to a safety report should be submitted as soon as the relevant information is available.

Submit

- MedWatch Report Form (FDA 3500A)
- FDA Form 1571
- Cover Letter

The IUSCC Protocol Development Coordinator should be contacted to assist with all FDA submissions and will be provided with a copy of all events that are reported to the FDA. All IND submissions will be maintained in a master file in the Clinical Trials Office of the IU Simon Cancer Center.

12.3.3 Reporting to Lilly

Study site personnel must notify Lilly of any SAE within 24 hours of investigator awareness of the event via the IUSCC SAE form. The form will be submitted with the Lilly study-specific cover letter via Lilly's Investigator Initiated Research (IIR) portal at http://LillyInvestigatorResearch.com. 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.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study. 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.

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

12.4 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. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance 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 regulations and associated detailed guidance.

12.5 Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to 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.

12.6 Treatment of Overdose

Refer to the relevant IB and/or Product Label for LY3214996 and abemaciclib.

13 Data and Safety Monitoring

This study will be conducted in accordance with the IU Simon Cancer Center Institutional DSMP for **High Risk Trials**.

Investigators will conduct continuous review of data and subject safety. **Weekly review meetings** for high risk trials are required and will include the principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion). **Weekly** meeting summaries should include review of data and subject safety by including for each dose level: the number of subjects, significant toxicities as described in the protocol, dose adjustments and responses observed. Study teams should maintain meeting minutes and attendance for submission to the DSMC upon request.

13.1 Data and Safety Monitoring Committee

The IUSCC Data and Safety Monitoring Committee (DSMC) is responsible for oversight of subject safety, regulatory compliance, and data integrity for this trial. The DSMC will review this study semi-annually to review overall trial progress, toxicity, compliance, data integrity, and accrual per the Institutional DSMP.

Furthermore, the DSMC conducts an administrative review of serious adverse events (SAEs), deviations, reportable events, and any other outstanding business. Major issues may require further DSMC review or action.

For any increase in frequency of grade 3 or above adverse events (above the rate reported in the Investigator Brochure or package insert), the principal investigator will notify the DSMC Chair immediately. The notification will include the incidence of study adverse events, grades, and attributions, as well as investigator statements regarding comparison with risks per the IB/ package insert.

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the subject warrant early closure of the study, the DSMC Chair and Compliance Officer must be notified within 1 business day via email, and the IRB must be notified within 5 business

days. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review.

13.2 IND Annual Reports

For trials with an IND held locally by the IU principal investigator or university, the IND Annual Report will be prepared and submitted to the Compliance Team. This report will be reviewed by the DSMC at the time of FDA submission.

13.3 Study Auditing and Monitoring

All trials conducted at the IUSCC are subject to auditing and/or monitoring per the Institutional DSMP. Reports will be reviewed by the full DSMC at the time of study review.

13.4 Data Management/ Oncore Reporting Requirements

The DSMC reviews data and study progress directly from Oncore; therefore, timely data entry and status updates are vital. Study data must be entered within Oncore promptly, no later than one week from study visit occurrence. Subject status in Oncore will be updated in real time, as this may affect overall trial enrollment status. Global SAEs and deviations will be reviewed on a monthly basis by the DSMC Chair directly from Oncore.

13.5 Study Accrual Oversight

Accrual data will be entered into the IU Simon Cancer Center OnCore system. The Protocol Progress Committee (PPC) reviews study accrual twice per year, while the PPC coordinator reviews accrual quarterly.

13.6 Oncore Safety Reporting

In addition to protocol- and regulatory-required safety reporting, all serious adverse events (SAEs) will be captured in the Oncore system within 1 business day of notification. Initial SAE reporting will include as much detail as available, with follow-up to provide complete information. Attributions will be assessed to study drugs, procedures, study disease, and other alternate etiology.

13.7 Protocol Deviation Reporting

Protocol deviations will be entered into OnCore within 5 days of discovery and reviewed by the DSMC Chair on a monthly basis. Findings will be reported to the full DSMC at the time of study review. For serious or repetitive protocol deviations, additional action may be required by the DSMC.

14 Statistical Considerations

14.1 Sample Size Determination

The primary end point is overall response rate (ORR), where overall response is defined as the complete or partial response per RECIST criteria. We will use the one stage design for the phase II trial. We will use the one stage design to test the null hypothesis that the true ORR is 5% versus the alternative hypothesis that that the true ORR is 19% using a one-sided test with the designing parameters type-I error=0.05 and type II error=0.2 (power=80%).

A total sample size of 28 evaluable patients will be accrued.The trial is considered a success when the null hypothesis is rejected, which is determined when 4 or more patients have an overall response among the 28 patients. Of note, an evaluable patient is defined as a patient who receives at least one dose of the study drug. Assuming a 20% drop-out rate, it is anticipated that the total accrual would be 35 patients.

We will add additional early stopping rules for the following subgroups of patients with pathogenic alterations in 1) BRAFV600E 2) BRAF nonV600E, RAF1 3) MEK1/2, ERK1/2 and 4) NF1. We will use the Bayesian posterior probability to monitor the response rates for those subgroups. A beta distribution of Beta (0.05,0.05) is assigned as the prior. Then, when every 5 evaluable patients have been enrolled in the specific subgroup under monitoring, we will calculaute the posterior probability that the ORR rate for that subgroup is less than 5%. If this posterior probability is greater than 90% during any interim analysis, we will claim that the drug is not promising for this subgroup and will stop any future enrollment for that subgroup of patients. That is, for the 5^{th}, 10^{th}, 15^{th}, 20^{th}, 25^{th}, 30^{th}, and 35^{th} patients in the subgroup, we will determine the enrollment for that subgroup if none of the patients report as tumor response. If the early stopping rule has been triggered, then at the end of the trial we will exclude all the patients in that subgroup from final analysis. We will use a binomal exact test to test the effectiveness of the drug for the remaining patients.

14.2 Populations for Analyses

The following populations 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.

Efficacy Population: will include all enrolled patients who received any quantity of study treatment, regardless of their eligibility for the study.

Biomarker population: will include the subset of patients from the safety population from whom a valid assay results have been obtained.

14.3 Statistical Analyses

Statistical analysis of this study will be the responsibility of Indiana University Department of Biostatistics 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. Additional exploratory analyses of the data will be conducted as deemed appropriate.

14.3.1 Safety Analyses

For safety analyses, CTCAE Version 5.0 will be used to summarize adverse events in the assessment of safety for incorporating LY3214996 in combination with abemaciclib. Summaries of treatment related adverse events in the population will be tabulated. All adverse events (AEs) will be presented in incidence tables coded by CTC term. An adverse event will be considered treatment related if it occurred on or after date of first dose of LY3214996 or abemaciclib and was possibly, probably, or definitely related to treatment. All adverse events will be recorded

until off study date. All deaths recoded in this study will be listed and summarized, and the cause documented.

14.3.2 Efficacy Analyses

14.3.2.1 Endpoints

Overall response rate is defined as the number of patients who achieve a best overall response of complete response (CR) or partial response (PR) divided by the total number of patients treated (efficacy population).

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

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

14.3.2.2 Analysis Planned

14.3.2.2.1 *The Analysis of Primary Endpoint*

The primary end point is overall response rate (ORR), where overall response is defined as the complete or partial response per RECIST v1.1 criteria. We will use the one stage design for the phase II trial. We will specify the null hypothesis that the true ORR is 5% versus the alternative hypothesis that that the true ORR is 19% using a one-sided test with the designing parameters type-I error=0.05 and type II error=0.2 (power=80%).

14.3.2.2.2 *The Analysis of Secondary Endpoint*

The safety and tolerability will be summarized and tabulated as in Section 14.3.1.

The secondary endpoint of progression free survival and the duration of response will be analyzed using the Kaplan-Meier method.

14.3.2.2.3 *The Analysis of Correlative Obejctives*

To identify potential predictive biomarkers beyond the genomic alteration, exploratory analysis of gene expression and DNA mutations will be analyzed to associated with ORR and PFS. In this exploratory analysis, the association of DNA mutations in genes and pathways of interest with ORR and PFS will be performed using logistic regression, and Cox regression model. High-dimentional data in these regression models will be dealt using Lasso and Elastic-Net Regularized Generalized Linear Models (glmnet package in R) For gene expression, differential expression between responders and non-responders will be identified using the DESeq package in R.

Plasma concentrations of LY3214996, abemacicilib and its metabolites will be summarized using descriptive longitudinal and statistics. Further PK/PD analyses will be analyszed using linear mixed effect model, in particular, the AUC will be estimated and summarized. However, all of these analyses will be exploratory.

14.3.2.3 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 discontinuing (overall and by reason for discontinuation). A listing of all important protocol deviations will be provided.

14.3.2.4 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.

14.3.2.5 Concomitant Therapy

A summary of prior and concomitant medications will be reported.

14.3.2.6 Post study-Treatment-Discontinuation Therapy

The numbers and percentages of patients receiving post study-treatment-discontinuation anticancer therapies will be provided by type of therapy (surgery, radiotherapy, or systemic therapy), and by drug class and/or name, overall and by line of therapy.

14.3.2.7 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 parts.
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.

15 Patient Consent and Peer Judgement

The protocol and informed consent form for this study must be approved in writing by the appropriate Institutional Review Board (IRB) prior to any patient being registered on this study. Changes to the protocol, as well as a change of principal investigator, must also be approved by the Board. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator (housed in the Clinical Trials Office) and are subject to inspection at any time during the study.

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

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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 that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
$AUC_{0\text{-}tlast}$, $AUC_{0\text{-}\infty}$	area under the concentration-time curve
ATP	adenosine triphosphate
BCOP	bovine corneal opacity and permeability
BID	twice a day
CDK4	cyclin-dependent kinase-4
CI	confidence intervals
CIOMS	Council for International Organizations of Medical Sciences
CL/F	apparent clearance
Cmax	maximum concentration
CR	complete response
CRC	colorectal cancer
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.
CTCAE	Common Terminology Criteria for Adverse Events
CTS	change in tumor size
CVw	coefficients of variations
DDI	drug-drug interactions
DLT	dose limiting toxicity

ECG	electrocardiogram
eCRF	electronic case report form
ECG	electrocardiogram
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.
EGFR	epidermal growth factor receptor
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review boards
ERK	extracellular signal regulated kinase
FDA	Food and Drug Administration
G-CSF	granulocyte-colony stimulating factor (G-CSF
GCP	good clinical practice
GI	gastrointestinal
GnRH	gonadotropin-releasing hormone
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
interim analysis	An interim analysis is an analysis of clinical trial data conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
LC-MS/MS	liquid chromatography-tandem mass spectrometry
MAPK	mitogen-activated protein kinase
mCRC	metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities

MN	micronucleus
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NF1	Neurofibromin-1
NOEL	no-observed-effect level
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PD	pharmacodynamics
PDAC	pancreatic ductal adenocarcinoma
PET	positron emission tomography
PFS	progression free survival
PI	principal investigator
PK	pharmacokinetics
PR	partial response
QD	once daily
QTc	corrected QT interval
QW	every week
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
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	Statistical Analysis Plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
screen failure	patient who does not meet one or more criteria required for participation in a trial

SUSARs	Suspected unexpected serious adverse reactions
$t_{1/2}$	half-life
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.
TTR	time to response
US	United States
V/F	apparent volume of distribution

Appendix 2. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

Investigators are responsible for:

- ensuring that the patient understands the potential risks and benefits of participating in the study
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any study 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 his or her participation in the trial.

Ethical Review

Documentation of IRB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). The sponsor-investigator or representative must approve the ICF, including any changes made by the IRB, before it is used at the investigative site. All ICFs must be compliant with the International Conference on Harmonisation (ICH) guideline on GCP.

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

- the current IB or package labeling, Patient Information Leaflet, Package Insert, or Summary of Product Characteristics and updates during the course of the study
- the ICF
- relevant curricula vitae

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 (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations.

Investigator Information

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

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 sponsor-investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study. If this investigator is unable to fulfill this function, another investigator will be chosen by Indiana University to serve as the clinical study report coordinating investigator.

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

The study will be discontinued if Lilly or the sponsor-investigator judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GC

Appendix 3. Creatinine Clearance Formula

For serum creatinine concentration in mg/dL:

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

For serum creatinine concentration in μmol/L:

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

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

Source: Cockcroft and Gault 1976.

Appendix 4. Dose Modification of LY3214996 & Abemaciclib

Neutropenia	Abemaciclib	LY3214996
≤ Grade 1/2	No change in dose.	No change in dose.
Grade 3	Hold* until ≤ Grade 2. Resume at same dose level.	No change in dose.
Recurrent Grade 3 or Grade 4	Hold* until ≤ Grade 2. Reduce by 1 dose level.	No change in dose.
*Patients requiring a delay of all protocol therapy > 3 weeks due to toxicity should go off protocol therapy. **NOTE:** Use of prophylactic granulocyte colony stimulating factor is permitted per investigator discretion. Use of ASCO guidelines is recommended. Suspend therapy for at least 48 hours after the last dose of a blood cell growth factor was administered and until toxicity resolves to at least Grade 2.		

Abbreviation: ASCO = American Society of Clinical Oncology

Thrombocytopenia	Abemaciclib	LY3214996
≤ Grade 1/2	No change in dose.	No change in dose.
Grade 3	Hold* until ≤ Grade 2. Resume at same dose level.	No change in dose.
Recurrent Grade 3 or Grade 4	Hold* until ≤ Grade 2. Reduce by 1 dose level.	No change in dose.
*Patients requiring a delay of all protocol therapy > 3 weeks due to toxicity should go off protocol therapy.		

Anemia	Abemaciclib	LY3214996
Supportive transfusion is permitted after cycle 1, day 1 and future cycles for subjects who do not meet hemoglobin parameters for retreatment.		
Hemoglobin	**Abemaciclib**	**LY3214996**
Grade 1/2	No change in dose	No change in dose.
Grade 3	Hold* until ≤ Grade 2. Resume at same dose level.	No change in dose.
Recurrent Grade 3 or Grade 4	Hold* until ≤ Grade 2. Reduce by 1 dose level.	No change in dose.
Patient requires administration of a blood cell growth factor	Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2. Resume abemaciclib at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor.	No change in dose.
*Patients requiring a delay of all protocol therapy > 3 weeks due to toxicity should go off protocol therapy. Supportive transfusion is permitted after cycle 1, day 1 and future cycles for subjects who do not meet hemoglobin parameters for retreatment.		

Recurrent in the context of dose interruptions and delays refer to the same event occurring within the next 8 weeks (as measured from the stop date of the first event). This does not include events in the same class (for example, neutropenia followed by anemia 1 month later).

As a general approach, based on the **risk/benefit balance assessment per the investigator**: for a patient who experiences a new episode of Grade 3 hematological toxicity after more than 8 weeks following the last episode of **same** Grade 3 hematological toxicity, the investigator may consider resuming the patient on the same drug dose if the patient satisfies the following conditions:

- The patient showed stable hematological counts (≤Grade 2) during that time frame
- In the absence of any infectious sign or risk factor
- The patient is getting benefit from study treatment.

Non-Hematologic Toxicity:

Nausea**	**Abemaciclib**	**LY3214996**
≤ Grade 1	No change in dose.	No change in dose.
Grade 2	Hold* until ≤ Grade 1. Resume at same dose level.	Hold* until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Reduce by 1 dose level.	Hold* until ≤ Grade 1. Reduce by 1 dose level.
*Patients requiring a delay of all protocol therapy > 3 weeks due to toxicity should go off protocol therapy. ** After optimal anti-emetic therapy. Please refer to Section 8.6.1. Use of prophylactic or scheduled antiemetics are recommended in future cycles for patients experiencing grade 2 or higher nausea.		

Vomiting**	**Abemaciclib**	**LY3214996**
≤ Grade 1	No change in dose.	No change in dose.
Grade 2	Hold* until ≤ Grade 1. Resume at same dose level.	Hold* until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Reduce by 1 dose level.	Hold* until ≤ Grade 1. Reduce by 1 dose level.
Grade 4	Hold* until ≤ Grade 1. Reduce by 1 dose level.	Hold* until ≤ Grade 1. Reduce by 1 dose level.
*Patients requiring a delay of all protocol therapy > 3 weeks due to toxicity should go off protocol therapy. ** After optimal anti-emetic therapy. Please refer to Section 8.6.1. Use of prophylactic or scheduled antiemetics are recommended in future cycles for patients experiencing grade 2 or higher vomiting.		

Diarrhea**	Abemaciclib	LY3214996
≤ Grade 1	No change in dose.	No change in dose.
Grade 2 (1st episode)	Hold* until ≤ Grade 1. Resume at same dose level.	Hold* until ≤ Grade 1. Resume at same dose level.
Grade 2 (Persistent or recurrent following resumption of therapy)	Hold* until ≤ Grade 1. Reduce by 1 dose level.	Hold* until ≤ Grade 1. Reduce by 1 dose level.
Grade 3	Hold* until ≤ Grade 1. Reduce by 1 dose level.	Hold* until ≤ Grade 1. Reduce by 1 dose level.
Grade 4	Hold* until ≤ Grade 1. Reduce by 1 dose level.	Hold* until ≤ Grade 1. Reduce by 1 dose level.
*Patients requiring a delay of all protocol therapy > 3 weeks due to toxicity should go off protocol therapy. ** After optimal anti-diarrheal therapy. Please refer to Section 8.6.1. Use of prophylactic or scheduled anti-diarrheals are recommended in future cycles for patients experiencing grade 2 or higher diarrhea.		

Hepatotoxicity is a known adverse drug reaction of abemaciclib. Additional information is in the IB. Should a patient experience ≥ Grade 2 increase in AST and/or ALT we recommend holding therapy with dosing guidelines below. Please follow AST, ALT, and total bilirubin at least weekly until ≤ Grade 1 prior to re-initiating study therapy. Liver function can be monitored more frequently per investigator discretion.

AST and/or ALT Elevations**	Abemaciclib	LY3214996
≤ Grade 1 (>ULN-3.0x ULN)	No change in dose.	No change in dose.
Grade 2 (>3.0-5.0 x ULN) (without increase in total bili > 2 x ULN)	Hold* until meets treatment criteria. Resume at same dose level.	Hold* until meets treatment criteria. Resume at same dose level.
Grade 2 (without increase in total bili >2 x ULN; recurrent or persistent)	Hold* until ≤ Grade 1. Reduce by 1 dose level.	Hold* until ≤ Grade 1. Reduce by 1 dose level.
Grade 3 (>5.0-20.0 x ULN) (without increase in total bili > 2 x ULN)	Hold* until ≤ Grade 1. Reduce by 1 dose level.	Hold* until ≤ Grade 1. Reduce by 1 dose level.
Grade 2 (with increase in total bili > 2x ULN)	Discontinue therapy	Discontinue therapy
Grade 3 (with increase in total bili >2 x ULN)	Discontinue therapy	Discontinue therapy
Grade 4 (>20.0 x ULN)	Discontinue therapy	Discontinue therapy
*Patients requiring a delay of all protocol therapy > 3 weeks due to toxicity should go off protocol therapy. ** Use ULN unless baseline is greater than ULN, then use baseline for grading.		

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

Ask your patients to report any new or worsening respiratory symptoms such as cough, dyspnea, fever, and investigate and treat as per your local clinical practice, including corticosteroids as appropriate. If interstitial lung disease/pneumonitis is suspected, investigations may include imaging, such as high-resolution CT scans, bronchoalveolar lavage, and biopsy as clinically indicated. Please refer to dosing guidelines below for respiratory toxicity.

ILD/Pneumonitis	**Abemaciclib**	**LY3214996**
≤ Grade 1	No change in dose.	No change in dose.
Grade 2 (>7 days despite maximal supportive measures or recurrent)	Hold* until ≤ Grade 1 or baseline. Reduce by 1 dose level.	Hold* until ≤ Grade 1 or baseline. Resume at same dose level.
Grade 3/4	Discontinue therapy.	Discontinue therapy.
*Patients requiring a delay of all protocol therapy > 3 weeks due to toxicity should go off protocol therapy.		

Cutaneous toxicity should be managed per guidelines in Section 8.6.1.1. In the event of grade 3 or higher dermatologic toxicity, hold abemaciclib and LY3214996 until dermatologic toxicity resolves to ≤ grade 2 or pre-treatment baseline. Subsequent LY3214996 treatment should be dose reduced by one dose level. Abemaciclib does not require dose reduction. Treatment may be held for up to 21 days. If the toxicity is not improved to ≤ grade 2 or pre-treatment baseline within the 21-day period, the patient will discontinue therapy. Additionally, a one level dose reduction of LY3214996 is permitted for intolerable grade 2 dermatologic toxicity, at the discretion of the treating physician. Such dose reductions should be undertaken in conjunction with management of cutaneous toxicity as described in Section 8.6.1.1.

For any grade 3 or 4 toxicity, not mentioned above, the treatment should be withheld until the patient recovers to grade 1 or less toxicity. The treatment may then be resumed at one dose level reduction. For intolerable grade 2 toxicities, withhold treatment until the patient recovers, then resume treatment at a one dose level reduction. Dose reduction will be done for the drug that is most likely to have caused the toxicity. For grade 1 or tolerable grade 2 toxicities or clinically insignificant laboratory changes, no dose reduction should be made.

Dose adjustments as outlined in the table below are allowed both within a cycle and between cycles for abemaciclib. Abemaciclib must be reduced sequentially by 1 dose level.

Dose Adjustment	**Oral Dose**	**Frequency**
0	150 mg	Q12H
-1	100 mg	Q12H
-2	50 mg	Q12H

Dose adjustments as outlined in the table below are allowed both within a cycle and between cycles for LY3214996. LY3214996 must be reduced sequentially by 1 dose level.

Dose Adjustment	Oral Dose	Frequency
0	200 mg	Daily
-1	100 mg	Daily

If a patient receiving the 50-mg Q12H dose of abemaciclib requires further dose reduction, abemaciclib should be discontinued. Patients may remain on single agent treatment with LY3214996 if the investigator determines the patient is receiving clinical benefit.
Dose omissions are allowed within a cycle. If a patient requires omission of more than 25% of doses during a cycle for tolerability, then treatment may continue if the investigator determines the patient is receiving clinical benefit.

Appendix 5. Sensitive CYP3A Substrates and Narrow Therapeutic Range Drugs

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

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

Moderate Inducers of CYP3A
Bosentan
Lenisurad
Modafinil
Primidone
Telotristat ethyl

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

This table is prepared to provide examples of clinical CYP3A-sensitive substrates and narrow therapeutic range drugs that are CYP3A substrates and is not intended to be an exhaustive list. Concomitant therapy with sensitive substrates of CYP3A4, particularly those that also have a narrow therapeutic range, should be used with caution for all patients.

Appendix 6. Patient Dosing Instructions and Diary

Subject ID: _____Cycle:_____

Date Medication Dispensed _____/_____/_____
LY3214996 _____
Abemaciclib Dose: _____

Dosing Instructions

LY3214996

- You will take LY3214996 once daily on days 1 through 28 of your 28 day cycle
- LY3214996 can be taken with or without food
- You should take your dose about the same time each day (± 2 hours) as much as possible
- If you miss or vomit a dose, you should not take another dose to try and make it up
- LY3214996 should be taken at the same time as either the a.m. or p.m. dose of abemaciclib

Abemaciclib

- You will take abemaciclib twice a day on days 1 through 28 of your 28 day cycle
- You should take your doses 12 hours apart (±2 hours) and at about the same time each day
- Abemaciclib can be taken with or without food
- If you miss or vomit a dose, you should not take another dose to try and make it up

Dosing Diary

Subject ID: _____Cycle:_____

Use the table below to record each dose of LY3214996 and each dose of Abemaciclib you take. Record the date and the time of each dose in the space provided. Return your diary to the study team at the end of each cycle.

Day	LY3214996	Abemaciclib	Day	LY3214996	Abemaciclib
Example Day 1 *01/01/2001*	*8:00 am*	*8:00 am* *8:00 pm*			
Day 1: ___/___/____	_____:____	_____:_____ _____:_____	Day 15:___/___/____	_____:____	_____:_____ _____:_____
Day 2: ___/___/____	_____:_____	_____:_____ _____:_____	Day 16:___/___/____	_____:_____	_____:_____ _____:_____
Day 3: ___/___/____	_____:_____	_____:_____ _____:_____	Day 17:___/___/____	_____:_____	_____:_____ _____:_____
Day 4: ___/___/____	_____:_____	_____:_____ _____:_____	Day 18:___/___/____	_____:_____	_____:_____ _____:_____
Day 5: ___/___/____	_____:_____	_____:_____ _____:_____	Day 19:___/___/____	_____:_____	_____:_____ _____:_____
Day 6: ___/___/____	_____:_____	_____:_____ _____:_____	Day 20:___/___/____	_____:_____	_____:_____ _____:_____
Day 7: ___/___/____	_____:_____	_____:_____ _____:_____	Day 21:___/___/____	_____:_____	_____:_____ _____:_____
Day 8: ___/___/____	_____:_____	_____:_____ _____:_____	Day 22:___/___/____	_____:_____	_____:_____ _____:_____
Day 9: ___/___/____	_____:_____	_____:_____ _____:_____	Day 23:___/___/____	_____:_____	_____:_____ _____:_____
Day 10: ___/___/___	_____:_____	_____:_____ _____:_____	Day 24:___/___/____	_____:_____	_____:_____ _____:_____
Day 11:___/___/____	_____:_____	_____:_____ _____:_____	Day 25:___/___/____	_____:_____	_____:_____ _____:_____
Day 12:___/___/____	_____:_____	_____:_____ _____:_____	Day 26:___/___/____	_____:_____	_____:_____ _____:_____
Day 13:___/___/____	_____:_____	_____:_____ _____:_____	Day 27:___/___/____	_____:_____	_____:_____ _____:_____
Day 14:___/___/____	_____:_____	_____:_____ _____:_____	Day 28:___/___/____	_____:_____	_____:_____ _____:_____