UCSF Helen Diller Family Comprehensive Cancer Center

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A Study of the Safety, Immunopharmacodynamics and Anti-tumor Activity of Ibrutinib Combined with Gemcitabine and Nab-Paclitaxel in Patients with Metastatic Pancreatic Adenocarcinoma

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Protocol Signature Page

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1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Committee on Human Research (CHR), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable CHR requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
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Principal Investigator **Site**

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Abstract

Title	A Study of the Safety, Immunopharmacodynamics and Anti-tumor Activity of Ibrutinib Combined with Gemcitabine and Nab-Paclitaxel in Patients with Metastatic Pancreatic Adenocarcinoma
Patient population	Patients with previously untreated metastatic pancreatic adenocarcinoma
Rationale for Study	Gemcitabine and nab-paclitaxel is a standard regimen (NCCN, Category 1) for patients with metastatic pancreatic ductal adenocarcinoma (PDAC). However, further improvement in treatment is needed. Increasingly, the nature of the immune infiltrate in PDAC appears to be tumor promoting. In preclinical studies, ibrutinib treatment, presumably by reprogramming B cells, results in increased CD8+ T cells to assist in tumor control. Preclinical studies of ibrutinib plus gemcitabine show superior antitumor effects compared to gemcitabine alone in both orthotopic murine pancreatic cancer cell line grafts and in genetically engineered mouse models. Thus, we propose a clinical trial of ibrutinib plus the standard gemcitabine based regimen of gemcitabine and nab-paclitaxel, evaluating safety, then efficacy and including correlative studies.
Primary Objectives	Phase Ib: • To determine the maximum tolerated dose of ibrutinib in combination with albumin bound paclitaxel and gemcitabine in patients with metastatic pancreatic adenocarcinoma. Immune Response Study: • To monitor the changes in the patients' immune profiles during treatment with ibrutinib, alone and in combination with gemcitabine and nab-paclitaxel, in the pancreatic tumor micro-environment (TME) and in the peripheral blood. • To confirm the pharmacodynamics of ibrutinib at dosing level 560 mg/day • To explore the relationships between the pharmacodynamics of ibrutinib in combination with nab-paclitaxel and gemcitabine and response prediction biomarkers in patients with metastatic pancreatic adenocarcinoma.
Secondary Objectives	Phase Ib: • To evaluate the safety of treatment with ibrutinib in combination with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic adenocarcinoma. • To evaluate the potential drug-drug interaction of ibrutinib in combination with nab-Paclitaxel and gemcitabine in patients with metastatic pancreatic

	adenocarcinoma. • To clinically assess the anti-tumor effects of treatment with ibrutinib in combination with nab-Paclitaxel and gemcitabine. Immune Response Study: • To verify and confirm the safety of ibrutinib in combination with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic adenocarcinoma. • To estimate the CA19-9 clinical response rate of patients with metastatic pancreatic adenocarcinoma treated with ibrutinib in combination with nab-Paclitaxel and gemcitabine. • To estimate the Progression-Free Survival and Time-to-Progression and Overall survival of patients with metastatic pancreatic adenocarcinoma treated with ibrutinib in combination with nab-Paclitaxel and gemcitabine.
Study Design	This is a **phase open-label study**, designed to assess the safety and immunopharmicodynamics of ibrutinib in combination with the standard doses of gemcitabine and nab-paclitaxel for treating advanced pancreatic adenocarcinoma. **Phase Ib**: Patients will be enrolled in the 3+3 dose escalation cohort to assess the safety and tolerability of the combination therapy of ibrutinib, gemcitabine and nab-paclitaxel*. Dosing escalation will commence at the 560 mg/day dose, and if no DLT is identified in the first 3 patients, the next dosing cohort will receive ibrutinib at 840 mg/day. If a DLT is identified at 560 mg/day or at 840 mg/day, dose de-escalation will begin with dosing cohorts receiving 560 mg/day, 420 mg/day, and 280 mg/day as necessary. Grade 4 hematologic adverse events are expected based on prior experience with gemcitabine and nab-paclitaxel, and support with colony stimulating factor will be allowed. If no DLT is identified at 840 mg/day, then 840 mg/day will be considered the Maximum Tolerated Dose. **Immune Response Study**: Patients will begin treatment with a one-week run-in of 560 mg/day of ibrutinib only. Each patient will undergo two EUS-guided biopsies, at least 5 days before and at least 5 days after the one-week run-in of ibrutinib. Combination therapy with gemcitabine and nab-paclitaxel will begin no later than 3 days after the second biopsy, and treatment with ibrutinib will resume 5-7 days after biopsy. The tissue samples acquired through biopsy will be used to assess the pharmacodynamic relationship between treatment with ibrutinib alone and changes in the tumor microenvironment. Serial blood samples will be taken to monitor changes in circulating cytokines, to define the B and T cell receptor repertoires and the characteristics of circulating myeloid cells. Patients enrolled and treated in thephase Ib dose escalation and the Immune Response cohorts will continue to receive combination therapy until

	documented disease progression, unless discontinuing therapy for the following reasons: • Irreversible or intolerable toxicity or clinically significant abnormal laboratory values thought to be related to drug toxicity • Patient withdraws consent • Treatment-related toxicities that require a delay in scheduled dosing for ≥21 days* • Documented symptomatic deterioration defined as global or severe deterioration of health status such that it requires discontinuation of trial treatment without evidence of disease progression at that time. • Inability of the patient to comply with trial requirements or lost to follow-up • Conditions requiring a therapeutic intervention not permitted by the protocol • Intercurrent illness (this will be at the investigator's discretion) *In the event that a drug must be held for intolerability (ie neuropathy for nab-paclitaxel or rash for gemcitabine) for more than 21 days, patients may continue on study receiving the other drugs, including ibrutinib.
Number of patients	29-50
Duration of Therapy	*10 months*
Duration of Follow up	1 year
Duration of study	5 yrs
Study Drugs	Ibrutinib, in combination with gemcitabine and nab-paclitaxel Ibrutinib (IMBRUVICA®) will be supplied as 140 mg hard gelatin capsules for oral (PO) administration.
Inclusion Criteria	1. Histologically or cytologically confirmed pancreatic adenocarcinoma 2. Stage IV disease (measurable disease NOT required) 3. Intact primary tumor (for Immune Response Cohort only) 4. ECOG performance score of 0-1

	5. At least 18 years of age 6. Female patients who are not of child-bearing potential, and fertile female patients of child-bearing potential, who agree to use adequate contraceptive measures, who are not breastfeeding, and who have a negative serum or urine pregnancy test within 72 hours prior to start of randomization. 7. Fertile male patients willing to use adequate contraceptive measures. 8. Adequate bone marrow function: • Absolute neutrophil count (ANC) ≥ 1500/uL • Platelet count ≥ 100,000/uL • Hemoglobin ≥ 9.0 g/dL 9. Adequate hepatic function: • Total bilirubin ≤ 1.5 X ULN (unless bilirubin rise due to Gilbert's syndrome • AST ≤ 3.0 X ULN (≤5.0X ULN if liver metastases are present). • ALT ≤ 3.0 X ULN (≤5.0X ULN if liver metastases are present). 10. Adequate renal function (defined as serum creatinine ≤ 1.5 X ULN) 11. Ability to understand the nature of this study protocol, comply with study and/or follow-up procedures, and give written informed consent 12. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures. 13. The calculated QTcF average of the triplicate screening ECGs must be <470 msec.
Exclusion Criteria	1. Any prior systemic or investigational therapy for metastatic pancreatic cancer. Systemic therapy administered alone or in combination with radiation in the adjuvant or neoadjuvant setting is permissible as long as it was completed > 6 months prior to the time of study registration. 2. History of other diseases, metabolic dysfunction, physical examination findings, or clinical laboratory findings giving reasonable suspicion of a disease or condition that, in the opinion of the investigator, renders the subject at high risk from treatment complications or might affect the interpretation of the results of the study. 3. History of previous malignancy (except in-situ cancer or basal or squamous cell skin cancer) within past 3 years. 4. Life expectancy of <3 months.

	5. Inability to undergo two sequential EUS-directed core biopsies of the primary tumor (for Immune Response Cohort only). 6. Presence of known central nervous system or brain metastases. 7. Known human immunodeficiency virus (HIV) infection. 8. History of stroke or intracranial hemorrhage within 6 months prior to enrollment. 9. Known bleeding disorders (e.g., von Willebrand's disease or hemophilia). 10. Patients receiving warfarin or other Vitamin K antagonists. However, if therapeutic anticoagulation is necessary, LMWH is the anticoagulant of choice. 11. 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 randomization. 12. Current peripheral sensory neuropathy > Grade 1 13. Major surgery within 4 weeks of the start of study treatment (defined as those surgeries that require general anesthesia. Insertion of a vascular access device is NOT considered major surgery. 14. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor. 15. Unable to swallow capsules or has 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.

List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the curve
BUN	blood urea nitrogen
CA19-9	cancer antigen 19-9
CBC	complete blood cell (count)
Cmax	maximum drug concentration
CMP	comprehensive metabolic profile
CR	complete response
CRF	case report form
CT	computerized tomography
CTCs	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
D5W	dextrose 5% in water
DLT	dose limiting toxicity
DSMC	Data and Safety Monitoring Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IND	investigational new drug application
IRB	Institutional Review Board
IV	Intravenous
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NE	non-evaluable
OS	overall survival
PD	progressive disease
PR	partial response
PTT	partial thromboplastin time
RECIST	Response Evaluation Criteria in Solid Tumors
SD	stable disease

SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
ULN	upper limit of normal

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1 Introduction

1.1 Background Current Treatment of Advanced Pancreatic Adenocarcinoma

Pancreatic adenocarcinoma (PDAC) represents the fourth leading cause of cancer-related mortality in the United States, with an estimated 39,950 deaths attributable to PDAC in 2014 (http://seer.cancer.gov/statfacts/html/pancreas.html). Over 90% of patients have inoperable disease at presentation, at which point systemic therapy becomes the primary form of treatment.

Treating PDAC has been challenging and few approved drugs are available. Recently, however, some breakthroughs have occurred, raising hope that this aggressive disease can be better controlled. FOLFIRINOX, a combination of 5FU, oxaliplatin, and irinotecan, has been found to be substantially superior to treatment of gemcitabine alone in patients with metastatic disease and good performance status [1]. Similarly, gemcitabine and nab-paclitaxel, a regimen with less non-hematologic toxicity, demonstrated improved overall survival and progression-free survival compared to gemcitabine alone [2]. Both of these combinations or modifications of these combinations are now front line options for patients with good performance status. Furthermore, these improvements in survival, however incremental, now afford patients with pancreatic cancer time to participate in and possibly benefit from clinical trials of novel therapeutics.

1.2 Immunotherapy for Pancreatic Adenocarcinoma

Immunotherapy—recruiting a patient's immune system to recognize and destroy malignant cells and control their spread—has been an ideal pursued by clinical researchers for decades. However, there have been very few clinical successes in the treatment of solid tumors with immunotherapeutic agents such as tumor-specific (TSA) and tumor-associated antigen (TAA) vaccines, cytokines, interleukins and other immune-modulators. One explanation for the lack of success for patients with pancreatic cancer may be that global depression of the immune state is a characteristic of the disease—this is supported by reports of depressed or anergic immune responses to both common and tumor antigens in PDAC patients [3, 4]. And yet there have also been reports of pre-existing or natural functional tumor-reactive T cells in the peripheral blood and bone marrow of PDAC patients [5-7]. Furthermore, responses to tumor antigens, i.e.anti-TAA antibodies or TAA-reactive T-cells, have been detected in the peripheral blood of PDAC patients treated with tumor-derived vaccines, and in some cases these responses appear to correlate with better outcomes [8-10]. However, significant improvements in patient survival have yet to be confirmed in randomized well-controlled clinical trials.

It is now widely appreciated that the stromal environment of pancreatic tumors and other solid tumors is highly immune-suppressive relative to normal tissue. There is a greater density of the immune suppressive FOXP3+ regulatory T cells (Tregs) in the human pancreatic tumor infiltrate compared to normal pancreatic tissue [11-13]. While T cells comprise the majority of the tumor infiltrate, surprisingly, the most prevalent are CD8+ T cells of the antigen-experienced effector phenotype, capable of producing IFN-γ once removed from the influence of the regulatory factors of the tumor stroma [14]. The presence of FOXP3+Tregs as well as Th17 and myeloid-derived suppressor cells in the PDAC stroma [14] suggests that there are several immune suppressive mechanisms and checkpoints protecting pancreatic tumor cells from destruction. Checkpoint-directed therapies such as ipilimumab (CTLA-4) and nivolumab (PD-1) have been evaluated clinically and have shown activity in other solid tumors, but none have demonstrated efficacy in PDAC cohorts as single-agents [15, 16]. Making headway in the treatment of PDAC

will most likely require combination therapies with check-point inhibitors, vaccines and other agents designed to alter the immune program of the tumor-associated stroma [8, 17-19].

1.3 Rationale for Targeting Regulatory B Cells in Treating Pancreatic Cancer

Preliminary preclinical data indicate that B cells may play an important pro-tumor role in PDAC. It was previously reported that B cells promote squamous cell carcinogenesis (SCC) via Fcγ receptor-dependent activation of tumor-infiltrating myeloid cells, mediated by immunoglobulin (Ig)-containing immune complexes deposited in (pre)malignant tissue [20, 21]. More recently, the same model was used to evaluate this neoplastic cell-extrinsic pathway as an anti-cancer target using B-cell depleting αCD20 monoclonal antibodies. In prevention and intervention mouse models, neoplastic progression stopped at an early hyperplastic stage subsequent to B cell depletion [22].

The presence of B cell infiltration in human PDAC has been confirmed *ex vivo* (Coussens, et al.manuscript in preparation) (Figure 1*)*: tumor tissue analyzed by Affymetrix U133 Plus 2 microarrays and by immunohistochemical methods exhibited the molecular and histopathologic characteristics of B cell or plasma cell infiltration, i.e. increased expression of CD20 or Ig mRNA in tumor lysates, as well as a significantly increased presence of CD20-positive B cells in tumor relative to normal pancreas in tissue sections. Furthermore, the density of B cell infiltration significantly correlated with decreased overall survival.

Figure 1. Leukocytes in Human PDAC

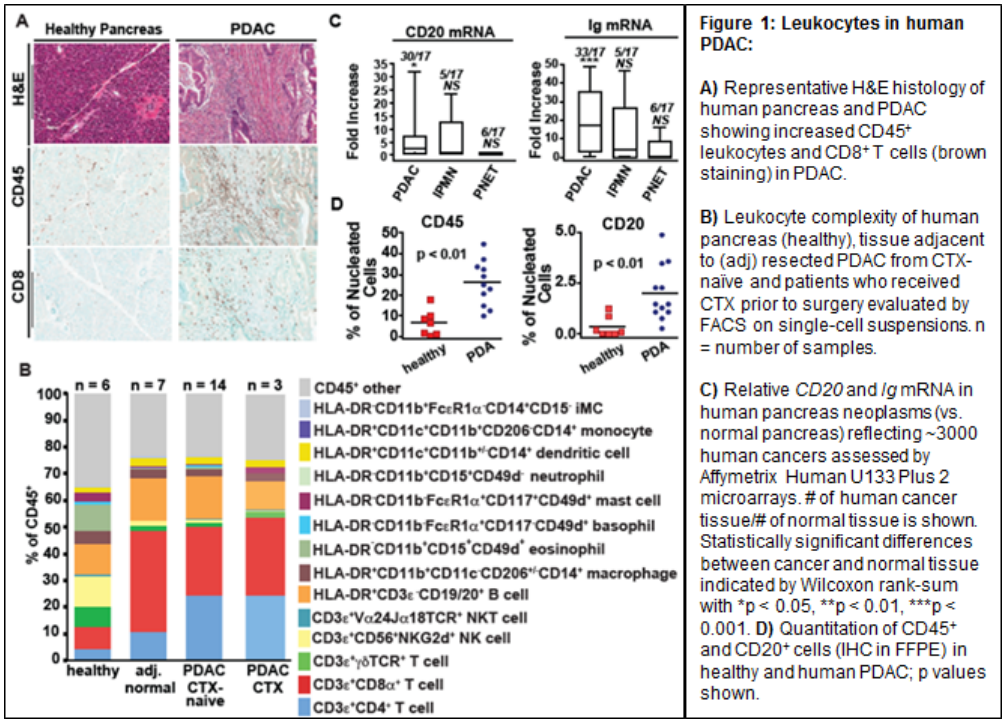


Figure 1: Leukocytes in human PDAC:

A) Representative H&E histology of human pancreas and PDAC showing increased CD45+ leukocytes and CD8+ T cells (brown staining) in PDAC.

B) Leukocyte complexity of human pancreas (healthy), tissue adjacent to (adj) resected PDAC from CTX-naïve and patients who received CTX prior to surgery evaluated by FACS on single-cell suspensions. n = number of samples.

C) Relative *CD20* and *Ig* mRNA in human pancreas neoplasms (vs. normal pancreas) reflecting ~3000 human cancers assessed by Affymetrix Human U133 Plus 2 microarrays. # of human cancer tissue/# of normal tissue is shown. Statistically significant differences between cancer and normal tissue indicated by Wilcoxon rank-sum with *p < 0.05, **p < 0.01, ***p < 0.001. **D)** Quantitation of CD45+ and CD20+ cells (IHC in FFPE) in healthy and human PDAC; p values shown.

To investigate the B-cell specific contribution to PDAC tumor growth *in vivo*, B cell- and/or FcγR-deficient mice were assessed for their ability to support growth of syngeneic orthotopic PDAC

(Figure 2). Growth of PDAC tumors in mice homozygous for FcγR deficiency was significantly attentuated compared to the the tumors in their wild-type and heterozygous littermates. Moreover, αCD20 mAb-mediated B cell depletion slowed growth of preexisting PDACs. Macrophages isolated from PDAC tumors of αCD20 mAb -treated mice displayed characteristics indicative of functional type 1 re-education, concomitant with an increased presence of CD8+ T cells (data not shown). These data indicate that B cells, and the downstream myeloid-based pathways they regulate, represent tractable targets for anti-cancer therapy, and suggest that the immune TME in susceptible solid tumors can be effectively re-educated to promote productive anti-tumor immune responses.

Figure 2. B cells and FcRγ regulate PDAC

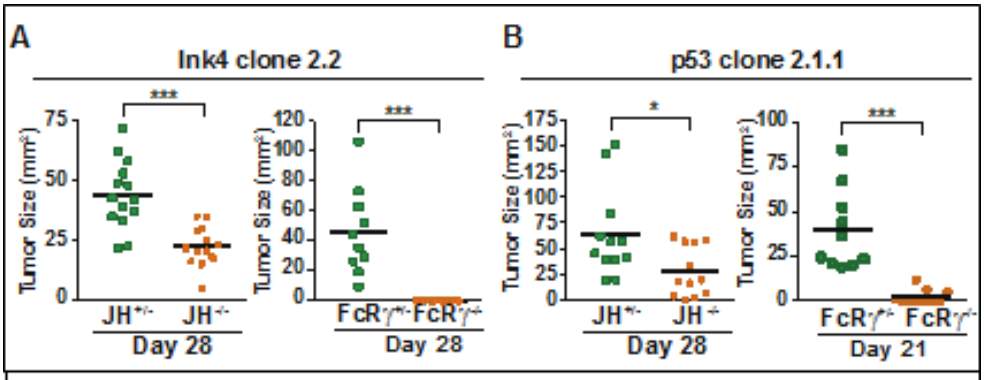


Figure 2. B cells and FcRg-regulate PDAC. End-stage orthotopic tumor growth from two PDAC cell lines injected into syngeneic $JH^{+/-}$, $JH^{-/-}$, $FcgR^{+/-}$ or $^{-/-}$ mice. * p < 0.05, ** < 0.01, *** < 0.001

1.4 Rationale for Targeting Bruton's Tyrosine Kinase with Ibrutinib to Alter TME of PDA

Normal and malignant B cells are dependent on functional Bruton's tyrosine kinase (Btk) for activation, maturation and survival. Coussins et al evaluated the presence of active Btk (pBtk) in immune cells infiltrating orthotopic murine PDAC tumors by flow cytometry, and immunohistochemically in human PDAC tissue sections (Figure 3A and B). Results from these studies indicate that pBtk is present in B cells and myeloid cells of murine and human PDAC. Based on these results, mice harboring syngeneic orthotopic PDAC at late-stage were treated with an FDA-approved BTK inhibitor (BTKi) (PCI-32765, ibrutinib) as monotherapy and in combination with gemcitabine, which resulted in significant reductions in tumor burden at end stage (Fig. 3C). Moreover, treatment of KPC transgenic mice predisposed to *de novo* pancreatic carcinogenesis with ibrutinib plus gemcitabine lead to significantly improved OS as compared to gemcitabine alone (Fig. 3D). By using a $CD8^+$ T cell-depleting mAb, it was revealed that improved outcomes of mice treated with ibrutinib/gemcitabine are dependent on $CD8^+$ T cells (Fig. 3E).

Figure 3. Btk as a therapeutic target in PDAC

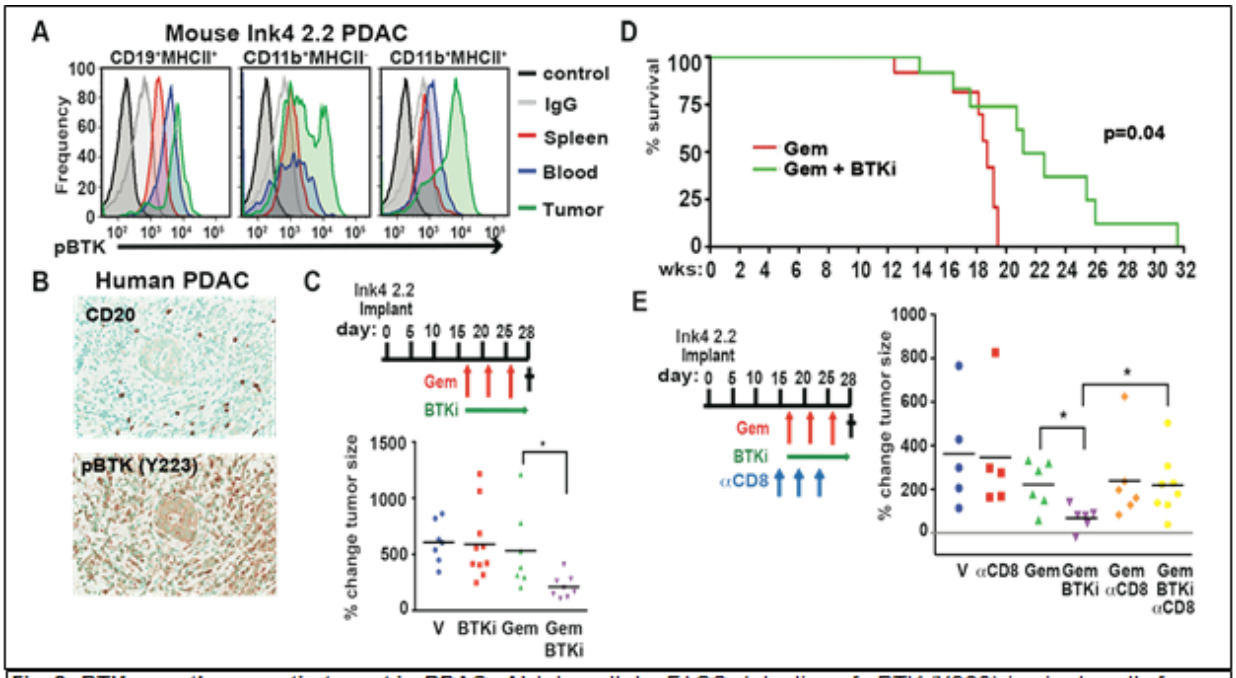


Fig 3: BTK as a therapeutic target in PDAC: A) Intracellular FACS detection of pBTK (Y223) in single cells from peripheral blood, spleen, and orthotopic PDAC, gated on $CD19^+MHCII^+$ B cells, $CD11b^+MHCII^-$ or $CD11b^+MHCII^+$ myeloid cells. Also shown are unstained and IgG control-stained cells. **B)** Immune-detection of $CD20^+$ B vs. $pBTK^+$ cells in adjacent serial sections of human PDAC. **C)** % change in tumor size measured by ultrasound following treatment as depicted. * $p < 0.05$. **D)** KPC transgenic mice aged to 8 wks then given oral ibrutinib (25 mg/day) or Gem (76 mg/kg, i.v., biw 3q) until all mice (8-9 per group) were out of study. p value by Log rank (data courtesy of L. Soucek). **E)** Similar study as shown in C with addition of CD8 T cell-depleting mAb. * $p < 0.05$.

Inhibition of Btk has additional immune effects which have the potential to translate into anti-tumor activity. Btk plays a critical role in inducible degranulation of Mast Cells [23], a process which has been shown to promote stromal changes that contribute to neoplastic transformation and tumor neoangiogenesis [24]. Systemic treatment with ibrutinib blocks mast cell degranulation *in vivo*, triggering collapse of tumor vasculature as well as tumor regression in insulinoma-bearing mice [24]. In another preclinical model (Massó-Vallés, et al, submitted manuscript), pancreatic ductal adenocarcinoma (PDAC)-bearing mice treated with Ibrutinib survived longer and presented with reduced tumor stroma, suggesting that targeting Mast Cells in patients with pancreatic cancer may positively alter the stromal architecture that protects and supports the growth of tumor tissue.

Ibrutinib also targets structural homologues of Btk, and has been shown to irreversibly bind and inhibit interleukin 2-inducible T cell kinase (ITK)[25]. Activated ITK is implicated in maintaining dysregulated Th2-biased immunosuppression of T cell-mediated anti-tumor responses. Inhibition with ibrutinib selectively reversed Th2 bias to favor activation of Th1 t cells, further augmenting the immunotherapeutic effect.

1.5 Rationale of Combining Ibrutinib with Gemcitabine and nab-Paclitaxel

Gemicitabine plus nab-paclitaxel is currently one of the two standard 1st line treatments for PDAC, and is regarded as a less toxic and more tolerable regimen than the combination

chemotherapy FOLFIRINOX. Clinically, gemcitabine may be the chemotherapeutic of choice for combination with immunotherapeutics: Treating PDAC patients with single agent gemcitabine does not appear to significantly alter the absolute number of functional CD8 and CD4 T cells, B cells or dendritic precursors in the peripheral blood, although a decrease in the number of memory T-cells and an increase in naïve T-cell activation was observed [26] and; treatment with gemcitabine-based therapies was reported to significantly decrease both the percentage and number of Tregs in the peripheral blood while having no effect on the number and function of other immune cells[27] [28]. Adding nab-paclitaxel to gemcitabine significantly extends survival, providing PDAC patients much needed time to mount effective anti-tumor responses, and pre-clinical studies suggest that nab-paclitaxel may accelerate depletion of the PDAC tumor stroma which supports tumor growth and immune tolerance [29]. The ability of Btk inhibitors to reprogram B cells and to block activation of signaling pathways downstream of Btk in both B cells and myeloid cells suggests that combining ibrutinib with gemcitabine and nab-paclitaxel to treat patients with PDAC may promote an anti-tumor immune response in the clinical setting.

1.6 Ibrutinib

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 US Food and Drug Administration (FDA) for the treatment of : 1) mantle cell lymphoma (MCL) in patients who have received at least one prior therapy, 2) chronic lymphocytic leukemia (CLL) , and 3) Waldenström's Macroglobulinemia.. 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 [30].

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 [31]. 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 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 [32].

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.

1.7 Summary of Non-Clinical Data

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

1.7.1 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 (IC50 = 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 (IC50 = 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. For additional information, see FDA's Guidance Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories and CTEP's Guidelines for Correlative Studies in Clinical Trials. 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 560 mg daily, respectively.

1.7.2 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.

1.8 Summary of Clinical Data

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

1.8.1 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 (t1/2) of ibrutinib across 3 clinical studies ranged from 4 to 9 hours, with a median time to maximum plasma concentration (Tmax) of 2 hours. Taking into account the approximate doubling in mean systemic exposure when dosed with food and the favorable safety profile, ibrutinib can be dosed with or without food. Ibrutinib is extensively metabolized primarily by cytochrome P450 (CYP) 3A4. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure. Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) >30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. A higher proportion of Grade 3 or higher adverse reactions were reported in patients with B-cell malignancies (CLL, MCL and WM) with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function.

1.8.2 Summary of Clinical Studies Evaluating the Safety and Efficacy of Ibrutinib

A brief summary of safety data from monotherapy and combination therapy studies is provided in below. For more comprehensive safety information please refer to the current version of the IB. Additional safety information may be available for approved indications in regional prescribing labels where the study is conducted (eg, USPI, SmPC).

1.8.2.1 Monotherapy Studies

Pooled safety data for a total of 1071 subjects treated with ibrutinib monotherapy from 9 studies in B-cell malignancies, which includes subjects from 2 randomized-control studies who crossed over from comparator treatment or placebo to receive ibrutinib monotherapy, are summarized below.

Most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1071):

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >2%	Most frequently reported Serious TEAEs >1%
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Anemia	Hypertension	
Pyrexia	Atrial fibrillation	
Neutropenia		

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

1.8.2.2 Combination Therapy Studies

Pooled safety data for a total of 423 subjects treated with various therapies in combination with ibrutinib from 4 studies conducted in B-cell malignancies, which included 1 randomized-control study, are summarized below. Therapies used in combination with ibrutinib in these studies, included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

Most frequently reported TEAEs in subjects receiving ibrutinib in combination therapy (N=423):

Most frequently reported TEAEs >10%	Most frequently reported Grade 3 or 4 TEAEs >2%	Most frequently reported Serious TEAEs >1%
Neutropenia	Neutropenia	Febrile neutropenia
Diarrhea	Thrombocytopenia	Pneumonia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Hypertension	

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

1.8.3 Treatment Discontinuations

As of 6 April 2013, 71/636 subjects discontinued treatment due to an adverse event, across the monotherapy and combination therapy ibrutinib studies (excluding Study PCYC-1103-CA); 62 subjects receiving monotherapy population and 9 subjects receiving combination therapy. The

most frequently reported adverse events that led to treatment discontinuations were pneumonia (13 subjects), respiratory failure (4 subjects), and cardiac arrest and Richter's Syndrome (3 subjects each).

1.8.4 Bleeding-related events

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, 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.

1.8.5 Cardiac

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 with a history of cardiac arrhythmias should be monitored closely.

1.8.6 Rash

Mild to moderate rashes have been observed with ibrutinib alone or in combination with other drugs. A single case of Stevens-Johnson Syndrome (SJS) was reported in a male subject with CLL treated with ibrutinib 420 mg/day. The subject was also receiving multiple concomitant medications known to be associated with SJS. Subjects should be monitored closely for signs and symptoms suggestive of SJS.

1.8.7 Non-Melanoma Skin Cancer

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

1.8.8 Infections

Fatal and non-fatal infections have occurred with ibrutinib therapy. At least 25% of subjects with MCL and 35% of subjects with CLL had Grade 3 or greater infections per NCI Common Terminology Criteria for Adverse Events (CTCAE v4.02). The most commonly reported infections include pneumonia, cellulitis, urinary tract infection and sepsis. Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in patients treated with ibrutinib.

1.8.9 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib.

1.8.10 Diarrhea

Diarrhea is the most frequently reported non-hematologic 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.

1.8.11 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.

1.8.12 Ongoing Combination Clinical Studies in Solid Tumors*

Three sponsored clinical trials of ibrutinib in are reported in the 2016 Ibrutinib Investigator's Brochure (version 10, 29 August 2016*). Included in the listing below is a phase 2/3, randomized, placebo-controlled, study of ibrutinib or placebo in combination with nab-paclitaxel and gemcitabine in 1st line treatment of metastatic pancreatic adenocarcinoma. The safety run-in of 6 subjects at the 560 mg/day dose was completed without DLTs. As of August 2016, at least 100 subjects have been randomized to receive either ibrutinib or placebo with nab-paclitaxel and gemcitabine.

Study Number	Description	Number of Subjects Planned/Exposed[a]	Study Drug(s); Dose Regimen; Duration of Treatment	Enrollment/Study Status[b]
Solid Tumors				
1135	Phase 1b/2, open-label study of the safety and efficacy ibrutinib + MEDI4736 in subjects with solid tumors.	Phase 1b: 6-36/6 Phase 2: 130/111	ibrutinib capsules (oral) Cohort 1: 560 mg or 420 mg daily in combination with MEDI4736 at 10 or 3 mg/kg IV q2 weeks in 28-day cycles until DLT or disease progression	Enrolling/Ongoing
1137	Phase 2/3, double-blind, randomized, placebo-controlled, study of ibrutinib in combination with nab-paclitaxel and gemcitabine versus placebo in combination with nab-paclitaxel and gemcitabine, in the first line treatment of patients with metastatic pancreatic adenocarcinoma	326/106	Arm A Ibrutinib (PO) 560 mg daily (4 capsules) until PD or unacceptable toxicity in combination with: Nab-paclitaxel (IV) 125 mg/m2 and gemcitabine (IV) 1000 mg/m2 given on Days 1, 8, and 15 of each 28-day cycle, until evidence of progressive disease (PD) or is no longer tolerated by the subject. Arm B Placebo (PO) 4 matched capsules until PD or unacceptable toxicity in combination with: Nab-paclitaxel (IV) 125 mg/m2 and gemcitabine (IV) 1000 mg/m2 given on Days 1, 8, and 15 of each 28-day cycle, until evidence of PD or is no longer tolerated by the subject.	Enrolling/Ongoing

Study Number	Description	Number of Subjects Planned/Exposed[a]	Study Drug(s); Dose Regimen; Duration of Treatment	Enrollment/Study Status[b]
1128	A Phase 1b/2 Study of Ibrutinib Combination Therapy in Selected Advanced Gastrointestinal and Genitourinary Tumors	189/3	Phase 2 - recommended Phase 2 Dose established in Phase 1b for ibrutinib (840 mg, 700 mg, or 560 mg) PO daily, in combination with specified anticancer agent, will be given in 21-day cycles until disease progression or unacceptable toxicity. Anticancer agents: RCC - everolimus:10 mg PO qd Urethelial - paclitaxel:80 mg/m2 IV qweek Gastric - docetaxel:75 mg/m2 IV q3weeks CRC - cetuximab:400 mg/m2 IV, then 250 mg/m2 qweek	Enrolling/Ongoing

2 Objectives of the Study

2.1 Phase Ib

Primary Objective:

- To determine the maximum tolerated dose of ibrutinib in combination with albumin bound paclitaxel and gemcitabine in patients with metastatic pancreatic adenocarcinoma

Secondary Objectives:

- To evaluate the safety of treatment with ibrutinib in combination with nab-Paclitaxel and gemcitabine in patients with metastatic pancreatic adenocarcinoma.
- To evaluate the potential drug-drug interaction of ibrutinib in combination with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic adenocarcinoma.
- To clinically assess the anti-tumor effects of treatment with ibrutinib in combination with nab-Paclitaxel and gemcitabine.

2.2 Immune Response Cohort

Primary Objectives:

- To monitor the changes in the patients' immune profiles during treatment with ibrutinib, alone and in combination with gemcitabine and nab-paclitaxel, in the pancreatic tumor micro-environment (TME) and in the peripheral blood.
- To confirm the pharmacodynamics of ibrutinib at dosing level 560 mg/day
- To explore the relationships between the pharmcodynamics of ibrutinib in combination with nab-paclitaxel and gemcitabine and response prediction biomarkers in patients with metastatic pancreatic adenocarcinoma.

Secondary Objectives:

- To verify and confirm the safety of ibrutinib in combination with nab-Paclitaxel and gemcitabine in patients with metastatic pancreatic adenocarcinoma.
- To estimate the CA19-9 clinical response rate of patients with metastatic pancreatic adenocarcinoma treated with ibrutinib in combination with nab-Paclitaxel and gemcitabine.
- To estimate the Progression-Free Survival (PFS),Time-to-Progression (TTP), and Overall Survival (OS) of patients with metastatic pancreatic adenocarcinoma.treated with ibrutinib in combination with nab-paclitaxel and gemcitabine.

2.3 Exploratory Objectives, Other Assessments

Immunologic studies will explore immune responses in the peripheral blood and the PDAC tumor micro-environment (TME).

Table 1. Acquisition of Specimens and Analytical Procedures for Immunologic Studies

Timepoint	Specimen	Analyses
At Baseline and after 1 wk run-in Ibrutinib-only for Immune Response cohort only.	EUS guided biopsy tissue	Qualitative immunohistological assessment of immune cell subsets, i.e, T effectors, Tregs, NK cells, myeloid subsets, B cells; Expression of immune checkpoint targets such as PD-1 and PD-L1, and $CD40^{+}$ cells; distribution of Btk and p-Btk.
Baseline, monthly for the first 3 cycles, then every 3 months	EDTA Plasma	Blood based biomarkers quantified by Luminex technology for changes in 30 cytokines over time; Assessment of cell-free DNA
Baseline, monthly for the first 3 cycles, then every 3 months	PBMC	Flow cytometry-based immune phenotyping and quantification; Functional T-Cell responses to mitogens and candidate tumor antigens (tetramer analysis); Deep sequencing to detect specific T cell and B-cell receptor clones; Quantitative evaluation of gene and/or protein expression patterns of peripheral blood myeloid cells.

3 Study Design

3.1 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed

about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.1.1 Inclusion Criteria

1. Histologically or cytologically confirmed pancreatic adenocarcinoma

2. Stage IV disease (measurable disease NOT required)

3. Intact primary tumor (for Immune Response Cohort only)

4. ECOG performance score of 0-1

5. At least 18 years of age

6. Female patients who are not of child-bearing potential, and fertile female patients of child-bearing potential who agree to use adequate contraceptive measures, who are not breastfeeding, and who have a negative serum or urine pregnancy test within 72 hours prior to start of randomization.

7. Fertile male patients willing to use adequate contraceptive measures.

8. Adequate bone marrow function:

   - Absolute neutrophil count (ANC) ≥ 1500/uL
   - platelet count ≥ 100,000/uL
   - hemoglobin ≥ 9.0 g/dL

9. Adequate hepatic function:

   - Total bilirubin ≤ 1.5 X ULN (unless bilirubin rise due to Gilbert's syndrome)
   - AST ≤ 3.0 X ULN (≤5.0X ULN if liver metastases are present.)
   - ALT ≤ 3.0 X ULN (≤5.0X ULN if liver metastases are present.)

10. Adequate renal function (defined as serum creatinine ≤ 1.5 X ULN)

11. Ability to understand the nature of this study protocol, comply with study and/or follow-up procedures, and give written informed consent

12. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.

13. The calculated QTcF average of the triplicate ECGs must be <470 msec.

3.1.2 Exclusion Criteria

1. Any prior systemic or investigational therapy for metastatic pancreatic cancer. Systemic therapy administered alone or in combination with radiation in the adjuvant or neoadjuvant setting is permissible as long as it was completed > 6 months prior to the time of study registration.
2. History of other diseases, metabolic dysfunction, physical examination findings, or clinical laboratory findings giving reasonable suspicion of a disease or condition that, in the opinion of the investigator, renders the subject at high risk from treatment complications or might affect the interpretation of the results of the study.
3. History of previous malignancy (except in-situ cancer or basal or squamous cell skin cancer) within past 3 years.
4. Life expectancy of <3 months.
5. Inability to undergo two sequential EUS-directed core biopsies of the primary tumor (for Immune Response Cohort only).
6. Presence of known central nervous system or brain metastases.
7. Known human immunodeficiency virus (HIV) infection.
8. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
9. Known bleeding disorders (e.g., van Willebrand's disease or hemophilia).
10. Patients receiving warfarin or other Vitamin K antagonists. However, if therapeutic anticoagulation is necessary, LMWH is the anticoagulant of choice.
11. 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 randomization.
12. Current peripheral sensory neuropathy > Grade 1
13. Major surgery within 4 weeks of the start of study treatment (defined as those surgeries that require general anesthesia. Insertion of a vascular access device is NOT considered major surgery.
14. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor.
15. Unable to swallow capsules or has 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.

3.1.3 Duration of and Discontinuation from Protocol Therapy

Patients will be treated until disease progression, or will be discontinued from protocol treatment for any of the following reasons:

- Documented disease progression

- Irreversible or intolerable toxicity or clinically significant abnormal laboratory values thought to be related to drug toxicity (per section 6.2)
- Patient requests to withdraw from the trial or discontinue treatment
- Treatment-related toxicities that require a delay in scheduled dosing for ≥21 days*
- Documented symptomatic deterioration defined as global or severe deterioration of health status such that it requires discontinuation of trial treatment without evidence of disease progression at that time.
- Inability of the patient to comply with trial requirements or lost to follow-up
- Conditions requiring a therapeutic intervention not permitted by the protocol
- Intercurrent illness (this will be at the investigator's discretion)

*In the event that a drug must be held for intolerability (ie neuropathy for nab-paclitaxel or rash for gemcitabine) for more than 21 days, patients may continue on study receiving the other drugs, including ibrutinib.

After discontinuation from protocol treatment, patients must be followed for AEs for 30 calendar days after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patients' medical records and as a comment on the Case Report Form (CRF).

All patients who have Grade 3 or 4 laboratory abnormalities (Common Terminology Criteria for Adverse Events [CTCAE] v 4.03) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the investigator, not likely that these values are to improve. In this case, the investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment on the CRF.

3.1.4 Pregnancy

During the course of the study, all female patients of childbearing potential (the definitions of "women of childbearing potential" are listed in Appendix 3) must contact the treating investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period).

If an investigator suspects that a patient may be pregnant prior to administration of study drug(s), the study drug(s) must be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the patient must not receive any study drug(s), and must be discontinued from the study.

If an investigator suspects that a patient may be pregnant after the patient has been receiving study drug(s), the study drug(s) must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the study drug(s) must be immediately and permanently stopped, the patient must be discontinued from the study, and the investigator must notify. If a patient becomes pregnant while enrolled in the study, a Pregnancy Form (a

paper report form) should be completed. For more details regarding handling and reporting of pregnancies that occur during treatment, see Section 11.4.

4 Trial Registration

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks and discomforts. Human protection committee approval of this protocol and consent form is required.

5 Treatment Plan

This is a phase Ib/Immune Response study of ibrutinib in combination with nab-paclitaxel and gemcitabine in the management of patients with metastatic pancreatic adenocarcinoma.

The objective of the phase Ib is to confirm the safety and toxicity of the combination of gemcitabine, nab-paclitaxel and ibrutinib in the management of patients with metastatic pancreatic adenocarcinoma. In the first part of phase Ib, 15-30 patients will be enrolled in 3+3 dose escalation cohorts to evaluate the safety of up to four doses of ibrutinib (280 mg, 420 mg, 560 mg, and 840 mg QD), doses previously shown to be safe in healthy subjects and safe and effective in the management of patients with CLL and MCL. The first dosing cohort of 3 patients will receive 560 mg QD of ibrutinib in combination with gemcitabine and nab-paclitaxel. Dose escalation will proceed to 840 mg QD unless a dose limiting toxicity is identified, in which case 3 additional patients will receive 560 mg QD. If 2 or more of 6 patients experience a DLT at 560 mg QD, dosing will de-escalate to 420, and to 280 mg QD if necessary. The dose level at which fewer than 2 of 6 patients experience a DLT will be designated as the Maximum Tolerated Dose (MTD).

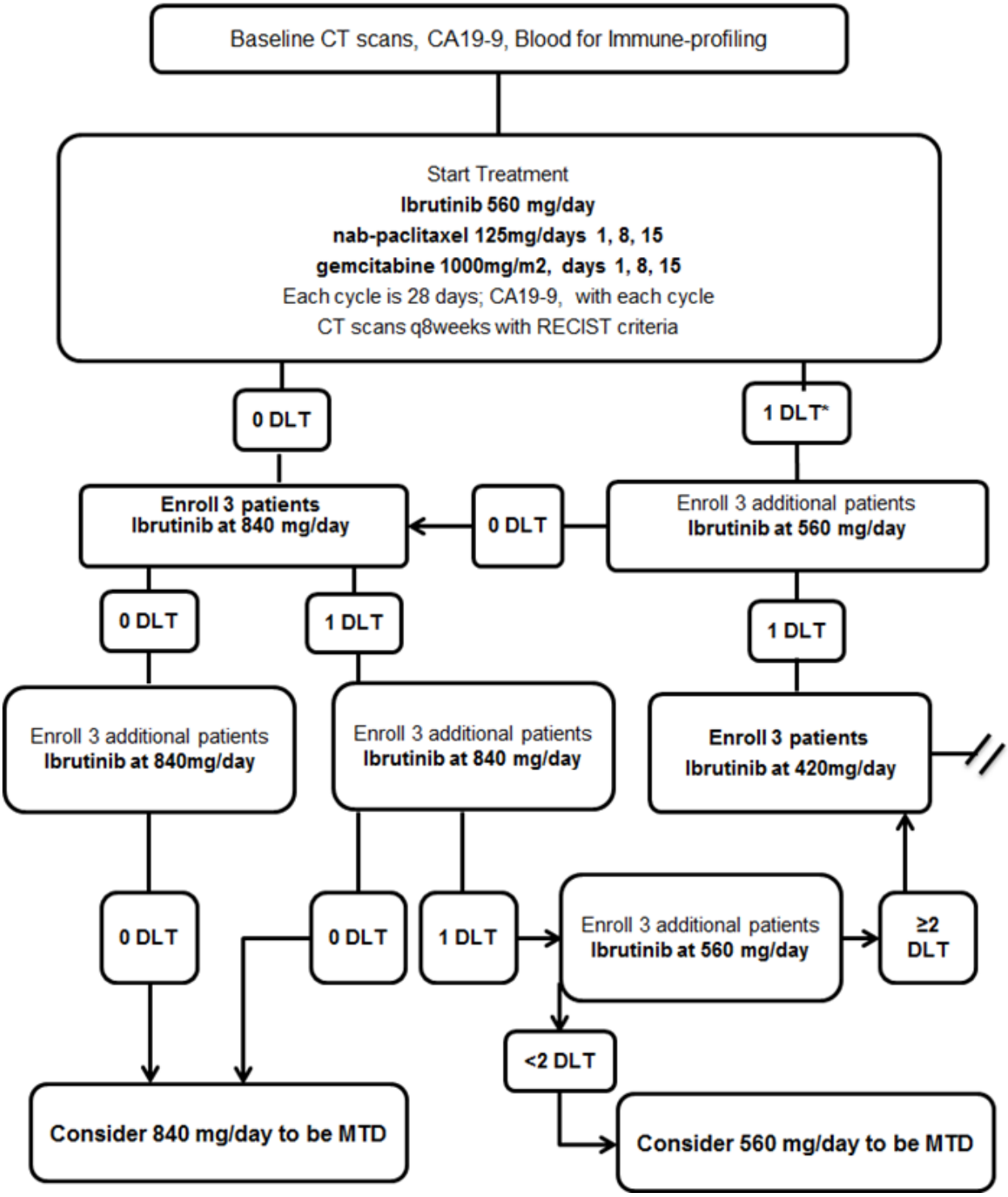
All patients in phase Ib will start treatment with daily dosing of ibrutinib concurrently with standard doses of gemcitabine and nab-paclitaxel. A cycle is defined as 28 days. Ibrutinib (560 mg/day, 840 mg/day, or 420 and 280 mg/day if de-escalation is necessary) will be started on day 1. Gemcitabine (1000 mg/m2) and nab-paclitaxel (125 mg/m2) will be given day 1, 8 and 15 of each cycle. Since grade 4 hematologic adverse events are expected based on prior experience with gemcitabine and nab-paclitaxel, and support with colony stimulating factor will be allowed.

Once the safety of the combination therapy is verified at the MTD, 20 patients will be enrolled in into the Immune Response Study. The objectives of the Immune Response Study are to assess the immunologic responses to and pharmacodynamics effects of pretreatment with ibrutinib alone. To address these objectives, the 20 patients will be enrolled, and will undergo two EUS-guided biopsies, one before and one after one week of treatment with ibrutinib-only, after which the patients begin the combination treatment regimen. Patients in the Immune Response study will be treated with 560 mg/day, unless 420 mg/day or 280 mg/day ibrutinib is determined to be the MTD in phase Ib.

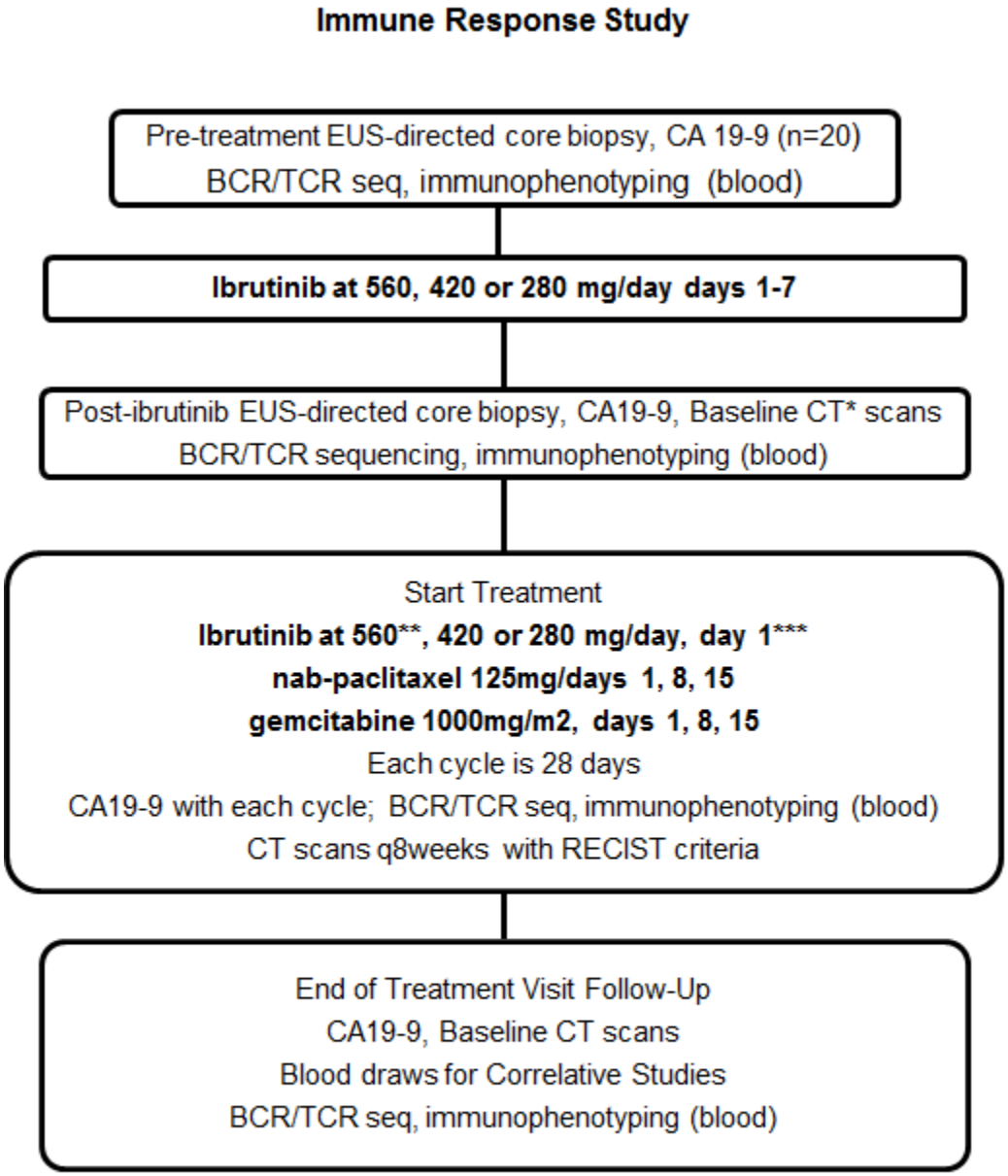
In both study phases and treatment cohorts, treatment effect will be monitored every 28 days by clinical exam and CA 19-9. CT scans will be performed every other 28 day cycle and tumor measurements will be assessed using standard RECIST criteria. Patients will continue on treatment until clinical or radiographic evidence of disease progression or until tolerance to treatment has been exceeded.

5.1 Study Schema

Phase Ib: Safety and Toxicity



5.1 Study Schema (cont'd)



***Non-hematologic DLT**
****560 mg/day unless 420 or 280 mg/day determined to be MTD**
*****Ibrutinib to start 5-7 days after post-run in biopsy.**

5.2 Dosage and administration of Ibrutinib

Treatment will be administered on an outpatient basis.

Table 2. Dose Escalation Schedule*

Dose Level	Dose of Study Drug	Minimum Number of Patients
1	560 mg/d	3
2	840 mg/d	6

*Daily dosing in combination with nab-Paclitaxel at 125mg/m^2 and Gemcitabine at 1000mg/m^2 IV on day 1, 8, and 15. If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day.

5.2.1 Phase Ib Dose escalation

No more than two dose levels of ibrutinib will be evaluated in dose escalation. If a DLT is identified at the 840 mg/d level, then 3 more patients will receive ibrutinib at the 560 mg/d dose to confirm that dosage as the maximum tolerated dose.

Patients within a given dose cohort may be enrolled concurrently given the well-established safety profile of ibrutinib and non-overlapping toxicities with chemotherapy. Although the safety profile of gemcitabine/nab-paclitaxel plus ibrutinib (560 mg daily) has been established on a separate, currently enrolling, company-sponsored phase II/III trial of this combination in pancreatic cancer, the patients in the 840 mg/day dose cohort cannot be enrolled until the DSMC has completed the monitoring of the 560 mg/day cohort dose level patients and there is DSMC Chair approval for dose escalation to the next dose level (840 mg/day).

If DLT is identified at the 560 mg/d dose level (2 or more DLTs out of 6 patients dosed), a dosing de-escalation will begin at the 420 mg/d dose. The lowest acceptable dose level is 280 mg/d.

5.2.2 Dose Limiting Toxicity

(DLT) will be defined as any unexpected grade 3 non-hematologic toxicity not reversible to grade 2 or less within 96 hours, or any grade 4 toxicity. Grade 4 hematological toxicities will not be considered dose limiting in this trial since a significant fraction of patients who are treated with gemcitabine and nab-paclitaxel are expected to experience these toxicities. Likewise, grade 3 peripheral neuropathy, a common and expected toxicity of treatment with nab-paclitaxel, will not be considered a DLT. DLT will be based on the first course of treatment.

Toxicity will be graded according to the NCI CTCAE version 4.03. To be evaluable for toxicity, a patient must receive at least one dose of any component of study therapy (ibrutinib, gemcitabine, or nab-paclitaxel). All patients enrolled are to be fully followed for DLT, and any patients who are not evaluable for toxicity will be replaced.

The maximum tolerated dose of ibrutinib will be that dose at which fewer than one-third of patients experience a dose limiting toxicity. If multiple toxicities are seen, the presence of dose limiting toxicity should be based on the most severe toxicity experienced.

5.2.3 Combination Therapy for Phase Ib and Immune Response cohorts

All patients in the Phase Ib safety and dose expansion and in Immune Response Study will received ibrutinib with nab-paclitaxel and gemcitabine in cycles of approximately 28 days in length. Nab-paclitaxel and gemcitabine are administered intravenously on days 1, 8 and 15 of each cycle.

Table 3. Dose, Route and Schedule for Combination Therapy

Study Drug	Dose	Route	Schedule	Cycle Length
Ibrutinib	560, 840, 420, or 280 mg	Oral	Continuous daily dosing	4 weeks (28 days)
Nab-Paclitaxel	125 mg/m^2	Intravenous	Days 1, 8, and 15	
Gemcitabine	1000 mg/m2	Intravenous	Days 1, 8, and 15	

5.2.4 One week run-in with Ibrutinib-only for the Immune Responses Study Cohort

Ibrutinib will be taken orally once per day during a 7 day run-in. Due to increased risk of bleeding when taking ibrutinib, Day 1 of the run-in will begin no earlier than 5 days after the pretreatment biopsy. Likewise, the post-run-in biopsy should be performed no earlier than 5 days after the last dose of the 7 day run-in treatment period. First infusions of gemcitabine and nab-paclitaxel may commence within 1-5 days after the post-run-in biopsy, but ibrutinib must be held until 5-7 days post-biopsy.

5.3 Study Treatment phase

Each treatment cycle generally is 28 days in length. Treatment may be administered +/-2 days of the scheduled date without constituting a protocol violation. Following the 1 week run-in with ibrutinib in the Immune Response cohort, the combination therapy treatment cycles will begin no earlier than 5 days after the 2nd biopsy, in 28-day cycles.

Treatment may be administered +/-2 days of the scheduled date without constituting a protocol violation. Ibrutinib is taken once daily; Nab-paclitaxel and gemcitabine are administered on Day 1, 8, and 15 of each cycle. Patients will continue 28 day treatment cycles until disease progression or until other reasons for discontinuation from treatment.

Ibrutinib: 560, 840, 420, or 280 or mg, orally once per day:

All doses of ibrutinib will be supplied by Pharmacyclics and dispensed by the Investigational Pharmacist or designee, and self-administered on an outpatient basis. Each dose should be taken with approximately 8 ounces of water at the same time each day.

Nab-Paclitaxel: 125mg/m^2 IV Day 1, 8, and 15:

Infuse over approximately 30-40 minutes or according to institutional standards.

Gemcitabine: 1000mg/m^2 IV Day 1, 8, and 15:

Infuse over approximately 30 minutes or according to institutional standards within following the completion of the nab-paclitaxel.

5.4 Restaging During the Combination Therapy Treatment Phase

Restaging by CT scans per RECIST version 1.1 (see Appendix 4) will occur every 2 cycles.

5.5 Assessments for Exploratory Endpoints

Immunologic studies will explore immune responses in the peripheral blood and the PDAC tumor micro-environment (TME). The biopsy specimen, blood and serum samples will be collected at baseline and various key times during the course of treatment will be evaluated. Peripheral blood lymphocytes at each pre- and post each vaccination time-points will be collected and analyzed at USCF, OHSU, and UCSD.

Biopsy analyses will include: qualitative assessment of immune cell subsets such as T effectors, Tregs, NK cells, myeloid subsets, B cells and expression of immune checkpoint targets such as PD-1 and PD-L1, and CD40+ cells.

Blood-based biomarkers, and serum will be analyzed by Luminex technology for changes in 30 cytokines over time. Quantitative and avidity evaluation of tumor infiltrating and peripheral blood mesothelin, Kras, and patient-specific mutation antigen-specific T cells will be analyzed.

PBMC will undergo flow cytometry-based immune phenotyping and quantification. T cells will be isolated for functional responses to mitogens as well as antigen specific functional responses to candidate pancreatic cancer antigens such as mesothelin or Kras using available peptide libraries and pMHC tetramers in response to treatment.

DNA isolated from PBMCs and tissue will be analyzed by deep sequencing to detect and track specific T cell and B cell receptor clones. Gene and/or protein expression of circulating myeloid cells will be quantitatively evaluated. All biopsies in the safety and efficacy portion of the study will be assessed by IHC. Findings will be correlated with clinical endpoints.

5.6 General Concomitant Medication and Supportive Care Guidelines

All concomitant medications taken during the study will be documented in the CRF with the indication, dose information, and dates of administration.

- Patients should receive full supportive care during the study, including transfusion of blood and blood products, treatment with antibiotics, anti-emetics, anti-diarrheals, analgesics, erythropoietin, or bisphosphonates, when appropriate.

- Alternatives should be sought for strong and moderate CYP3A inhibitors.

- Primary prophylaxis with granulocyte colony stimulating factors (G-CSF) is not allowed but G-CSF may be used during the course of treatment per ASCO guidelines and the dose modification guidelines in Table 6 below if severe cytopenias develop.

Antiplatelet Agents and Anticoagulants

- Low molecular weight (LMW) heparin may be used as an anticoagulant for thromboembolic events during the study. NOTE: receiving coumadin is an exclusion criterion and is not permitted on study.

Coumadin or vitamin K antagonists *should not* be administered concomitantly with ibrutinib. 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. Subjects with congenital bleeding diathesis have not been studied. For 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..

- No other investigational therapy should be given to patients. No anticancer agents other than the study medications administered as part of this study protocol should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the study.

6 Dose Modifications and Dosing Delays

6.1 Dose Modifications of Ibrutinib for the Immune Response cohort

The following dose modifications of ibrutinib apply to the subjects who are enrolled in the Immune Response cohort only, during the 1 week run-in of ibrutinib only. The dose of study drug should be modified according to the dose modification guidelines in Table 4 if any of the following toxicities occur:

- Grade 4 ANC (<500/μL) for more than 7 days. See Section 5.6 for instructions regarding the use of growth factor support.
- 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.

Table 4. 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

6.2 Dose Modifications for Dose Escalation and Immune Response Cohorts during Combination Therapy

Treatment cycles are fixed at 28 days in length. If neither of the chemotherapies (gemcitabine or nab-paclitaxel) can be administered on Day 1 of a new cycle (due to toxicity or any other reason), that new cycle will not be considered to start until the day that one or both of the chemotherapies is administered to the patient. If the start of a new cycle is postponed due to toxicities, the day 1 procedures for that cycle do not need to be repeated at the time of resuming treatment, except for any relevant blood tests that caused that cycle to be postponed in the first place.

Missed doses of any/all components of treatment on Days 8, 15 and 22 of a cycle will not be made up; i.e., cycle length will not be extended beyond 28 days. Example: On day 15 of a cycle, if gemcitabine and nab-paclitaxel are held due to hematologic toxicity, ibrutinib may be given as deemed appropriate. On Day 22, even if counts have recovered, treatment per protocol on that day would consist only of Day 22 ibrutinib; the gemcitabine/nab-paclitaxel would not be 'made up' on that day. Treatment with all study components would resume on Day 1 of the next cycle.

Brief treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation but should be recorded in CRF.

Table 5. Dose Reductions for Gemcitabine, Nab-paclitaxel, and Ibrutinib

	Gemcitabine	Nab-paclitaxel	Ibrutinib
Starting dose level	1,000 mg/m2	125 mg/m2	840 mg*
Dose level -1	800 mg/m2	100 mg/m2	560 mg**
Dose level -2	600 mg/m2	75 mg/m2	420 mg

Dose level -3	600 mg/m2	75 mg/m2	280 mg

*Highest dose level for Phase Ib dose escalation cohort only.

**Highest dose level for Immune Response cohort

6.3 Dose Modifications Tables

The following dose modification rules will be used with respect to potential toxicity. Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE v4.03).

Patients experiencing treatment-related toxicities that require a delay in scheduled dosing for >21 days will be discontinued from further study participation. In the event that a drug must be held for intolerability (ie neuropathy for nab-paclitaxel or rash for gemcitabine) for more than 21 days, patients may continue on study receiving the other drugs, including ibrutinib. Once a dose reduction is required at any point, no dose re-escalation will be permitted for the duration of study treatment. For hematologic toxicities, dose adjustments will be made as per Table 5 below.

When a dose reduction of ibrutinib is indicated, the treating physician will write an order to "decrease ibrutinib by one dose reduction". The drug should be labeled "first dose reduction" or "second dose reduction".

6.3.1 Dose Modifications and Schedule for Hematologic Toxicities

Dose level modifications for nab-paclitaxel and gemcitabine and ibrutinib where appropriate are found in Table 4 and 5.

Grade 3 and 4 anemia will be treated per ASCO and Institutional Guidelines.

Both ibrutinib and the combination of nab-paclitaxel and gemcitabine are potentially myelotoxic, and because of this overlapping toxicity, it may be difficult for the investigator to determine whether hematological toxicity is due to ibrutinib, or the nab-paclitaxel-gemcitabine combination. Because of the uncertainty in determining causality, the investigator should assume that any hematological toxicity which occurs is due to both ibrutinib and nab-paclitaxel + gemcitabine and should follow the recommendations directly below for ibrutinib, and in tables 6 and 7 for nab-paclitaxel and gemcitabine.

Ibrutinib

- Grade 4 ANC (<500/μL) for more than 7 days. See Section 5.6 for instructions regarding the use of growth factor support.
- Grade ≥3 thrombocytopenia (<50,000/μL)

Hematologic dose modifications for ibrutinib should follow the schedule and dose levels recommended in tables 4 and 5.

Nab-Paclitaxel and Gemcitabine

The tables below reflect rules for modifying/holding chemotherapy identical to those used in the registrational phase III trial of gemcitabine/nab-paclitaxel (MPACT) in metastatic pancreatic

cancer. Of note, the treating physician has the prerogative to take the more conservative approach (e.g., hold treatment on day 8 or 15 in the face of borderline blood counts) if felt appropriate for safety reasons.

Table 6. Day 1 Hematologic Dose Modifications for both Nab-Paclitaxel and Gemcitabine

Treatment Day Counts and Toxicity			
ANC		**Platelets**	**Timing**
≥1.5 x 10^9/L	And	≥100 x 10^9/L	Treat on time, continue at 100% of present dose
≤1.5 x 10^9/L	Or	≤100 x 10^9/L	Delay by 1 week intervals until recovery.

Table 7. Day 8 and 15 Hematologic Dose Modifications for Nab-Paclitaxel and Gemcitabine

Day 8 Blood Counts	**Day 8** **Dose Modification**	**Day 15** **Blood Counts**	**Day 15** **Dose Modification**
ANC > 1000 and Platelets > 75,000	Maintain dose level	ANC > 1000 and Platelets > 75,000	Maintain dose level
		ANC 500-1000 or Platelets 50,000 -74,999	Hold+ consider G-CSF[a] Upon count recovery, when safe to resume, maintain same dose level
		ANC < 500[a] or Platelets <50,000	Hold+ consider G-CSF[a] Upon count recovery, when safe to resume, decrease by 1 dose level
ANC 500-1000 or Platelets 50,000 -74,999	Hold+ consider G-CSF[a]	ANC > 1000 and Platelets ≥ 75,000	Maintain dose level (treat on time)

Day 8 Blood Counts	Day 8 Dose Modification	Day 15 Blood Counts	Day 15 Dose Modification
		ANC 500-1000 or Platelets 50,000 -74,999	Hold+ consider G-CSF[a] Upon count recovery, when safe to resume, decrease by 1 dose level
		ANC < 500[a] or Platelets <50,000	Hold+ consider G-CSF[a] Upon count recovery, when safe to resume, decrease by 1 dose level
ANC < 500 or Platelets <50,000	Hold+ consider G-CSF[a]	ANC > 1000 and Platelets ≥ 75,000	Decrease by 1 dose level (treat on time)
		ANC ≤1000 or Platelets 50,000 -74,999	Hold+ consider G-CSF[a] Upon count recovery, when safe to resume, decrease by 1 dose level
		ANC < 500[a] or Platelets <50,000	Hold+ consider G-CSF[a] Upon count recovery, when safe to resume, decrease by 1 dose level

Abbreviations: G-CSF = Granulocyte colony stimulating factor.
a G-CSF is optional if descent only affects platelets. The use of G-CSF should be according to Investigator preference and institutional standards. Prophylactic antibiotics are recommended in the setting of ANC <1.0 x 10^9/L.
b If patients do not experience resolution of neutropenia >21 days, despite uninterrupted G-CSF treatment, study treatment will be discontinued.
c Febrile patients (regardless of neutrophil count) should have their chemotherapy treatment held. A full sepsis diagnostic work-up should be performed while continuing broad spectrum antibiotics. If cultures are positive, the antibiotic may or may not be changed, depending on the sensitivity profile of the isolated organism. Patients with persistent fever after 3 weeks, despite uninterrupted antibiotic treatment, will discontinue study treatment. Febrile neutropenic patients can also receive G-CSF, in addition to antibiotic treatment, to hasten the resolution of their febrile neutropenia (following current institutional guidelines). In all cases, ANC must have returned to >1500 and platelet count >100,000before resuming chemotherapy treatment.

6.3.2 Dose Modifications and Schedule for Non-Hematologic Toxicities

Dose level modifications for non-hematologic toxicities for nab-paclitaxel, gemcitibine and ibrutinib where appropriate are found in Tables 7 and 8.

The start of a new treatment cycle with gemcitabine and/or nab-paclitaxel should not begin until any treatment-related non-hematologic toxicity has resolved to < Grade 1 or baseline. In general all study drugs will be held. However, if the investigator determines that the non-hematologic toxicity was due to one study drug and not the others, treatment with the remaining study drugs may continue as clinically appropriate.

Based upon maximum non-hematologic toxicities experienced during the previous cycle, dose adjustments for subsequent cycles are to be made according to the following criteria (unless specified per unique toxicities as noted below):

Table 8. Day 1 Non-Hematologic Dose Modifications

CTC Grade	Gemcitabine	Nab-paclitaxel	Ibrutinib
0-2	Same as Day 1 previous cycle (except for Grade 2 cutaneous toxicity where doses of gemcitabine and nab-paclitaxel should both be reduced to next lower dose level)		
3[a, b, c]	Hold Once the AE has been resolved to <Grade 1 or baseline, reduce by one dose level at the next administration		
4[c]	Off protocol therapy		

a The decision as to which drug (any or all three) should be modified will depend upon the type of non-hematologic toxicity seen and which course is medically most sound in the judgment of the physician/investigator e.g., if the toxicity only affects neuropathy, then only nab-paclitaxel should be reduced.

b A pulmonary embolism that is Grade 3 and will be exempt from this requirement at the investigator's discretion.

c Patients who manifest a Grade 3 electrolyte value(s) i.e., hypokalemia, do not require a dose reduction once the electrolyte issue is resolved. Patients do not have to be removed from protocol for a Grade 4 electrolyte value i.e., Grade 4 elevated glucose in a patient with diabetes mellitus.

Dose modifications may also be made for non-hematologic toxicity occurring WITHIN a cycle, as specified below:

Table 9. Non-Hematologic Dose Modifications within a Cycle (Days 8 and 15)

CTC Grade	Dose modification of gemcitabine and/or nab-paclitaxel	Dose modification of Ibrutinib
0-2[a]	Maintain at same dose level	
3[b, c, d]	Hold	

	Once the AE has been resolved to <Grade 1 or baseline, reduce by one dose level at the next administration
4[d]	Off protocol therapy

a. Except for cutaneous toxicity where the dose of Gemcitabine and Nab-paclitaxel should be decreased one level.
b. This decision as to which drug (either or both) should be modified will depend upon the type of non-hematologic toxicity seen and which course is medically most sound in the judgment of the physician/investigator. Once doses are reduced, they should not be re-escalated.
c. A pulmonary embolism that is Grade 3 will be exempt from this requirement at the investigator's discretion.
d. Patients who manifest a Grade 3 electrolyte value(s) i.e., hypokalemia, do not require a dose reduction once the electrolyte issue is resolved. Patients do not have to be removed from protocol for a Grade 4 electrolyte value i.e., Grade 4 elevated glucose in a patient with diabetes mellitus.

6.3.2.1 Atrial Fibrillation

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 6.0). If the dose of ibrutinib is reduced, at the investigator's discretion, the dose of ibrutinib may be re-escalated after 2 cycles of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. The PI should be consulted before dose reescalation.

6.3.2.2 Peripheral neuropathy

Nab-paclitaxel should be held in patients who experience ≥ Grade 3 peripheral sensory neuropathy and may be resumed at the next lower dose level of nab-paclitaxel in subsequent cycles after the peripheral neuropathy improves to ≤ Grade 1. If the toxicity does not resolve within 21 days, the patient will be removed from further treatment with nab-paclitaxel and may continue treatment with gemcitabine and ibrutinib at the discretion of the care provider, based on the clinical status of the patient. Patients discontinued from study will be followed for progression-free survival.

6.3.2.3 Hypersensitivity Reactions

Hypersensitivity reactions are graded as follows:

- Grade 1: Mild transient reaction; infusion interruption not indicated; intervention not indicated.

- Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids indicated for ≤24 hours).

- Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae. Note: any infusion that is interrupted and not resumed within the visit will be considered a Grade 3 reaction.

- Grade 4: Life-threatening consequences; urgent intervention indicated.

Hypersensitivity reactions are not expected with either gemcitabine or nab-paclitaxel or ibrutinib, and, if they do occur, are generally minor. However, in rare instances, more severe reactions may occur. A patient who experiences a Grade 3 infusion reaction may either be taken off study protocol at the discretion of the treating physician or be rechallenged at one dose level lower. A patient who experiences a Grade 4 infusion reaction should be taken off study protocol.

6.3.2.4 Hepatic toxicity

Ibrutinib is metabolized in the liver. 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). For subjects who develop moderate liver impairment (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, and could be re-treated according to resolved hepatic conditions (ie, 140 mg or 280 mg for moderate or mild.)

Table 10. Dose Modifications for Hepatic Toxicities: Gemcitabine and nab-Paclitaxel

AST and/or ALT		Total bilirubin	Gemcitabine	Nab-paclitaxel
Grade 0-2 (up to 5x ULN)	AND/OR	Grade 0-1 (up to 1.5x ULN)	Maintain at same dose level	
Grade 0-2 (up to 5x ULN)	AND/OR	Grade 2 (>1.5-3.0 x ULN)	Hold treatment; resume all drugs once total bilirubin resolves to Grade ≤1 1st episode: resume at same dose level Recurrent episodes: resume at one dose level lower	
Grade 3 (>5-20x ULN)	AND/OR	Grade 3 (>3-10x ULN)	Hold treatment; resume both drugs at one dose level lower once total bilirubin resolves to Grade ≤1 and AST/ALT to Grade ≤2.	
Grade 4 (>20x ULN)	OR	Grade 4 (>10x ULN)	Remove from study treatment	

Note: If elevated liver function tests (LFTs) are related to biliary obstruction and are corrected after appropriate intervention (e.g. stenting), no dose reductions are required.

6.3.2.5 Cutaneous Toxicity

Patients who develop Grade 2 or 3 cutaneous toxicity should have their dose reduced to the next lower dose level for nab-pa. If the patient continues to experience Grade 2 or 3 reactions,

despite dose reduction, treatment should be discontinued. Patients who develop Grade 4 cutaneous toxicity should have treatment discontinued.

6.3.2.6 Pulmonary Embolism

A patient with a grade 3 pulmonary embolism can remain in therapy despite need for anticoagulation. Low molecular weight (LMW) heparin may be used as an anticoagulant for thromboembolic events during the study. NOTE: Coumadin treatment is not allowed during the study.

6.3.2.7 Nausea/Vomiting/Diarrhea

For nausea, vomiting, and diarrhea that are attributed to one or more of the study drugs, maximal medical management should be employed prior to dose reductions. If the toxicities persist at Grade 3 or greater despite optimal medical management, then appropriate dose holds and reductions should be performed.

7 Study Procedures and Observations

7.1 Overview

All patients should visit the trial center on the days specified within this protocol. The baseline medical history, physical examination, ECOG PS, complete blood counts (CBC) with 3-part differential and platelets, comprehensive metabolic profile (CMP), coagulation tests and CA19-9 should be done ≤ 14 days prior to initiation of treatment. Informed consent and scans must be performed within 28 days prior to randomization. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

7.2 Pre-treatment Assessments

- Informed consent form prior to any other study related procedures
- Medical history and demographics*
- Physical examination including measurements of height (first visit), weight, and vital signs (resting heart rate, blood pressure, oral temperature)*
- ECOG PS (see Appendix 1)*
- 12-lead ECG
- Concomitant medication and vitamin supplement review
- CBC including 3-part differential and platelets*
- CMP (see Section 7.8)*
- CA19-9 blood sample*
- PT/INR and PTT
- Serum or urine pregnancy test for women of child-bearing potential (must be performed within 72 hours prior to randomization)

- Archived tumor tissue if available (either FFPE tissue block or 15 or more unstained slides see Section 5.4.1)
- Tumor Evaluation
- CT Scan of chest, abdomen and pelvis with contrast
- MRI may be used if any contraindications to CT
- All sites of disease must be documented at baseline and followed during the trial per RECIST 1.1

*Must be done within <14 days prior to initiation of study treatment.

7.3 Study Treatment Assessments

7.3.1 Immune Response Cohort: One Week Ibrutinib-only Period

If any of the assessments were performed during the screening period within 14 days preceding the day of Loading Dose 1, they do not have to be repeated.

- Physical examination (Loading Dose 1 only) including measurements of height (first visit), weight, and vital signs (resting heart rate, blood pressure, oral temperature)
- ECOG PS (See Appendix 1) (Loading Dose 1 only)
- Concomitant medication review (Loading Dose 1 only)
- AE assessment
- CBC including 3-part differential and platelets (Loading Dose 1 only)
- CMP (See Section 7.8) (Loading Dose 1 only)
- CA19-9 blood sample (only for patients with elevated levels ≥ 2 x ULN at baseline) (Loading Dose 1 only)
- 70 mL blood for correlates
- EUS Guided Biopsies*

*EUS Guided biopsies should be performed at least 5 days before day 1 and at least 5 days after day 7 of the ibrutinib-only run-in.

7.4 Combination Therapy Treatment Period

7.4.1 Day 1 of all Cycles

- Physical examination including measurement of weight and vital signs
- ECOG PS (see Appendix 1)
- AE assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets

- CMP
- PT/INR and PTT (see tables 11 and 12 for phase 1b and immune response cohorts)
- CA19-9 blood sample (only for patients with elevated levels ≥ 2 x ULN at baseline)
- 70 mL blood for correlates analyses

7.4.2 Day 8 of all Cycles

- AE assessment
- CBC, including 3-part differential and platelets
- CMP

7.4.3 Cycles 1 and 2, Day 15

- Physical examination including measurement of weight and vital signs (Cycle 1 only)
- ECOG PS (see Appendix 1)
- AE assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets
- CMP (See Section 7.8)

7.4.4 Day 22 of all Cycles

- AE assessment

7.4.5 Cycle 3 and beyond Day 15

- AE assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets
- CMP (See Section 7.8)

7.5 Every 2 Cycles (8 weeks)

Patients will be evaluated for response to treatment at the end of every 2 cycles (e.g. end of Cycles 2, 4, 6, etc.), during the last week of the cycle (Day 22-28). The evaluations should be completed at the end of every 2 cycles regardless of any treatment delays. The following assessments will be performed:

- CT scan of chest, abdomen/pelvis. (MRI acceptable alternative for patients in whom CT scan cannot be performed).
- Patients without measurable disease at baseline will still be evaluated every 2 cycles (e.g. end of Cycles 2, 4, 6, etc.) for progressive disease per RECIST 1.1 criteria.

7.6 End-of-Treatment

Patients will return to the study center within 30 days after discontinuation of study treatment for an End of Treatment Visit. In the event that the patient is too ill or frail to return to clinic for this

End of Treatment visit, the End of Treatment assessment can be performed on the same day the patient is removed from study therapy.

- Physical examination including measurement of weight and vital signs
- ECOG PS (see Appendix 1)
- AE assessment
- Concomitant medication review
- CBC, including 3-part differential and platelets
- CMP
- PT/INR and PTT
- CA19-9 blood sample (only for patients with elevated levels ≥ 2 x ULN at baseline)
- CT Scan of chest, abdomen/pelvis if abnormal at baseline or clinically indicated if not performed within last 30 days. MRI is an acceptable alternative for patients in whom CT scan cannot be performed).

7.7 Follow-up

7.7.1 Progression-Free Survival Follow-up

Patients who discontinue study treatment prior to the occurrence of disease progression will be followed approximately every 8 weeks in the same modality from the date of last dose of ibrutinib, gemcitabine and nab-paclitaxel until disease progression or for up to 2 years whichever comes first. Assessments at these visits will be performed as described in Tables 11 and 12. Any subsequent cancer therapy will be documented.

7.7.2 Survival Follow-up

Following documented disease progression, patients will be followed every 2 months for 2 years for subsequent anticancer therapy, secondary malignancies, and survival status. Information on the start date, type and duration of any subsequent anticancer therapy will be collected. This follow-up may be accomplished through routine clinic follow up visits, documented telephone contact with the patient or through contact with the primary practitioner or caregiver.

7.8 Comprehensive Metabolic Profile Assessment

The comprehensive metabolic profile (CMP) panel can sometimes vary by institution. The following laboratory tests should be performed for each patient for assessment of CMP:

- glucose
- blood urea nitrogen (BUN)
- creatinine
- sodium
- potassium
- chloride
- calcium
- carbon dioxide (CO2)
- alkaline phosphatase
- AST (SGOT)

- ALT (SGPT)
- total bilirubin
- total protein
- albumin

8 Drug Formulation, Availability, Administration and Toxicity Information

8.1 Description, Supply and Storage of ibrutinib

Ibrutinib (IMBRUVICA®) will be supplied to the investigational pharmacy by Pharmacyclics, Inc.

8.1.1 Supply, Packaging and Storage

Ibrutinib (IMBRUVICA®) 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 drug 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.

8.1.2 Dose and Administration

Ibrutinib (92ct, 140-mg capsules for 280, 420, 840 mgs and 120ct, 140-mg capsules for 560mgs) 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 patients 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 8).

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 patient 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 patients in bottles at each visit. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records (Section 8.1.3) updated at each visit. Returned capsules must not be redispensed to anyone.

8.1.3 Accountability

The pharmacist(s) must confirm the quantity of ibrutinib received with each shipment. The Investigator or designee will maintain records to confirm that the product was stored at 15-30°C, product delivery to the trial site, product inventory at the site, the dose given to each patient, and the destruction of unused vials. .

8.1.4 Precautions and Risks

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.There is no specific antidote for ibrutinib. In the event of an overdose, subjects should be closely monitored and given appropriate supportive treatment.

Refer to Section 11 for further information regarding AE reporting.

Risks and Side effects

The risks and side effects that have been seen in patients who have been treated with **ibrutinib alone** that have been felt to be possibly, probably, or definitely related to ibrutinib are defined below.

Very likely (At least 20% of patients):

Diarrhea
Fatigue
Nausea
Infection
Arthralgia and Myalgia

Less likely (At least 10% of patients):

- Cough
- Stomatitis
- Sinusitis
- Anemia
- Pyrexia
- Neutropenia
- Dizziness
- Thrombocytopenia
- Constipation
- Peripheral edema
- Upper respiratory tract infection
- Vomiting
- Urinary tract infection

- Dyspnea
- Skin infection
- Petechiae
- Pneumonia
- Headache
- Muscle spasms
- Epistaxis
- Decreased appetite
- Hypertension

Rarely (but may be serious) (At least 1% of patients):

- Dyspepsia
- Blurry vision
- Atrial fibrillation
- Acute renal failure
- Lymphocytosis and/or Leukocytosis
- Sepsis
- Febrile neutropenia
- Subdural hematoma
- Abdominal pain
- Hyperuricemia
- Dehydration
- Asthenia
- Dyspepsia
- Dry mouth
- Skin redness
- Pleural effusion
- Respiratory failure

Rare serious side effects (less than 1% of patients):
Hypersensitivity
Cerebrovascular accident with hemorrhage
Hemorrhagic colitis
Pancytopenia
Splenomegaly
Systemic inflammatory response syndrome

8.2 Gemcitabine

Gemcitabine (2'-Deoxy-2', 2'-difluorocytidine monohydrochloride, Gemzar) exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S phase) and also blocking the progression of cells through the G1/S phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate

(dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

8.2.1 Drug Storage and Stability

Gemcitabine is commercially available in 200 mg and 1 gm vials and will be obtained from commercial supply. Gemcitabine should be prepared as per institutional standards.

8.2.2 Drug Administration

Gemcitabine should be prepared as per institutional standards.

8.2.3 Side Effects

Most common side effects include myelosuppresion, rash, nausea/vomiting, fever, fatigue, flu-like symptoms, fluid retention, diarrhea, and transaminitis. Rare but serious side effects include pulmonary syndromes, bronchospasm, and hemolytic-uremic syndrome. For more information please see the prescribing information.

8.3 Nab-paclitaxel (Abraxane)

Abraxane (nab-paclitaxel, nanoparticle albumin-bound paclitaxel), when released as the active drug (paclitaxel), blocks cell replication in the G2 mitotic phase by promoting microtubule assembly, stabilizing existing microtubules, and inhibiting disassembly of microtubles. Binding of abraxane by an albumin specific receptor (gp60) leads to activation of caveolin-1, a protein which mediates internalization of the compound into the endothelial cell and transport to the tumor interstitium. Secreted Protein And Rich in Cysteine (SPARC), a tumor-secreted protein, binds albumin, releasing the active drug at the tumor cell membrane, thereby increasing its concentration at the target site of action.

8.3.1 Drug Storage and Stability

Abraxane (nab-paclitaxel, nanoparticle albumin-bound paclitaxel), when released as the active drug (paclitaxel), blocks cell replication in the G2 mitotic phase by promoting microtubule assembly, stabilizing existing microtubules, and inhibiting disassembly of microtubles. Binding of abraxane by an albumin specific receptor (gp60) leads to activation of caveolin-1, a protein which mediates internalization of the compound into the endothelial cell and transport to the tumor interstitium. Secreted Protein And Rich in Cysteine (SPARC), a tumor-secreted protein, binds albumin, releasing the active drug at the tumor cell membrane, thereby increasing its concentration at the target site of action.

8.3.2 Drug Administration

Abraxane should be prepared as per institutional standards.

8.3.3 Side Effects

Most common side effects include myelosuppresion, nausea/vomiting, diarrhea, mucositis, sensory neuropathy, myalgia/arthralgia, infections, hypotension, abnormal ECG changes, cough, dyspnea, edema, bilirubin/liver enzyme elevations, allergic reactions, alopecia, asthenia. Rare but serious side effects include hypersensitivity reactions and cardiovascular events. For more information please see the prescribing information.

9 Response Evaluations And Measurements

All patients with measurable disease will be evaluated for response using the RECIST version 1.1 (Appendix 4) (Eisenhauer et al. 2009).

10 Statistical Considerations

10.1 Study Design

This is a phase Ib/Immune Response study of ibrutinib in combination with nab-paclitaxel and gemcitabine in the management of patients with metastatic pancreatic adenocarcinoma. Phase Ib is a standard dose-confirmation schema with 3 to 6 patients per cohort (3+3 dose escalation/de-escalation design). There are two planned dose cohorts, with two additional cohorts at de-escalated doses if necessary. The objective of the part Ib is to confirm the safety and toxicity of the combination of gemcitabine and nab-paclitaxel with the doses and schedule of ibrutinib previously shown to be safe and effective in the management of patients with CLL and Mantle Cell Lymphoma,and to determine the Maximum Tolerated Dose (MTD),. See section 5.0 and section 5.1 for more details. At least six patients total will have received the MTD to verify and confirm the safety and toxicity of ibrutinib in combination with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic adenocarcinoma. These 6 patients will also be followed for overall survival and included in efficacy and clinical benefit analysis of the study.

The 20 patients enrolled and treated in the Immune Response study cohort will be evaluated for safety and followed for survival.

10.2 Study Endpoints

Phase Ib, Dose Escalation

Primary endpoints:

- Safety and tolerability of ibrutinib in combination with gemcitabine and nab-paclitaxel

Immune Response Study

Primary endpoint:

- Changes in the immune profile of peri-tumoral environment and peripheral blood during and after treatment with ibrutinib, alone and in combination with gemcitabine and nab-paclitaxel.

Secondary endpoints:

- Median time-to-progression (TTP)
- Median progression-free survival (PFS)
- Median overall survival (OS)

10.3 Pharmacodynamic (PD) Analysis

- Btk occupancy ratio (PBMC)

10.4 Exploratory Endpoints

- Changes in T cell and B cell frequency
- Changes in T cell and B cell clonality
- Changes in T cell and B cell function
- Changes in circulating myeloid cell gene and protein expression profiles

10.5 Randomization

Not Applicable

10.6 Stratification

Not applicable

10.7 Missing Data and Replacement Policy

Data for all patients will be summarized and analyzed to the extent the available data allow. Missing data will not be imputed or replaced.

10.8 Interim Analyses and Stopping Rules

Not applicable for phase Ib study design. Stopping rules are already included as part of standard 3+3 design.

10.9 Analyses Plans

Descriptive statistics will be used to summarize baseline subject characteristics, treatment administration, efficacy, and safety outcomes. Summaries of discrete data will include number of subjects and incidence as a frequency and as a percentage. Summaries of continuous data will include mean, standard deviation, median, minimum, maximum, and sample size.

10.10 Primary Analysis (or Analysis of Primary Endpoints)

Phase Ib: Safety will be assessed through summaries of DLTs and other adverse events. Tolerability will be described using summaries of dose reductions, dose delays, discontinuations for toxicity, and overall dose exposure. The safety of the MTD will be established after review by

the Study Team (comprised of Principal Investigator, Investigational Pharmacist, Study Statistician, and Site Committee quorum) taking into account the the severity and causal relationship for all DLTs and other AEs, and tolerability. Review of PD parameters at each dose level may also be used to inform determination of MTD. Eligible patients who receive at least one dose of the study drug are evaluable for safety from the date and time of their first dose of the study drug until 30 days after last dose of study drug.

10.11 Secondary Analysis (or Analysis of Secondary Endpoints)

Kaplan-Meier methods will be used to summarize median TTP, PFS, and OS with 95% confidence intervals. The proportion of patients with TTP and PFS equal to or exceeding 6 months will also be calculated and reported along with 95% confidence intervals.

CA19-9 Response Rate

The CA19-9 Response Rate is defined as the percentage of CA 19-9 evaluable treated patients (baseline CA19-9 > 75 units) who have confirmed CA19-9 reduction of 75% from baseline value. Patients who have missing CA19-9 measurements will be treated as non-responders, i.e., they will be included in the denominator when calculating the percentage. The CA19-9 Response Rate, along with exact one-sided 95% confidence intervals, will be reported for the study.

Time to Progression (TTP)

TTP is defined as the duration from date of first dose of protocol therapy to date of removal from study for radiographic (per RECIST 1.1) and/or clinical progression including death attributed to progression. Eligible patients are evaluable for TTP who are response-evaluable and who are removed from study for radiographic or clinical progression. For patients removed from study for other reasons (such as for toxicity, withdrawal of consent, death without documented progression, or other reasons without clinical or radiographic evidence of tumor progression), TTP will be censored at the date of study discontinuation.

Progression-Free Survival (PFS)

PFS is defined as the duration of time from date of first dose of protocol therapy to time of documented radiographic and/or clinical disease progression or death from any cause. Eligible patients are evaluable for PFS who are response-evaluable and who are removed from study for radiographic or clinical progression and/or who experience death from any cause during study follow up. Patients who have not progressed or died are censored at the date last known to be progression-free.

Overall Survival (OS)

Median OS for all enrolled patients will be calculated from date of first dose of protocol therapy until date of death, using chart review and/or follow up phone calls to determine date of death in patients after removal from study. The survival of patients still alive after 2 years of follow up post study discontinuation will be censored. Alive patients are censored at the date last known alive

10.12 Analyses of Exploratory Endpoints

Identification of myeloid cell biomarkers by flow cytometry: FACS will be used to

quantitatively evaluate abundance, complexity, phenotype and functional status of myeloid cells (T_H1, T_H2, T_H17) using blood leukocytes from patients. Multiplex ELISA and RT-PCT will be used to assess a broad spectrum of T_H cell responses in peripheral blood leukocytes. These parameters will be compared to expression levels of biomarkers and cytokines in frozen and/or FFPE-embedded tumor tissue from pre- and post-treatment PDA patients vs. archived PDA and normal pancreas tissues. Globin mRNA will be extracted using anti-globin magnetic beads prior to multiplex PCR analysis.

T cell frequency, clonality and function

Polychromatic flow cytometry: Abundance, complexity, phenotype and functional status of T cells in peripheral blood leukocytes and tumor cell suspensions will be analyzed by FACS quantitation of Ag-specific CD8+ T cells in using peptide epitope-MHC class I tetramers. Tetramer+ and (-) CD8+ T cells will be stained for accepted markers reporting functional status of Ag-specific CD8+ T cells, the proliferation Ki-67, and the cellular activation markers.

T cell frequency and function: In addition to FACS, the EPIMAX platform will be used, allowing assessment of a broad spectrum of T cell responses both by epitope mapping and by cytokine profiling[33, 34] (e.g., TNFα, IFNγ, IL2, IL4, IL10, IL17) using 9-10mer ($CD8^+$ T cells) or 20mer libraries ($CD4^+$ T cells). Morisita's distances will be calculated for serial blood and tumor samples

TCR deep sequencing of tissue and blood: T cell responses, their clonality, and expansion or contraction over time will be monitored globally by deep sequencing of TCRβ chains to identify and track unique T cell clones in tissue and blood.

Changes in Circulating and Intra-tumoral B-Cell Receptors

B cell frequency and phenotype: B cell abundance, complexity, phenotype and functional status of B cells will be quantitatively evaluated by FACS analysis of blood leukocytes and tumor cell suspensions before and after therapy with ibrutinib-only.

BCR sequencing: Immuno-receptor loci rearrangements from genomic DNA samples reflecting pre- vs. post-treatment PB and tumor will be sequenced using V and J segment consensus primers. Sequences will be analyzed using standardized algorithms for clonotype determination.

Clonotype identification and enumeration: The frequency of each clonotype in a sample will be determined by calculating the number of sequencing reads for each clonotype divided by the total number of passed sequencing reads in the sample, with algorithmic methods utilized for clonotype determination as described previously. Low quality reads, those that do not map to a J and a V segment and do not demonstrate high-quality sequence data in the clone-defining region, will be excluded. Sequence data will be analyzed to determine clonotype sequences including mapping to germline V and J consensus sequences.

Determination of repertoire diversity and repertoire change: Diversity of individual sample repertoires will be assessed by calculating the number of unique clonotypes comprising the top 25th % of cumulative reads after sorting by clone abundance. Repertoire change between sequential experiments will be measured using Morisita's distance, which is not significantly

influenced by sample size1, 2, and reported as a continuous variable from 0-1 with1 indicating maximal dissimilarity.

Statistical Analysis

Analyses for diversity, repertoire change and identification of differentially abundant clonotypes will be performed as described above. In the Immune Response Study, 20 patients will be enrolled and their B and T cell repertoires measured at time points, including pre-, post-, start of, during, and end of treatment. Changes in B and T cell repertoire parameters over time will be modeled using mixed effects models to account for an intra-subject correlation. A binary and ordinal logistic regression analyses will be performed to evaluate effect of pre-treatment B and T cell repertoire parameters on tumor response (PD, SD, PR, CR), while Cox regression analysis will be performed to evaluate their impacts on disease free survival. Due to the limited sample size, multivariate analyses will be primarily exploratory, and include an examination of the joint effects of several B and T cell repertoires parameters on the clinical outcome.

10.13 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the NCI CTCAE v4.03.

11 Safety Reporting And Analyses

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.

Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB) according to the policies of the responsible IRB.

11.1 Adverse Events

The Principal Investigator is responsible for recognizing and reporting AEs. It is the Principal Investigator's responsibility to report relevant SAEs to the applicable local and national regulatory bodies.

Definitions of Adverse Events

An AE is any untoward medical occurrence in a patient 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 patient and/or observed by the Investigator or study staff including laboratory abnormalities of clinical significance.
- Any AEs experienced by the patient through the completion of final study procedures.
- AEs not previously observed in the patient 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 (documented on the medical history CRF) 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.

Recording and Reporting of Adverse Events

All AEs of any subject during the course of the study will be recorded in the CRF, and the investigator will give his or her opinion as to the relationship of the AE to the study drug treatment (i.e., whether the event is related or unrelated to study drug administration).

All AEs should be documented. A description of the event, including its date of onset and resolution, whether it constitutes an SAE or not, any action taken (e.g., changes to study treatment), and outcome, should be provided, along with the investigator’s assessment of causality (i.e., the relationship to the study treatment[s]). For an AE to be a suspected treatment-related event there should be at least a reasonable possibility of a causal relationship

between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE 4.03.

If the AE is serious, it should be reported immediately to IRB of record. Other untoward events occurring in the framework of a clinical study are also to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that are related to a study-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Any clinically significant signs and symptoms; abnormal test findings; changes in physical examination; hypersensitivity; and other measurements that occur will be reported as an AE, and collected on the relevant CRF.

Test findings will be reported as an AE if the test result requires an adjustment in the study drug(s) or discontinuation of treatment; and/ or test findings require additional testing, treatment, or surgical intervention; a test result or finding is associated with accompanying symptoms; or a test result is considered to be an AE by the investigator.

All AEs regardless of seriousness or relationship to study treatment, spanning from the start of study treatment, until 30 calendar days after discontinuation or completion of study treatment as defined by the clinical study for that subject, are to be recorded in the CRF.

Handling of Adverse Events

All AEs resulting in discontinuation from the trial should be followed until resolution or stabilization. Patients must be followed for AEs for 30 calendar days after discontinuation or completion of clinical trial-specific treatment (e.g., chemotherapy, radiation, oral medications, targeted therapy, and surgery). All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the subject's medical record and as a comment on the CRF. After 30 days of completion of study-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

11.2 Serious Adverse Events

Definitions of Serious Adverse Events

The definitions of SAEs are given below. The Principal Investigator is responsible for ensuring that all staff involved in the trial is familiar with the content of this section.

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 that:

- Results in death
- Is a life-threatening adverse event. Life-threatening is defined as an AE in which the patient 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 at least a 24-hour inpatient hospitalization or prolongation of existing hospitalization

- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- Results in 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 patient or patient 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.

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room

- Outpatient or same-day surgery units

- Observation or short-stay unit

- Rehabilitation facility

- Hospice or skilled nursing facility

- Nursing homes, custodial care or respite care facility

Hospitalization during the trial for a pre-planned surgical or medical procedure (one which was planned prior to entry in the trial) does not require reporting as an SAE to the local IRB. Deaths that are attributed by the Investigator solely to the progression of disease do not require reporting as an SAE to the the local IRB.

Serious Adverse Event Reporting by Investigators

It is important to distinguish between "serious" and "severe" adverse events, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs on the CRF and SAEs on the SAE Report Form.

Adverse events classified by the treating investigator as serious require expeditious handling and reporting to the sponsor in order to comply with regulatory requirements. Serious adverse events may occur at any time from the start of study treatment through the 30-day follow-up period after the last study treatment. The sponsor must be notified of all SAEs, regardless of

causality, within one business day of the first knowledge of the event by the treating physician or research personnel.

To report an SAE, the SAE Report Form should be completed with the necessary information. All SAEs occurring from the start of study treatment, until 30 calendar days of last study treatment must be reported to the chair, Dr. Margaret Tempero as SAEs on the SAE Report Form and followed until resolution (with autopsy report if applicable).

Deaths and other SAEs occurring >30 calendar days after last study treatment that are deemed 'possibly' or 'probably' related to study drug must be reported as SAEs on the SAE Report Form within 1 day of first knowledge of the event by the treating physician or research personnel (with an autopsy report if available).

Deaths occurring >30 calendar days after last study treatment and not attributed to study treatment (e.g., disease progression) need not be reported as SAEs, but simply captured on the appropriate CRF.

To report an SAE, the SAE Report Form should be completed with the necessary information.

The SAE report Form should be sent to the study coordination site via e-mail using the following contact information (during both business and non-business hours):

[redacted]

[redacted]

[redacted]

Emailof the SAE report Form should be confirmed by the site personnel submitting the report.

Reporting to Regulatory Agencies:

Serious adverse events will be forwarded to FDA by the IND Sponsor according to 21 CFR 312.32.

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.

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. Refer to http://evs.nci.nih.gov/ftp1/CTCAE/About.html for the grading of hematologic AEs. The CTCAE v4.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a patient 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 patient's daily activities

- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the patient, 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 patient's usual daily activity, and require systemic drug therapy or other treatment

- Grade 4 (Life-threatening or disabling AE) – experiences which cause the patient to be in imminent danger of death

- Grade 5 (Death related to AE) – experiences which result in patient death

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: 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.

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.

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

Assessment of Adverse Events

Investigators will assess the occurrence of adverse events and serious adverse events at all subject evaluation time points 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, clinically significant laboratory test, 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.

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.

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. For 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.

Non-melanoma Skin Cancer and Other Malignancies

Non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma of the skin) have been reported with more frequency and may be related to the use of ibrutinib. Other cancers have been been reported such as solid tumors and hematologic malignancies, and 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.

Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities. These events (regardless of seriousness) will be reported to the local IRB per the SAE reporting timelines.

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 v4.02.

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

Expediting Reporting Requirements for Serious Adverse Events

All serious adverse events and AESIs (initial and follow-up information) will be reported on FDA Medwatch (Form 3500A) or Suspect Adverse Event Report (CIOMS Form 1) IRB Reporting Form and sent sent via email (AEintakePM@pcyc.com) or fax ((408) 215-3500), to Pharmacyclics Drug Safety, or designee, within 24 hrs 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)

11.3 Usage of Concurrent/Concomitant Medications

11.3.1 Medications to be Used With Caution

CYP3A- Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

- If a strong CYP3A inhibitor (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, or cobicistat) must be used, reduce ibrutinib dose to 140 mg or withhold treatment for the duration of inhibitor use. Subjects should be monitored for signs of ibrutinib toxicity.
- If a moderate CYP3A inhibitor (eg, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, or dronedarone) must be used, reduce ibrutinib to 140 mg (for 840 mg/day dose, reduce to 280 mg) for the duration of the inhibitor use. Avoid grapefruit and Seville oranges during ibrutinib/placebo treatment, as these contain moderate inhibitors of CYP3A (see Section 5.3.1.2).
- No dose adjustment is required in combination with mild inhibitors.

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

11.4 Dietary Restrictions

- Ibrutinib should be taken with water.
- Seville oranges or grapefruit juice should be avoided

12 Reporting and Documentation of Results

12.1 Evaluation of Efficacy (or Activity)

12.1.1 Antitumor Effect – Solid Tumors

Response and progression in this study will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria (or International Workshop on Chronic Lymphocytic Leukemia [IWCLL]).

12.1.1.1 Definitions

Evaluable for toxicity

All patients will be evaluable for toxicity from the time of their first treatment with the study drug.

Evaluable for objective response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

12.1.1.2 Disease Parameters

Measurable disease

Measurable disease is defined as lesions (or tumors) that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm), 10mm caliper measurement by clinical exam (when superficial), and/or 20mm by chest X-ray (if clearly defined and surrounded by aerated lung).

All tumor measurements will be recorded in millimeters or decimal fractions of centimeters. Previously irradiated lesions are considered non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Target lesions

All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). 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 response.

Non-target lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”). Bone lesions may be measureable if ≥ 1 cm on MRI. Measurements of these lesions are not required, but the presence or absence of each will be noted throughout follow-up.

Non-measurable disease (Tumor Markers)

Non-measurable disease is all other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan). Leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniquesare all non-measurable. (e.g. PSA, CA-125, CA19-9, CEA)

12.2 Evaluation of Safety

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE v4.03 for reporting of non-hematologic adverse events and modified criteria for hematologic adverse events, see Section 6.3.

12.3 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

12.4 Adverse Events Monitoring

All adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, as noted above.

The Investigator will assess all adverse events and determine reportability requirements to the UCSF Data and Safety Monitoring Committee (DSMC) and UCSF's Institutional Review Board, the Committee on Human Research (CHR); and, when the study is conducted under an Investigational New Drug Application (IND), to the Food and Drug Administration (FDA) if it meets the FDA reporting criteria..

All adverse events entered into OnCore® will be reviewed by the Helen Diller Family Comprehensive Cancer Center Site Committee on a weekly basis. The Site Committee will review and discuss at each weekly meeting the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

In addition, all adverse events and suspected adverse reactions considered "serious," entered into OnCore® will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis, discussed at DSMC meetings which take place every six (6) weeks, and prior to dose escalation. At the time of dose escalation, a written report will be submitted to the DSMC Chair (or qualified alternate) describing the cohorts, dose levels, adverse events, safety reports, and any Dose Limiting Toxicities observed, in accordance with the protocol. The report will be reviewed by the DSMC Chair (or qualified alternate). Approval for the dose escalation by the DSMC Chair (or qualified alternate) must be obtained prior to implementation. For a detailed description of the Data and Safety Monitoring Plan for a Multicenter Phase 1 Dose Escalation Institutional Study at the Helen Diller Comprehensive Cancer Center please refer Appendix 2 Data and Safety Monitoring Plan for Phase 1 Dose Escalation.

12.5 Expedited Reporting

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s)

or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF Committee on Human Research (Institutional Review Board)

The Principal Investigator must report events meeting the UCSF CHR definition of "Unanticipated Problem" (UP) within 10 business days of his/her awareness of the event.

Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

Suspected adverse reaction (as defined in 11.1)

Unexpected (as defined in 11.2)

Serious (as defined in 11.2)

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the

13 Study Management

13.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory

requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

13.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF CHR (UCSF Institutional Review Board). Prior to obtaining CHR approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

13.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the CHR-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

13.4 Changes in the Protocol

Once the protocol has been approved by the UCSF CHR, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the CHR prior to implementation.

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. If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to CHR approval. In this circumstance, however, the Investigator must then notify the CHR in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

13.5 Handling and Documentation of Clinical Supplies

The UCSF Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

13.6 Case Report Forms (CRFs)

The Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar, using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as

possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

13.7 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 5 Data and Safety Monitoring Plan for Phase 1 Dose Escalation Institutional Study, for additional information.

13.8 Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center for Phase II studies will also coordinate, at minimum, monthly conference calls with the participating sites at the completion of each cohort or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study.

13.9 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, CHR correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

13.10 Coordinating Center Documentation of Distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

13.11 Regulatory Documentation

Prior to implementing this protocol at UCSF HDFCCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the UCSF Committee on Human Research (CHR). Prior to implementing this protocol at the participating sites, approval for the UCSF CHR approved protocol must be obtained from the participating site’s IRB.

The following documents must be provided to UCSF HDFCCC before the participating site can be initiated and begin enrolling participants:

- **Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization**
- **Participating Site IRB approved consent form**

- **Participating Site IRB membership list**
- **Participating Site IRB's Federal Wide Assurance number and OHRP Registration number**
- **Curriculum vitae and medical license for each investigator and consenting professional**
- **Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site**
- **Participating site laboratory certifications and normals**

Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment.

14 Protection of Human Subjects

14.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the CHR mechanism and the process of informed consent. The CHR reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The CHR also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

14.2 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

Table 11. Schedule of Events and Procedures: Phase Ib Dose escalation

Period/Procedure	Screening[a]	Treatment Cycles 1-2[c] (Cycle is 28 days)				Treatment Cycles 3 and beyond[c] (Cycle is 28 days)				End of Study Treatment[d]	Follow-up	
Study Day/Visit Day	**-14 to 0**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**		**Prior to PD[k]**	**After PD[l]**
Tests and Observations												
Informed consent	X											
Medical history and Demographic	X											
Physical exam, weight	X	X[f]		X		X				X	X	
Vital signs[e]	X	X[e]	X[e]	X[e]		X[e]	X[e]	X[e]		X	X	
Height[e]	X											
ECOG PS	X	X[f]		X		X				X	X	
Concomitant medications	X	X		X		X		X		X		
AE assessment		X	X	X	X	X	X	X	X	X	X	
Archival Tissue Collection (if available) [i]	X											
12-lead ECG	X[m]					X[n]						
Subsequent Cancer Treatment											X	X
Survival Status												X
Treatment/Drug Administration												
Ibrutinib[b]		X	X	X	X	X	X	X	X			
Gemcitabine		X	X	X		X	X	X				
Nab-Paclitaxel		X	X	X		X	X	X				
Laboratory procedures												
CBC w/ 3 part Diff	X	X[f]	X	X		X	X	X		X		
CMP[g]	X	X[f]	X	X		X	X	X		X		
Urine or serum Pregnancy test	X											

Period/Procedure	Screening[a]	Treatment Cycles 1-2[c] (Cycle is 28 days)				Treatment Cycles 3 and beyond[c] (Cycle is 28 days)				End of Study Treatment[d]	Follow-up	
Study Day/Visit Day	**-14 to 0**	**D1**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**		**Prior to PD[k]**	**After PD[l]**
Hepatitis (HBV, HCV)	X[O]											
Coagulation (INR Pt/PTT)	X	X[f]								X		
CA19-9	X	X[f,f2]				X[f2]				X[f2]		
Blood collection for correlative studies, BTK occupancy assays		X[h]				X						
Imaging procedures												
Imaging (CT or MRI) every 8 wks[j]	X				X				X		X	

a. Pre-treatment assessments will be completed within 14 days of start of therapy. The Informed Consent and scans can be completed within 28 days of start of therapy. The pregnancy test (for women of child-bearing potential) should be completed within 72 hours prior start of therapy.

b. Daily dosing with ibrutinib should begin day 1 of cycle 1, and should continue through-out the 28 day cycles until patient is off study treatment.

c. Treatment with gemcitabine and nab-paclitaxel is to be administered on days 1, 8, 15 of each 28 day cycle. Ibrutinib will be taken orally, each day of the 28 day treatment cycle. While every effort should be made to adhere to this schedule, +/- 2 days from any scheduled treatment is acceptable due to holidays, travel issues, or other logistics.

d. End of study visit should be completed within 30 days of the last dose. In the event that the patient is too ill or frail to return to clinic for this EOT visit, this will *not* constitute a protocol violation.

e. Vital signs including BP, pulse and temperature should be documented with each PE. Vital signs should also be documented with any signs or symptoms during or immediately after an infusion. Perform complete physical examination at screening. A limited PE will be repeated on Day 15 of Cycle 1 only. A limited PE related to signs, symptoms and concurrent illnesses is appropriate during Study Treatment. Height only required during Pre-treatment.

f. These procedures to not need to be repeated if they were performed within the preceding 14 days (eg during the pre-treatment period).

f.2. Only for patients with elevated levels ≥ 2 x ULN at baseline.

g. CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO2, ALP, AST (SGOT), ALT (SGPT), total bilirubin, total protein, and albumin.

h. EDTA blood collection for baseline cytokine, B an T cell receptor profiling, and myeloid cell characterization and BTK occupancy assays should be drawn before beginning combination therapy on day 1 cycle 1, and day 1 of the subsequent cycles before infusion of gemcitabine and nab-paclitaxel . The correlative blood samples will be processed at UCSF before shipping to other sites for analyses.

i. Archived tumor tissue will be collected for this study. Tissue may be collected at Pre-treatment or at any time during the study.

j. Tumor assessment occurs at the end of every 2 cycles, during the last week of the cycle. The evaluations should be completed at the end of every 2 cycles regardless of any treatment delays. This typically will consist of CT scans of the chest/abdomen/pelvis. MRI represents an acceptable alternative for patients with increased risk of contrast related nephropathy or other contraindications. Baseline and subsequent imaging must be by the same type of procedure (e.g. CT vs. MRI scan).

k. Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 8 weeks from the date of last dose of trial drug until disease progression or for up to 2 years whichever comes first. Any subsequent cancer therapy will be documented.

l. Patients with documented disease progression will be followed every 2 months for survival status (e.g., date and cause of death) for up to 2 years or death whichever comes first. Information on the start date, type and duration of any subsequent anticancer therapy will be collected. Patients may be contacted during outpatient visits, by documented telephone contact with the patient or through contact with the primary practitioner or caregiver

m. 12-lead ECGs will be done in triplicate (≥1 minute apart); the calculated QTcF average of the 3 ECGs must be <470 msec for eligibility. Abnormalities noted at Screening should be included in the medical history.

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

o. Screening tests for Hepatitis Virus to include HBsAg, Hepatitis B core antibody (HBcAb), total, and HCV Antibody. If either of the HBV tests are positive, order HBV DNA quantification by PCR. If HBV DNA positive, determine if anti-viral therapy if DNA is necessary.

Table 12. Schedule of Events and Procedures: Immune Response Study

Period/Procedure	Screening[a]	Ibrutinib Run-in Period[b]	Treatment Cycles 1-2[c] (Cycle is 28 days)				Treatment Cycles 3 and beyond[c] (Cycle is 28 days)				End of Study Treatment[d]	Follow-up	
Study Day/Visit Day	**-14 to 0**	**Wk1D1**	**D1[b]**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**		**Prior to PD[k]**	**After PD[l]**
Tests and Observations													
Informed consent	X												
Medical history and Demographic	X												
Physical exam, weight	X	X[f]	X		X		X				X	X	
Vital signs[e]	X	X	X[e]	X[e]	X[e]		X[e]	X[e]	X[e]		X	X	
Height[e]	X												
ECOG PS	X	X[f]	X		X		X				X	X	
Concomitant medications	X	X[f]	X		X		X		X		X		
AE assessment		X	X	X	X	X	X	X	X	X	X	X	
Archival Tissue Collection (if available) [i]	X												
12-lead ECG	X[m]	X[f]					X[n]						
Subsequent Cancer Treatment												X	X
Survival Status													X
EUS-guided biopsy		X[b]											
Treatment/Drug Administration													
Ibrutinib[b]		X	X	X	X	X	X	X	X	X			
Gemcitabine			X	X	X		X	X	X				

Period/Procedure	Screening[a]	Ibrutinib Run-in Period[b]	Treatment Cycles 1-2[c] (Cycle is 28 days)				Treatment Cycles 3 and beyond[c] (Cycle is 28 days)				End of Study Treatment[d]	Follow-up	
Study Day/Visit Day	**-14 to 0**	**Wk1D1**	**D1[b]**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**		**Prior to PD[k]**	**After PD[l]**
Nab-Paclitaxel			X	X	X		X	X	X				
Laboratory procedures													
CBC w/ 3 part Diff	X	X[f]	X	X	X		X	X	X		X		
CMP[g]	X	X[f]	X	X	X		X	X	X		X		
Urine or serum Pregnancy test	X												
Hepatitis (HBV, HCV)	X												
Coagulation (INR, Pt, PTT)	X	X[f]	X								X		
CA19-9	X	X[f,f2]					X [f2]				X [f2]		
Blood collection for correlative studies,BTK occupancy assays		X[h]	X[h]				X[h]						
Imaging procedures													
Imaging (CT or MRI) every 8 wks[j]	X					X				X		X	

a. Pre-treatment assessments will be completed within 14 days of start of therapy. The Informed Consent and scans can be completed within 28 days of start of therapy. The pregnancy test (for women of child-bearing potential) should be completed within 72 hours prior start of therapy.

b. Day 1 of the 7 day ibrutinib-only run-in period should begin at least 5 days after the pretreatment EUS guided biopsy. Dosing with ibrutinib should be stopped for at least 5 day before performing the post-ibrutinib EUS-guided biopsy. Day 1 Cycle 1 of the combination treatment with gemcitabine and nab-paclitaxel may occur at 1-3 days after the post-ibrutinib run-in biopsy, and daily oral dosing with ibrutinib may commence 5-7 days post-biopsy.

c. Treatment with gemcitabine and nab-paclitaxel is to be administered on days 1, 8, 15 of each 28 day cycle. Ibrutinib will be taken orally, each day of the 28 day treatment cycle. While every effort should be made to adhere to this schedule, +/- 2 days from any scheduled treatment is acceptable due to holidays, travel issues, or other logistics.

d. End of study visit should be completed within 30 days of the last dose. In the event that the patient is too ill or frail to return to clinic for this EOT visit, this will *not* constitute a protocol violation.

e. Vital signs including BP, pulse and temperature should be documented with each PE. Vital signs should also be documented with any signs or symptoms during or immediately after an infusion. Perform complete physical examination at screening. A limited PE will be repeated on Day 15 of Cycle 1 only. A limited PE related to signs, symptoms and concurrent illnesses is appropriate during Study Treatment. Height only required during Pre-treatment.

f. These procedures to not need to be repeated if they were performed within the preceding 14 days (eg during the pre-treatment period).

f.2. Only for patients with elevated levels ≥ 2 x ULN at baseline.

g. CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO2, ALP, AST (SGOT), ALT (SGPT), total bilirubin, total protein, and albumin.

h. EDTA Blood collection for baseline cytokine, B and T cell receptor profiling, and myeloid cell characterization and BTK occupancy assays should be drawn before and after the 7 day ibrutinib run-in, before the EUS-guided biopsies are performed. Blood collection for the correlative analyses will also occur on day 1 of cycle 2 and subsequent cycles of combination therapy before infusion of gemcitabine and nab-paclitaxel begins. The correlative blood samples will be processed at UCSF before shipping to other sites for analyses.

i. Archived tumor tissue will be collected for this study. Tissue may be collected at Pre-treatment or at any time during the study.

j. Tumor assessment occurs at the end of every 2 cycles, during the last week of the cycle. The evaluations should be completed at the end of every 2 cycles regardless of any treatment delays. This typically will consist of CT scans of the chest/abdomen/pelvis. MRI represents an acceptable alternative for patients with increased risk of contrast related nephropathy or other contraindications. Baseline and subsequent imaging must be by the same type of procedure (e.g. CT vs. MRI scan).

k. Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 8 weeks from the date of last dose of trial drug until disease progression or for up to 2 years whichever comes first. Any subsequent cancer therapy will be documented.

l. Patients with documented disease progression will be followed every 2 months for survival status (e.g., date and cause of death) for up to 2 years or death whichever comes first. Information on the start date, type and duration of any subsequent anticancer therapy will be collected. Patients may be contacted during outpatient visits, by documented telephone contact with the patient or through contact with the primary practitioner or caregiver.

m. 12-lead ECGs will be done in triplicate (≥1 minute apart); the calculated QTcF average of the 3 ECGs must be <470 msec for eligibility. Abnormalities noted at Screening should be included in the medical history.

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

o. Screening tests for Hepatitis Virus to include HBsAg, Hepatitis B core antibody (HBcAb), total, and HCV Antibody. If either of the HBV tests are positive, order HBV DNA quantification by PCR. If HBV DNA positive, determine if anti-viral therapy is necessary.

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Appendices

Appendix 1 Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity 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	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time Ambulatory and capable of all self-care, 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 his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 2 New York Heart Association (NYHA) Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix 3 Guidelines for Women of Child-Bearing Potential

Women of Child-Bearing Potential are Defined as Follows:

- Any female who has experienced menarche and does not meet the criteria for "Women Not of Childbearing Potential".

Women Not of Childbearing Potential are Defined as Follows:

- Women who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
- Women who are >45 years of age, not using hormone replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40pg/mL (140 pmol/L)
- Women who are >45 years of age, using hormone replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone replacement therapy

Acceptable Contraception Methods:

Male patients with female partners of child-bearing potential and women patients of childbearing potential are required to use two forms of acceptable contraception, including one barrier method, during their participation in the trial and for 6 months (women) or 6 months (men) following discontinuation of study treatment. Male patients must also refrain from donating sperm for 6 months following discontinuation of study treatment.

The following are acceptable forms of barrier contraception:

- Latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/film/cream/suppository

The following are acceptable forms of secondary contraception, when used with a barrier method and spermicide:

- True abstinence. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are **not** acceptable methods of contraception

Appendix 4 Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

Patients with Measureable Disease

Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

Baseline Eligibility

Measurable Disease:	Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: 10 mm by CT scan (CT scan slice thickness no greater than 5 mm). 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable). 20 mm by chest X-ray. Skin lesions: Documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Disease:	All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with >10- to <15-mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses, and abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging requirements.

Target Lesions:	Selected lesions, up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), should be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. Pathological nodes which are defined as measurable and that may be identified as target lesions must meet the criterion or a short axis of >15 mm by CT scan. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor response.
Non-Target Lesions:	All other lesions should be identified as non-target lesions at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Guidelines for Evaluation of Measurable Disease

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, as per study screening requirements.

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. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical Lesions:	Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
Chest X-ray:	Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI:	CT is the best currently available and reproducible method to measure target lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. MRI of the chest should only be performed in extenuating circumstances. Even if IV contract cannot be administered (for example, in the situation of allergy to contract), a non-contrast CT of the chest is still preferred over MRI.
Ultrasound:	Ultrasound should not be used to measure tumor lesions. Ultrasound may be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
Endoscopy and Laparoscopy:	Use of endoscopy and laparoscopy should not be used to measure tumor lesions. Such techniques can be useful in confirming complete pathological response when biopsies are obtained.
Tumor Markers:	Tumor markers alone cannot be used to assess response. If markers are initially above the upper limit of normal, they must normalize for a subject to be considered in complete clinical response when all lesions have disappeared.
Cytology and Histology:	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).

Response Criteria

Evaluation of Target Lesions

Complete Response:	Complete disappearance of all target lesions. Any pathological lymph node (target or non-target) must have a reduction in short axis to < 10 mm).
Partial Response:	A decrease from baseline of ≥30% of the diameter(s) of all target lesions.
Stable Disease:	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest (nadir) sum of the diameters of target lesions while on study.
Progressive Disease:	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest (nadir) sum while on study (this includes the baseline sum if that is the smallest on study), or the appearance of one or more new lesions. Requires not only 20% increase, but absolute increase of a minimum of 5 mm over sum.

Evaluation of Non-Target Lesions

Complete Response:	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).
Stable Disease:	Persistence of one or more non-target lesions.
Progressive Disease:	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. When the subject also has measurable disease, to achieve “unequivocal progression” on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

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 progressive disease the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	NO	CR
CR	SD	NO	PR
CR	NE	NO	PR
PR	SD OR NE	NO	PR
SD	SD OR NE	NO	SD
PD	ANY	YES OR NO	PD
ANY	PD	YES OR NO	PD
ANY	ANY	YES	PD
NE	SD	NO	NE

Abbreviations: CR=complete response; NE=not evaluable; PD = progressive disease; PR=partial response; SD=stable disease.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of a CR depends upon this determination, it is recommended that the residual lesion be investigated by fine needle aspirate or biopsy to confirm the CR status.

When nodal disease is included in the sum of target lesions, and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression, should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Appendix 5 Data and Safety Monitoring Plan for a Multicenter Institutional Study (Phase 1 Dose Escalation Institutional Study)

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

• Review of subject data in each cohort

• Review of suspected adverse reactions considered “serious”

• Approval of dose escalation by DSMC Chair (or qualified alternate)

• Monthly monitoring (depending on study accrual)

• Minimum of a yearly regulatory audit

Monitoring and Reporting Guidelines

All institutional Phase 1 therapeutic studies are designated with a high risk assessment. The data is monitored monthly as subjects are enrolled and includes all visits monitored up through the Dose Limiting Toxicity (DLT) period. At the time of dose escalation, a written report will be submitted to the DSMC Chair outlining the cohort dose, all adverse events and suspected adverse reactions considered “serious”, and any Dose Limiting Toxicity as described in the protocol. The report will be reviewed by the DSMC Chair or qualified alternate and written authorization to proceed or a request for more information will be issued within 2 business days of the request. The report is then reviewed at the subsequent DSMC meeting. In the event that the committee does not concur with the DSMC Chair’s decision, further study accrual is held while further investigation takes place.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and subject safety and discuss each subject’s treatment at weekly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes. For each dose level, the discussion will include the number of patients, significant toxicities in accordance with the protocol, doses adjustments, and observed responses.

Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate, at minimum, monthly conference calls with the participating sites at the completion of each cohort or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Cohort updates (i.e. DLTs)
- Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

Dose Level Considerations

The PI/Study Chair, participating investigators, and research coordinators from each site will review enrollment for each dose level cohort during the regularly scheduled conference calls. The dose level for ongoing enrollment will be confirmed for each subject scheduled to be enrolled at a site. Dose level assignments for any subject scheduled to begin treatment must be confirmed by the UCSF Coordinating Center via fax or e-mail.

If a Dose Limiting Toxicity (DLT) arises in a subject treated at a study site, all sites must be notified immediately by the UCSF Coordinating Center. The Study Chair has 1 business day (after first becoming aware of the event at either the UCSF Coordinating Center or the participating site) in which to report the information to all participating sites. If the DLT occurs at a participating site, the local investigator must report it to the UCSF Coordinating Center within 1 business day, after which the UCSF Coordinating Center will notify the other participating sites.

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites. The data (i.e. copies of source documents) from the participating sites will be faxed over to the UCSF Coordinating Center prior to the monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol, patient safety, and to verify data entry.

All clinically significant adverse events (AEs), whether or not unexpected, and whether or not considered to be associated with the use of study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

All clinically significant adverse events entered into OnCore® will be reviewed on a weekly basis at the UCSF Coordinating Center's Site Committee. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

In addition, all suspected adverse reactions considered "serious" are entered into OnCore® and will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meetings, which take place every six (6) weeks.

All suspected adverse reactions considered "serious" should be reported to the UCSF Coordinating Center within 1 business day of becoming aware of the event or during the next scheduled conference call, whichever is sooner.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The contact may be by phone or e-mail.

Increase in Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert), the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail. The DSMC must receive a formal letter within 10 business days and the CHR must be notified

Data and Safety Monitoring Committee Contacts:

DSMC Chair: [redacted]
Phone: [redacted]
Email: [redacted]
Address: [redacted]

DSMC Monitors
[redacted]
UCSF Helen Diller Family
Comprehensive Cancer Center
San Francisco, CA 94143

*** DSMP approved by NCI 09/February2012**

Appendix 6 UCSF Policy/Procedure for Required Regulatory Documents for a UCSF Investigator-Initiated Oncology Clinical Trials with an Investigator held Investigational New Drug (IND)

Purpose

This policy defines the required Regulatory Documents for Single Site and Multicenter Investigator Initiated Oncology Clinical Trials at the Helen Diller Family Comprehensive Cancer Center (HDFCCC) where the Principal Investigator (PI) holds the IND.

Background

The International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines define Essential Regulatory Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of GCP and with all applicable regulatory requirements. Filing essential documents in a timely manner can greatly assist in the successful management of a clinical trial.

The Regulatory Documents will consist of electronic files in both iMedRIS and OnCore®, as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

Procedures

1. HDFCCC Essential Regulatory Documents

Documents Filed in iMedRIS:

- CHR approvals for initial submission of application, all modifications, and continuing annual renewals
- Current and prior approved protocol versions with signed protocol signature page(s)
- Committee for Human Research (CHR) approval letters and Informed Consent Form(s) (ICF)
- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event Reporting
- Protocol Violations and Single Patient Exception (SPE) Reports to CHR with supporting fax documentation

Documents Filed in OnCore®:

- Package Insert (if the study drug is commercial) or Investigator Brochure
- Protocol Review Committee (PRC) approved protocols, protocol amendments and Summary of Changes (SOC)
- Patient handouts
- Screening/enrollment log
- Data and Safety Monitoring Committee (DSMC) monitoring reports
- DSMC dose escalation approvals with study status summary forms
- OnCore® Case Report Form (CRF) completion manual

Documents Filed in Regulatory Binder:

- Completed Food and Drug Administration (FDA) 1572 document with Principal Investigator's signature
- For all Principal Investigators and Sub-Investigators listed on the FDA 1572, will need Financial Disclosure Forms, CVs, MD Licenses, Drug Enforcement Agency (DEA) Licenses, and Staff Training Documents (i.e. Collaborative Institute Training Initiative (CITI), etc.)
- Site Initiation Visit (SIV) minutes and correspondence with participating site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center
- Serious Adverse Event (SAE) reports to CHR and sponsor.
- MedWatch reporting to FDA and sponsor
- Delegation of Authority Form
- Drug Destruction Standard Operating Procedure (SOP)
- For all laboratories listed on the FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges

Appendix 7 Data and Safety Monitoring Plan for Multicenter Institutional Study (Phase 2 or 3 Institutional Study)

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- **Review of subject data**
- **Review of suspected adverse reactions considered "serious"**
- **Monthly monitoring (depending on study accrual)**
- **Minimum of a yearly regulatory audit**

Monitoring and Reporting Guidelines

All institutional Phase 2 or 3 therapeutic studies are designated with a moderate risk assessment. The data is monitored every six months, with twenty percent of the subjects monitored (or at least three subjects if the calculated value is less than three).

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate quarterly conference calls with the participating sites to communicate the review of adverse events, safety data, and other study matters.

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the study and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and subject safety and discuss each subject's treatment at monthly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

<u>Multicenter communication</u>

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate, at minimum, monthly conference calls with the participating sites at the completion of each cohort or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- **Enrollment information**
- **Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)**
- **Protocol violations**
- **Other issues affecting the conduct of the study**

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites. The data (i.e. copies of source documents) from the participating sites will be sent electronically or faxed over

to the UCSF Coordinating Center prior to the monitoring visits in order for the DSMC to monitor the participating site's compliance with the protocol, patient safety, and to verify data entry.

Adverse Event Review and Monitoring

Adverse Event Monitoring

All Grade 3-5 Adverse Events, whether or not unexpected, and whether or not considered to be associated with the use of study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the UCSF Site Committee meetings. All clinically significant adverse events must be reported to the UCSF Coordinating Center by the participating sites within 10 business days of becoming aware of the event or during the next scheduled quarterly conference call, whichever is sooner. The UCSF Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s) from the UCSF Coordinating Center and the participating sites.

In addition, all suspected adverse reactions considered "serious" must be entered in OnCore® and reported to the UCSF Coordinating Center within 1 business day. The suspected adverse reactions considered "serious" will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at the DSMC meeting, which take place every six (6) weeks.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair or qualified alternate within 1 business day of this notification. The contact may be by phone or e-mail.

Increase in Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert), the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Study Chair stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail. The DSMC must receive a formal letter within 10 business days and the CHR must be notified.

Data and Safety Monitoring Committee Contacts:

DSMC Chair:
Phone:
Email:
Address:

DSMC Monitors

UCSF Helen Diller Family
Comprehensive Cancer Center
San Francisco, CA 94143

* DSMP approved by NCI 09/February2012

Appendix 8 UCSF Policy/Procedure for Required Regulatory Documents for a UCSF Multicenter Investigator-Initiated Oncology Clinical Trials with an Investigator held Investigational New Drug (IND)

Purpose

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Background

The International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines define Essential Regulatory Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of GCP and with all applicable regulatory requirements. Filing essential documents in a timely manner can greatly assist in the successful management of a clinical trial.

The Regulatory Documents will consist of electronic files in both iMedRIS and OnCore®, as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

Procedures

1. HDFCCC Essential Regulatory Documents

Documents Filed in iMedRIS:

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- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event Reporting
- Protocol Violations and Single Patient Exception (SPE) Reports to CHR with supporting fax documentation

Documents Filed in OnCore®:

- Package Insert (if the study drug is commercial) or Investigator Brochure
- Protocol Review Committee (PRC) approved protocols, protocol amendments and Summary of Changes (SOC)
- Patient handouts
- Screening/enrollment log
- Data and Safety Monitoring Committee (DSMC) monitoring reports
- OnCore® Case Report Form (CRF) completion manual

Documents Filed in Regulatory Binder:

- Completed Food and Drug Administration (FDA) 1572 document with Principal Investigator's signature
- For all Principal Investigators and Sub-Investigators listed on the FDA 1572, will need Financial Disclosure Forms, CVs, MD Licenses, Drug Enforcement Agency (DEA) Licenses, and Staff Training Documents (i.e. Collaborative Institute Training Initiative (CITI), etc.)
- Site Initiation Visit (SIV) minutes and correspondence with participating site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center
- Serious Adverse Event (SAE) reports to CHR and sponsor.
- MedWatch reporting to FDA and sponsor
- Delegation of Authority Form
- Drug Destruction Standard Operating Procedure (SOP)
- For all laboratories listed on the FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges

2. Additional Essential Documents for Multicenter Trials for the Coordinating Center (filed in Regulatory Binder or OnCore)

- Institutional Review Board (IRB) approval letters, IRB roster, Informed Consent Form (ICF), and Health Insurance Portability and Accountability Act (HIPAA) Consent Form for the Participating Site(s)
- For all Principal Investigators and Sub-Investigators listed on the 1572 at the Participating Site(s) – Financial Disclosure Forms, CVs, MD Licenses, and Staff Training documents (i.e. Collaborative Institute Training Initiative (CITI), etc.) (for Investigational New Drug Application
- Site Initiation Visit (SIV) minutes and correspondence with Participating Site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center for the Participating Site(s)
- Protocol Violations and Single Patient Exception (SPE) reports to IRB with supporting fax documentation for Participating Site(s)
- Drug Destruction Standard Operating Procedure (SOP) for the Participating Site(s)
- Data and Safety Monitoring Committee (DSMC) monitoring reports for the Participating Site(s)
- For all laboratories listed on FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges for the Participating Site(s)
- Copy of the Data and Safety Monitoring Plan (DSMP) Monitoring Plan for all participating site(s) in Multicenter studies or Contract Research Organization (CRO) Monitoring Plan (if an outside CRO is used for the study)
- Serious Adverse Event (SAE) forms submitted to both the IRB and the sponsor for the Participating Site(s)

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Appendix 9 Required Regulatory Documents for Sub-sites Participating in a UCSF Investigator Initiated Multicenter Trial (Checklist)

Directions:

1) Fax the documents listed below to the UCSF Coordinating center [redacted] *or*

2) Scan the documents and upload to OnCore® and create a Note to File for the on-site Regulatory binder to indicate where these documents may be found

1572

☐ PI and Sub investigators:

CV and Medical license

Financial disclosure form

NIH or CITI human subject protection training certification

☐ Laboratories

CLIA and CAP

CV of Lab Director and Lab Licenses

Laboratory reference ranges

Local Institutional Review Board

☐ IRB Approval letter

☐ Reviewed/Approved documents

- Protocol version date: _____
- Informed consent version date: _____
- Investigator Brochure version date: _____
- HIPAA

☐ Current IRB Roster

Other

☐ Delegation of Authority Log

- Include NIH or CITI human subject protection training certificates or GCP training certification

☐ Pharmacy

- Drug destruction SOP and Policy

☐ Protocol signature page

☐ Executed sub contract

27.apr.2012

Appendix 10 Inhibitors and Inducers of CYP3A

Strong inhibitors	Moderate inhibitors	Weak inhibitors	All Other Inhibitors
Indinavir	Aprepitant	Cimetidine	Chloramphenicol
Nelfinavir	Amprenavir	fluvoxamine	Delaviridine
Ritonavir	Atzanavir		Diethyl-Dithiocarbamate
Clarithromycin	Ciprofloxacin		Gestodene
Itraconazole	Crizotinib		Mifepristone
Ketoconazole	Darunavir		Norfloxacin
Nefazodone	Diltiazem		Norfluoxetine
Saquinavir	dronedarone		
Suboxone	Erythromycin		
Telithromycin	Fluconazole		
cobicistat	Grapefruit Juice		
boceprevir	Seville Orange Juice		
mibefradil	Verapamil		
telaprevir	Voriconazole		
Troeandomycin	imatinib		
posaconazole			
Inducers			
Carbamazepine	Oxcarbarzepine	Rifabutin	
Efavirenz	Phenobarbital	Rifampin	
Nevirapine	Phenytoin	St. John's Wort	
Barbiturates	Pioglitazone	Troglitazone	
Glucocorticoids			
Modafinil			
Oxcarbarzepine			
Phenobarbital			
Phenytoin			
Pioglitazone			