Protocol Title

PSCI 18-052 A Pilot Study to Evaluate the Response and Tolerability of Verzenio™ (Abemaciclib) in Patients with Advanced Biliary Tract Carcinoma

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TABLE OF CONTENTS

Title	A Pilot Study to Evaluate the Response and Tolerability of Verzenio™ (Abemaciclib) in Patients with Advanced Biliary Tract Carcinoma
Phase	Pilot study
Objectives	**Primary Objectives:** • To estimate the overall response rate (ORR) **Secondary Objectives:** • To determine progression free survival (PFS) • To determine the disease control rate (DCR) • To determine the overall survival (OS) rate at 6 and 12 months • To determine quality of life (QoL) using EORTC-QLQ-C30 (see Appendix C) **Exploratory Objectives:** • To determine the efficacy and safety of abemaciclib with regard to the subtypes of biliary tract carcinoma (BTC) including intrahepatic cholangiocarcinoma (IHCC), extra-hepatic cholangiocarcinoma (EHCC), ampullary carcinoma, and gall bladder carcinoma (GBC). • Analyze the biopsied tumor tissues for molecular profiling (by Caris Life Sciences, Inc ®) including genetic mutation in *K-RAS*, *B-RAF*, *TP53*, *INK4A/p16*, *CDKN1A*/*p21*, *cyclin D*, and *RB* by DNA sequencing (clinical routine). • Correlate the efficacy of abemaciclib with the mutational status of *K-RAS*, *B-RAF*, *TP53*, *INK4A*/*p16*, *CDKN1A*/*p21*, *cyclin D* and *RB* genes. • Analyze the collected blood samples for characterization of extracellular vesicles (EVs).
Study Design	Open label, Pilot Study
Total # of Subjects	N = 10, Approximately up to 20 subjects may be enrolled to attain at least 10 evaluable participants.
Estimated Enrollment Period	36 months
Estimated Study Duration	48 months

KEY ELIGIBILITY CRITERIA	Inclusion Criteria 1. Male or female, age ≥ 18 years at the time of informed consent. 2. Capable and willing to sign informed consent form prior to performing any

	protocol-related procedures. 3. Histologic or cytologic evidence of advanced or metastatic biliary tract cancer, including cholangiocarcinoma (intra-hepatic or extra-hepatic bile ducts), ampullary carcinoma, or gallbladder carcinoma. 4. Evidence of recurrent, locally advanced, unresectable, or metastatic disease. 5. Progressed following or intolerant to one or more lines of systemic therapy, or treatment-naïve subjects who either decline or being considered not a good candidate first-line systemic chemotherapy per the opinion of the treating physician 6. Per the opinion of the physician investigator, predicted life expectancy > 3 months. 7. Presence of at least 1 lesion that is measurable or evaluable using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. 8. Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2. 9. Per the opinion of the physician investigator, acute toxicities relating to any prior anticancer treatment have improved to Grade 1 or baseline. Exceptions include residual alopecia or Grade 2 peripheral neuropathy. 10. Ability to swallow capsules. 11. Adequate organ function as evidenced by the laboratory parameters noted in Section 3.0 Study Eligibility. 12. Women of childbearing potential (WOCP) defined as not surgically sterile (hysterectomy, tubal ligation, or oophorectomy), or at least 1 year postmenopausal, must have a negative serum pregnancy test before study drug administration on cycle 1 day 1. 13. WOCP must use a medically acceptable method of contraception and must agree to continue used of this method for the duration of the study and for 3 weeks after last dose of study drug. Acceptable methods of contraception include abstinence, barrier method with spermicide, intrauterine device (IUD) known to have a failure rate of less than 1% per year, or steroidal contraceptive (oral, transdermal, implanted, or injected) in conjunction with a barrier method. 14. Male, capable of producing offspring, must use a medical acceptable method of contraception and agree to continued use of this method for the duration of the study and for 3 weeks after last dose of study drug because of the possible effects on spermatogenesis. Acceptable methods of contraception include abstinence, WOCP partner's use of barrier method with spermicide, WOCP partner's use of an IUD known to have a failure rate of less than 1% per year, WOCP partner's use of steroidal contraceptive (oral, transdermal, implanted or injected) or WOCP partner is surgically sterile or at least 1 year post-menopausal. In addition, male subjects may not donate sperm for the duration of the study and for 30 days after last dose of study drug. 15. Must be willing and able to comply with the protocol, including adhering to study restrictions, remaining at the clinic as required during the study period, and willing to return to the clinic for the follow-up evaluation.

	16. Patients who received chemotherapy must have recovered (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≤1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy. 17. Patients who received radiotherapy must have completed and fully recovered from the acute effects of radiotherapy. A washout period of at least 14 days is required between end of radiotherapy and randomization. 18. Completed last dose of myelosuppressive chemotherapy greater than 21 days prior to first dose of study drug. 19. Completed last dose of non-myelosuppressive biological or monoclonal antibody therapy greater than 14 days prior to first dose of study drug. **Exclusion Criteria:** 1. Ongoing or active infection requiring systemic antibiotics. 2. Uncontrolled hypertension despite adequate therapy (systolic blood pressure higher than 150 mm Hg or diastolic blood pressure higher than 90 mm Hg found on 2 separate occasions separated by 1 week). 3. Diabetes mellitus and occurrence of more than 2 episodes of ketoacidosis in the 12 months prior to the first dose of study drug. 4. Active second malignancy other than curatively resected basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ carcinoma of the cervix, or other cancers treated with curative intent, and no known active disease in the 3 years prior to enrollment. 5. Primary brain tumor or brain metastases from another primary site. 6. Known history of human immunodeficiency virus (HIV). 7. Known active viral hepatitis B or viral hepatitis C. 8. History of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. Subjects with controlled atrial fibrillation for more than 30 days are permitted. 9. Congestive heart failure (New York Heart Association [NYHA] Class III or IV), or acute coronary syndromes within 6 months of enrollment. 10. Female subjects who are pregnant or breastfeeding. 11. Any other medical, psychiatric, or social condition, which in the opinion of the physician investigator, would preclude participation in the study, pose an undue medical hazard, interfere with the conduct of the study, or interfere with interpretation of the study results. For example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy. 12. Use of an investigational drug within 1 month before the screening visit or currently participating in another investigational study. 13. Any disorder that may interfere with drug absorption, distribution, metabolism, or excretion (including extensive gastrointestinal surgery that

	involves removal of the entire stomach or most of the small intestine or large intestine, bariatric surgery, uncontrolled active Crohn's Disease or ulcerative colitis, or preexisting condition resulting in baseline Grade 2 or higher diarrhea). History of Whipple's procedure is permitted. 14. Known hypersensitivity to any of the components in abemaciclib including micro-crystalline cellulose 102, microcrystalline cellulose 101, lactose monohydrate, croscarmellose sodium, sodium stearyl fumarate, silicon dioxide. Color mixture ingredients—polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, and iron oxide red. 15. The patient has serious and/or uncontrolled preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (for example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, severe renal impairment [e.g. estimated creatinine clearance <30ml/min].
STATISTICS	The data will be summarized in tables listing the mean, standard deviation, median, minimum, maximum and number of subjects for continuous data, or in tables listing count and percentage for categorical data where appropriate. The primary endpoint is overall response rate (ORR). This pilot study of 10 subjects will generate data preliminary data regarding ORR and tolerability with this patient population. The secondary endpoints, which include progression-free survival (PFS), disease control rate (DCR), and overall survival (OS) rate, will be tabulated and graphed as appropriate. The Kaplan-Meier survival curve will be graphed with confidence intervals. A 5% level test of the median survival, based on an exponential maximum likelihood estimator test, will be conducted to determine if median survival is statistically greater than 2.8 months. Adverse events (AEs) and serious adverse events (SAEs) will be annotated and tabulated to allow for a quantitative assessment of the safety and tolerability of abemaciclib. Potential factors associated with the efficacy of abemaciclib, including subtypes of BTC subtypes, and tumor molecular profiles, will be explored with a Cox proportional hazards model. Reproducible statistical reports will be produced.

1.0 STUDY PURPOSE AND STUDY OBJECTIVES/ENDPOINTS

1.1 Study Purpose:

The primary purpose of this study is to determine the objective response rate of abemaciclib in participants with biliary tract carcinoma that are locally advanced, unresectable or metastatic and have failed first-line therapy.

1.2 Study Objectives

1.2.1 Primary Objectives:

- To estimate ORR

1.2.2 Secondary Objectives

- To determine PFS
- To determine the DCR
- To determine the OS rate at 6 and 12 months
- To determine QoL using EORTC-QLQ-C30 (see Appendix C)

1.2.3 Exploratory Objectives:

- Determine the efficacy and safety of abemaciclib with regard to the subtypes of BTC including IHCC, EHCC, ampullary carcinoma, and GBC.
- Analyze the biopsied tumor tissues for molecular profiling including genetic mutation in *K-RAS*, *B-RAF*, *TP53*, *INK4A*/*p16*, *CDKN1A*/*p21, cyclin D* and *RB* by DNA sequencing (clinical routine).
- Correlate the efficacy of abemaciclib with the mutational status of *K-RAS*, *B-RAF*, *TP53*, *INK4*A/*p16*, *CDKN1A*/*p21, cyclin D*, and *RB*.
- Analyze the collected blood samples for characterization of EVs including genetic mutations and metabolic profiles.

1.3 Study Endpoints

1.3.1 Primary Efficacy Variable and Endpoints:

- ORR as estimated by the proportion of subjects with a best response of CR or PR during study.

1.3.2 Secondary Efficacy Variable and Endpoints:

- PFS as determined by the time interval from the date of first dose of study drug to first documented disease progression or death from any cause, whichever occurs first, if evaluable.
- DCR as determined by the proportion of subjects with CR, PR, or SD.
- OS rate at 6 and 12 months defined as determined by the proportion of subjects who are alive at 6 months and 12 months from the date of first dose of study drug, respectively.
- QoL as measured from the date of baseline and then every 4 weeks using the EORTC-QLQ-C30 (see Appendix C).

1.3.3 Safety Variable and Endpoints:

The safety and tolerability of abemaciclib will be assessed at specified times throughout the study, at the End of Treatment (EOT) visit and at the follow up visit, by evaluating AEs (type, frequency, severity, and causality), concomitant medication usage or any subsequent anticancer therapies (after the EOT visit), clinical laboratory test results, vital sign measurements, ECG findings, ECOG Performance Status, and physical examination results.

1.3.4 Exploratory Endpoints:

- Efficacy and safety of abemaciclib with regard to the subtypes of biliary tract carcinoma (BTC) including intrahepatic cholangiocarcinoma (IHCC), extra-hepatic cholangiocarcinoma (EHCC), ampullary carcinoma, and gall bladder carcinoma (GBC).
    - Molecular profiles of the biopsied tumor tissues (by Caris Life Sciences®) including genetic mutation in *K-RAS*, *B-RAF, TP53*, *INK4A/p16*, *CDKN1A/*p21, *cyclin D* and *RB* by DNA sequencing (clinical routine).
- Efficacy of abemaciclib with regard to the mutational status of *K-RAS*, *B-RAF, TP53*, *INK4A/p16*, *CDKN1A/p2*1, *cyclin D*, and *RB* genes.
- Genetic mutations and metabolic profiles in the extracellular vesicles from blood-based biopsies.

2.0 BACKGROUND INFORMATION

2.1 Introduction

BTC is a leading cause of cancer-related mortality. Except in the patients with localized disease for which surgical resection with curative intent is feasible, the prognosis of patients with recurrent, advanced unresectable, or metastatic BTC is generally poor. Standard treatment involves palliative systemic chemotherapy using gemcitabine and cisplatin, which produces limited benefit of tumor response and survival. Typically tumors progress following first-line chemotherapy. Currently there is no standard effective second-line treatment. The molecular basis of chemoresistance is poorly understood. Genetic mutations in *K-RAS*, *B-RAF*, *TP53*, *RB*, and *INK4A/p16* are variably present in BTC, but their contributory roles in resistance to chemotherapy and tumor progression are unclear. Targeted therapeutics has been clinically investigated in advanced BTC, but their clinical benefits remain to be demonstrated.

The newly developed small molecule inhibitor of cyclin-dependent kinases (CDK4 and CDK6), abemaciclib, provides a new opportunity of treating patients with BTC. The goal of this clinical study is to determine the efficacy and safety of abemaciclib in patients with advanced or metastatic BTC that has progressed or intolerant following one line of chemotherapy. This research work is important because this is anticipated to generate evidence for supporting the potential use of abemaciclib as a treatment of patients with advanced BTC by overcoming chemoresistance through inhibition of CDK4/6, which act downstream of mutant *K-RAS, B-RAF, TP53, RB*, and *INK4A/p16*. Besides, the data from this study are expected to generate insight into the roles of CDK4/6 in the pathogenesis of BTC with mutations in *K-RAS*, *B-RAF*, *TP53*, *RB*, or *INK4A/p16*. Moreover, successful completion of this study is expected to pave the way to future investigation of abemaciclib in combination with chemo-, targeted, or immuno- therapeutics for improving treatment response and survival in patients with BTC.

2.2 Biliary Tract Cancers - Cholangiocarcinoma (intra/extrahepatic bile ducts), ampullary carcinoma, gallbladder carcinoma

Approximately 10,000 new cases of BTC are reported each year within the United States (Siegel et al, 2017). For patients with BTC, the majority (80-90%) is diagnosed with locally advanced or metastatic disease, for which surgical resection with curative intent is not feasible (Marks and Yee, 2015a). Palliative systemic chemotherapy with or without radiation therapy remains the only treatment option (Wyluda and Yee, 2015). However, the literature regarding treatment results is limited because most studies are small, reports consist of treatment of bile duct carcinoma, gallbladder carcinoma, ampullary carcinoma, and pancreatic or hepatocellular carcinoma due to paucity of patients. Despite being in a similar anatomic location, the biological behavior may vary. In general, though, no single drug or combination has consistently increased survival beyond the expected 6-8 months.

The current standard first-line chemotherapy using gemcitabine and cisplatin produces limited survival benefits, with an overall survival of 12.7 months and progression-free survival of 8 months, as compared to gemcitabine, 8.1 months and 5 months, respectively (Valle et al, 2010). Typically, the disease will progress, and currently there is no standard second-line treatment. Despite treatment, the clinical outcomes of patients with BTC are generally poor, with a 2-year survival rate of 13% for patients with gallbladder carcinoma and less than 5% for cholangiocarcinoma (Marks and Yee, 2015b).

Clinical studies have been attempted to improve treatment response in patients with BTC by using various combinations of chemotherapeutic drugs and targeted agents, though with limited success (Wyluda and Yee, 2015; Marks and Yee, 2015a; Marks and Yee, 2015b). While epidermal growth factor receptors (ERBB-1, ERBB-2) are aberrantly over-expressed or amplified in BTC, the combination of either erlotinib or cetuximab with cytotoxic drugs have not produced significant clinical benefits (Lee et al, 2012; Malka et al, 2014). Conceivably, resistance of biliary tract tumors may be related to underlying genetic mutations, particularly *K-RAS*, *B-RAF*, *TP53*, *INK4A*/*p16*, and *RB*. Tumors with these mutations are typically aggressive and resistant to chemotherapy-induced apoptosis. Currently, there are no actionable agents that effectively target mutated K-RAS, p53, INK4A/p16, or RB. Targeting the oncogenes and tumor suppressor genes that control tumor growth may provide new opportunities to improve treatment responses for patients with BTC. Mutations in *K-RAS*, *B-RAF*, *TP53*, and *INK4A*/*p16* have been demonstrated in BTC (Chang et al, 2014; Hanada et al, 1999; Rashid et al, 2002; Robertson et al, 2013; Saetta et al, 2004; Suto et al, 2000; Tannapfel et al, 2000; Tannapfel et al, 2003; Tian et al, 2006; Marks and Yee, 2015a), and they may play important roles in development and progression of BTC.

The incidence of oncogenic mutations in *K-RAS* has been reported to be 17% to 59% of gallbladder carcinoma (GBC), 23% to 100% of extra-hepatic cholangiocarcinoma (EHCC), and 0% to 56% in intra-hepatic cholangiocarcinoma (IHCC). At a relatively low frequency, mutations in *B-RAF* were found in 1% of GBC, 3% of EHCC, and 5% of IHCC. Similarly, mutations in *PI3KCA* are present in 14% of GBC, 7% of EHCC, and 5% of IHCC. The reported incidence of mutations in *TP53* is 31% to 92% in GBC, 33% to 73% in EHCC, and 11% to 37% in IHCC. In BTC, inactivation of INK4A/p16 has been shown to occur through distinct mechanisms including deletion or point mutation of the *INK4A*/*p16* gene, and hypermethylation of the 5' regulatory regions of *INK4A*/*p16*.

In particular, 60-80% of BTC exhibit point mutations in the *INK4A*/*p16* gene. These data suggest that the mutated K-RAS, p53, and INK4A/p16 are potential therapeutic targets in BTC.

CDK4 and CDK6 are regulated either directly or indirectly by p53 and INK4A/p16, and small molecule inhibitors targeting CDK4/6 may produce anti-tumor effect in BTC by causing cell cycle arrest and apoptotic cell death. The major mitogenic signaling pathways such as those of EGF typically involve K-RAS that lead to activation of the CDK4/6 and cyclin D1 complex. This in turns phosphorylates and inactivates retinoblastoma (RB), enabling the transcription factor E2F to transcribe the targets genes that promote cell cycle progression, survival, and suppression of senescence. Activation of the INK4A/p16-CDKs-retinoblastoma (RB)-E2F pathway has been demonstrated to induce cell cycle arrest and apoptosis. This pathway is in parallel to that involves p53-CDKN1A/p21-mediated cell cycle arrest and apoptosis (Sherr and McCormick, 2002). By inhibiting CDKs, one can expect to induce cell cycle arrest and apoptosis in cancer cells that carry activating mutation in K-RAS and inactivating mutations in p53 and INK4A/p16 (Sherr et al, 2016). Thus, CDK inhibitors may be effective for treatment of patients with tumors carrying mutations in *K-RAS, B-RAF*, *TP*53, and *INK4A/p16*. Besides, synthetic lethal interaction between oncogenic K-RAS and CDK4 has been demonstrated (Puyol et al, 2010), such that inhibition of CDK4 in tumors with mutant K-RAS produces enhanced anti-tumor effect.

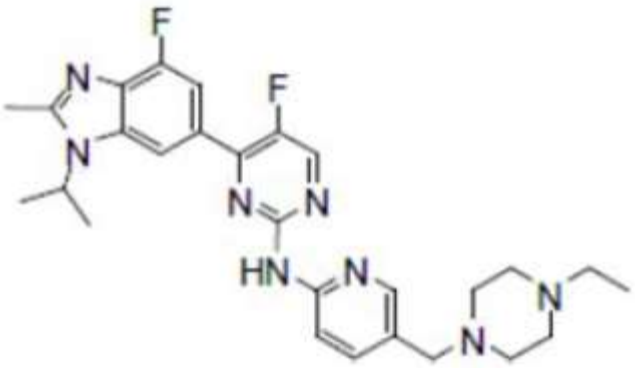
Small molecule inhibitors of cyclin-dependent kinases (CDKs) may produce anti-tumor effect in BTC by causing cell cycle arrest and apoptotic cell death. CDK inhibitors such as abemaciclib may help overcome therapeutic resistance by targeting CDK4/6 that act down-stream of mutated K-RAS, B-RAF, p53, or INK4A/p16 and impairing cell cycle progression. These activities have recently been reported in a variety of malignant diseases, but it has not been investigated in BTC. Besides, accumulating evidence indicates that serum metabolites are potential biomarkers of BTC (Liang et al, 2016, Lee et al, 2018). How serum metabolites are altered in patients treated with CDK inhibitors such as abemaciclib has not been studied. These observations form the basis of the hypothesis that inhibitors of CDKs such as abemaciclib may produce treatment response and prolong survival in patients with BTC, particularly those tumors that carry mutations in *K-RAS, B-RAF*, *TP*53, or *INK4A/p16*.

2.3 Abemaciclib: Drug Information

Abemaciclib is an orally available cyclin-dependent kinase (CDK) inhibitor that targets the CDK4 (cyclin D1) and CDK6 (cyclin D3) cell cycle pathway, with potential antineoplastic activity. Abemaciclib specifically inhibits CDK4 and CDK6, thereby inhibiting retinoblastoma (RB) protein phosphorylation in early G2. Inhibition of RB phosphorylation prevents CDK-mediated G1-S phase transition, thereby arresting the cell cycle in the G1 phase, suppressing DNA synthesis and inhibiting cancer cell growth. Overexpression of the serine/threonine kinases CDK4/6, as seen in certain types of cancer, causes cell cycle deregulation.

2.3.1 Abemaciclib Formulation

Abemaciclib is a kinase inhibitor for oral administration. It is a white to yellow powder with chemical name is 2-Pyrimidinamine, *N*-[5-[(4-ethyl-1-piperazinyl)methyl]-2-pyridinyl]-5-fluoro-4-[4-fluoro-2-methyl-1-(1-methylethyl)-1*H*-benzimidazol-6-yl]-. Abemaciclib has the following structure:



Empirical formula: $C_{27}H_{32}F_2N_8$ - Molecular weight: 506.59

Abemaciclib capsules are provided as immediate-release oval white, beige, or yellow capsules. Inactive ingredients are as follows: Excipients—microcrystalline cellulose 102, microcrystalline cellulose 101, lactose monohydrate, croscarmellose sodium, sodium stearyl fumarate, silicon dioxide. Color mixture ingredients—polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, and iron oxide red.

2.3.2 Pharmacology studies

2.3.2.1 Abemaciclib is currently indicated for the following:

• In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

• In combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.

• As monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

2.3.2.2 Mechanism of Action:

Cyclin dependent kinases 4 and 6 (CDK4/6) in complex with D-type cyclins promote cell cycle entry. Most human cancers contain overactive CDK4/6 cyclin D and thus CDK4/6 specific inhibitors are now approved for use as anti-cancer therapeutics. Abemaciclib is an inhibitor of CDK4 and CDK 6. CDK4 and CDK6, in breast cancer cell lines, promote phosphorylation of the retinoblastoma protein (RB), cell cycle progression and cell proliferation. In vitro, continuous exposure to abemaciclib inhibited RB phosphorylation and thus blocked progressed from G1 into the S phase of the cell cycle. This subsequently resulted in cell death/apoptosis.

2.3.2.3 Drug Metabolism and Pharmacokinetic Studies

The pharmacokinetics of abemaciclib have been characterized in patients with solid tumors, including metastatic breast cancer, and in normal healthy volunteers. Following single and repeated

twice daily administration of 50 mg (0.3 times the approved recommended 150 mg dose) to 200 mg of abemaciclib, the increase in plasma exposure (AUC) and Cmax was approximately dose proportional. Steady state was achieved within 5 days following twice daily dose exposure and the estimated geometric mean accumulation ratio was 2.3 (60% CV) and 3.2 (59% CV) based on Cmax and AUC, respectively.

The absolute bioavailability of abemaciclib after a single oral dose of 200 mg is 45% (19% CV). The median Tmax of abemaciclib is 8.0 hours (range 4.1-24 hours). A high fat, high calorie meal (800-1000 calories with 150 calories from protein, 250 calories from carbohydrate, and 500-600 calories from fat) administered to healthy volunteers increased the AUC of abemaciclib plus its active metabolites by 9% and increased Cmax by 26%.

In vitro abemaciclib was bound to human plasma proteins, serum albumin and alpha-1-acid glycoprotein in a concentration independent manner from 152 ng/mL to 5066 ng/mL. In a clinical study the mean (standard deviation, SD) bound fraction was 96.3% (2.10 for abemaciclib, 93.4% (2.3) for M2, 96.8% (0.8) for M18 and 97.8% (0.6) for M20. The geometric mean systemic volume of distribution is approximately 690.3 L (49% CV). In patients with advanced cancer, concentrations of abemaciclib and its active metabolites M2 and M20 in cerebrospinal fluid were comparable to unbound plasma concentrations. The geometric mean hepatic clearance (CL) of abemaciclib in patients was 26 L/H (51% CV) and the mean plasma elimination half-life for abemaciclib in patients was 18.3 hours (72% CV).

Hepatic metabolism is the main route of clearance of abemaciclib. Abemaciclib is metabolized to several metabolites primarily by cytochrome P450 3A4 (CYP 3A4) with formation of N-desethylabemaciclib (M2) representing the major metabolism pathway. Additional metabolites include hydroxyabemaciclib (M20), hydroxyl-N-desethylabemaciclib (M18) and an oxidative metabolite (M1). M2, M18 and M20 are equipotent to abemaciclib and their AUCs accounted for 25%, 13% and 26% of the total circulating analytes in plasma, respectively. After a single 150 mg oral dose of radiolabeled abemaciclib, approximately 81% of the dose was recovered in feces and approximately 3% recovered in urine. The majority of the dose eliminated in feces was metabolites.

2.3.2.4 Toxicology Studies

According to the bacterial reverse mutation (Ames) assay, abemaciclib and its active metabolites M2 and M20 did not display mutagenic properties. Abemaciclib was not clastogenic *in vitro* rat bone marrow micronucleus assay. Repeat-dose toxicity studies were performed to assess the effects of abemaciclib in testis, epididymis, prostate, and seminal vesicle at doses ≥10 mg/kg/day in rats and ≥0.3 mg/kg/day in dogs which exceed the recommended therapeutic doses in humans. The findings included decreased organ weights, intratubular cellular debris, hypospermia, tubular distillation, atrophy and degeneration or necrosis.

From the nonclinical safety report from Eli Lilly on 8/13/2020, the increased incidences of interstitial (Leydig) cell hyperplasia and interstitial (Leydig) cell adenoma were observed in rats treated with LY2835219 at clinically relevant LY2835219 exposure levels. Interstitial cell hyperplasia occurred in male rats at exposures below typical human exposures achieved when administered at 150 mg twice daily, and benign interstitial cell adenomas occurred in male rats at exposure levels that were 1.5-fold or 1.1-fold higher than typical human exposure at 150 mg or 200 mg twice daily respectively. Sponsors-Investigators are advised to instruct patients to conduct regular self-

examination of their testicles and report any new symptoms or changes to their investigator during clinical trial visits.

2.4 Findings from nonclinical and clinical studies

2.4.1 Nonclinical studies

Pre-clinical studies have demonstrated that inhibitors of CDK4/6 such as abemaciclib, produced anti-tumor effects by inducing cell cycle arrest and apoptosis and overcoming therapeutic resistance (Gelbert et al, 2014; Viluda and Rugo, 2016). Biochemical assays indicate that abemaciclib is a potent and selective inhibitor of CDK4 (IC_{50} 2 nM) and CDK6 (IC_{50}: 10 nM) by competing for ATP (KiATP: 0.6 nM and 2.4 nM for CDK4/cyclin D1 and CDK6/cyclin D1, respectively) (Gelbert et al, 2014). In cancer cells (of colon, breast, acute myelogenous leukemia) and human colorectal xenografts, abemaciclib produced cellular arrest in G1 phase of the cell cycle with inhibited phosphorylation of RB (Gelbert et al, 2014). Studies in mouse xenograft of melanoma with acquired resistance to vemurafenib that targets B-RAF V600E mutation, abemaciclib induced regression of tumor growth through targeting the up-regulated cyclin D1-CDK4/6 signaling from MAPK reactivation (Yadav et al, 2014). Besides, the human colorectal xenografts model indicates that chronic dosing of abemaciclib achieved minimum steady-state trough plasma concentrations of 200 ng/ml is required to maintain cell cycle arrest (Tate et al, 2014). Taken together, the pre-clinical data support the anti-tumor activity of abemaciclib through inhibition of CDK4/6-cyclin D1 and suggest a strategy for dosing abemaciclib in the clinical studies. From the Eli Lilly abemaciclib Investigator's Brochure (v. 12/2/2021): In a 2-year carcinogenicity study in rats, interstitial (Leydig) cell hyperplasia and benign interstitial (Leydig) cell adenomas in the testes were observed at clinically relevant exposure levels. Male patients should be instructed to conduct regular self-examination of their testicles and report any new symptoms or changes. In rodents, cataracts/lens fiber degeneration, retinal atrophy, and corneal inflammation have been observed at clinically relevant abemaciclib exposure levels. Patients who experience changes in vision or develop eye redness and symptoms such as eye pain should undergo ophthalmological investigations as clinically indicated.**2.4.2 Clinical Studies**

Abemaciclib is approved to treat: Breast cancer that is hormone receptor positive (HR+) and HER2 negative (HER2-) and is advanced or has metastasized (spread to other parts of the body). It is used with fulvestrant in women who progressed on prior hormonal therapy.

The safety of abemaciclib (150 mg twice daily) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in MONARCH 2. The data described below reflect exposure to abemaciclib in 441 patients with HR-positive, HER2-negative advanced breast cancer who received at least one dose of abemaciclib plus fulvestrant in MONARCH 2.

Median duration of treatment was 12 months for patients receiving abemaciclib plus fulvestrant and 8 months for patients receiving placebo plus fulvestrant.

Dose reductions due to an adverse reaction occurred in 43% of patients receiving abemaciclib plus fulvestrant. Adverse reactions leading to dose reductions in ≥5% of patients were diarrhea and neutropenia. Abemaciclib dose reductions due to diarrhea of any grade occurred in 19% of patients receiving abemaciclib plus fulvestrant compared to 0.4% of patients receiving placebo and

fulvestrant. Abemaciclib dose reductions due to neutropenia of any grade occurred in 10% of patients receiving abemaciclib plus fulvestrant compared to no patients receiving placebo plus fulvestrant.

Permanent study treatment discontinuation due to an AE were reported in 9% of patients receiving abemaciclib plus fulvestrant and in 3% of patients receiving placebo plus fulvestrant. Adverse reactions leading to permanent discontinuation for patients receiving abemaciclib plus fulvestrant were infection (2%), diarrhea (1%), hepatotoxicity (1%), fatigue (0.7%), nausea (0.2%), abdominal pain (0.2%), acute kidney injury (0.2%), and cerebral infarction (0.2%).

Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 18 cases (4%) of abemaciclib plus fulvestrant treated patients versus 10 cases (5%) of placebo plus fulvestrant treated patients. Causes of death for patients receiving abemaciclib plus fulvestrant included: 7 (2%) patient deaths due to underlying disease, 4 (0.9%) due to sepsis, 2 (0.5%) due to pneumonitis, 2 (0.5%) due to hepatotoxicity, and one (0.2%) due to cerebral infarction.

The most common adverse reactions reported (≥20%) in the abemaciclib arm were diarrhea, fatigue, neutropenia, nausea, infections, abdominal pain, anemia, leukopenia, decreased appetite, vomiting, and headache (Table 6). The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, anemia, and infections.

Table 1: Adverse Reactions ≥10% in Patients Receiving Abemaciclib (Verzenio®) plus Fulvestrant and ≥2% Higher than Placebo plus Fulvestrant in MONARCH 2

	VERZENIO plus Fulvestrant N=441			Placebo plus Fulvestrant N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders						
Diarrhea	86	13	0	25	<1	0
Nausea	45	3	0	23	1	0
Abdominal pain[a]	35	2	0	16	1	0
Vomiting	26	<1	0	10	2	0
Stomatitis	15	<1	0	10	0	0
Infections and Infestations						
Infections[b]	43	5	<1	25	3	<1
Blood and Lymphatic System Disorders						
Neutropenia[c]	46	24	3	4	1	<1
Anemia[d]	29	7	<1	4	1	0
Leukopenia[e]	28	9	<1	2	0	0
Thrombocytopenia[f]	16	2	1	3	0	<1
General Disorders and Administration Site Conditions						
Fatigue[g]	46	3	0	32	<1	0
Edema peripheral	12	0	0	7	0	0
Pyrexia	11	<1	<1	6	<1	0
Metabolism and Nutrition Disorders						
Decreased appetite	27	1	0	12	<1	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	13	0	0	11	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	16	0	0	2	0	0
Pruritus	13	0	0	6	0	0
Rash	11	1	0	4	0	0
Nervous System Disorders						
Headache	20	1	0	15	<1	0
Dysgeusia	18	0	0	3	0	0
Dizziness	12	1	0	6	0	0
Investigations						
Alanine aminotransferase increased	13	4	<1	5	2	0
Aspartate aminotransferase increased	12	2	0	7	3	0
Creatinine increased	12	<1	0	<1	0	0
Weight decreased	10	<1	0	2	<1	0

[a] Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, abdominal tenderness.
[b] Includes upper respiratory tract infection, urinary tract infection, lung infection, pharyngitis, conjunctivitis, sinusitis, vaginal infection, sepsis.
[c] Includes neutropenia, neutrophil count decreased.
[d] Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.
[e] Includes leukopenia, white blood cell count decreased.
[f] Includes platelet count decreased, thrombocytopenia.
[g] Includes asthenia, fatigue.

Additional adverse reactions in MONARCH 2 include venous thromboembolic events (deep vein thrombosis, pulmonary embolism, cerebral venous sinus thrombosis, subclavian vein thrombosis, axillary vein thrombosis, and DVT inferior vena cava), which were reported in 5% of patients treated with abemaciclib plus fulvestrant as compared to 0.9% of patients treated with fulvestrant plus placebo.

Table 2: Laboratory Abnormalities ≥10% in Patients Receiving Abemaciclib (Verzenio®) plus Fulvestrant and ≥2% Higher than Placebo plus Fulvestrant in MONARCH 2

	VERZENIO plus Fulvestrant N=441			Placebo plus Fulvestrant N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Creatinine increased	98	1	0	74	0	0
White blood cell decreased	90	23	<1	33	<1	0
Neutrophil count decreased	87	29	4	30	4	<1
Anemia	84	3	0	33	<1	0
Lymphocyte count decreased	63	12	<1	32	2	0
Platelet count decreased	53	<1	1	15	0	0
Alanine aminotransferase increased	41	4	<1	32	1	0
Aspartate aminotransferase increased	37	4	0	25	4	<1

Abemaciclib Administered as a Monotherapy in Metastatic Breast Cancer (MONARCH 1)

Patients with HR-positive, HER2-negative breast cancer who received prior endocrine therapy and 1-2 chemotherapy regimens in the metastatic setting

Safety data below are based on MONARCH 1, a single-arm, open-label, multicenter study in 132 women with measurable HR-positive, HER2-negative metastatic breast cancer. Patients received 200 mg abemaciclib orally twice daily until development of progressive disease or unmanageable toxicity. Median duration of treatment was 4.5 months.

Ten patients (8%) discontinued study treatment from adverse reactions due to (1 patient each) abdominal pain, arterial thrombosis, aspartate aminotransferase (AST) increased, blood creatinine increased, chronic kidney disease, diarrhea, ECG QT prolonged, fatigue, hip fracture, and lymphopenia. Forty-nine percent of patients had dose reductions due to an adverse reaction. The most frequent adverse reactions that led to dose reductions were diarrhea (20%), neutropenia (11%), and fatigue (9%).

Deaths during treatment or during the 30-day follow up were reported in 2% of patients. Cause of death in these patients was due to infection.

The most common reported adverse reactions (≥20%) were diarrhea, fatigue, nausea, decreased appetite, abdominal pain, neutropenia, vomiting, infections, anemia, headache, and thrombocytopenia (Table 3). Severe (Grade 3 and 4) neutropenia was observed in patients receiving abemaciclib.

Table 3: Adverse Reactions in ≥10% of Patients Receiving Abemaciclib (Verzenio®) in MONARCH 1

	VERZENIO N=132		
	All Grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders			
Diarrhea	90	20	0
Nausea	64	5	0
Abdominal pain	39	2	0
Vomiting	35	2	0
Constipation	17	<1	0
Dry mouth	14	0	0
Stomatitis	14	0	0
Infections and Infestations			
Infections	31	5	2
General Disorders and Administration Site Conditions			
Fatigue[a]	65	13	0
Pyrexia	11	0	0
Blood and Lymphatic System Disorders			
Neutropenia[b]	37	19	5
Anemia[c]	25	5	0
Thrombocytopenia[d]	20	4	0
Leukopenia[e]	17	5	<1
Metabolism and Nutrition Disorders			
Decreased appetite	45	3	0
Dehydration	10	2	0
Respiratory, Thoracic and Mediastinal Disorders			
Cough	19	0	0
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	15	0	0
Nervous System Disorders			
Headache	20	0	0
Dysgeusia	12	0	0
Dizziness	11	0	0
Skin and Subcutaneous Tissue Disorders			
Alopecia	12	0	0
Investigations			
Creatinine increased	13	<1	0
Weight decreased	14	0	0

[a] Includes asthenia, fatigue.
[b] Includes neutropenia, neutrophil count decreased.
[c] Includes anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased.
[d] Includes platelet count decreased, thrombocytopenia.
[e] Includes leukopenia, white blood cell count decreased.

Table 4: Laboratory Abnormalities for Patients Receiving Abemaciclib (Verzenio®) in MONARCH 1

	VERZENIO N=132		
	All Grades %	Grade 3 %	Grade 4 %
Creatinine increased	98	<1	0
White blood cell decreased	91	28	0
Neutrophil count decreased	88	22	5
Anemia	68	0	0
Lymphocyte count decreased	42	13	<1
Platelet count decreased	41	2	0
ALT increased	31	3	0
AST increased	30	4	0

Creatinine Increased

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function. In clinical studies, increases in serum creatinine (mean increase, 0.2-0.3 mg/dL) occurred within the first 28-day cycle of abemaciclib dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as BUN, cystatin C, or calculated GFR, which are not based on creatinine, may be considered to determine whether renal function is impaired.

Abemaciclib is also being studied in the treatment of other types of cancer. In a multicenter study that involved phase I dose escalation followed by tumor-specific cohorts, anti-tumor activity of abemaciclib was observed in patients with advanced solid tumors. These include breast cancer, non-small cell lung cancer, colorectal carcinoma, melanoma, ovarian cancer, endometrial cancer, and glioblastoma. Importantly, this study demonstrates a better disease control rate in patients with lung adenocarcinoma carrying *K-RAS* mutation than in those with wild-type *K-RAS* treated with abemaciclib (Patnaik et al, 2016). Similarly, patients who responded to abemaciclib include one with metastatic melanoma harboring both *N-RAS* mutation and loss of *INK4A/p16* gene. In this clinical study, the dose-limiting toxicity was grade 3 fatigue. Other common treatment-related AEs occurred in the gastrointestinal, renal, or hematopoietic systems. An acceptable safety profile and antitumor activity of abemaciclib were also demonstrated in another clinical study (Fujiwara et al, 2016). This is a phase I study using dose escalation of abemaciclib as a single agent for Japanese patients with advanced cancer. In this study of 12 patients, tumor response was demonstrated in two patients, one with breast cancer and one with neuroendocrine carcinoma. Taken together, abemaciclib produces anti-tumor effect as a single agent in various malignancies, and it possibly overcomes therapeutic resistance due to mutations in *K-RAS* and *INK4A/p16*.

It is known that BTC carry mutations in oncogenes and tumor suppressor genes that directly or indirectly regulate CDK4 and CDK6, but the efficacy of abemaciclib has not been investigated in BTC. Clinical study (as in this proposal) is indicated to test the hypothesis that abemaciclib prolongs

PFS in patients with advanced BTC by improving anti-tumor response. Exploring the potential therapeutic use of abemaciclib and correlation of its efficacy with tumor molecular profiles in advanced BTC is expected to create new treatment options, and generate insight into the roles of CDK4/6 in the pathogenesis of BTC. Furthermore, this study will help pave the way to future investigation of combination therapy using abemaciclib for improving treatment response and survival in patients with BTC.

2.5 Selection of Drugs/Doses

When used as monotherapy, the recommended dose of abemaciclib is 200 mg taken orally twice daily. Abemaciclib may be taken with or without food.

3.0 SELECTION OF PARTICIPANTS/ELIGIBILITY

3.1 Inclusion Criteria:

1. Male or female, age ≥18 years at the time of informed consent.
2. Capable and willing to sign informed consent form prior to performing any protocol-related procedures.
3. Histologic or cytologic evidence of advanced or metastatic biliary tract cancer including cholangiocarcinoma (intra-hepatic or extra-hepatic), ampullary carcinoma, or gallbladder carcinoma.
4. Evidence of recurrent, locally advanced, unresectable, or metastatic disease.
5. Progressed following or intolerant to one or more lines of systemic therapy, or treatment-naïve subjects who either decline or being considered not a good candidate first-line systemic chemotherapy per the opinion of the treating physician
6. Per the opinion of the physician investigator, predicted life expectancy of >3 months.
7. Presence of at least 1 lesion that is measurable or evaluable using RECIST v1.1.
8. ECOG performance score ≤ 2.
9. Per the opinion of the physician investigator, acute toxicities relating to any prior anticancer treatment have improved to Grade 1 or baseline. Exceptions include residual alopecia or Grade 2 peripheral neuropathy.
10. Ability to swallow capsules.
11. Adequate organ function, as evidenced by all of the following:

System	Laboratory value
Hematologic	
ANC	≥1500/μL
Platelets	≥75,000/μL
Hemoglobin	≥8.0 g/dL (Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator. Initial treatment may not begin earlier than the day after the erythrocyte transfusion.)

System	Laboratory value
Hepatic	
Serum total bilirubin	≤2 times the ULN; Patients with Gilbert's syndrome with a total bilirubin ≤3.0 times ULN and direct bilirubin within normal limits are permitted.
AST and ALT	≤3 times the ULN, ≤ 5 times ULN for subjects with liver metastasis

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

12. WOCP defined as not surgically sterile (hysterectomy, tubal ligation, oophorectomy) or at least 1 year postmenopausal must have a negative serum pregnancy test before study drug administration on cycle 1 day 1.
13. WOCP must use a medically acceptable method of contraception and must agree to continued use of this method for the duration of the study and for 3 weeks after last dose of study drug. Acceptable methods of contraception include abstinence, barrier method with spermicide, intrauterine device (IUD) known to have a failure rate of less than 1% per year, or steroidal contraceptive (oral, transdermal, implanted, or injected) in conjunction with a barrier method.
14. Male subjects capable of producing offspring, must use a medically acceptable method of contraception and agrees to continued use of this method for the duration of the study and for 3 weeks after last dose of study drug because of the possible effects on spermatogenesis). Acceptable methods of contraception include abstinence, use of barrier method with spermicide, WOCP partner's use of an IUD known to have a failure rate of 1% per year, WOCP partner's use of steroidal contraceptive (oral, transdermal, implanted, or injected) in conjunction with a barrier method, or WOCP partner is surgically sterile or at least 1 year post-menopausal. In addition, male subjects may not donate sperm for the duration of the study and for 30 days after last dose of study drug.
15. Must be willing and able to comply with the protocol, including adhering to study restrictions, remaining at the clinic as required during the study period, and willing to return to the clinic for the follow-up evaluation.
16. Patients who received chemotherapy must have recovered (Common Terminology Criteria for Adverse Events [CTCAE] Grade ≤1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy.
17. Patients who received radiotherapy must have completed and fully recovered from the acute effects of radiotherapy. A washout period of at least 14 days is required between end of radiotherapy and randomization.
18. Completed last dose of myelosuppressive chemotherapy greater than 21 days prior to first dose of study drug.
19. Completed last dose of non-myelosuppressive biological or monoclonal antibody therapy greater than 14 days prior to first dose of study drug.

3.2 Exclusion Criteria:

1. Ongoing or active infection requiring systemic antibiotics.

2. Uncontrolled hypertension despite adequate therapy (i.e., systolic blood pressure higher than 150 mm Hg or diastolic blood pressure higher than 90 mm Hg found on 2 separate occasions separated by at least 1 week).
3. Diabetes mellitus and occurrence of more than 2 episodes of ketoacidosis in the 12 months prior to the first dose of study drug.
4. Active second malignancy other than curatively resected basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ carcinoma of the cervix, or other cancers for which they are treated with curative intent, and no known active disease in the 3 years prior to enrollment.
5. Primary brain tumor or brain metastases from another primary site.
6. Known history of HIV.
7. Known active viral hepatitis B or viral hepatitis C.
8. History of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), or sudden cardiac arrest. Subjects with controlled atrial fibrillation for more than 30 days are permitted.
9. Congestive Heart Failure (NYHA Class III or IV), or acute coronary syndromes within 6 months of enrollment.
10. Female subjects who are pregnant or breastfeeding.
11. Any other medical, psychiatric, or social condition, which in the opinion of the investigator, would preclude participation in the study, pose an undue medical hazard, interfere with the conduct of the study, or interfere with interpretation of the study results. For example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy.
12. Use of an investigational drug within 1 month before the screening visit or currently participating in another interventional investigational study.
13. Any disorder that may interfere with drug absorption, distribution, metabolism, or excretion (including extensive gastrointestinal surgery that involves removal of the entire stomach or most of the small intestine or large intestine, bariatric surgery, uncontrolled active Crohn's disease or ulcerative colitis, or preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea). History of Whipple's procedure is permitted.
14. Known hypersensitivity to any of the components in abemaciclib, including: micro-crystalline cellulose 102, microcrystalline cellulose 101, lactose monohydrate, croscarmellose sodium, sodium stearyl fumarate, silicon dioxide. Color mixture ingredients—polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, and iron oxide red.
15. The patient has serious and/or uncontrolled preexisting medical condition(s) that, in the judgement of the investigator, would preclude participation in this study (for example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, severe renal impairment [e.g. estimated creatinine clearance <30ml/min].

3.3 Registration Procedures

Eligible participants will be enrolled on study by the Penn State Cancer Institute, Clinical Trials Office (PSCI-CTO) by the designated Research Study Coordinator. The protocol specific Eligibility Checklist Worksheet must be completed in its entirety prior to enrollment, and source documentation verifying each eligibility criterion must be available. The physician investigator will sign this document acknowledging accuracy of the data including any subjective variables. Following verification of eligibility, it is preferred that participants begin the investigational treatment as soon as possible.

3.4 Early Withdrawal /Discontinuation of the Study Treatment

A participant will be withdrawn from study treatment for any of the following reasons:

- Withdrawal of consent from the study by the participant at any time and for any reason. The reason for elective withdrawal will be documented in the research record if known.
- Unacceptable toxicity in the judgement of the Principal Investigator.
- Toxicity possibly related to abemaciclib does not resolve in14 days.
- Progression of disease requiring alternative systemic treatment.
- Significant participant or protocol noncompliance that, in the opinion of the Principal Investigator, warrants withdrawal of treatment. For example, participant is noncompliant in taking prescribed study medication or fail to return for scheduled follow up visits.
- Development of intercurrent, non-cancer related illnesses or complications that prevent either continuation of therapy or regular follow up.
- In the opinion of the Principal Investigator, it is inappropriate for the participant to continue on the study.
- Best medical interest of the participant at the discretion of the Principal Investigator.
- Subject becomes pregnant.
- Participant become lost to follow up. Participants who are unable to be located despite 3 documented attempts at contact (telephone, mail, or email) followed by a certified letter will be considered lost to follow up and rendered off study.
- Premature study closure.

Every effort should be done to help assure participants who are withdrawn from study treatment undergo the planned end of study follow up, end of treatment follow-up as outlined.3.4.1 Follow-up

An EOT visit will occur 30 ± 7 days from the last study treatment. Follow-up visits will occur every 3 months (+/- 7 days) x2, beginning 3 months after last dose of the study drug, then every 6 months (± 7 days) thereafter.

4.0 RECRUITMENT METHODS

4.1 Identification/Screening of Subjects

Patients seen at Penn State Cancer Institute with the disease of study may be pre-screened through the electronic medical record or in the clinic by research team members for basic variables such as age and ability to sign consent. Those patients deemed by this pre-screening effort to meet these basic criteria will be approached for consideration of participation.

This clinical trial will be available for potential patient candidates to view on clinicaltrials.gov.

Formal screening for participation will not be initiated until an IRB approved informed consent form has been signed.. All subjects who sign consent will be assigned a study ID number.

Subjects who consent to participate in the clinical trial but who are not subsequently assigned to the study intervention or registered will be considered screen failures. Subject may be re-screened. All re-screened subjects will be assigned the same subject ID number as was assigned during the initial screening.

4.2 Recruitment Process

Potential participants will be approached for possible participation in the PSCI outpatient clinic or the inpatient setting if applicable. The protocol may be initially presented to the patient by the Principal Investigator or Sub-Investigator. A member of the study team will discuss the protocol further with the patient.

4.3 Recruitment Materials

No recruitment materials will be used for the purpose of this clinical trial.

5.0 CONSENT PROCESS AND DOCUMENTATION

5.1 Informed Consent Process

The informed consent process will be carried out in compliance with federal regulations. A copy of the signed IRB approved consent document will be provided to the patient. The original document will be maintained in the protocol specific regulatory files with copies in the Cerner electronic medical record and research chart.

5.2 Coercion and Undue Influence

During the consent conference, all patients will be made aware that this is a research investigation and participation is optional. Their medical care at Penn State Health will not be affected by their decision to participate or not participate.

5.3 Consent Other Considerations

5.3.1 Non-English-Speaking Participants

Non-English-speaking patients are eligible for participation in this trial. Protocol and related information will be provided to the patient orally in their language using a certified interpreter prior to and throughout the course of the study. In the event that a non-English speaking patient is identified, the consent process and ongoing research process will be carried out in compliance with federal regulations, as well as the following institutional policies and procedures.

5.3.2 Cognitively Impaired Adults/Unable to consent

Not applicable. Eligibility requires that patients are able to understand the requirements for the study and provide consent themselves.

6.0 HIPAA RESEARCH AUTHORIZATION AND/OR WAIVER OR ALTERATION OF AUTHORIZATION

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI. Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or alteration of authorization statements of agreement

Not applicable.

7.0 STUDY DESIGN AND PROCEDURES

This is a open label pilot study of abemaciclib administered orally to participants with recurrent, locally advanced, unresectable, or metastatic BTC. This study consists of a screening period of up to 28 days, up to eight 28-day treatment cycles, an EOT visit and follow-up visits every 3 months (± 7 days) 6 months after last dose of the study drug then every 6 months(± 7 days) thereafter until death .

The Principal Investigator will determine whether the participant meets all inclusion/exclusion criteria.

Each cycle will consist of 28 days of twice daily dosing of abemaciclib. Participants must receive a minimum of two 28 day cycles to be considered evaluable for the primary endpoint of ORR unless they withdraw earlier due to rapid disease progression. If a participant is deriving clinical benefit, he or she may receive additional cycles until one of the criteria for discontinuation is met.

Participants who are deriving clinical benefit after completing the treatment period may continue on additional cycles of therapy at the discretion of the sponsor and the medical monitor from the DSMC. Any participant that continues on abemaciclib after completing the treatment period will be monitored and assessed for tumor response per clinical routine per principal investigator.

Participants who complete treatment or who are withdrawn from treatment early will have an end of treatment visit. Participants with measurable disease who end treatment on a cycle at which a tumor response assessment is not planned should have end of treatment CT scans/MRI scans. Follow up visits will be performed every three months +/- 7 days 6 months for the subsequent anticancer therapy and survival then thereafter every 6 months (± 7 days) for survival only till death. It will be done by either clinic visit or phone call.

7.1 General Design/Phase/Schema

This is an open label pilot study to determine the efficacy and safety/tolerability of abemaciclib in participants with locally advanced, unresectable, or metastatic biliary tract cancer who have failed one or more lines of systemic therapy, or treatment-naïve subjects who either decline or being considered not a good candidate first-line systemic chemotherapy per the opinion of the treating physician**7.1.1 Enrollment/Randomization**

This is a non-randomized study and thus participants will be enrolled sequentially. Participants will be screened for eligibility after signing the informed consent form.

7.1.2 Participant Population

Participants with histologically confirmed advance or metastatic biliary tract cancer including cholangiocarcinoma (intra-hepatic or extra-hepatic bile ducts), ampullary carcinoma, or gallbladder carcinoma who progressed following one or more lines of systemic therapy, will be enrolled if they meet eligibility criteria.

7.1.3 Number of sites/number of participants

This is a single center study that will be conducted at the Penn State Cancer Institute. In the future, additional study sites may be added if needed to assist with accrual numbers. Any addition of new sites and related modification to the protocol will be reviewed and approved in advance by the IRB and other applicable oversight bodies. Approximately up to 20 subjects may be enrolled to attain at least 10 evaluable participants.

7.1.4 Sample Size consideration

Refer to section 8.1.

7.1.5 Study Treatment

Abemaciclib will be given as a single oral agent. The starting dose will be 200 mg twice daily. One cycle = 28 days. There will be no protocol scheduled hiatus and daily dosing will be continuous unless there is unacceptable toxicity, disease progression, or death.

7.1.6 Dosing Adjustments, Delays and Discontinuation

Abemaciclib Dose Modification for Grade 3 or 4 AEs

Dose Level	Abemaciclib Dose
Recommended starting dose	200 mg twice daily
First dose reduction	150 mg twice daily
Second dose reduction	100 mg twice daily
Third dose reduction	50 mg twice daily

Complete blood counts with differentials and complete metabolic panel will be monitored every 2 weeks for the first 2 months, then monthly for the next 2 months, at the beginning of every cycle.

7.1.7 Subject Evaluability and Subject Replacement

Approximately up to 20 subjects will be enrolled to attain at least 10 evaluable participants. Participants who voluntarily withdraw from the study for a reason other than tumor progression or inability to tolerate treatment may be replaced.

7.1.8 Safety Analysis

A safety analysis will be requested to review all safety data following the recruitment of 5 participants. The study may be terminated early if unexpected toxicities are observed. Following study termination, the internal PSCI DSMC will complete an expedited review of all efficacy and safety data; All regulatory bodies will be notified of study termination within no more than 2 business days of such a decision.

7.1.9 Safety Monitoring and Study Stopping Rules

In accordance with administrative, legal and ethical requirements documented in this protocol, safety monitoring will be performed by an internal Data Safety Monitoring Committee (DSMC). The DSMC of PSCI will review safety data per DSMC charter. The principal investigator (PI) will continuously monitor study progress for safety and will hold routine meetings with the study team and disease center personnel to review overall conduct and progress of this study. The frequency of such meetings will be dependent upon accrual to the trial and issues that arise. Study team meetings will include discussion of accrual, adverse events/safety issues, response and overall progress of the trial. Unexpected and related adverse events will be reported as they arise as well as any significant literature reporting developments that may affect the safety of participants in this study. Serious and unexpected adverse events will be reported to PSCI DMSC.

This study will be suspended or terminated prematurely for any of the following reasons:

- A death that is unexpected and at least probably related to abemaciclib
- Severe anaphylactic reaction to abemaciclib, either active ingredient, metabolites or excipients
- Any event, that, in the opinion of the Principal Investigator, or internal monitoring team, warrant immediate review by the PSCI DSMC
- Any other safety finding assessed as related to abemaciclib that, in the opinion of the PSCI DSMC, contraindicates further dosing of any participant.
- Any interim finding that, in the opinion of the Principal Investigator, suggests that the study has no clinical benefit for the participants.

7.1.10 Study Duration

- Enrollment period: 36 months
- Length of study: 48 months
- Anticipated length of study for each participant: 6 months

7.1.11 Study Drug

Abemaciclib will be stored in the limited access Penn State Health Investigational Drug Pharmacy. Maintenance, secure storage, and accountability of abemaciclib will be ensured according to institutional policies and procedures for investigational medications.

Abemaciclib is stored at room temperature. Refer to package label for specific storage conditions and instructions. Abemaciclib will be provided in 50 mg capsules in 60 count bottles. The Investigational pharmacist may dispense the medication directly to the research participant or the designated research team member.

7.2 Study Procedures and Assessments

Refer to Appendix B: *Protocol Required Interventions and Assessments*.

7.2.1 Procedures at Screening

A signed and dated informed consent form will be obtained before screening procedures commence. Evaluations obtained as part of routine medical care and performed during the screening period may be used for the protocol required evaluations.

After informed consent is obtained, participants who are screened will be assigned a unique identifier number such that all participants are given consecutive identification numbers in successive order.

A participant who is screened but not enrolled may be re-screened.

<u>The following procedures and assessments will be performed within 28 days prior to C1D1 visit:</u>

- Obtain histology report confirming diagnosis of malignancy
- Review inclusion/exclusion criteria
- Tumor evaluation through diagnostic imaging and RECIST v1.1 reading, including CT or MRI scans of chest, abdomen, and pelvis with contrast, and brain MRI, or PET CT scan
- Archival tumor samples will be collected for subjects for confirmation of diagnosis, as well as, for determination of exploratory mutational analysis.
- If no archival tumor samples are available, fresh biopsy will be collected for subjects for confirmation of diagnosis, as well as, for determination of exploratory mutational analysis.
- Review medical history (to include demographics, tobacco use (if smokes or smoked, and smoking pack year), surgical and psychiatric history and cancer treatment history)
- Review prior medication history (those medications taken within the last 28 days before the start of study treatment)
- Full physical examination including height, weight and vital signs measurements (temperature, heart rate, respiration rate and blood pressure).
- ECOG performance status
- Triplicate 12-lead ECG
- Clinical laboratory tests include hematology (complete blood counts with differential), serum chemistry (complete metabolic panel including Na, K, Cl, CO2, blood urea nitrogen, creatinine, glucose, aspartate aminotransferase, total bilirubin, alkaline phosphatase, alanine aminotransferase, albumin), coagulation profile including prothrombin time (PT), international normalized ratio (INR), partial thromboplastin time (PTT), CA 19-9, urinalysis)

<u>The following procedures and assessments will be performed within 7 days prior to C1D1 visit:</u>

- Serum pregnancy test.

Participants who continue to meet all inclusion and exclusion criteria will be enrolled in the study.

7.2.2 Procedures During Study Drug Treatment

7.2.2.1 Procedures During Treatment Cycles (28-Day Cycles)

Study procedures and assessments will be performed as described below. No extra capsules of abemaciclib will be distribute to participants for each cycle.

The following procedures and assessments will be performed on C1D1 and C2D1:

- Physical examination, including weight and vital signs measurements.
- ECOG performance status
- AEs
- Concomitant medication
- 12-lead ECG (C1D1 and subsequent cycles if clinically indicated)
- Clinical laboratory tests
- EORTC-QLQ-C30 (see Appendix C)
- Dispense Abemaciclib
- Collect unused Abemaciclib (C2D1 only)
- Review participant drug diary and compliance with study medication (C2D1 only)
- Extracellular vesicle detection (C1D1 only)

The following procedures and assessments will be performed on C1D15 and C2D15:

- Physical examination, including vital signs measurements.
- ECOG performance status
- AEs
- Concomitant medication
- Clinical laboratory tests

The following procedures and assessments will be performed on C3-C8D1:

- Physical examination, including weight and vital signs measurements. Vital signs include temperature, heart rate, respiration rate and blood pressure.
- ECOG performance status
- AEs
- Concomitant medication
- Tumor evaluations every 8 weeks through diagnostic imaging and RECIST v1.1 reading, including CT or MRI of abdomen and pelvis with contrast every 8 weeks (± 7 days).
- Clinical laboratory tests
- EORTC-QLQ-C30

- Dispense Abemaciclib
- Collect unused Abemaciclib
- Review participant drug diary and compliance with study medication
- Extracellular vesicle detection will be performed every 8 weeks (± 3 days) until objective disease progression or study completion.

7.2.3 Procedures During the End-of-Treatment Visit

For participants who complete the study or withdraw prematurely, final evaluations will be performed at the EOT visit or on the last day the participant receives the study drug.

Participants with ongoing AEs or clinically significant abnormal laboratory test results (as interpreted by the Principal Investigator) will be monitored per the Principal Investigator and AEs will be recorded and reported per protocol Section 10.1.2.

If a participant withdraws from the study during the treatment period, the reason must be determined and recorded on the participant's electronic case report form (eCRF). For participants who withdraw consent, every attempt will be made to determine the cause.

The following procedures will be performed at the EOT visit (up to 30 days ± 7 days) from last dose of study drug), unless otherwise specified:

- Physical examination including body weight and vital sign measurements
- ECOG performance status
- AEs
- Concomitant medication
- Collect unused Abemaciclib
- Review participant drug diary and compliance with study medication
- Tumor evaluations through diagnostic imaging (CT/MRI/PET) every 8 weeks (± 3 days) until objective disease progression.
- Subsequent post-study treatment anti-cancer therapy
- Clinical laboratory tests
- 12-lead ECG if clinically indicated
- EORTC-QLQ-C30
- Extracellular vesicle detection will be performed every 8 weeks (± 3 days) until objective disease progression or study completion

7.2.4 Procedures at Follow-Up Visits

- Tumor evaluations: every 3 months (± 7 days) beginning 3 months after the last dose of study drug for subjects who have not progressed.
- Survival/death assessment, including data and cause of death if applicable. Every 3 months (± 7 days) x2, beginning 3 months after last dose of the study drug then every 6 months (± 7 days) thereafter. The assessment can be performed at standard of care visits or any other possibly treatments, or via phone calls.

- Subsequent post-study treatment anticancer therapy: every 3 months (± 7 days) x2, beginning 3 months after last dose of the study drug then every 6 months (± 7 days) thereafter.

7.2.5 Unscheduled Visits

An unscheduled visit may be performed at any time during the study at the request of the participant or as deemed necessary by the Principal Investigator. The date and reason for the unscheduled visit will be recorded on the CRF, as well as any other data obtained (e.g. AEs, concomitant medications and treatments, and results from procedures or tests).

7.3 Treatment of participants

7.3.1 Study Drugs Administered

The investigational drug, abemaciclib, will be administered as 50 mg capsules.

7.3.2 Study drug information

When used as monotherapy, the recommended dose of abemaciclib is 200 mg taken orally twice daily. Continue treatment until disease progression or unacceptable toxicity.

7.3.3 Packaging/Preparation/Dispensing/Storage

Abemaciclib 50 mg capsules are oval beige. Capsules are suppled in 60 count bottles. Drug is to be stored at room temperature.

7.3.4 Administration

Participant will be administered a 200 mg dose (i.e., four 50 mg capsules) of abemacilib orally twice daily. The participant will be instructed to swallow abemaciclib as a whole capsule and not to chew, crush or split capsules before swallowing. Participants should not ingest abemaciclib capsules if broken, cracked, or otherwise not intact. Doses should be taken at approximately the same time every day, twice daily. Capsules can be taken orally with or without food. If the participant vomits or misses a dose of abemaciclib, the participant will be instructed to take the next dose at its scheduled time.

Participants will also be provided with a diary and instructed to keep a twice daily record of the times they have taken their medications and any other events such as vomiting, diarrhea, etc.

7.3.5 Overdose

There is no known antidote for abemaciclib. The treatment of overdose of abemaciclib should consist of general supportive measures.

7.3.6 Missed doses

If a participant vomits or misses a dose, the participant will be instructed to take the next dose at its scheduled time.

7.3.7 Restriction on Concomitant Therapies

Effect of Other Drugs on Abemaciclib

Strong CYP3A Inhibitors

Strong CYP3A4 inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity. all strong CYP3A inhibitors are excluded from use during this clinical trial. Patients should avoid grapefruit, orange juice, pomelo products.

Ketoconazole

Avoid concomitant use of the strong CYP3A4 inhibitor ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold.

Itraconazole (a strong CYP3A inhibitor) is predicted to increase the relative potency adjusted unbound AUC of abemaciclib plus its active metabolites (M2, M18 and M20) by 2.2-fold. Co-administration of 500 mg twice daily doses of clarithromycin (a strong CYP3A inhibitor) with a single 50 mg dose of abemaciclib (0.3 times the approved recommended 150 mg dosage) increased the relative potency adjusted unbound AUC0-INF of abemaciclib plus its active metabolites (M2, M18, and M20) by 1.7-fold relative to abemaciclib alone in cancer patients.

Moderate CYP3A Inhibitors: Diltiazem and verapamil (moderate CYP3A inhibitors) are predicted to increase the relative potency adjusted unbound AUC of abemaciclib plus its active metabolites (M2, M18, and M20) by 1.7-fold and 1.3-fold, respectively.

Strong CYP3A Inducers

Co-administration of 600 mg daily doses of rifampin (a strong CYP3A inducer) with a single 200 mg dose of abemaciclib decreased the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2, M18, and M20) by 67% in healthy subjects.

Moderate CYP3A Inducers: The effect of moderate CYP3A inducers on the pharmacokinetics of abemaciclib is unknown.

Loperamide: Co-administration of a single 8-mg dose of loperamide with a single 400-mg dose of abemaciclib in healthy subjects increased the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites (M2 and M20) by 12%, which is not considered clinically relevant.

Fulvestrant: In clinical studies in patients with breast cancer, fulvestrant had no clinically relevant effect on the pharmacokinetics of abemaciclib or its active metabolites.

Effects of Abemaciclib on Other Drugs

Loperamide: In a clinical drug interaction study in healthy subjects, co-administration of a single 8 mg dose of loperamide with a single 400 mg abemaciclib (2.7 times the approved recommended 150 mg dosage) increased loperamide $AUC_{0\text{-}INF}$ by 9% and C_{max} by 35% relative to loperamide alone. These increases in loperamide exposure are not considered clinically relevant.

Metformin: In a clinical drug interaction study in healthy subjects, co-administration of a single 1000 mg dose of metformin, a clinically relevant substrate of renal OCT2, MATE1, and MATE2-K

transporters, with a single 400 mg dose of abemaciclib (2.7 times the approved recommended 150 mg dosage) increased metformin $AUC_{0\text{-}INF}$ by 37% and C_{max} by 22% relative to metformin alone. Abemaciclib reduced the renal clearance and renal secretion of metformin by 45% and 62%, respectively, relative to metformin alone, without any effect on glomerular filtration rate (GFR) as measured by iohexol clearance and serum cystatin C.

Fulvestrant: In clinical studies in patients with breast cancer, abemaciclib had no clinically relevant effect on fulvestrant pharmacokinetics.

In Vitro Studies

Transporter Systems: Abemaciclib and its major active metabolites inhibit the renal transporters OCT2, MATE1, and MATE2-K at concentrations achievable at the approved recommended dosage. The observed serum creatinine increase in clinical studies with abemaciclib is likely due to inhibition of tubular secretion of creatinine via OCT2, MATE1, and MATE2-K [see Adverse Effects (7.1)]. Abemaciclib and its major metabolites at clinically relevant concentrations do not inhibit the hepatic uptake transporters OCT1, OATP1B1, and OATP1B3 or the renal uptake transporters OAT1 and OAT3.

Abemaciclib is a substrate of P-gp and BCRP. Abemaciclib and its major active metabolites, M2 and M20, are not substrates of hepatic uptake transporters OCT1, organic anion transporting polypeptide 1B1 (OATP1B1), or OATP1B3.

Abemaciclib inhibits P-glycoprotein (P-gp) and BCRP. The clinical consequences of this finding on sensitive P-gp and BCRP substrates are unknown.

CYP Metabolic Pathways: Abemaciclib and its major active metabolites, M2 and M20, do not induce CYP1A2, CYP2B6, or CYP3A at clinically relevant concentrations. Abemaciclib and its major active metabolites, M2 and M20, down regulate mRNA of CYPs, including CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6 and CYP3A4. The mechanism of this down regulation and its clinical relevance are not understood. However, abemaciclib is a substrate of CYP3A4, and time-dependent changes in pharmacokinetics of abemaciclib as a result of autoinhibition of its metabolism was not observed.

P-gp and BCRP Inhibitors: *In vitro*, abemaciclib is a substrate of P-gp and BCRP. The effect of P-gp or BCRP inhibitors on the pharmacokinetics of abemaciclib has not been studied.

Thus, all strong CYP3A inhibitors are excluded from use during this clinical trial. Patients should avoid grapefruit, orange juice, pomelo products.

Strong CYP3A Inducers

Coadministration of abemaciclib with rifampin, a strong CYP3A inducer, decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity. For the purpose of this study, all CYP3A inducers will not be permitted on this study; please see Appendix A and refer to crediblemeds.org for a more comprehensive list of prohibited medications.

7.3.8 Dose Delays/Modifications

Dose Modifications for Adverse Reactions

The recommended abemaciclib dose modifications for adverse events are provided in table below. Discontinue abemaciclib for participants unable to tolerate 50 mg twice daily. Once the drug is reduced, there is no dose re-escalation.

Abemaciclib Dose Modification for Adverse Reactions

Dose Level	Abemaciclib Dose
Recommended starting dose	200 mg twice daily
First dose reduction	150 mg twice daily
Second dose reduction	100 mg twice daily
Third dose reduction	50 mg twice daily

Guidelines for Dose Adjustments and Delays of Abemaciclib

Toxicity Type	Toxicity Profile and Severity	Dose Modification	Dose Reduction
Hematologic Toxicity	Grade 3	Dose **MUST** be held until toxicity resolves to ≤ Grade 2.	Dose **MAY** be reduced by 1 dose level at investigator's discretion.
Hematologic Toxicity (second or more recurrence)	Grade 3	Dose **MUST** be held until toxicity resolves to ≤ Grade 2.	Dose **MUST** be reduced by 1 dose level with each occurrence. Discontinue abemaciclib for participants unable to tolerate 50 mg twice daily
Hematologic Toxicity	Grade 4	Dose **MUST** be held until toxicity resolves to ≤ Grade 2.	Dose **MUST** be reduced by 1 dose level. Discontinue abemaciclib for participants unable to tolerate 50 mg twice daily

Nonhematologic Toxicity (except diarrhea and ALT increased)	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose **MUST** be held until toxicity resolves to either baseline or ≤ Grade 1.	Dose **MUST** be reduced by 1 dose level. Discontinue abemaciclib for participants unable to tolerate 50 mg twice daily
Nonhematologic Toxicity (except diarrhea and ALT increased)	Grade 3 or 4 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose **MUST** be held until toxicity resolves to either baseline or ≤ Grade 1.	Dose **MUST** be reduced by 1 dose level. Discontinue abemaciclib for participants unable to tolerate 50 mg twice daily
Diarrhea	Grade 2 that does not resolve within 24 hrs to at least Grade 1	Dose **MUST** be held until toxicity resolves to ≤Grade 1.	Dose **MAY** be reduced by 1 dose level.
Diarrhea	Grade 3 or 4 that does not resolve with maximal supportive measures within7 days or requires hospitalization.	Dose **MUST** be held until toxicity resolves to ≤ Grade 1.	Dose **must** be reduced by 1 dose level - Discontinue abemaciclib for participants unable to tolerate 50 mg twice daily

ALT/AST increased	Grade 2 (>3.0-5.0xULN) that does not resolve within 7 days to baseline or ≤ Grade 1	Dose **MUST** be held until toxicity resolves to baseline or Grade 1	Dose **MUST** be reduced by 1 dose level
	Grade 3 (>5.0-20.0xULN) with total bilirubin >2xULN, in the absence of cholestasis	Abemaciclib therapy MUST be discontinued	Abemaciclib therapy MUST be discontinued
	Grade 4 (>20.0xULN)	Abemaciclib therapy MUST be discontinued	Abemaciclib therapy MUST be discontinued

Abbreviations: ALT = alanine aminotransferase, AST=aspartate aminotransferase, ULN = upper limit of normal.

Monitor ALT, AST, and serum bilirubin prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly following cycle 2, and as clinically indicated.

7.4 Supportive Care Guidelines

7.4.1 Guidelines for Diarrhea Management

Clinical trial data indicates the majority of patients who receive abemaciclib will develop diarrhea. Early identification and intervention for the management of diarrhea has been helpful to patients

At enrollment, participants should receive instructions on the prompt management of diarrhea. In the event of diarrhea, supportive care measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the participant should initiate antidiarrheal therapy (e.g. loperamide) and notify the investigator for further instructions and appropriate follow-up.
- Participants should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- (Refer to Dose Modification Table above for more information on dose modification).

7.4.2 Guidance for Increases in Serum Creatinine and Assessment of Renal Insufficiency

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting glomerular function. In vitro studies have indicated that abemaciclib and its major metabolites LSN2839567 and LSN3106726 inhibit the renal transporters OCT2, MATE1, and MATE2-K at clinically relevant concentrations. Thus, increases in serum creatinine observed following dosing with abemaciclib, in the absence of simultaneous increases in BUN or

development of an abnormal urinalysis, are most likely due to inhibition of its tubular secretion via OCT2, MATE1, and MATE2-K and may not reflect a decline in renal function, making serum creatinine level an unreliable measurement for renal function.

Increases in serum creatinine occurred within the first 28-day cycle of dosing remained stable through the treatment period and were reversible upon treatment discontinuation.

If deterioration of renal function is suspected, measures other than those relying on assessment of serum creatinine should be used to determine renal function. No dosage adjustment is required for patients with mild or moderate renal impairment (CLcr ≥30-89 mL/min, estimated by Cockcroft-Gault [C-G]). The pharmacokinetics of abemaciclib in patients with severe renal impairment (CLcr <30 mL/min, C-G), end stage renal disease, or in patients on dialysis is unknown; hold abemaciclib unless Clcr improves to ≥30 mL/min.

7.4.3 General Guidance for Hepatic Monitoring

To ensure patient safety the investigator should collect specific recommended clinical information and follow-up laboratory tests as shown below in Table 5.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. If a study patient experiences elevated ALT 5×ULN and elevated total bilirubin (TB) 2×ULN, or ALT 8×ULN, liver tests, including ALT, AST, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests below.

Table 5 Hepatic Monitoring Tests for a Hepatic Treatment Emergent Abnormality.

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

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

a Reflex/confirmation dependent on regulatory requirements and/or testing availability.

7.4.4 General Guidance for Hematology Toxicity

7.4.4.1 Neutropenia

Severe (Grade 3 and 4) neutropenia was observed in participants receiving abemaciclib-see Tables 1-4. If a participant requires blood cell growth factors, these should be administered according to ASCO Guidelines. Abemaciclib must be held for at least 48 hours after the last dose of blood cell growth factors is administered and until toxicity resolves to at least Grade 2. When abemaciclib is resumed, the dose must be reduced by 1 dose level unless already performed for incidence of toxicity that led to the use of growth factor.

7.4.5 General Guidance for Interstitial lung disease (ILD)/Pneumonitis events

Interstitial lung disease (ILD) / pneumonitis has been identified as an adverse drug reaction for abemaciclib. Adverse events reported included events such as interstitial lung disease, pneumonitis, obliterative bronchiolitis, organizing pneumonia, pulmonary fibrosis. The majority of events were Grade 1 or Grade 2 with serious cases and fatal events reported.

Monitor for clinical symptoms or radiological changes indicative of ILD/pneumonitis and please ask patients to report any new or worsening pulmonary symptoms. Symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams.; these symptoms should be investigated and treated as per local clinical practice and/or guidelines (including corticosteroids as appropriate). Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations. Investigations may include imaging such as high resolution computer tomography (HRCT), bronchoalveolar lavage (BAL), and biopsy as clinically indicated (see also Table 7: *refer to dose adjustment table for interstitial lung disease/pneumonitis*).

Dose Modification and Management — Interstitial Lung Disease/Pneumonitis

CTCAE Grade	Abemaciclib Dose Modifications
Grade 1 or 2	No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Hold dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 or 4	Discontinue abemaciclib.

Dose Modification and Management — Nonhematologic Toxicities Excluding Diarrhea, ALT Increased, and ILD/Pneumonitis

CTCAE Grade	Abemaciclib Dose Modifications
Grade 1 or 2	No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Hold dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 or 4	

7.4.6. General Guidance for Concomitant Therapy

Abemaciclib is predominantly cleared by oxidative metabolism via CYP3A4. Clinical drug interaction studies with a CYP3A inhibitor and CYP3A inducer significantly altered the PK of abemaciclib and its circulating major metabolites.

CYP3A inducers

Avoid concomitant use of CYP3A inducers and consider alternative agents.

CYP3A inhibitors

Avoid concomitant use of strong CYP3A inhibitors (for example, voriconazole) and use caution with coadministered moderate (for example, ciprofloxacin) or weak (for example, ranitidine) CYP3A inhibitors. If coadministration with a strong CYP3A inhibitor is unavoidable, reduce the abemaciclib dose to 100 mg twice daily or, in the case of ketoconazole, reduce the abemaciclib dose to 50 mg twice daily. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the abemaciclib dose to 50 mg twice daily. Avoid grapefruit or grapefruit juice. If a CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor.

7.4.7 General Guidance for use of Radiotherapy in Combination with Abemaciclib

Limited data are available on the use of radiotherapy in combination with abemaciclib or alternate dosing schedules (e.g. induction phase). Caution should be exercised with co-administering abemaciclib with radiotherapy.

7.5 Use in Special Populations

7.5.1 Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action, abemaciclib can cause fetal harm when administered to a pregnant woman. There are no available human data informing the drug-associated risk. Advise pregnant women of the potential risk to a fetus. In animal reproduction studies, administration of abemaciclib during organogenesis was teratogenic and caused decreased fetal weight at maternal exposures that were similar to human clinical exposure based on AUC at the maximum recommended human dose.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4% and of miscarriage is 15 to 20% of clinically recognized pregnancies.

Data

Animal Data

In an embryo-fetal development study, pregnant rats received oral doses of abemaciclib up to 15 mg/kg/day during the period of organogenesis. Doses ≥4 mg/kg/day caused decreased fetal body weights and increased incidence of cardiovascular and skeletal malformations and variations. These findings included absent innominate artery and aortic arch, malpositioned subclavian artery, unossified sternebra, bipartite ossification of thoracic centrum, and rudimentary or nodulated ribs. At 4 mg/kg/day in rats, the maternal systemic exposures were approximately equal to the human exposure (AUC) at the recommended dose.

7.5.2 Lactation

Risk Summary

There are no data on the presence of abemaciclib in human milk, or its effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions in breastfed infants from abemaciclib, advise lactating women not to breastfeed during abemaciclib treatment and for at least 3 weeks after the last dose.

7.5.3 Females and Males of Reproductive Potential

Pregnancy Testing

Based on animal studies, abemaciclib can cause fetal harm when administered to a pregnant woman Pregnancy testing is recommended for WOCP prior to initiating treatment with abemaciclib.

Contraception

Females

Abemaciclib can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during abemaciclib treatment and for at least 3 weeks after the last dose.

Infertility

Males

Based on findings in animals, abemaciclib may impair fertility in males of reproductive potential [see Nonclinical Toxicology].

7.5.4 Pediatric Use

The safety and effectiveness of abemaciclib have not been established in pediatric patients.

7.5.5 Geriatric Use

Of the 900 patients who received abemaciclib in MONARCH 1, MONARCH 2, and MONARCH 3, 38% were 65 years of age or older and 10% were 75 years of age or older. The most common adverse reactions (≥5%) Grade 3 or 4 in patients ≥65 years of age across MONARCH 1, 2, and 3 were neutropenia, diarrhea, fatigue, nausea, dehydration, leukopenia, anemia, infections, and ALT increased. No overall differences in safety or effectiveness of abemaciclib were observed between these patients and younger patients.

7.5.6 Renal Impairment

No dosage adjustment is required for patients with mild or moderate renal impairment (CLcr ≥30-89 mL/min, estimated by Cockcroft-Gault [C-G]). The pharmacokinetics of abemaciclib in patients with severe renal impairment (CLcr <30 mL/min, C-G), end stage renal disease, or in patients on dialysis is unknown.

7.5.7 Hepatic Impairment

No dosage adjustments are necessary in patients with mild or moderate hepatic impairment (Child-Pugh A or B).

Reduce the dose when administering abemaciclib to patients with severe hepatic impairment (Child-Pugh C).

7.6 Procedures for Monitoring Participant Compliance

The Principal Investigator will be responsible for monitoring participant compliance. If the Principal Investigator determines that the participant is not in compliance with the study protocol, the Principal Investigator should determine whether the participant should be withdrawn.

The investigator or designee will instruct the participants on how to take the study drug, demonstrate how to complete the participant's diary card with a record of the number of capsules of abemaciclib that he or she has taken daily at home, and instruct him or her to bring the diary card back for each study visit. The investigator or designee will be responsible for checking the return of study drug and the participant's diary card for completeness at each study visit.

7.7 Assessment of Efficacy

Efficacy of treatment with abemaciclib will be assessed by tumor response. Tumor response assessments for participants with measurable disease will be performed every 8 weeks ± 7 days for the duration of the treatment period and compared with assessments performed at screening. Tumor response is defined for each participant as the best response during the study as determined using RECIST v 1.1 criteria and tumor specific criteria as described below. Responses will be confirmed with a subsequent radiographic evaluation which would be performed 4 weeks after response is declared. Responses will be recorded as CR, PR, Stable Disease (SD) or Progressive Disease (PD).

7.7.1 Assessment of Tumors by RECIST v 1.1

Tumor assessments that are made after administration of study drug will be compared with those obtained at baseline or the smallest sum since treatment started, to determine whether CR, PR, SD or PD has occurred.

Measurable disease, measurable lesions, and non-measurable lesions are defined as follows:

- Measurable disease: presence of at least 1 measurable lesion after the histological diagnosis and staging of disease
- Measurable lesions: lesions that can be accurately measured in at least 1 dimension as 10 mm or greater and lymph nodes ≥ 15 mm in shortest axis by CT scan measurements (or MRI, as appropriate); prior sites of loco-regional therapy (e.g., fibrosis from radiation) should not be considered measurable lesions
- Non-measurable lesions: all other lesions including skin lesions, small lesions (less than 10 mm), lymph nodes ≤ 15 mm and ≥ 10 mm in shortest axis, ascites, pleural/pericardial effusions, etc.

Documentation of lesions should include date, site, dimensions, description, and diagnostic method. The same method of assessment and technique should be used at baseline and during follow-up to characterize each identified and reported lesion.

Baseline documentation of target and non-target lesions is as follows: all measurable lesions up to a maximum of 5 lesions total and a maximum of 2 lesions per organ representative of all involved organs should be identified as target lesions.

Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.1)

Measurable tumor burden	Maximum 5 target lesions in total (up to 2 per organ) can be identified at baseline and measured through the course of therapy
Minimum size of measurable lesions	≥10 mm in LD and 2 times the slice thickness for extranodal lesions ≥15 mm in short axis diameter (SAD) for nodal lesions ≥10 mm in LD for clinical lesions (must be measured using electronic calipers) ≥20 mm in LD for chest X-ray (if clearly defined and surrounded by aerated lung): CT scan is preferable Ultrasound cannot be used to measure lesions
Lymph nodes	Lymph nodes are considered pathologically enlarged if >10 mm in SAD. To be measurable, nodal lesions must be ≥15 mm in SAD. Nodal lesions with SAD >10 mm and <15 mm are non-measurable. The sum of the diameters (LD for extranodal target lesions, SAD for nodal lesions) is followed through the course of therapy.
Bone lesions	A lytic or mixed lytic-blastic bone lesion with a soft tissue component assessed on CT scan/MRI can be measurable if the minimum size criteria are met. Blastic bone lesions and bone lesions assessed on bone scan, PET, or plain film are non-measurable.
Cystic lesions	Lesions that meet the criteria for radiographically defined simple cysts are not malignant. Cystic lesions thought to be metastases can be measurable if they meet the minimum size criteria. Non-cystic lesions are preferable.
Lesions with prior local therapy	Lesions in previously irradiated areas (or areas treated with local therapy) are not measurable unless the lesion has progressed since therapy. Conditions should be defined in study protocols.
Too small to measure	If a target lesion becomes too small to measure, a default value of 5 mm is assigned. If the lesion disappears, the measurement is recorded as 0 mm.
FDG/PET	New lesions can be assessed using FDG-PET: (–) PET at baseline and (+) PET at follow-up is PD based on a new lesion. No PET at baseline and (+) PET at follow-up is PD if the new lesion is confirmed on CT. If a subsequent CT confirms the new lesion, the date of PD is the date of the initial PET scan, not the CT scan. No PET at baseline and a (+) PET at follow-up corresponding to a pre-existing lesion on CT that is not progressing: not PD

(Eisenhauer et al 2009) LD=longest diameter; SAD=short axis diameter; CT=computed tomography; MRI=magnetic resonance imaging; PET=positron emission tomography; FDG=fluorodeoxyglucose

Evaluation of Target Lesions

Target lesions will be evaluated as follows:

Response	Criteria
CR	Disappearance of all target lesions
PR	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD

Response	Criteria
PD	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of Nontarget Lesions

Nontarget lesions will be evaluated as follows:

Response	Criteria
CR	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete response/SD	Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
PD	Appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions. (Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel [or study chair].)

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the participant's best response assessment will depend on the achievement of both measurement and confirmation criteria, as follows:

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment. In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm CR status.

7.7.2 Primary Efficacy Endpoint

- ORR defined above as estimated by the proportion of subjects with a best response of CR or PR during the study.

7.7.3 Secondary Efficacy Endpoint

- OS rate at 6 and 12 months defined as determined by the proportion of subjects who are alive at 6 months and 12 months from the date of first dose of study drug, respectively.
- PFS as determined by the time interval from the date of first dose of study drug to first documented disease progression or death from any cause, whichever occurs first, evaluable.
- DCR as determined by the proportion of subjects with CR, PR, or SD.
- QoL as measured from the date of first dose of study drug/baseline and then every 4 weeks using the EORTC-QLQ-C30 (see Appendix C)

7.7.4 Exploratory Efficacy Variables

- Determine the Efficacy and safety of abemaciclib with regard to the subtypes of biliary tract carcinoma (BTC) including intrahepatic cholangiocarcinoma (IHCC), extra-hepatic cholangiocarcinoma (EHCC), ampullary carcinoma, and gall bladder carcinoma (GBC).
- Analyze the biopsied tumor tissues for molecular profiling (by Caris Life Sciences, Inc®) including genetic mutation in *K-RAS*, *B-RAF, TP53*, *INK4A/p16*, *CDKN1A/*p21, *cyclin D,* and *RB* by DNA sequencing (clinical routine).
- Correlate the efficacy of abemaciclib with the mutational status of *K-RAS*, *B-RAF, TP53*, *INK4A/p16*, *CDKN1A/p21*, *cyclin D*, and *RB* genes.
- Analyze the collected blood samples for characterization of extracellular vesicles (EVs).Three lavender-top EDTA glass tubes will be used to collect approximately 5 ml of blood in each tube, and one 10-ml green-top sodium heparin tube will be used to collect approximately 7.5 ml of blood in the tube. The collected blood specimens will be processed as described in the Study 18-052 Lab Manual, and the frozen specimens will be stored in freezer boxes and sent to Dr. Hongzhang He (phone number 949-878-2679), or Dr. He's research staff. The blood specimens will be processed by and stored in Dr. He's laboratory (Captis Diagnostics, Inc., 5000 Forbes Avenue, Scott Hall 4N211, Pittsburgh, PA 15213) for characterization of EVs.

8.0 STATISTICAL PLAN

This is a pilot study to confirm tolerability of abemaciclib and provide an estimate of the overall response rate. A sample size of 10 subjects is determined to be minimally sufficient for these pilot study objectives. The primary objective of this study is objective response rate in locally advanced and metastatic biliary tract carcinoma that have failed (tumor progression or patient intolerance) one or more lines of systemic therapies. All participants will be treated with 200 mg twice daily of oral abemaciclib for 28 days being one cycle. Participants will be treated up to 8 cycles or until progression, untoward toxicities or death. Antitumor activities will be evaluated using RECIST v1.1.

8.1 Sample Size and Power Considerations

The primary endpoints is overall response rate (ORR). A sample size of 10 subjects is determined to be minimally sufficient for these pilot study objectives.

8.2 Analysis Sets/Populations

8.2.1 Enrolled Participants

The set of enrolled participants includes all participants who provide informed consent to participate in the study and who meet all inclusion and exclusion criteria, regardless of whether or not a participant took any study drug.

8.2.2. Safety Analysis Set

The safety analysis set for this study will include participants who receive 1 or more doses of study drug.

8.2.3 Data Handling Conventions

For all variables, only the observed data from the participants will be used in the statistical analyses. There is no plan to estimate missing data. Treated participants without response assessment after dosing will be considered as non-responders.

8.3 Study Population

The set of enrolled participants will be used for all study population summaries unless otherwise noted.

8.3.1 Participant Disposition

Data from participants who are screened, participants screened but not enrolled, reason for non-enrollment, participants enrolled, participants enrolled but not treated, participants in the safety sets, participants who complete the study, and participants who withdraw from the study will be summarized using descriptive statistics. Data from participants who withdraw from the study will also be summarized by reason for withdrawal using descriptive statistics.

8.3.2 Demographic and Baseline Characteristics

Participant demographic and baseline characteristics, including age, sex, race, medical history, disease types, biomarkers, prior medications, and ECG and physical examination findings, will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation, standard error, median, minimum, and maximum) will be provided. For categorical variables, participant counts and percentages will be provided. Categories for missing data will be presented if necessary.

8.4 Efficacy Analysis

8.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is ORR evaluated using RECIST v1.1. A responder is defined as a participant with a best response of CR and PR during study. Confirmation of CR and PR as assessed by RECIST v1.1 is needed no sooner than 4 weeks after the initial observation of response.

8.4.2 Secondary Endpoints

The secondary efficacy endpoints are as follows:

- OS rate at 6 and 12 months defined as determined by the proportion of subjects who are alive at 6 months and 12 months from the date of first dose of study drug, respectively.
- PFS as determined by the time interval from date of first dose of study drug to first documented disease progression or death from any cause, whichever occurs first.
- DCR as determined by the proportion of subjects with CR, PR, or SD.
- QoL as measured from the date of first dose of study drug/baseline and then every 4 weeks using the EORTC-QLQ-C30 (see Appendix C). The EORTC QLQ-C30 is a copyrighted instrument, which has been translated and validated in over 100 languages and is used in more than 3,000 studies worldwide. Presently QLQ-C30 Version 3.0 is the most recent version. It is supplemented by disease-specific modules for e.g. Breast, Lung, Head & Neck, Esophageal, Ovarian, Gastric, Cervical cancer, Multiple Myeloma, Esophago-Gastric, Prostate, Colorectal Liver Metastases, Colorectal and Brain cancer which are distributed by the EORTC Quality of Life Department. Other disease specific modules are under development but not yet validated.

8.4.3 Planned Method of Analysis

The primary and secondary efficacy endpoints, which include PFS, DCR, OS and QoL will be tabulated and graphed as appropriate. The Kaplan-Meier survival curve will be graphed with confidence intervals. A 5% level test of the median survival, based on an exponential maximum likelihood estimator test, will be conducted to determine if median survival is statistically greater than 2.8 months. Adverse events and serious adverse events will be annotated and tabulated to allow for a quantitative assessment of the safety and tolerability of abemaciclib. Potential factors associated with the efficacy of abemaciclib, including subtypes of BTC subtypes, and tumor molecular profiles, will be explored with a Cox proportional hazards model. Reproducible statistical reports will be produced.

The QLQ-C30 is composed of both multi-item scales and single-item measures including a global health status/QoL scale, five functional scales and three multi-item symptom scales and six single item scales. For the multi-item scales, the raw score, RS, is calculated by taking the mean of the individual item scores. Then a linear transformation is applied to standardize the raw score so that scores range from 0 to 100. The linear transformations for each scale type (functional/symptom/global health status) are different and clearly documented in the EORTC QLQ-C30 Scoring Manual. Descriptive statistics of the QLQ-C30 scales will be reported and Spaghetti plot graphics will be produced to visualize the responses. No statistical analyses are planned for this secondary measure.

8.5 Safety Variables and Analysis

8.5.1 Safety Variables

The safety and tolerability of abemaciclib treatment will be assessed throughout the study by evaluating AEs.

8.5.2 Safety Analysis

The safety analysis set will be used for all safety analyses.

All AEs will be graded by CTCAE v 5.0. Summaries will be presented for all AEs (overall and by severity), AEs determined by the investigator to be related or not related to study treatment (overall and by severity), SAEs, serious treatment-related AEs, AEs leading to withdrawal, and Grade 3 and 4 AEs. Participant listings of AEs, SAEs, Grade 3 and 4 AEs, and AEs leading to withdrawal will be presented.

The number and percentage of participants with Grade 3 or 4 values will be tabulated. Summaries of laboratory values for laboratory parameters will be completed as applicable. Vital signs abnormalities will be categorized and tabulated. Summaries of the vital signs measurements will be provided.

The use of concomitant medications will be summarized by therapeutic class using descriptive statistics. Concomitant medications will include all medications taken while the participant is treated with study drug.

For continuous variables, descriptive statistics (n, mean, standard deviation, standard error, median, minimum, and maximum) will be provided for actual values and changes from baseline to each time point. For categorical variables, participant counts and percentages will be provided. Descriptive summaries of SAEs, participant withdrawals due to AEs, and potentially clinically significant abnormal values (clinical laboratory or vital signs) based on predefined criteria will also be provided.

If any participant dies during the study, a listing of deaths will be provided and all relevant information will be discussed in the participant narrative.

8.6 Safety Analysis

The data safety monitoring committee (DSMC) will review all safety data following recruitment of the 5 subjects. If the DSMC requests earlier views of the safety data, the appropriate data will be cleaned and provided. The study may be terminated early if unexpected toxicities are observed, but this should be unanticipated. No interim analyses are planned for this pilot study.

9.0 CONFIDENTIALITY, PRIVACY, AND DATA MANAGEMENT

The Principal Investigator will strictly adhere to the research data security and integrity plan put forth in the following Penn State Health Institutional policy “HRP-598 – Research Data Plan Review Form”.

9.1 Patient Identifiers associated with data and/or specimens

Participants will be identified in all reports using a protocol specific unique patient identification number. A Master list linking these unique identification numbers and the participant is maintained in the limited access, password protected Cancer Institute OnCore Clinical Trials Management System (CTMS).

9.2 Data Storage

Data will be maintained in the OnCore CTMS per institutional requirements for data access and security. OnCore is a limited access, password protected system maintained in the Cancer Institute.

All data will be retained in the CTMS until the time period required by the FDA and institutional IRB. Data destruction will be completed according to institutional policies.

10.0 ASSESSMENT OF SAFETY AND ADVERSE EVENT REPORTING

In this study, safety will be assessed by the PI by evaluating results of assessments including but not limited to verbal inquiries, physical examinations, clinical laboratory test results, vital signs measurements, ECG findings, and concomitant medication usage.

10.1 Adverse Events

10.1.1 Definition of an AE

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of whether it has a causal relationship with this treatment.

An AE can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of the study, or significant worsening of the disease under study or of any concurrent disease, whether or not considered related to the study drug. A new condition or the worsening of a pre-existing condition will be considered an AE. Stable chronic conditions (such as arthritis) that are present before the participant signs the informed consent form and do not worsen during the study will not be considered AEs.

Accordingly, an AE can include any of the following:

- Intercurrent illnesses
- Physical injuries
- Events possibly related to concomitant medication
- Significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions. (Note: A condition recorded as pre-existing that is intermittently symptomatic [e.g., headache] and which occurs during the study should be recorded as an AE.)
- Drug interactions
- Events occurring during diagnostic procedures
- Laboratory or diagnostic test abnormalities that result in the withdrawal of the participant from the study, are associated with clinical signs and symptoms or an SAE, or require medical treatment or further diagnostic work-up, or are considered by the Principal Investigator to be clinically significant. Note: Abnormal laboratory test results at the screening visit that preclude a participant from entering the study or receiving study treatment are not considered AEs, but will be evaluated to monitor data from participants who do not meet screening criteria.
- All events of possible drug-induced liver injury with hyperbilirubinemia (defined as aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥3 times the upper limit of the normal range [ULN], plus either bilirubin ≥2 times the ULN or international normalized ratio [INR]>1.5) or Hy's Law events require immediate study treatment cessation and reporting as a SAE.
- Disease progression (or progressive disease) or death due to disease progression will not be considered an AE or a SAE in this study, but will be collected as an efficacy assessment.

10.1.2 Recording and Reporting AEs

In this study, any AE occurring after the study participant has signed the informed consent form but *prior to* the initiation of study medication will be recorded as medical history. The commencement of AE collection will begin at the time of initiation of study medication (Cycle 1, Day 1). AE collection will continue up to and including the EOT visit. Those AEs that are determined to be related to the study treatment that are ongoing at the time of the EOT visit, will continue to be monitored until the event resolves or improves to baseline or Grade 1. For this study, the EOT visit may occur up to approximately 30 days after the last dose of study drug.

All AEs that occur during the defined study period must be recorded in the source documentation.

Signs and symptom will be recorded and entered into the database individually, except when considered manifestations of a medical condition or disease state. When such a diagnosis is made, all related signs, symptoms, and any test findings will be recorded collectively as a single diagnosis. A precise medical diagnosis will be recorded whenever possible.

Abnormal laboratory values or diagnostic test results will constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests. Disease progression will not be recorded as an AE.

When known, the onset and end dates, duration, action taken regarding study drug, and outcome for each AE should be recorded on the source documentation and entered in the study database. The guidelines relating to expectedness of each AE, relationship of each AE to study drug treatment and study procedures, and the severity and seriousness of each AE, as judged by the investigator, is described below.

10.1.3 Expectedness of an AE

An AE that is not included in the Listing of Adverse Drug reactions in the Investigator's Brochure for Abemaciclib, by its specificity, severity, outcome, or frequency, is considered an unexpected AE.

If necessary, Lilly's U.S. Pharmacovigilance Department may assist the Principal Investigator, to determine the expectedness for SAEs especially in the event it is related, unexpected and of special interest.

10.1.4 Relationship of an AE to the Study Drug

The relationship of an AE to the study drug is characterized as follows:

Term	Definition	Clarification

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to AEs which, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to AEs, which, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug.	The relationship of an AE may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the test drug. • It could readily have been produced by the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant. • It does not follow a known pattern of response to the test drug. • It does not reappear or worsen when the drug is re-administered.
Reasonable possibility (related)	This category applies to AEs for which, after careful medical consideration at the time they are evaluated, a connection with the test drug administration cannot be ruled out with certainty nor felt with a high degree of certainty to be related to the study drug.	The relationship of an AE may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the drug. • It cannot be reasonably explained by the known characteristics of the participant's clinical state, environmental or toxic factors, or other modes of therapy administered to the participant. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists. • It follows a known pattern of response to the test drug.

10.1.5 Severity of an AE

The severity of each AE will be graded according to the National Cancer Institute Common Terminology Criteria for AEs, current version 5.0 (NCI CTCAE version 5.0).

AEs that are not included in the NCI CTCAE lists will be graded according to the NCI CTCAE general guideline for grades as follows:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2 Moderate; minimal, local intervention, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL), e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL, e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Grade 4 Life-threatening consequences; urgent intervention indicated

Grade 5 Death related to AE

10.2 Serious Adverse Events

10.2.1 Definition of a SAE

A SAE is an AE occurring at any dose that results in any of the following outcomes or actions:

- Death
- A life-threatening AE (i.e., the participant was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- Inpatient hospitalization or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of an AE, or that they occurred as a consequence of the event. Hospitalizations scheduled for an elective procedure or for treatment of a pre-existing condition that has not worsened during participation in the study will not be considered SAEs.
- Persistent or significant disability or incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- A congenital anomaly or birth defect
- An important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the participant and may require medical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse. Note: Any suspected transmission of an infectious agent via a medicinal product is considered an important medical event.

Reportable AEs, UAP, SAEs and Protocol Violation reporting to DSMC

Type of Event	To whom will it be reported	Time Frame for Reporting	How to report?

Death of a research participant unless the death is expected (e.g., due to disease progression).	PSCI DSMC and designated IRB, if applicable per IRB policy.	DSMC: Within 24 hours	DSMC: Email to PSCI-DSMC@pennstatehealth.psu.edu
Serious Adverse Event, *regardless of relatedness of expectedness*	PSCI DSMC and designated IRB, if applicable per IRB policy.	DSMC: Within 10 working days from the time the study team received knowledge of the event.	DSMC: Email to PSCI-DSMC@pennstatehealth.psu.edu
Unanticipated Problems that are not adverse events or protocol deviations	PSCI DSMC and designated IRB, if applicable per IRB policy.	DSMC: Within 10 working days from the time the study team received knowledge of the event.	DSMC: Email to PSCI-DSMC@pennstatehealth.psu.edu

10.3 Reporting of AEs and SAEs

10.3.1 Investigator Responsibility

An unanticipated AE is one that is deemed to be unexpected and related (reasonable possibility) to the investigational medication. All unanticipated AEs that occur during the protocol specific AE observation time period must be reported to the Principal Investigator immediately. If a serious unexpected AE is believed to be related to the study drug or study procedures, the Principal Investigator will take appropriate steps to notify all the appropriate regulatory authorities.

All SAEs will be reported to the sponsor within 24 hours of knowledge. SAEs will be reported to the sponsor using the MedWatch Form 3500A. Updates to the SAE should be made as events change.

The Sponsor-Investigator will submit a written IND Safety Report (i.e., completed FDA Form 3500A) to the responsible new drug review division of the FDA for any observed or volunteered adverse event that is determined to be a serious and unexpected, suspected adverse reaction. Each IND Safety Report will be prominently labeled, “IND Safety Report”, and a copy will be provided to all participating investigators (if applicable) and sub-investigators.

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the Sponsor-Investigator’s receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

For each written IND Safety Report, the Sponsor-Investigator will identify all previously submitted IND Safety Reports that addressed a similar suspected adverse reaction experience and will provide an analysis of the significance of newly reported, suspected adverse reaction in light of the previous, similar report(s) or any other relevant information.

Relevant follow-up information to an IND Safety Report will be submitted to the applicable review division of the FDA as soon as the information is available and will be identified as such (i.e., "Follow-up IND Safety Report").

If the results of the Sponsor-Investigator's follow-up investigation show that an adverse event that was initially determined to not require a written IND Safety Report does, in fact, meet the requirements for reporting; the Sponsor-Investigator will submit a written IND Safety Report as soon as possible, but in no event later than 15 calendar days, after the determination was made.

In addition to the subsequent submission of a written IND Safety Report (i.e., completed FDA Form 3500A), the Sponsor will notify the responsible review division of the FDA of any unexpected, fatal or life-threatening suspected adverse reaction.

The telephone or facsimile transmission of applicable IND Safety Reports will be made as soon as possible but in no event later than 7 calendar days after the Sponsor-Investigator's receipt of the respective adverse event information and determination that it meets the respective criteria for reporting.

Unexpected and related AEs as defined by Penn State IRB (regardless of grades) and SAEs will be reported to the Penn State IRB expeditiously per their requirements. The study funder, Eli Lilly, will be notified within one business day of Investigator and/or Institution receiving notification of any "serious" adverse event experienced by a patient participating in the Study and receiving Study Drug. For purposes of this requirement, "serious" means: (1) death; (2) in-patient hospitalization or prolonged hospitalization; (3) life-threatening; (4) persistent or significant disability or incapacity; (5) congenital anomaly or birth defect; or (6) other serious events that may jeopardize the patient and may require medical or surgical intervention to prevent one of the other five listed outcomes. Serious adverse events should be reported to Lilly using a MedWatch 3500A Form (FAX #: 866-644-1697). Investigator and Institution further agree to make available promptly to Lilly such records as may be necessary and pertinent for Lilly to further investigate an adverse event in the Study that is possibly associated with the Study Drug.

Based on the unanticipated toxicity, the Sponsor/Investigator, Dr Nelson Yee may take the following steps where applicable:

- Amending the current protocol
- Discontinuing or suspending the study
- Altering the process of informed consent by modifying the existing informed consent form and informing current study participants of any new findings. This includes modifying listings of expected toxicities to include AEs newly identified as related to the study medication.

The Principal Investigator must ensure that the IRB and DSMC are also informed of the event, in accordance with local regulations.

10.4 Pregnancy

All pregnancies (pregnancies of women participating in the study and partners of men participating in the study) that occur during the study, or 30 days after last dose of the study drug, are to be reported immediately to the individual identified in the clinical study personnel contact information section of this protocol, and the Principal Investigator must provide the Eli Lilly's USA Pharmacovigilance Department with MedWatch 3500A form (FAX: 866-644-1697). Although pregnancy is not a SAE, the process for reporting a pregnancy is the same as that for reporting a SAE.

Any participant becoming pregnant during the study will be withdrawn. All participants (or partners) who become pregnant will be monitored to the completion or termination of the pregnancy. If the pregnancy continues to term, the outcome (health of the infant up to 8 weeks of age), including spontaneous or voluntary termination, details of birth, and presence or absence of any birth defect, congenital abnormalities, or maternal and newborn complications, will be reported to Eli Lilly. Any complication of pregnancy will be reported as an AE or SAE, as appropriate.

If the pregnancy does not continue to term, 1 of the following actions will be taken:

- For a spontaneous abortion, report as a SAE.
- For an elective abortion due to developmental anomalies, report as a SAE.
- For an elective abortion not due to developmental anomalies, report on the pregnancy form.

11.0 STUDY MONITORING, AUDITING, AND INSPECTION

11.1 **Protocol Amendments**

No changes from the final approved protocol will be initiated without the prior written approval or favorable opinion of a written amendment by the IRB/IEC, except when necessary to address immediate safety concerns to the participants or when the logistical or administrative changes are required.

11.2 Information to Study Personnel

The Principal Investigator is responsible for administering information about the study to all staff members involved in the study or in any element of participant management, both before starting the study and during the course of the study (e.g., when new staff become involved). The Principal Investigator must assure that all study staff members are qualified by education, experience, and training to perform their specific responsibilities. Study staff members must be listed on the Delegation of Authority Log, which includes a clear description of each staff member's responsibilities. This list must be reviewed and updated throughout the study, as necessary.

The Principal Investigator is responsible for explaining the protocol to all study staff, including any sub-investigators, and for ensuring they comply with the protocol. Additional information will be made available during the study when new staff becomes involved in the study.

At monthly intervals, routinely scheduled meetings with the study staff members will be conducted at the Penn State Cancer Institute. All sub-Investigators and study staff members will be notified of new information regarding the safety of the study drug and presented updates on the study. Written documentation of such notifications will be maintained in the regulatory files of the Clinical Trials Office.

11.3 Study Monitoring

The Principal Investigator will ensure that this study is conducted and that the data are collected, documented, and reported in compliance with this protocol, federal regulations, institutional and IRB policies and procedures. Good Clinical Practice guidelines and any other applicable regulatory requirements. The study will be monitored by the PSCI Quality Assurance Department. The monitors will provide an independent review of the regulatory and subject records and associated data collected to assure appropriate compliance, ensuring human subject's protection, examine the quality, reliability, and integrity of data collected and provide opportunities for corrective action while the study is ongoing. Comprehensive monitoring will be conducted by a PSCI Quality Assurance monitor specifically for the PSCI-CTO and planned visits will start at Site Initiation Visit (SIV), a visit will take place within two weeks after the first subject receives protocol treatment; every 6-8 weeks until the last subject is enrolled, and thereafter every 4-6 months until all subjects have come off active treatment. Once all subjects are on long term follow-up monitoring visits will occur annually; the remaining visits will happen for close out; and ad-hoc for any study based on findings.

The investigational site will provide direct access to all trial-related sites, source data/ documents, and reports for the purpose of auditing by the DSMC, and inspection by local and regulatory authorities.

11.4 Audit and Inspection

The Principal Investigator will allow for auditing and inspecting by all applicable federal, state and local entities at any time. Lilly Pharmaceuticals, the pharmaceutical manufacturer of abemaciclib who is providing funding for this study, may audit the investigational center to evaluate study conduct and compliance with protocols, SOPs, GCPs, and applicable regulatory requirements. The Quality Assurance Unit at Lilly, independent of the PSCI Quality Assurance will be responsible for determining the need for (and timing of) an investigational center audit.

The Principal Investigator and Sub-Investigators must accept that regulatory authorities and Eli Lilly representatives may conduct inspections to verify compliance of the study with GCP guidelines.

The DSMC, study monitors from Penn State Cancer Institute Quality Assurance Department, any auditors, the PSCI IRB, or any other health authority inspectors (or their agents) will be given direct access to source data and documentation (e.g., medical charts/records, laboratory test results, printouts, videotapes) for source data verification, provided that participant confidentiality is maintained.

The Principal Investigator and any Sub-investigator must maintain all original source documents of each participant's data at all times. Examples of source documents are hospital records, office visit records, examining physician's finding or notes, consultant's written opinion or notes, laboratory reports, drug inventory, study drug label records, diary data, protocol required worksheets, and eCRFs that are used as the source.

12.0 DATA HANDLING, DATA QUALITY ASSURANCE, AND RECORD KEEPING

12.1 Data Collection

Direct data entry into to the Penn State Cancer Institute OnCore CTMS will be utilized for this study. In addition to demographics, medical history, concomitant medications, and safety data, only those data needed to answer the study objectives will be included in the study database. The assessments and interventions noted in the *Protocol Required Interventions and Assessments* (Appendix B) will not be entered into the database. This data includes dates and results of physical examinations, vital signs, performance status, and laboratory results (CBC, Chemistry). Any abnormal results of the assessments will be captured as an AE according to the criteria noted in Section 10. Any concomitant medications administered for the purpose of procedures (anesthetics, etc.) will not be included in the data collection. AEs and SAEs will be recorded after the start of study drug until 30 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first. AE that are ongoing at time will be checked or ongoing with no stop date. Unanticipated SAEs (ie. Serious, unexpected, and related (even remotely)) will be reported on the SAE Submission Form and entered in Oncore within 1 business day of discovery of the event. All other SAEs will be entered in the Oncore system within 5 business days. For screen failures (participants who sign the informed consent form but do not meet eligibility criteria), data relating to failure reason and demography will be captured.

Data will be reviewed for consistency by Data Management using both automated logical checks and manual review. The data collected will be reviewed and approved by the Principal Investigator or designated Co-investigator on an approximately quarterly basis depending on enrollment. Evidence of the Principal Investigator or Co-investigator review and approval may be done electronically in the OnCore CTMS. This approval acknowledges the Principal Investigator's review and acceptance of the data as being, to the best of his knowledge, complete, accurate, and current per the date documented on the form. Data will be verified using source documentation by the Study Monitor.

12.2 Reporting and Publication of Results

The Principal Investigator is responsible for ensuring that the public has access to the appropriate information about the study by conforming to requirements for registration and publication of results. The data of this study will be submitted to American Society of Clinical Oncology Gastrointestinal Cancers Symposium and American Society of Clinical Oncology Annual Meeting for presentation. In addition, the data will be written in a manuscript and submitted to journals such as Journal of Clinical Oncology, Cancer, Lancet Oncology, World Journal of Gastroenterology, and World Journal of Clinical Oncology.

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APPENDIX A

Drugs That Could Inhibit or Induce Cytochrome P450 When Administered With Abemaciclib *See also www.crediblemeds.org*

SUBSTRATES							
1A2 amitriptyline caffeine clomipramine clozapine cyclobenzaprine estradiol fluvoxamine haloperidol imipramine-N-DeMe mexilletine naproxen olanzapine ondansetron phenacetin_acetaminophen→NAPQI propranolol riluzole ropivacaine tacrine theophylline tizanidine verapamil (R)warfarin zileuton zolmitriptan	**2B6** bupropion cytoxan efavirenz ifosfamide methadone	**2C8** paclitaxel torsemide amodiaquine cerivastatin repaglinide	**2C9** **NSAIDs:** diclofenac ibuprofen lornoxicam meloxicam S-naproxen_Nor piroxicam suprofen **Oral Hypoglycemic Agents:** tolbutamide glipizide **Angiotensin II Blockers:** losartan irbesartan **Sulfonylureas:** glyburide glibenclamide glipizide glimepiride tolbutamide amitriptyline celecoxib fluoxetine fluvastatin glyburide nateglinide phenytoin-4-	**2C19** **Proton Pump Inhibitors:** lansoprazole omeprazole pantoprazole rabeprazole **Anti-epileptics:** diazepam→Nor phenytoin(O) S-mephenytoin phenobarbitone amitriptyline carisoprodol citalopram chloramphenicol clomipramine cyclophosphamide hexobarbital imipramine N-DeME indomethacin R-mephobarbital moclobemide nelfinavir nilutamide primidone progesterone proguanil propranolol teniposide R-warfarin→8-	**2D6** **Beta Blockers:** carvedilol S-metoprolol propafenone timolol **Antidepressants:** amitriptyline clomipramine desipramine imipramine paroxetine	**Antipsychotics:** haloperidol perphenazine risperidone→9OH thioridazine zuclopenthixol alprenolol amphetamine aripiprazole atomoxetine bufuralol chlorpheniramine chlorpromazine codeine (→O-desMe) debrisoquine dexfenfluramine dextromethorphan duloxetine encainide flecainide fluoxetine fluvoxamine lidocaine metoclopramide methoxyamphetamine mexilletine minaprine nebivolol nortriptyline ondansetron	**Antipsychotics (continued):** sparteine tamoxifen tramadol venlafaxine

			OH2 rosiglitazone tamoxifen torsemide S-warfarin	OH	oxycodone perhexiline phenacetin phenformin promethazine propranolol

SUBSTRATES (Continued)			
2E1	**3A4,5,7**		
Anesthetics: enflurane halothane isoflurane methoxyflurane sevoflurane acetaminophen→NAPQI aniline2 benzene chlorzoxazone ethanol N,N-dimethyl formamide theophylline→8-OH	**Macrolide antibiotics:** clarithromycin erythromycin (not 3A5) NOT azithromycin telithromycin **Anti-arrhythmics:** quinidine→3OH (not 3A5) **Benzodiazepines:** alprazolam diazepam→3OH midazolam triazolam **Immune Modulators:** cyclosporine tacrolimus (FK506) **HIV Antivirals:** indinavir nelfinavir ritonavir saquinavir	**Calcium Channel Blockers:** amlodipine diltiazem felodipine lercanidipine nifedipine2 nisoldipine nitrendipine verapamil **HMG CoA Reductase Inhibitors:** atorvastatin cerivastatin lovastatin NOT pravastatin simvastatin **Steroid 6beta-OH:** estradiol hydrocortisone progesterone testosterone **Miscellaneous:** alfentanyl aprepitant aripiprazole buspirone cafergot	**Miscellaneous (continued):** dextromethorphan docetaxel domperidone eplerenone fentanyl finasteride gleevec haloperidol irinotecan LAAM lidocaine methadone nateglinide ondansetron pimozide propranolol quetiapine quinine risperidone NOT rosuvastatin salmeterol sildenafil sirolimus tamoxifen taxol

	Prokinetic: cisapride **Antihistamines:** astemizole chlorpheniramine terfenadine	caffeine_TMU cilostazol cocaine codeine-Ndemethylation dapsone dexamethasone	terfenadine trazodone vincristine zaleplon ziprasidone zolpidem

INHIBITORS

1A2	**2B6**	**2C8**	**2C9**	**2C19**	**2D6**	**2E1**	**3A4,5,7**
fluvoxamine ciprofloxacin cimetidine amiodarone fluoroquinolones furafylline interferon methoxsalen mibefradil	thiotepa ticlopidine	gemfibrozil trimethoprim glitazones montelukast quercetin	fluconazole amiodarone fenofibrate fluvastatin fluvoxamine isoniazid lovastatin phenylbutazone probenicid sertraline sulfamethoxazole sulfaphenazole teniposide voriconazole zafirlukast	**PPIs:** lansoprazole omeprazole pantoprazole rabeprazole chloramphenicol cimetidine felbamate fluoxetine fluvoxamine indomethacin ketoconazole modafinil oxcarbazepine probenicid ticlopidine topiramate	bupropion fluoxetine paroxetine quinidine duloxetine terbinafine amiodarone cimetidine sertraline celecoxib chlorpheniramine chlorpromazine citalopram clemastine clomipramine cocaine diphenhydramine doxepin doxorubicin escitalopram halofantrine histamine H1 receptor antagonists hydroxyzine levomepromazine methadone metoclopramide mibefradil midodrine moclobemide perphenazine ranitidine red-haloperidol	diethyl-dithiocarbamate disulfiram	**HIV Antivirals:** indinavir nelfinavir ritonavir clarithromycin itraconazole ketoconazole nefazodone saquinavir telithromycin aprepitant erythromycin fluconazole grapefruit juice verapamil diltiazem cimetidine amiodarone NOT azithromycin chloramphenicol ciprofloxacin delaviridine diethyl-dithiocarbamate fluvoxamine gestodene imatinib mibefradil mifepristone norfloxacin norfluoxetine star fruit voriconazole

					ritonavir ticlopidine tripelennamine		

INDUCERS							
1A2	**2B6**	**2C8**	**2C9**	**2C19**	**2D6**	**2E1**	**3A4,5,7**
broccoli brussel sprouts char-grilled meat insulin methylcholanthrene modafinil nafcillin beta-naphthoflavone omeprazole tobacco	phenobarbital rifampin	rifampin	rifampin secobarbital	carbamazepine norethindrone NOT pentobarbital prednisone rifampin	dexamethasone rifampin	ethanol isoniazid	**HIV Antivirals:** efavirenz nevirapine barbiturates carbamazepine efavirenz glucocorticoids modafinil nevirapine oxcarbazepine phenobarbital phenytoin pioglitazone rifabutin rifampin St. John's wort troglitazone

APPENDIX B – PROTOCOL REQUIRED INTERVENTIONS AND ASSESSMENTS

BASELINE ASSESSMENTS

DAYS PRIOR TO C1D1	≤28	≤7	COMMENTS
Informed Consent	X		
Assessment of eligibility	X		
Enrollment path report	X		
Diagnostic Imaging for Tumor Evaluation–RECIST v. 1.1 Reading	X		Baseline CT or MRI scans of chest, abdomen, and pelvis with contrast, brain MRI or PET CT scans with contrast are performed if symptomatic. If hypersensitivity or known serious allergic reaction to CT contrast, consider MRI scans with gadolinium, or alternatively chest CT scans without contrast and abdomen/pelvic MRI scans with contrast.
Medical History	X		including demographics, tobacco use (if smokes or smoked, and smoking pack year), surgical and psychiatric history and cancer treatment history
Physical Examination	X		Height, weight and vital signs (temperature, heart rate, respiration rate, blood pressure).
Concomitant Medications	X		
ECOG Performance Status	X		
Triplicate 12-lead ECG	X		Any ECG abnormalities at baseline will be followed up according to standard of care.
Hematology	X		
Serum Chemistry	X		Complete metabolic profile
Coagulation Profile	X		
Urinalysis	X		Basic and microscopic if abnormal sample is collected.
CA 19-9	X		
Archival Tumor Samples	X		Formalin-fixed paraffin-embedded tumor is requested following confirmation of study eligibility.
Fresh Tumor Samples	X		If archival tissue is unavailable or insufficient, repeat biopsy of tumor is as clinically indicated.
Pregnancy Test		X	WOCP must have a negative serum pregnancy test between Day -7 to Day -1.

Notes:

- Physical examination, including body weight
- Hematology: complete blood counts with differential

- Serum Chemistry: complete metabolic panel including Na, K, Cl, CO2, blood urea nitrogen, creatinine, glucose, aspartate aminotransferase, total bilirubin, alkaline phosphatase, alanine aminotransferase, albumin Coagulation Profile = PT,INR, PTT
- Urinalysis - In case of abnormal parameters microscopic evaluation should be performed.
- Tumor Samples (clinical routine) - Archival or fresh tumor tissue is required for subjects with confirmation of diagnosis, as well as, for determination of exploratory mutational analysis as described in Section 1.3.4.
- Biomarker Blood Sample (extracellular vesicles (EV) isolation) - will be collected at baseline (within 28 days prior to C1D1 visit) and every 8 weeks (at the onset of every 3rd cycle). Three lavender-top EDTA glass tubes will be used to collect approximately 5 ml of blood in each tube, and one 10-ml green-top sodium heparin tube will be used to collect approximately 7.5 ml of blood in the tube.

ON STUDY TREATMENT SCHEDULE OF ASSESSMENTS

	Cycle 1	**Cycle 1**	**Cycle 2**	**Cycle 2**	**Cycle 3 – 8**	**Instructions**
Day within Cycle	**1(+/-3)**	**15(+/-3)**	**1(+/-3)**	**15(+/-3)**	**1(+/-3)**	
Physical Examination	X	X	X	X	X	Including vital signs (temperature, heart rate, respiration rate, blood pressure).
Weight	X		X		X	
ECOG Performance Status	X	X	X	X	X	
Adverse Events	X	X	X	X	X	CTCAE 5.0
Concomitant Medication	X	X	X	X	X	
Diagnostic Imaging for Tumor Evaluation –RECIST v1.1 Reading					X	CT or MRI scans of chest, abdomen and pelvis with contrast are performed every other cycle (every 8 weeks ± 7 days). If hypersensitivity or known serious allergic reaction to CT contrast, consider MRI scans with gadolinium; alternatively chest CT scans without contrast and abdomen/pelvic MRI scans with contrast.
12-lead ECG	X					ECG as a baseline and subsequently if clinically indicated.
Hematology	X	X	X	X	X	≤ 3 days prior to day 1 of each cycle, unless more frequent assessment is clinically indicated.
Serum Chemistry	X	X	X	X	X	≤ 3 days prior to day 1 of each cycle, unless more frequent assessment is clinically indicated.
CA 19-9	X		X		X	
EORTC-QLQ-C30	X		X		X	

Dispense Abemaciclib	X		X		X	Abemaciclib is taken orally every 12 hours on days 1 through 28 of each cycle regardless of food intake.
Collection of Unused Study Drug			X		X	
Study Drug Diary			X		X	
Extracellular vesicles	X				X	Every 8 weeks (±3 days) until disease progression or End of Treatment visit.

- Participants who are deriving clinical benefit after completing the treatment period may continue on additional cycles of therapy at the discretion of the sponsor and medical monitor. Any participant on abemaciclib after completing the treatment period will be monitored and assessed for tumor response .
-

POST-TREATMENT FOLLOW-UP SCHEDULE OF ACTIVITIES

	EOT [a]	**Long-Term Follow-Up** [c]	**Instructions**
Physical Examination	X		Including vital signs measurements (temperature, heart rate, respiration rate, blood pressure).
Weight	X		
ECOG Performance Status	X		
Adverse Events	X		Only collected for unresolved AEs ≥ Grade 3 and related to the study drug.
Concomitant Medication	X		
Collection of Unused Study Drug	X		
Diagnostic Imaging –for Tumor Evaluation RECIST v.1.1 Reading	X	X	Every 3 months (± 7 days) beginning 3 months after last dose of the study drug for subjects who have not progressed.
Survival information		X	Every 3 months (± 7 days) x2, beginning 3 months after last dose of the study drug then every 6 months (± 7 days) thereafter.
Post-Study Treatment Anti-Cancer Therapy	X	X	Every 3 months (± 7 days) x2, beginning 3 months after last dose of the study drug, then every 6 months (± 7 days) thereafter.
Hematology	X		

Serum Chemistry	X		
Coagulation Profile	X		
Urinalysis	X		
CA 19-9	X		
12-lead ECG[b]	X		
EORTC-QLQ-C30	X		
Collection of Unused Study Drug	X		
Study Drug Diary	X		
Extracellular vesicles	X		

[a] End-of-treatment (EOT) visit will be completed up to 30 days (± 7 days) after last dose study drug.
[b] as clinical indicated.
[c.] A follow-up visit will be conducted every 3 months (± 7 days) x2, beginning 3 months after last dose of the study drug then every 6 months (± 7 days) thereafter.

APPENDIX C. EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent