IST PROTOCOL

TITLE: Phase Ib/II trial of Ibrutinib plus Nivolumab in Patients with Previously-treated Metastatic Renal Cell Cancer

PROTOCOL NUMBER: UCDCC#262

STUDY DRUGS: Ibrutinib (PCI-32765) and Nivolumab (Opdivo)

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Amendment 6.0 / May 10, 2017
Amendment 7.0/ June 15, 2017

Participating Centers: TBD

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SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

_____
Signature of Site Principal Investigator

_____
Date

_____
Printed Name of Site Principal Investigator

Institution Name: _____

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, instructions from Pharmacyclics representatives, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

SYNOPSIS

Study Title:	A Phase Ib/II trial of Ibrutinib plus Nivolumab in Patients with Previously-treated Metastatic Renal Cell Cancer
Protocol Number:	*UCDCC#262*
Study Phase:	1b/2
Study Duration:	30 months
Number of Subjects:	30
Investigational Product and Reference Therapy:	Ibrutinib will be supplied as 140 mg hard gelatin capsules for oral (PO) administration. Ibrutinib will be supplied by Pharmacyclics. Nivolumab will be administered at 240 mg as an intravenous infusion over 60 minutes every 2 weeks. Nivolumab is commercially available.
Objectives:	**Primary Objective:** To assess in a preliminary fashion the feasibility and efficacy of ibrutinib in combination with nivolumab in patients with previously-treated metastatic renal cell cancer (mRCC). **Secondary Objectives**: To evaluate the safety of the combination of ibrutinib and nivolumab in patients with previously treated mRCC. **Exploratory Objectives:** Archival tumor specimens will be collected for potential BTK.ETK and PD1 correlative studies.
Study Design:	Prospective, open-label, non-randomized, US multicenter study
Population:	Adult subjects with metastatic renal cell carcinoma of any histologic subtype who have completed at least one line of prior systemic therapy are potentially eligible for this trial.
Centers:	UC Davis and one additional site (TBD)
Inclusion Criteria: *Refer to* Section 4.0 *for the complete and detailed list of inclusion/exclusion criteria.*	*Disease Related* Patients with metastatic renal cell carcinoma of any histologic subtype with measurable and/or evaluable disease who have completed at least one line of prior systemic therapy are potentially eligible for this trial. *Laboratory* • Adequate hematologic function defined as: Absolute neutrophil count >750 cells/mm^3 (0.75 x 10^9/L). Platelet count >50,000 cells/mm^3 (50 x 10^9/L). Hemoglobin >8.0 g/dL.

	• Adequate hepatic and renal function defined as: Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 3.0 x upper limit of normal (ULN). Estimated (measured or calculated) Creatinine Clearance ≥30 ml/min (Cockcroft-Gault) Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin) • PT/INR <1.5 x ULN and PTT (aPTT) <1.5 x ULN. *Demographic* • Men and women ≥ 18 years of age. • Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
Exclusion Criteria:	*Concurrent Conditions* • Cytotoxic chemotherapy ≤21 days prior to first administration of study treatment and/or monoclonal antibody ≤ 4 weeks prior to first administration of study treatment and/or other RCC-directed systemic therapy ≤ 2 weeks prior to first administration of study treatment • Any known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy. • Concurrent systemic immunosuppressant therapy (eg, cyclosporine A, tacrolimus, etc., or chronic administration of >10mg/day of prednisone) within 28 days of the first dose of study drug. • Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug. • Recent infection requiring systemic treatment that was completed ≤14 days before the first dose of study drug. • Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4), grade 0 or 1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia. • Known bleeding disorders (eg, von Willebrand's disease) or hemophilia. • History of stroke or intracranial hemorrhage within 6 months

	prior to enrollment. • Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody or hepatitis B surface antigen must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded. • Any uncontrolled active systemic infection. • Major surgery within 4 weeks of first dose of study drug. • Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk. • Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to enrollment. • Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction. • Lactating or pregnant. • Unwilling or unable to participate in all required study evaluations and procedures. • Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations) • Concomitant use of warfarin or other Vitamin K antagonists. Note: Subjects receiving antiplatelet agents in conjunction with ibrutinib should be observed closely for any signs of bleeding or bruising, and ibrutinib should be withheld in the event of any bleeding events. Supplements such as fish oil and vitamin E preparations should be avoided. • Requires treatment with a strong cytochrome P450 (CYP) 3A4/5 inhibitor. (see Appendix 3) • QT prolongation and/or familiar history of QT prolongation

	and uncontrolled cardiac arrhythmias that in the opinion of the investigator would interfere with the patient's safety or compliance on trial. • Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child Pugh classification (Appendix10).
Study Treatment:	Ibrutinib 420-560mg PO daily Nivolumab 240 mg IV q2weeks Cycles repeated every 28 days
Concomitant Therapy:	*Refer to Section 6 for information on concomitant therapy.*
Safety Plan:	Adverse events and serious adverse events (SAEs) will be reviewed by the Data and Safety Monitoring Committee on an ongoing basis to identify safety concerns.
Statistical Methods and Data Analysis:	**Primary Efficacy Analysis:** RECIST criteria will be used to assess efficacy (i.e., progression free survival rate.) **Safety Analysis:** Adverse events will be evaluated and recorded using CTCAE version 4.
Interim Analysis	No interim analysis is planned.
Sample Size Determination:	30

ABBREVIATIONS

CRF	case report form
DCF	data clarification form
DMC	Data Monitoring Committee
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4th edition)
ECG	Electrocardiogram
eDC	electronic data capture
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
IAC	Interim Analysis Committee
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
MedDRA	Medical Dictionary for Regulatory Activities
MRU	medical resource utilization
PD	Pharmacodynamic
PK	Pharmacokinetic
PQC	Product Quality Complaint
PRO	patient-reported outcome(s)
RCC	Renal cell carcinoma
TF	Treatment Failure
TSH	Thyroid Steroid Hormone
USP	United States Pharmacopeia

1. BACKGROUND

1.1. Disease/Histology

Renal cell carcinoma (RCC) is diagnosed in over 330,000 patients diagnosed globally and is responsible for over 140,000 deaths. One-third of patients are typically diagnosed with overt metastases at initial presentation. Additionally, in those patients initially diagnosed with organ-confined RCC and who are surgically treated with a curative intent, approximately one-third will relapse and subsequently succumb to the disease.

Mutation or inactivation of von Hippel-Lindau (VHL) tumor suppressor gene is found in over 80% of clear cell RCC tumors. This leads to accumulation of hypoxia inducible factor (HIF) and the upregulation of vascular endothelial growth factor (VEGF) production. Thus, agents that modulate or inhibit VEGF and its receptors and cellular pathways have been shown to be highly efficacious in metastatic RCC. Systemic therapies directed against angiogenesis are commercially available and are in wide use for the treatment of metastatic RCC. These agents include sunitinib, sorafenib, pazopanib, axitinib, and bevacizumab. Of note, sunitinib, pazopanib, and bevacizumab (plus interferon-alpha) were investigated in the first-line setting, while sorafenib and axitinib were investigated following progression with a first-line treatment. Also approved for the treatment of mRCC are the mammalian target of rapamycin (mTOR) inhibitors temsirolimus (first-line, poor risk patients) and everolimus (second line and beyond).

Universally, the vast majority of patients treated with one or more of these drugs will experience disease progression either after an initial response or tumor stabilization, or at the outset. The median progression-free survival time ranges from 8 through 11 months for first-line sunitinib or pazopanib, and from 3 through 5 months with sorafenib or axitinib following progression with first-line sunitinib treatment. Everolimus improved progression-free survival compared to placebo in a phase 3 trial in RCC patients who previously progressed on sunitinib and/or sorafenib.

Mechanisms of resistance to VEGF-directed therapy are not fully known. Some evidence points to revascularization as an escape mechanism. Activity of other anti- VEGF agents after development of resistance to VEGF-R blockade suggests that complete independence from VEGF does not develop in the resistant state. In the case of VEGF-R TKIs, the substantial variability in their target profiles and binding specificity suggests that resistance to another in-class agent is not implicit. Numerous trials have shown clinical activity of VEGF-pathway agents in disease that has progressed despite initial VEGF-blockade. Maintaining VEGF inhibition in this setting may be a productive strategy. Such may be the case in colorectal cancer, where some evidence has suggested that continuing bevacizumab in the face of disease progression may be associated with better outcome. Axitinib was shown to have a PFS benefit when compared to sorafenib in the AXIS trial of predominantly second-line mRCC patients.

While continued VEGF inhibition has theoretical rationale, changing therapeutic drug class upon progression is an approach that has been validated in the case of mTOR inhibition after VEGF-

TKI therapy. Everolimus demonstrated a PFS advantage over placebo after sunitinib and/or sorafenib therapy and is a valid treatment choice in this setting.

1.1.1. Treatment Options

Multiple combinations of the new agents are being explored in ongoing studies. Minimal randomized data are yet available regarding relative efficacy of such combinations. The optimal strategy in managing progressive RCC after resistance to initial therapy is in rapid evolution. Recent trials of the PD1 inhibitor Nivolumab and the VEGFR/MET TKI Cabozantinib in the previously treated setting showed efficacy benefit for these agents when compared to everolimus; however, as of this writing, neither of these newer agents have been FDA-approved for metastatic RCC. Since the availability of multiple agents, switching drugs in the face of progression has instead become a standard practice.

Checkpoint inhibitor therapy is also particularly active in RCC, particularly with PD1 inhibitors. A recent paper by Motzer et al (JCO 2014) reported the results of a randomized phase II trial testing the BMS PD1 inhibitor Nivolumab in mRCC. A total of 168 patients were randomly assigned to three dose levels of nivolumab 0.3- (n = 60), 2- (n = 54), and 10-mg/kg (n = 54). Median PFS was 2.7, 4.0, and 4.2 months, respectively (P = .9). Respective ORRs were 20%, 22%, and 20%. Median OS was 18.2 months (80% CI, 16.2 to 24.0 months), 25.5 months (80% CI, 19.8 to 28.8 months), and 24.7 months (80% CI, 15.3 to 26.0 months), respectively. Nivolumab was also recently reported to improve OS compared to everolimus in a large randomized phase III trial.

1.1.2. Role of BTK in Disease/Histology

The Btk family kinases represent members of non-receptor tyrosine kinases, which include Btk/Atk, Itk/Emt/Tsk, Bmx/ETK, and Tec. Similar to Src-family kinases, Btk family kinases play central but diverse modulatory roles in various cellular processes, particularly in transformed or malignant cells. There is now convincing evidence that Btk family kinases (particularly ETK) are over-expressed in renal cell cancer. A recent paper by Zhuang et al (J Exp Clin Cancer Res 2014) reported the results of preclinical studies in 90 human RCC tumor specimens and 30 normal tissues. In this study, ETK expression by IHC was found to be increased in RCC as compared to normal controls. Furthermore, there was a positive correlation between ETK expression and increasing clinical stage, grade and metastasis. In addition, ETK expression appeared to have prognostic relevance: overall survival appeared to be shorter for patients whose tumors had higher ETK expression. In RCC cell line models, downregulation of ETK resulted in significant tumor growth inhibition as well as reduction in migration/invasion. There was also note of enhanced apoptosis when ETK was downregulated.

These early data suggest that ETK may be a reasonable therapeutic target in RCC.

1.2. Investigational Product Name and Description

Ibrutinib is a first-in-class, potent, orally administered covalently-binding inhibitor of Bruton's tyrosine kinase (BTK). Inhibition of BTK blocks downstream B-cell receptor (BCR) signaling pathways and thus prevents B-cell proliferation. In vitro, ibrutinib inhibits purified BTK and selected members of the kinase family with 10-fold specificity compared with non-BTK kinases. Ibrutinib (IMBRUVICA®) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of: 1) mantle cell lymphoma (MCL) in patients who have received at least one prior therapy based on overall response rate, 2) chronic lymphocytic leukemia (CLL) including patients with 17p deletion or a TP53 mutation 3) Waldenström's Macroglobulinemia (WM). Ibrutinib is currently under investigation in various indications.

B cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B-cells express cell surface immunoglobulins comprising the B-cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways (Bishop 2003).

The process of B-cell maturation, including immunoglobulin chain rearrangement and somatic mutation, is tightly regulated. It is thought that B-cell lymphomas and CLL result from mutations and translocations acquired during normal B-cell development (Shaffer 2002). Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies.

The role of BTK in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease X-linked agammaglobulinemia and the mouse genetic disease X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by reduced BCR signaling and a failure to generate mature B-cells. The BTK protein is expressed in most hematopoietic cells with the exception of T-cells and natural killer cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signaling in B-cells (Satterthwaite 2000).

Data from Study PCYC-04753 demonstrate that although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours postdose at dose levels ≥2.5 mg/kg. In Study PCYC-04753, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts and for the 560 mg continuous dosing cohort, were all above 90% at either 4 or 24 hours after drug administration.

For the most comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, and in vitro and in vivo preclinical activity and toxicology of ibrutinib, refer to the latest version of the ibrutinib Investigator's Brochure.

1.3. Summary of Nonclinical Data

For the most comprehensive nonclinical information regarding ibrutinib, refer to the current version of the Investigator's Brochure.

1.3.1. Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of the Btk (Pan 2007). In vitro, ibrutinib is a potent inhibitor of Btk activity (IC_{50} = 0.39 nM). The irreversible binding of ibrutinib to cysteine-481 in the active site of Btk results in sustained inhibition of Btk catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the B-cell receptor and blocks primary B-cell activation (IC_{50} = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression (Herman 2011)

For more detailed and comprehensive information regarding nonclinical pharmacology, refer to the current Investigator's Brochure.

1.3.2. Toxicology

In safety pharmacology assessments, no treatment-related effects were observed in the central nervous system or respiratory system in rats at any dose tested. Further, no treatment-related corrected QT interval (QTc) prolongation effect was observed at any tested dose in a cardiovascular study using telemetry-monitored dogs.

Based on data from rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog).

In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. In a rat embryo-fetal toxicity study ibrutinib administration was associated with fetal loss and malformations (teratogenicity) at ibrutinib doses that result in approximately 6 times and 14 times the exposure (AUC) in patients administered the dose of 420 and 560 mg daily, respectively.

1.3.2.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib.

Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg.

Fertility studies with ibrutinib have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs.

1.4. Summary of Clinical Data

For the most comprehensive clinical information regarding ibrutinib, refer to the current version of the Investigator's Brochure.

1.4.1. Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging from 1.25 to 12.5 mg/kg/day as well as fixed dose levels of 420, 560, and 840 mg/day, exposure to ibrutinib increased as doses increased with substantial intersubject variability. The mean half life ($t_{1/2}$) of ibrutinib across 3 clinical studies ranged from 4 to 9 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Administration of 420 mg ibrutinib with a high-fat breakfast in subjects with CLL approximately doubled the mean systemic exposure compared to intake after overnight fasting with median time to T_{max} delayed from 2 to 4 hours. Ibrutinib was extensively metabolized to the dihydrodiol metabolite PCI-45227, a reversible inhibitor of Btk, with approximately 15 times lower inhibitory potency compared to ibrutinib. The metabolite-to-parent AUC ratio ranged from 0.7 to 3.4. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure.

The results of human mass balance study of [^{14}C]-ibrutinib conducted in six healthy male subjects demonstrated that less than 10% of the total dose of [^{14}C]-ibrutinib is renally excreted, whereas approximately 80% is recovered in feces. Subjects with mild and moderate renal insufficiency (creatinine clearance > 30 mL/min) were eligible to enroll in Study PCYC-1102-CA in which pharmacokinetic (PK) assessments were included. No dose adjustment is needed for mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). There is no data in patients with severe renal impairment or patients on dialysis. The study of ibrutinib in hepatic impaired subjects is currently in progress.

1.5. Summary of Clinical Safety

For more detailed information refer to the current version of the IB.

Pooled safety data for a total of 423 subjects treated with various therapies in combination with ibrutinib from 4 studies, which included1 randomized-control study, are summarized below. Therapies used in combination with ibrutinib in these studies, included BR, FCR, ofatumumab, and R-CHOP. The median duration of treatment for this pool was 14.0 months (range: 0.2 to 27.1 months). Refer to the ibrutinib IB, edition 9.0, dated 30 June 2015 for additional details concerning these studies

Most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib in combination therapy (N=423):

Most frequently reported TEAEs ≥ 20% [a]	Most frequently reported Grade 3 or 4 TEAEs ≥ 3% [b]	Most frequently reported Serious TEAEs ≥ 2% [c]
Neutropenia	Neutropenia	Pneumonia
Diarrhea	Thrombocytopenia	Febrile neutropenia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Neutrophil count decreased	Cellulitis
Anemia	Anemia	
Pyrexia	Fatigue	
	Hypertension	
	Diarrhea	

[a] Source is Table 10 of IB (v10), [b] Source is Table 12 of IB (v10), [c] Source is Table 13 of IB (v10).

For more detailed information refer to the current version of the IB.

1.5.1. Risks

1.5.2. Bleeding-related events

There have been reports of hemorrhagic events in subjects treated with ibrutinib both with and without thrombocytopenia. These include primarily minor hemorrhagic events such as contusion, epistaxis, and petechiae; and some major hemorrhagic events including gastrointestinal bleeding, intracranial hemorrhage and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied.

1.5.3. Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset of dyspnea should be evaluated clinically, and if indicated, have an ECG performed. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines.

1.5.4. Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib. Subjects should be monitored for fever, weakness, or easy bruising and/or bleeding.

1.5.5. Diarrhea

Diarrhea is the most frequently reported nonhematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe. Should symptoms be severe or prolonged follow the protocol dose modification guidelines.

1.5.6. Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these reported infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections (reference Section 6.1). Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib. Subjects should be monitored for symptoms (fever, chills, weakness, confusion) and appropriate therapy should be instituted as indicated.

1.5.6.1. Non-melanoma skin cancer

Non-melanoma skin cancers have occurred in patients treated with IMBRUVICA. Monitor patients for the appearance of non-melanoma skin cancer.

1.5.7. Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

1.5.8. Tumor Lysis Syndrome

There have been reports of tumor lysis syndrome (TLS) events in subjects treated with single-agent ibrutinib or in combination with chemotherapy. Subjects at risk of tumor lysis syndrome are those with comorbidities and/or risk factors such as high tumor burden prior to treatment,

increased uric acid (hyperuricemia), elevated lactate dehydrogenase (LDH), bulky disease at baseline, and pre-existing kidney abnormalities.

1.5.9. Interstital Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in patients treated with ibrutinib. Monitor patients for pulmonary symptoms indicative of ILD. Should symptoms develop follow the protocol dose modification guidelines (see Section 5.3.1.4).

1.5.10. Hypertension

Hypertension has been commonly reported in subjects treated with ibrutinib. Monitor subjects for new onset of hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

1.6. Study Rationale

The open-label, parallel assignment CheckMate-025 trial randomized 821 previously treated patients with advanced or metastatic clear-cell RCC to 3 mg/kg of IV nivolumab every 2 weeks or 10 mg of oral everolimus daily until progression or unacceptable toxicity. A trial combining nivolumab with the BTK/ETK inhibitor ibrutinib would be of great interest to the mRCC community.

2. STUDY OBJECTIVE

2.1. Primary Objective

To assess in a preliminary fashion the feasibility and efficacy of ibrutinib in combination with nivolumab in patients with previously-treated metastatic renal cell cancer (mRCC).

2.2. Secondary Objective(s)

To evaluate the safety of the combination of ibrutinib and nivolumab in patients with previously treated mRCC.

2.3. Exploratory Objective(s)

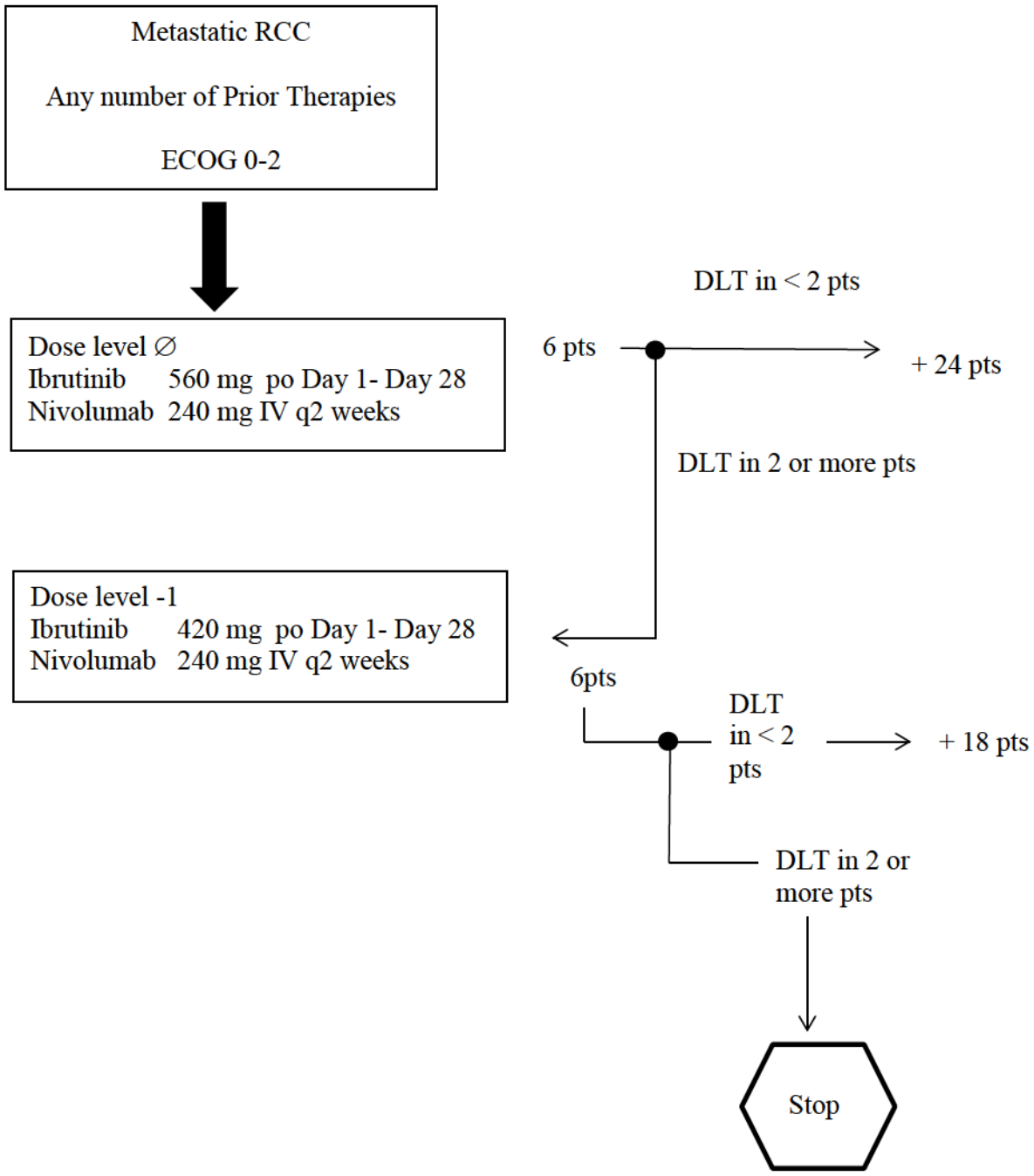
Archival tumor specimens will be collected for potential BTK.ETK and PD1 correlative studies.

3. STUDY DESIGN

3.1. Overview of Study Design

This is a prospective Phase Ib/II open-label, non-randomized, US multicenter study that is designed to test the efficacy of the addition of ibrutinib to nivolumab for the treatment of renal cell cancer.

3.1.1. Study Schema



*DLT assessment after 1 cycle (4 weeks)
*DLT = Grade III or higher SAE attributed to treatment
**Patients will have two de-escalation dose levels for (-1 and -2) for all patients based on interim toxicities.

3.2. Study Design Rationale

This is a prospective Phase Ib/II open-label, non-randomized, US multicenter study that is designed to test the efficacy of the addition of ibrutinib to nivolumab for the treatment of previously-treated renal cell cancer. The overall study plan will consist of a screening period, a study treatment phase, a follow up phase, if applicable, a safety follow-up and a survival follow-up. For safety, all patients will be followed for 30 days after the last dose of study treatment or until all treatment related clinical significant toxicities resolve to ≤ grade 1. Survival status (date of death or date of last contact) will be recorded.

3.2.1. Study Population And Treatment

The study will enroll adult subjects with pathologically determined renal cell cancer. This study will be conducted at the University of California Davis Comprehensive Cancer Center and at another site that is yet to be determined. There will be a total of 2 US sites.

Ibrutinib in combination with nivolumab will be investigated. The assigned treatment (Ibrutinib in combination with nivolumab) will continue in subjects for a maximum of 1 year or until progression, unacceptable or intolerable toxicity, physician choice (if in best interest of patient), or patient withdrawal for any reason. In the event that the patient is unable (due to toxicity or tolerability issues) or unwilling to receive both agents concurrently after the first two cycles, then single agent nivolumab can be administered at the investigator's discretion to complete one year of therapy. Treatment with ibrutinib will continue until either disease progression OR physician/patient choice OR unacceptable or intolerable toxicities.

3.2.2. Dose Selection

The selected dose of ibrutinib ranges from 420-560 mg (2-4 x 140 mg capsules) once daily. Although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours postdose at dose levels ≥2.5 mg/kg. A dose greater than 2.5 mg/kg was considered necessary to achieve consistent, full BTK occupancy, in previous PCYC studies. In Study PCYC-04753, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts and for the 560 mg continuous dosing cohort, were all above 90% at either 4 or 24 hours after drug administration.

4. SUBJECT SELECTION

Patients will be recruited in the medical, urology, and radiation oncology clinics of the University of California Davis Medical Center and participating centers.

4.1. Inclusion Criteria

To be enrolled in the study, each potential subject must satisfy all of the following inclusion criteria.

Disease Related

Metastatic renal cell cancer patients (any histologic subtype) with measurable and/or evaluable disease who have completed at least one line of prior systemic therapy are potentially eligible for this trial. Any number of prior systemic therapies are allowed, including prior nivolumab.

Laboratory

1. Adequate hematologic function defined as:
    - Absolute neutrophil count >750 cells/mm^3 (0.75 x 10^9/L).
    - Platelet count >50,000 cells/mm^3 (50 x 10^9/L).
    - Hemoglobin >8.0 g/dL.
2. Adequate hepatic and renal function defined as:
    - Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 3.0 x upper limit of normal (ULN).
    - Estimated Creatinine Clearance ≥30 ml/min (Cockcroft-Gault)
    - Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
3. PT/INR <1.5 x ULN and PTT (aPTT) <1.5 x ULN.

Demographic

4. Men and women ≥ 18 years of age.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

Ethical/Other

6. Female subjects who are of non-reproductive potential (ie, post-menopausal by history - no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). Female subjects of childbearing potential must have a negative serum pregnancy test upon study entry.
7. Male and female subjects who agree to use both a highly effective methods of birth control (eg, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence, or sterilized partner) and a barrier method (eg, condoms, cervical ring, sponge, etc) during the period of therapy and for 30 days after the last dose of study drug

4.2. Exclusion Criteria

To be enrolled in the study, potential subjects must meet NONE of the following exclusion criteria:

Concurrent Conditions

1. Cytotoxic chemotherapy ≤21 days prior to first administration of study treatment and/or monoclonal antibody ≤ 4 weeks prior to first administration of study treatment and/or other RCC-directed systemic therapy <= 2 weeks prior to first administration of study treatment
2. Any known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.
3. Concurrent systemic immunosuppressant therapy (eg, cyclosporine A, tacrolimus, etc., or chronic administration [>14 days] of >10 mg/day of prednisone) within 28 days of the first dose of study drug.
4. Vaccinated with live, attenuated vaccines within 4 weeks of first dose of study drug.
5. Recent infection requiring systemic treatment that was completed ≤14 days before the first dose of study drug.
6. Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4), grade ≤1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia.
7. Known bleeding disorders (eg, von Willebrand's disease) or hemophilia.
8. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
9. Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). *Subjects who are positive for hepatitis B core antibody or hepatitis B surface antigen must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.*
10. Any uncontrolled active systemic infection.
11. Major surgery within 4 weeks of first dose of study drug.
12. Any life-threatening illness, known autoimmune disease, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
13. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to enrollment.
14. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic

inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.

15. Lactating or pregnant.
16. Unwilling or unable to participate in all required study evaluations and procedures.
17. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).
18. Concomitant use of warfarin or other Vitamin K antagonists. Note: Subjects receiving antiplatelet agents in conjunction with ibrutinib should be observed closely for any signs of bleeding or bruising, and ibrutinib should be withheld in the event of any bleeding events. Supplements such as fish oil and vitamin E preparations should be avoided.
19. Requires treatment with a strong cytochrome P450 (CYP) 3A4/5 inhibitor. (see Appendix 3)
20. QT prolongation and/or familiar history of QT prolongation and uncontrolled cardiac arrhythmias that in the opinion of the investigator would interfere with the patient's safety or compliance on trial.
21. Currently active, clinically significant hepatic impairment Child-Pugh class B or C according to the Child Pugh classification (Appendix 10).

5. TREATMENT OF SUBJECTS

5.1. Treatment allocation and blinding (if appropriate)

N/A

5.2. Study treatment

This will be a non-randomized open-label prospective phase 1b/II study of the combination of ibrutinib with nivolumab in mRCC. See Section 3.1.1 Study Schema.

5.2.1. Route and schedule

Repeat every 28 days

Dose Level	Nivolumab dose	Ibrutinib dose (days 1-28)*
Level 0	240 mg IV q2 weeks	560mg PO
Level -1	240 mg IV q2 weeks	420mg PO

*should be taken at the same time every day

Dose limiting toxicity (DLT) must be treatment-related (possibly, probably, or definitely). To be evaluable for DLT, the subject must have had one dose of Nivolumab and at least 3 weeks of Ibrutinib.

Dose limiting toxicity (DLT) is defined as:

1) Grade 4 absolute neutrophil count with fever (>101.4 F) or documented infection;

2) Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding;

3) Any grade 3 or greater non-hematologic toxicity excluding alopecia.

DLT will be assessed after 1 cycle (4 weeks).

5.3. Study Medication

5.3.1. Ibrutinib

5.3.1.1. Formulation/Packaging/Storage

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib Investigator's Brochure for a list of excipients.

The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies. All study drugs will be dispensed in child-resistant packaging.

Refer to the pharmacy manual/site investigational product manual for additional guidance on study drug storage, preparation and handling.

Study drug labels will contain information to meet the applicable regulatory requirements.

5.3.1.2. Dose and Administration

Ibrutinib is administered orally once daily. The capsules are to be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (Appendix 3).

If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

The first dose will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis. Ibrutinib will be dispensed to subjects in bottles at each visit. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records (Section 12.8) updated at each visit. Returned capsules must not be redispensed to anyone.

5.3.1.3. Overdose

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any Serious Adverse Event criterion must be reported as a Serious Adverse Event in the appropriate time frame and documented as clinical sequelae to an overdose.

There is no specific experience in the management of ibrutinib overdose in patients. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day). Healthy subjects were exposed up to single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

Refer to Section 11.3 for further information regarding special reporting situations as a result of overdose.

5.3.1.4. Dose Modification for Adverse Reactions

The dose of study drug should be modified according to the dose modification guidelines in Table 1 if any of the following toxicities occur:

- Grade 4 ANC (<500/µL) for more than 7 days or fibroneutropenia.
- Grade 3 thrombocytopenia (<50,000/µL) in the presence of clinically significant bleeding events.
- Grade 4 thrombocytopenia (<25,000/µL).
- Grade 3 or 4 nausea, vomiting, or diarrhea if persistent, despite optimal anti-emetic and/or anti-diarrheal therapy.
- Any other Grade 4 or unmanageable Grade 3 toxicity.

For Grade 3 or 4 atrial fibrillation or persistent atrial fibrillation of any grade, consider the risks and benefits of ibrutinib treatment. If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (Section 6.2.4).

Note: After a dose reduction, dose escalation of ibrutinib to a previous higher dose is NOT allowed.

Table 1. Ibrutinib Dose Modifications

Occurrence	Action to be Taken
First	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie, 280 mg/day for 420 mg/day dose; 420 mg/day for 560 mg /day dose)
Third	Withhold study drug until recovery to Grade ≤1 or baseline; may restart at 1 dose level lower (ie, 140 mg/day for 420 mg/day dose; 280 mg/day for 560 mg /day dose)
Fourth	Discontinue study drug

5.3.1.5. Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver and therefore subjects with clinically significant chronic hepatic impairment at the time of screening (Child- Pugh class B or C) are excluded from study participation. For subjects with existing chronic mild hepatic impairment (Child-Pugh class A) at enrollment, the starting dose has to be adjusted to a level of 280 mg daily (two capsules). For subjects who develop mild liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib is to a level of 280 mg daily (two capsules) unless lower doses had already been implemented. For subjects who develop moderate liver impairment while on study (Child-Pugh class B), the recommended dose reduction is to a level of 140 mg daily (one capsule). Subjects who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) or better. Monitor subjects for signs of toxicity and follow dose modification guidance as needed (Refer to Appendix 10 and Section 5.3.1.4).

5.3.2. Nivolumab

5.3.2.1. Formulation/Packaging/Storage

Nivolumab (also referred to as BMS-936558 or MDX-1106) 40 and/or 100 mg vials (10 mg/mL) will be supplied using commercial supply. Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody. Nivolumab vials must be stored in the refrigerator at 2-8oC, protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton. The product does not contain a preservative, and as such after preparation, nivolumab infusions should be stored at room temperature for no more than 4 hours from time of preparation. This includes room temperature storage of infusion in IV container and time for administration of infusion. Alternatively, nivolumab infusion can be stored under refrigeration at 2 to 8 degrees C (36-46°F) for no more than 24 hours from the time of infusion preparation. The infusion should not be frozen.

Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves. For complete details on drug preparation, administration, storage conditions, clinical pharmacology, pharmacokinetics, and known precautions and adverse reactions please refer to the Nivolumab package insert.

5.3.2.2. Dose and Administration

The drug product solution should be visually inspected for particulate matter and discoloration prior to administration. Nivolumab is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloud, is discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

The required volume of nivolumab should be withdrawn and transferred into an intravenous container. Nivolumab should be then be diluted with either 0.9% sodium chloride injection, USP or 5% dextrose injection, USP, to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. Diluted solution should be mixed by gentle inversion, but should not be shaken. Partially used or empty vials of nivolumab should be discarded.

Patients should be administered nivolumab 240 mg as an in intravenous infusion over 60 minutes every 2 weeks. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressures, and temperature) should be determined within 60 minutes before, during (every 15 [±5] minutes), and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before infusion. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop acute symptoms.

Administer the infusion over 60 minutes through an intravenous line containing a sterile, nonpyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer).

Do not coadminister other drugs through the same intravenous line.

Flush the intravenous line at end of infusion.

5.3.3. Management of Nivolumab-Specific Adverse Events

Toxicities associated or possibly associated with nivolumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology.

Although most immune-related adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of nivolumab may not have an immediate therapeutic effect and in severe cases, immune-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, mycophenolate, or TNF-α inhibitors.

The primary approach to Grade 1-2 immune-related adverse events is supportive and symptomatic care with continued treatment with nivolumab; for higher grade immune-related adverse events, nivolumab should be held and oral/parental steroids administered. Recurrent Grade 2 immune-related adverse events may also mandate holding nivolumab or the use of steroids. Consideration for benefit/risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of nivolumab. Nivolumab should be permanently discontinued in patients with life-threatening irAEs.

See Prescribing Information for full details.

5.3.4. Guidelines for Dosage Modification and Treatment Interruption or Discontinuation

Nivolumab treatment will be given for up to one year.

Patients may temporarily suspend study treatment for up to 42 days from the last dose if they experience toxicity that is considered related to the study drug and requires a dose to be held. If nivolumab is held because of adverse events for >42 days beyond the last dose, then the patient will be discontinued from nivolumab.

If a patient must be tapered off steroids used to treat adverse events, nivolumab may be held for additional time beyond 42 days from the last dose until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤10 mg/day. The acceptable length of interruption will depend on an agreement between the investigator and the Principal Investigator.

Dose interruptions for reason(s) other than toxicity, such as surgical procedures, may be allowed with Principal Investigator approval. The acceptable length of interruption will depend on agreement between the investigator and the Principal Investigator.

Any toxicities associated or possibly associated with nivolumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology.

Patients should be assessed clinically (including review of laboratory values) for toxicity prior to, during, and after each infusion. If unmanageable toxicity due to nivolumab occurs at any time during the study, treatment with nivolumab should be discontinued.

Management of potential immune related AEs are described in the following sections.

5.3.4.1. Management of infusion-related reaction

No premedication will be allowed for the first dose of nivolumab. Premedication may be administered for 2 doses or greater at the discretion of the treating physician. Patients who experience infusion-associated symptoms may be treated symptomatically with antipyretics

(ibuprofen preferred), diphenhydramine, and/or cimetidine or another H2 receptor antagonist, as per standard practice.

The management of infusion-related reactions will be according to severity as per institutional guidelines.

5.3.4.2. Gastrointestinal Toxicity

Immune-mediated colitis has been associated with the administration of nivolumab. Diarrhea or colitis was reported in 21% of patients in two trials of nivolumab. Immune-mediated colitis occurred in 2.2% of patients in one trial- of these one patient had Grade 2 colitis, and five had Grade 3 colitis. In the other trial, Grade 3 immune-mediated colitis occurred in 0.9% of patients.

Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild. Range for time to onset of symptoms of colitis has been 1-6 months.

If the event is of significant duration or magnitude or is associated with signs of systemic inflammation or acute phase reactants (e.g. increased CRP or platelet count or bandemia), it is recommended that sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy with three to five specimens for standard paraffin block be performed.

Treatment may be restarted following the resolution of colitis. In addition, if the patient is being managed with corticosteroids, treatment should not be restarted until the steroids have been tapered down to a prednisone dose $\leq$ 10 mg/day. Patients who resume treatment should be monitored closely for signs of renewed diarrhea.

Table 2 provides a summary of dose modification guidelines for gastrointestinal toxicities.

Table 2 Dose Modification Guidelines for Gastrointestinal Toxicity

Symptoms	Management	Follow-up
Grade 1 diarrhea: <4 stools per day over baseline Grade 1 colitis: asymptomatic colitis	Continue nivolumab Administer symptomatic treatment	- Close monitoring for worsening symptoms - Educate patients to report worsening immediately
Grade 2 diarrhea: 4-6 stools per day over baseline - IV fluids indicated <24 hrs - Not interfering with ADL Grade 2 Colitis: abdominal pain, blood in stool	Withhold nivolumab Administer symptomatic treatment If symptoms persist >5 days or recur: 0.5 to 1 mg/kg/day prednisone equivalents	If improved: - resume nivolumab - if steroids have been administered, taper steroids over at least 1 month before resuming nivolumab If symptoms worsen or persist >3-5 days with oral steroids: - treat as Grade 3 or 4
Grade 3 or 4 Grade 3 diarrhea: $\geq$ 7 stools per day over baseline, incontinence - IV fluids $\geq$ 24 hs - Interferes with ADLs Colitis Grade 3: severe abdominal pain, medical intervention indicated, peritoneal signs present Colitis Grade 4: life threatening symptoms, perforation	Grade 3: withhold nivolumab until symptoms are Grade 1 Grade 3 persists or worsens, or Grade 4: permanently discontinue nivolumab Administer 1-2 mg/kg/day prednisone equivalents Consider lower-GI endoscopy	If improved from Grade 3: - when at Grade 1, taper steroids over 1 month before resuming nivolumab If improved from persistent Grade 3 or Grade 4 - continue steroids until Grade 1, then taper over at least 1 month If symptoms persist >3-5 days, or recur after improvement - add non-corticosteroid immunosuppressive medication

5.3.4.3. Hepatotoxicity

Immune-mediated hepatitis has occurred with the administration of nivolumab.

Patients should be monitored for abnormal liver tests prior to and periodically during treatment. While on this study, patients presenting with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately and LFTs should be reviewed before administration of the next dose of study drug.

If LFTs increase, neoplastic, concurrent medications, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other causes for the increased LFTs. Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-liver-kidney microsomal antibodies, and anti-smooth muscle antibody tests should be performed in an autoimmune etiology is considered.

Patients with LFT abnormalities should be managed according to the guidelines in Table 3.

Table 3 Dose Modification Guidelines for Hepatotoxicity

Symptoms	Management	Follow-up
Grade 1: AST or ALT >ULN to 3xULN and/or T Bili >ULN to 1.5xULN	Continue nivolumab Regularly monitor LFTs	Continue monitoring LFTs
Grade 2: AST or ALT >3 to ≤5 x ULN and/or T Bili >1.5 to ≤ 3 ULN	- Withhold nivolumab - Increase frequency of monitoring to every 3 days - 1 to 2 mg/kg/day prednisone equivalents	If improved to Grade 1 or baseline, resume nivolumab. If steroids have been administered, taper steroids over at least 1 month before resuming nivolumab. Resume routine LFT monitoring
Grade 3 or 4: AST or ALT >5x ULN and/or T Bili >3x ULN	- Permanently discontinue nivolumab - Increase frequency of monitoring to every 1-2 days - Gastroenterology consult - Treat with 1-2 mg/kg/day prednisone equivalent	If improved to <Grade 2, taper steroids over at least 1 month If labs persist >3-5 days, worsen or rebound: add non-corticosteroid immunosuppressive medication
IV = intravenous; LFT = liver function test; ULN = upper limit of normal.		

5.3.4.4. Renal Toxicity

Immune-mediated nephritis or renal dysfunction occurred with nivolumab treatment. Patients should be monitored for elevated serum creatinine prior to and periodically during treatment and clinically monitored for symptoms of decreased volume of urination, hematuria, peripheral edema, and loss of appetite.

In one trial, there was increased incidence of elevated creatinine in the nivolumab-treated group as compared to chemotherapy (13% v 9%). Grade 2 or 3 immune-mediated nephritis or renal dysfunction occurred in 0.7% (2/268) of patients. In another trial, the incidence of elevated creatinine was 22%, with Grade 2 immune-mediated renal dysfunction occurring in 0.9% (1/117) patients.

Renal toxicity should be managed according to the guidelines in Table 4.

Table 4 Dose Modification Guidelines for Renal Toxicity

Toxicity, Grade	Management	Follow-up
Grade 1 - Creatinine >ULN and >baseline but ≤ 1.5x baseline	Continue nivolumab - Monitor creatinine weekly	If improved to baseline, resume routine creatinine monitoring.
Grade 2 or 3 - Creatinine >1.5 to ≤ 6x ULN or >1.5 x baseline	Withhold nivolumab - Monitor creatinine every 2-3 days - Treat with 0.5 to 1 mg/kg/day prednisone equivalents - Consider renal biopsy	If improved to Grade 1, taper steroids over at least 1 month before resuming nivolumab with routine creatinine monitoring. If elevations persist >7 days or worsen, treat as Grade 4
Grade 4 - Creatinine >6x ULN	Permanently discontinue nivolumab - Monitor creatinine daily - Nephrology consult - Treat with 1-2 mg/kg/day prednisone equivalents - Consider renal biopsy	If improved to Grade 1, taper steroids over at least 1 month

5.3.4.5. Endocrine Toxicity

Immune-mediated hypothyroidism and hyperthyroidism has been associated with the administration of nivolumab. In one trial, Grade 1 or 2 hypothyroidism occurred in 8% (21/268) of patients receiving nivolumab. Grade 1 or 2 hyperthyroidism occurred in 3% (8/268) of patients on nivolumab on that trial, and in 1% (1/102) patients receiving chemotherapy. In another trial, hypothyroidism occurred in 4.3% (5/117) of patients. Hyperthyroidism occurred in 1.7% (2/117) of patients. One patient experienced Grade 2 hyperthyroidism.

Patients with unexplained symptoms such as fatigue, headaches, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies, as well as for hyponatremia or hyperkalemia. An endocrinologist should be consulted if an endocrinopathy is suspected. TSH and free T4 levels should be obtained to determine if thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

Hypothyroidism should be managed according to the guidelines in Table 5.

Table 5 Dose Modification Guidelines for Endocrine Toxicity

Toxicity Grade	Management	Follow-up
Asymptomatic endocrinopathy (e.g hypothyroidism or hyperthyroidism)	- Continue nivolumab - If TSH <0.5 xLLN or TSH >2x ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated - Consider endocrinology consult	Continue standard monitoring
Symptomatic endocrinopathy – either hypothyroidism or hyperthyroidism	- continue nivolumab for hypothyroidism or hyperthyroidism - withhold nivolumab for other endocrinopathies with abnormal lab/pituitary scan - evaluate endocrine function - consider pituitary scan - repeat labs in 1-3 weeks - repeat MRI in 1 month if symptoms persist but normal lab/pituitary scan - consider endocrinology consult	If improved (with or without hormone replacement)- resume nivolumab Continue standard monitoring Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis: - severe dehydration - hypotension - shock out of proportion to current illness	- withhold nivolumab - rule out sepsis - consult endocrinology - stress-dose IV steroids with mineralocorticoid activity (may be switched to an equivalent dose of oral corticosteroids at start of tapering or earlier, once sustained clinical improvement observed) - administer IV fluids	When adrenal crisis ruled out, treat as symptomatic endocrinopathy
TSH = thyroid-stimulating hormone.		

5.3.4.6. Pulmonary Toxicity

Severe pneumonitis or interstitial lung disease, including fatal cases, have occurred with nivolumab treatment. As such, patients must be monitored for signs and symptoms of pneumonitis. Across clinical trial experience in 691 patients with solid tumors, fatal immune mediated pneumonitis occurred in 0.7% (5/691) of patients receiving nivolumab. In one trial 2.2% (6/268) of patients receiving nivolumab developed immune-mediated pneumonitis, one with Grade 3 and with Grade 2 cases. In another trial, immune-mediated pneumonitis occurred in 6% (7/117) of patients receiving nivolumab including five Grade 3 and two Grade 2 cases.

Pulmonary toxicity should be managed according to the guidelines in Table 6.

Table 6 Dose Modification Guidelines for Pulmonary Toxicity

Description	Management	Follow-up
Grade I- radiographic changes only	- Consider withholding nivolumab. - Monitor every 2-3 days - consider pulmonary and infectious disease consults.	- Reassess at least every 3 weeks - If improved, resume nivolumab (if it has been discontinued) when symptoms stabilized - If worsens, treat as Grade 2 or above
Grade 2: - mild to moderate symptoms - radiographic changes	- withhold nivolumab - monitor daily - consult Pulmonary and Infectious diseases - treatment with 1 mg/kg/day prednisone or equiv - consider bronchoscopy/lung biopsy	If improved to baseline: - taper steroids over at least 1 month before resuming nivolumab If not improving after 2 weeks or worsening: - treat as Grade 3 or 4
Grade 3 or 4: - severe symptoms - new/worsening hypoxia - life-threatening symptoms	- Hospitalize patient - Permanently discontinue nivolumab - Monitor daily - Obtain Pulmonary and Infectious Disease consults - Treat with 1-2 mg/kg/day prednisone or equivalent - Consider bronchoscopy, lung biopsy	If improved to baseline: - taper steroids over at least 1 month If persists or worsens after 2 days - add non-corticosteroid immunosuppressive medication

5.3.4.7. Pericardial and Pleural Effusions

Pericardial and pleural involvement with associated effusions is common in patients with NSCLC and have the theoretical potential to be exacerbated by inflammation associated with antitumor immunity following PD-L1 blockade. Patients presenting with dyspnea, chest pain, or unexplained tachycardia should be evaluated for the presence of a pericardial effusion. Patients with preexisting pericardial effusion should be followed closely for pericardial fluid volume measurements and impact on cardiac function. When intervention is required for pericardial or pleural effusions, appropriate workup includes cytology, LDH, glucose, cholesterol, protein concentrations (with pleural effusions), and cell count. For patients with a pericardial effusion causing end-diastolic right ventricular collapse, treatment may be restarted following the placement of a pericardial window, demonstrations of hemodynamic stability, and resolution of right ventricular dysfunction.

6. CONCOMITANT MEDICATIONS/PROCEDURES

6.1. Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines (Smith 2006). Transfusions may be given in accordance with institutional policy.

Short courses (≤14 days) of steroid treatment for non-cancer related medical reasons (eg, joint inflammation, asthma exacerbation, rash, antiemetic use and infusion reactions) at doses that do not exceed 100mg per day of prednisone or equivalent are permitted.

6.2. Medications to be Used with Caution

6.2.1. CYP3A- Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong CYP3A inhibitor (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, cobicistat, posaconazole, and nefazadone) or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. If a strong CYP3A inhibitor must be used, either reduce ibrutinib dose to 140 mg or withhold treatment temporarily (for 7 days or less). Subjects should be monitored for signs of ibrutinib toxicity. If a moderate CYP3A inhibitor (eg. Fluconazole, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone, and dronedarone) must be used, reduce ibrutinib to 140mg for the duration of the inhibitor use. No dose adjustment is required in combination with mild inhibitors. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A (see Section 5.3.1.2).

Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

A list of common CYP3A inhibitors and inducers is provided in Appendix 3. A comprehensive list of inhibitors, inducers, and substrates may be found at
http://medicine.iupui.edu/clinpharm/ddis/main-table/

This website is continually revised and should be checked frequently for updates.

6.2.2. Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor (with an IC_{50} of 2.15 µg/mL). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit

intestinal P-gp after a therapeutic dose. There is no clinical data available; therefore, to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin, should be taken at least 6 hours before or after ibrutinib.

6.2.3. QT Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic ECG and electrolyte monitoring should be considered.

6.2.4. Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Bleeding events of any grade, including bruising and petechiae, occurred in subjected treated with ibrutinib. Subjects with congenital bleeding diathesis have not been studied. For guidance on ibrutinib and the use of anticoagulants during procedures/surgeries see Section 6.4.

Subjects requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

6.3. Prohibited Concomitant Medications

Any chemotherapy, experimental therapy, or radiotherapy are prohibited while the subject is receiving study treatment.

Corticosteroids for the treatment of the underlying disease is prohibited except when required to treat Nivolumab toxicity. Corticosteroids for the treatment of non-cancer related reasons for longer than 14 days and/or at doses >100mg of prednisone or its equivalent are prohibited.

6.4. Guidelines for Ibrutinib Management with Surgeries or Procedure

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib.

6.4.1. Minor Surgical Procedures

For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be

restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib for these procedures.

6.4.2. Major Surgical Procedures

For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

6.4.3. Emergency Procedures

For emergency procedures, ibrutinib should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

7. STUDY EVALUATIONS

7.1. Description of Procedures

A cycle has a duration of 28 days throughout this study.

All screening clinical and laboratory assessments must be performed within 28 days of Study Day 1 and prior to the first dose of study treatment.

All study tests and procedures should be evaluated at the study center at which the subject was enrolled.

7.1.1. Assessments

7.1.1.1. Informed Consent Form

The subject must read, understand, and sign the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) approved informed consent form (ICF) confirming his or her willingness to participate in this study before any study-specific screening procedures are performed.

Subjects must also grant permission to use protected health information per the Health Insurance Portability and Accountability Act (HIPAA). In addition, subjects must sign all approved ICF amendments per the site IRB/REB/IEC guidelines during the course of the study.

The subject may be enrolled in the study only after signing the ICF and being deemed eligible for entry based on screening procedures and history review.

7.1.1.2. Confirm Eligibility

All necessary screening procedures and evaluations, along with review of medical history, must be performed to document that the subject meets all of the inclusion criteria and none of the exclusion criteria (Section 4). In addition to the review of screening procedures and results, documentation of pathologic confirmation of eligible disease (Section 4) is required for confirmation of eligibility prior to enrollment.

7.1.1.3. Medical History

The subject's complete history through review of medical records and by interview will be collected and recorded. Concurrent medical signs and symptoms during screening and prior to first dose of study treatment must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and a list of all prior anticancer treatments, dates administered, response, and duration of response to these treatments is required to be clearly documented in the subject's medical record.

7.1.1.4. Concomitant Medications

All medications from the signing of ICF through 30 days after the last dose of study drug will be documented in the subject's medical record.

7.1.1.5. Adverse Events

The accepted regulatory definition for an adverse event is provided in Section 11.1. All medical occurrences that meet the adverse event definition will be documented in the source documents from the time of first dose of study treatment until 30 days following the last dose of study drugs. SAEs will be reported to the Pharmacyclics and the study sponsor from the time of first dose of study treatment.

Both serious and non-serious AEs will be recorded in the CRF from the first dose of study drug until 30 days after the last dose of study drug(s).

Additional important requirements for adverse event and serious adverse event reporting are explained in Section 11.

7.1.1.6. Physical Examination

The Screening and End-of-Treatment physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight (on Nivolumab dosing days), and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

7.1.1.7. Vital Signs

Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature and will be assessed after the subject has been resting in the sitting position for at least 3 minutes.

7.1.1.8. Performance Status

This assessment must be performed during the screening assessments as well as the day of the first study treatment and prior to the first dose. Subsequent assessments will be performed as per the Schedule of Assessments (Appendix 1).

The ECOG and KPS performance indices are provided in Appendix 2.

7.1.2. Laboratory

7.1.2.1. Hematology

Hematology parameters will include a complete blood count including platelets and differential.

7.1.2.2. Chemistry (Serum)

Serum chemistry parameters will include sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), phosphate, uric acid, magnesium and bicarbonate. Baseline TSH will also be required. If TSH is abnormal, further evaluation of serum T3, T4 will be at investigator's discretion.

7.1.3. Diagnostics/Procedures

7.1.3.1. Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.

7.1.3.2. Pregnancy Test

Serum or urine pregnancy test will be required at Screening by local laboratory only for women of childbearing potential. A serum or urine pregnancy test will also be performed on Day 1 prior to first dose. If positive, pregnancy must be ruled out by ultrasound to be eligible.

7.1.3.3. ECG

ECGs should be performed at screening and subsequently at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset dyspnea.

Subjects should be in supine position and resting for at least 10 minutes before study-related ECGs. During visits in which both ECGs and blood draws are performed, ECGs should be performed first. Abnormalities noted at Screening should be included in the medical history.

7.2. Efficacy Evaluations (Histology Specific)

Archival specimens will be obtained at screening within 28 days before the first dose of ibrutinib and nivolumab.

7.3. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in source documents for transcription to the CRF or laboratory requisition form. Refer to the Schedule of Assessments (Appendix 1) for the timing and frequency of all sample collections.

8. STUDY PROCEDURES

8.1. Screening Phase

Screening procedures will be performed up to 28 days prior to the first dose of study treatment, unless otherwise specified. Obtain written informed consent as indicated by subject's signature on the IRB approved ICF.

- Informed Consent
- Medical history
- Review of eligibility criteria
- Review and recording of all current, ongoing medications and any medications taken within 30 days prior to start of study medication (including over-the-counter drugs, vitamins and herbs)
- Complete physical exam including height and weight
- Vitals signs (including blood pressure, heart rate, respiratory rate, and body temperature)
- Performance Status
- CT/MRI scan
- 12-lead ECG. Subjects should be in a supine position and resting for at least 10 minutes before obtaining the ECG.
- Archival specimen
- Urine test
- Pregnancy Test
- Blood for translational studies
- Urine for translational studies
- Creatinine Clearance (measured or calculated)
- Laboratory tests for:
    - Hematology including differential
    - Serum chemistries (including TSH)
    - Serum pregnancy test (for women of childbearing potential only)
    - PT/INR and PTT

  - Hepatitis serologies
- Confirm eligibility – complete enrollment checklist prior to enrollment

8.2. Treatment Phase

Treatment with ibrutinib in combination with nivolumab will continue for a maximum of one year or until 1) tumor progression; 2) unacceptable or intolerable toxicity; 3) patient withdrawal for any reason; 4) physician choice if in the best interest of the patient. Treatment with Ibrutinib will continue until either disease progression, or physician choice, or patient choice, or unacceptable or intolerable toxicities. Investigator discretion as to continuing single agent nivolumab for a maximum of one year will be allowed for patients who are unable to receive the doublet due to toxicity or patient preference.

8.2.1. Cycle 1, Day 1 Visit

Following completion of the Screening Visit and once eligibility has been confirmed, subjects are enrolled. Enrollment should occur as close to the time of the expected first dose as possible.

- Confirm eligibility criteria
- Review of current medications and any new medications since screening visit
- Review of current signs/symptoms including any new untoward events since screening
- Complete physical exam and weight
- Vital signs
- Performance status
- Pregnancy Test
- Laboratory tests for:
  - Hematology including differential
  - Serum chemistry
- Dose administration – ibrutinib
- Dose administration – nivolumab
- Provide drug diary and dosing instructions to subject
- Dispense study drugs

8.2.2. Cycle 1, Day 15 Visit

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Physical exam
- Vital signs
- Performance Status
- Blood for translational studies
- Urine for translational studies
- Lab sample collection for
  - Hematology
  - Serum chemistry

8.2.3. Cycle 2, Day 1 Visit

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary and dispense new diary
- Physical exam
- Vital signs
- Performance Status
- Lab sample collection for
    - Hematology
    - Serum chemistry

8.2.4. Cycle 2, Day 15 Visit

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary
- Physical exam
- Vital signs
- Performance Status
- Lab sample collection for
    - Hematology including differential

8.2.5. Cycle 3-7, Day 1 Visit

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary and dispense new diary
- Physical exam
- Vital signs
- Performance Status
- Disease assessment
- Lab sample collection for
    - Hematology including differential
    - Serum chemistry

8.2.6. Cycle 3- 7, Day 15 Visit

- Review of concomitant medications
- Review of adverse events
- Vital signs
- Lab sample collection for
    - Hematology including differential

8.2.7. Cycle 8 and Beyond

- Review of concomitant medications
- Review of adverse events
- Review returned subject dosing diary and dispense new diary
- Disease assessment
- Lab sample collection for
    - Hematology including differential
    - Serum chemistry

8.2.8. End of Treatment (EOT) Visit

- Review of concomitant medications
- Review of adverse events
- Blood for translational studies
- Urine for translational studies
- Lab sample collection for
    - Hematology including differential
    - Serum chemistry

8.3. Follow-up Phase

Once a subject has completed the End-of-Treatment Visit they will enter the Follow-up Phase. Once subjects experience TF, relapse, or start use of alternative anticancer therapy (for subjects who have not withdrawn consent), they will be contacted approximately every 3 months (±14 days) by clinic visit or telephone until death, subject withdrawal, lost to follow-up, study termination by the study sponsor, or up to 6 months whichever occurs first.

- Survival status, including other malignancies
- Subsequent anticancer therapy

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Completion

A subject will be considered to have completed the study if he or she has died before the end of the study, has not been lost to follow up, or has withdrawn consent before the end of study.

9.2. Withdrawal from Study Treatment

Study treatment will be discontinued in the event of any of the following events:

1. Unacceptable toxicity
2. Treatment failure or no evidence of clinical benefit per investigator assessment
3. An intercurrent illness or adverse event that prevents further ibrutinib administration.

4. Withdrawal of consent for treatment by subject
5. Investigator decision (such as chronic noncompliance, significant protocol deviation, or best interest of the subject)
6. Study termination by Pharmacyclics or study sponsor
7. Subject becomes pregnant
8. Nivolumab is held for greater than 42 days (the subject can stay on study with Ibrutinib only)
9. Ibrutinib is held for greater than 4 weeks. If lbrutinib therapy is held for greater than 4 weeks, then the subject must discontinue from the nivolumab as well

All subjects, regardless of reason for discontinuation of study treatment will undergo an End of Treatment Visit and be followed for treatment failure and survival.

9.3. Withdrawal from Study

Withdrawal from study (including all follow-up) will occur under the following circumstances:

1. Withdrawal of consent for follow-up observation by the subject
2. Lost to follow-up
3. Study termination by Pharmacyclics or study sponsor
4. Death

If a subject is lost to follow-up, every reasonable effort should be made by the study site personnel to contact the subject. The measures taken to follow up should be documented.

When a subject withdraws before completing the study, the following information should be documented in the source documents:

1. Reason for withdrawal
2. Whether the subject withdraws full consent (i.e. withdraws consent to treatment and all further contact) or partial consent (i.e. withdraws consent to treatment but agrees to participate in follow-up visits)

10. STATISTICAL METHODS AND ANALYSIS

10.1. Subject Information

All patients receiving at least one cycle of therapy and are evaluable for response will be assessable for the primary endpoint of progression free survival (evaluable population).

10.2. Endpoints

10.2.1. Primary Endpoint

The primary analytic objective of this Phase IB/II study is provide a preliminary assessment of the efficacy of this treatment combination, as measured by Progression-Free Survival (PFS).

10.2.2. Secondary Endpoints

Secondary analytic objectives are to provide preliminary assessments of the RECIST Response Rate, Overall Survival, and Safety of this treatment combination.

10.2.3. Other Secondary Endpoints

N/A

10.2.4. Exploratory Endpoints

N/A

10.3. Sample Size Determination

In the RECORD-1 trial, PFS at 6 months was approximately 40%. Assuming that the ibrutinib plus nivolumab combination will increase the PFS rate from 40 to 70% at the 6 month timepoint, a sample size of 25 patients will provide 90% power and one-sided level 0.034 to detect this difference, with a critical value of 15 or more patients out of 25 experiencing PFS at 6 months. To account for dropouts, a total of 30 patients will be accrued. Efficacy analysis will be performed on all patients enrolled in the study regardless of dose level assignment; i.e., patients from each of the completed dose levels will be pooled as described in the study schema.

10.4. Analysis Populations

10.4.1. Safety Population

The safety population will include all patients who receive at least one dose of either study drug. A baseline measurement and at least one laboratory, vital sign, or other safety-related measurement obtained after at least one dose of study medication may be required for inclusion in analyses of a specific safety parameter.

10.4.2. Efficacy populations

Evaluable population:

The evaluable population will be the basis for the primary analysis of efficacy (progression-free survival). This population will include all patients who complete at least one cycle of therapy at either of the two planned dose levels and are evaluable for the primary response (progression-

free survival). Secondary analyses may require instead that patients be evaluable for secondary efficacy analyses (RECIST response, overall survival.)

Per-protocol population:

A supportive analysis may be carried out using the per-protocol population, defined as a subset of the evaluable population that further excludes patients who experienced deviations from protocol that may affect primary or secondary outcomes.

10.5. Statistical Methods

Primary endpoint: Progression-free survival (PFS) as the number of months from baseline to death or progression, defined in Appendix 4. The duration of PFS will be summarized descriptively using Kaplan-Meier survival plots and life tables. The number and proportion with PFS of 6 months or more will be reported, adjusting for censoring using the life-table approach. If the number with PFS at least six months is 15 or more out of 25 evaluable patients, this will constitute evidence supporting an improvement over historic PFS rates.

Secondary endpoints: RECIST response will be calculated as in Appendix 4, and will be summarized by the number and percentage of patients, accompanied by 2-sided exact 95% confidence intervals. Overall survival will be summarized descriptively by Kaplan-Meier curves and life table estimates, as for PFS. Number and type of adverse events will be summarized descriptively by system organ class affected and by grade of event, overall and by dose. Vital signs and laboratory test results will be summarized descriptively (mean, SD, range) overall and by dose.

11. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

11.1. Definitions

11.1.1. Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug (ICH-E2A, 1995).

For the purposes of this clinical study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions.

The term "disease progression" should not be reported as an adverse event term. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression should be reported.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms provided by the subject and/or observed by the Investigator or study staff including laboratory abnormalities.
- Any AEs experienced by the subject through the completion of final study procedures.
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the underlying disease that were not present before the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies).

The following are NOT considered AEs:

- **Pre-existing condition:** A pre-existing condition is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Pre-planned or elective hospitalization:** A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- **Diagnostic Testing and Procedures:** Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.

11.1.2. Serious Adverse Events

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death (ie, the AE actually causes or leads to death).
- Is life-threatening. Life-threatening is defined as an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have

caused death if it were more severe. If either the Investigator or the IND Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.

- Requires in-patient hospitalization >24 hours or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject or subject may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsion that does not result in hospitalization; or development of drug dependency or drug abuse.

11.1.3. Severity Criteria (Grade 1-5)

Definitions found in the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) will be used for grading the severity (intensity) of *nonhematologic* AEs. The CTCAE v4.03 will be used for the grading of hematologic AEs when applicable. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE v4.03, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

11.1.4. Causality (Attribution)

The Investigator is to assess the causal relation (ie, whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

Not Related (unrelated): Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.

Unlikely: The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.

Possibly Related: There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.

Related: The AE is clearly related to use of the investigational product.

11.2. Unexpected Adverse Events

An “unexpected” AE is an AE that is not listed in the Investigator's Brochure/package insert or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be “unexpected” (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be “unexpected” (by virtue of greater specificity) if the Investigator's Brochure/package insert listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

11.3. Special Reporting Situations

Special reporting situation on a Sponsor study may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of any study drug
- Suspected abuse/misuse of a study drug
- Inadvertent or accidental exposure to a study drug

- Medication error involving a product (with or without subject exposure to the study drug, e.g., name confusion)

If any special reporting situations meet the criteria of an AE, it should be reported on the Serious Adverse Event Report Form. The Serious Adverse Event Form should be sent via email or fax to Pharmacyclics Drug Safety or designee within 15 days of awareness.

11.4. Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators

11.4.1. Assessment of Adverse Events

Investigators will assess the occurrence of adverse events and serious adverse events at all subject evaluation timepoints during the study. All adverse events and serious adverse events whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, all abnormal laboratory values, or other means, will be recorded. Each recorded adverse event or serious adverse event will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

11.4.2. Adverse Event Reporting Period

All AEs whether serious or non-serious, will be captured from the time signed and dated ICF is obtained until 30 days following the last dose of study drug.

Serious adverse events reported after 30 days following the last dose of study drug should also be reported if considered related to study drug. Resolution information after 30 days should be provided.

Progressive disease should NOT be reported as an event term, but instead symptoms/clinical signs of disease progression may be reported. (See Section 11.1.1)

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection").

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself.

If a death occurs within 30 days after the last dose of study drug, the death must be reported as a serious adverse event.

11.4.3. Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject must immediately inform the Investigator if she becomes pregnant from the time of consent to 30 days after the last dose of study drug. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 3 months after the last dose of study drug. Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days after the last dose of study drug must be reported. Any occurrence of pregnancy must be reported to Pharmacyclics Drug Safety, or designee, per SAE reporting timelines. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. Pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old and this must be reported to Pharmacyclics Drug Safety, or designee, per SAE reporting timelines. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

11.4.4. Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

11.4.5. Eye-Related Adverse Events

New or worsening eye-related symptoms that are Grade 2 or higher, or a symptom that was Grade 2 or higher at baseline worsens, should be evaluated by an ophthalmologist.

11.4.6. Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities by the Sponsor. These events (regardless of seriousness) will be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety or designee within 15 days of awareness.

11.4.6.1. Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic adverse events of Grade 3 or higher*. Any treatment-emergent serious adverse events of bleeding of any grade
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells should be reported as grade 3 or higher AE per CTCAE v4.03.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 11.3.6 above.

11.4.7. Expediting Reporting Requirements for Serious Adverse Events

All serious adverse events and AESIs as per Section 11.3.6 (initial and follow-up information) will be reported on FDA Medwatch and sent via email (AEintakeCT@pcyc.com) or fax ((408) 215-3500) to Pharmacyclics Drug Safety, or designee, within 15 days of the event. Pharmacyclics may request follow-up and other additional information from the Sponsor Investigator.

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts)

It is the responsibility of the Investigator and the research team to ensure that serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices (GCP), the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

12. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

12.1. Regulatory and Ethical Compliance

This clinical study was designed and will be implemented in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practices, with applicable local regulations including US Code of Federal Regulations [CFR] Title 21 and with the ethical principles laid down in the Declaration of Helsinki.

12.2. Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s). In accordance with UCD OCR policy an original signed and dated participant Informed Consent document will reside in a secured location within the UCD OCR. Participating sites will store original signed and dated informed consent per its policies. Copies of the signed and dated Informed Consent document will be provided to the study participant and UCD Health System Information Management for inclusion in the participant's UCD Health System Medical Record or per participating site's policies.

12.3. Quality Control and Quality Assurance

Quality assurance audits of select patients and source documents may be conducted by the UC Davis Cancer Center Quality Assurance Committee as outlined in the UC Davis Cancer Center Data and Safety Monitoring plan.

Quality control will be maintained by the OCR Quality Assurance team according to OCR policy.

Quality assurance audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are mailed/sent by from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites.

12.4. Data and Safety Monitoring

In addition to the requirements for adverse event reporting as outlined in Section 11, this protocol is also subject to the UC Davis Cancer Center's (UCDCC) Data and Safety Monitoring Plan. The UCDCC is committed to pursuing high-quality patient-oriented clinical research and has established mechanisms to ensure both scientific rigor and patient safety in the conduct of clinical research studies. The UCDCC relies on a multi-tiered committee system that reviews and monitors all cancer clinical trials and ensures the safety of its participants, in compliance with institutional and federal requirements on adverse event (AE) reporting, verification of data

accuracy, and adherence to protocol eligibility requirements, treatment guidelines, and related matters. The Scientific Review Committee (SRC) assumes overall oversight of cancer studies, with assistance and input from two independent, but interacting, committees: the Quality Assurance Committee and the Data Safety Monitoring Committee. A multi-level review system strengthens the ability of the UCDCC to fulfill its mission in conducting high quality clinical cancer research.

As per University of California Davis Cancer Center (UCDCC) Office of Clinical Research (OCR) SOP AM 506: Protocol Specific Meetings, the principal investigator (PI) and clinical research coordinator (CRC) meet at least monthly for ongoing study information, to discuss patient data and adverse events and to determine if dose escalation is warranted, when applicable.

According to the UCDCC Data and Safety Monitoring Plan (DSMP), any new serious adverse events related to the drugs being used on this trial are reviewed monthly by the UCDCC Data and Safety Monitoring Committee (DSMC) and any applicable changes to the study are recommended to the PI, if necessary.

The UCDCC Scientific Review Committee (SRC) determines if a UCDCC Data and Safety Monitoring Board (DSMB) is required. If required, the DSMC will appoint a DSMB. The DSMB is responsible for reviewing study accrual logs, adverse event information and dose escalation meeting minutes (where applicable) to ensure subject safety and compliance with protocol defined guidelines.

12.5. Protected Subject Health Information Authorization

In order to maintain patient privacy, all study reports and communications will identify the patient by initials and the assigned patient number. Data capture records and drug accountability records will be stored in secure cabinets in the UCD OCR or at the participating institution(s). Medical records of patients will be maintained in strict confidence according to legal requirements. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

12.6. Study Files and Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

12.7. Case Report Forms and Record Maintenance

All data will be collected using UC Davis data collection forms. The collection forms are pdf editable forms that can be faxed/emailed to UCD. Copies of the completed forms will be submitted to UC Davis data coordinating center for data entry and storage in a secure location. The original data collection forms will reside in secure location.

- SUBMIT WITHIN 24 HOURS OF REGISTRATION:
  Patient Registration Form
- SUBMIT WITHIN 14 DAYS OF REGISTRATION:
  Pre-Study Evaluation Form (IH-102)
- SUBMIT WITHIN 7 DAYS OF SCREENING FAILURE:
  Patient Screen Failure Form
- SUBMIT WITH 14 DAYS OF CYCLE COMPLETION:
  Adverse Event/Drug Relationship Form
- SUBMIT WITHIN 14 DAYS OF END OF EACH TREATMENT CYCLE:
  Treatment Cycle Form - Oral
  Treatment Cycle Form - Infusion
- SUBMIT WITHIN 14 DAYS OF EACH RESPONSE ASSESSMENT:
  Tumor Measurement Log
- SUBMIT WITHIN 14 DAYS OF OFF TREATMENT:
  Off Treatment/In Follow-up/Off Study/Expiration Form (IH-301)
- SUBMIT WITHIN 14 DAYS OF KNOWLEDGE OF DEATH IF PATIENT IS STILL ON STUDY OR 30–DAYS IF OFF STUDY:
  Off Treatment/In Follow-up/Off Study/Expiration Form (IH-301)
- SUBMIT WITHIN 2 DAYS OF KNOWLEDGE OF PROTOCOL DEVIATION:
  Notice of Protocol Deviation
- SUBMIT WITHIN 14 DAYS OF EACH REQUIRED FOLLOW-UP ENCOUNTER:
  Follow-Up Form (IH-302)
- ALL SERIOUS ADVERSE EVENTS MUST BE REPORTED AS OUTLINED IN THE PROTOCOL

12.8. Investigational Study Drug Accountability

Ibrutinib will be supplied by Pharmacyclics. Ibrutinib must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the Investigator or other site personnel supply ibrutinib to other Investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from Pharmacyclics.

An Investigational Drug Accountability Log must be used for drug accountability. For accurate accountability, the following information must be noted when drug supplies are used during the study:

1. Study identification number

2. Subject identification number

3. Lot number(s) of ibrutinib or comparator dispensed for that subject

4. Date and quantity of drug dispensed

5. Any unused drug returned by the subject

12.9. Protocol Amendments

Per the IST Agreement, any amendments to the Protocol or Informed Consent Form protocol must be sent to Pharmacyclics for review and approval prior to submission to the IRB. Written verification of IRB approval will be obtained before any amendment is implemented.

12.10. Publication of Study Results

Per the IST Agreement, the Investigator is required to submit to Pharmacyclics a copy of a planned publication (abstract, poster, oral presentation or manuscript) prior to the submission thereof for publication or disclosure. Pharmacyclics may provide scientific comments and suggestions understanding that the Investigator has sole editorial responsibility, and retains the authority to make the final determination on whether or not to incorporate Pharmacyclics comments or requests for additional information.

12.11. Study Discontinuation

Per the IST Contract, the Investigator reserves the right to terminate the study at any time. Should this be necessary, both the Investigator will arrange discontinuation procedures in partnership with Pharmacyclics. In terminating the study, the Investigator will assure that adequate consideration is given to the protection of the subjects' interests. Pharmacyclics may terminate the study for reasons including, but not limited to: evidence that the PI or an involved investigator is unqualified to conduct research or fulfill sponsor responsibilities (e.g., is listed on

a debarment or ineligible investigator list); failure to meet timelines or achieve agreed upon milestones; a known or perceived risk to patient well-being is identified; or breach of contract. Additional grounds for termination are outlined in the IST Agreement.

13. REFERENCES

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Satterthwaite AB, Witte ON. The role of Bruton's tyrosine kinase in B cell development and function: a genetic perspective. Immunol Rev 2000;175:120-127.

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Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187-205.

Stevenson FK, Krysov S, Davies AJ, et al. B-cell receptor signaling in chronic lymphocytic leukemia. Blood 2011;118: 4313-4320.Zhuang, et al. The expression and role of tyrosine kinase ETK/BMX in renal cell carcinoma. Expt Clin Cancer Res 2014.

14. APPENDICES

Appendix 1. Schedule of Assessments

Study Visits	Screening Phase	Treatment Phase (1 cycle = 28 days)								Suspected PD	End-of-Treatment[a]	FU[b]
		Cycle 1		Cycle 2		Cycles 3–7		Cycles 8 and beyond				
		D1 (baseline)	D15	D1	D15	D1	D15	D1		Any time	30 days after treatment d/c	q 3 mos
Study Visit Windows	-28 days	± 3 days								Any time	± 7 days	± 7 days
Informed consent	x											
Confirm eligibility	x	x										
Medical history	x											
Review concomitant medications	x	x	x	x	x	x	x	x			x	
Review adverse events[c]		x	x	x	x	x	x	x			x	
Study drug compliance review[d]		x	x	x	x	x		x				
Height	x											
Physical exam, vital signs, weight, ECOG	x	x	x	x	x	x		x		x	x	x
Disease assessment[†]:												
CT/MRI scan	x					x		x		x		x
Overall response assessment						x		x		x		x
Hematology	x	x	x	x	x	x	x	x		x	x	
Serum chemistry*	x	x	x	x		x		x		x	x	
TSH[f]	x	x				x		x			x	
Creatinine clearance (Cockcroft-Gault)	x										x	
PT/INR and PTT	x											
Hepatitis serologies	x											
Pregnancy test	x	x										
12 lead ECG	x	As clinically indicated[¥]										
Urine test	x											
Archival Specimen	x											
Blood for Translational Studies[e]	x		x								x	
Urine for Translational Studies	x		x								x	
Any new anticancer therapy												x
Study Drug Administration												
Nivolumab infusion		Every 2 weeks										
Ibrutinib (continuous)		x	x	x	x	x	x	x	x			

Abbreviations: D = day; d/c = discontinuation; PD = progressive disease; FU = follow-up, TSH = thyroid stimulating hormone.
Nivolumab: 240 mg IV every 2 weeks

[†]Disease assessment to be performed every 8 weeks
*Laboratory testing prior to Nivolumab treatment (will be done before every 2 doses of Nivolumab treatment, every 4 weeks).
[¥] ECG's may be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset dyspnea
a. An EOT visit will occur 30 ± 7 days from the last dose of study drug or prior to the start of a new anticancer treatment.
b. Once subjects experience TF, relapse, or start use of alternative anticancer therapy (for subjects who have not withdrawn consent), they will be contacted approximately every 3 months (±14 days) by clinic visit or telephone until death, subject withdrawal, lost to follow-up, study termination by the study sponsor, or up to 6 months whichever occurs first.
c. AEs are reported from the time the patient signs the Informed Consent Form until 30 days following last dose of study drug.
d. Includes patient instruction and routine review of study drug diary and evaluation of contents of study drug containers from home administration
e. See Appendix 8 for collection and processing instructions
f. TSH will be measured at screening, every other cycle starting at Cycle 1, and at the end of treatment visit.

Appendix 2. ECOG and Karnofsky Performance Status Scores[1,2]

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
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	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

1. Karnofsky D, Burchenal J, The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, ed. Evaluation of Chemotherapeutic Agents. New York, NY: Columbia University Press; 1949:191–205.
2. Zubrod C, et al. Appraisal of methods for the study of chemotherapy in man: Comparative therapeutic trial of nitrogen mustard and thiophosphoramide. Journal of Chronic Diseases; 1960:11:7-33.

Appendix 3. Inhibitors and Inducers of CYP3A

Inhibitors of CYP3A are defined as follows. A comprehensive list of inhibitors can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx . The general categorization into strong, moderate, and weak inhibitors according to the website is displayed below. Refer to Section 6.2.1 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib.

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors (SHOULD AVOID):	Carbamazepine
INDINAVIR	Efavirenz
NELFINAVIR	Nevirapine
RITONAVIR	Barbiturates
CLARITHROMYCIN	Glucocorticoids
ITRACONAZOLE	Modafinil
KETOCONAZOLE	Oxcarbarzepine
NEFAZODONE	Phenobarbital
SAQUINAVIR	Phenytoin
SUBOXONE	Pioglitazone
TELITHROMYCIN	Rifabutin
Moderate inhibitors:	Rifampin
Aprepitant	St. John's Wort
Erythromycin	Troglitazone
diltiazem	
Fluconazole	
grapefruit juice	
Seville orange juice	
Verapamil	
Weak inhibitors:	
Cimetidine	
All other inhibitors:	
Amiodarone	
NOT azithromycin	
Chloramphenicol	
Boceprevir	
Ciprofloxacin	
Delaviridine	
diethyl-dithiocarbamate	
Fluvoxamine	
Gestodene	
Imatinib	
Mibefradil	
Mifepristone	
Norfloxacin	
Norfluoxetine	
star fruit	
Telaprevir	
Troleandomycin	
Voriconazole	

Source: http://medicine.iupui.edu/clinpharm/ddis/table.aspx.

Appendix 4. Response Criteria

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (25). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Disease Parameters

Measurable Disease
The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable Lesions
Lesions that can be accurately measured in at least one dimension with longest diameter 20mm using conventional techniques or 10mm with spiral CT scan.

Non-Measurable Lesions
All other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow up.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline Documentation of "Target" and "Non-Target" Lesions

As per RECIST 1.1: When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

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.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted in Section 3, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum.

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions
- **Partial Response (PR):** At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
- **Progressive Disease (PD):** At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of Non-Target Lesions

- **Complete Response (CR**): Disappearance of all non-target lesions and normalization of tumor marker level
- **Incomplete Response/ Stable Disease (SD):** Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
- **Progressive Disease (PD):** Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of Best Overall Response

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

Table 3. Best Overall Response Evaluation

Target Lesion	Non-Target Lesion	New Lesion	Overall Response
CR	CR	No	CR
CR	Incomplete Response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having

"symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Appendix 5: Pill Diary

PROTOCOL NUMBER: UCDCC# 262
PATIENT NAME: _____
MEDICAL RECORD NUMBER: _____

INVESTIGATIONAL AGENT: Oral ibrutinib

CYCLE #: _____ **START DATE:** _____ **DOSE:** _____

Instructions: Ibrutinib is an oral agent that should be taken once daily every day on a 28-day cycle. *It should be taken around the same time each day*. Please indicate in the corresponding box using a check mark the days that you took ibrutinib. If you miss a dose, do not double up the next dose. Just leave the corresponding box for the missed dose blank.

Day of Cycle	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Please initial in each box to indicate you took dose																												

PATIENT SIGNATURE:_____

Appendix 6: NCI CTC Version 4.03

Toxicity will be scored using NCI CTC Version 4.03 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.03 can be downloaded from the CTEP homepage: (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTC Version.

Appendix 7: Registration Guidelines

A. Before registration, the site study coordinator should check to make sure that the corresponding Investigational Drug Service or equivalent has study drug in stock.

B. Registrations for this Phase I protocol must be made through the Office of Clinical Research of the University of California, Davis Comprehensive Cancer Center between the hours of 9am and 3pm (Pacific Time), Monday through Friday (except holidays). Documentation of current IRB approval of this protocol by non-UC Davis institutions must be on file prior to registration of patients at these institutions.

C. Pre-study laboratory tests, scans, and x-rays, must be completed prior to registration, within the time frame specified in the protocol. The eligibility checklist must be completed. Patients must sign an informed consent prior to registration.

D. Patients may be registered up to 72 hours prior to treatment initiation. All pages of the signed consent, completed checklist and reports from all pre-study laboratory tests, scans and x-rays must be faxed to UC Davis OCR [redacted] or emailed to UCD in order to register the patient. These documents are to be redacted and "patient initials" or "a participating site subject identifier" will be written on the documents until the Study Subject ID is issued. The UC Davis Study Coordinator will review these documents and fax/email a registration confirmation within 24 hours.

   Reminder: Confirm eligibility for ancillary studies and willingness to participate at the same time as eligibility for the treatment study.

E. If the patient is to be registered the same day as the proposed treatment start date, the UC Davis Study Coordinator must be notified by fax 24 hours prior to proposed treatment start date that the site has a patient to register.

F. The Study Coordinator will verify that the patient is eligible, that pre-study tests have been completed, and that the forms are complete. The Study Coordinator will then register the patient and assign a patient accession number. The Study Coordinator will fax or email a registration confirmation including the patient accession number within 24 hours.

G. A patient failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, contact the coordinating site PI or Study Coordinator.

NOTE: Administration of study medication may not be initiated until the registration confirmation has been received.

Appendix 8: Molecular Correlative Sample Handling

Specimen Submission for Correlative Studies:
With the patient's consent, tissue and blood specimens will be submitted as outlined below.

Specimen Collection, Storage, Shipping and Submission Requirements

- **Archival tumor specimens**: If available, 1 - 2 paraffin-embedded tissue blocks containing formalin-fixed tumor or needle aspirate from time of diagnosis (or subsequent, but prior to therapy) should be submitted for evaluation of expression of or mutations in relevant molecular pathways. Paraffin blocks may be processed according to standard institutional protocols. If blocks are unavailable, 16 unstained slides are acceptable alternatives. If submitting slides, please include a single H&E stained slide that has been reviewed by a pathologist for adequacy. A copy of the corresponding Pathology Report should be submitted with all tumor specimens.

- **Blood specimens**: Blood will be collected from each patient prior to initiating treatment (baseline), prior to treatment on Cycle 1 Day 15, and when the patient is removed from study treatment. Each blood draw will consist of 3 x 10 ml, purple top K2 EDTA tubes

  Plasma & Buffy Coat:
  - Blood collected into one of the 10 ml K2 EDTA tubes should be inverted several times, and placed on wet ice until centrifugation. The tubes should be centrifuged as soon as possible at approximately 800 x g for 10 minutes. Plasma should be removed and transferred to a 15 ml conical tube. This tube will centrifuged a second time to pellet any remaining cellular debris. The second centrifugation should be done at 800 – 1500 (preferred) x g for 10 minutes. Resulting plasma is to be transferred in 500 µl aliquots in labeled cryotubes. Buffy coat cells should be separately removed and placed in labeled cryotubes. **All specimens must be labeled with protocol number, patient registration number, and date of specimen collection.** All tubes are then to be frozen and stored at or below -70°C.

  PBMC Isolation:
  - Blood collected into the remaining two 10 mL K2 EDTA tubes should be processed for viable PBMCs according to the Molecular Pharmacology Shared Resource (MPSR) SOP for PBMC Isolation from Whole Blood. Briefly, blood will be diluted with RPMI or PBS, layered over Ficoll, and spun at 400 x g for 30 minutes with no brake to separate PBMCs from RBCs. The PBMCs will be carefully collected and washed in PBS 2x and resuspended in RPMI for cell counting (using a Scepter automated counter). Cells will be stepwise frozen at about 1.0 e^7 in FBS/DMSO (10% final concentration of DMSO) using a Mr. Frosty freezing container. Frozen cells must be shipped to UC Davis within one week of collections so that they can be transferred to liquid Nitrogen for long-term storage. SOP will be emailed to participating sites upon request - see contact information in Appendix 9 (Specimen Submission Form).

  - **If participating sites are unable to process blood for PBMCs**, whole blood should be shipped directly to UC Davis Comprehensive Cancer Center via overnight courier for processing. Blood should be collected and shipped M-Th ONLY and notification of

shipment must be sent to processing lab. **See Appendix 9 (Specimen Submission Form) for shipping and contact information.**

- **Urine Specimen:** Urine will be collected from each patient prior to initiating treatment (baseline), prior to treatment on Cycle 1 Day 15, and when the patient is removed from study treatment. Approximately 10 mL of sample with be transferred to a 15 mL conical and centrifuged at 3000 x g for 5-10 minutes. Immediately after centrifugation, transfer 1.5 mL of urine to each cryovial, maximum of 5 cryovials. Cryovials must be labeled as above and stored at or below -70°C.

- **Shipping Instructions:** All archival paraffin block or slide specimens should be sent at ambient temperature. Frozen specimens should be shipped on **dry ice**. These should be shipped by overnight courier Monday through Wednesday only, according to the instructions in **Appendix 9**.

- **A Specimen Submission Form must be submitted with each specimen**. Institutions should notify the recipient by either phone or fax prior to shipping specimens. This will allow the recipient to track the package in the event that there are any problems in delivery.

The Federal Guidelines for Shipment are as follows (these periodically change, please check for the most current guidelines):

1. The specimen must be wrapped in an absorbable material
2. The specimen must then be placed in an AIRTIGHT container (resealable bag)
3. Pack the resealable bag and specimen in a styrofoam shipping container
4. Pack the styrofoam shipping container in a cardboard box
5. The cardboard box should be labeled "UN3373 Biological Substance, Category B" "BIOHAZARD"

Appendix 9: Submission Form

UCDCC#262 Blood Submission Form

Phase Ib/II trial of Ibrutinib plus Nivolumab in Patients with Previously-treated Metastatic RCC

Patient Information:

Patient Study ID# _____ **Pt Initials (FML):** _____

Timepoint: ☐ Baseline ☐ Cycle 1 Day 15 _____
☐ Early Removal ☐ Progression

Draw Date: _____ **Time of Draw:** _____

Shipper Contact Information:

Packaged by: _____ Phone #: _____ Email Address: _____

Specimen Collection and Processing Instructions:

Draw: 3 x 10 ml Purple EDTA Tube (BD# 366643)
*****Process tubes according to Appendix 8 instructions*****

If shipping JUST whole blood for PBMC isolation, ship at room temperature with a *room temperature cool pack* to protect sample from temperature fluctuations.

If shipping frozen PBMCs, plasma, buffy, and urine: Please ship on dry ice within one week of collection as the PBMCs must be transferred to liquid nitrogen to remain viable for immunoresponse assays.

If shipping JUST frozen plasma, buffy, and urine: If PBMCs were submitted to UCD as whole blood, and the only specimens on-site are plasma, buffy, and urine, frozen specimens should be batched on site and shipped on dry ice to UC Davis periodically (approximately quarterly).

Packaged Specimens should be shipped using **FedEx Priority Overnight to:**

Dr. Philip Mack, PhD / Anthony Martinez
UC Davis Comp. Cancer Center
[redacted]

Samples should be **shipped M-Th only**.

Notify receiving laboratory with sample and tracking information at the time of shipment.

Email: [redacted]

UC-Davis Correlative Lab Use Only

Lab Specimen #_____
Condition of Specimen:
☐ **Usable as received**
☐ **Usable, not optimal:** _____
☐ **Not usable, insufficient or incorrect**
☐ **Not usable, other:**_____

Date Received: ☐☐/☐☐/☐☐
Received/Logged By: _____
FedEx Tracking #: _____

Contact [redacted] **with questions**

Appendix 10: Child-Pugh Score

Measure	1 point	2 points	3 points
Total bilirubin, µmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/L (g/dL)	>35 (>3.5)	28-35 (2.8-3.5)	<28 (<2.8)
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5-6	A
7-9	B
10-15	C

Source:

1. Child CG, Turcotte JG. "Surgery and portal hypertension". In Child CG. *The liver and portal hypertension.* Philadelphia:Saunders. 1964. pp. 50-64.
2. Pugh RN, Murray-Lyon IM, Dawson L, Pietroni MC, Williams R . "Transection of te oesophagus for bleeding oesophageal varices". *The British journal of surgery*, 1973;60: 646-9.