PROTOCOL

TITLE:	A randomized, multicenter, double-blind, placebo-controlled, Phase 3 study of the Bruton's Tyrosine Kinase inhibitor 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
PROTOCOL NUMBER:	**PCYC-1137-CA**
STUDY DRUG:	Ibrutinib (PCI-32765)
IND NUMBER:	124,674
EudraCT NUMBER:	2014-002069-31
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SPONSOR:	Pharmacyclics LLC 995 East Arques Avenue Sunnyvale, CA 94085-4521 United States of America
DATE FINAL:	17 March 2015
Amendment 1:	15 June 2015
Amendment 2:	25 August 2015
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PROTOCOL APPROVAL PAGE

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I have carefully read Protocol PCYC-1137-CA entitled: **"A randomized, multicenter, double-blind, placebo-controlled, Phase 3 study of the Bruton's Tyrosine Kinase inhibitor 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"**.

I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the Sponsor, Pharmacyclics, and the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of Pharmacyclics. All data pertaining to this study will be provided to Pharmacyclics. The policy of Pharmacyclics LLC requires that any presentation or publication of study data by clinical Investigators be reviewed by Pharmacyclics, before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

The following Pharmacyclics LLC representative is authorized to sign the protocol and any amendments:

DocuSigned by:
George Cole Jul-20-2017
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Medical Monitor's Signature Date
George Cole, MD
Clinical Development, Pharmacyclics LLC

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SYNOPSIS

Study Title:	A randomized, multicenter, double-blind, placebo-controlled, Phase 3 study of the Bruton's Tyrosine Kinase inhibitor 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
Protocol Number:	PCYC-1137-CA
Study Phase:	3
Study Duration:	Estimated to be 38 months
Number of Subjects	Approximately 426 (6 subjects in the Safety Run-in Phase and 420 subjects in the Double-blind Randomized Phase)
Investigational Product and Reference Therapy:	**Ibrutinib (IMBRUVICA®)** will be supplied as 140 mg hard gelatin capsules for oral (PO) administration at a dose of 560 mg daily, in combination with nab-paclitaxel and gemcitabine **Placebo** will be supplied as matched hard gelatin capsules for oral (PO) administration, in combination with nab-paclitaxel and gemcitabine **Gemcitabine:** is available as 200 mg or 1000 mg lyophilized powder single use vials for reconstitution and intravenous (IV) administration **Nab-paclitaxel:** is available as 100 mg lyophilized powder single use vials for reconstitution and intravenous (IV) administration
Objectives:	**Primary Objective:** To evaluate the efficacy of ibrutinib in combination with nab-paclitaxel and gemcitabine versus placebo in combination with nab-paclitaxel and gemcitabine, based on investigator assessment of progression-free survival (PFS) and overall survival (OS), for the first line treatment of patients with metastatic pancreatic adenocarcinoma **Secondary Objectives:** • Clinical benefit response (CBR) rate • Overall response rate (ORR): complete response (CR) + partial response (PR), *per* investigator assessment • Carbohydrate antigen 19-9 (CA19-9) response • Patient-reported outcomes (PRO) by EORTC QLQ-C30 • Rate of venous thromboembolic events (VTE) • To evaluate the safety and tolerability of ibrutinib in combination with nab-paclitaxel and gemcitabine *versus* placebo in combination with nab-paclitaxel and gemcitabine
Study Design:	The study will consist of **two phases**: **Safety Run-in Phase:** Six subjects will initially be recruited to receive open-label ibrutinib in combination with nab-paclitaxel and gemcitabine. The independent Data Monitoring Committee (DMC) will review data on the safety of ibrutinib combined with nab-paclitaxel and gemcitabine, after the first 6 subjects have completed at least 28 days of follow-up after the

	initiation of combination therapy as detailed in Section 10.8. Following DMC review and confirmation, the study may proceed to the Double-blind Randomized Phase. **Double-blind Randomized Phase:** The Double-blind Randomized Phase will compare ibrutinib in combination with nab-paclitaxel and gemcitabine *versus* placebo in combination with nab-paclitaxel and gemcitabine Approximately 420 subjects will be randomized between Arm A (ibrutinib in combination with nab-paclitaxel and gemcitabine) and Arm B (placebo in combination with nab-paclitaxel and gemcitabine). Randomization will be stratified according to: • Karnofsky performance status (KPS) 70-80 *vs* KPS 90-100 • Liver metastasis (present or absent) • Age ≤65 years vs age >65 years Subjects will be treated until unacceptable toxicity or disease progression, whichever occurs first. If nab-paclitaxel and/or gemcitabine or ibrutinib/placebo are discontinued prior to disease progression, the remaining agents will be continued until unacceptable toxicity or disease progression.
Population:	Subjects with previously untreated metastatic pancreatic adenocarcinoma who, in the opinion of the investigator, are candidates for nab-paclitaxel and gemcitabine combination chemotherapy.
Centers:	Multicenter
Inclusion Criteria:	*Disease-related* 1. Histologically or cytologically confirmed diagnosis of pancreatic adenocarcinoma. 2. Stage IV disease diagnosed **within 6 weeks of randomization.** 3. Disease which is evaluable according to RECIST 1.1, with at least one measurable metastatic lesion (not in a previously irradiated area). 4. Disease status for which, in the opinion of the investigator, nab-paclitaxel and gemcitabine is considered an appropriate treatment choice. 5. No previous radiotherapy, surgery, cytotoxic chemotherapy or investigational therapy for the treatment of **metastatic** pancreatic adenocarcinoma. 6. No prior **neo-adjuvant, peri-operative or adjuvant chemotherapy** for primary disease of pancreatic adenocarcinoma. Prior treatment with 5-Fluorouracil (5-FU), gemcitabine or capecitabine administered as a radiation sensitizer (at non-cytotoxic doses) in the adjuvant setting is allowed, provided at least 6 months have elapsed since completion of the last dose. 7. No clinically significant third-space fluid accumulation (eg, ascites or pleural effusion).

	8. Male and female subjects of reproductive potential who agree to use highly effective methods of birth control (eg, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence[1], or sterilized partner) and a barrier method (eg, condoms, cervical ring, sponge, etc) during the period of therapy and for 6 months for males and females after the last dose of study medication. 9. Ability to provide written informed consent and to understand and comply with the requirements of the study. *Laboratory* 10. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to randomization: • Absolute neutrophil count (ANC) ≥1.5 x 10^9/L • Platelet count ≥100 x 10^9/L • Hemoglobin ≥9 g/dL 11. Adequate hepatic and renal function defined as: • Serum aspartate transaminase (AST) and/or alanine transaminase (ALT) ≤5.0 x upper limit of normal (ULN) if liver metastases, or ≤3 x ULN without liver metastases • Alkaline phosphatase <3.0 x ULN or ≤5.0 x ULN if liver or bone metastases present • Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin, such as hemolysis) • Estimated Creatinine Clearance ≥30 mL/min (Cockcroft-Gault) 12. PT/INR <1.5 x ULN and PTT (aPTT) <1.5 x ULN *Demographic* 13. Men and women ≥18 years of age 14. Karnofsky performance status (KPS) ≥70. 15. ECOG 0-1
Exclusion Criteria:	*Disease Related* 1. Prior radiotherapy to any measurable lesion at any time. 2. Radiotherapy in the adjuvant setting, or earlier, within the last 6 months. 3. Previous cytotoxic chemotherapy for primary disease of pancreatic adenocarcinoma. 4. Neuroendocrine (carcinoid, islet cell) or acinar pancreatic carcinoma

[1] Complete abstinence is a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01 About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

	Concurrent Conditions 5. Known brain or leptomeningeal disease (CT or MRI scan of the brain required only in case of clinical suspicion of central nervous system [CNS] involvement). 6. Prior exposure to Bruton's tyrosine kinase (BTK) inhibitor. 7. A documented ≥10% decrease in KPS between Screening visit and within 72 hours prior to randomization. 8. History of other malignancies, except: • Malignancy treated with curative intent and with no known active disease present for ≥3 years before the first dose of study drug and felt to be at low risk for recurrence by investigator. • Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease. • Adequately treated carcinoma *in situ* without current evidence of disease. 9. Known bleeding disorders (eg, von Willebrand's disease or hemophilia). 10. Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded. 11. Live vaccination within 4 weeks prior to randomization. 12. Any uncontrolled active systemic infection including any infection requiring systemic IV treatment which was completed ≤7 days before randomization. 13. Major surgery within 4 weeks of first dose of study drug. 14. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk. 15. History of stroke or intracranial hemorrhage within 6 months prior to enrollment. 16. 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. 17. History of interstitial lung disease, idiopathic pulmonary fibrosis, or pulmonary hypersensitivity pneumonitis. 18. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction. 19. Concomitant use of warfarin or other Vitamin K antagonists.

	20. Known hypersensitivity to any study drug (nab-paclitaxel, gemcitabine or ibrutinib). 21. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor. 22. Currently active, clinically significant hepatic impairment (Class B or C according to the Child-Pugh classification [Appendix I]). 23. Lactating or pregnant. 24. Unwilling or unable to participate in all required study evaluations and procedures. 25. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations). 26. Decline in serum albumin ≥20% from Screening to study randomization (both labs at Screening and prior to randomization may be confirmed locally).
Study Treatment:	**1:1 Randomization between Arm A & Arm B** Study medication should commence within 3 days of randomization. **Arm A** **Ibrutinib** (PO) 560 mg daily (4 capsules) until PD or unacceptable toxicity in combination with: **Nab-paclitaxel** (IV) 125 mg/m^2 and **gemcitabine** (IV) 1000 mg/m^2 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/m^2 and **gemcitabine** (IV) 1000 mg/m^2 given on Days 1, 8, and 15 of each 28-day cycle, until evidence of PD or is no longer tolerated by the subject. **Dose Modifications** Dose modifications for toxicity will be made **separately for each agent** as detailed in Section 5.3.1.4 for ibrutinib/placebo and Section 5.3.2.4 for nab-paclitaxel and gemcitabine.
Concomitant Therapy:	Avoid co-administration with strong CYP3A or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Any non-study protocol related chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited while the subject is receiving study medication. Corticosteroids (at dosages equivalent to prednisone >20 mg/day) for >14 days should be avoided.

Safety Plan:	The safety of this study will be monitored by an independent data monitoring committee (DMC) as outlined in the DMC charter and in accordance with the Sponsor's Pharmacovigilance procedures. The DMC will consist of at least two clinicians including one medical expert in the management of pancreatic adenocarcinoma and at least one statistician. **Safety Run-in Phase:** The DMC will review data on the safety of ibrutinib in combination with nab-paclitaxel and gemcitabine, after the first six subjects have completed at least 28 days of follow-up after the initiation of combination therapy. Further enrollment will be suspended until the safety data have been reviewed. Depending on the outcome of their review, the DMC may recommend that: 1. The study continue to the Double-blind Randomized Phase. 2. Prior to commencing the Double-blind Randomized Phase, an additional safety review is performed after a total of up to 12 subjects have been treated with ibrutinib (560 mg) in combination with nab-paclitaxel and gemcitabine. 3. Prior to commencing the Double-blind Randomized Phase, the dose level of ibrutinib should be reduced to 420 mg and an additional 6 subjects should be studied at this dose level, in combination with nab-paclitaxel and gemcitabine. **Double-blind Randomized Phase:** The DMC will review **unblinded** safety data on subjects randomized to each arm at periodic intervals during the study, as detailed in the DMC charter. The Sponsor will be reviewing blinded safety data on an ongoing basis and if a potential safety signal arises, additional *ad hoc* meetings may be convened, if requested by the DMC or the Sponsor.
Statistical Methods:	All efficacy analyses will be performed using the **Intent-To-Treat (ITT) Population** (consisting of all subjects randomized). *Efficacy data from subjects in the open label safety run-in phase will be presented separately from the double-blind randomized phase.* **Primary Endpoints:** The primary endpoints of this study are PFS by investigator assessment, according to RECIST 1.1 criteria, and OS. Both PFS and OS will be analyzed comparing the 2 treatment arms using the log-rank test stratified by the stratification factors. **Secondary Endpoints:** • Clinical benefit response (CBR) rate will be compared using a chi-square test. • Overall response rate (ORR) will be compared using a chi-square test. • Carbohydrate antigen 19-9 (CA19-9) response will be compared using a chi-square test.

	• Patient-reported outcomes (PRO) by EORTC QLQ-C30 will be summarized with descriptive statistics by treatment arm. Longitudinal analysis with repeated measures may be used as appropriate. • Rate of venous thromboembolic events (VTE) Multiplicity adjustment will be considered for the analysis of primary and secondary endpoints to control the overall Type I error. Details will be specified in the statistical analysis plan. **Safety Analysis:** **Safety Run-in Phase:** Safety data from subjects in the open label run-in phase will be presented separately from the randomized Safety Population. **Double-blind Randomized Phase:** Safety data will be generated from the Safety Population (consisting of all subjects randomized and receiving at least one dose of any study drug).
DMC Review	A DMC review of safety data including all death events will be performed approximately every 6 months after the first subject is randomized.
Sample Size Determination	The sample size calculation is based on a 2-sided family-wise Type I error rate (FWER) of 0.05 for two primary endpoints, PFS and OS. The FWER is controlled at 0.05 with 0.007 allocated to the PFS analysis and 0.043 allocated to the OS analysis. As of 24 April 2017, a total of 424 subjects have been randomized with a 1:1 allocation to the two treatment arms. The calculations are based on the following assumptions using EAST software version 6.3.1 and the actual enrollment rates. **For PFS:** • Median PFS is 5.5 months for the control arm (nab-paclitaxel and gemcitabine) (Von Hoff 2013). • Target hazard ratio is 0.66 which corresponds to a 51% improvement in median PFS (eg, from 5.5 months to 8.33 months) for the ibrutinib + nab-paclitaxel + gemcitabine arm compared to the placebo + nab-paclitaxel + gemcitabine arm • 2-sided $\alpha = 0.007$ A total of 350 PFS events will provide approximately 88% power. **For OS:** • Median OS is 8.5 months for the control arm (nab-paclitaxel and gemcitabine) (Von Hoff 2013). • Target hazard ratio is 0.735 which corresponds to approximately 36% improvement in median OS (eg, from 8.5 months to 11.6 months) for the ibrutinib + nab-paclitaxel + gemcitabine arm compared to the placebo + nab-paclitaxel + gemcitabine arm • 2-sided $\alpha = 0.043$

	• A group sequential design with one interim analysis is planned when at least 250 deaths occur (approximately 71% of the deaths occur). Lan-DeMets alpha spending function with O'Brien-Fleming boundary for efficacy is used. • A total of 353 OS events will provide approximately 80% power for the study.

ABBREVIATIONS

AE	adverse event
AESI	Adverse Events of Special Interest (AESI)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-24}	area under the curve from zero to 24 hours
BCR	B-cell receptor
CYP	cytochrome P
BTK	Bruton's tyrosine kinase
CA 19-9	Carbohydrate antigen 19-9
CBR	clinical benefit response
CI	confidence interval
CLL	chronic lymphocytic leukemia
CNS	central nervous system
C_{max}	maximum observed plasma concentration
CR	complete response
CRF	case report form (paper or electronic as appropriate for this study)
CT	Computerized Tomography
CTCAE	NCI Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	Disease Control Rate
DMC	Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group performance status
ECG	Electrocardiogram
eDC	electronic data capture
EFS	Event free survival
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End-of-Treatment
FWER	family-wise Type I error rate
5-FU	5-Fluorouracil
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act
HUS	Hemolytic Uremic Syndrome
IC_{50}	concentration that inhibits a process by 50%
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normal ratio
IB	Investigator's Brochure
ILD	interstitial lung disease
IRB	Institutional Review Board
ITK	interleukin-2-inducible kinase

ITT	Intent-to-treat
IV	intravenous
IWRS	interactive web response system
KPS	Karnofsky Performance Status
LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MPAC	Memorial Pain Assessment Card
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NSCLC	non small cell lung cancer
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PO	oral
PR	partial response
PRO	patient-reported outcome(s)
aPTT	activated partial thromboplastin time
PT	prothrombin time
REB	Research Ethics Board
RECIST	Response Evaluation Criteria In Solid Tumors
QLQ-C30	EORTC core quality of life questionnaire
QTc	QT interval corrected for heart rate
SCARs	severe cutaneous adverse reactions
SAE	serious adverse event
SD	stable disease
SJS	Steven-Johnson syndrome
SLL	small lymphocytic lymphoma
SP	Safety Population
$t_{1/2}$	half-life
T_{max}	time to maximum plasma concentration
TDP	Time to diminished pain
TGI	tumor growth inhibition
TLS	tumor lysis syndrome
VTE	venous thromboembolic events
ULN	upper limit of normal
USP	United States Pharmacopeia

1. BACKGROUND

1.1. Pancreatic Adenocarcinoma

Pancreatic adenocarcinoma remains one of the most intractable of all malignancies. The diagnosis is almost universally associated with exceptionally poor outcomes, resulting in an extremely short survival and substantial concomitant burden of both disease and treatment related morbidity. The bleakness of the prognosis is exemplified by the profound depression characterizing the condition (Boyd 2012) with suicide rates in those with pancreatic cancer eleven times greater than within the general population (Turarga 2011).

Worldwide, approximately 300,000 new cases of pancreatic cancer are recorded annually, with over 90% being ductal adenocarcinomas. In the United States despite accounting for less than 5% of malignancies in total, the disease remains the fourth leading cancer-related cause of death in both men and women (World Cancer Research Fund International 2013, Siegel 2014). The American Cancer Society estimates that approximately 45,000 patients were diagnosed with pancreatic cancer in 2013, with over 37,000 of them surviving less than a year (American Cancer Society 2013).

It is therefore a devastating disease and within the entire spectrum of neoplastic conditions, pancreatic adenocarcinoma is a malignancy characterized by the most intractable biology and refractory clinical course, resulting in a rapid natural history of disease progression and death.

In the US, the average lifetime risk for developing pancreatic cancer is 1%–2% and unlike most other malignancies, the incidence has been slowly increasing over the last decade (Malvezzi 2014).

Identified risk factors are wide ranging and include chronic pancreatitis, smoking, diabetes mellitus, significant family history of the disease and certain genetic disorders such as cystic fibrosis, hereditary pancreatitis, Peutz-Jeghers syndrome, and Lynch syndrome (Zavoral 2011, Alsamarrai 2014, Larsson 2005, Li 2009). An excess incidence of pancreatic adenocarcinoma also appears to occur in patients with BRCA-1 and BRCA-2 mutations (Easton 1999, Al-Sukhni 2008). The median age at detection is 71 and the disease is extremely rare in those aged less than 40 (Raimondi 2009).

The two major precursors of pancreatic adenocarcinoma are pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. These antecedent conditions are associated with a stepwise pattern of histological deterioration, combined with progressively worsening genetic mutational alterations (Canto 2012, Hustinx 2005), ultimately resulting in overt carcinoma typically possessing considerable intratumoral genomic heterogeneity and multiple distinct subclones (Iacobuzio-Donahue 2009).

Characteristic features of the disease include a high rate of activating mutations in KRAS (>90%), progression from distinct types of precursor lesions, a propensity for both local invasion and distant metastasis, an extensive stromal reaction (desmoplasia) resulting in a hypovascular and hypoxic microenvironment, reprogramming of cellular metabolism, and evasion of tumor immunity (Ryan 2014, Feig 2012, Vonderheide 2013, Ogura 2013). These disease characteristics collectively combine to present major challenges to the development of effective therapeutic strategies.

Despite the recent evolution of more sophisticated imaging modalities aimed at earlier detection, including high-resolution computed tomography (CT) scanning and endoscopic ultrasound (Langer 2009, Poley 2009), the overall 5-year survival for patients with pancreatic cancer is less than 5%. This poor prognosis is predominantly influenced by the majority of patients being diagnosed late in the disease process. Unlike many other gastrointestinal malignancies, pancreatic cancer tends to remain asymptomatic and undiagnosed until significant locoregional or distant disease is present (Furukawa 2001, Hruban 2014, Enewold 2015) with four out of five initially presenting with unresectable tumor burden. One-third of this advanced patient population will have inoperable locally-advanced disease, while the remaining two-thirds will have evidence of stage IV metastases at diagnosis (Brunner 2010).

Approximately 85% of patients with distant disease will present with liver metastases, a finding known to be associated with poor outcomes (Papadoniou 2008, Hawes 2000, Park 2008). In contrast, a small proportion of patients have disseminated disease limited to isolated pulmonary metastases and in this sub group, a more favorable prognosis with prolonged survival has been reported (Katz 2009, Arnaoutakis 2011).

Complete resection with histologically negative margins is the only intervention offering the possibility of long-term survival for the 20% or so of cases presenting without overt advanced inoperable disease at diagnosis. While early detection is rare, those with tumors limited to the pancreas without nodal involvement and who undergo successful resection can experience a median survival of over 30 months with 1-, 3-, and 5-year survivals of 80%, 49%, and 41%, respectively (Cameron 2006). In contrast however, many patients are unfortunately discovered to have extensive lymph node involvement and/or microscopically positive operative margins at the time of surgery (Konstantinidis 2013), findings which are incompatible with a favorable longer term course.

Due to the technical challenges of surgery, only 15% of patients actually undergoing operative intervention achieve a sufficiently prolonged remission to be consistent with a curative outcome (Lowy 2008). Despite these favorable results in a few, the majority of patients receiving surgery will ultimately develop locoregional recurrence and/or distant metastases. In view of the limited overall disease control obtained with surgery alone, both chemoradiation and chemotherapy have therefore been utilized as adjuncts to resection, in an attempt to minimize subsequent locoregional and distant recurrence (Kalser 1985, Oettle 2007, Neoptolemos 2004).

Despite a lack of consensus over the most appropriate adjuvant intervention, clinically significant improvements with adjuvant therapy are clearly obtainable in some situations, especially in carefully selected patient sub-groups (such as those with R1 resections, or positive lymph nodes) with reported hazard ratios for death, compared to no adjuvant treatment, in the range 0.5-0.7 (Corsini 2008, Butturini 2008, Oettle 2007, Oettle 2013).

However, any overall advantage conferred by adjuvant treatment is unfortunately constrained by the small proportion of the total patient population for whom it is a realistic therapeutic option. Additionally, the benefits that such adjuvant treatment strategies bring is modest compared to similar adjuvant interventions in many other solid tumor settings (Liao 2013, Raigani 2014).

Delayed detection and hence the limited utility of surgical and adjuvant strategies is one of the two major drivers underlying the aggressive natural history of pancreatic adenocarcinoma. The second is the lack of effective chemotherapeutic strategies, most markedly in the advanced setting. Current chemotherapy regimens are only marginally effective in extending survival, a finding which has not changed in over three decades (Loc 2014, Oberstein 2013, Falconi 2003), underscoring the ongoing unmet medical need for novel and innovative new approaches for advanced disease in this most challenging of malignancies.

1.2. Current Treatment Options for Advanced Pancreatic Adenocarcinoma

1.2.1. Regional Therapy

A number of evolving radiotherapy techniques are being deployed in the first line management of locally advanced, unresectable disease, such as intensity modulated radiotherapy (IMRT) (Yovino 2011), stereotactic body radiotherapy (SBRT) (Chang 2009) and intraoperative radiation therapy (IORT) (when used in patients found to have unresectable disease at the time of surgery) (Jingu 2012, Ashman 2013).

While these modalities can achieve enhanced dose delivery to the tumor site, with reduced collateral irradiation of non-malignant tissue, and correspondingly improved local control, there is to date little evidence that this translates into an improvement in survival, possibly due to a confounding increase in the frequency of metastatic disease, at least in some reported series (Gunderson 1987, Mohuiddin 1995).

The uncertainty around the clinical benefit of these approaches, as well as methodological complexities in defining optimal total and fractional radiotherapy doses, severely constrain the widespread application of such treatment strategies in the management of locally advanced unresectable disease. In general, suitable patients would only have access to such techniques through participation in clinical trials at specialized centres (NCCN Guidelines 2016).

1.2.2. Chemoradiotherapy

Chemoradiation (involving sensitizers such as 5-Fluorouracil (5-FU) [Moertel 1981, Crane 2002], gemcitabine [Murphy 2007, Girard 2010] or capecitabine [Mukherjee 2013]) has established a role in the initial management of certain patient subsets with unresectable locally advanced disease, in particular those who do not develop metastatic dissemination during preceding chemotherapy. However, as with many treatment strategies in advanced pancreatic cancer, the utility of this approach remains controversial (Kim 2007, Cavalcante 2014).

The choice of initial management of patients with unresectable locally advanced disease is further complicated by the lack of consensus over the optimal sequencing of employing chemoradiation at the outset versus initial chemotherapy followed by subsequent chemoradiation (Jones 2014, Huguet 2014). The former approach is probably most suited to selected patients with poorly controlled pain and/or locally invasive disease resulting in bleeding (Blackstock 2003) while the latter appears to confer greatest benefit in those with a good performance status, no detectable metastatic burden and little probability of disease reverting to a resectable status (Huguet 2007, Krishnan 2007).

Overall, the balance of available evidence seems to suggest that chemoradiation is superior to radiation alone but there is no convincing advantage established to date for chemoradiation versus chemotherapy alone (Chen 2013, Hammel 2013, Azria 2014), typically with similar median overall survival (OS) figures of less than 12 months for either regimen. Given the marginal benefits of treatment, it is clear that careful selection of appropriate patient populations for any give modality is essential for maximizing the modest results that can be expected.

1.2.3. Systemic Chemotherapy

Patients with advanced pancreatic disease most frequently receive chemotherapy in the first line setting, with the aim of prolonging survival and providing palliative relief of symptoms such as pain, weight loss, biliary obstruction and declining performance status (NCCN Guidelines 2016, Seufferlein 2012).

Gemcitabine monotherapy was the original standard of care for patients with metastatic pancreatic cancer for several years. Although it only showed a marginal survival benefit over treatment with bolus 5-FU (5.6 *versus* 4.4 months), there was a significantly higher proportion of patients who achieved clinical benefit with gemcitabine compared to 5-FU (23.8% versus 4.8%) (Aapro 1998, Burris 1997).

The limited efficacy of gemcitabine monotherapy appears to be improved by administering the drug at a fixed dose rate (FDR), rather than the standard 30 minute infusion conventionally utilized, resulting in a 25% improvement in median survival (6.2 months versus 4.9 months) (Poplin 2009). This differential activity is probably due to greater intracellular concentrations of the phosphorylated active form of gemcitabine achievable with FDR (eg, 10 mg/m^2/min) delivery techniques (Grunewald 1991).

Numerous combination strategies with a range of chemotherapy agents, including cisplatin, oxaliplatin, capecitabine, 5-FU, epirubicin, paclitaxel and docetaxel (Poplin 2009, Reni 2005) have been studied in combination with gemcitabine in an attempt to improve treatment outcomes. However, despite the variety of combination approaches examined, little benefit has been seen over gemcitabine monotherapy in the advanced disease setting, with a significant increase in toxicity in all cases (Ciliberto 2013, Sun 2012). Furthermore, where any benefit has been seen with gemcitabine-combination therapy, it has been restricted to the small proportion of patients with a good performance status (Heinemann 2008, Herrmann 2007, Heinemann 2006, Whitehead 1997). Combination regimens which are currently endorsed by the National Comprehensive Cancer Network (NCCN) Pancreatic Adenocarcinoma Guidelines (NCCN Guidelines: Pancreatic Adenocarcinoma 2016) for this prognostically more favorable group include gemcitabine plus capecitabine (Li 2014) and the combination of gemcitabine, docetaxel and capecitabine (the GTX regimen) (Fine 2008, De Jesus-Acosta 2012).

Gemcitabine and cisplatin combinations are also recommended for selected patients who may harbor *BRCA* mutations, based on empirical findings of superior efficacy of this approach in patients with a family history of pancreatic cancer (Lowery 2011).

Despite generally highly variable results reported for taxanes when used as monotherapy (Androulakis 1999a, Rougier 2000, Gebbia 1996), or when given with gemcitabine (Jacobs 1999, Androulakis 1999b) recently the combination of gemcitabine plus nab-paclitaxel (albumin bound paclitaxel particles) has shown an increased median survival of 1.8 months, with improved OS at 1 and 2 years, when compared to gemcitabine alone. Furthermore, compared to the significant toxicity of the FOLFIRINOX regimen discussed below, adverse effects were acceptable, mainly consisting of cytopenias and peripheral neuropathy (Von Hoff 2013).

In addition to chemotherapeutic regimens, gemcitabine has also been examined in combination with more targeted approaches, including a number of kinase inhibitors. The range of agents studied encompasses bevacizumab (Kindler 2011), cetuximab (Philip 2010), saridegib (Richards 2012), axitinib (Kindler 2011), sorafenib (Goncalves 2012), aflibercept (Rougier 2013), tipifarnib (Van Cutsem 2004), marimastat (Philip 2008), pemetrexed (Oettle 2005) and erlotinib (Moore 2007), amongst others. Despite the mechanistic variety of targeted agents, erlotinib was the only combination to show a statistically significant survival advantage over gemcitabine monotherapy, although this was by only two weeks. However, the minimal survival benefit seen with this combination has been tempered by both a significant side effect profile and the high cost of treatment, leading to limited uptake of this combination in clinical practice.

Additionally, a number of *non-gemcitabine* based regimens have also been examined in advanced pancreatic cancer, including capecitabine plus continuous infusional 5-FU (Boeck 2010, Cartwright 2002) and the combination of a fluoropyrimidine (5-FU/leucovorin or capecitabine) with oxaliplatin (Pelzer 2011, Xiong 2008).

Of particular note, the multidrug combination of leucovorin, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) was recently reported to provide an increased median survival of 4.3 months when compared to gemcitabine monotherapy. However, given its significant side effect profile, it is effectively available only to a select group of patients with advanced pancreatic cancer who are able to tolerate such an intensive intervention (Conroy 2011).

Overall, current NCCN and ESMO guidelines detail a wide range of treatment options for patients with advanced pancreatic cancer, with the exception of those with a poor performance status, where gemcitabine monotherapy is essentially the only recommendation. The broad variety of possible treatment choices is however an indication of the dissatisfaction with each individually. Choosing an appropriate treatment regimen therefore remains complicated and uncertain and in the absence of randomized comparative trials, there is no consensus on first-line therapy for these patients. Treatment choices are therefore guided empirically and pragmatically without evidence based, well-defined and validated treatment algorithms.

Currently the three most widely used chemotherapy combinations for patients with a good performance status (ie, ECOG PS of 0 or 1, adequate pain control, a patent biliary stent and adequate nutritional intake), are FOLFIRINOX, gemcitabine plus nab-paclitaxel and gemcitabine plus erlotinib (Seufferlein 2012, NCCN Guidelines: Pancreatic Adenocarcinoma 2016). Out of over thirty phase 3 studies in pancreatic adenocarcinoma over the last decade, these are the only ones to have reported a statistically significant improvement in survival, when compared to gemcitabine alone.

Results of Phase 3 trials for these three regimens are summarized in Table 1 below:

Table 1. Summary of Phase 3 Trial Results of FOLFIRINOX, Gemcitabine Plus Nab-paclitaxel and Gemcitabine Plus Erlotinib in Pancreatic Adenocarcinoma

REGIMEN	**FOLFIRINOX *vs* G**			**NAB-PAC + G *vs* G**			**ERL + G *vs* G**		
GROUP	F	G	*p* value	Nab+G	G	*p* value	ERL	G	*p* value
PFS (ms)	6.4	3.3	<0.001	5.5	3.7	<0.0001	3.75	3.55	0.004
OS (ms)	11.1	6.8	<0.001	8.5	6.7	<0.0001	6.24	5.91	0.038
	12.5* 13.7**								
ORR (%)	31.6	9.4	<0.001	23	7	<0.0001	8.6	8	n/a

Abbreviations: F = FOLFIRINOX, G=gemcitabine; ERL=erlotinib; Nab-PAC= nab-paclitaxel; ORR=overall response rate; OS=overall survival; PFS=progression-free survival

* OS in *metastatic disease* from single centre MSKCC study of FOLFIROX

** OS in *locally advanced disease* from single centre MSKCC study of FOLFIROX (Lowery 2012)

Although comparison across trials is limited by methodological variations, greatest efficacy was seen with the FOLFIRINOX regimen although at the cost of a substantially higher burden of Grade 3/4 toxicity (45.7% neutropenia, 12.7% diarrhea, 9.1% thrombocytopenia, 9% sensory neuropathy). However, although clearly more toxic, it is notable that significantly fewer patients

had an impaired quality of life at six months in the FOLFIRINOX group compared to the gemcitabine one (31% versus 66%, p <0.001). Furthermore, a subsequent more detailed analysis of patient outcomes showed that patients in the FOLFIRINOX group actually maintained or even improved quality of life compared to those treated with gemcitabine (Gourgou-Bourgade 2013).

Erlotinib and gemcitabine reported minimal improvement in efficacy (although greater activity was seen in patients developing a skin rash early on in treatment, this being a recognized surrogate of EGFR inhibition) (Moore 2007, Van Cutsem 2009). Furthermore the marginal efficacy advantage was abrogated by the finding that whilst toxicities were fairly comparable between the two groups, three times as many patients required a dose reduction in the erlotinib and gemcitabine arm, compared to gemcitabine alone (16% versus 5%).

The Phase 3 trial of nab-paclitaxel and gemcitabine (Von Hoff 2013) reported efficacy improvements over gemcitabine alone.

A total of 861 patients were randomly assigned to either nab-paclitaxel and gemcitabine (n=431) or gemcitabine alone (n=430). Median OS was 8.5 months with nab-paclitaxel and gemcitabine versus 6.7 months with gemcitabine alone (hazard ratio 0.72; 95% CI 0.62 to 0.83; P<0.001). The survival rate was 35% versus 22% at 1 year, and 9% versus 4% at 2 years, respectively. Median progression-free survival was 5.5 months for nab-paclitaxel and gemcitabine versus 3.7 months for gemcitabine alone (hazard ratio, 0.69; 95% CI, 0.58 to 0.82; P<0.001) with a similar benefit (hazard ratio) for both median PFS and median OS. The rate of progression-free survival was 44% versus 25% at 6 months and 16% versus 9% at 1 year, respectively.

Overall, treatment effects for both OS and PFS consistently favored the nab-paclitaxel and gemcitabine group across most protocol prespecified subgroups. Patients with more advanced disease (poorer performance status, presence of liver metastasis, more than three sites of metastatic disease, metastatic pancreatic cancer at initial diagnosis, or a CA19-9 level that was ≥59 times the upper limit of the normal) had the highest reduction in the risk of death and greatest prolongation of PFS with nab-paclitaxel and gemcitabine compared to gemcitabine alone.

The overall response rate (ORR) was 23% versus 7% in the two groups (P<0.001) while the rate of disease control (confirmed response or stable disease for ≥16 weeks) was 48% versus 33% respectively (P<0.001).

In addition, 61% of patients in the nab-paclitaxel and gemcitabine group, versus 44% of those in the gemcitabine alone group, had a serum carbohydrate antigen CA19-9 decrease from baseline of at least 20% (P<0.001) and 31% versus 14% had a decrease of at least 90% (P<0.001). Patients in both treatment groups who achieved a decrease of at least 90% in the CA19-9 level had a median survival of 13.5 months, as compared with 8.2 months among those with a decrease of less than 90% (hazard ratio, 0.53; 95% CI, 0.43 to 0.67; P<0.001).

The most common adverse events (AEs) of grade 3 or higher severity were neutropenia (38% in the nab-paclitaxel and gemcitabine group versus 27% in the gemcitabine alone group), fatigue (17% versus 7%), and neuropathy (17% versus 1%). Febrile neutropenia occurred in 3% versus 1% of the patients in the two groups respectively. In the nab-paclitaxel and gemcitabine group, neuropathy of grade 3 or higher improved to grade 1 or lower in a median of 29 days.

Although first line therapy with regimens such as nab-paclitaxel plus gemcitabine and FOLFIRINOX provide improved outcomes versus gemcitabine monotherapy, the limited extent of any gains and the toxicity afforded by these regimens has led to the exploration of maintenance strategies in those patients with stable disease or better following initial chemotherapy. The recently reported Phase 2 PACT-12 trial of sunitinib maintenance therapy in patients who had not progressed after 6 cycle of chemotherapy (Reni 2013) demonstrated a 6-fold increase in PFS at 6 months, when compared to an observation only arm (3.6% vs 22.2%) and a 3-fold increase in two year OS (7.1% vs 22.9%).

The promising nature of these results suggests that the use of targeted agents after initial chemotherapy is a potentially useful new treatment construct which should be explored further in future trials of new therapeutic approaches to advanced pancreatic adenocarcinoma.

In view of the limited clinical activity and variable burden of toxicity with all currently available first line regimens and the potential promise of the combination of chemotherapy and targeted agent strategies, there is therefore a clear need for new treatment options with a more favorable efficacy-toxicity profile and improved quality of life for patients with advanced pancreatic adenocarcinoma, such as that presented by the addition of ibrutinib to the combination of nab-paclitaxel and gemcitabine.

1.3. Potential Role of Ibrutinib in the Treatment of Pancreatic Adenocarcinoma

With respect to the anti-tumor activity of ibrutinib, there are three potential mechanisms that may be operative in pancreatic adenocarcinoma: 1) changes in the tumor microenvironment, eg, inhibition of mast cell function, 2) changes in immune profiles, eg, alteration of Th1/Th2 polarity, and 3) direct inhibition of Epidermal Growth Factor Receptor (EGFR) kinase activity.

Several emerging lines of evidence suggest that BTK inhibition in solid tumors may be relevant due to modulation of the tumor microenvironment. These mechanisms may be applicable for a wide range of solid tumor types. Ibrutinib has been shown to inhibit *in vivo* tumor growth in a *myc*-driven genetically engineered pancreatic islet cell carcinoma model, and more recently in a KRAS driven pancreatic ductal adenocarcinoma model. This was attributed in both models to inhibition of mast-cell degranulation with a resulting anti-angiogenic effect (Soucek 2011, Masso-Valles 2013). New data have just been published showing that treating *p53ER/ER;LSLKRasG12D;pdx1-Cre* mice with both ibrutinib and standard of care gemcitabine, ameliorated the toxicity and significantly extended survival when compared to gemcitabine alone. Additionally, in subcutaneous xenografts (PDX) of a patient derived tumor in the

NOD/SCID mouse model a significant survival advantage was seen in single agent ibrutinib treated mice compared to control mice (Masso-Valles 2015).

Extensive correlative evidence points to a role of infiltrating mast cells in progression of numerous tumor types (Dalton 2012), as does direct functional evidence from genetically engineered models (Soucek 2007, Chang 2011, Ma 2013). BTK is known to be essential for IgE-stimulated basophile degranulation (Iwaki 2005), a function which has been shown to be inhibited by ibrutinib (MacGlashan 2011), and which was also inhibited in mast-cell models (Soucek 2011, Masso-Valles 2013). Ibrutinib treatment in these reports was also associated with decreases of $Gr1^+$ infiltrating myelomonocytic cells which may contribute pro-angiogenic and pro-proliferative signaling. All described mechanisms may contribute to an anti-tumor effect.

Mast cells have previously been proposed as targets for cancer therapy (Soucek 2007). Soucek et al. have shown that the oncogene *myc* can instruct a complex inflammatory program involving recruitment of mast cells, which are necessary in the tumor microenvironment for the physical expansion and maintenance of tumors. In a mouse pancreatic ductal adenocarcinoma model comprised of transgenic animals with pancreas-specific expression of $KRAS^{G12D}$ (Hingorani 2003), which is one of the most common mutations in pancreatic cancer, it was shown that inflammatory cells including mast cells are present in the tumor microenvironment. With ibrutinib monotherapy, general tumor size was reduced (Soucek 2012) while the combination of ibrutinib and gemcitabine significantly improved survival compared to gemcitabine alone (P=0.02) (Masso-Valles 2013). BTK is required for mast cell degranulation and when given in approved doses, ibrutinib achieves nearly complete BTK occupancy for 24 hours. In the model, mast cells are still recruited to the tumor microenvironment, but are no longer degranulating (Soucek 2012). Further, ibrutinib was shown to reduce tumor proliferation and tumor vasculature (Soucek 2012). Ibrutinib also reduced inflammatory cell infiltration and reduced collagen deposition. Mice that were treated with ibrutinib had a survival benefit (Soucek 2012).

Ibrutinib is also an irreversible inhibitor of interleukin-2-inducible kinase (ITK) (Iwaki 2005, Dubovsky 2013). ITK is a member of the TEC family of kinases and retains close homology with the BTK active site including conservation of the cysteine residue which ibrutinib binds to covalently. Patients with CLL treated with ibrutinib have been shown to have shifts of T-helper (Th) polarization to a more favorable Th1 bias (Dubovsky 2013). In addition, studies of T-cell function in vitro and in murine neoplastic (CLL), parasitic infection (Leishmania major), and infectious disease (Listeria monocytogenes) models *in vivo*, analyses have confirmed ibrutinib as a clinically relevant and physiologically potent ITK inhibitor (Dubovsky 2013). ITK inhibition reduces Th2-dominant immune responses and potentiates Th1-based responses (Dubovsky 2013). This shift in the Th1/Th2 ratio may directly potentiate anti-tumor activity through an increased tumor influx of cytotoxic $CD8^+$ T cells, as well as augmenting the effects of concomitantly administered cytotoxic chemotherapy.

Ibrutinib has been shown to inhibit EGFR (Honigberg 2010) and to inhibit growth of non small cell lung cancer (NSCLC) cells carrying EGFR gene mutations both *in vitro* and *in vivo* (Gao 2014), suggesting ibrutinib can function as an EGFR inhibitor.

Human EGFR is over-expressed in many pancreatic tumors (Fjällskog 2003, Tobita 2003) and is associated with poor prognosis and disease progression (Xiong 2004, Ueda 2004). Treatment with erlotinib, an EGFR inhibitor, has shown benefit in patients with pancreatic adenocarcinoma in a clinical trial, although the efficacy was limited to a small subpopulation (<10%) (Moore 2007). Mechanistically, mutations in KRAS, known to occur in about 90% of patients with pancreatic cancer, has been associated with up-regulation of EGFR in pancreatic tumors presumably leading to enhancement of KRAS-mediated oncogenic signal(s) (Siveke 2012). TGFα, one of the EGFR ligands, is also known to be over-expressed in ductal epithelial cells of pancreatic tumors from patients (Barton 1991). In experimental models of pancreatic cancer in mice, pharmacological (Bruns 2000, Ng 2002, Ardito 2012) or genetic (Ardito 2012) inactivation of EGFR decreased the growth and metastasis of human pancreatic tumor xenografts and improved the anticancer effects of gemcitabine. Collectively, these results suggest that expression of EGFR and its activity are critical for pathogenesis of pancreatic adenocarcinoma in human.

The fact that pancreatic cancer has a poor prognosis is in part related to its relative resistance to chemotherapy. New approaches are therefore needed to treat this aggressive disease. The effect of ibrutinib on mast cells and other cells in the tumor microenvironment and its potential to augment the antitumor activity of conventional chemotherapy combinations, such as nab-paclitaxel plus gemcitabine, the chemotherapy combination examined in the current study, provide a potential alternative approach to existing therapies for this disease.

1.4. Ibrutinib

Ibrutinib (IMBRUVICA®) is a first-in-class, potent, orally administered, covalently binding inhibitor of Bruton's tyrosine kinase (BTK) co-developed by Pharmacyclics LLC and Janssen Research and Development LLC for the treatment of B-cell malignancies.

Ibrutinib has been approved in many regions including the United States (US) and European Union (EU), for indications including treatment of patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy, patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), including CLL/SLL with a deletion of the short arm of chromosome 17 (del17p), patients with Waldenström's Macroglobulinemia (WM), and patients with Marginal Zone Lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy.

For the most up to date and comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, *in vitro* and *in vivo* preclinical activity and toxicology of ibrutinib, always refer to the latest version of the ibrutinib Investigator's Brochure (IB) and/or the applicable regional labeling information.

1.4.1. Summary of Nonclinical Data

1.4.1.1. Pharmacology

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

Ibrutinib has also been reported to be an irreversible inhibitor of ITK (IC_{50}=2-10 nM) in enzymatic assays and exhibiting 50% ITK occupancy in Jurkat whole cell lysates at 100 nM (Duvousky 2013).

For more detailed and comprehensive information regarding nonclinical pharmacology and toxicology, please refer to the current ibrutinib IB.

1.4.1.2. Toxicology

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

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

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

1.4.1.3. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib.

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

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

1.4.2. Summary of Clinical Data

For the most comprehensive clinical information regarding ibrutinib, please refer to the current version of the ibrutinib IB.

1.4.2.1. Pharmacokinetics and Product Metabolism

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

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

1.4.3. Summary of Clinical Safety

For more comprehensive safety information please refer to the current version of the ibrutinib IB.

1.4.3.1. Monotherapy Studies

Pooled safety data from a total of 1318 subjects treated with ibrutinib monotherapy in 13 studies that have completed primary analysis or final analysis included in the CSR as of the 31 May 2016 cutoff date for the current ibrutinib IB update in B-cell malignancies are summarized below.

The most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1318):

Most frequently reported TEAEs ≥15% [a]	Most frequently reported Grade 3 or 4 TEAEs ≥3% [b]	Most frequently reported Serious TEAEs ≥2% [c]
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Febrile neutropenia
Cough	Anemia	Pyrexia
Pyrexia	Hypertension	
Anemia	Diarrhea	
Neutropenia	Atrial fibrillation	
Upper respiratory tract infection		
Thrombocytopenia		
Oedema peripheral		

[a] Source is Table 6 of ibrutinib IB (v10); [b] Source is Table 8 of ibrutinib IB (v10); [c] Source is Table 9 of ibrutinib IB (v10).

1.4.3.2. Combination Studies

Pooled safety data from a total of 423 subjects treated with various therapies in combination with ibrutinib from 4 studies conducted in subjects with B-cell malignancies are briefly 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).

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

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

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

1.4.4. Risks

1.4.4.1. 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, subdural 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. See Section 6.2.4 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 6.4 for guidance on ibrutinib management with surgeries or procedures.

1.4.4.2. Atrial Fibrillation

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset of dyspnea should be evaluated clinically, and if indicated, have an ECG performed. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 5.3.1.4).

1.4.4.3. Cytopenias

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

1.4.4.4. 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 (see Section 5.3.1.4).

1.4.4.5. Infections

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

1.4.4.6. Interstitial Lung Disease (ILD)

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

1.4.4.7. Rash

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

1.4.4.8. Tumor Lysis Syndrome

There have been reports of tumor lysis syndrome (TLS) events in subjects treated with single-agent ibrutinib or in combination with chemotherapy. Subjects at risk of tumor lysis

syndrome are those with comorbidities and risk factors such as high tumor burden prior to treatment, increased uric acid (hyperuricemia), elevated LDH, bulky disease at baseline, and pre-existing kidney abnormalities.

1.4.4.9. Hypertension

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

1.4.4.10. Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (ie, ≥50% increase from baseline and an absolute count >5,000/µL), often associated with reduction of lymphadenopathy, has been observed in most subjects with CLL/SLL treated with ibrutinib. This effect has also been observed in some subjects with MCL treated with ibrutinib. This observed lymphocytosis (increase in the number of circulating lymphocytes eg, >400,000/µL) is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first month of ibrutinib therapy and typically resolves within a median of 8 weeks in subjects with MCL and 14 weeks in subjects with CLL/SLL. This pharmacodynamic effect was less prominent or not observed in other indications.

1.4.4.11. Non-melanoma Skin Cancer

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

1.4.5. Summary of Clinical Data in Pancreatic Adenocarcinoma

To date, there is no clinical experience with ibrutinib, either as monotherapy or in combination, in patients with pancreatic adenocarcinoma.

1.5. Nab-paclitaxel

Nab-paclitaxel (ABRAXANE®) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a noncrystalline, amorphous state. The chemical name for paclitaxel is 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine.

Paclitaxel is a microtubule inhibitor that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for

vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

1.5.1. Summary of Clinical Data

Nab-paclitaxel (ABRAXANE®) is indicated for use in the following conditions:

- Metastatic breast cancer, after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.
- Locally advanced or metastatic non-small cell lung cancer (NSCLC), as first-line treatment in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy
- Metastatic adenocarcinoma of the pancreas as first-line treatment, in combination with gemcitabine.

For more information on clinical data for nab-paclitaxel, please refer to the ABRAXANE® product labeling.

1.5.2. Summary of Clinical Safety

Hematologic Effects

Bone marrow suppression (primarily neutropenia) is dose-dependent and a dose-limiting toxicity of nab-paclitaxel. In clinical studies, Grade 3-4 neutropenia occurred in 34% of patients with metastatic breast cancer, 47% of patients with non-small cell lung cancer (NSCLC), and 38% of patients with pancreatic cancer.

Nervous System

Sensory neuropathy is dose- and schedule-dependent. The occurrence of Grade 1 or 2 sensory neuropathy does not generally require dose modification. If Grade ≥3 sensory neuropathy develops, nab-paclitaxel treatment should be withheld until resolution Grade ≤1 for pancreatic cancer followed by a dose reduction for all subsequent courses.

Sepsis

Sepsis occurred in 5% of patients with or without neutropenia who received nab-paclitaxel in combination with gemcitabine. Biliary obstruction or presence of biliary stent were risk factors for severe or fatal sepsis. If a patient becomes febrile (regardless of ANC) treatment should be initiated with broad spectrum antibiotics. For febrile neutropenia, nab-paclitaxel and gemcitabine should be interrupted until fever resolves and ANC ≥1500/µL and then resumed at a reduced dose.

Pneumonitis

Pneumonitis, including some cases that were fatal, occurred in 4% of patients receiving nab-paclitaxel in combination with gemcitabine. Patients should be monitored for signs and symptoms of pneumonitis and there should be an interruption of nab-paclitaxel and gemcitabine during evaluation of suspected pneumonitis. After ruling out infectious etiology and upon making a diagnosis of pneumonitis, treatment should be permanently discontinued.

Hypersensitivity

Severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported. Patients who experience a severe hypersensitivity reaction to nab-paclitaxel should not be re-challenged with the drug.

Hepatic Impairment

Because the exposure and toxicity of paclitaxel can be increased with hepatic impairment, administration of nab-paclitaxel in patients with hepatic impairment should be performed with caution. Nab-paclitaxel is **not** recommended in patients with pancreatic carcinoma who have moderate or severe hepatic failure.

Albumin (Human)

Nab-paclitaxel contains albumin (human), a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries a remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

Use in Pregnancy

Nab-paclitaxel can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel protein-bound particles to rats during pregnancy at doses lower than the maximum recommended human dose, based on body surface area, caused embryofetal toxicities, including intrauterine mortality, increased resorptions, reduced numbers of live fetuses, and malformations.

There are no adequate and well-controlled studies in pregnant women receiving nab-paclitaxel. If the drug is used during pregnancy, or if a patient becomes pregnant while receiving the drug, the patient should be apprised of the potential hazard to the fetus.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving nab-paclitaxel.

Use in Men

Men should be advised not to father a child while receiving nab-paclitaxel.

For more information on clinical safety data for nab-paclitaxel, please refer to the ABRAXANE® product labeling.

1.5.3. Summary of Clinical Data in Pancreatic Adenocarcinoma

A multicenter, multinational, randomized, open-label study was conducted in 861 patients comparing nab-paclitaxel and gemcitabine versus gemcitabine monotherapy as first-line treatment of metastatic adenocarcinoma of the pancreas.

Key eligibility criteria were Karnofsky Performance Status (KPS) ≥70, normal bilirubin level, transaminase levels ≤2.5 times the upper limit of normal (ULN) or ≤5 times the ULN for patients with liver metastasis, no prior cytotoxic chemotherapy in the adjuvant setting or for metastatic disease, no ongoing active infection requiring systemic therapy, and no history of interstitial lung disease. Patients with rapid decline in KPS (≥10%) or serum albumin (≥20%) during the 14-day Screening period prior to study randomization were ineligible. A total of 861 patients were randomized (1:1) to the nab-paclitaxel and gemcitabine arm (n=431) or to the gemcitabine arm (n=430).

Randomization was stratified by geographic region (Australia, Western Europe, Eastern Europe, or North America), KPS (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no). Patients randomized to nab-paclitaxel and/gemcitabine received nab-paclitaxel 125 mg/m^2 as an intravenous infusion over 30-40 minutes followed by gemcitabine 1000 mg/m^2 as an intravenous infusion over 30-40 minutes on Days 1, 8, and 15 of each 28-day cycle. Patients randomized to gemcitabine received 1000 mg/m^2 as an intravenous infusion over 30-40 minutes weekly for 7 weeks followed by a 1-week rest period in Cycle 1 then as 1000 mg/m^2 on Days 1, 8 and 15 of each subsequent 28-day cycle.

Patients in both arms received treatment until disease progression or unacceptable toxicity. The major efficacy outcome measure was OS. Additional outcome measures were progression-free survival (PFS) and overall response rate (ORR), both assessed by independent, central, blinded radiological review using Response Evaluation Criteria In Solid Tumors (RECIST) criteria (version 1.0).

In the intent-to-treat (all randomized) population, the median age was 63 years (range 27–88 years) with 42% ≥65 years of age; 58% were men; 93% were White and KPS was 90-100 in 60%. Disease characteristics included 46% of patients with 3 or more metastatic sites; 84% of patients had liver metastasis; and the location of the primary pancreatic lesion was in the head of pancreas (43%), body (31%), or tail (25%).

Results of this study are summarized in Table 2 below:

Table 2. Efficacy Results from Randomized Study in Patients with Pancreatic Adenocarcinoma

	Nab-paclitaxel and gemcitabine (N=431)	Gemcitabine (N=430)
Overall Survival		
Number of deaths, n (%)	333 (77)	359 (83)
Median Overall Survival (Months)	**8.5**	**6.7**
95% CI	7.9,9.5	6.0,7.2
HR (95% CI)	0.72 (0.06,0.83)	
p-value	<0.0001	
Progression-free Survival		
Death or progression, n (%)	277 (64)	265 (62)
Median Progression-free survival	**5.5**	**3.7**
95% CI	4.5, 5.9	3.6, 4.0
HR (95% CI)	0.69 (0.58, 0.82)	
p-value	<0.0001	
Overall Response Rate		
Confirmed complete or partial overall response, n (%)	**99 (23)**	**31 (7)**
95% CI	19.1. 27.2	5.0, 10.1
p-value	<0.0001	

Abbreviations: CI = confidence interval; HR = hazard ratio;
Reference: ABRAXANE® prescribing information

1.6. Gemcitabine

Gemcitabine (GEMZAR®) is a nucleoside metabolic inhibitor that exhibits antitumor activity. Gemcitabine HCl is 2′-deoxy-2′,2′-difluorocytidine monohydrochloride (β-isomer).

1.6.1. Summary of Nonclinical Data

Gemcitabine kills cells undergoing DNA synthesis and blocks the progression of cells through the G1/S-phase boundary.

Gemcitabine is metabolized by nucleoside kinases to diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. Gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme responsible for catalyzing the reactions that generate deoxynucleoside triphosphates for DNA synthesis, resulting in reductions in deoxynucleotide concentrations, including dCTP.

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, which eventually results in the initiation of apoptotic cell death.

1.6.2. Summary of Clinical Data

Gemcitabine is indicated:

- In combination with carboplatin, for the treatment of advanced ovarian cancer that has relapsed at least 6 months after completion of platinum based therapy
- In combination with paclitaxel, for first-line treatment of metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated
- In combination with cisplatin for the treatment of non-small cell lung cancer
- As a single agent for the treatment of pancreatic cancer

For more information on clinical data for gemcitabine, please refer to the most current local gemcitabine product labeling.

1.6.3. Summary of Clinical Safety

Schedule-dependent Toxicity

In clinical trials evaluating the maximum tolerated dose of gemcitabine, prolongation of the infusion time beyond 60 minutes or more frequent than weekly dosing resulted in an increased incidence of clinically significant hypotension, severe flu-like symptoms, myelosuppression, and asthenia. The half-life of gemcitabine is influenced by the length of the infusion.

Myelosuppression

Myelosuppression manifested by neutropenia, thrombocytopenia, and anemia occurs with gemcitabine as a single agent and the risks are increased when gemcitabine is combined with other cytotoxic drugs.

In clinical trials, Grade 3-4 neutropenia, anemia, and thrombocytopenia occurred in 25%, 8%, and 5%, respectively of patients receiving single-agent. The frequencies of Grade 3-4 neutropenia, anemia, and thrombocytopenia varied from 48% to 71%, 8 to 28%, and 5 to 55%, respectively, in patients receiving gemcitabine in combination with another drug.

Pulmonary Toxicity and Respiratory Failure

Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS), has been reported. In some cases, these pulmonary events can lead to fatal respiratory failure despite discontinuation of therapy.

The onset of pulmonary symptoms may occur up to 2 weeks after the last dose of gemcitabine. Gemcitabine should be discontinued in patients who develop unexplained dyspnea, with or without bronchospasm, or have any evidence of pulmonary toxicity.

Hemolytic Uremic Syndrome (HUS)

Hemolytic Uremic Syndrome (HUS), including fatalities from renal failure or the requirement for dialysis can occur in patients treated with gemcitabine. In clinical trials, HUS was reported in 6 of 2429 patients (0.25%). Most fatal cases of renal failure were due to HUS. Renal function should be assessed prior to initiation of gemcitabine and periodically during treatment.

The diagnosis of HUS should be considered in patients who develop anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, or reticulocytosis; severe thrombocytopenia; or evidence of renal failure (elevation of serum creatinine or BUN). Gemcitabine should be permanently discontinued in patients with HUS or severe renal impairment. Renal failure may not be reversible even with discontinuation of therapy.

Hepatic Toxicity

Drug-induced liver injury, including liver failure and death, has been reported in patients receiving gemcitabine alone or in combination with other potentially hepatotoxic drugs.

Administration of gemcitabine in patients with concurrent liver metastases or a pre-existing medical history or hepatitis, alcoholism, or liver cirrhosis can lead to exacerbation of the underlying hepatic insufficiency.

Hepatic function should be assessed prior to initiation of gemcitabine and periodically during treatment. Gemcitabine should be discontinued in patients who develop severe liver injury.

Embryofetal Toxicity

Gemcitabine can cause fetal harm when administered to a pregnant woman, based on its mechanism of action. Gemcitabine was teratogenic, embryotoxic, and fetotoxic in mice and rabbits. If this drug is used during pregnancy, or if a woman becomes pregnant while taking gemcitabine, the patient should be apprised of the potential hazard to a fetus.

Exacerbation of Radiation Therapy Toxicity

Gemcitabine is not indicated for use in combination with radiation therapy.

Concurrent (given together or ≤7 days apart)

Life-threatening mucositis, especially esophagitis and pneumonitis occurred in a trial in which gemcitabine was administered at a dose of 1000 mg/m^2 to patients with non-small cell lung cancer for up to 6 consecutive weeks concurrently with thoracic radiation.

Non-concurrent (given >7 days apart)

Excessive toxicity has not been observed when gemcitabine is administered more than 7 days before or after radiation. Radiation recall has been reported in patients who receive gemcitabine after prior radiation.

Capillary Leak Syndrome

Capillary leak syndrome (CLS) with severe consequences has been reported in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents. Gemcitabine should be discontinued if CLS develops during therapy.

For more information on clinical safety data for gemcitabine, please refer to the local gemcitabine product labeling.

1.6.4. Summary of Clinical Data in Pancreatic Adenocarcinoma

1.6.4.1. Summary of Clinical Data: Gemcitabine Monotherapy

The safety and efficacy of gemcitabine was evaluated in two studies, a randomized, single-blind, two-arm (gemcitabine *versus* 5-fluorouracil), active-controlled trial conducted in patients with locally advanced or metastatic pancreatic cancer who had received no prior chemotherapy and in a single arm, open-label, multicenter trial conducted in patients with locally advanced or metastatic pancreatic cancer previously treated with 5-FU or a 5-FU-containing regimen.

The primary efficacy outcome measure in both trials was clinical benefit response (CBR).

In the randomized study, patients treated with gemcitabine had statistically significant increases in clinical benefit response, survival, and time to disease progression compared to those randomized to receive 5-FU. No confirmed objective tumor responses were observed in either treatment arm.

Efficacy outcome results are summarized in the Table 3 below.

Table 3. Randomized Trial of Gemcitabine versus 5-Fluorouracil in Pancreatic Adenocarcinoma

Efficacy Outcomes	Gemcitabine (n =63)	5-FU (n=63)
Clinical Benefit Response	22.2%	4.8%
p-value	0.004	
Overall Survival		
Median (months)	5.7	4.2
(95% CI)	4.7, 6.9	3.1, 5.1
p-value	0.0009	
Time to Disease Progression		
Median (months)	2.1	0.9
(95% CI)	1.9, 3.4	0.9, 1.1
p-value	0.0013	

Reference: GEMZAR® prescribing information

1.7. Study Rationale

Advanced pancreatic adenocarcinoma is one of the most aggressive malignancies and even with the most intensive chemotherapeutic strategies median survival is less than one year, often with a significantly impaired quality of life. Treatment options remain limited and the combination of nab-paclitaxel and gemcitabine represents one of the most widely used therapeutic strategies in patients with a better performance status. However, outcomes with this regimen are limited to a median survival of less than nine months and a progression-free interval of only five and a half months.

There is therefore an overwhelming and urgent need for more effective and innovative approaches with acceptable toxicity, such as the proposed three agent combination of ibrutinib, nab-paclitaxel and gemcitabine which will be examined in the current trial. The nab-paclitaxel and gemcitabine regimen is considered the most appropriate combination with which to evaluate ibrutinib, as the pattern of significant efficacy and manageable toxicity facilitate its first line use in the widest range of patients with advanced pancreatic disease (Hoy 2014, Cecco 2014, Al-Batran 2014).

Addition of ibrutinib to a nab-paclitaxel and gemcitabine chemotherapy backbone is supported by the biologic rationale that ibrutinib exerts direct anti-tumor, collagen-induced platelet aggregation inhibition (Ninomoto 2017) and antivascular effects via mast cell stabilization (Masso-Valles 2015) and also modifies the tumor microenvironment and associated immune profile through alteration of Th1/Th2 polarity, with a concomitant cytotoxic T cell influx. The immuno-mediated anti-tumor effects of ibrutinib appear to be mechanistically distinctive to and separate from the cytotoxic activity of nab-paclitaxel and gemcitabine. The direct anti-tumor, collagen-induced platelet aggregation inhibition (Ninomoto 2017), and antivascular properties of

ibrutinib should further augment the existing efficacy of the nab-paclitaxel and gemcitabine combination.

2. STUDY OBJECTIVE

2.1. Primary Objective

The primary objective of the study is to evaluate the efficacy of ibrutinib in combination with nab-paclitaxel and gemcitabine *versus* placebo in combination with nab-paclitaxel and gemcitabine, based on investigator assessment of progression-free survival (PFS) and overall survival (OS), for the first line treatment of patients with metastatic pancreatic adenocarcinoma.

2.2. Secondary Objective(s)

- Clinical benefit response (CBR) rate
- Overall response rate (ORR): complete response (CR) + partial response (PR), per investigator assessment
- Carbohydrate antigen 19-9 (CA19-9) response
- Patient-reported outcome (PRO) by EORTC QLQ-C30
- Rate of venous thromboembolic events (VTE)
- To evaluate the safety and tolerability of ibrutinib in combination with nab-paclitaxel and gemcitabine *versus* placebo in combination with nab-paclitaxel and gemcitabine

2.3. Exploratory Objectives

To compare the treatment arms in terms of the following:

- Time to diminished pain: time to 50% reduction in pain score as assessed on MPAC pain assessment tool
- Disease control rate (DCR): the proportion of subjects who achieve a best response of complete response (CR), partial response (PR) or stable disease (SD) (≥8 weeks) per investigator assessment, in accordance with RECIST 1.1 criteria.
- Exploratory tumor and circulating biomarkers
- Pharmacokinetic (PK) parameters of ibrutinib, gemcitabine and paclitaxel when dosed in combination

3. STUDY DESIGN

3.1. Overview of Study Design

This is a randomized, multicenter, double blind placebo-controlled, Phase 3 study comparing ibrutinib in combination with nab-paclitaxel and gemcitabine versus placebo in combination with

nab-paclitaxel and gemcitabine, in the first line treatment of subjects with metastatic pancreatic adenocarcinoma. The primary endpoints are PFS as determined by investigator assessment according to RECIST 1.1 and OS. The secondary endpoints will evaluate clinical benefit rate, overall response, carbohydrate CA19-9 response, patient-reported outcomes, and VTE rate.

A Data Monitoring Committee (DMC) review of safety data including death events will be performed approximately every 6 months after the first subject is randomized.

The study will consist of **two phases.**

Safety Run-in Phase:

Six subjects will initially be recruited to receive open-label ibrutinib in combination with nab-paclitaxel and gemcitabine. The independent Data Monitoring Committee (DMC) will review data on the safety of ibrutinib combined with nab-paclitaxel and gemcitabine, after the first 6 subjects have completed at least 28 days of follow-up after the initiation of combination therapy as detailed in Section 10.8.

Depending on the outcome of their review, the DMC may recommend that:

a) the study continue to the Double-blind Randomized Phase.
b) prior to commencing the Double-blind Randomized Phase, an additional safety review is performed after a total of up to 12 subjects have been treated with ibrutinib (560 mg) in combination with nab-paclitaxel and gemcitabine.
c) prior to commencing the Double-blind Randomized Phase, the dose level of ibrutinib should be reduced to 420 mg and an additional 6 subjects should be studied at this dose level, in combination with nab-paclitaxel and gemcitabine prior to a subsequent review by the DMC.

Double-blind Randomized Phase

The second phase of the study will be a randomized, double-blind comparison of ibrutinib in combination with nab-paclitaxel and gemcitabine *versus* placebo in combination with nab-paclitaxel and gemcitabine.

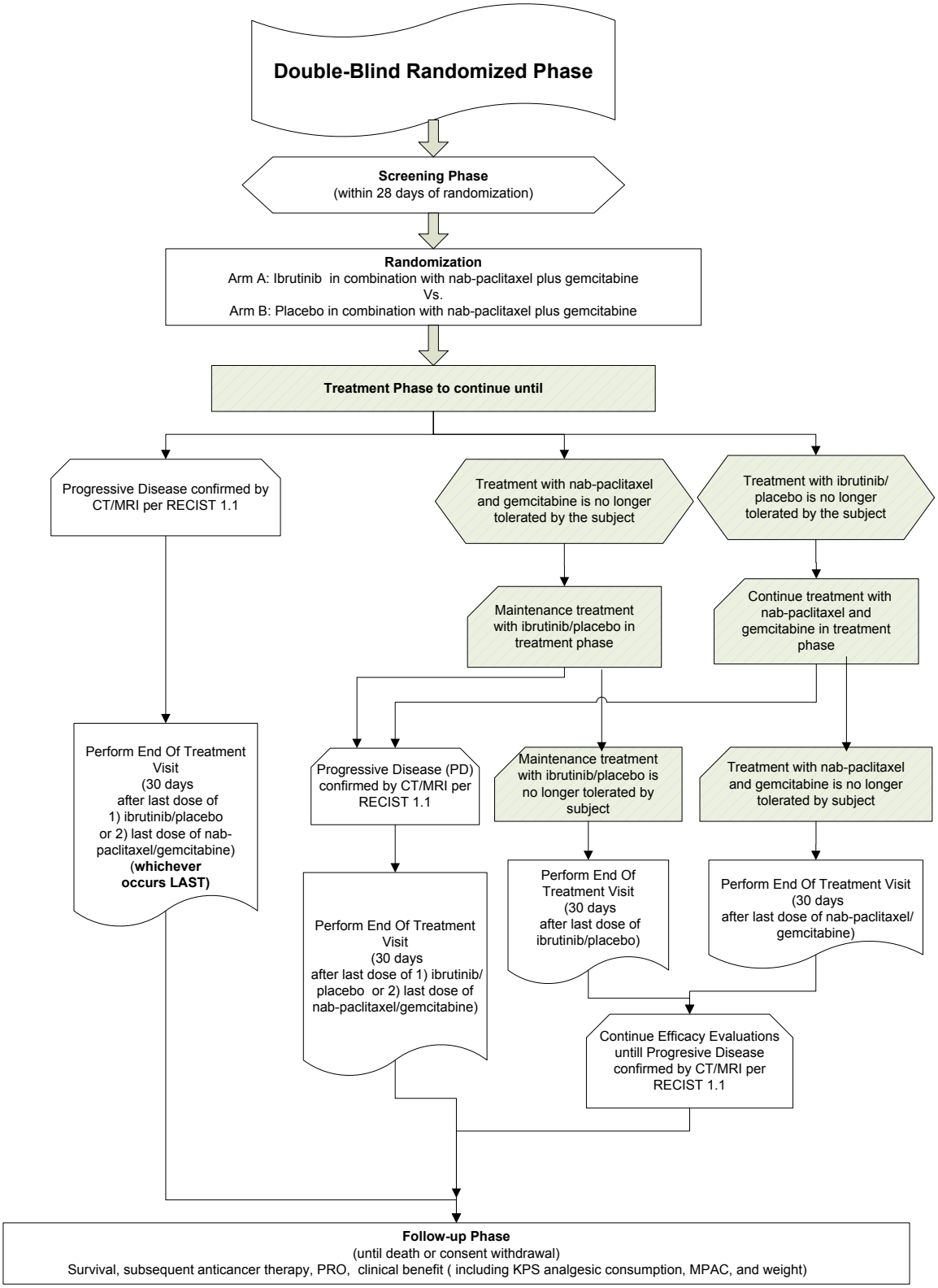
Approximately 420 subjects will be randomized between Arm A (ibrutinib in combination with nab-paclitaxel and gemcitabine) and Arm B (placebo in combination with nab-paclitaxel and gemcitabine).

Randomization will be stratified according to:

- KPS 70-80 *vs* KPS 90-100
- Liver metastasis (present or absent)
- Age ≤65 years *vs* age >65 years

Subjects will be treated until unacceptable toxicity or disease progression, whichever occurs first. If nab-paclitaxel and/or gemcitabine or ibrutinib/placebo are discontinued prior to disease progression, the remaining agents will be continued until unacceptable toxicity or disease progression.

3.2. Study Schema



Note: Shaded box represents Treatment Phase. See Schedule of Assessment (Appendix A) for details of procedures.

3.3. Study Design Rationale

This is a double-blind, randomized, placebo-controlled trial, comparing ibrutinib in combination with the established regimen of nab-paclitaxel and gemcitabine to placebo in combination with nab-paclitaxel and gemcitabine in subjects with advanced pancreatic adenocarcinoma, with primary endpoints of PFS as determined by investigator assessment according to RECIST 1.1 and OS.

While there is no agreed standard of care in the management of advanced pancreatic adenocarcinoma, nab-paclitaxel and gemcitabine is a very widely used regimen in patients with a good performance status and hence is considered to be a suitable comparator control regimen for this trial.

Progression-free survival (PFS) is considered an appropriate primary endpoint in a patient population which has an exceptionally limited life expectancy and for whom a prolonged period of disease control, with a corresponding stabilization of quality of life, is probably the most important outcome of therapeutic intervention, given the very modest improvements in OS afforded by existing treatment options. Subsequently this study is designed to detect a clinically meaningful difference in PFS (Ellis 2014) target hazard ratio (0.6 to 0.75) with OS as an additional primary endpoint.

As this is a novel combination, an initial open-label Safety Run-in Phase of 6 subjects is considered an appropriate means of establishing the safety and tolerability of ibrutinib in combination with nab-paclitaxel and gemcitabine. Safety data from this initial cohort will be reviewed by an independent DMC, prior to enrollment continuing. Furthermore, the DMC will have the authority to request that safety and tolerability are examined in additional subjects, at the same or a lower dose of ibrutinib, before proceeding to the Double-blind Randomized Phase of the study.

The double-blind, placebo-controlled study design is considered the optimal means for comparatively assessing the efficacy, safety and tolerability of the two treatment arms.

3.3.1. Study Population and Treatment

Subjects with previously untreated metastatic pancreatic adenocarcinoma who, in the opinion of the investigator, are candidates for nab-paclitaxel and gemcitabine combination chemotherapy.

Subjects will be randomized to treatment with either continuous daily ibrutinib or placebo, in combination with nab-paclitaxel and gemcitabine given on Days 1, 8, and 15 of continual 28-day cycles, until disease progression, or unacceptable toxicity, whichever occurs first. If clinically appropriate, the investigator may start dosing with the oral study drug (ibrutinib/placebo) up to 48 hours before beginning chemotherapy.

Subjects will be treated until unacceptable toxicity or disease progression, whichever occurs first. If nab-paclitaxel and/or gemcitabine or ibrutinib/placebo are discontinued prior to disease progression, the remaining agents will be continued until unacceptable toxicity or disease progression.

3.3.2. Dose Selection

3.3.2.1. Ibrutinib

Ibrutinib has been FDA-approved for MCL at a dose of 560 mg and for CLL and WM at a dose of 420 mg. In 2 studies in subjects with B-cell malignancies, the pharmacodynamics of ibrutinib were determined by monitoring the BTK active-site occupancy in subjects' peripheral blood mononuclear cells (PBMC) before and after ibrutinib treatment (ibrutinib IB). Doses tested in the first-in-human ascending-dose study were 1.25, 2.5, 5.0, 8.3 and 12.5 mg/kg ibrutinib PO given non-continuously in 35-day cycles (28 days on, 7 days off) as well as 8.3 mg/kg and 560 mg ibrutinib PO given continuously (Advani 2013). With respect to safety, no maximum tolerated dose (MTD) was identified. Subjects administered drug at doses of 2.5 mg/kg/day or higher achieved BTK occupancy at or above 90% at 4 and 24 hours after drug administration (Advani 2013). Absolute doses in the 2.5 and 5 mg/kg cohort ranged from 40 to 320 mg/day and from 280 to 600 mg/day, respectively. The highest dose administered was 1,400 mg of ibrutinib. Based on this data, fixed dose levels of >280 mg are expected to be necessary to ensure achievement of the full pharmacodynamic effect in the vast majority of patients. The sustained pharmacodynamic effect despite a relative rapid elimination of ibrutinib is secondary to irreversible inhibition of BTK in subjects' PBMCs (ibrutinib IB). Consistent with this, once-a-day oral dosing resulted in 24-hour sustained target inhibition in these trials.

In contrast to studies in B-cell malignancies, there are multiple possible enzymatic targets whose inhibition may contribute to efficacy in solid tumors. *In vitro* and preclinical studies have shown that ibrutinib covalently binds to the cysteine-481 amino acid of the BTK enzyme and inhibits numerous processes, including ERK signaling, NF-κB DNA binding, cytosine–phosphate–guanine (CpG)-mediated CLL-cell proliferation, and tumor-cell migration (ibrutinib IB). For solid tumors, the key target for mast cells and infiltrating myelomonocytic cells in the tumor microenvironment is BTK, whose inhibition can be reliably achieved at well tolerated doses. In addition, a high level of occupancy of the T-cell specific kinase ITK has been achieved in a study with CLL patients using ibrutinib doses of 420 mg once daily. The enzymatic IC_{50} of ibrutinib for EGFR and HER2 are higher than that for BTK, however the concentrations required for enzymatic inhibition in cells, and inhibition of cellular growth of sensitive cell lines *in vitro*, is similar to or only slightly higher than that required for BTK (Elias 2013, Chen 2014). Growth inhibition of a breast cancer xenograft *in vivo* has furthermore been noted with doses that are effective, but not fully optimal, for BTK occupancy or for *in vivo* inhibition of lymphoma xenografts. Therefore, the approved doses of 560 or 420 mg/day may be effective in suppressing growth of tumors that are driven by ErbB receptors (epidermal growth factor receptor [EGFR; ErbB1], HER-2 [ErbB2], ErbB3, and ErbB4) (Yarden 2001, Olayioye 2000).

Due to the extensive clinical experience with the 560 mg dose in terms of safety and efficacy, and due to variability in the sensitivity of solid tumors studied to date, a dose of 560 mg/day has been chosen for this study involving pancreatic ductal adenocarcinoma.

3.3.2.2. Nab-paclitaxel and Gemcitabine

The schedule of **nab-paclitaxel** (IV) 125 mg/m^2 and **gemcitabine** (IV) 1000 mg/m^2 given on Days 1, 8 and 15 of each 28-day cycle is the schedule of administration in the approved US Prescribing Information for nab-paclitaxel when given in combination with gemcitabine for the treatment of pancreatic adenocarcinoma (ABRAXANE® Prescribing Information) and hence is considered appropriate for the current study.

4. SUBJECT SELECTION

4.1. Inclusion Criteria

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

Disease-related

1. Histologically or cytologically confirmed diagnosis of pancreatic adenocarcinoma.
2. Stage IV disease diagnosed **within 6 weeks of randomization**.
3. Disease which is evaluable according to **RECIST 1.1, with at least one measurable** metastatic lesion (not in a previously irradiated area).
4. Disease status for which, in the opinion of the investigator, nab-paclitaxel and gemcitabine is considered an appropriate treatment choice.
5. No previous radiotherapy, surgery, cytotoxic chemotherapy or investigational therapy for the treatment of **metastatic** pancreatic adenocarcinoma.
6. No **prior neo-adjuvant, peri-operative or adjuvant chemotherapy** for primary disease of pancreatic adenocarcinoma. Prior treatment with 5-FU, gemcitabine or capecitabine administered as a radiation sensitizer (at non-cytotoxic doses) in the adjuvant setting is allowed, provided at least 6 months have elapsed since completion of the last dose.
7. No clinically significant third-space fluid accumulation (eg, ascites or pleural effusion).
8. Male and female subjects of reproductive potential who agree to use highly effective methods of birth control (eg, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence [2], or sterilized partner) and a barrier

[2] Complete abstinence is a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01 About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

method (eg, condoms, cervical ring, sponge, etc) during the period of therapy and for 6 months for males and females after the last dose of study medication.

9. Ability to provide written informed consent and to understand and comply with the requirements of the study.

Laboratory

10. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to randomization:
    - Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
    - Platelet count ≥100 x 10^9/L
    - Hemoglobin ≥9 g/dL
11. Adequate hepatic and renal function defined as:
    - Serum aspartate transaminase (AST) and/or alanine transaminase (ALT) ≤5.0 x upper limit of normal (ULN) if liver metastases, or ≤3 x ULN without liver metastases
    - Alkaline phosphatase <3.0 x ULN or ≤5.0 x ULN if liver or bone metastases present
    - Bilirubin ≤1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin, such as hemolysis)
    - Estimated Creatinine Clearance ≥30 mL/min (Cockcroft-Gault)
12. PT/INR <1.5 x ULN and PTT (aPTT) <1.5 x ULN

Demographic

13. Men and women ≥18 years of age.
14. Karnofsky performance status (KPS) ≥70. Two observers will be required to assess KPS at Screening. If discrepant, the one with the lowest assessment will be accepted.
15. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1

4.2. Exclusion Criteria

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

Disease-related

1. Prior radiotherapy to any measurable lesion at any time.
2. Radiotherapy in the adjuvant setting, or earlier, within the last 6 months.
3. Previous cytotoxic chemotherapy for primary disease of pancreatic adenocarcinoma.
4. Neuroendocrine (carcinoid, islet cell) or acinar pancreatic carcinoma.

Concurrent Conditions

5. Known brain or leptomeningeal disease (CT or MRI scan of the brain required only in case of clinical suspicion of central nervous system involvement).
6. Prior exposure to BTK inhibitor.
7. A documented ≥10% decrease in KPS between Screening visit and within 72 hours prior to randomization.
8. History of other malignancies, except:
    - Malignancy treated with curative intent and with no known active disease present for ≥3 years before the first dose of study drug and felt to be at low risk for recurrence by investigator.
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
    - Adequately treated carcinoma *in situ* without current evidence of disease.
9. Known bleeding disorders (eg, von Willebrand's disease or hemophilia).
10. Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.
11. Live vaccination within 4 weeks prior to randomization.
12. Any uncontrolled active systemic infection including any infection requiring systemic IV treatment which was completed ≤7 days before randomization.
13. Major surgery within 4 weeks of first dose of study drug.
14. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
15. History of stroke or intracranial hemorrhage within 6 months prior to enrollment.
16. 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.
17. History of interstitial lung disease, idiopathic pulmonary fibrosis, or pulmonary hypersensitivity pneumonitis.
18. Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
19. Concomitant use of warfarin or other Vitamin K antagonists.

20. Known hypersensitivity to any study drug (nab-paclitaxel, gemcitabine, or ibrutinib).
21. Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor.
22. Currently active, clinically significant hepatic impairment (Class B or C according to the Child-Pugh classification [Appendix I]).
23. Lactating or pregnant.
24. Unwilling or unable to participate in all required study evaluations and procedures.
25. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations).
26. Decline in serum albumin ≥20% from Screening to study randomization (both labs at Screening and prior to randomization may be confirmed locally).

5. TREATMENT OF SUBJECTS

5.1. Treatment Allocation and Blinding

5.1.1. Safety Run-in Phase

Six subjects will be enrolled to receive open-label ibrutinib in combination with nab-paclitaxel and gemcitabine. Prior to enrollment, all subjects must receive approval from the Sponsor's Medical Monitor or designee.

5.1.2. Randomized Double-blind Phase

After the subject has completed all baseline (screening) procedures and met all requirements of the inclusion/exclusion criteria study personnel will register the subject into the Interactive Web Response System (IWRS); subsequently the study personnel will answer key questions to randomize the subject and have drug assigned. The first dose of study drug must be administered after randomization, which should be no more than 72 hours after the subject has been randomized by IWRS.

Approximately 420 subjects will be randomized in a 1:1 ratio to each of the 2 treatment arms.

Treatment Arm A: ibrutinib in combination with nab-paclitaxel and gemcitabine

Treatment Arm B: placebo in combination with nab-paclitaxel and gemcitabine

Randomization will be stratified according to:

- KPS 70-80 *vs* KPS 90-100
- Liver metastasis (present or absent)
- Age ≤65 years *vs* age >65 years

5.1.2.1. Blinding

This is a double-blind study; therefore, subjects, investigators, and the Sponsor's study team members will remain blinded to treatment assignment. The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject if necessary to appropriately manage or treat the subject. Data that may potentially unblind the treatment assignment (ie, study drug plasma concentrations) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized.

It is recommended that the investigator contact the Sponsor or its designee to discuss the particular situation before breaking the blind whenever possible. Telephone contact with the Sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the Sponsor must be informed as soon as possible. The date, time, and reason for the unblinding must be documented within the IWRS in the appropriate section of the eCRF and in the source document. The confirmation received from the IWRS indicating the code break must be retained with the subject's source documents in a secure manner. A subject whose treatment assignment has been unblinded may continue the study treatment if the subject is expected to continue receiving clinical benefit. The subject should continue to return for scheduled study visits. The single-blind (ie, subject remains blinded to treatment assignment) should be maintained provided the subject's safety is not compromised.

5.2. Study Treatment

Ibrutinib (560 mg) or matching placebo will be given orally once daily continuously starting on Cycle 1 Day 1 until disease progression is documented or unacceptable toxicity.

Nab-paclitaxel (IV) 125 mg/m^2 and **gemcitabine** (IV) 1000 mg/m^2 will be given on Days 1, 8, and 15 of each 28-day cycle until disease progression or unacceptable toxicity.

5.3. Study Medication

5.3.1. Ibrutinib

5.3.1.1. Formulation/Packaging/Storage

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

The ibrutinib (**or placebo**) 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.

5.3.1.2. Dose and Administration

The first dose of study treatment including ibrutinib should be given no more than 72 hours after randomization. Ibrutinib 560 mg (4 x 140-mg capsules) (**or placebo**) will be administered orally once daily beginning on Day 1 of Cycle 1 of the Treatment Phase.

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

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

Dosing on days which coincide with administration of nab-paclitaxel and gemcitabine will be given in the clinic. On all other days, dosing will be on a domiciliary basis.

On Day 1 of Cycle 1 **only**, all subjects will be observed for 2 hours after completion of nab-paclitaxel and gemcitabine administration, to ensure that there are no acute clinical effects of co-administering ibrutinib/placebo in combination with nab-paclitaxel and gemcitabine.

On Day1 of Cycle 2 **only**, subjects will be on site for 6 hours after initiation of nab-paclitaxel and gemcitabine administration, to allow collection of blood samples for PK analysis (see Appendix B).

Ibrutinib/placebo will be dispensed to subjects in bottles at the beginning of each cycle. Unused ibrutinib/placebo must be returned to the site (Section 12.8) at each visit. All returned ibrutinib/placebo will be reconciled and documented at the end of each cycle. Returned ibrutinib/placebo capsules must not be redispensed to anyone.

5.3.1.3. Overdose

Any dose of study drug administered 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 MTD was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day

(1400 mg/day). Healthy subjects were exposed up to single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

Refer to Section 11.4 for further information regarding AE reporting.

5.3.1.4. Dose Modification for Adverse Reactions

The dose of ibrutinib/placebo 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 6.1 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 (>3 days), despite optimal anti-emetic and/or anti-diarrheal therapy.
- Any other Grade 4 or unmanageable Grade 3 toxicity.

Persistent atrial fibrillation of any grade continuing despite adequate treatment, consider the risks and benefits of ibrutinib treatment. If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (Section 6.2.4).

In the event that the investigator manages dose modifications differently than what is outlined in Section 5.3.1.4 please consult the medical monitor.

If the dose of ibrutinib/placebo is reduced, at the investigator's discretion, the dose of ibrutinib/placebo 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 medical monitor should be consulted before dose re-escalation. Dose changes must be recorded in the Dose Administration eCRF.

Table 4. Ibrutinib/Placebo 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, 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, 280 mg/day for 560 mg /day dose)
Fourth	Discontinue study drug

5.3.1.5. Dose Modification for Chronic Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver. For subjects with existing chronic mild hepatic impairment (Child-Pugh class A) the starting dose has to be adjusted to a level of 280 mg daily (two capsules). For subjects with a history of chronic liver impairment who develop liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib/placebo 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 impairment, respectively). In the case of South Korea, dose modification for subjects with chronic hepatic impairment should follow the approved regional label in South Korea for Imbruvica®. Monitor subjects for signs of toxicity and follow dose modification guidance as needed (refer to Appendix I).

5.3.2. Nab-paclitaxel and Gemcitabine

5.3.2.1. Formulation/Packaging/Storage

5.3.2.1.1. Nab-paclitaxel (ABRAXANE®)

Nab-paclitaxel is available as lyophilized powder containing 100 mg of paclitaxel in single-use vial for reconstitution.

Vials should be stored in original cartons at 20ºC to 25ºC (68ºF to 77ºF) and retained in the original package to protect from bright light.

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

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

5.3.2.1.2. Gemcitabine

Gemcitabine for injection, USP, is available in sterile single-use vials individually packaged in a carton containing: *either* 200 mg *or* 1000 mg white to off-white, lyophilized powder in a sterile single-use vial.

Unopened vials of gemcitabine are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C (68° to 77°F) and that allows for excursions between 15° and 30°C (59° and 86°F).

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

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

5.3.2.2. Dose and Administration

Nab-paclitaxel 125 mg/m^2 and **gemcitabine** 1000 mg/m^2 will be administered on Days 1, 8, and 15 of each 28-day cycle, each as a 30-40 minute intravenous infusion, with gemcitabine administration initiating immediately (or as soon as practically possible) after the nab-paclitaxel infusion has ended. On nab-paclitaxel and gemcitabine administration days, ibrutinib/placebo will be given immediately ***prior to*** initiation of the nab-paclitaxel infusion.

Nab-paclitaxel and gemcitabine will be administered in the chemotherapy suite, in accordance with local institutional policies and procedures. Pre-medication will be given in accordance with the ABRAXANE® package insert and local institutional policies and procedures.

On Day 1 of Cycle 1 only, subjects will be observed for 2 hours after completion of nab-paclitaxel and gemcitabine administration, to ensure that there are no acute clinical effects of co-administering ibrutinib/placebo in combination with nab-paclitaxel and gemcitabine.

On Day1 of Cycle 2 only, subjects will be on site for 6 hours after initiation of nab-paclitaxel and gemcitabine administration, to allow collection of blood samples for PK analysis (see Appendix B).

5.3.2.3. Overdose

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. Signs and symptoms of an overdose that meet any Serious Adverse Event criterion must be reported as a Serious Adverse Event in the appropriate time frame and documented as clinical sequelae to an overdose. In the event of an overdose, subjects should be closely monitored and given appropriate supportive treatment.

5.3.2.3.1. Nab-paclitaxel Overdose

There are no specific antidotes for nab-paclitaxel. The primary anticipated complications of overdosage would consist of bone marrow suppression, sensory neurotoxicity, and mucositis.

5.3.2.3.2. Gemcitabine Overdose

There are no specific antidotes for gemcitabine. Myelosuppression, paresthesias, and severe rash were the principal toxicities seen when a single dose as high as 5700 mg/m^2 was administered by intravenous infusion over 30 minutes every 2 weeks to several patients in a dose-escalation study (gemcitabine prescribing information).

5.3.2.4. Dose Modification for Adverse Reactions

Recommended dose reductions and/or delays for nab-paclitaxel and gemcitabine for **hematological toxicity** at the start of, or within, a cycle are summarized in Table 5 below.

Table 5. Nab-paclitaxel and Gemcitabine Dose Modifications for Hematological Toxicity

Cycle Day	ANC (cells/mm^3)		Platelet Count (cells/mm^3)	Nab-paclitaxel + Gemcitabine
Day 1	<1500	OR	<100,000	Delay doses until recovery
Day 8	500 to <1000	OR	50,000 to <75,000	Reduce one dose level
	<500	OR	<50,000	Withhold doses
Day 15: If Day 8 doses were reduced or given without modification				
	500 to <1000	OR	50,000 to <75,000	Reduce one dose level from Day 8
	<500	OR	<50,000	Withhold doses
Day 15: If Day 8 doses were withheld				
	≥1000	OR	≥75,000	Reduce one dose level from Day 1
	500 to <1000	OR	50,000 to <75,000	Reduce two dose levels from Day 1
	<500	OR	<50,000	Withhold doses

Recommended dose reductions and/or delays for nab-paclitaxel and gemcitabine for **non-hematological toxicity** are summarized in Table 6 below.

Table 6. Nab-paclitaxel and Gemcitabine Dose Modifications for Non-Hematological Toxicity

Adverse Drug Reaction	Nab-paclitaxel	Gemcitabine
Febrile Neutropenia Grade 3 or 4	Withhold until fever resolves and ANC ≥1500/μL; resume at next lower dose level	
Peripheral Neuropathy Grade 3 or 4	Withhold until improves to Grade ≤1; resume at next lower dose level	No dose reduction
Cutaneous Toxicity Grade 2 or 3	Reduce to next lower dose level; discontinue of toxicity persists	
Gastrointestinal Toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to Grade ≤1; resume at next lower dose level	

Dose reductions for nab-paclitaxel and gemcitabine referred to in Table 5 and Table 6 are summarized below in Table 7.

Table 7. Dose Reduction for Nab-paclitaxel and Gemcitabine

Dose Level	Nab-paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)
Full dose	125	1000
1st dose reduction	100	800
2nd dose reduction	75	600
If any additional dose reduction required	Discontinue	Discontinue

5.4. Criteria for Continuation of Remaining Study Treatment(s), if One or More Study Treatments are Discontinued

Subjects will be treated until disease progression in the absence of unacceptable toxicity (see separate dose management guidelines for toxicity for each agent). If nab-paclitaxel and/or gemcitabine or ibrutinib/placebo are discontinued prior to disease progression, the remaining agents will be continued until unacceptable toxicity or disease progression.

5.5. Criteria for Permanent Discontinuation of Study Treatment

Investigators are encouraged to keep a subject who in the judgment of the investigator, is experiencing benefit on study treatment unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk. In addition, if a subject shows signs of disease progression on physical examination or laboratory assessment, the subject may continue study treatment until disease progression is confirmed by radiologic assessment (eg, CT/MRI) according to RECIST 1.1 criteria. If treatment is discontinued due to disease progression that is not confirmed by radiologic assessment the medical monitor should be notified within 24 hours.

For a complete list of criteria for permanent discontinuation of study treatment, refer to Section 9.2.

An End-of-Treatment Visit (Section 8.2.3) is required for all subjects once all study drugs have been discontinued except for those subjects who have withdrawn full consent.

6. CONCOMITANT MEDICATIONS/PROCEDURES

Concomitant therapies must be recorded from the time of ICF signing until 30 days after the last dose of study drugs.

6.1. Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted.

Use of antimicrobial prophylaxis in accordance with standard practice (eg, ASCO guidelines [Flowers 2013]) is permitted and should be considered in patients who are at increased risk for opportunistic infections.

Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines (Smith 2006). Transfusions may be given in accordance with institutional policy.

Corticosteroids at dosages equivalent to prednisone >20 mg/day administered consecutively for >14 days are to be avoided.

6.2. Medications to be Used with Caution

6.2.1. CYP3A Inhibitors/Inducers

Ibrutinib is metabolized primarily by CYP3A4. Concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure and therefore strong CYP3A inhibitors should be avoided.

- If a strong CYP3A inhibitor (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, cobicistat, and posaconazole) must be used, reduce ibrutinib/placebo dose to 140 mg for the duration of the inhibitor use or withhold ibrutinib treatment temporarily (for 7 days or less). Subjects should be monitored for signs of ibrutinib toxicity.
- If a moderate CYP3A inhibitor (eg, fluconazole, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, diltiazem, fosamprenavir, imatinib, verapamil, amiodarone, and dronedarone) is indicated, reduce ibrutinib dose to 140 mg for the duration of the inhibitor use. Avoid grapefruit or 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 systemic strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

A list of common CYP3A inhibitors and inducers is provided in Appendix G. For further information, please refer to the current version of the ibrutinib IB and examples of inhibitors, inducers, and substrates may be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

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

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor (with an IC_{50} of 2.15 μg/mL). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There are no clinical data available. Therefore, to avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin, should be taken at least 6 hours before or after ibrutinib/placebo.

6.2.3. QT Prolonging Agents

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

6.2.4. Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib/placebo. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib/placebo with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. For guidance on ibrutinib/placebo and the use of anticoagulants during procedures/surgeries see Section 6.4.

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

6.3. Prohibited Concomitant Medications

Chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited while the subject is receiving study medication. Live vaccinations are prohibited while the subject is receiving gemcitabine and for 6 weeks after last dose of gemcitabine.

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.4. Guidelines for Ibrutinib Management with Surgeries or Procedures

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

6.4.1. Minor Surgical Procedures

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

6.4.2. Major Surgical Procedures

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

6.4.3. Emergency Procedures

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

7. STUDY EVALUATIONS

7.1. Description of Procedures

Where appropriate, all procedures/assessments must be performed prior to dosing with any study drug at all clinic visits.

7.1.1. Assessments

7.1.1.1. ICF

The subject must read, understand, and sign the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) approved informed consent form (ICF)

confirming his or her willingness to participate in this study before any study-specific screening procedures are performed. All subjects must also grant permission to use protected health information per the Health Insurance Portability and Accountability Act (HIPAA). In addition, subjects must sign all approved ICF amendments per the site IRB/REB/IEC guidelines during the course of the study as additional information is provided.

7.1.1.2. Confirm Eligibility

All necessary procedures and evaluations must be performed to document that the subject meets all of the inclusion criteria and none of the exclusion criteria at Screening (Section 4). Blood samples for serum chemistry, hematology, coagulation, and hepatitis serologies will be evaluated by a central laboratory to confirm eligibility with the exception of albumin where eligibility can be determined based on local labs. If central laboratory evaluation is not available (eg, specimen clotted, hemolysis, or otherwise not resulted), the Medical Monitor may review and approve submitted local labs to support eligibility on a case by case basis provided another sample is redrawn and submitted to the central laboratory prior to treatment.

7.1.1.3. Medical History and Demographics

The subject's complete clinically relevant history will be collected and recorded through review of medical records and by interview. Details of any cancer risks will be identified (to include family history of cancer, history of being >30 lbs overweight, radiation therapy before the age of 30 [specify location], alcohol ingestion, smoking/tobacco use, chronic pancreatitis, known genetic abnormality [eg, KRAS etc]). Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and list of all prior anticancer treatments, dates administered, and responses and duration of response to these treatments, will also be recorded.

7.1.1.4. Prior and Concomitant Medications

All medications continuous from the signing of ICF or 14 days prior the first dose of study drug (whichever is greater) through 30 days after the last dose of study drug will be documented. After a subject discontinues study treatment, receipt of all subsequent anticancer therapies and analgesics consumption will be collected until death, subject withdrawal of full consent, lost to follow-up, or study termination by Sponsor, whichever comes first.

7.1.1.5. Adverse Events

The accepted regulatory definition for an adverse event is provided in Section 11.1. All medical occurrences that meet the adverse event definition must be recorded from the time the ICF is signed until 30 days after the last dose of study drug. Laboratory abnormalities designated clinically significant by the investigator will also be recorded as adverse events. Additional important requirements for adverse event and serious adverse event reporting are explained in Section 11.4.

In addition to all routine AE reporting, all new malignant tumors including solid tumors, skin malignancies and hematologic malignancies are to be reported as adverse events during all protocol-specified follow-up periods including post-progression follow-up for OS.

7.1.1.6. Study Drug Compliance Review

Study drug compliance should be assessed on Day 1 of each cycle while continuing to administer ibrutinib/placebo. The patient diary should be reviewed along with ibrutinib/placebo counts to ensure that all missed doses or dose changes have been documented.

7.1.1.7. Physical Examination

The Screening and End-of-Treatment Visit physical examination will include, at a minimum, the general appearance of the subject, height (Screening only), and examination of the general appearance, head, eyes, ears, nose and throat (HEENT), cardiovascular, dermatologic, lymphatic, respiratory, gastrointestinal, genitourinary, musculoskeletal, nervous, and lymphatic systems. Abnormalities at Screening should be reported as medical history.

A physical examination is required on Day 1 of each cycle, and Efficacy Follow-up Visits. All physical exams will include a pancreatic cancer disease assessment include the following; assessment of palpable masses and new sites of disease, hepatospenomegaly, third space fluid accumulation (ascites or pleural fluid), and signs of jaundice, cachexia, muscle atrophy, or lethargy. If ascites and/or pleural effusion fluid is removed/assessed cytology should be sent and volume of fluid removed quantified and entered into the eCRF. New metastatic sites should be biopsied with pathology information entered to eCRF.

7.1.1.8. Eye-related Symptom Assessment

The subjects will be asked about eye-related symptoms at Screening and with all subsequent physical exams while on treatment (refer to Appendix A).

If there are any eye-related symptoms of severity Grade ≥2 at Screening or if the subject develops any eye-related symptoms of severity Grade ≥2 while on study treatment, an ophthalmologic evaluation/consult must be performed and the outcome must be reported on the ophthalmologic eCRF.

7.1.1.9. Weight

Weight will be collected per visit schedule listed in Appendix A until death, subject withdrawal, lost to follow-up, or study termination by the Sponsor, whichever occurs first.

7.1.1.10. Eastern Cooperative Oncology Group (ECOG) Performance Status

The Eastern Cooperative Oncology Group Performance Status scale is provided in Appendix E. ECOG performance status will be assessed at Screening.

7.1.1.11. Karnofsky Performance Score (KPS)

The Karnofsky Performance Scale is provided in Appendix D. Performance score will be assessed at Screening, C1D1, and every 2 weeks until death, subject withdrawal, lost to follow-up, or study termination by the Sponsor, whichever occurs first. Two observers will be required to assess KPS at Screening. If discrepant, the one with the lowest assessment will be accepted.

7.1.1.12. Memorial Pain Assessment Card (MPAC)

The Memorial Pain Assessment Card (MPAC) is provided in Appendix F. Pain, mood and relief will be assessed prior to any other procedures (including investigator and staff interaction) at Screening and then every 2 weeks after the first dose, until death, subject withdrawal, lost to follow-up, or study termination by the Sponsor, whichever occurs first.

7.1.1.13. Patient-reported Outcomes (PRO) (EORTC QLQ-C30, version 3.0)

The EORTC Quality of Life Questionnaire (QLQ-C30) is provided in Appendix H. The QLQ-C30 questionnaire will be completed every 2 weeks immediately following the MPAC beginning on C1D1. The assessment will be completed until death, subject withdrawal, lost to follow-up, or study termination by the Sponsor, whichever occurs first. The QLQ-C30 questionnaire will be administered to all randomized subjects in this study. This is to be completed by the subject prior to any other study procedures at weeks specified in the Schedule of Assessments (Appendix A).

The QLQ-C30 questionnaire is an integrated modular tool incorporating nine multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social); 3 symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality-of-life scale. Several single-item symptom measures are also included (such as appetite loss, constipation, diarrhoea, dyspnea, financial impact and sleep disturbance).

Individual questions are answered within a 4-point scale (not at all, a little, quite a bit, very much) and typically patients can complete the entire questionnaire in about ten minutes with minimal assistance.

7.1.1.14. Vital Signs

Vital signs including blood pressure, heart rate, respiratory rate, and body temperature should be assessed after the subject has been resting in the sitting position for at least 3 minutes. Vital signs are taken during Screening, Day 1 of every cycle, and End-of-Treatment Visit.

7.1.2. Laboratory

All tests will be performed by a study specific central laboratory except serum/urine pregnancy and urinalysis testing which will be performed locally. Hematology for Cycle 1 and Cycle 2

Day 22 visits must be performed centrally. All subsequent Day 22 hematology labs from Cycle 3 onwards will be performed at the discretion of the investigator and may be performed locally.

7.1.2.1. Hematology

Hematology parameters will include a complete blood count: white blood cells, red blood cells, hemoglobin, hematocrit, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils and bands (if reported).

7.1.2.2. Comprehensive Chemistry Panel

Serum chemistry parameters will include sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, creatinine clearance (Cockroft-Gault) (done at Screening only), glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, lactate dehydrogenase (LDH), phosphate, uric acid, magnesium and bicarbonate.

7.1.2.3. Coagulation Studies

Measurement of prothrombin time (PT)/INR, and activated partial thromboplastin time (aPTT) will be performed at Screening using a study specific central laboratory.

7.1.2.4. Hepatitis Serologies

Hepatitis serologies include hepatitis C antibody, hepatitis B surface antigen, and hepatitis B core antibody will be evaluated. If hepatitis B core antibody, hepatitis B surface antigen or hepatitis C antibody is positive, then PCR to quantitate hepatitis B/C DNA can be performed locally and must be negative prior to randomization/enrollment.

7.1.2.5. Urinalysis

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

7.1.2.6. Pregnancy Test

A serum or urine pregnancy test will be required at Screening and on Day 1 prior to the first dose for women of childbearing potential (ie, post-menopausal by history - no menses for ≥1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). If positive, pregnancy must be ruled out by ultrasound to be eligible for randomization. This test will also be performed at End-of-Treatment visit and may be performed more frequently if required by local regulatory authorities.

7.1.3. Diagnostics/Procedures

7.1.3.1. ECG

At Screening, 12-lead ECGs will be done in triplicate (≥1 minute apart). ECG abnormalities noted at Screening must be included in the medical history.

Subsequent ECGs should be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset dyspnea with results noted collected in the eCRF.

Subjects should be in supine position and resting for at least 10 minutes before all study-related ECGs.

7.1.3.2. CT/MRI

Documented tumor measurement is required using CT scans, PET/CT or MRI, as appropriate, and is to be performed at Screening and every 8 weeks following initiation of study drug until documented disease progression by RECIST 1.1, death, withdrawal of consent for further follow up, or lost to follow up, whichever occurs first. The same method of assessment (CT, PET/CT, or MRI) and the same technique for acquisition of data must be used to characterize each identified and reported lesion at baseline and at follow-up visits.

Pretreatment tumor assessment will be performed within 28 days before the first dose of study drug. A CT scan (with contrast unless contraindicated) of thorax, liver, abdomen and other areas if clinically indicated, is required for the pretreatment tumor assessment. An adequate volume of contrast should be given to ensure metastases are well-visualized and the method of administration (dose and rate) should be consistent for subsequent examinations. Lesions in anatomical locations that are not well visualized by CT may be measured by MRI instead.

In the case where CT with contrast is contraindicated, an alternative would be MRI of the abdomen and pelvis and CT of the chest without contrast.

NOTE: PET/CT hybrid scanners may be used to acquire the required CT images only if the CT produced by the scanner is of diagnostic quality, adheres to specified slice thickness/scan parameters, and includes the use of IV contrast. The PET scan must be performed **prior** to CT with IV contrast as to not compromise PET results. Additionally, the CT images must be separated from the PET data prior to submitting the data, and cannot be transmitted as fused CT/PET images.

If independent CT and PET scanners are used, and the subject is receiving both scans on the same day, the PET scan must be performed prior to CT with IV contrast.

Subjects who refuse CT/MRI scans and/or miss more than one scan may be removed from the study, at the discretion of the investigator and following discussion with the medical monitor.

De-identified copies of all scans-(including those from Screening and any unscheduled scans) must be provided to the Sponsor or designee (eg, central imaging vendor). At the Sponsor's discretion, the Sponsor or designee may conduct an independent review of the investigator assessments.

7.1.4. Pharmacokinetics

Refer to the Laboratory Manual for instructions on collecting and processing these samples. PK samples will be taken from all subjects except for gemcitabine PK, which will be collected in subjects enrolled in selective regions only. Prior to Cycle 2 Day 1 (C2D1) visit, the clinical staff will instruct the subject not to take the ibrutinib dose before arrival at the clinic on C2D1. The actual time (versus requested time) that each sample is drawn must be recorded using a 24 hour format. The same clock should be used for recording the time of dosing.

Plasma concentrations of ibrutinib and metabolite PCI-45227, gemcitabine and metabolite 2',2'-difluorodeoxyuridine (dFdU), and nab-paclitaxel will be determined using validated analytical methods. Other potential metabolites of ibrutinib may be explored. Refer to the Table 8 and Appendix B for Pharmacokinetics Sampling Schedule.

Table 8. Pharmacokinetics Sampling Schedule for Cycle 2 Day 1 Only

Study Cycle & Day	Time points	Ibrutinib/ Placebo	Nab-Paclitaxel	Gemcitabine[c]
Cycle 2 Day 1	Predose [a]	X	X	X
	Drug Administration/Infusion (Time 0)	Drug Administration	Start Infusion	
	Infusion (Time 0.5 hr)		End of Infusion X[b]	Start of Infusion
	Infusion (Time 1.0 hr)			End of Infusion X[b]
	0.5 hr post end of dose/infusion (±5 min)		X	
	1.0 hr post end of dose/infusion (±15 min)	X		X
	1.5 hr post end of dose/infusion (±15 min)		X	
	2.0 hr post end of dose/infusion (±15 min)	X		
	3.0 hr post end of dose/infusion (±15 min)			X
	3.5 hr post end of dose/infusion (±15 min)		X	
	4.0 hr post end of dose/infusion (±15 min)	X		
	5.0 hr post end of dose/infusion (±15 min)			X
	5.5 hr post end of dose/infusion (±15 min)		X	
	6.0 hr post end of dose/infusion (±15 min)	X		

a. Predose samples should be collected prior to the administration of any drug.
b. End of infusion samples for both gemcitabine and nab-paclitaxel should be collected within **5 minutes before the infusion is stopped**.
c. Gemcitabine PK samples will be collected only in selective regions.

Note:
- Ibrutinib/placebo should be dosed at clock time zero. Immediately following ibrutinib/placebo administration, nab-paclitaxel infusion should begin. Once nab-paclitaxel infusion is stopped (30-40 minutes after infusion start), gemcitabine infusion should be started immediately thereafter (infusion time is about 30-40 minutes).
- Clock times are approximate and assumes a 30 minute infusion for both gemcitabine and nab-paclitaxel
- X indicates timepoint after the administration of ibrutinib/placebo that associated PK should be drawn and likewise time after each infusion is completed that the associated PK is drawn.

7.1.5. Biomarkers

7.1.5.1. Carbohydrate Antigen 19-9 (CA 19-9)

Blood samples for serum carbohydrate antigen 19-9 (CA 19-9) levels will be collected and sent to the central lab at Screening and prior to dosing on Day 1 of each cycle. If study drugs are discontinued, blood samples for CA 19-9 will be collected and sent to a central laboratory every 4 weeks.

7.1.5.2. Immunophenotyping

Blood sample(s) for T/B/NK cell count ($CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, $CD16/56^+$) must be collected and sent to the central lab prior to dosing on Day 1 of each cycle of nab-paclitaxel and gemcitabine for the first 3 cycles and then every 3 cycles thereafter until treatment discontinuation. Percentages and absolute counts of $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$ and $CD16/56^+$ cells will be determined. Additional assessment of T, B, macrophages subsets may also be performed.

7.1.5.3. Molecular Markers

Blood and urine samples will be collected and sent to the central laboratory prior to dosing on Day 1 of each cycle of nab-paclitaxel and gemcitabine for the first 3 cycles and then only blood sample will be collected every 3 cycles thereafter until documented disease progression per RECIST 1.1. Buccal swabs will be collected from all subjects on Cycle 1 Day 1. Archival tumor tissue will be provided if available and/or fresh tumor tissue will be collected at Screening if consented by subject. If a fresh tumor biopsy is performed at Screening, it should be at least 7 days prior to the first dose of study drug or at least 3 days prior to the first dose of study drug for a fine needle aspiration (FNA). Upon RECIST 1.1 documented disease progression, an optional fresh tumor biopsy may be collected from consenting subjects.

Cytokines/chemokines, secreted protein markers and cell surface/genomic markers may be tested in peripheral blood and tumor tissue, respectively. In the presence of sufficient samples, tumor biopsies may be evaluated by qualitative immunohistological assessment of immune cell subsets, ie, T cells, B cells, NK cells, and macrophages. Expression of BTK and pBTK expression in tumor biopsies may be evaluated, and in addition staining for immune checkpoint targets such as PD-1 and PD-L1 may also be performed. Additional genomic analyses, TCRb and BCR sequencing may be performed on the tumor samples of some subjects to identify clonality of T and B cells in tumor tissues. Functional T-Cell responses to mitogens and candidate tumor antigens (tetramer analysis) may also be explored.

All sample types may undergo additional testing to evaluate other potential biomarkers related to disease and treatment response and to investigate potential mechanisms of treatment resistance. These samples may be characterized by techniques such as gene expression profiling, targeted sequencing for genomic alterations, and intracellular pathway analyses. Inhibition of BTK, ITK

and other relevant kinases may also be explored. These efforts may identify biomarkers that could assist with future development of ibrutinib.

Pharmacodynamics assays, including BTK and ITK occupancy, may be performed to correlate results of biomarker assessments to the clinical effects of ibrutinib in combination with nab-paclitaxel and gemcitabine.

Additional testing may be performed on stored samples as new methods are developed to further understand the origin, progression, and resistance of cancer and its relationship to the study drug(s). In addition, these samples may be used for research that may lead to the development of medical products or processes. All leftover samples will be de-identified prior to shipping to a central vendor and will be destroyed no later than 10 years after study completion.

See Appendix C for biomarker sampling schedule.

7.2. Efficacy Evaluations

All radiologic scans will be assessed for response or progression using RECIST 1.1 guidelines (Eisenhauer 2009). Grading for best response will be categorized as complete response (CR), partial response (PR), stable disease (≥8 weeks) (SD), or progressive disease (PD). Additional information can be found at https://www.eortc.be/Recist/documents/RECISTGuidelines.pdf.

7.2.1. Definitions

Response and progression will be evaluated in this study using RECIST 1.1 guidelines (Eisenhauer 2009). Changes in only the longest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1 guidelines to assess response, with the exception of lymph nodes, where changes in the shortest diameter are utilized.

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

7.2.1.1. Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size as follows:

- 10 mm with CT scan with a slice thickness of no greater than 5 mm. If the slice thickness is >5 mm, the minimum size for a measurable lesion is twice the slice thickness.
- 10 mm caliper measurement by clinical exam.
- If the CT slice thickness is >5 mm, the extranodal disease must be ≥ twice the slice thickness.

Lymph nodes can only be considered as target lesions if they are ≥15 mm in the short axis. Although lymph nodes ≥10 mm are considered pathological, they cannot be categorized as target lesions per RECIST 1.1 guidelines.

7.2.1.2. Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm using spiral CT scan or pathological nodes with ≥10 to <15 mm short access) as well as truly non-measurable lesions are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable disease.

7.2.1.3. Target Lesions

All measurable 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 the baseline/screening assessment. Target lesions should 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. Lesions that have been irradiated cannot be included in the tumor assessment, unless unequivocal tumor progression has been documented in these lesions after radiation therapy.

7.2.1.4. Non-target Lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at the baseline/screening assessment. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’. Recording several lesions involving the same organ as a single item is acceptable.

7.2.1.5. New Lesions

If new lesions appear and there is doubt as to whether a lesion is new or an inflammatory change, follow-up scans are required. If the new lesion is confirmed, as unequivocal (ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to be something other than the tumor by a scan obtained at least 4 weeks after the initial scan), the date of progression is taken to be the date on which the new lesion was first detected. If a lesion reappears after disappearing in a subject with complete response, progressive disease is declared.

However, if such a lesion behaves in this manner in a subject with stable disease or partial response, it is the change in sum of target disease that defines the response or progression.

A lesion found in a follow-up study in a region that was not scanned at baseline is still considered a new lesion and will indicate progressive disease, if confirmed by a repeat scan obtained at least 4 weeks after the initial scan.

7.2.2. Guidelines for Evaluation of Measurable Disease

Standard training on RECIST 1.1 guidelines and implementation of the guidelines will be provided to clinical trial sites. All measurements for target lesions should be taken and recorded in metric notation using a ruler or calipers.

Measurements need not be along the same axis (as measured at baseline), but should always be the longest axis of the lesion at that point in time. It does not have to be at the same slice position, provided the measurement is of the same lesion. However, if the initial measurements are in the axial plane, all further measurements of that lesion must remain in the axial plane. Likewise, if the initial measurements are in the coronal plane (this is acceptable), all further measurements of that lesion must be in the coronal plane.

If a lesion disappears, the measurement of that lesion is clearly 0 mm, however, if the lesion remains present, but is too small to measure accurately, a default measurement of 5 mm should be given, regardless of slice thickness. If lymph nodes decrease to <10 mm, these are considered to be disease free, but remain target lesions. If lesions merge, the long axis of the resulting lesion is measured as one lesion in place of the individual lesions. If lesions split, the long axis of each individual lesion is added together.

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

Nodal lesions: If lymph nodes are chosen as target lesions and decrease to normal size (<10 mm), the measurement of the lesion must still be included in the sum of the target lesions. This means that subjects may still meet the criteria for CR even if the sum of target lesions is not zero.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (eg, 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.

Tumor markers: Tumor markers alone cannot be used to assess response.

NOTE: The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable

disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

7.2.3. Response Criteria

7.2.3.1. Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in the short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

7.2.3.2. Evaluation of Non-target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions and appearance of one or more new lesions.

Note: To be considered unequivocal progression on the basis of non-target lesions only, the overall tumor burden must have increased.

In the event that worsening in non-target disease cannot be easily quantified for unequivocal progression, it is appropriate to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for radiographically measurable disease. For example, an increase in a malignant pleural effusion from ‘trace’ to ‘large’ or an increase in lymphangitic disease from localized to widespread. If ‘unequivocal progression’ is seen, the subject should be considered to have had overall PD at that point.

7.2.3.3. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the

treatment started). The subject's best response assignment will depend on meeting RECIST 1.1 criteria (Table 9).

Subjects who have signs and symptoms of progression outside of the scheduled assessment, should be evaluated by the investigator and a CT/MRI scan performed to determine if disease progression can be confirmed by RECIST 1.1 criteria.

If a subject shows signs or symptoms of disease progression, the subject may continue study treatment with ibrutinib/placebo until disease progression is confirmed by radiologic assessment (eg, CT/MRI) according to RECIST 1.1 criteria. If a subject experiences clinical deterioration consistent with progression but does not clearly meet progression by RECIST 1.1 by CT or MRI, when clinically appropriate, based on investigator perceived risk benefit assessment, the subject may continue treatment until progression can be confirmed by a repeat scan unless considered medically contraindicated.

Subjects may continue study treatment until progression is confirmed by a serial exam at least 2 weeks later. New anticancer therapy should be withheld if clinically appropriate in the absence of confirmed progressive disease by CT/MRI per RECIST 1.1 criteria.

In order to accommodate the potential for pseudoprogression, treatment with ibrutinib + nab-paclitaxel + gemcitabine or placebo + nab-paclitaxel + gemcitabine may continue between the initial assessment of suspected progression and confirmation of progression. Subjects with suspected progressive disease who, in the Investigator's opinion, continue to receive clinical benefit from their treatment may continue to receive therapy as dictated in the protocol after consultation with the Sponsor and at the Investigator's discretion. In the absence of symptomatic deterioration, a biopsy (if lesion is assessable) should be performed at the time of suspected pseudoprogression (in order to rule out tumor necrosis and/or an inflammatory reaction) or the investigator may continue dosing and a CT/MRI scan *or physical examination (if the lesion is not assessable by CT/MRI)* should be performed at least 4 weeks later to confirm PD. If PD is confirmed at the later time point, PD should be assigned to the prior time point at which PD criteria were met. Therapy should be discontinued if there is confirmed PD per RECIST 1.1 guidelines or other clinical data suggest clear evidence of progression (symptomatic deterioration).

Table 9. Time Point Response: Subjects with Target (+/– Non-target) Disease

Target Lesions	Non Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or Not All Evaluated	No	PR
SD	Non-PD or Not All Evaluated	No	SD
Not all Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

NOTE: Subjects that require discontinuation of treatment for progression without CT or MRI confirmation or biopsy to document at that time should be classified as having disease progression. Every effort should be made to document progression by CT scan or MRI even after discontinuation of treatment. If a subject has evidence of disease progression and is unable to obtain CT or MRI for radiology confirmation of disease progression, data to support disease progression must be entered into the eCRF. For example, laboratory assessments, physical exam findings including the pancreatic disease assessment, and findings from third space fluid accumulation or biopsies must be provided to support disease progression.

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

7.2.3.4. Missing Assessments or Inevaluable Lesions

When an imaging assessment is not done or a lesion is not evaluable at a particular time point, the subject is not evaluable (NE) at that time point.

7.3. Sample Collection and Handling

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

Instructions for the collection, handling, and shipment of samples are found in the Laboratory Manual.

8. STUDY PROCEDURES

8.1. Screening Phase (Within 28 Days of Randomization)

8.1.1. Screening/Consenting Visit

- Informed Consent
- Confirmation of eligibility criteria
- Medical history
- Adverse Events (including new malignant tumors)
- Complete physical exam
- Eye-related symptoms assessment (ophthalmic exam for any eye related symptoms of severity Grade ≥2)
- Weight
- Vitals signs
- Review of prior medications (including analgesic consumption)
- Eastern Cooperative Oncology Group Performance Status (ECOG)
- Karnofsky performance status (KPS)
- Memorial Pain Assessment Card (MPAC)
- 12-lead ECG (in triplicate, ≥1 minutes apart)
- Clinical laboratory tests for:
  - Hematology
  - Comprehensive chemistry panel
  - Coagulation panel (PT, aPTT, INR)
  - Hepatitis serologies
  - Creatinine clearance
  - Urinalysis
  - Serum pregnancy test (for women of childbearing potential only)
  - Serum CA-19-9
- Imaging by CT, PET/CT, MRI of thorax/liver/abdomen + other areas if clinically indicated, as described in Section 7.1.3.2
- Biomarkers

- Confirmation of tumor tissue availability
  - Archival tissue, or
  - Fresh tumor biopsy (optional) collected at least 7 days prior to dosing, or
  - FNA at least 3 days prior to dosing (refer to Section 7.1.5.3)

8.2. Treatment Phase

8.2.1. Treatment Visits

8.2.1.1. Cycle 1 Day 1 (C1D1)

Laboratory assessments performed within 48 hours of C1D1 may be used as pre-dose C1D1 laboratory assessments and are not required to be repeated. Refer to Sections 5.1.1 and 5.1.2 for details regarding enrollment and randomization process.

Eligibility must be confirmed by the investigator prior to randomization. Eligibility Worksheet must be submitted for Safety Run-in Phase (within 48 hours of anticipated enrollment) and approved by the Sponsor or designee prior to enrollment in IWRS.

Pre-dose

- Eligibility confirmation
- Memorial Pain Assessment Card (MPAC)
- PRO (QLQ-C30)
- Symptom directed physical exam
- Eye-related symptom assessment (ophthalmic exam for any eye-related symptoms of severity Grade ≥2)
- Weight
- Vital signs
- Review of concomitant medications (including analgesic consumption)
- Review of adverse events (including any new malignant tumors)
- Karnofsky Performance Status (KPS)
- Clinical laboratory tests for:
  - Hematology
  - Comprehensive chemistry panel
  - Urine pregnancy test (for women of childbearing potential only)
  - Urinalysis
  - Serum CA 19-9

- Biomarker sampling
  - Blood and urine sample collection for immunophenotyping and molecular markers
  - Buccal swab

Dosing

- Dispense ibrutinib/placebo (optional to be provided 48 hours prior to C1D1 administration of chemo if appropriate, C1D1 labs should be obtained for baseline prior to administration of any study drug)
- In-clinic administration of ibrutinib/placebo (prior to commencement of nab-paclitaxel infusion)
- In-clinic administration of nab-paclitaxel and gemcitabine

Post-dose

- Assessment of adverse events for 2 hours post completion of nab-paclitaxel and gemcitabine administration
- Subject may leave clinic at the discretion of the investigator, 2 hours post completion of nab-paclitaxel and gemcitabine administration

8.2.1.2. Cycle 1 Day 8 (and Subsequent Cycles)

Pre-dose

- Clinical laboratory tests for:
  - Hematology
  - Comprehensive chemistry panel
  - Urinalysis
- Review of concomitant medications (including analgesic consumption)
- Weight
- Review of adverse events (including any new malignant tumors)

Dosing

- Assess need for dose modification/dose delay for ibrutinib/placebo based on laboratory test results and reported AEs, if any
- Assess need for dose modification/dose delay for nab-paclitaxel and gemcitabine based on laboratory test results and reported AEs, if any
- In-clinic administration of ibrutinib/placebo (immediately prior to commencement of nab-paclitaxel infusion)
- In-clinic administration of nab-paclitaxel and gemcitabine

Post-dose

- Subject may leave clinic after completion of nab-paclitaxel and gemcitabine administration

8.2.1.3. Cycle 1 Day 15 (and Subsequent Cycles)

Pre-dose

- Memorial Pain Assessment Card (MPAC)
- PRO (QLQ-C30)
- Clinical laboratory tests for:
  - Hematology
  - Comprehensive chemistry panel
  - Urinalysis
- Review of concomitant medications (including analgesic consumption)
- Weight
- Review of adverse events (including any new malignant tumors)
- Karnofsky Performance Status (KPS)

Dosing

- Assess need for dose modification/dose delay for ibrutinib/placebo based on laboratory test results and reported AEs, if any
- Assess need for dose modification/dose delay for nab-paclitaxel and gemcitabine based on laboratory test results and reported AEs, if any
- In-clinic administration of ibrutinib/placebo (immediately prior to commencement of nab-paclitaxel infusion)
- In-clinic administration of nab-paclitaxel and gemcitabine

Post-dose

- Subject may leave clinic after completion of nab-paclitaxel and gemcitabine administration

8.2.1.4. Cycle 1 Day 22 (and Subsequent Cycles)

- Laboratory tests for:
  - Hematology for Cycles 1 and 2, Day 22 visits must be performed centrally. All subsequent Day 22 hematology labs from Cycle 3 onwards will be performed at the discretion of the investigator and may be performed locally.

8.2.1.5. Cycle 2 Day 1 (and Subsequent Cycles)

Pre-dose

- Memorial Pain Assessment Card (MPAC)
- PRO (QLQ-C30)
- Clinical laboratory tests for:
  - Hematology
  - Comprehensive chemistry panel
  - Urinalysis
  - Urine pregnancy test (for women of child bearing potential)
- Symptom directed physical exam
- Weight
- Vital signs
- Review of concomitant medications (including analgesic consumption)
- Review of ibrutinib/placebo compliance
- Review of adverse events (including new malignant tumors)
- Karnofsky Performance Status (KPS)
- Serum CA 19-9 on Day 1 of each Cycle until disease progression)
- Blood and urine sample collection for immunophenotyping and molecular markers (Cycles 2 and 3 and then only blood sample will be collected every THIRD cycle thereafter until disease progression)
- PK sampling for ibrutinib/placebo, nab-paclitaxel, and gemcitabine* on Cycle 2 Day 1 ONLY - must collect pre-dose samples prior to any study drug administration (including ibrutinib/placebo)
  *Note: gemcitabine PK sampling will be collected in selective regions only.
- Imaging by CT, PET/CT, MRI (every 8 weeks, starting with Cycle 3. Scan to be performed within +/- 7 days of scheduled dosing visit)
- RECIST 1.1 response evaluation (every 8 weeks, starting with Cycle 3)

Dosing

- Assess need for dose modification/dose delay for ibrutinib/placebo based on laboratory test results and reported AEs, if any
- Assess need for dose modification/dose delay for nab-paclitaxel and gemcitabine based on laboratory test results and reported AEs, if any
- In-clinic administration of ibrutinib/placebo (immediately prior to commencement of nab-paclitaxel infusion)

- In-clinic administration of nab-paclitaxel and gemcitabine
- PK sampling for ibrutinib/placebo, nab-paclitaxel, gemcitabine* on Cycle 2 Day 1 ONLY
  * Note: gemcitabine PK sampling will be collected in selective regions only.

Post-dose

- Dispense ibrutinib/placebo
- Subject may leave clinic after completion of nab-paclitaxel and gemcitabine administration (other than Cycle 2 Day1)
- PK sampling for ibrutinib/placebo, nab-paclitaxel, gemcitabine* up to 5.0 hr after end of gemcitabine infusion on Cycle 2 Day 1 ONLY
  * Note: gemcitabine PK sampling will be collected in selective regions only.

8.2.2. Efficacy Evaluations

Efficacy evaluations will be performed per the schedule outlined in Appendix A. The following procedures will be performed in conjunction with standard visits as follows:

- Radiologic exam by CT, PET/CT, and/or MRI should be performed every 8 weeks and to confirm progressive disease
- RECIST 1.1 Evaluation (to correspond with radiological exam)

8.2.3. End-of-Treatment (EOT) Visit

An End-of-Treatment (EOT) Visit should occur 30 days (+7 days) after all study drugs have been discontinued or prior to starting any new anticancer treatment.

Subjects who withdraw consent to treatment should still have an EOT Visit, if subject consents. The following procedures will be performed at the EOT Visit:

- Memorial Pain Assessment Card (MPAC)
- PRO (QLQ-C30)
- Complete physical exam
- Eye-related symptoms assessment (ophthalmic exam for eye related symptoms Grade ≥2)
- Weight
- Vital signs
- Karnofsky Performance Status (KPS)
- Clinical laboratory tests for:
  - Hematology
  - Comprehensive chemistry panel

  - Urine pregnancy test
  - Serum CA 19-9
- Blood and urine sample collection for immunophenotyping and molecular markers
- Review of AEs and concomitant medications (including analgesic consumption and new malignant tumors)
- Optional fresh tumor biopsy in consenting subjects (if RECIST 1.1 determined disease progression has been documented at the time of the EOT visit).

8.3. Follow-up Phase

After completing the EOT Visit, subjects will enter the Long-term Follow-up Phase provided they have RECIST1.1 documented disease progression at the EOT Visit. Subjects who withdraw from treatment for reasons other than RECIST1.1 documented progressive disease will participate in the Efficacy Follow-ups.

8.3.1. Efficacy Follow-up

Subjects who discontinue treatment for reasons other than RECIST1.1 documented disease progression will continue to have normally scheduled clinical assessments (every 2 weeks or as specified below) until RECIST1.1 disease progression is documented, death, withdrawal of consent for further follow up, or lost to further follow up.

- Physical exam
- Radiological disease assessments (CT, PET/CT, or MRI) every 8 weeks
- Serum CA 19-9 measurements every 4 weeks.
- Clinical benefit, including:
  - KPS
  - MPAC
  - Analgesic consumption
  - PRO (QLQ-C30)
  - Weight
- Optional fresh tumor biopsy in consenting subjects (if RECIST 1.1 determined disease progression has been documented)

8.3.2. Long-term Follow-up

For subjects who terminate study treatment, have documented RECIST1.1 disease progression, and have not withdrawn consent for Long-term Follow-up, they (or a partner/relative where appropriate) will be contacted approximately every 2 weeks (±7 days) by clinic visit or telephone to assess.

- Survival
- Use of subsequent anticancer therapy
- Clinical benefit (if visit is done in the clinic, not applicable for phone follow up), including:
  - KPS
  - MPAC
  - Analgesic consumption
  - PRO
  - Weight

Subjects will be contacted until death or complete withdrawal of consent.

9. SUBJECT COMPLETION AND WITHDRAWAL

9.1. Completion

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

9.2. Withdrawal from Study Treatment

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

- Radiologically confirmed progressive disease (PD).
- Unacceptable drug related toxicity, or other event that prevents further administration of any study medication (ie, so that the subject can no longer tolerate ibrutinib/placebo and nab-paclitaxel and gemcitabine).
- Death
- Withdrawal of consent for treatment with any further study medications. If a subject withdraws consent for all further treatment with study medication, the site must clarify with the subject whether their intent is to i) withdraw from the study (as detailed in Section 9.3) ii) permit continuing protocol specified follow-up visits (including assessment for progression) or iii) permit only protocol specified follow up for survival status.

  The study medical monitor should be notified wihin 24 hours of a patient modifying their consent.
- Investigator decision (such as chronic noncompliance, significant protocol deviation, or best interest of the subject including clinical deterioration without progression)
- Study termination by Sponsor
- Subject becomes pregnant

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

If a subject shows signs of disease progression on physical examination or laboratory assessment, the subject may continue study treatment, at the discretion of the investigator, until disease progression is confirmed by radiologic assessment (eg, CT/MRI) according to RECIST 1.1 criteria.

In order to accommodate the potential for pseudoprogression, treatment with ibrutinib + nab-paclitaxel + gemcitabine or placebo + nab-paclitaxel + gemcitabine may continue between the initial assessment of suspected progression and confirmation of progression. Subjects with suspected progressive disease who, in the Investigator's opinion, continue to receive clinical benefit from their treatment may continue to receive therapy as dictated in the protocol after consultation with the Sponsor and at the Investigator's discretion. In the absence of symptomatic deterioration, a biopsy (if lesion is assessable) should be performed at the time of suspected pseudoprogression (in order to rule out tumor necrosis and/or an inflammatory reaction) or the investigator may continue dosing and a CT/MRI scan *or physical examination (if the lesion is not assessable by CT/MRI)* should be performed at least 4 weeks later to confirm PD. If PD is confirmed at the later time point, PD should be assigned to the prior time point at which PD criteria were met. Therapy should be discontinued if there is confirmed PD per RECIST 1.1 guidelines or other clinical data suggest clear evidence of progression (symptomatic deterioration).

9.3. Withdrawal from Study

Withdrawal from study will occur under the following circumstances:

- Withdrawal of consent for follow-up observation by the subject. If a subject withdraws from treatment only, then this is not considered to be a withdrawal from study.
- Lost to follow-up
- Study termination by Sponsor
- Death

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

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

- Reason for withdrawal
- Given that OS is a primary endpoint of this study and a critical endpoint to understand if ibrutinib improves outcomes for pancreatic cancer patients – physicians and subjects should be encouraged to allow for survival follow-up as deemed appropriate and agreeable to subjects.

10. STATISTICAL METHODS AND ANALYSIS

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

10.1. Subject Information

10.1.1. Intention-to-treat Population (ITT)

The ITT Population is defined as all subjects who are randomized to study medication.

The ITT population will be used as the primary population for analysis of efficacy.

10.1.2. Safety Population (SP)

The Safety Population will consist of all randomized subjects who received at least one dose of any study treatment. The Safety Population will be used for the analysis of safety data.

10.1.3. Additional Analysis Populations

Additional analysis populations, which may be used in sensitivity analyses for primary and secondary efficacy objectives and for analyses of exploratory objectives, will be defined in the statistical analysis plan.

Safety and efficacy data from subjects in the open label run-in phase will be presented descriptively and separately from the randomized efficacy ITT and Safety Populations.

10.1.4. Replacement of Subjects

Subjects who are randomized but subsequently withdrawn for any reason will not be replaced.

10.2. Endpoints

10.2.1. Primary Endpoints

The primary endpoints are progression-free survival (PFS), as determined by investigator assessment, according to RECIST 1.1 criteria and overall survival (OS).

10.2.2. Secondary Endpoints

- Clinical benefit response (CBR) rate
- Overall response rate (ORR): CR + PR, per investigator assessment
- Carbohydrate antigen 19-9 (CA19-9) response
- Patient-reported outcomes (PRO): global health status based on QLQ-C30

- Rate of venous thromboembolic events (VTE)

10.2.3. Other Secondary Endpoints

The safety and tolerability of ibrutinib/placebo in combination with nab-paclitaxel and gemcitabine *versus* the combination of placebo with nab-paclitaxel and gemcitabine

10.2.4. Selected Exploratory Endpoints

- Overall survival maintenance in a subgroup of subjects, who are progression-free and alive at 6 months of treatment. This subgroup is defined as no PD or death at 6 months who continue on ibrutinib/placebo after having discontinued nab-paclitaxel and gemcitabine.
- Exploratory tumor and circulating biomarkers
- Pharmacokinetic (PK) parameters of ibrutinib, gemcitabine and paclitaxel

10.3. Sample Size Determination

The sample size calculation is based on a 2-sided family-wise Type I error rate (FWER) of 0.05 for two primary endpoints, PFS and OS. The FWER is controlled at 0.05 with 0.007 allocated to the PFS analysis and 0.043 allocated to the OS analysis.

As of 24 April 2017, a total of 424 subjects have been randomized with a 1:1 allocation to the two treatment arms. The calculations are based on the following assumptions and a sample size of 424 subjects, using EAST software version 6.3.1 and the actual enrollment rates.

For PFS:

- Median PFS is 5.5 months for the control arm (nab-paclitaxel and gemcitabine) (Von Hoff 2013).
- Target hazard ratio is 0.66 which corresponds to a 51% improvement in median PFS (eg, from 5.5 months to 8.33 months) for the ibrutinib + nab-paclitaxel + gemcitabine arm compared to the placebo + nab-paclitaxel + gemcitabine arm
- 2-sided $\alpha = 0.007$
- A total of 350 PFS events will provide approximately 88% power. No interim analysis is planned.

For OS:

- Median OS is 8.5 months for the control arm (nab-paclitaxel and gemcitabine) (Von Hoff 2013).
- Target hazard ratio is 0.735 which corresponds to approximately 36% improvement in median OS (eg, from 8.5 months to 11.6 months) for the ibrutinib + nab-paclitaxel + gemcitabine arm compared to the placebo + nab-paclitaxel + gemcitabine arm
- 2-sided $\alpha = 0.043$
- A group sequential design with one interim analysis is planned when at least 250 deaths occur (approximately 71% of death events). Lan-DeMets alpha spending function with O'Brien-Fleming boundary for efficacy is used.
- A total of 353 OS events will provide approximately 80% power for the study.

10.4. Efficacy Analysis

10.4.1. Primary Endpoints and Methods

A primary efficacy endpoint , PFS, is defined as the time from the date of randomization until disease progression *per* RECIST 1.1 criteria assessed by investigator, or death from any cause, whichever occurs first.

The additional primary endpoint, OS, is defined as the time from date of randomization until date of death from any cause. The primary analyses of PFS and OS will be performed in the ITT population using the log-rank test stratified by the stratification factors. PFS final analysis and OS interim analysis will be carried out at the same time after at least 350 PFS events and 250 death events (approximately 71% of death events) are observed.

To control the family-wise Type I error rate the fallback method as specified in the FDA Draft Guidance (Multiple Endpoints in Clinical Trials, 2017), will be used to test the two primary endpoints. A 2-sided family-wise Type I error rate (FWER) of 0.05 will be used with 0.007 allocated to the PFS hypothesis testing and 0.043 allocated to the OS hypothesis testing. Lan-DeMets alpha spending function with O'Brien-Fleming boundary for efficacy will be used to determine the Type I error rate for the interim and final OS analyses depending on whether an alpha of 0.043 or 0.05 is used.

Additional details will be provided in the SAP.

10.4.2. Secondary Endpoints and Methods

Multiplicity adjustment will be made for the analysis of the primary and secondary endpoints to control the overall Type I error. Following statistically significant test results for one or both primary endpoints, the secondary endpoints will be tested sequentially in a pre-defined order as outlined in the SAP.

10.4.2.1. Clinical Benefit Response

Clinical benefit response (CBR) is defined as:

Subject achieved a ≥50% reduction in pain intensity (Memorial Pain Assessment Card [MPAC]) or analgesic consumption, or a 20-point or greater improvement in KPS for a period of at least 4 consecutive weeks, without showing any sustained worsening in other parameters.

OR

Subject was stable on all of the aforementioned parameters, and showed a marked, sustained weight gain (≥7% increase maintained for ≥4 weeks) not due to fluid accumulation (Burris 1997).

A chi-square test will be used to compare the two treatment arms.

10.4.2.2. Overall Response Rate

Overall response rate (ORR) is defined as the proportion of subjects who achieve a complete response or partial response, based on investigator assessment according to RECIST 1.1. A chi-square test will be used to compare the two treatment arms.

10.4.2.3. Carbohydrate Antigen 19-9 (CA19-9) Response

CA19-9 response rate will be the proportion of subjects with a decline of 20%, 90% and other thresholds considered clinically meaningful, from baseline. The rate will be compared between the two treatment arms using the chi-square test (details will be pre-specified in the SAP).

10.4.2.4. Patient-reported outcomes (PRO) as measured by EORTC QLQ-C30

Scores and change from baseline for EORTC QLQ-C30 will be descriptively summarized by treatment group and visit. Longitudinal analysis with repeated measures may be used as appropriate.

10.4.2.5. Rate of venous thromboembolic events (VTE)

The occlusion, or partial occlusion of a vessel by a thrombus which subsequently migrates to a distal site in a vessel is a known complication of patients with pancreatic carcinoma. This includes venous thrombosis and pulmonary emboli. The VTE rate is defined as proportion of subjects with VTE (details will be pre-specified in the SAP). A 30% relative reduction from the control arm is considered clinically meaningful.

10.4.3. Exploratory Endpoints and Methods

Exploratory endpoints will be evaluated to compare treatment effects between the two treatment arms. Descriptive statistics will be used to summarize these exploratory endpoints. Further details will be provided in the SAP.

10.5. Safety Analysis

Analysis of safety data will be conducted primarily on the safety population, which includes all randomized subjects who receive at least one dose of any study drug.

Safety Run-in Phase:

Safety data from subjects in the open label run-in phase will be presented separately from the randomized Safety Population.

Double-blind Randomized Phase:

Safety data will be generated from the Safety Population (SP) (consisting of all subjects randomized and receiving at least one dose of any study drug).

The safety variables to be analyzed include adverse events, clinical laboratory test results (hematology and chemistry), and vital signs measurements. No formal statistical testing is planned.

10.5.1. Adverse Events

The verbatim terms used in the eCRF by Investigators will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are those adverse events that emerge during treatment, having been absent pretreatment, or worsen relative to the pretreatment state. All treatment-emergent adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized. The number and percent of subjects with treatment-emergent adverse events will be summarized according to intensity (NCI CTCAE v4.03) and drug relationship as well as categorized by system organ class and preferred term. Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

10.5.2. Clinical Laboratory Tests

Laboratory tests will be summarized separately for hematology and serum chemistry. Laboratory values will be converted to standard international units and will be graded using the NCI CTCAE v4.03 for those to which a grade can be applied.

10.6. Pharmacokinetic Analyses

10.6.1. Ibrutinib

Ibrutinib and PCI-45227 bioanalytical data will be used in noncompartmental PK analysis. Plasma concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the PK report.

Descriptive statistics will be used to summarize ibrutinib and PCI-45227 concentrations at each sampling time point and PK parameters of ibrutinib and PCI-45227 (including, but not limited to: C_{max}, T_{max}, AUC_{last}, and $t_{1/2}$).

Individual and mean plasma ibrutinib and PCI-45227 concentration time profiles will be plotted.

Ibrutinib data from this study may also be combined with data from other studies performed with ibrutinib in subjects with hematologic malignancies as part of a population-PK analysis using nonlinear mixed effects models. For the population-PK analysis, covariates that could potentially correlate with plasma PK parameters will be evaluated. The results of the population-PK analyses (if performed) will be presented in a separate report.

Ibrutinib PK data in this study will be compared to observed/reported concentration data for ibrutinib and/or population PK models to explore the potential for a pharmacokinetic interaction between ibrutinib in combination use with gemcitabine and nab-paclitaxel. Gemcitabine and nab-paclitaxel PK data in this study will be compared between two arms with and without ibrutinib to explore the potential for a pharmacokinetic interaction between gemcitabine and nab-paclitaxel in combination use with ibrutinib.

For the drug combination of ibrutinib, paclitaxel, and gemcitabine, model-derived exposure parameters (PK parameters) may be used to explore PK/PD correlation between the exposure of ibrutinib and its active metabolites with relevant clinical or biomarker information to assess effectiveness and toxicity.

10.6.2. Gemcitabine

Individual gemcitabine and dFdU concentrations will be tabulated along with descriptive statistics. Individual and mean concentration-time profiles will be generated and included in the report. Pharmacokinetic parameters will be determined using standard non-compartmental methods. The following PK parameters will be determined: peak concentration (C_{max}), time to peak concentration (T_{max}) and area under the curve (AUC), as data allow. Descriptive statistics of non-compartmental PK parameters will be provided.

10.6.3. Nab-paclitaxel

Individual nab-paclitaxel concentrations will be tabulated along with descriptive statistics. Individual and mean concentration-time profiles will be generated and included in the report. Pharmacokinetic parameters will be determined using standard non-compartmental methods. The following PK parameters will be determined: peak concentration (C_{max}), time to peak concentration (T_{max}) and area under the curve (AUC), as data allow. Descriptive statistics of non-compartmental PK parameters will be provided.

10.7. DMC Review

A DMC review of safety data including all death events will be performed approximately every 6 months after the first subject is randomized.

10.8. Data Monitoring Committee (DMC)

An independent DMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled/randomized in this study and to evaluate safety and efficacy results. Further details will be provided in the DMC Charter.

Safety Run-in Phase:

The DMC will review data on the safety of ibrutinib combined with nab-paclitaxel and gemcitabine, after the first 6 subjects have either completed at least 28 days of follow-up after the initiation of combination therapy or terminated therapy at an earlier time point due to toxicity. If a subject discontinues treatment before 28 days (eg, death due to PD), subjects may be replaced. Following DMC review and confirmation, the study may proceed to the Double-blind Randomized Phase.

The DMC assessment will focus on deaths, treatment discontinuations, SAEs, AEs of special interest (see Section 11.4.7) and Grade 3/4 AEs to identify any potential added toxicity when ibrutinib is combined with nab-paclitaxel and gemcitabine.

Adverse events including grade 3/4 myelotoxicity, nausea, vomiting, diarrhea and peripheral neuropathy are expected with the combination of nab-paclitaxel and gemcitabine and therefore will not be considered a safety signal unless the duration is unusually prolonged, or unexpected increase in frequency observed and/or unresponsive to supportive management. For example, all grades of venous thromboembolism are frequent and expected complications of metastatic pancreatic cancer regardless of therapy and will not be considered a safety signal unless occurring at an unexpectedly high rate. These and other appropriate factors will be considered by the DMC when reviewing the safety data of the subjects treated with the combination of ibrutinib and nab-paclitaxel plus gemcitabine during the safety run in stage of the study.

Depending on the outcome of their review, the DMC may recommend that:

a) the study continues to the Double-blind Randomized Phase

b) prior to commencing the Double-blind Randomized Phase, an additional safety review is performed after a total of up to 12 subjects have been treated with ibrutinib (560 mg) in combination with nab-paclitaxel and gemcitabine (with all subjects having either completed at least 28 days of follow-up after the initiation of combination therapy or terminated therapy at an earlier time point due to toxicity).

c) Prior to commencing the Double-blind Randomized Phase, the dose level of ibrutinib should be reduced to 420 mg and an additional 6 subjects should be studied at this dose level, in combination with nab-paclitaxel and gemcitabine (with all subjects having either completed at least 28 days of follow-up after the initiation of combination therapy or terminated therapy at an earlier time point due to toxicity) prior to a subsequent review by the DMC.

Double-blind Randomized Phase:

The DMC will review unblinded safety data on subjects randomized to each arm at periodic intervals during the study, as detailed in the DMC charter. The Sponsor will assess blinded safety data on an ongoing basis and all deaths, treatment discontinuations, and SAEs will be reviewed by the Sponsor's responsible physician to identify safety concerns. If a potential safety signal is identified, additional *ad hoc* meetings may be convened, if requested by the DMC or the Sponsor.

The DMC will consist of at least one medical expert in the management of pancreatic adenocarcinoma and at least one statistician. The DMC responsibilities, authorities, and procedures will be documented in the DMC charter.

10.9. Independent Review

Investigator assessed PFS is one of the primary endpoints in this double blinded study. Scans (CT/PET-CT/MRI) will be collected and held for blinded independent review and assessment of disease progression events if necessary, the details of which will be outlined in a separate independent review committee charter.

11. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

11.1. Definitions

11.1.1. Adverse Events

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

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

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

Adverse events may include, but are not limited to:

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

The following are NOT considered AEs:

- **Pre-existing condition:** A pre-existing condition (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.

11.1.2. Serious Adverse Events

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

- Results in death (ie, the AE actually causes or leads to death).
- Is life-threatening. Life-threatening is defined as an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the investigator or the Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.
- Requires in-patient hospitalization >24 hours or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject or subject may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsion that does not result in hospitalization; or development of drug dependency or drug abuse.

Given that the investigator's perspective may be informed by having actually observed the event, and the Sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event, if either the Sponsor or the investigator believes that the event is serious, the event will be considered serious.

11.1.3. Severity Criteria (Grade 1-5)

Definitions found in the CTCAE v4.03 will be used for grading the severity (intensity) of AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE v4.03, the following grading system should be used to assess severity:

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

- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

11.1.4. Causality (Attribution)

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

Not Related:	Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Unlikely:	The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.
Possibly Related:	There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.
Related:	The AE is clearly related to use of the investigational product.

11.2. Unexpected Adverse Events

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

11.3. Special Reporting Situations

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

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

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

Occurrence of any special reporting situations should be recorded in the eCRF. If any special reporting situation meets the criteria of an adverse event, it should be recorded on the adverse events eCRF. If the adverse event is considered serious, it should be recorded on the adverse events eCRF as serious and should be reported on the Serious Adverse Event Report Form. The SAE Report Form should be sent via email or fax to Pharmacyclics Drug Safety or designee within 24 hours of awareness.

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

11.4.1. Assessment of Adverse Events

Investigators will assess the occurrence of adverse events and serious adverse events at all subject evaluation timepoints during the study. All adverse events and serious adverse events whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded in the subject's medical record and on the Adverse Event CRF and, when applicable, on the Serious Adverse Event Report Form.

Each recorded adverse event or serious adverse event will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

11.4.2. Adverse Event Reporting Period

All AEs whether serious or non-serious, will be documented from the time signed and dated ICF is obtained until 30 days following the last dose of study drug. SAEs will be reported to the Sponsor Drug Safety via an SAE reporting form and will be recorded in the eCRF from the time of ICF signing. Non-serious AEs will be recorded in source documents from the time of ICF signing and will be recorded in the eCRF from the first 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"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

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. Autopsy and postmortem reports must be forwarded to the Sponsor, or designee, as outlined above, if allowed per local regulatory guidelines.

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

11.4.3. Expediting Reporting Requirements for Serious Adverse Events

All serious adverse events (initial and follow-up information) will be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of the discovery of the event or information. Pharmacyclics may request follow-up and other additional information from the Investigator (eg, hospital admission/discharge notes and laboratory results). The contact information (phone, email and fax) for Pharmacyclics Drug Safety can be found on the Serious Adverse Event Report Form and instructions.
(See Section 5.1.2.1 for unblinding details.)

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)

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities and governing bodies according to the local regulations.

The investigator (or sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol

unless otherwise required and documented by the IEC/IRB.

11.4.4. 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 initial dose to 6 months after the last dose of study drug. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of initial dose to 6 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 female subject or female partners of male subjects from the time of initial dose to 6 months after the last dose of study drug must be reported. Any occurrence of pregnancy must be recorded on the Pregnancy Report Form Part I and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of learning of the event. 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 by completing the Pregnancy Report Form Part II. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

11.4.5. Other Malignancies

All new primary malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for OS. If observed, relevant data will be entered in the corresponding eCRF.

11.4.6. Eye-Related Adverse Events

New or worsening eye-related symptoms that are Grade 2 or higher, or a symptom that was Grade 2 or higher at baseline worsens, should be evaluated by an ophthalmologist whose findings should be reported on the ophthalmologic eCRF.

11.4.7. Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities by the Sponsor. These events (regardless of seriousness) should be reported

on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, or designee, within 24 hours of awareness.

11.4.7.1. Major Hemorrhage

Major hemorrhage is defined as any one of the following:

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

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

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 11.4.7 above.

12. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

12.1. Regulatory and Ethical Compliance

This clinical study was designed and will be implemented in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practices, with applicable local regulations (including US Code of Federal Regulations [CFR] Title 21 and European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

12.2. Institutional Review Board (IRB), Research Ethics Board (REB) and Independent Ethics Committee (IEC) Approval

The investigator will submit this protocol, the ICF, IB, and any other relevant supporting information (eg, all advertising materials or materials given to the subject during the study) to the appropriate IRB/REB/IEC for review and approval before study initiation. Amendments to the protocol and informed consent form must also be approved by the IRB/REB/IEC before the implementation of changes in this study.

The Investigator is responsible for providing the IRB/REB/IEC with any required information before or during the study, such as SAE expedited reports or study progress reports.

The IRB/REB/IEC must comply with current United States (US) regulations (§21 CFR 56) as well as country-specific national regulations and/or local laws.

The following documents must be provided to Pharmacyclics or its authorized representative before entering subjects in this study: (1) a copy of the IRB/REB/IEC letter that grants formal approval; and (2) a copy of the IRB/REB/IEC-approved ICF.

12.3. Informed Consent

The ICF and process must comply with the US regulations (§ 21 CFR Part 50) as well as country specific national regulations and/or local laws. The ICF will document the study-specific information the investigator or his/her designee provides to the subject and the subject's agreement to participate.

The Investigator or designee (designee must be listed on the Delegation of Authority log), **must** explain in terms understandable to the subject the purpose and nature of the study, study procedures, anticipated benefits, potential risks, possible AEs, and any discomfort participation in the study may entail. This process must be documented in the subject's source record. Each subject must provide a signed and dated ICF before any study-related (nonstandard of care) activities are performed. The original and any amended signed and dated consent forms must remain in each subject's study file at the study site and be available for verification by study monitors at any time. A copy of each signed consent form must be given to the subject at the time that it is signed by the subject.

12.4. Quality Control and Quality Assurance

Sponsor shall implement and maintain quality control and quality assurance procedures to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2008) and all revisions thereof, and in accordance with the FDA regulations (21 CFR Parts 11, 50, 54, 56, and 312, Subpart D – Responsibilities of Sponsors and Investigators) and with the ICH guidelines on GCP (ICH E6).

12.5. Protected Subject Health Information Authorization

Information on maintaining subject confidentiality in accordance to individual local and national subject privacy regulations must be provided to each subject as part of the informed consent process (refer to Section 12.3), either as part of the ICF or as a separate signed document (for example, in the US, a site-specific HIPAA consent may be used). The investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Pharmacyclics and its designees, regulatory agencies, and IRBs/REBs/IECs. As the study Sponsor, Pharmacyclics will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject. If a subject withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject **and** to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

During the review of source documents by the monitors or auditors, the confidentiality of the subject will be respected with strict adherence to professional standards and regulations.

12.6. Study Files and Record Retention

The investigator **must** keep a record that lists **all** subjects considered for enrollment (including those who did not undergo screening) in the study. For those subjects subsequently excluded from enrollment, the reason(s) for exclusion is to be recorded.

The investigator/study staff must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Essential documentation includes, but is not limited to, the IB, signed protocols and amendments, IRB/REB/IEC approval letters (dated), signed Form FDA 1572 and Financial Disclosures, signed ICFs (including subject confidentiality information), drug dispensing and accountability records, shipping records of investigational product and study-related materials, signed (electronically), dated and completed CRFs, and documentation of CRF corrections, SAE forms transmitted to Pharmacyclics and notification of SAEs and related reports, source documentation, normal laboratory values, decoding procedures for blinded studies, curricula vitae for study staff, and all relevant correspondence and other documents pertaining to the conduct of the study.

All essential documentation will be retained by the investigator for at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated and until there are no pending or contemplated marketing applications; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the drug.

The investigator must notify Pharmacyclics and obtain written approval from Pharmacyclics before destroying any clinical study documents or images (eg, scan, radiograph, ECG tracing) at any time. Should an investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to Pharmacyclics. Pharmacyclics will inform the investigator of the date that study records may be destroyed or returned to Pharmacyclics.

Pharmacyclics must be notified in advance of, and Pharmacyclics must provide express written approval of, any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the investigator and Pharmacyclics to store such documents in sealed containers away from the study site so that they can be returned sealed to the investigator for audit purposes.

12.7. Case Report Forms and Record Maintenance

CRFs will be used to collect the clinical study data and must be completed for each enrolled subject with all required study data accurately recorded such that the information matches the data contained in medical records (eg, physicians' notes, nurses' notes, clinic charts and other study-specific source documents). Authorized study site personnel (ie, listed on the Delegation of Authority log) will complete CRFs designed for this study according to the completion guidelines that will be provided. The investigator will ensure that the CRFs are accurate, complete, legible, and completed within a reasonable period of time. At all times, the investigator has final responsibility for the accuracy and authenticity of all clinical data.

The CRFs exists within an electronic data capture (EDC) system with controlled access managed by Pharmacyclics or its authorized representative for this study. Study staff will be appropriately trained in the use of CRFs and application of electronic signatures before the start of the study and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The investigator attests that the information contained in the CRFs is true by providing electronic signature within the EDC system. After database lock, the investigator will receive a copy of the subject data (eg, paper, CD, or other appropriate media) for archiving at the study site.

12.8. Investigational Study Drug Accountability

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

Accountability records for all study drugs must be maintained and readily available for inspection by representatives of Pharmacyclics and are open to inspections by regulatory authorities at any time.

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

1. Study identification number (PCYC-1137-CA)
2. Subject identification number
3. Lot number(s) of ibrutinib/placebo and nab-paclitaxel plus gemcitabine dispensed for that subject
4. Date and quantity of drug dispensed
5. Any unused drug returned by the subject

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with Pharmacyclics' requirements. If the site cannot meet Pharmacyclics' requirements for disposal/destruction, arrangements will be made between the site and Pharmacyclics or its representative, for return of unused investigational product. Before disposal/destruction, final drug accountability and reconciliation must be performed by the monitor.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

12.9. Study Monitoring/Audit Requirements

Representatives of Pharmacyclics or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the investigator and site staff, remote monitoring, as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions and regulatory guidelines, and to ensure the quality and integrity of the data. This study is also subject to reviews or audits.

To assure the accuracy of data collected in the CRFs, it is mandatory that the monitor/auditor have access to all original source documents, including all electronic medical records (EMR) at reasonable times and upon reasonable notice. During the review of source documents, every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/REB/IEC, representatives of Pharmacyclics, its designated agents and authorized employees of the appropriate Regulatory Authority to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

Pharmacyclics or its authorized representative may perform an audit at any time during or after completion of this study. All study-related documentation must be made available to the designated auditor. In addition, a representative of the FDA or other Regulatory Agencies may choose to inspect a study site at any time before, during, or after completion of the clinical study. In the event of such an inspection, Pharmacyclics will be available to assist in the preparation. All pertinent study data should be made available as requested to the Regulatory Authority for verification, audit, or inspection purposes.

12.10. Investigator Responsibilities

A complete list of investigator responsibilities are outlined in the clinical trial research agreement and the Statement of Investigator Form FDA 1572, both of which are signed by the investigator before commencement of the study. In summary, the investigator will conduct the study according to the current protocol; will read and understand the IB; will obtain

IRB/REB/IEC approval to conduct the study; will obtain informed consent from each study participant; will maintain and supply to the Sponsor or designee, auditors and regulatory agencies adequate and accurate records of study activity and drug accountability for study-related monitoring, audits, IRB/REB/IEC reviews and regulatory inspections; will report SAEs to the Sponsor or designee and IRB/ REB/IEC according to the specifics outlined in this protocol; will personally conduct or supervise the study; and will ensure that colleagues participating in the study are informed about their obligations in meeting the above commitments.

12.11. Sponsor Responsibilities

A complete list of the Sponsor responsibilities is outlined in the clinical trial research agreement and in the laws and regulation of the country in which the research is conducted. In summary, the Sponsor will select qualified investigators, provide them with the information they need to properly conduct the study, ensure adequate monitoring of the study, conduct the study in accordance with the general investigational plan and protocols and promptly inform investigators, health and regulatory agencies/authorities as appropriate of significant new adverse effects or risks with respect to the drug.

12.12. Financial Disclosure

A separate financial agreement will be made between each principal investigator and Pharmacyclics or its authorized representative before the study drug is delivered.

For this study, each investigator and subinvestigator (as designated on the Form FDA1572) will provide a personally signed Financial Disclosure Form in accordance with § 21 CFR 54. Each investigator will notify Pharmacyclics or its authorized representative of any relevant changes in financial disclosure information during the conduct of the study and for 1 year after the study has been completed.

12.13. Liability and Clinical Trial Insurance

In the event of a side effect or injury, appropriate medical care as determined by the investigator/ designee will be provided.

The ICF will include a description of treatment in the event of a study related injury and handling of the costs associated therewith, incorporating country-specific national regulations and/or local laws. Financial compensation for lost wages, disability or discomfort due to the study is not available.

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

12.14. Protocol Amendments

Pharmacyclics will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/REB/IEC together with, if applicable, a revised model ICF. Written documentation of IRB/REB/IEC and required site approval must be received by Pharmacyclics before the amendment may take effect at each site. Additionally under this circumstance, information on any change in risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand and sign each revised ICF confirming willingness to remain in the trial.

No other significant or consistent change in the study procedures, except to eliminate an immediate hazard, shall be effected without the mutual agreement of the investigator and Pharmacyclics.

12.15. Publication of Study Results

Pharmacyclics may use the results of this clinical study in registration documents for Regulatory Authorities in the US or abroad. The results may also be used for papers, abstracts, posters, or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by an investigator. In all cases, to avoid disclosures that could jeopardize proprietary rights and to ensure accuracy of the data, Pharmacyclics reserves the right to preview all manuscripts and abstracts related to this study, allowing Pharmacyclics sufficient time to make appropriate comments before submission for publication.

In most cases, the Investigators at the sites with the highest accruals of eligible subjects and those with substantial input to study design shall be listed as lead authors on manuscripts and reports of study results. The Medical Monitor, study director and/or lead statistician may also be included in the list of authors. This custom can be adjusted upon mutual agreement of the authors and Pharmacyclics and in accordance with current standards for authorship as recorded in professional conference and journal submission instructions.

12.16. Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, both the Sponsor and the investigator will arrange discontinuation procedures. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

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14. APPENDICES

Appendix A. Schedule of Assessments

	Screening Phase	Treatment Phase [c]									Follow-up Phase (refer to protocol Sections 7 & 8)		
		Cycle 1				Cycle 2 through Treatment Discontinuation				Efficacy Evaluations	End-of-Treatment	Efficacy Follow-up (until PD)	Long Term Follow-up
		D1 Baseline	D8	D15	D22	D1	D8	D15	D22	Every 8 weeks	30 days after treatment d/c	Every 2 weeks or as specified	Every 2 weeks
Visit Window	**-28 days**	**-2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±7d**	**+7d**	**±3d**	**±7d**
Informed consent	X												
Confirmation of eligibility criteria	X	X											
Randomization		X											
Medical history and demographics	X												
Physical exam (including disease related symptoms)	X	X[a]				X[a]					X	X[a]	
Eye-related symptom assessment	X	X				X					X		
Vital Signs[d]	X	X				X					X		
Weight	X	X	X	X		X	X	X			X	X	X[t]
Concomitant medications [q]	X	X	X	X		X	X	X			X	X[r]	X[r]
ECOG Performance Status	X												
Karnofsky Performance Status (KPS)	X	X		X		X		X			X	X	X[t]
MPAC Pain Assessment Card[b]	X	X		X		X		X			X	X	X[t]
PRO (QLQ-C30)[b]		X		X		X		X			X	X	X[t]
Adverse events[e]	X	X[k]	X	X		X	X	X			X		
12-lead ECG[i]	X	If clinically indicated (eg, subjects with palpitations, lightheadedness)											
Laboratory:													
Hematology	X	X	X	X	X[n]	X	X	X	X[n]		X		
Serum chemistry	X	X	X	X		X	X	X			X		
Coagulation panel	X												
Hepatitis serologies[f]	X												
Creatinine clearance (Cockcroft-Gault)	X												
Urinalysis [g]	X	X	X	X		X	X	X					
Pregnancy Test[h]	X	X				X					X		
Carbohydrate antigen (CA) 19-9	X	X				X					X	X[p]	
Disease Assessment:													
CT, PET/CT, MRI scan	X									X		X[m]	
RECIST 1.1 Overall efficacy assessment										X		X[m]	

	Screening Phase	Treatment Phase [c]									Follow-up Phase (refer to protocol Sections 7 & 8)		
		Cycle 1				Cycle 2 through Treatment Discontinuation				Efficacy Evaluations	End-of-Treatment	Efficacy Follow-up (until PD)	Long Term Follow-up
		D1 Baseline	D8	D15	D22	D1	D8	D15	D22	Every 8 weeks	30 days after treatment d/c	Every 2 weeks or as specified	Every 2 weeks
Visit Window	**-28 days**	**-2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±7d**	**+7d**	**±3d**	**±7d**
Pharmacokinetics/Biomarkers													
Pharmacokinetics (PK) (See Appendix B)						X							
Immunophenotyping [o]		X[r]				X					X		
Molecular markers - blood & urine[o]		X				X					X		
Buccal Swab		X											
Tumor biopsy (archival/fresh) [j]	X										X		
Study Drug Administration													
Dispense ibrutinib/placebo		X				X							
In-clinic administration of ibrutinib / placebo		X[s]	X	X		X	X	X					
In-clinic administration of nab-paclitaxel + gemcitabine		X[s]	X	X		X	X	X					
Study drug compliance review[n]						X							
Survival and subsequent anticancer therapy													X
CT = computed tomography, D or d = day(s), d/c = discontinuation; ECG = electrocardiogram, FU = follow-up, ibr = ibrutinib, ICF = informed consent form, MRI = magnetic resonance imaging, PD = progressive disease, PK = pharmacokinetics, RECIST = response evaluation criteria in solid tumors													

Footnotes:

a. A symptom-directed physical examination is required on Day 1 of each cycle and Efficacy Follow Up visits. These physical exams will include pancreatic cancer disease related symptoms assessment and ascities/pleural effusion assessment (if applicable).

b. To be completed prior to any other procedures or physician interactions. MPAC to be performed first.

c. All assessments are to be performed prior to dosing unless otherwise specified.

d. Vital signs will be assessed after the subject has been resting in the sitting position for at least 3 minutes.

e. AEs are reported from the time the subject signs the Informed Consent Form until 30 days following last dose of study drug. All new malignant tumors are to be reported as adverse events through Long Term Follow-up for OS.

f. Hepatitis serologies evaluated by central laboratory. If hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody is positive, then PCR to quantitate hepatitis B/C DNA must be performed and must be negative prior to randomization/enrollment.

g. Tests will be performed locally.

h. Serum or urine pregnancy test will be required at Screening and on Day 1 prior to first dose for women of childbearing potential. The test will be performed locally.

i. At Screening, 12-lead ECGs will be done in triplicate (≥1 minute apart). Abnormalities noted at Screening should be included in the medical history.

[j.] Archival tumor biopsy tissue may be provided if available and/or fresh tumor tissue will be collected at Screening if consented by subject. If a fresh tumor biopsy is performed at Screening, it should be at least 7 days prior to the first dose of study drug or at least 3 days prior to the first dose of study drug for a fine needle aspiration (FNA). Upon RECIST 1.1 documented disease progression, an optional fresh tumor biopsy may be collected from consenting subjects.

[k.] Cycle 1 Day 1 ONLY: Assessment of adverse events for 2 hours post completion of nab-paclitaxel and gemcitabine administration. At the discretion of the investigator, subject may leave clinic 2 hours post completion of nab-paclitaxel and gemcitabine administration.

[l.] Subjects who are withdrawn for reasons other than RECIST1.1 documented disease progression will continue to have normally scheduled clinical and radiological disease assessments (CT, CT/PET or MRI) until disease progression is documented, death, withdrawal of consent for further follow up, or lost to follow up, whichever occurs first.

[m.] To be performed every 8 weeks until disease progression is documented, death, withdrawal of consent for further follow up, or lost to follow up, whichever occurs first. Optional fresh tumor biopsy in consenting subjects (if RECIST 1.1 documented disease progression).

[n.] Cycle 1 and Cycle 2 Day 22 hematology assessments must be performed centrally. Subsequent assessments may be performed locally and at the discretion of the investigator.

[o.] Blood and urine samples for biomarkers will be collected prior to dosing on Day 1 for the first 3 cycles and then only blood sample will be collected every 3 cycles thereafter until RECIST 1.1 documented disease progression.

[p.] CA 19-9 will be collected every 4 weeks during efficacy follow up.

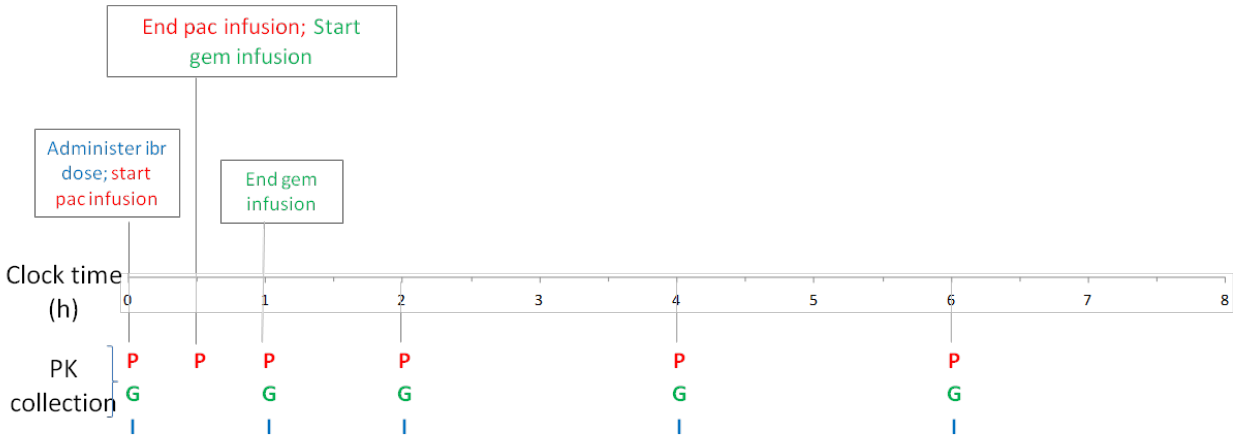
[q.] Continuous from the signing of ICF or 14 days prior to the first dose of study drug (whichever is greater) through 30 days after the last dose of study drug.

[r.] Analgesic consumption only.

[s.] Must be administered on Cycle 1 Day 1.

[t.] Not required if Follow-up visit was done via the telephone.

Appendix B. Pharmacokinetics Sample Collection Based on Clock Time for Cycle 2 Day 1



-All PKs at time 0 must be collected prior to dosing with any drug
-End of Infusion (EOI) PK samples collected within 5 minutes before the infusion is stopped
-PK collection times within 6 h window
- Pac: up to 5.5 h post-infusion (6 time points)
- Gem: up to 5 h post-infusion (5 time points)
- Ibr: up to 6 h post-infusion (5 time points)
- Total number of blood draws: 6

Note: Gemcitabine PK samples will be collected only in selective regions.

Appendix C. Biomarker Sampling Schedule

	Screening	Cycle 1	Cycle 2	Cycle 3 and Every 3 Cycles until Treatment Discontinuation
		Day 1	Day 1	Day 1
Immunophenotyping		X[a]	X[a]	X[a]
Molecular markers		X[a]	X[a]	X[a]
Buccal swab		X[a]		
Tumor biopsy[b]	X[b]			X[b] End-of-Treatment Visit Only

a. Collected predose. Urine sample is required only on Cycles 1 to 3 visits and End of Treatment Visit.

b. Archival tumor biopsy tissue may be collected where available and optional fresh tumor biopsies will be collected on consenting subjects at Screening and on documented progression.

Appendix D. Karnofsky Performance Status

%	Karnofsky Performance Status
100	Normal; no complaints; no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Care for self. Unable to carry on normal activity or do active work.
60	Requires occasional assistance but is able to care for most of his or her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled; hospitalization is indicated though death not imminent.
20	Hospitalization necessary; very sick; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.

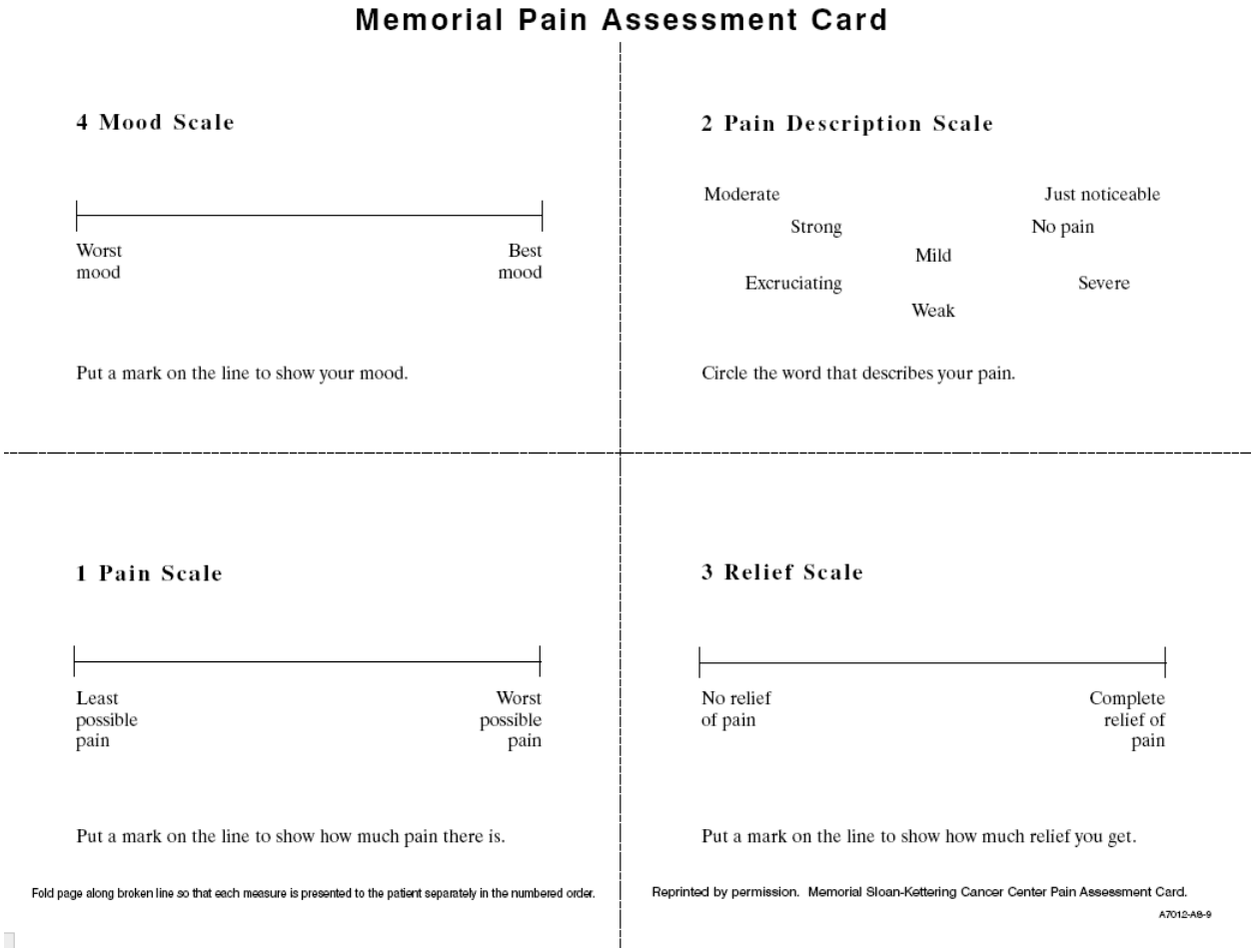
Appendix E. ECOG Performance Status Scores

Status	Eastern Cooperative Oncology Group (ECOG) Performance Status[a]
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

a. Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Available at: http://www.ecog.org/general/perf_stat.html. Accessed January 4, 2008.

Appendix F. Memorial Pain Assessment Card (MPAC)



Reference:

1. Fishman B, Pasternak S, Wallenstein SL, Houde RW, Holland JC, Foley KM. The Memorial Pain Assessment Card. A valid instrument for the evaluation of cancer pain. Cancer. 1987;60:1151-8.

Appendix G. Inhibitors and Inducers of CYP3A

Inhibitors and inducers of CYP3A enzymes are defined as follows. Refer to Section 6.2.1 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib. Further information can be found at the following website: http://medicine.iupui.edu/clinpharm/ddis/main-table/.

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors:	carbamazepine
indinavir	efavirenz
nelfinavir	nevirapine
ritonavir	barbiturates
clarithromycin	glucocorticoids
itraconazole	modafinil
ketoconazole	oxcarbarzepine
nefazodone	phenobarbital
saquinavir	phenytoin
suboxone	pioglitazone
telithromycin	rifabutin
cobicistat	rifampin
boceprevir	St. John's Wort
mibefradil	troglitazone
telaprevir	
troleandomycin	
posaconazole [a]	
Moderate inhibitors:	
aprepitant	
amprenavir	
amiodarone	
atazanavir	
ciprofloxacin	
crizotinib	
darunavir	
dronedarone	
erythromycin	
diltiazem	
fluconazole	
fosamprenavir	
grapefruit juice	
Seville orange juice	
verapamil	
voriconazole [a]	
imatinib	
Weak inhibitors:	
cimetidine	
fluvoxamine	
All other inhibitors:	
chloramphenicol	
delaviridine	
diethyl-dithiocarbamate	
gestodene	
mifepristone	
norfloxacin	
norfluoxetine	
star fruit	

a. Classification based on internal data. .

Appendix H. EORTC QLQ-C30

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: |_|_|_|

Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|

Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|_|_|

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

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

Please go on to the next page

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Appendix I. Child-Pugh Score for Subjects with Chronic Liver Impairment

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

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

Source:

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