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PHASE II TRIAL OF ABEMACICLIB AND NIVOLUMAB FOR SUBJECTS WITH HEPATOCELLULAR CARCINOMA

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List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CRF	Case report form
CT	Computed tomography
CTCAE	(National Cancer Institute) Common Toxicity Criteria For Adverse Events
CXR	Chest X-Ray
DNA	Deoxyribonucleic acid
DOR	Duration of Response
EKG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
GCP	Good clinical practice
HCC	Hepatocellular carcinoma
IB	Investigator's Brochure
ICF	Informed Consent Form
IHC	Immunohistochemistry
IP	Investigational Product
IV	Intravenous
LFTs	Liver function tests
LLN	Lower limit of normal
MRI	Magnetic Resonance Imaging
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PI	Principal Investigator
PR	Partial Response
PS	Performance Status
RNA	Ribonucleic Acids
SAE	Serious adverse event
SD	Stable disease
SUSAR	Suspected unexpected serious adverse reaction
TSH	Thyroid Stimulating Hormone
ULN	Upper limit of normal
WBC	White blood cell count

Study Summary

Title	Phase II Trial of Abemaciclib and Nivolumab for Subjects with Hepatocellular Carcinoma
Short Title	Abemaciclib and Nivolumab for HCC
IRB Number	Pending
Protocol Number	Pending
Phase	Phase II
Methodology	Single-arm open-label
Study Duration	24 months (18 months for accrual and 6 additional months for follow-up)
Study Center(s)	University of Pennsylvania Abramson Cancer Center
Objectives	Primary: • To determine the overall response rate Secondary: • To determine progression-free survival, duration of response, and overall survival • To determine toxicity Exploratory: • To explore potential biomarkers of anti-tumor immunity in peripheral blood and paired tissue biopsies
Number of Subjects	27 evaluable

Main Inclusion and Exclusion Criteria	1. Advanced HCC with histologic confirmation 2. Retinoblastoma (RB) positive by immunohistochemistry 3. ECOG PS 0 or 1 4. Childs-Pugh A or B7 5. ANC $\geq$ 1500 x 10^9/L 6. Platelets $\geq$ 75,000 x 10^9/L 7. No prior therapy with a PD-1, PD-L1, or CDK4/6 inhibitor 8. No uncontrolled ascites 9. No esophageal varices requiring treatment in the past 6 months 10. No serious autoimmune disease, interstitial lung disease, or solid organ transplant 11. No use of systemic corticosteroids other than for adrenal hormone replacement
Investigational Product	Abemaciclib 150mg by mouth twice daily
Duration of administration	Until progression, intolerance, or withdrawal of consent
Reference therapy	Historic results from nivolumab in HCC
Statistical Methodology	Primary endpoint will be overall response rate (ORR) by RECIST v. 1.1. This will be compared to historical ORR with nivolumab. Toxicity rates will be calculated using CTCAE v. 5.0. Kaplan-Meier methods will be used to calculate PFS, DOR, and OS using RECIST v. 1.1 and iRECIST criteria With 27 subjects, a one-sided binomial test with alpha = 0.10 will have 81% power to detect an improvement in ORR from 18% (H0) to 36% (H1).

BACKGROUND AND STUDY RATIONALE

This study will be conducted in full accordance all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations.

1 Introduction

Hepatocellular carcinoma is the second leading cause of cancer deaths worldwide, resulting in an estimated 810,000 deaths in 2015 [1]. Even as deaths from other common cancers have declined in the United States, mortality from HCC has doubled in the past two decades, and HCC is now the fifth-leading cause of cancer deaths in the U.S. [2]. For patients with advanced HCC not amenable to ablation, surgical resection, or transplant, median survival is less than one year. The accelerated approval of the PD-1 inhibitor nivolumab by the FDA in 2017 illustrates the benefit of immunotherapy for advanced HCC, but, with an overall response rate (ORR) of only 15-20% in studies of pembrolizumab and nivolumab in HCC, more effective combinations are clearly needed [3, 4].

1.1 Background and Relevant Literature

Recent preclinical studies have demonstrated potentiation of anti-tumor immunity and increases in tumor-infiltrating lymphocytes by CDK4/6 inhibitors as well as synergy between PD-1 and CDK4/6 inhibitors [5-8]. Mechanisms demonstrated have included inhibition of proliferation of regulatory T cells (Treg), enhanced antigen presentation and type III interferon production, decreased PD-L1 degradation, decreases in myeloid-derived suppressor cells (MDSCs), and increased IL-2 production due to derepression of nuclear factor of activated T cells (NFAT) pathways. Improvement in response has been shown with an initial 7-day run-in of abemaciclib prior to PD-L1 therapy compared to concurrent or sequential administration [9]. Additionally, single agent activity of CDK4/6 inhibitors has been demonstrated in RB-positive HCC, which account for about 70% of tumors, with impaired tumor growth and improved survival in murine models [10]. A single-arm phase II trial of palbociclib showed a median progression-free survival of nearly 6 months, but the clinical efficacy of CDK4/6 inhibitors has never been further explored in a randomized study in HCC [11]. As a single agent in HCC, nivolumab has demonstrated an overall response rate of 15-20% [3] and received accelerated approval from the FDA in HCC based on the results of the Checkmate-040.

We hypothesize that the addition of abemaciclib to nivolumab in advanced HCC will double the overall response rate (ORR) compared to nivolumab alone by both enhancing anti-tumor immunity and inhibiting cell cycle progression.

Ongoing studies in breast cancer and non-small cell lung cancer have demonstrated the safety of abemaciclib and pembrolizumab at standard doses, and it is assumed that the combination of abemaciclib and nivolumab will be similarly tolerable in an HCC population [12]. This will be a single-arm phase II trial to test the initial efficacy of this combination and elucidate the immune effects of abemaciclib in HCC.

1.2 Name and Description of the Investigational Product

Abemaciclib is an oral inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6). These kinases are activated upon binding to D-cyclins. Cyclin D1 and CDK4/6 promote phosphorylation of the retinoblastoma protein (Rb), cell cycle progression, and cell proliferation. In vitro, continuous exposure to abemaciclib inhibited Rb phosphorylation and blocked progression from G1 into S phase of the cell cycle, resulting in senescence and apoptosis.

1.2.1 Clinical Data to Date

1.2.1.1 Human Pharmacokinetics

The pharmacokinetics of abemaciclib were characterized in patients with solid tumors, including metastatic breast cancer, and in healthy subjects. Following single and repeated twice daily dosing of 50 mg (0.3 times the approved recommended 150 mg dosage) 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

repeated twice daily dosing, and the estimated geometric mean accumulation ratio was 2.3 (50% CV) and 3.2 (59% CV) based on Cmax and AUC, respectively.

Absorption
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: 4.1-24.0 hours).

Effect of Food
A high-fat, high-calorie meal (approximately 800 to 1000 calories with 150 calories from protein, 250 calories from carbohydrate, and 500 to 600 calories from fat) administered to healthy subjects increased the AUC of abemaciclib plus its active metabolites by 9% and increased Cmax by 26%.

Distribution
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% (1.1) for abemaciclib, 93.4% (1.3) 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, including breast cancer, concentrations of abemaciclib and its active metabolites M2 and M20 in cerebrospinal fluid are comparable to unbound plasma concentrations.

Elimination
The geometric mean hepatic clearance (CL) of abemaciclib in patients was 26.0 L/h (51% CV), and the mean plasma elimination half-life for abemaciclib in patients was 18.3 hours (72% CV).

Metabolism: Hepatic metabolism is the main route of clearance for abemaciclib. Abemaciclib is metabolized to several metabolites primarily by cytochrome P450 (CYP) 3A4, with formation of N-desethylabemaciclib (M2) representing the major metabolism pathway. Additional metabolites include hydroxyabemaciclib (M20), hydroxy-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.

Excretion: 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.

Specific Populations
Age, Gender, and Body Weight Based on a population pharmacokinetic analysis in patients with cancer, age (range 24-91 years), gender (134 males and 856 females), and body weight (range 36-175 kg) had no effect on the exposure of abemaciclib.

Patients with Renal Impairment: In a population pharmacokinetic analysis of 990 individuals, in which 381 individuals had mild renal impairment (60 mL/min ≤ CLcr <90 mL/min) and 126 individuals had moderate renal impairment (30 mL/min ≤ CLcr <60 mL/min), mild and moderate renal impairment had no effect on the exposure of abemaciclib. The effect of severe renal impairment (CLcr <30 mL/min) on pharmacokinetics of abemaciclib is unknown.

Patients with Hepatic Impairment: Following a single 200 mg oral dose of abemaciclib, the relative potency adjusted unbound AUC 0-INF of abemaciclib plus its active metabolites (M2, M18, M20) in plasma increased 1.2-fold in subjects with mild hepatic impairment (Child-Pugh A, n=9), 1.1-fold in subjects with moderate hepatic impairment (Child-Pugh B, n=10), and 2.4-fold in subjects with severe hepatic impairment (Child-Pugh C, n=6) relative to subjects with normal hepatic function (n=10). In subjects with severe hepatic impairment, the mean plasma elimination half-life of abemaciclib increased to 55 hours compared to 24 hours in subjects with normal hepatic function.

Drug Interaction Studies

Effects of Other Drugs on Abemaciclib

Strong CYP3A Inhibitors:

- Ketoconazole (a strong CYP3A inhibitor) 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.
- Coadministration 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 AUC 0-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:

- Coadministration of 600 mg daily doses of rifampin (a strong CYP3A inducer) with a single 200 mg dose of VERZENIO decreased the relative potency adjusted unbound AUC0-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 AUC0-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, coadministration 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 AUC0-INF by 9% and Cmax 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, coadministration 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 AUC0-INF by 37% and Cmax 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. 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-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, downregulate 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.

1.2.1.2 Clinical Studies in Adults

MONARCH 1 (NCT02102490) was a single-arm, open-label, multicenter study in women with measurable HR-positive, HER2-negative metastatic breast cancer whose disease progressed during or after endocrine therapy, had received a taxane in any setting, and who received 1 or 2 prior chemotherapy regimens in the metastatic setting [13]. A total of 132 patients received 200 mg abemaciclib orally twice daily on a continuous schedule until development of progressive disease or unmanageable toxicity. The median duration of treatment was 4.5 months. The most common grade 3/4 toxicities with abemaciclib were diarrhea (20% Grade 3), neutropenia (19% Grade 3, 5% Grade 4), nausea (5% Grade 3), infections (5% Grade 3, 2% Grade 4), fatigue (13% Grade 3), anemia (5% Grade 3), thrombocytopenia (4% Grade 3), and decreased appetite (3% Grade 3).

MONARCH 2 (NCT02107703) was a randomized, placebo-controlled, multicenter study in women with HR-positive, HER2-negative metastatic breast cancer in combination with fulvestrant in patients with disease progression following endocrine therapy who had not received chemotherapy in the metastatic setting [14]. A total of 669 patients were randomized to receive abemaciclib or placebo orally twice daily plus intramuscular injection of 500 mg fulvestrant on days 1 and 15 of cycle 1 and then on day 1 of cycle 2 and beyond (28-day cycles). Patients remained on continuous treatment until development of progressive disease or unmanageable toxicity. MONARCH 2 met its primary endpoint with an improvement in PFS (median 16.4 vs. 9.3 months, HR 0.553, $p<0.0001$). The most common grade 3/4 toxicities with abemaciclib in MONARCH 2 were neutropenia (24% Grade 3, 3% Grade 4) and diarrhea (13% Grade 3). anemia (7% Grade 3, <1% Grade 4), thrombocytopenia (2% Grade 3, 1% Grade 4), infections (5% Grade 3, <1% Grade 4), nausea (3% Grade 3), ALT increase (4% Grade 3, <1% Grade 4) and fatigue (3% Grade 3). Further details about MONARCH 1 and MONARCH 2 are available in the FDA package insert for abemaciclib.

1.3 Nivolumab Mechanism of Action

PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, ICOS, and BTLA. PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes. These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

In vitro, nivolumab (BMS-936558) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 + 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02). Clinical efficacy has been demonstrated in a variety of tumor types, and it is currently FDA approved for the treatment of melanoma, non-small cell lung cancer, Hodgkin's lymphoma, renal cell carcinoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, microsatellite instability-high tumors, and hepatocellular carcinoma

1.3.1 Nivolumab In Hepatocellular Carcinoma

Nivolumab was initially tested in hepatocellular carcinoma in the phase I/II Checkmate-040 study [3]. This was an open-label, non-comparative dose escalation and expansion trial. A total of 262 subjects were treated in the two phases of the study. In the dose-escalation portion, the overall response rate was 15%, with a disease control rate of 58% and a median overall survival of 15.0 months. In the dose expansion phase, an objective response rate of 20% was demonstrated, and median survival was not reached in the overall population. Response rates were similar regardless of viral hepatitis status or prior treatment with sorafenib. Toxicity was manageable, with 25% grade 3/4 adverse events, most commonly rash (23%), AST increase (21%), ALT increase (15%), lipase increase (21%), amylase increase (19%), and pruritis (19%). Treatment-related serious adverse events were seen in 6% of patients in the dose-escalation of cohort. Only 20% of subjects had PD-L1 expression of > 1% by IHC, and this did not correlate with response rate. Based on the results of this study, nivolumab received accelerated approval from the FDA for HCC. A phase III trial (Checkmate-459) comparing sorafenib to nivolumab for the initial treatment of advanced HCC is ongoing.

1.4 Dose Rationale

A phase 1b study of abemaciclib 150mg twice daily with the PD-1 inhibitor pembrolizumab 200mg every 3 weeks in women with breast cancer demonstrated tolerability, with no additional toxicity expected from either therapy as single agents [12]. The toxicities of pembrolizumab and nivolumab are expected to be similar in this study population and thus abemaciclib 150mg twice daily is expected to be similarly tolerable. The initial 7-day run-in of abemaciclib prior to starting nivolumab is based on preclinical data showing enhanced synergy compared to concurrent or sequential dosing [9].

The Checkmate-040 study which led to the accelerated approval of nivolumab in HCC used a dose of 240mg every 2 weeks. More recently, the FDA label for nivolumab has added the option of 480mg every 4 weeks for most nivolumab indications, including in hepatocellular carcinoma. The nivolumab doses of 480 mg Q4W was selected for this study based on clinical pharmacokinetic data and modeling showing similar drug exposure and no change in safety compared to dosing every 2 weeks using either weight-based (3mg/kg) or flat dose (240mg) regimens.

2 Study Objectives

2.1 Primary Objective

- To determine ORR of abemaciclib plus nivolumab in HCC as measured by RECIST v. 1.1

2.2 Secondary Objectives

- To determine PFS and DOR of abemaciclib plus nivolumab in HCCas measured by both RECIST v 1.1 and iRECIST. To measure ORR by iRECIST. To summarize OS using Kaplan-Meier methods
- To determine toxicity rates by category using CTCAE v. 5.0

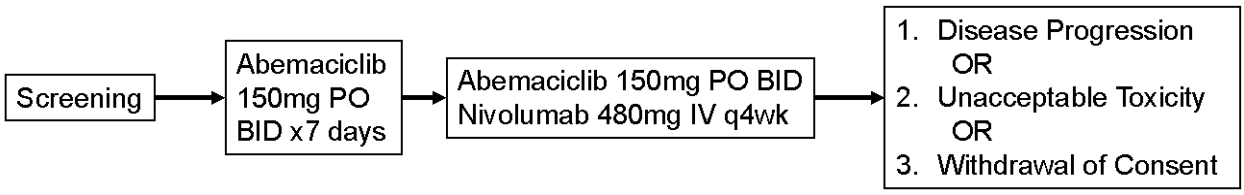
2.3 Exploratory Objective

- To correlate outcomes with blood and tumor tissue immune markers pre- and post-therapy to explore potential biomarkers of anti-tumor response

3 Investigational Plan

Subjects with advanced hepatocellular carcinoma will be enrolled in this single-arm open-label phase II study. Subjects will receive abemaciclib monotherapy 150mg twice daily for seven days then will initiate nivolumab 480mg IV every 28 days while continuing twice daily abemaciclib. Subjects will continue therapy until progression of disease, unacceptable toxicity, or withdrawal of consent.

Figure 1: Treatment Schema



3.1 Abemaciclib Dose and Schedule

Abemaciclib will be given at a dose of 150mg by mouth twice daily continuously for the duration of trial therapy.

3.1.1 *Dose Modifications for Abemaciclib*

If a subject experiences any of the following toxicities (grading per CTCAE v. 5.0) that are considered at least possible related to abemaciclib, abemaciclib will be modified as follows:

Table 1: Dose Levels for Abemaciclib

Dose Level	Dose of abemaciclib
0	150mg twice daily
-1	100mg twice daily
-2	50mg twice daily
If further dose-reduction beyond 50mg twice daily is required, discontinue abemaciclib permanently	

Hematologic toxicities

- Grade 1 or 2: No abemaciclib dosage adjustment necessary

- Grade 3: Withhold abemaciclib until toxicity resolves to ≤ Grade 2; no dose reduction of abemaciclib is necessary
- Grade 4 or recurrent Grade 3: Withhold abemaciclib until toxicity resolves to ≤ Grade 2 and then resume abemaciclib at the next lower dose (see **Table 1**)

If blood cell growth factors (e.g. filgrastim) are administered, hold abemaciclib for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤ grade 2. Resume at next lower dose (see **Table 1**) unless already performed for the toxicity that led to the use of the growth factor.

Non-hematologic toxicities:

- Diarrhea: At the first sign of loose stools, begin management with antidiarrheal agents and increase oral fluid intake. Response should be assessed within 24 hours.
    - Grade 1: No abemaciclib dosage adjustment necessary
    - Grade 2: If toxicity does not resolve to ≤ Grade 1 within 24 hours, withhold abemaciclib until resolution (no abemaciclib dosage reduction is necessary)
    - Grade 2 that persists or recurs after resumption at the same dose (despite maximal supportive measures): Withhold abemaciclib until toxicity resolves to ≤ Grade 1 and then resume abemaciclib at the next lower dose (see **Table 1**)
    - Grade 3 or 4 or requires hospitalization: Withhold abemaciclib until toxicity resolves to ≤ Grade 1 and then resume abemaciclib at the next lower dose (see **Table 1**)
- Hepatotoxicity:

Table 2: Dose Modifications and Management Of Abemaciclib For Hepatotoxicity

Monitor ALT prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	
CTCAE Grade	**Abemaciclib Dose Modifications**
Grade 1 (>ULN-3.0 x ULN) Grade 2 (>3.0-5.0 x ULN)	No dose modification is required.
Persistent or Recurrent Grade 2, or Grade 3 (>5.0-20.0 x ULN) that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 (>5.0 x ULN) with total bilirubin >2 x ULN, in the absence of cholestasis	Discontinue abemaciclib.
Grade 4 (>20.0 x ULN)	Discontinue abemaciclib.

To ensure patient safety the investigator should collect specific recommended clinical information and follow-up laboratory tests as shown below in Table 3.

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 TBL 2×ULN, or ALT 8×ULN, liver tests, including ALT, AST, TBL, 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.

In the event that hepatotoxicity requiring discontinuation of abemacicilib is observed, a complete laboratory evaluation as detailed in **Table 3** should be performed.

Table 3: 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.

Table 4: Dose Modification and Management — Hematologic Toxicities

Monitor complete blood counts prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	
CTCAE Grade	**Abemaciclib Dose Modifications**
Grade 1 or 2	No dose modification is required.
Grade 3	Suspend dose until toxicity resolves to ≤Grade 2. Dose reduction is not required.
Grade 3, recurrent, or Grade 4	Suspend dose until toxicity resolves to ≤Grade 2. Resume at next lower dose.
Patient requires administration of a blood cell growth factor	Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤Grade 2.

	Resume abemaciclib at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor.

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 infliltrates 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), broncheoalveolar lavage (BAL), and biopsy as clinically indicated (see also Table 7: *refer to dose adjustment table for interstitial lung disease/pneumonitis*).

Table 5: 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	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 or 4	Discontinue abemaciclib.

Table 6: 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	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 or 4	

- Other toxicities attributable to abemaciclib:
  - 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: Withhold abemaciclib until toxicity resolves to baseline or ≤ Grade 1. Resume at next lower dose (see **Table 1**).

- Grade 3 or 4: Withhold abemaciclib until toxicity resolves to baseline or ≤ Grade 1. Resume at next lower dose (see **Table 1**).

For any toxicity of abemaciclib (regardless of grade) that, despite optimal supportive care, is felt by the treating Investigator to present a risk to safety of the study subject, additional dose reduction, treatment delay, or treatment discontinuation is permitted at the discretion of the treating Investigator. Subjects in whom abemaciclib is held or discontinued may continue to receive nivolumab and remain on study.

3.1.2 *General Guidance for Increases in Serum Creatinine and Assessment of Renal Insufficiency with Abemaciclib*

Elevation of serum creatinine is observed with abemaciclib and is due to a pharmacological inhibitory effect of abemaciclib on renal tubular transporters without affecting glomerular function. The rise in serum creatinine (mean increase, 0.2 mg/dL) occurs within the first 28-day cycle of abemaciclib, and remains elevated but stable throughout the treatment period, and is reversible upon treatment discontinuation. Alternative markers (such as BUN, cystatin C level, or cystatin C calculated GFR) which are not based on creatinine, may be considered to determine whether renal function is impaired.

3.2 Nivolumab Dose and Schedule

Nivolumab will be administered at a dose of 480mg IV every 28 days. Treatment with nivolumab will begin after an initial 7-day treatment period with abemaciclib monotherapy (see Figure 1: Treatment Schema). No dose modifications of nivolumab are permitted. Subjects who experience toxicity related to nivolumab will be managed in accordance with guidelines in the management algorithms provided in the nivolumab package label, with modifications relevant to the treatment population

Table 4: Dose Modifications and Delays For Nivolumab Toxicity

Adverse Reaction	Severity	Dose Modificaiton
Colitis	Grade 2 diarrhea or colitis	Withhold dose
	Grade 3 diarrhea or colitis	Withhold dose
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose
	Grade 3 pneumonitis	Permanently discontinue
Hepatitis	• If AST/ALT is within normal limits at baseline and increases to more than 3 and up to 5 times the ULN • If AST/ALT is more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 20 times the ULN	Withhold dose
	If AST or ALT increases to more than 20 times the ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2	Withhold dose
	Grade 3 or 4	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose

	Grade 4 hyperglycemia	Permanently discontinue
Nephritis	Serum creatinine more than 1.5 and up to 6 times the ULN	Withhold dose
	Serum creatinine more than 6 times the ULN	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 Adverse Reaction (except for amylase or lipase elevations in absence of clinical pancreatitis)	• Withhold dose for first occurrence • Permanently discontinue for recurrence of same Grade 3 adverse event
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Grade 3 myocarditis	Permanently discontinue
	Requirement for 10mg per day or greater of prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

These dose adjustments are for AEs deemed related to nivolumab using CTCAE v. 5.0. If in the opinion of the treating Investigator, a toxicity is thought to be unrelated to nivolumab, no dose delay for nivolumab is necessary. If treatment is withheld per the above table, it should be held until the toxicity has returned to Grade $\leq$ 1.

Subjects with drug-related endocrinopathies controlled with hormone replacement such as insulin or adrenal replacement-dose steroids may resume treatment when toxicity has improved to Grade $\leq$ 1. Dose interruption is not required for hyper- or hypothyroidism but supportive care (e.g. thyroid replacement) should be started per institutional standards.

Corticosteroids are frequently indicated for Grade 3 or greater toxicities, and are necessary at times for lower grade toxicities. Guidance for their use and dosing is available in nivolumab package label. For any toxicity of nivolumab (regardless of grade) that, despite optimal supportive care, is felt by the treating Investigator to present a risk to safety of the study subject, additional treatment delay or treatment discontinuation is permitted at the discretion of the treating Investigator.

3.3 Treatment Duration and Follow-Up

Subjects will remain on study therapy until disease progression, unacceptable progression, or withdrawal of consent. Subjects who discontinue either abemaciclib or nivolumab may remain on study. Subjects with

radiographic progression with clinical stability may continue on treatment and have repeat imaging in 4-8 weeks per iRECIST criteria [15] (see section 7.10.5.3 for details).

3.4 Study Endpoints

3.4.1 Primary Study Endpoint

The primary study endpoint is overall response rate by investigator review using RECIST v. 1.1

3.4.2 Secondary Study Endpoints

1. Toxicity rates is an ordinal measure, graded using CTCAE v. 5.0, or dichotomized (binary)
2. Overall response rate using iRECIST criteria (binary)
3. Progression-free survival (time to event)
4. Duration of response (time to event)
5. Overall survival (time to event)

4 Study Population

4.1 Inclusion Criteria

1. Subjects must have hepatocellular carcinoma (HCC) that is inoperable (where surgery is not indicated due to disease extent, co-morbidities, or other technical reasons)
2. Histologic confirmation of HCC is not required for screening but is required prior to initiation of study treatment. Subjects with hepatocholangiocarcinoma or cholangiocarcinoma are not eligible.
3. Tumor must be positive for retinoblastoma (RB) expression by immunohistochemistry
4. Age $\geq$ 18 years and ability to understand and the willingness to sign a written informed consent document.
5. ECOG performance status of 0 or 1
6. Childs-Pugh score of $\leq$7
7. Life expectancy of at least 12 weeks
8. Must be able to swallow tablets
9. Must be willing to comply with protocol procedures (including completion of diaries and outcome measures)
10. Local or loco-regional therapy to the liver (i.e. surgery, radiation therapy, hepatic arterial embolization, chemoembolization, radiofrequency ablation, percutaneous ethanol injection, or cryoablation) must have been completed $\geq$ 4 weeks prior to enrollment
11. Must be willing to undergo a pretreatment and on-treatment biopsy and have a tumor site that is accessible for core needle biopsy
12. Measurable or evaluable disease as defined by RECIST v. 1.1
13. Women of childbearing potential must have a negative serum pregnancy test performed within 7 days of the first dose of abemaciclib (see Appendix A for definition of childbearing potential). Female subjects of childbearing potential must use an approved contraceptive method (detailed in Appendix A) for the duration of the study and an additional 3 weeks after the final dose of abemaciclib.
14. Subjects with hepatitis B must have an HBV viral load < 100 IU/mL by PCR during screening
15. Must have adequate organ and hematopoietic function as defined below:

Table 5: Baseline Laboratory Parameters

Laboratory Test	Required Value
Absolute neutrophil count (ANC)	$\geq$ 1.5 x 10^9/L
Platelet count	$\geq$ 75,000 x 10^9/L
Hemoglobin	$\geq$ 8.0 x 10^9/L

Alanine aminotransferase (ALT)	≤ 3 x ULN
Aspartate aminotransferase (AST)	≤ 3 x ULN
Serum creatinine OR creatinine clearance (CrCl)	≤ 1.5 x ULN OR CrCl ≥ 50mL/min by Cockcroft-Gault Formula
Total bilirubin	≤ 2.0 x ULN
Serum albumin	≥ 2.8 g/dL
INR	< 1.5 (FFP permitted if elevated)

4.2 Exclusion Criteria

1. Any history of a serious medical or psychiatric condition that would prevent the subject from signing the informed consent form
2. Pregnant or breastfeeding
3. Use of any chemotherapy within 3 weeks prior to the first study treatment date
4. Use of any experimental therapy within 4 weeks or 5 half-lives, whichever is longer, prior to the first study treatment date
5. Use of radiation within 2 weeks prior to the first study treatment date (4 weeks if radiation to liver as per section 4.1)
6. Prior treatment with a CDK 4/6 inhibitor
7. Prior treatment with a PD-1 or PD-L1 inhibitor
8. Those who have not recovered from adverse events ≤ Grade 1 from prior therapy, with the exceptions of alopecia of any grade or stable peripheral neuropathy ≤ Grade 2
9. Subjects may not receive concomitant anticancer agents or radiation. Antiviral agents aimed at treating infectious hepatitis are permitted
10. History of or suspected hypersensitivity to nivolumab or abemaciclib
11. Uncontrolled ascites
12. Esophageal varices requiring treatment within the past 6 months (banding or medication)
13. Subjects with uncontrolled brain metastases. Subjects with brain metastases must have stable neurological status following local therapy (surgery or radiation) for at least 4 weeks prior to first study treatment and must be off of steroids related to the brain metastases.
14. Any concurrent condition requiring the continued or anticipated use of systemic steroids beyond physiologic replacement dosing (excluding non-systemic inhaled, topical skin, nasal, and/or ophthalmic corticosteroids). All other systemic corticosteroids above physiologic replacement dosing must be discontinued at least 4 weeks prior to first study treatment
15. Active drug or alcohol use or dependence as documented in the chart that, in the opinion of the investigator, would interfere with adherence to study requirements
16. Active bacterial or fungal infection requiring IV therapy at the start of protocol treatment
17. A second primary malignancy that, in the judgment of the investigator, may affect the interpretation of results
18. Any illness or condition that in the opinion of the investigator may affect the safety of the subject or the evaluation of any study endpoint (e.g. interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea)
19. Personal history of ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest
20. Prior organ allograft or allogeneic bone marrow transplantation
21. Pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range with medication

22. Active autoimmune disease, except for vitiligo, type 1 diabetes mellitus, asthma, atopic dermatitis, or endocrinopathies manageable by hormone replacement; other autoimmune conditions may be allowable at the discretion of the Principal Investigator
23. Any other conditions judged by the investigator that would limit the evaluation of the subject
24. HIV positive by PCR

4.3 Subject Recruitment

Subjects will be identified through the clinical practices of the Abramson Cancer Center and the Hospital of the University of Pennsylvania and its affiliated hospitals and through referrals from outside hospitals and physicians. The trial will be publicized on the websites of the Abramson Cancer Center and the Hospital of the University of Pennsylvania. This protocol will also be listed in the ClinicalTrials.gov database. Subjects will be required to give written consent to participate before any screening tests or evaluations are conducted.

4.4 Total Number of Subjects and Sites

Twenty-seven evaluable subjects will be enrolled. Subjects may be enrolled at the University of Pennsylvania or at the Penn Presbyterian Medical Center.

4.5 Vulnerable Populations

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study

Note: Subjects who become imprisoned or are court-ordered to attend residential alcohol and other drug treatment facilities will be considered prisoners under Subpart C of the federal regulations 45CFR46. Such subjects cannot be continued in the research unless an amendment to the protocol is submitted and approved by the IRB and certification is submitted to the federal Office of Human Research Protections if the research is supported by the Department of Health and Human Services.

5 Study Intervention

5.1 Description

Abemaciclib is an oral tablet that is available in four dosage forms and strengths:
-50 mg tablets: oval beige table with “Lilly” debossed on one side and “50” on the other side

5.2 Intervention Regimen

Abemaciclib will be taken by mouth twice daily

5.3 Receipt

Abemaciclib will be receive to the Investigational Drug Service (IDS) and will be stored at room temperature as per standard pharmacy practice

5.4 Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)

5.5 Preparation and Packaging

Abemaciclib is supplied for clinical use in bottles containing 60 tablets (tablets described in section 5.1).

5.6 Administration and Accountability

Upon completion of study participation or termination of the study, all unused and/or partially-used abemaciclib will be destroyed by IDS.

5.7 Subject Compliance Monitoring

Subjects will be required to maintain a pill diary documenting adherence to twice daily oral administration of abemaciclib. Study medication bottles will be brought to study visits at the start of each 28-day cycle and study diaries will be reviewed at the start of each cycle.

6 Study Procedures

Table 6: Schedule of Study Procedures

All labs and study visits have a window of +/- 4 days. All imaging has a window of +/- 7 days

Study Phase	**Screening**	**Cycle 1 (35 days)**				**Cycle 2+ (28 days)**		**End of Study Visit[2]**	**Follow-up[3]**
Study Days	**-28 to 0**	**1**	**8**	**15[1]**	**29[1]**	**1**	**15[1]**		
Treatment									
Abemaciclib		X----------					----------X		
Nivolumab			X			X			
Tests and Procedures									
Informed Consent	X								
Review Inclusion/ Exclusion Criteria	X								
Demographics/Medical History	X								X[3]
Physical Examination	X	X	X			X		X	
Vital Signs: BP, HR, RR	X	X	X			X		X	
Height	X								
Weight	X	X				X		X	
ECOG PS	X	X	X			X		X	
Concomitant Medications	X	X				X		X	
IP Compliance						X		X	
AE Assessment		X	X			X		X	
CBC with differential[4]	X	X	X	X	X	X	X[4]	X	
Serum Chemistries[5]	X	X	X	X	X	X	X[5]	X	
TSH	X					X		X	
PT/aPTT[6]	X					X[6]		X[6]	
Serum Pregnancy Test[7]	X	X				X		X	
AFP[8]	X	X[8]				X[8]		X[8]	
HIV Screening[9]	X								
Hepatitis B/C Screening[10]	X	X[10]				X[10]		X[10]	
Disease Assessment (CT or MRI)[11]	X					X		X	
Research Correlates									
Blood sample (50cc)[12]	X		X	X[12]		X		X	

Tumor biopsy[13]	X			X					

[1] Lab visit only
[2] Should occur within 30 days of end of protocol therapy
[3] Follow-up will be through review of the available medical record and/or phone calls every 6 months for up to 2 years
[4] CBC with differential including hemoglobin, white blood count, absolute neutrophil count, and platelet count. CBC will be repeated on day 15 of cycle 2 but is required on day 15 of subsequent cycles only if hematologic toxicity ≥ Grade 2 by CTCAE v 5.0
[5] Serum chemistries including sodium (Na), potassium (K), chloride (Cl), bicarbonate (HCO3), blood urea nitrogen (BUN), creatinine (Cr), albumin, total bilirubin, AST, ALT, and alkaline phosphatase. Chemistries will be repeated on day 15 of cycle 2 but are required on day 15 of subsequent cycles only if hepatotoxicity ≥ Grade 1 by CTCAE v 5.0 or other toxicity measured by the panel ≥ Grade 2 by CTCAE v 5.0 are present on day 1 of that cycle.
[6]PT/INR will be done at screening, day 1 of cycle 2 and subsequent cycles, and at the end of study visit. Activated thromboplastin time (aPTT) is required only at screening
[7]Women of childbearing potential per Appendix A
[8]AFP will be repeated only if abnormal at screening
[9]HIV screening with HIV1/2 antibody screening and HIV RNA PCR if antibody screen positive
[10]Hepatitis B screening with hepatitis B surface antigen, surface antibody, and core antibody (IgG or total antibody, not IgM); if hepatitis B surface antigen or core antibody is positive, HBV DNA PCR will be performed. Hepatitis C screening with HCV antibody; if positive, HCV RNA PCR will be performed. Subjects who are positive for HBV core antibody and/or surface antigen at screening must have HBV viral load checked on day 1 of each cycle and at the end of treatment visit.
[11]Baseline imaging assessment to be performed within 21 days of cycle 1 day 1. Subsequent imaging on cycle 3 day 1 and on day 1 of every other subsequent cycle (cycles 5, 7, etc.), and at end of study visit if not performed within prior 28 days.
[12] Baseline research blood samples can be drawn during screen or prior to treatment on cycle 1 day 1, then on cycle 1 day 8 prior to nivolumab treatment, cycle 1 day 15-19 (on same day as research tumor biopsy when possible), day 1 of each subsequent cycle, and at the end of study visit. Procedures for sample handling are described in the laboratory manual.
[13]Core or surgical tumor biopsy must occur at baseline after completion of most recent therapy and between days 15 and 19 of cycle 1. Biopsies outside of this window for scheduling, safety, or other reasons will not be considered deviations but should be discussed with the Principal Investigator.

6.1 Screening (Within 28 days of First Dose)

- Signed written and informed consent
- Review and confirm all inclusion/exclusion criteria
- Complete medical history and demographics
- Complete physical examination including but not limited to: height, weight, vital signs (oxygen saturation, heart rate, respiration rate, blood pressure, and oral temperature)
- ECOG performance status
- Concomitant medications
- Clinical laboratory testing including but not limited to:
    - CBC with differential and platelet count
    - Serum chemistries: sodium (Na), potassium (K), chloride (Cl), bicarbonate (HCO_3), blood urea nitrogen (BUN), creatinine (Cr), calcium (Ca), albumin (Alb), total serum bilirubin (TBili), AST (SGOT), ALT (SPGT), alkaline phosphatase (ALP)
    - Prothrombin time (PT)/International normalized ratio (INR)
    - Activated thromboplastin time (aPTT)
    - Thyroid stimulating hormone (TSH)
        - If abnormal, free thyroxine will be performed
- Alpha fetoprotein (AFP)
- HIV serology
    - HIV 1/2 antibody screen; HIV viral load by PCR if antibody screen positive
- Serum pregnancy test for beta HCG (for women of childbearing potential, defined in Appendix A)
- Serologic testing for hepatitis C and hepatitis B:
    - Hepatitis B screening with hepatitis B surface antigen, surface antibody, and core antibody (IgG or total antibody, not IgM); if hepatitis B surface antigen or core antibody is positive, HBV DNA PCR will be performed
    - Hepatitis C screening with HCV antibody; if positive, HCV RNA PCR will be performed. HCV RNA PCR can also be performed on cycle 1 day 1, and results are not required prior to initiating therapy.
    - For subjects known to be positive for hepatitis B or hepatitis C by medical history, viral PCR should be performed concurrently to antibody studies
- Blood draw (50cc) for correlative research studies (procedures described in laboratory manual)
- Per standard of care, baseline imaging including but not limited to chest CT (with or without contrast) and triphasic abdominopelvic CT or MRI, if subject does not have previous documentation within 3 weeks of first dose
- Core or surgical tumor biopsy (procedures described in laboratory manual)

6.2 Study Intervention Phase

All labs and study visits have a window of +/- 4 days. All imaging has a window of +/- 7 days

6.2.1 Cycle 1

6.2.1.1 Day 1 - Baseline Visit

- Focused physical exam
- Vital signs and weight
- ECOG PS
- CBC with differential and platelet count and serum chemistries (Na, K, Cl, HCO_3, BUN, Cr, Ca, Alb, TBili, AST, ALT, ALP)
- AFP (only if elevated at screening)
- Serum pregnancy test for beta HCG (for women of childbearing potential, defined in Appendix A)
- Review of concomitant medications
- HCV and HBV viral PCR if indicated:
    - HBV DNA PCR only if hepatitis B surface antigen or core antibody positive
    - HCV RNA PCR if hepatitis C antibody positive and not performed at screening
- Dispensing of abemaciclib

- Baseline AE assessment

6.2.1.2 Day 8

- Focused physical exam
- Vital signs and weight
- ECOG PS
- CBC with differential and platelet count and serum chemistries (Na, K, Cl, HCO_3, BUN, Cr, Ca, Alb, TBili, AST, ALT, ALP)
- Blood draw (50cc) for correlative research studies (procedures described in laboratory manual)
- AE assessment
- Nivolumab treatment

6.2.1.3 Day 15 (biopsy and lab visit when possible on same day between days 15 and 19)

- CBC with differential and platelet count and serum chemistries (Na, K, Cl, HCO_3, BUN, Cr, Ca, Alb, TBili, AST, ALT, ALP)
- Core or surgical tumor biopsy (procedures described in laboratory manual)
- Blood draw (50cc) for correlative research studies (procedures described in laboratory manual)

6.2.1.4 Day 29 (lab visit only)

- CBC with differential and platelet count and serum chemistries (Na, K, Cl, HCO_3, BUN, Cr, Ca, Alb, TBili, AST, ALT, ALP)

6.2.2 Cycle 2

6.2.2.1 Day 1

- Focused physical exam
- Vital signs and weight
- ECOG PS
- CBC with differential and platelet count and serum chemistries (Na, K, Cl, HCO_3, BUN, Cr, Ca, Alb, TBili, AST, ALT, ALP)
- TSH
- PT/INR
- AFP (only if elevated at screening)
- Serum pregnancy test for beta HCG (for women of childbearing potential, defined in Appendix A)
- HBV DNA PCR if hepatitis B surface antigen or core antibody previously positive
- Review of concomitant medications
- Review of abemaciclib pill diary
- Dispensing of abemaciclib and return of unused pills
- AE assessment
- Nivolumab treatment
- Blood draw (50cc) for correlative research studies (procedures described in laboratory manual)

6.2.2.2 Day 15 (lab visit only)

- CBC with differential and platelet count and serum chemistries (Na, K, Cl, HCO_3, BUN, Cr, Ca, Alb, TBili, AST, ALT, ALP)

6.2.3 Cycle 3 and beyond

6.2.3.1 Day 1

- Focused physical exam
- Vital signs and weight
- ECOG PS
- CBC with differential and platelet count and serum chemistries (Na, K, Cl, HCO_3, BUN, Cr, Ca, Alb, TBili, AST, ALT, ALP)
- TSH

- PT/INR
- AFP (only if elevated at screening)
- Serum pregnancy test for beta HCG (for women of childbearing potential, defined in Appendix A)
- HBV DNA PCR if hepatitis B surface antigen or core antibody previously positive
- Review of concomitant medications
- Review of abemaciclib pill diary
- Dispensing of abemaciclib and return of unused pills
- AE assessment
- Nivolumab treatment
- Blood draw (50cc) for correlative research studies (procedures described in laboratory manual)
- Disease assessment (CT or MRI) with 7 days of day 1 of cycle 3, 5, and every other subsequent cycle

6.2.4 End of Study Visit (within 30 days of end of protocol therapy)

- Focused physical exam
- Vital signs and weight
- ECOG PS
- CBC with differential and platelet count and serum chemistries (Na, K, Cl, HCO_3, BUN, Cr, Ca, Alb, TBili, AST, ALT, ALP)
- TSH
- AFP (only if elevated at screening)
- Serum pregnancy test for beta HCG (for women of childbearing potential, defined in Appendix A)
- HBV DNA PCR if hepatitis B surface antigen or core antibody previously positive
- Review of concomitant medications
- Review of abemaciclib pill diary
- Return of unused abemaciclib pills
- AE assessment
- Blood draw (50cc) for correlative research studies (procedures described in laboratory manual)
- Disease assessment (CT or MRI) if not performed within prior 28 days

The end of study visit can be conducted during a scheduled office visit (such as to review scans demonstrating progression) or separately.

6.2.5 Follow-Up Phase of the Study

All subjects will be followed for survival, disease status and new anti-cancer treatment information unless the subject requests to be withdrawn from follow-up or the study is terminated by the Principal Investigator. Follow-up information will be collected via telephone or subject medical records until death, loss to follow-up, or study termination by the Prinicipal Investigator, whichever occurs first. Subjects will be followed every 6 months up for a maximum of 24 months from the end of protocol therapy. If the subject no longer wishes to be contacted but maintains his or her consent, the study staff may use a public information source (e.g. newspaper or electronic obituary, county records) to obtain information about survival status only as per local data protection laws and approval from the relevant ethics committee.

6.2.6 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or study procedures or visit schedules or unacceptable toxicity of the therapy. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each subject completes the clinical study. Subjects who withdraw early will have one final visit to collect investigational product and to follow up regarding adverse events.

If a subject permanently discontinues all study treatment for reasons other than disease progression, such as toxicity, the state of disease in terms of progression should be noted at this time point. Ideally formal

imaging should occur at this point to document the state of disease. Alternatively, the previous scan should be used. Where possible scanning should continue as per normal practice (RECIST v1.1) until progression has been reached as per protocol or the subject has started other anti-cancer treatment. The date of progression of disease should be recorded in the eCRF. Further treatment is at the treating doctor's discretion.

6.2.7 Data Collection and Follow-Up for Withdrawn Subjects

Subjects who withdraw consent to participate in the study will be seen for one final visit to collect the investigational product. During this visit they will be asked for permission to have the study team look into their survival status via publicly available means.

7 Study Evaluations and Measurements

7.1 Informed Consent

Study personnel will obtain written informed consent from each subject **prior** to participation in this study, following adequate explanation of the aims, eligibility criteria, treatment and follow-up procedures, anticipated benefits and potential risks of the study.

7.2 Medical History and Demographic Data

A complete medical history will be obtained including details of any relevant medical conditions occurring prior to consent. Details will be collected on the subject's cancer diagnosis including site, date of diagnosis, radiological tumor size, prior anti-cancer treatment (if any) and outcome, medications and their indications, history of alcohol use, history of viral hepatitis (including prior and/or ongoing treatments and current disease status), history of non-alcoholic steatohepatitis (NASH), history of autoimmune liver disease, history of liver cirrhosis, and Child-Pugh score. Demographic data collected will include sex, date of birth and race/ethnicity.

7.3 Physical Examination

A complete physical examination will be conducted at specified visits. A focused physical assessment will be performed at other visits as determined by the Investigator or directed per subject complaints

7.4 Vital Signs, Height, and Weight

Vital signs including oxygen saturation, heart rate, respiration rate, blood pressure, and oral temperature will be measured at specified visits. Height will be collected at the baseline or screening visit. Weight will be collected at specified visits.

7.5 ECOG Performance Status

ECOG performance status will be measured at specified visits according to **Table 7**

Table 7: ECOG Performance Status

ECOG Grade	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

7.6 Concomitant Medications

All medications (including prescription medications and over the counter preparations), taken by the subject from the day of consent to the safety visit will be documented as concomitant medications. All medication should be recorded to clearly allow identification of prohibited medications. If a subject is taking any of the medications defined as prohibited for use during the study, then these will be documented during screening. Subjects must stop taking any prohibited medications prior to starting study treatment within the specified wash out periods of the prohibited medications. The following details will be collected: drug name, reason for treatment, dose/units, route of administration, frequency, start and end date of therapy.

Patients must be instructed not to take any medications, including over-the-counter products such as vitamins, minerals and other dietary supplements, without first consulting the Investigator. All concomitant medications must be recorded on the relevant eCRF.

Supportive care and other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator and recorded in the relevant eCRF.

Patients who use oral contraceptives, hormone replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low molecular weight heparin or warfarin at a stable dose level), or other allowed maintenance therapy should continue their use.

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. Therefore, drugs that are strong and moderate inducers of CYP3A and/or strong inhibitors of CYP3A should be avoided or substituted if necessary.

If concomitant use cannot be avoided, abemaciclib dose adjustments may be required:

- Patients who must take CYP3A inhibitors such as clarithromycin, diltiazem, or verapamil should reduce the abemaciclib dose to 100 mg twice daily.
- Patients who must take itraconazole should reduce the abemaciclib dose to 50 mg twice daily.
- Patients should avoid using ketoconazole
- Patients should avoid grapefruit or grapefruit juice.

7.7 Laboratory Evaluations

Blood samples will be taken to be tested in the clinical laboratory at intervals specified in **Table 4**

Complete Blood Count:
White blood cell (WBC) count with differential, hemoglobin, hematocrit, and platelet count

Serum Chemistry:
Sodium (Na), potassium (K), chloride (Cl), bicarbonate (HCO_3), calcium (Ca), blood urea nitrogen (BUN), creatinine (Cr), total bilirubin(Tbili), alkaline phosphatase (ALP), AST (SGOT), ALT (SGPT), albumin (Alb)

Coagulation Studies (Screening only):
Prothrombin time (PT) with international normalized ratio (INR), activated thromboplastin time (aPTT)

Tumor Markers:
Alpha fetoprotein (AFP). Repeat per **Table 6** schedule only if abnormal at screening.

Thyroid Stimulating Hormone (TSH):
Thyroid stimulating hormone (TSH); if abnormal, check free thyroxine (T4)

Viral Hepatitis Serology and PCR(Screening Only):
Hepatitis B surface antigen (HbSAg), hepatitis B surface antibody (HbSAb), hepatitis B core antibody (HbCAb) total or IgG (IgM only not acceptable), hepatitis C antibody (HCV Ab); if HbSAg or HbCAb positive, check HBV viral load; if HCV Ab positive, check HCV viral load.

Subjects with active hepatitis B and/or hepatitis C are eligible for the study but viral status must be verified using these screening tests. Testing must be sent but results are not required prior to the initiation of study therapy. For subjects known to be positive for hepatitis B or hepatitis C by medical history or prior available laboratory data, viral PCR may be checked concurrently with viral serologies at screening.

For subjects positive for hepatitis B (surface antigen or core antibody positive), HBV viral PCR will be checked on day 1 of every cycle and at the end of treatment visit.

HIV (Screening only):
HIV 1/2 antibody; if positive, check HIV viral load by PCR. Subjects with detectable HIV viral RNA by PCR are not eligible.

7.8 Pregnancy Testing

A serum pregnancy test will be performed at specified visits for female subjects of childbearing potential as defined in Appendix A. Female subjects of reproductive potential should use a highly effective means of contraception (see Appendix A) for the duration of the study and at least 3 weeks after the last dose of abemaciclib

7.9 Investigational Product Compliance

Subjects will maintain a diary documenting adherence to abemaciclib. This diary will be reviewed at the start of each treatment cycle (starting with cycle 2) and at the end of study visit.

7.10 Disease Assessments

7.10.1 Antitumor Effect

For the purpose of this study, patients will be evaluated for response every 8 weeks by CT scan of the chest with or without contrast and triphasic (non-contrast, arterial phase contrast, venous phase contrast) CT scan and/or MRI of the abdomen with IV contrast (pelvis required only if disease documented in pelvis on baseline scan). MRI scans of the abdomen are preferred if the patient is eligible to have this done. The same imaging modality should be used throughout the study.

7.10.2 Definition of Evaluable

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with abemaciclib.

Evaluable for efficacy endpoints, including overall response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy (including at least 50% of scheduled abemaciclib doses and at least 1 dose of nivolumab), and have had their disease re-evaluated by appropriate imaging after at least 4 and no more than 12 weeks from cycle 1 day 1 will be considered evaluable for efficacy endpoints including overall response. These patients will have their response classified according to the definitions stated below.

7.10.3 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable and/or evaluable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. In subjects who have received locoregional therapy to the liver, lesions that have not been treated locally should be preferentially chosen as target lesions. If a liver lesion that has been treated using locoregional therapy must be chosen as a target lesion, progression of the lesion is required after locoregional therapy, A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

7.10.4 Methods for Evaluation of Measurable Disease

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

7.10.5 Response Criteria

7.10.5.1 Evaluation of Target Lesions (RECIST 1.1)

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

7.10.5.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

7.10.5.3 Immune-Related Response in Measurable Lesions (iRECIST)

iRECIST guidelines were established in 2017 to guide response assessments in clinical trials testing immunotherapeutics. Full details of the iRECIST criteria for this study can be found in Seymour L et al, Lancet Oncology 2017 [15].

If initial RECIST 1.1-defined progression (ie, iUPD) is noted on imaging in the setting of clinical stability, subjects may remain on study treatment and have confirmatory imaging in 4-8 weeks (study specified scans every 8 weeks should continue on initial schedule if patient remains on study). An assignment of clinical stability requires that no worsening of performance status has occurred, that no clinically relevant increases in disease-related symptoms such as pain or dyspnea occur that are thought to be associated with disease progression, and that no requirement for intensified management of disease-related symptoms exists, including increased analgesia, radiotherapy, or other palliative care. The imaging findings and the recommendation to continue with treatment despite iUPD should be discussed with the patient before a decision is made about whether or not to continue therapy. Patients who have iUPD and are not clinically stable should be designated as not clinically stable in the case report form. This designation will allow the

best overall response to be calculated and the date of iUPD to be used in estimates of progression-free survival.

If radiologic progression is confirmed (iCPD), they will be determined to have progressive disease and discontinued from study therapy, but if repeat imaging shows stable disease or response by RECIST 1.1 they may remain on study therapy with imaging continuing as previously scheduled every 8 weeks (cycle 3 day 1, cycle 5 day 1, etc.).

Table 3: Comparison of RECIST 1.1 and iRECIST

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before CR, PR, or SD
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Consideration of clinical status	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

Table 4: Assignment of timepoint response using iRECIST

	Timepoint response with no previous iUPD in any category	Timepoint response with previous iUPD in any category
Target lesions: i CR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR

Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions: yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures >5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same.

*Previously identified in assessment immediately before this timepoint. “i” indicates immune responses assigned using iRECIST. iCR=complete response. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression. non-iCR/non-iUPD=criteria for neither CR nor PD have been met. iCPD=confirmed progression. RECIST=Response Evaluation Criteria in Solid Tumours.

7.10.5.4 Overall Response Rate

Overall response rate is defined as the proportion of subjects who achieve a complete or partial response during the course of the study. The best response experienced by a subject (CR > PR > SD > PD) will be used. Responses will be determined by investigator review. The primary study endpoint will be use RECIST v. 1.1 definitions (sections 7.10.5.1 and 7.10.5.2) to define overall response rate. Overall response rate by iRECIST criteria (section 7.10.5.3) will be a secondary endpoint.

7.10.5.5 Duration of Response

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

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

7.10.6 Toxicity Evaluation

All subjects entered into the study and who are given at least one dose of abemaciclib will have detailed information collected on adverse events for the overall study safety analysis. All adverse events will be categorized and tabulated using CTCAE v. 5.0.

7.10.7 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression using both RECIST v. 1.1 and iRECIST criteria [15], death, or last patient contact when progression-free. For patients who are progression-free, PFS will be censored at the most recent date which documents progression-free status (i.e., scan date or clinical visit date).

7.10.8 Overall Survival

OS is defined as the duration of time from start of treatment to death due to any cause or last patient contact alive. Public records (e.g. obituaries) may be used to ascertain dates of death for subjects where such data is not available in the medical record unless the subject withdraws consent for follow-up. For subjects who enroll in hospice care in whom the specific date of death cannot be determined, date of death will be recorded as the date the patient entered hospice. In subjects who are alive or lost to follow-up, OS will be censored at last date of contact alive.

7.11 Correlative Studies

7.11.1 Correlative Blood Samples

Research blood samples (50cc) will be drawn at baseline, on cycle 1 day 8, cycle 1 day 15, on day 1 of each subsequent cycle, and at the end of study visit. Immune markers such as multi-parameter flow cytometry, antigen-specific T-cell assays (to identify tumor-reactive T-cells), markers of APC activation, T-cell receptor sequencing, and/or cytokine assays will be performed. Depending on resource and sample availability, additional assays to further assess immune activation following treatment will be employed.

Further procedures for handling of research blood samples are described in the laboratory manual.

7.11.2 Tumor Biopsy

Tumor tissue samples will be obtained at baseline and between days 15 and 19 of cycle 1. Biopsies are mandatory but can be omitted if in the best interest of the subject after discussion with the Principal Investigator. At a minimum, tissue confirmation of histology (HCC) and RB status by immunohistochemistry is required prior to starting study therapy. Tissue will be analyzed by H&E, and by IHC for PD-L1 and for

immune markers (such as CD45, CD68, CD3, CD8, CD4, Foxp3, CD20, myeloperoxidase), tumor markers (AFP, Ki-67, cleaved caspase 3) , vascular (CD31) and stromal markers (collagen type I); and by Masson's trichrome. If sufficient material is available, the tumor may also be assessed by a next-generation sequencing panel, whole exome sequencing (WES), RNA sequencing, and/or by other techniques. When tumor WES sequencing, tumor RNAseq, and germline WES is feasible and successfully performed, patient specific neo epitopes arising from tumor somatic missense mutations will be predicted bioinformatically.

Depending on resource availability and tissue availability, additional assays to further assess immune activation following treatment will be employed. In some cases, germline whole exome sequencing will be performed to allow determination of HLA type and as needed for the bioinformatics pipeline to identify patient specific neo epitopes.

Further procedures for handling of tumor biopsy material is described in the laboratory manual.

8 Statistical Plan

8.1 Primary Endpoint

The primary endpoint is overall response rate (ORR) by investigator review using RECIST v. 1.1 (binary).

8.2 Secondary Endpoints

1. Toxicity rates is an ordinal measure, graded using CTCAE v. 5.0, or dichotomized (binary).
2. Overall response rate using iRECIST criteria (binary)
3. Progression-free survival (time to event)
4. Duration of response (time to event)
5. Overall survival (time to event)

8.3 Sample Size and Power Determination

Overall response rate to PD-1 therapy in HCC has varied in published studies from 15-20%. By combining available data from these studies, an overall response rate of 18% is estimated for PD-1 monotherapy. Doubling of this response rate, from 18% (H0) to at least 36% (H1) would be highly promising and worthy of additional study. With 27 subjects, a one-sided binomial test with alpha = 0.10 will have 81% power to detect an improvement in ORR from 18% (H0) to 36% (H1). For proportions, a sample of n=27 will provide 90% confidence intervals that are a maximum of 0.34 in width. For additional time to event variables, 27 subjects (21 events by 24 months) yields 90% confidence intervals for median survival that are approximately half of mean survival in width (assuming exponential survival).

8.4 Statistical Methods

ORR and other binary variables will be analyzed using binomial exact tests, using a one-sided 10% type one error. Progression-free survival, duration of survival, and overall survival will be analyzed using Kaplan-Meier methods. PFS and DOR will be summarized as medians with 90% confidence intervals. Toxicity rates will be summarized as binomial proportions with 90% confidence intervals.

8.4.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as gender).

8.4.2 Efficacy Analysis

To be eligible for efficacy endpoints (PFS, ORR, DOR, OS), subjects must have completed at least one cycle of therapy, and have had their disease re-evaluated by appropriate cross-sectional imaging (CT or MRI) at least 4 weeks and no more than 12 weeks after their baseline imaging. Subjects who do not meet criteria for the efficacy analysis will be replaced.

8.4.3 Safety Analysis

All subjects entered into the study and who are given at least one dose of abemaciclib will have detailed information collected on adverse events for the overall study safety analysis. All adverse events will be categorized by CTCAE v. 5.0,tabulated as ordinal, and summarized as binomial proportions.

8.4.4 Exploratory Endpoints

Analysis of Immune markers in tissue and blood will be a hypothesis-generating exploration of potential biomarkers. Logistic regression will be used to evaluate any association of response status with marker, and markers will be summarized by response status. Cox-proportional hazards regression models will be used to evaluate for any association with a marker and time to progression

9 Safety and Adverse Events

9.1 Definitions

9.1.1 Unanticipated Problems Involving Risk to Subjects or others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

9.1.2 Adverse Event

An **adverse event** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

9.1.3 Adverse Events of Special Interest

AESIs (serious or non-serious) are defined as AEs of scientific and medical concern specific to the investigational product or program, for which ongoing monitoring and rapid communication by the Principal Investigator to drug manufacturer can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the Principal Investigator to other parties (e.g., regulators) might also be warranted.

Details on currently agreed list of AESIs for abemaciclib can be found in the current IB. These AESIs are to be reported to Eli Lilly expeditiously within 1 business day of knowledge of the event, during the study through 30 days after receiving the last dose of study treatment, according to the procedures below

9.1.4 Serious Adverse Event

Serious Adverse Event

Adverse events are classified as serious or non-serious. A **serious adverse event** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity

- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life-threatening, but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as **non-serious adverse events**.

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Events of progression of the subject's underlying cancer as well as events clearly related to progression of the subject's cancer (signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. If the event has a fatal outcome within the safety reporting period, then the event of Progression of Disease must be recorded as an AE and as a SAE with CTC Grade 5 (fatal outcome) indicated.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Finding
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an AE must also be recorded and documented as an AE.

Abnormal Laboratory Values
An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- an action on the study drug is made as a result of the abnormality
- intervention for management of the abnormality is required
- at the discretion of the investigator should the abnormality be deemed clinically significant

9.2 Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

9.2.1 Post-Study Adverse Event

All unresolved AEs should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the Principal Investigator of any death or AE occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The Principal Investigator should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

9.3 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported immediately.

9.4 Relationship of AE to Study

The relationship of each adverse event to the study procedures should be characterized by the Investigator as definitely related, probably related, possibly related , unlikely or unrelated to study therapy.

9.5 Reporting of Adverse Events, Adverse Device Effects and Unanticipated Problems

Investigators must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible,

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study intervention was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study intervention

Additionally all other events (unanticipated problems, adverse reactions, unanticipated adverse device effects and subject complaints will be recorded and reported with respect to institutional and federal policies as described in the Penn Manual and below.

9.5.1 Follow-up report

If an SAE has not resolved at the time of the initial report and new information arises that changes the investigator's assessment of the event, a follow-up report including all relevant new or reassessed information (e.g., concomitant medication, medical history) should be submitted to the IRB. The investigator is responsible for ensuring that all SAE are followed until either resolved or stable.

9.5.2 Investigator Reporting: Notifying Drug Manufacturer (Eli Lilly)

All SAEs, AESIs, and pregnancies, regardless of relationship to study drug, must be reported to the drug manufacturer during the study through 30 days after receiving the last dose of study treatment within 1 business day, according to the procedures below. After the 30-day specified window, only SAEs considered to be treatment related and all AESIs, regardless of treatment relationship, should be reported. It is important that the investigator provide an assessment of relationship of the SAE or AESI to study treatment at the time of the initial report.

Serious adverse events should be reported to Lilly using a CIOMS Form or other form acceptable to Lilly. 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.

Investigator and Institution agree to provide Lilly with a copy of all information Investigator and/or Institution submit to regulators related to any adverse events for the Study Drug that occur during the Study that Investigator and/or Institution have not otherwise provided Lilly.

9.5.3 Investigator Reporting: Notifying the Penn IRB

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB. The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

Unexpected (An event is “unexpected” when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.)

AND

Related to the research procedures (An event is “related to the research procedures” if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

9.5.4 Reporting Process

Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the form: “Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events” or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator’s study file.

9.5.5 Other Reportable Events:

For clinical drug trials, the following events are also reportable to the Penn IRB:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
    - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
    - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
    - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
    - Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- Complaint of a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

9.6 Abramson Cancer Center Data Safety Monitoring Committee (DSMC):

Every effort should be made to report an event as a diagnosis, not as a list of symptoms. Symptoms that led to the diagnosis should be included in the event description but should not be the actual event.

Unless covered by exclusions below, Grade 3 or higher events must be reported within 10 days of knowledge.

All unexpected deaths within one business day of knowledge.

All other deaths within 30 days of knowledge. Deaths of subjects off-study for greater than 30 days from the last study treatment/intervention are not reportable unless a longer time frame is specified in the protocol.

EXCEPTIONS to AE/SAE Reporting:

Grade 3 or 4 events that are judged by a study investigator to be clearly unrelated to protocol therapy. The reason for determining that the event is unrelated must be clearly documented in the EMR.

Grade 3 or 4 events that are probably or definitely related to progression of disease as judged by a study investigator. The fact that this event is related to disease progression must be clearly document in the EMR.

Grade 3 or 4 events that are probably or definitely related to an FDA approved agent. The fact that this event is related to the FDA approved agent must be clearly documented in the EMR..

SAEs will be submitted to the DSMC through the Velos Clinical Trial Management System.

Reportable Events;

Exception

A one-time, intentional action (planned prospectively) or process that departs from the IRB and CTSRMC approved study protocol, intended for one occurrence. Advance documented IRB and DSMC approval is required.

For in-house studies with a Medical Monitor or Safety Monitoring Committee (not DSMB), approval must be obtained from the Medical Monitor or Safety Monitoring Committee prior to submitting your exception request to the DSMC.

The following information must be contained in your exception request:
- When it is needed and why it is needed in that timeframe
- Has the Medical Monitor or Sponsor approved and provide the documentation of approval
- Is this an exception from eligibility, treatment, disease progression, study calendar windows, etc.
- Why the exception is needed (cite the section(s) of the protocol) along with the full clinical details of the subject. This must be determined by the sub-Investigator or PI.
- The reason why the protocol currently doesn't allow the situation for which an exception is being requested. This must be determined by the sub-Investigator or PI.
- If there are plans to amend the protocol and if not, why not.
- If additional follow-up or interventions will be required in order to protect the subject as a result of this exception.

Study Exceptions the DSMC may Reject:

Exceptions to eligibility, treatment/dosing, contraindicated treatment/therapies/interventions or safety tests for the following types of studies may be rejected by the DSMC:

- Any investigator-initiated treatment study.
- Any treatment study involving on-campus manufacturing of any component, regardless of sponsor.

To seek approval, you must provide the DSMC with strong and compelling scientific and clinical information to support your request. You should also include a statement explaining whether or not the protocol will be amended. If the protocol will not be amended your reasoning must be provided. If this situation is likely to happen again, the DSMC will require a protocol amendment.

Deviation

Any unintentional action or process that departs from IRB approval and is identified retrospectively. The deviation is reportable to the DSMC and the IRB within 10 days from the time the event becomes known to the study team only when: one or more participants were placed at increased risk of harm, or, the event has the potential to occur again, or the event has the potential to qualify as serious or continuing noncompliance.

If the PI determines that a deviation has **any potential** to impact participant safety (harm and/or risk), or the integrity of data produced from the participant, or some other overall impact on the study, the PI must report the deviation to the IRB and DSMC as described above. The IRB will make the final assessment of the impact. The DSMC will assess for additional safety and scientific integrity concerns.

The following information must be contained in your deviation report:
- When it happened? When the study team (any member) became aware
- The full description of the deviation including important dates, test results, actions taken towards the subject, etc. Also, why it happened and how it was identified.
- Was the Medical Monitor or Sponsor notified. If so, their response?
- The PIs assessment of the impact on risk, safety and/or outcome. If no impact, why. If impact, what and what will happen next.
- The corrective actions that have been implemented to date and the impact of those corrective action plans.

- Future corrective action plans (if applicable) and the impact of those plans.
- If there are plans to amend the protocol (if applicable to prevent future deviations) and if not, why not.

If the PI determines that the event had no potential to impact participant safety (harm and/or risk) or the integrity of data produced from the participant, the PI must fully document his/her rationale for each category (risk, harm, and participant data).

10 Study Administration, Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period

10.2 Data Collection and Management

This study will use Velos as the data management system. The study case report form (CRF) is the primary data collection instrument for the study and will be electronically created and completed in Velos. CRFs will be provided for each subject. Subjects must not be identified by name on any CRFs. Subjects will be identified by their subject identification number (PID). All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done, or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A.”. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

11 Study Monitoring, Auditing, and Inspecting

11.1 Study Monitoring Plan

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment, at least every 6 months, of the number and type of serious adverse events by an independent clinician, David Vaughn, MD, Department of Medicine, Division of Hematology-Oncology. Additionally, the Medical Monitor will be consulted for protocol exceptions and deviations and as needed for decision-making regarding dose modifications, study eligibility, and any need to stop enrollment or the study for safety concerns.

This study will be monitored in accordance with the Cancer Center’s Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) Plan, approved by NCI during the Core Grant’s most recent review. This plan requires that the investigator submit a study-specific plan outlining how data will be reviewed In addition, the CTSRMC plan calls for an internal audit by the Cancer Center’s Data Safety Committee twice yearly. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above

noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 parts 50 and 56 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent IRB, in agreement with local legal prescriptions, for formal approval of the study conduct.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB and CTSRMC for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject and the investigator-designated research professional obtaining the consent.

13 Study Finances

13.1 Funding Source

This clinical study, including correlative work, will be supported by funds provided by Eli Lilly Pharmaceuticals, Inc.

13.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

14 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the Principal Investigator. Any investigator involved with this study is obligated to provide the Principal Investigator with complete test results and all data derived from the study.

15 References

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16 Appendix A: Definition of Non-Childbearing Potential and Medically Acceptable Methods of Birth Control

Non-childbearing potential is defined as any of the following (by other than medical reasons):

1. ≥45 years of age and has not had menses for >2 years

2. Amenorrhoeic for <2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone value in the postmenopausal range upon pre-study (screening) evaluation

3. Post hysterectomy, oophorectomy or tubal ligation

A female of childbearing potential, must have a negative serum pregnancy test within 7 days of the first dose of abemaciclib and agree to use a highly effective contraception method during the treatment period and for 3 weeks following the last dose of abemaciclib.

Acceptable methods include:
- Condoms
- Diaphragm
- Cervical cap
- Intra-uterine device
- Surgical sterilization (tubal ligation or vasectomy)
- Oral contraceptives

If condoms are used as a barrier method, a spermicidal agent should be added as a double barrier protection.

Cases of pregnancy that occur during maternal exposures to abemaciclib should be reported. If a patient is determined to be pregnant following abemaciclib initiation, she must discontinue treatment immediately. Data on fetal outcome and breast-feeding are to be collected for regulatory reporting and drug safety evaluation.

Abstinence at certain times of the cycle, such as during ovulation or after ovulation, or withdrawal are not acceptable methods. The list of methods above is not exhaustive and additional contraception methods may also be acceptable if approved by the study doctor.

NCT Number	NCT03781960
Protocol Official Title	PHASE II TRIAL OF ABEMACICLIB AND NIVOLUMAB FOR SUBJECTS WITH HEPATOCELLULAR CARCINOMA
Documents Included	UNIVERSITY OF PENNSYLVANIA RESEARCH SUBJECT COMBINED INFORMED CONSENT FORM AND HIPAA AUTHORIZATION
Document Date (mm/dd/yyyy)	12/14/2019

UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT
COMBINED INFORMED CONSENT FORM AND HIPAA AUTHORIZATION

Protocol Title:	A PHASE II TRIAL OF ABEMACICLIB AND NIVOLUMAB FOR SUBJECTS WITH HEPATOCELLULAR CARCINOMA
Sponsor Investigator:	Thomas Karasic, MD Abramson Cancer Center of the University of Pennsylvania Philadelphia, PA 19104 215-614-1858
Sub-investigators:	Mark O'Hara, MD; Kim Reiss-Binder, MD; Ursina Teitelbaum, MD; Charles Schneider, MD; Jennifer Eads, MD; Nevena Damjanov, MD; Ryan Massa, MD
Emergency Contact:	24 Hour Emergency – Call 215-662-4000 for HUP operator Ask for Oncologist On-Call

Why am I being asked to volunteer?

You are being asked to participate in this research study because you have Hepatocellular Carcinoma (HCC). Your participation is voluntary, which means you can choose whether or not you want to participate. If you choose not to participate, your clinical care will not be affected. Before agreeing to participate in this research study, it is important that you read the following explanation of the proposed procedures and how long you will be in the study. This document describes the purpose, procedures, benefits, risks, discomforts and precautions of the study. It also describes the alternative procedures that are available to you and your right to withdraw from the study at any time.

Please take time to read the following information carefully. You may wish to discuss it with your family, friends, and your personal doctor (i.e., your family doctor or primary care doctor). If you have any questions, you may ask your study doctor and/or the research team for more information. Take time to decide whether or not you wish to take part. If you decide to participate, you will be asked to sign this form. If you decide to participate, you can change your mind at any time and withdraw from the study without giving a reason.

What is the purpose of this research study? What does this study involve?

The main purpose of this study is:

- To evaluate the effectiveness of the combination of nivolumab and abemaciclib for the treatment of hepatocellular carcinoma

Other goals of this study are:

- To learn about the side effects that this combination of drugs may cause
- To learn more about how these drugs work by studying blood and tissue

During this study you will receive a combination of 2 medications:

1. Nivolumab (also known as Opdivo) is a cancer therapy that activates the immune system to attack tumor cells by "removing the brakes" of the immune system. Nivolumab is FDA-approved for the treatment of advanced HCC.

2. Abemaciclib (also known as Verzenio) is a cancer therapy that slows cancer growth by preventing cells from dividing. It has also been shown in laboratory studies to make the immune system more active. It is FDA-approved for the treatment of breast cancer but is not used for the standard treatment of HCC.

Who is sponsoring this study?

Dr. Thomas Karasic, the Principal Investigator, is also the sponsor (entity responsible for the design, conduct and regulatory oversight of the study). Eli Lilly corporation is the manufacturer of the study drug, abemaciclib, and will be providing the drug during this research study. Dr. Karasic and the University of Pennsylvania will receive payments to cover some of the research costs such as the collecting/reporting study information associated with the conduct of the study.

Conflict of Interest:
In addition, one or more of the investigators (as listed on page 1 of this consent document) may receive extra money from Bristol-Myers Squibb (BMS) for work done which is not part of this study and/or may receive extra money from competitor companies who make similar therapies (drugs in the same class as the one evaluated in this study). These activities may include consulting, advisory boards, giving speeches or writing reports. If you would like more information, please ask a member of the research team.

How long will I be in the study?

You may continue to participate on this study until your disease gets worse, you experience unacceptable side effects, and/or your physician no longer believes the therapy is of benefit to you (whichever occurs first).

What am I being asked to do?

If you meet all of the criteria for being in the study, you will be registered to participate.

Screening Procedures: These procedures are done to evaluate your cancer, overall health, and eligibility. If you have had some of these tests/procedures recently, they may not need to be repeated. These tests and procedures need to be done within 28 days before you receive your first dose of study drug, unless otherwise indicated.

- A review of your history to include:
    - A review of your medical and cancer history to make sure you do not have any conditions that could interfere with your taking part in this study (this will include the review of results from genetic testing you have already had)
    - A review of the medications you are taking, including all prescription medications and all non-prescription medications (such as vitamins, herbal supplements, aspirin, etc.)
    - A review of your social history (such as if you are a smoker and how much alcohol you may drink)
    - A review of any significant medical or surgical procedures you have had
- A complete physical examination including height and weight
- An assessment of how your disease affects your daily living abilities (called Performance Status).
- Measurement of your vital signs (blood pressure, pulse, and temperature)
- Prior and concomitant medications and any surgical procedure
- Approximately 4 teaspoons (tsp) of blood will be drawn to determine your eligibility. The routine tests being done to determine your eligibility and for safety purposes will test your blood cell counts (number of each type of blood cell), blood chemistry levels (to test your kidney and liver function and the minerals in your body), thyroid function, the ability of your blood to clot properly, whether

you have hepatitis B or C, whether you have HIV, and a serum pregnancy test for women of child bearing potential. If the pregnancy test comes back positive you will not be allowed to participate in this study.
    - If you test positive for hepatitis B, hepatitis C, or HIV, by law we have to report the positive test results to the City of Philadelphia Health Department and/or the PA Department of Health. Personal identifiers such as name, sex, date of birth, address, and phone number will be reported. For more information about the requirements reporting infectious diseases to the City of Philadelphia Health Department, please visit https://hip.phila.gov/ReportDisease. For more information about the requirements reporting infectious diseases to the PA Health Department, please visit http://www.health.pa.gov/Your-Department-of-Health/Offices%20and%20Bureaus/epidemiology/Pages/Reportable-Diseases.aspx#.V620aZ3D9eU.
    - In the case of HIV, reporting is used to keep track of how many people in the U.S. have HIV infection. It is also to make sure that states get enough money from the federal government to support the medical care of people living with HIV. The Health Department does not share the names of HIV infected people with anyone else. It removes all personal identifiers, such as your name, before giving information on the number of HIV infections to the federal government.
- Approximately 10 teaspoons of blood will be drawn for research purposes
    - This would not typically be done as a part of your standard of care treatment.
- Radiology tests - to assess your disease. These assessments may include a CT (computed tomography) scan or MRI (magnetic resonance imaging) scan
- You will be asked to allow your doctor to complete a tumor biopsy and remove a small amount of tumor before you start study treatment. Providing this type of tumor sample is essential in helping us learn about your specific disease and how we can help other patients like you.
    - This would not typically be done as a part of your standard of care treatment.

Procedures associated with the administration of the study drug(s)

When all of the above tests/procedures have been completed, you have been found eligible to enter this study, and you agree to participate, you will be scheduled to receive study drug.

Treatment will be provided as cycles, with each cycle comprised of 4 weeks (28 days), except for the first cycle, which will be 5 weeks (35 days). Cycles will continue until your cancer gets worse, you experience unacceptable side effects, your doctor no longer believes the therapy is in your best interest, or you no longer want to participate in the study.

Nivolumab will be administered intravenously (IV) into a vein every 4 weeks. This will require approximately 30 minutes to administer in the infusion center.

Abemaciclib will be administered by mouth twice per day every day of each treatment cycle.

You will be given a diary to record when you take your abemaciclib. You will be asked to bring this completed diary and your remaining study drug and/or empty pill bottles to each study visit. When you return this study drug kit and diary, the study team will review everything to make sure you are taking the drug appropriately and completing this diary as requested

Study Tests/Procedures

These exams, tests, and procedures are being done to evaluate your health and response to the study drug(s). At each of these study visits you will be asked how you are feeling, if you have had any side effects, if you may be pregnant, if you have had any medical procedures, and about any medications you are taking. It is important you check with your study doctor before starting any new medications. Taking

other drugs (including alcohol, over-the-counter medications, herbal preparations, illegal drugs, or nutritional supplements) may cause additional side effects or even life-threatening reactions when combined with the drugs being used in this study. If you experience side effects, changes in your health and/or changes in medications, please contact your study doctor or a study team member.

You will have the following tests, procedures, and assessments done at the time points below:

	Cycle 1				Cycle 2 and later (28 days)	
	Day 1	**Day 8**	**Day 15**	**Day 29**	**Day 1**	**Day 15**
Office Visit	X	X			X	
Treatment						
Abemaciclib	X[1]----------					----------X[1]
Nivolumab		X			X	
Tests and Observations						
Physical exam	X	X				
Vital signs	X	X	X			
Weight	X	X				
Performance status	X	X			X	
Blood sample collection for blood cell count testing (1 tsp)	X	X	X	X	X	X[2]
Blood sample collection for blood chemistry testing (1 tsp)	X	X	X	X	X	X[2]
Blood sample collection to test blood clotting (1 tsp)					X	
Blood sample collection for thyroid function testing (1 tsp)					X	
Tumor Marker (1 tsp)	X				X	
Blood sample collection for pregnancy testing (women of childbearing potential) (1 tsp)	X				X	
CT/MRI					X[3]	
Blood sample for research testing (10 tsp)		X	X		X	
Tumor biopsies for research testing			X[4]			

1. Abemaciclib will be administered by mouth twice per day every day of each treatment cycle
2. These lab tests will be required on Cycle 2 Day 15 but will only be required on Day 1 of Cycle 3 and later cycles if the testing is normal or near-normal
3. CT/MRI scans will be done approximately at Cycle 3 Day 1, Cycle 5 Day 1, then every 8 weeks
4. A tumor biopsy will be collected during cycle 1 between days 15 and 19

End of Study Visit:
You will be asked to come in again 30 days after you have finished study treatment with abemaciclib for a Review of your general health and to see whether anything new has happened to you since your last study visit, including any side effects you may be experiencing.

Post-Study Procedures:
After your last study visit we will look into your medical records approximately every 6 months to gather information related to your overall health and any additional cancer treatments/procedures you may have undergone.

What are the possible risks or discomforts?

While on the study, you are at risk for the following side effects. Some of these side effects may be potentially serious or life-threatening, and may include death. You should discuss these with the study doctor. There also may be other side effects that are not known and other very rare side effects that are known but not included in this list. If you experience side effects from the study drug(s), your study doctor may delay or skip a dose of the study drug, or ask you to stop taking study drug. Your doctors may also give you other drugs to help lessen these side effects. Many side effects go away shortly after the study drug is stopped, but in some cases side effects can be serious, long lasting or permanent.

As there is little experience using nivolumab in combination with abemaciclib (the study drug), it is not yet clear how they will work together. This means that it is possible that the study drug may change how well the routine care drugs work in treating your disease (i.e. may make it more or less effective).

Possible risks or discomforts with abemaciclib:

Abemaciclib may cause one or more of the side effects listed below. This information is based on data from cancer subjects in other clinical trials with abemaciclib. In addition, there may be side effects that are not yet known that may occur. You should tell your doctor or nurse right away about any possible side effects you experience.

- Gastrointestinal (GI) tract (stomach and intestines):
  - Diarrhea (90%)
  - Nausea (64%)
  - Decreased appetite (45%)
  - Abdominal pain (39%)
  - Vomiting (35%)
  - Constipation (17%)
  - Dry mouth (14%)
  - Mouth pain or sores (14%)
  - Weight loss (14%)
  - Abnormal taste (12%)
- Bone marrow (which produces blood cells):
  - Low red blood cell count (anemia) (25%)
  - Low platelet count with increased risk of bleeding (20%)
  - Low neutrophil or white blood count with increased risk of infection (37%)
- Kidney:
  - Worsened kidney function (13%)
  - Dehydration (10%)
- Lungs and Respiratory System
  - Cough (19%)
- Muscle and Bone
  - Joint pain (15%)
- Nervous System
  - Headache (20%)
  - Dizziness (11%)
- Fatigue (65%)
- Infection (31%)
- Hair loss (12%)
- Fever (11%)

Liver problems

Abemaciclib can cause serious liver problems. Your healthcare provider should do blood tests to check your liver before and during treatment with Abemaciclib. If you develop liver problems during treatment with Abemaciclib, your healthcare provider may reduce your dose or stop your treatment. Tell your healthcare provider right away if you have any of the following signs and symptoms of liver problems:

- feeling very tired
- pain on the upper right side of your stomach area (abdomen)
- loss of appetite
- bleeding or bruising more easily than normal

Blood clots in your veins, or in the arteries of your lungs.
Abemaciclib may cause serious blood clots that have led to death. Tell your healthcare provider right away if you get any of the following signs and symptoms of a blood clot:

- pain or swelling in your arms or legs
- shortness of breath
- chest pain

Possible risks or discomforts with Nivolumab:
Nivolumab may cause one or more of the side effects listed below. This information is based on data from cancer subjects in other clinical trials with nivolumab. In addition, there may be side effects that are not yet known that may occur. You should tell your doctor or nurse right away about any possible side effects you experience.Very common side effects of Nivolumab are: [greater than or equal to 10%]

- Fatigue
- Itching
- Rash
- Diarrhea

Common side effects of Nivolumab are: [greater than or equal to 1% and less than 10%]

- Abdominal pain
- Alkaline phosphatase increased: lab test result associated with liver or bone abnormalities
- Allergic reaction/hypersensitivity
- ALT increased: lab test result associated with abnormal liver function
- Amylase increased: lab test result associated with pancreas inflammation
- AST increased: lab test result associated with abnormal liver function
- Bilirubin (liver function blood test) increased
- Chills
- Constipation
- Cough
- Creatinine increased: lab test result associated with decreased kidney function
- Decreased appetite
- Dizziness or vertigo (feeling off balance which can lead to dizziness)
- Dry mouth
- Dry skin
- Fever
- Headache
- Increased blood sugar
- Inflammation of the colon
- Inflammation of the mouth
- Infusion related reaction
- Lipase increased: lab test result associated with pancreas inflammation
- Loss of color (pigment) from areas of skin

- Lung inflammation (pneumonitis - see details below)
- Musculoskeletal pain
- Nausea
- Redness (of the skin)
- Shortness of breath
- Sodium levels in the blood low
- Swelling, including face, arms, and legs
- Thyroid gland function decreased/ thyroid stimulating hormone increased: lab test result associated with abnormal thyroid function
- Thyroid gland function increased
- Tingling, burning, numbness or weakness, possibly in arms, legs, hands and feet
- Vomiting

Uncommon side effects of Nivolumab include:[Less than 1%]

- Adrenal gland function decreased
- Bronchitis
- Dehydration
- Diabetes
- Double Vision
- Dry Eye
- Erythema multiforme (A skin disorder characterized by bullseye-shaped lesions)
- Hair loss
- Heart rate increased
- Heart rythym abnormal
- High blood pressure
- Hives
- Inflammation of the eye
- Inflammation of the kidney
- Inflammation of the pancreas
- Inflammation of the pituitary gland
- Inflammation of the stomach
- Inflammation of the thyroid gland
- Joint pain or stiffness
- Liver inflammation
- Low blood pressure
- Muscle inflammation
- Pemphigoid: blistering of the skin or mouth caused by the immune system attacking healthy tissue.
- Pituitary gland function decreased
- Psoriasis: characterized by patches of abnormal, scaly skin
- Renal (kidney) failure or kidney injury
- Respiratory failure
- Upper respiratory tract infection
- Vision blurred
- Weight loss
- Blood chemistry abnormalities, including low blood phosphate, magnesium, and potassium levels.
- High blood uric acid level
- Abnormal taste
- Increased sensitivity of skin to sunlight
- Difficulty swallowing
- Heartburn

Rare but potentially serious side effects of Nivolumab include: [less than 0.1%]

- Lung infiltrates, associated with infection or inflammation
- Anaphylactic reaction (severe allergic reaction)
- Cranial nerve disorder
- Damage to the protective covering of the nerves in the brain and spinal cord
- Diabetes complications resulting in excess blood acidsGuillain-Barre syndrome, an autoimmune disorder associated with progressive muscle weakness or paralysis
- Sarcoidosis, a disease involving abnormal collections of inflammatory cells (granulomas) in organs such as lungs, skin, and lymph nodesDrug induced liver injuryAbnormal blood cell production
- Inflammation of blood vessels
- Sores in the mouth which may cause difficulty swallowing
- Back pain
- Autoimmune disorders, including Guillain-Barre syndrome (associated with progressive muscle weakness or paralysis)
- Chest discomfort
- Heart palpitations
- Inflammation of the heart (may be life threatening or fatal)
- Collection of fluid around the heart
- Infections: including sepsis, lung infections, and skin infections.
- Decreased movement of the intestines
- Disorientation
- Inflammationof the lining of the brain and spinal cord
- Inflammation of the brain, potentially life threatening or fatal
- Lung infiltrates, associated with infection or inflammation
- Polymyalgia rheumatic (muscle pain and stiffness around the shoulders and hips)
- Disease caused by the body's immune system attacking healthy organs
- Drug induced liver injury
- Stevens Johnson syndrome: inflammatory disorder of skin and mucous membranes, resulting in blistering and shedding of skin
- Syndrome associated with fever, white blood cell activation and abnormal function (including destruction of other blood cells by certain white blood cells), low blood cell counts, rash, and enlargement of the spleen
- Histiocytic necrotizing lymphadenitis or Kikuchi lymphadenitis: disorder of the lymph nodes which causes the lymph nodes to become enlarged, inflamed and painful, commonly affecting lymph nodes of the neck and possibly associated with fever or muscle and joint pains.
- Rosacea: acne-like skin condition resulting in redness of face
- Rupture of the intestine/hole in the intestine
- Drug reaction with rash, blood cell abnormalities, enlarged lymph nodes, and internal organ involvement (including liver, kidney, and lung); known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
- Myasthenia gravis, a nerve disease that may cause weakness of eye, face, breathing, and swallowing muscles. One death in a patient who received Nivolumab combined with Ipilimumab was considered due to myasthenia gravis and severe infection (sepsis).
- Toxic epidermal necrolysis, a potentially fatal disease characterized by blistering and peeling of the top layer of skin resembling a severe burn, has occurred in patients who received Nivolumab treatment.
- Rhabdomyolysis (muscle fiber released into the blood stream which could damage your kidney) and polymyositis (chronic muscle inflammation with muscle weakness) has been reported in one patient.

- Vogt Koyanagi Harada syndrome; a disease that affects the pigmented tissue; this may affect the eye leading to swelling, pain and/or blurred vision; the ear leading to hearing loss , ringing in the ears and /or the skin leading to loss of skin color

- **Lung Inflammation (Interstitial Lung Disease/ Pneumonitis):** It is possible that Nivolumab and Abemaciclib may cause inflammation of the tissues of the lung. This adverse effect has been reported infrequently in patients treated with Nivolumab. While many patients with x-ray or CT abnormalities have not developed any symptoms, some patients have developed mild to severe symptoms and in rare cases, death has occurred as a result of their lung inflammation. Signs and symptoms of lung inflammation may include difficulty breathing, pain or discomfort while breathing, chest pain, cough (with or without mucus), shortness of breath (while at rest or with low activity), increased rate of breathing, fever, low blood oxygen levels, or fatigue. Abemaciclib may also cause lung tissue scarring.

Your study doctor and nurse will watch you closely for changes in your ability to breathe and for other signs or symptoms that might show you are developing this type of lung inflammation and will perform regular tests including physical exams, measurement of oxygen levels through non-invasive testing (i.e., pulse oximeter), blood tests, chest x-rays and/or CT scans.

Please inform your study doctor or nurse <u>AT ONCE</u> if you experience any of the following:

- Any new or increased shortness of breath;
- Any new or increased chest pain;
- Any new or increased pain/difficulty while breathing;
- Any new or increased cough or any significant change in your type of cough; for example, any new or increased mucous or blood in your cough;
- Any change in the amount of oxygen you require;
- Any fever, fatigue, or other symptoms that occur at the same time as any changes to your breathing or other lung symptoms.

If you start to develop symptoms, your study doctor will ask you to return to the clinic for additional tests, which could include a physical exam, measurement of oxygen levels, blood tests, chest x-rays, and/or CT scans. You will be monitored very closely for changes in your overall lung symptoms, monitoring may require hospitalization. You may require specific treatment in order to control pneumonitis. You may also be seen by a special doctor called a pulmonologist, who has special training to be an expert in how your lungs work.

Prolonged treatment with medicines that suppress inflammation, sometimes needed to manage the side effects of Nivolumab treatment, may lower your body's ability to fight off certain infections (i.e., opportunistic infections). These infections may require treatment with antibiotic or antifungal medications and may be fatal.

<u>Other Study Related Risks</u>

<u>Risks of Blood Draws</u>

Blood samples will be taken for tests throughout this study. The amount of blood to be taken by these blood draws is very small, and may be associated with discomfort and/or bruising at the site where the needle is inserted; and less commonly, fainting, the formation of a small blood clot or swelling of the vein and surrounding tissue, bleeding, and infection from the injection site. The total volume to be collected will depend upon the number of treatment visits and the duration of safety follow-up.

Risk of IV
An IV line will be used to administer study drug through a vein in your arm. The use of an IV line may cause discomfort, irritation, mild bruising, bleeding, leakage of drug solution, and rarely infection, nausea, and lightheadedness.

Risks of Infusion-Related Reaction
Infusions of drugs can cause allergic reactions in people. Allergic reactions may include shortness of breath, itching, rash, low blood pressure, and fever during the infusion or shortly after. If you experience any of these symptoms, you should contact your doctor immediately. Sometimes these reactions can be serious and can result in death if not watched carefully. You will be watched by medical personnel for signs of allergic reactions, and you will be given medicine if you need it.

Risks of Imaging Tests
During your participation in this study, you may undergo routine radiology tests to assess your disease. These can include CT, x-rays and MRI scans. Each of these procedures has risks associated with it, and you should talk to your study doctor or the person doing these procedures about the risks before they start.

- Radiation Exposure: This research study involves exposure to radiation from the X-rays and CT. Therefore, you will receive a radiation dose. Some of these procedures may not be necessary for your medical care and will occur only as a result of your participation in the study. At exposure levels much higher than you will receive, radiation is known to increase the risk of developing cancer after many years. At the exposure level you will receive, it is very likely that you will see no effects at all.
- CT Scans: A CT scan is an imaging method that uses x-rays to create cross-sectional pictures of the body. You will be asked to lie on a narrow table that slides into the center of the CT scanner. Depending on the study being done, you may need to lie on your stomach, back, or side. Once you are inside the scanner, the machine's x-ray beam rotates around you. It is important to remain still during the exam, because movement causes blurred images. You may be told to hold your breath for short periods of time. The scans take about 15 minutes or less to complete.
    - It is important to inform your study doctor if you have had an allergic reaction to IV contrast material in the past, or if you have an allergy to iodine. Most CT contrast reactions (approximately 95%) are mild to moderate in degree and most resolve themselves without treatment. However, life-threatening reactions and fatalities, mostly of cardiovascular origin, have occurred. People with heart disease, kidney disease or allergies are more likely to have a more severe reaction to contrast agents. If you have a history of kidney disease, allergies or heart disease, please inform the study staff. Likely contrast reactions include feelings of overall warmth (especially in the bladder area after injection), a metallic taste during the injection, and warmth, burning sensation, or momentary pain during the contrast injection at the injection site. Less likely contrast reactions include nausea, vomiting, headache, hives, and itching. Rare but serious contrast reactions include faster than normal heart rate (tachycardia), high blood pressure (hypertension), low blood pressure (hypotension), heart attack, kidney failure, fluid in the lungs (pulmonary edema), serious allergic reaction, and death. There is also a risk that multiple needle sticks will be necessary to ensure proper intravenous line placement. There may be a small amount of pain or bruising with the placement of the intravenous catheter (IV) and a small risk of infection at the injection site.
- MRI: The known risks associated with a Magnetic Resonance Imaging (MRI) are minimal. The procedure uses radio waves and a magnetic field to take pictures. The greatest risk of having an MRI is the chance of metal objects flying through the air toward the magnet and hitting you. To reduce this risk, all people involved with the study are instructed to remove all metal from their clothing and all metal objects from their pocket. You must tell your study doctor if you have any metal plates or clips in your body. No metal objects are allowed to be brought into the magnet room

at any time. Metal objects inside your body can affect the test results and could lead to injury. Because the magnetic field of the MRI scanner attracts metal, these studies will not be performed on anyone with a pacemaker or any non-removable metallic foreign objects in their body. If you have any such object on your body, you will not receive the scan. You may feel claustrophobic (fear of being closed in) or anxious. You may experience some discomfort and fatigue from lying in a confined space. There are no known effects from exposure to the magnetic fields.

Risks of a Biopsy

A biopsy is an invasive test in which your cells and/or tissue are collected for examination. It involves the surgical removal of a small bit of tissue for examination. Your study doctor will explain this procedure to you in more detail, and you will be given a standard hospital consent form to sign detailing your specific type of biopsy prior to the procedure.

Risks of a biopsy include, but are not limited to:

Likely risks:
- Pain
- Discomfort
- Soreness
- Minor bleeding
- Bruising

Less likely risks:
- Redness
- Swelling
- Bleeding
- Lung collapse (pneumothorax) - air which leaks out of the lung and collects between the lung and the ribs, sometimes causing shortness of breath and chest pain, and which may require hospitalization admission and chest tube placement for the evacuation (release) of air

Rare risks:
- Bleeding, life threatening hemorrhage
    - Hemorrhage - bleeding around the lesion
    - Hemothorax - bleeding around the lung
- Possible damage to adjacent organs
- Drainage from the biopsy site
- Abnormal wound healing
- Fever
- Infection
- Allergic reaction to the medication used to numb the skin over the biopsy site

Rarely, these complications can lead to the need for intubation (placement of a breathing tube) or surgery. A very rare complication of lung biopsy is air embolism, defined as air that enters the blood stream, which can be life-threatening.

As with any invasive procedure and the use of sedation, additional risks include, but are not limited to: bleeding related to needle placement; injury to nearby organs, vessels and nerves; and breathing difficulties. In addition to these potential complications, there may be other unpredictable complications, including death.

It is also possible that the procedure may yield inconclusive results (“non-diagnostic”) due to sampling

limitations (not enough tissue to sample) or to limitations in being able to interpret the results of the sample in the laboratory.

Risks of Genetic Research

The research testing done as a part of this study includes genetic testing. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.

There can be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a research study. Even though your genes are unique, you share some of the same genes with your blood relatives. Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to you and your family are very low, because your samples will be coded. Research results will not be returned to you or your doctor.

Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, it could make it harder for you to get or keep a job or insurance, or life insurance companies may charge a higher rate based on this information. We believe the chance these things will happen is very small, but we cannot make guarantees.

A federal law (Genetic Information Non-Discrimination Act, GINA) helps reduce the risk from health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long term care insurance. If you want to learn more about GINA, you can find information about it on the internet or ask the study staff.

Reproductive Risks

Female Participants

You should not become pregnant while you or your sexual partner are taking Nivolumab and for 6 months after your last dose of study drug because the study drugs could have a negative effect on an unborn baby. In this case, we do not have enough information about Nivolumab to determine if it could cause problems for a pregnancy or developing baby. In addition, you should not breastfeed while on this study as these drugs may also affect a breast-feeding child. Pregnant women and women who are breast-feeding are not allowed to participate in this study. If you become pregnant, you will no longer be able to participate in this study.

If you are able to have children, you must agree to use a medically accepted form of birth control including condoms, diaphragms, cervical cap, an intra-uterine device (IUD), surgical sterility (tubal ligation or a partner that has undergone a vasectomy), or oral contraceptives, OR you must agree to completely abstain from intercourse during participation in this study and for 3 weeks after your last dose of study drug. Abstinence at certain times of the cycle only, such as during the days of ovulation, after ovulation and withdrawal are not acceptable methods of birth control. Ask your study doctor about the contraceptive methods that are available and which might be the best for you.

Even when you use an approved contraceptive method, there is always a small risk that you could still become pregnant. If you do become pregnant during the course of this study or up to 3 weeks after your last dose of study drug, you must discontinue study treatment, tell the investigator immediately, and consult an obstetrician or maternal-fetal specialist. If you become pregnant while on this study, we will ask permission to collect information about your pregnancy.

If you become pregnant during this study, suspect pregnancy or if you missed your period or it is late, or if you have a change in your usual menstrual cycle (e.g., heavier bleeding during your period or bleeding between periods), you should immediately contact your study doctor.

1. You will discontinue nivolumab immediately. When study drug is permanently discontinued, you may be instructed about continued use of other medications.
2. The study doctor will help you understand how nivolumab might affect your pregnancy. This will be based on all the information available at that time.
3. You will be referred to other doctors for pre-natal medical care. Your study doctor will be available to counsel other doctors about how nivolumab might affect your pregnancy.
4. The study doctor will ask for your permission to follow the progress of your pregnancy, provided it is safe for you and your unborn baby to do so. This information will be used to advise other women who might become pregnant while taking the study medication.

In case of a pregnancy, your pregnancy and its outcome will be reported to the study sponsor. Your doctor will discuss this with you, as well as options for additional appropriate care for your cancer.

The sponsor has not set aside any funds to pay for any aspects of obstetric, child or related care and does not plan to pay for them.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you (such as new information about how the drug works or newly discovered side effects). If we discover new information about the study that could affect your decision to stay in the study, you will be notified in a timely manner. You will be able to ask questions about this new information and can discuss it with your family, friends, or doctor.

What are the possible benefits of the study?

Taking part in this study may or may not make your health better. However, while you may not benefit personally, the knowledge learned from your participation in this research study may benefit other patients in the future. It is possible that your disease and/or health may worsen as a result of participating in this study.

What other choices do I have if I do not participate?

Your participation in this study is entirely voluntary. Other possible options include:

- Getting treatment or care for your cancer without being in a study.
- Taking part in another study.
- Not receiving treatment at this time.
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will I be paid for being in this study?

You will not be paid for taking part in this study.

Will I have to pay for anything?

Eli Lilly Corporation, the manufacturer of abemaciclib, is supplying abemaciclib for the purposes of this study at no cost to you. You and/or your insurance company will be responsible for the costs of nivolumab, including drug administration.

You will be responsible for any deductibles or applicable co-pays for the standard tests, exams or procedures that would be done for your routine clinical care, such as office visits, scans and blood work. You and/or your insurance provider will be responsible for standard tests, exams or procedures that would be done even if you were not in this study. Please talk to your doctor and study team about putting you in touch with a financial counselor to determine exactly what the deductible and co-pay will be for you; this is highly variable depending on your type of insurance. There will be no charge to you for those laboratory tests and other procedures that are being done specifically for the purposes of this research study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Website at: http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Website.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured or hurt during the study?

<u>All side effects, injuries or illnesses that occur while you are taking part in this research study:</u>
If you have a medical emergency during your participation on this study, you should go to the nearest emergency room. You should contact the Principal Investigator or Emergency contact listed on page one of this form. You may also contact your own doctor or seek treatment outside of the University of Pennsylvania. Be sure to tell the doctor or his/her staff that you are in a research study being conducted at the University of Pennsylvania. Ask them to call the telephone numbers on the first page of this consent form for further instructions or information about your care.

The University of Pennsylvania will offer you the care needed to treat side effects and/or injuries that occur while you are taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them. There are no plans for the University of Pennsylvania or Eli Lilly Corporation to pay you or give you other compensation for the injury.

You may receive bills for injuries/illnesses that occur during your participation in this study. If you have questions about these bills and whether or not they are covered by the research study, please bring copies of these bills to a member of the study team and they will be able to answer your questions.

Financial compensation for such things as traveling, parking, lost wages, disability or discomfort due to injury is not routinely available.

You will not lose any of your legal rights when you sign this form.

When is the Study over? Can I leave the Study before it ends?

You may stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first. You can also choose to leave the study at any time without giving a reason. It is important to tell the doctor if you are thinking about stopping so any risks for the treatments that you received can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you. Leaving the study will not affect your future medical care.

The doctor may stop you from taking part in this study at any time if he/she believes that it is in your best interest, if you do not follow the study rules, or if the study is stopped. If new information becomes available that might affect your choice to stay in the study, your study doctor will notify you as soon as possible.

This study may also be stopped at any time by your study doctor, the study Sponsor, or the Food and Drug Administration (FDA) without your consent because:

- The Principal Investigator or the sponsor feels that it is in your best interest to discontinue the study. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions, or you become pregnant
- The Sponsor, the study Principal Investigator, or the Food and Drug Administration (FDA) has decided to stop the study due to new information regarding side effects.
- It is determined that you are no longer benefiting from the study therapy
- For any other reason that is not known at this time

If you are removed from the research study, your study doctor will explain to you why you were removed. The study doctor and study team will help arrange for your continued care.

Who can see or use my information? How will my personal information be protected?

If you decide to participate in this study, the study doctor and staff will collect medical and personal information about you as part of completing the study. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. This study is being overseen by the Food and Drug Administration (FDA); therefore they may review your research records. Please refer to the information below which explains more specifically how your personal information will be protected. If you do not want to allow these uses, you should not participate in this study. Information identifying you will be kept confidential as described below.

<u>What personal health information is collected and used in this study, and might also be disclosed?</u>
The following personal health information will be collected and used for the purposes of this study.

- Name, address, telephone number, gender, date of birth
- The history and diagnosis of your disease
- Specific information about the therapy you received, including previous treatment(s) you may have had
- Information about other medical conditions that may affect your care
- Medical data including laboratory test results, health status, x-rays, CTs, MRIs, pathology results, etc.
- Information on side effects (adverse events) you may experience, and how these were treated
- Long-term information about your general health status and the status of your disease. This may include information from other health care providers.
- Data that may be related to tissue samples that may be collected from you
- Numbers or codes that will identify you, such as your medical record number
- Information related to study visits and other tests/procedures performed while you are participating on this study.

While collected as part of this study by your study doctor and study team, identifying information (including your name, address, telephone number, medical record number, or any number/codes that will directly identify you) will be kept as confidential as possible and will not be routinely disclosed outside of the University of Pennsylvania. Personal health information that could be used to identify you will not be sent to Eli Lilly Corporation, and/or their designated representatives.

You will be assigned a unique subject registration number upon enrollment. This number and your initials will be used to identify you throughout the course of this study so that your identity is protected. The key to this code (which links your name back to the personal health information collected during this study) will be stored in a secure area and only the University of Pennsylvania study team will have access to this code. However, some of the study data (e.g. date of birth) could be used in combination with other information, in order to identify you. If you have questions about the specific information that will be released, you should ask your study doctor.

Why is my personal health information being used?
Your personal contact information is important for the research team to contact you during the study. Your personal health information and results of tests and procedures are being collected as part of this research study, and will be used to conduct and oversee this research study, and to help guide your medical care.

Which personnel may use or disclose my personal health information?
The following individuals may use or disclose your personal health information for this research study:

- The Principal Investigator and the Investigator's study team
- Authorized members of the workforce of the UPHS and the School of Medicine, and University of Pennsylvania support offices, who may need to access your information in the performance of their duties (for example: for research oversight and monitoring, to provide care as part of this study or as part of your routine care, to manage accounting or billing matters, etc.). This includes members of the Institutional Review Board (IRB), an Ethics Committee at the University of Pennsylvania who are responsible for reviewing and overseeing research studies to ensure that they are safe and being well managed.
- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB

Who, outside of UPHS and the School of Medicine, might receive my personal health information?
As part of the study, the Principal Investigator, the study team and others listed above, may disclose your study-related records, including the results of the research study tests and procedures, to those listed below. This study data may be processed and transmitted using secure computer systems. In all disclosures outside of the University of Pennsylvania Health System and School of Medicine, you will not be identified by name, medical record number, address, telephone number, or any other direct personal identifier unless disclosure of the direct identifier is required by law. In records and information disclosed outside of the University of Pennsylvania Health System and School of Medicine, you will be assigned a unique code number.

Your original medical records also may be reviewed by the sponsor of this study or its designated representatives, the Institutional Review Board overseeing this study, and any of the regulatory or safety oversight organizations outlined below. They may review these records for the purpose of checking data collected for the study, to make sure the study is being done properly, and to analyze the results of the study.

Individuals or organizations responsible for administering the study:

- The Principal Investigator and the Investigator's study team
- Eli Lilly Corporation (who may receive serious side effect information)

Regulatory and safety oversight organizations

- The U.S. Food and Drug Administration (FDA)
- Other regulatory agencies and/or their designated representatives, including international agencies
- Public Health agencies and other government agencies (including non-U.S.) as authorized or required by law

Once your personal health information is disclosed to others outside of UPHS or the School of Medicine, it may no longer be covered by United States federal privacy protection regulations.

The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may UPHS and the School of Medicine be able to use or disclose my personal health information?
Your authorization for use of your personal health information for this specific study does not expire. If you sign this form, we will collect your health information until the end of the research study. We may collect some information from your medical records even after you finish taking part in this study or after your death. We will keep all of the information forever in case we need to look at it again. We will protect this information and keep it confidential.

Your information may be held in a research database. However, UPHS and the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization to do so
- The University of Pennsylvania's Institutional Review Board grants permission after ensuring that appropriate privacy safeguards are in place
- As permitted by law

The data from this study may be published or used for teaching purposes, however you will not be personally identified in any publication. Your identity will remain confidential unless disclosure is required by law.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

Can I change my mind?
You have the right to withdraw your permission for the use of your personal health information, but if you do so, you must stop taking part in this study. You must do so in writing to the Principal Investigator at the address on the first page. Even if you withdraw your permission, your personal health information that was collected before we received your written request may still be used and disclosed, as necessary for the study. If you withdraw your permission to use your personal health information, you will also be withdrawn from the research study and no new information will be collected. However, even if you do withdraw your permission to use the data about you, we are required by the FDA and other national regulatory authorities to record anything that relates to the safety of the investigational drug under study.

Will I be able to access my research records?
You have the right to see and get a copy of your medical records kept by the University of Pennsylvania. However, you will not be able to review or receive some of your records related to the study until after the entire study has been completed. When the study is over, you may write to the study doctor to ask to see or copy all of your medical information that was collected during the study. You also have the right to say how your medical information may be used, and to have any incorrect data about yourself updated or corrected.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by US Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

By signing this document, you are permitting the UPHS and the School of Medicine to use and disclose personal health information collected about you for research purposes as described above.

What is an electronic medical record and/or a clinical trial management system?

An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.
A clinical trial management system (CTMS) is used to register your information as a participant in a study and to allow for your research data to be entered/stored for the purposes of data analysis and any other required activity for the purpose of the conduct of the research.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, information related to your participation in the research (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing EMR maintained by UPHS. Information related to your participation in clinical research will also be contained in the CTMS.

If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any information produced from your participation in this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). Information related to your participation in the study (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in this EMR.

Once placed in your EMR or in the CTMS, your information may be accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc.).

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?

If you have questions, concerns or complaints regarding your participation in this research study you should speak with the Principal Investigator listed on page one of this form. If you have any questions about your rights as a research subject, you may contact the Office of Regulatory Affairs at the University of Pennsylvania with any questions, concerns or complaints by calling (215) 898-2614.

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237). You may also visit the NCI website at http://cancer.gov/. For NCI's clinical trials information, go to http://cancer.gov/clinicaltrials/. For NCI's general information about cancer, go to http://cancer.gov/cancerinfo.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, the study has been explained to you, your questions have been answered, you have had time to make your decision, and you have decided to volunteer to participate. You have been given the names of study staff that you can contact if you need assistance or if you have any additional questions or concerns. You agree to follow all of the instructions of your study doctor to the best of your ability, and report any changes in your health that may occur during the study.

Your signature also means that you are permitting the University of Pennsylvania Health System and the School of Medicine to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania Health System and the School of Medicine to disclose that personal health information to outside organizations or people involved with the operations of this study.

You agree that your primary care physician can be informed about your participation in this clinical trial.

A copy of this signed and dated consent form will be given to you.

Name of Subject (Print)	Signature of Subject	Date
Name of Person Obtaining Authorization (Print)	Signature of Person Obtaining Authorization	Date