BOSTON BIOMEDICAL
Sumitomo Dainippon Pharma Global Oncology

TITLE:	**A Phase III Study of BBI-608 plus nab-Paclitaxel with Gemcitabine in Adult Patients with Metastatic Pancreatic Adenocarcinoma.**
PROTOCOL NUMBER:	**CanStem111P**
FDA IND Number	**100,887**
EudraCT Number	**2016-004359-57**
STUDY DRUG:	**BBI-608 (aka BBI608, Napabucasin)**
SPONSOR:	**Boston Biomedical, Inc.**
	[redacted]
DATE OF PROTOCOL:	**October 18th, 2016**
DATE OF AMENDMENT:	**July 31st, 2019**
AMENDMENT:	**5**

This clinical study protocol is subject to critical review and has been approved by the Sponsor. The following personnel have approved this protocol:

[redacted]

Confidentiality Statement

DOCUMENT REVISION HISTORY

Document	Version Date
Original protocol	18 October 2016
Original protocol (Rev.1)	18 October 2016
Amendment 1	23 February 2017 (Local – USA)
Amendment 2	16 June 2017
Amendment 3	16 February 2018
Amendment 4	4 December 2018
Amendment 5	31 July 2019

ABBREVIATIONS & DEFINITIONS

ADLs	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BMI	Body Mass Index
BP	Blood pressure
CHF	Congestive Heart Failure
CR	Complete Response
CRC	Colorectal cancer
CRO	Contract Research Organization
CSC	Cancer Stem Cell
DCR	Disease Control Rate
DSMB	Data Safety and Monitoring Board
EDC	Electronic Data Capture
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
FFPE	Formalin Fixed Paraffin Embedded
FOLFIRINOX	5-FU, leucovorin, irinotecan and oxaliplatin
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HCG	Human Chorionic Gonadotropin
HED	Human Equivalent Dose
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
ICH	International Conference on Harmonization
IHC	Immunohistochemical
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intention to Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
MMP7	Matrix Metalloproteinase-7
mOS	Median Overall Survival
mPFS	Median Progression-Free Survival
MTD	Maximum Tolerated Dose
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NOAEL	No Observed Adverse Effect Level
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PDAC	Pancreatic ductal adenocarcinoma
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response

PS	Performance Status
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QoL	Quality of Life
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase 2 Dose
RTSM	Randomized Trial Supply Management
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Study Day
SD	Stable Disease
SU	Safety Updates
TCPS	Tri-Council Policy Statement
ULN	Upper Limit of Normal
WOCBP	Women of Child Bearing Potential

STUDY SYNOPSIS

Study Title:	**A Phase III Study of BBI-608 plus nab-Paclitaxel with Gemcitabine in Adult Patients with Metastatic Pancreatic Adenocarcinoma.**
Study Number:	*CanStem111P*
Study Phase:	III
Study Drug:	BBI-608 (also called napabucasin, BBI608, BB608) is a small molecule that is hypothesized to affect multiple oncogenic cellular pathways, including inhibition of the STAT3 pathway, which has been implicated in cancer stem cell viability.
Primary Objective:	To compare overall survival (OS) of patients with metastatic pancreatic adenocarcinoma (PDAC) treated with BBI-608 plus weekly nab-paclitaxel with gemcitabine (Arm 1) versus weekly nab-paclitaxel with gemcitabine (Arm 2).
Secondary Objectives:	Key Secondary Objectives • To compare Progression-Free Survival (PFS) in patients with metastatic PDAC treated with BBI-608 plus weekly nab-paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine. • To compare Disease Control Rate (DCR) in patients with metastatic PDAC treated with BBI-608 plus weekly nab-paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine. • To compare Overall Response Rate (ORR) in patients with metastatic PDAC treated with BBI-608 plus weekly nab-paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine. Other Secondary Objectives • To evaluate the safety profile of BBI-608 administered daily plus weekly nab-paclitaxel and gemcitabine in patients with metastatic PDAC with safety assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.0. • To compare the Quality of Life (QoL), as measured using the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC-QLQ-C30), in patients with metastatic PDAC treated with BBI-608 plus weekly nab-paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine. Exploratory Objectives • To compare OS in patients treated with BBI 608 plus weekly nab paclitaxel with gemcitabine (Arm 1) versus weekly nab paclitaxel with gemcitabine (Arm 2) in biomarker positive PDAC patients. • To compare PFS in patients with metastatic PDAC treated with BBI 608 plus weekly nab paclitaxel with gemcitabine versus weekly nab paclitaxel with gemcitabine in biomarker positive patients. • To compare DCR in patients with metastatic PDAC treated with BBI 608 plus weekly nab paclitaxel with gemcitabine versus weekly nab paclitaxel with gemcitabine in biomarker positive patients.

	• To compare ORR in patients with metastatic PDAC treated with BBI 608 plus weekly nab paclitaxel with gemcitabine versus weekly nab paclitaxel with gemcitabine in biomarker positive patients.
Study Design:	This is a randomized, open-label, multi-center, phase III study of BBI-608 plus weekly nab-paclitaxel with gemcitabine (Arm 1) vs. weekly nab-paclitaxel with gemcitabine (Arm 2) for adult patients with metastatic PDAC. 1132 patients will be randomized in a 1:1 ratio, stratified according to geographical region (North America/Western Europe/Australia vs. Japan/Korea vs. Rest of the World), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1), and presence of liver metastases (yes vs. no). Enrollment was completed prior to this amendment. Until the time of this amendment, the study proceeded in 28-day (4-week) cycles. BBI-608 was administered orally, twice daily, with doses separated by approximately 12 hours. BBI-608 administration began 2-5 days prior to the first nab-paclitaxel with gemcitabine infusion. Nab-paclitaxel 125 mg/m^2 immediately followed by gemcitabine 1000 mg/m^2 were administered on Days 1, 8 and 15 of every 28-day cycle via intravenous infusion. From the time of this amendment, and since the outcome of the interim analysis which was futile, patients may continue protocol therapy if it is believed to be in their best interest by the investigator and patient, and with the patient's informed consent. Patients will receive BBI-608, nab-paclitaxel and/or gemcitabine at the same dose and schedule that they were receiving prior to the amendment. Patients on Arm 1 may continue BBI-608 with the Sponsor's approval. Patients on Arm 1 may also discontinue BBI-608 but choose to continue with nab-paclitaxel and gemcitabine alone. Tumor assessments will be performed every 8 weeks after randomization until objective disease progression or treatment discontinuation due to toxicity. The protocol will continue to be followed for all endpoints until study completion. The study is planned for completion on February 28th, 2020.
Study Population:	This study will enroll patients with histologically or cytologically confirmed adenocarcinoma of the pancreas that is metastatic (Stage IV). Patients with local recurrence following surgical resection will be excluded. At randomization, patients will not have received systemic chemotherapy for metastatic pancreatic adenocarcinoma previously (with a fluoropyrimidine or gemcitabine administered as a radiation sensitizer in the adjuvant setting allowed). Other inclusion criteria for all patients include: age ≥ 18 years; ECOG performance status ≤ 1; and adequate hepatic, renal, and bone-marrow function.
Test Product, Dose, and Mode of Administration:	Until the time of this amendment, patients randomized to Arm 1 on this study received BBI-608 orally, daily, at 240 mg bid (480 mg total daily dose). BBI-608 was taken daily continuously throughout each 4 week (28 day) study cycle in combination with nab-paclitaxel and gemcitabine. BBI-608 was administered twice daily, one hour prior or two hours after meals, with the first dose taken in the morning and doses separated by approximately 12 hours. Patients randomized to Arm 1 received BBI-608 in combination with nab-paclitaxel and gemcitabine. Patients randomized to Arm 2 received nab-paclitaxel and gemcitabine alone. Nab-paclitaxel 125 mg/m^2 was administered intravenously starting

	on Day 1 of Cycle 1. Gemcitabine 1000 mg/m^2 was administered intravenously following nab-paclitaxel infusion. This regimen was repeated on Days 1, 8 and 15 of every 28-day cycle. Dose modification of BBI-608 and/or nab-paclitaxel and/or gemcitabine was allowed. There were no dose reductions or adjustments for lymphopenia or alopecia. From the time of this amendment, and since the outcome of the interim analysis was communicated to investigators, patients may continue protocol therapy if it is believed to be in their best interest by the investigator and patient, and with the patient's informed consent. Patients will receive BBI-608, nab-paclitaxel and/or gemcitabine at the same dose and schedule that they were receiving prior to the amendment. Patients on Arm 1 may continue BBI-608 with the Sponsor's approval. Patients on Arm 1 may discontinue BBI-608 but choose to continue with nab-paclitaxel and gemcitabine..
Duration of Treatment:	Patients may continue to receive assigned protocol therapy as long as they have not experienced any adverse events requiring permanent discontinuation of study medication, have not demonstrated disease progression based on Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria, it is believed to be in the patient's best interest by the investigator and patient, or until February 28th, 2020, whichever occurs first. If nab-paclitaxel and/or gemcitabine is/are discontinued due to toxicity, BBI-608 may be continued until another discontinuation criterion is met with the Sponsor's approval, if it is believed to be in the patient's best interest by the investigator and patient, and with the patient's informed consent. If BBI-608 is discontinued due to toxicity, nab-paclitaxel and gemcitabine may be continued until another discontinuation criterion is met. The study is planned for completion on February 28th, 2020.
Statistical Methods:	The primary study endpoint is Overall Survival (OS), defined as the time from randomization until death from any cause. A multiplicity adjustment strategy will be applied to control the overall Type I error rate with respect to several sources of multiplicity in the trial. This multiplicity adjustment will account for the analysis of the treatment effect on the primary (OS) and key secondary (PFS, DCR, ORR) endpoints. The study is designed to have a power of 90% and a one-sided alpha of 2.5% to detect a 20% reduction in the continuous risk of death (HR 0.80, which corresponds to an increase of median survival from 8.5 to 10.63 months) in the Intention to Treat (ITT) general study population. It is estimated that 864 events will be required to detect this reduction which would be observed by randomizing 1132 patients enrolled over 24 months with patient follow up for an additional 12 months, for total study duration of 36 months. It is anticipated that up to 5% dropout rate will occur for the entire study. The primary hypothesis is: H_0: BBI-608 + nab-paclitaxel with gemcitabine ≤ nab-paclitaxel with gemcitabine versus H_1: BBI-608+ nab-paclitaxel with gemcitabine > nab-paclitaxel with gemcitabine. This hypothesis will be evaluated for the superiority of BBI-608 by performing a stratified log-rank test adjusting for the stratification variables at randomization. The final analysis will be performed when 864 OS events have been observed.

	The overall power of the study will be approximately 90% after the multiplicity control procedure is considered. Prior to this amendment, there was one interim analysis presented to the independent Data Safety and Monitoring Board (DSMB). Additionally, the DSMB reviewed safety during conduct of the study. The role and responsibility of the DSMB are defined in a separate Charter. The interim analysis involved a stratified log-rank test. Nominal p-values were based on the Lan-DeMets error spending function using an O'Brien-Fleming stopping boundary in order to preserve the overall one-sided alpha level at 0.025. The interim analysis was performed when approximately 432 deaths (50% of the required events) were observed. The interim analysis was for futility only, with the futility boundary set at HR $\geq$ 1.

TABLE OF CONTENTS

STUDY ACKNOWLEDGMENT/DISCLOSURE

I understand that this protocol contains information that is confidential and proprietary to Boston Biomedical, Inc.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined herein, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any Investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents. I will complete any protocol specific training required by the sponsor and that I understand the requirement to inform additional site personnel with delegated duties of this information.

I will provide copies of the protocol and access to all information furnished by Boston Biomedical, Inc. and/or the designated Contract Research Organization (CRO) to the study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I understand that this trial will be registered on a public trial registry and that my contact information and site name will be included in the registry listing.

The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of Boston Biomedical, Inc. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to Boston Biomedical, Inc. of any such disclosure.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice to Boston Biomedical Inc., and/or the designated CRO. The study may be terminated at any time by Boston Biomedical, Inc. with or without cause.

Any supplemental information that may be added to this document is also confidential and proprietary to Boston Biomedical, Inc. and must be kept in confidence in the same manner as the contents of this protocol.

_____ _____

Principal Investigator
(Printed Name and Signature)

Date

Site Name: _____

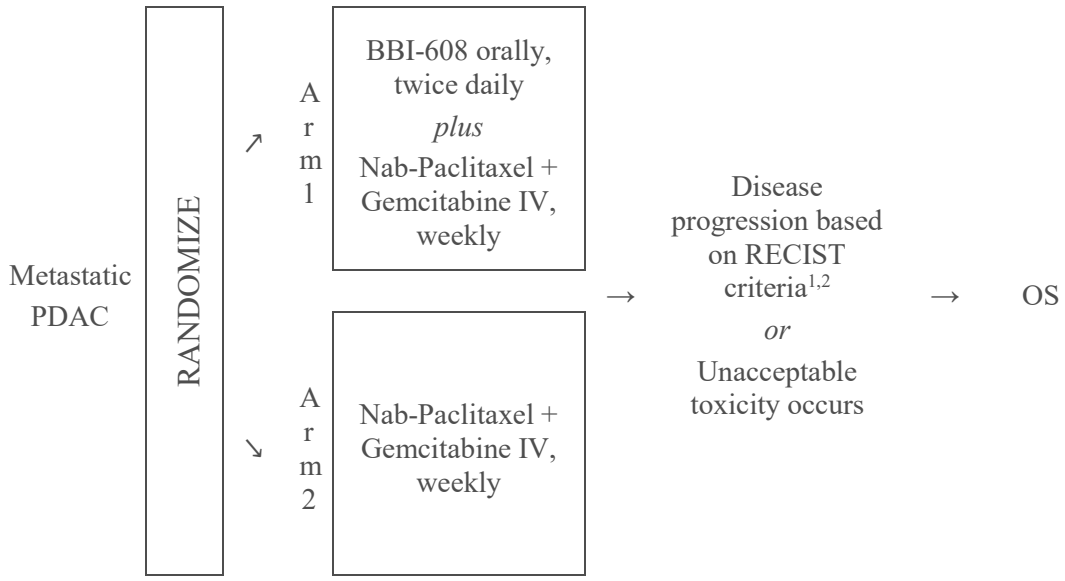
Protocol Number: CanStem111P

TREATMENT SCHEMA

This is an international multi-center, prospective, open-label, randomized phase III trial of the cancer stem cell inhibitor BBI-608 plus nab-paclitaxel with gemcitabine (Arm 1) *versus* nab-paclitaxel with gemcitabine (Arm 2) in patients with metastatic PDAC.

Stratification:

- Geographical region (North America/Western Europe/Australia vs. Japan/Korea vs. Rest of the World)
- ECOG performance status (0 *versus* 1)
- Presence of liver metastases (yes *versus* no)



[1]If no other standard therapies are available at the time of disease progression, and the patient has not experienced any adverse events requiring permanent discontinuation, BBI-608 may be continued in monotherapy.
[2]From the time of this amendment, and since the outcome of the interim analysis was communicated to investigators, patients may continue protocol therapy if it is believed to be in their best interest by the investigator and patient, and with the patient's informed consent. Patients on Arm 1 may continue BBI-608 with the Sponsor's approval. Patients on Arm 1 may discontinue BBI-608 but choose to continue with nab-paclitaxel and gemcitabine.

Primary Objective:

- Overall Survival in the general study population

Key Secondary Objectives:

- Progression-Free Survival (PFS) in the general study population.

- Disease Control Rate (DCR) in the general study population.
- Objective Response Rate (ORR) in the general study population.

Other Secondary Objectives:

- Safety profile
- QoL in the general study population

Exploratory Objectives:

- OS in the predefined biomarker sub population[¥]
- PFS in the predefined biomarker positive sub population[¥]
- DCR and ORR in the predefined biomarker positive sub population[¥]

[¥]This biomarker-positive sub-population is defined as those patients with phospho-STAT3 positivity on immunohistochemical (IHC) staining of Formalin Fixed Paraffin Embedded (FFPE) tumor tissue.

Sample Size:

Planned sample size is 1132 patients (566 on Arm 1 and 566 on Arm 2).

1.0 OBJECTIVES

1.1 PRIMARY OBJECTIVE

To compare overall survival (OS) of patients with metastatic (Stage IV) PDAC treated with BBI-608 plus weekly nab-paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine.

1.2 SECONDARY OBJECTIVES

Key Secondary Objectives

- To compare Progression Free Survival (PFS), in patients treated with BBI-608 plus weekly nab-paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine.
- To compare DCR in patients treated with BBI-608 plus weekly nab-paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine.
- To compare ORR in patients treated with BBI-608 plus weekly nab-paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine.

Other Secondary Objectives

- To evaluate the safety profile of BBI-608 administered daily plus weekly nab-paclitaxel with gemcitabine, with safety assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.0.
- To compare the Quality of Life (QoL), as measured using the EORTC-QLQ-C30, in patients with treatment-naive metastatic PDAC treated with BBI-608 plus weekly nab-paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine.

Exploratory Objectives:

- To compare the OS in patients treated with BBI 608 plus weekly nab paclitaxel with gemcitabine (Arm 1) versus weekly nab-paclitaxel with gemcitabine (Arm 2) in biomarker positive PDAC patients.
- To compare the PFS in patients treated with BBI 608 plus weekly nab paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine in biomarker positive PDAC patients.
- To compare the ORR and DCR in patients treated with BBI 608 plus weekly nab paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine in biomarker positive PDAC patients.

2.0 BACKGROUND INFORMATION AND RATIONALE

2.1 PANCREATIC DUCTAL ADENOCARCINOMA

Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic cancer with the worst prognosis of all solid tumors *(Corbo, 2012; Klimstra, 2007)*. PDAC is the fourth leading cause of cancer death in the United States with an estimate of 38,460 deaths closely following the number of 45,220 diagnoses in 2013 *(Siegel, 2013)*. Surgery is considered the only potentially curative treatment, however, more than 80% of patients present with locally advanced or metastatic disease *(Davis, 2012)*. Out of the minority of presenting patients who qualify for curative surgery, most will develop disseminated advanced disease with a 5-year survival rate of less than 5% *(Hidalgo, 2010)*.

Standard treatment for unresectable and metastatic disease currently includes first-line combination regimen with FOLFIRINOX (5-FU, leucovorin, irinotecan and oxaliplatin), a regimen that provides a median overall survival (OS) of 11.1 months in patients with treatment-naïve disease *(Conroy, 2011)*. Moreover, a number of uncontrolled studies have shown that modified FOLFIRINOX (mFOLFIRINOX) regimen results in decreased toxicity while maintaining efficacy in patients with pancreatic adenocarcinoma *(Blazer, 2015; Mahaseth, 2013)*. Most recently, a liposomal irinotecan formulation was shown to improve overall survival by 1.9 months (6.1 months vs 4.2 months) in combination with 5-FU and leucovorin in patients with metastatic PDAC progressing on gemcitabine-based first-line treatment as compared to patients treated with 5-FU and leucovorin alone *(Chen, 2015).* An alternative regimen for this patient population is a combination of nab-paclitaxel with gemcitabine. A recent updated survival analysis of the phase II/III study, MPACT *(Von Hoff, 2013)*, randomizing 861 patients with metastatic PDAC to gemcitabine versus gemcitabine in combination with nab-paclitaxel, revealed a sustained difference in OS between the 2 arms with median survival of 8.7 months in the combination group compared to 6.6 months in the gemcitabine monotherapy group and more importantly a first ever 3-year survival rate of 4% in the combination treatment group *(Goldstein, 2014)*. These results encourage continued efforts to build upon these backbones to further extend survival. Currently, a patient with advanced disease progressing in first-line therapy has limited treatment options. Given the morbidity associated with this disease, there is an urgent need to identify novel therapies to improve the outcome of patients with advanced unresectable PDAC.

2.2 CANCER STEM CELLS (CSC) AND PDAC

CSCs or cancer cells with stemness phenotypes are a sub-population of cancer cells that have self-renewal capability, are highly malignant and are considered to be fundamentally responsible for malignant growth, recurrence, drug-resistance and metastasis. Moreover, CSCs are highly resistant to chemotherapies and current targeted agents. CSCs have been isolated from almost all major tumor types, including PDAC *(Lee, 2008; Boman, 2008; Clevers, 2011; Gupta, 2009; Hanahan, 2011; Gupta, 2011)*.

Accumulating evidence indicates that CSCs may play a key role in the pathogenesis of PDAC (*Lee, 2008)*. Cancer stem cells have been isolated from human pancreatic adenocarcinomas using a combination of three cell surface markers including CD44, CD24, and ESA *(Li, 2007).* These CSCs isolated from pancreatic adenocarcinoma patients display tumour-initiating properties (*Shah, 2007; Li, 2007)*. Additionally, the CD133 cell surface marker also discriminates for pancreatic cancer cells with potent proliferative capacity *(Hermann, 2007)* and pancreatic cancer cells positive for both CD133 and CXCR4 cell surface markers have the ability to migrate and metastasize in addition to having a potent

proliferative capacity (*Hermann, 2007)*. Moreover, CSCs in PDAC display resistance to therapeutics as it has been observed that treatment with ionizing radiation and chemotherapy results in enrichment of cancer stem cells in pancreatic adenocarcinoma. Exposure of pancreatic cancer cell line to gemcitabine results in enrichment of the CSC population (*Hermann, 2007; Hong, 2009)*. Finally, as is the case with other cancers including colorectal, breast, prostate, and ovarian carcinoma, expression of CSC markers in pancreatic tumors correlates with diminished survival *(Rasheed, 2012; Maeda, 2008; Ohara, 2013)*. These findings suggest that the development of cancer stem cell inhibitors may represent a novel strategy for potential use in the treatment of PDAC.

2.3 BBI-608

BBI-608 (also called napabucasin, BBI608, BB608) is a small molecule that is hypothesized to affect multiple oncogenic cellular pathways, including inhibition of the STAT3 pathway, which has been implicated in cancer stem cell viability. For further pre-clinical information, please refer to the Investigator Brochure.

BBI-608 has been evaluated in multiple clinical trials as both a monotherapy and as a component of combination therapy with standard anti-cancer therapeutics. Available data from many of these trials, including detailed adverse event (AE) tables and pharmacokinetic information, can be found in the IB.

Highlighted below are general information on the BBI-608 safety profile and a summary of the BBI608-118 (aka BBI608-201PANC) phase I/II clinical trial of BBI-608 in combination with standard chemotherapy for advanced PDAC.

2.3.1 Pre-Clinical Rationale

The pre-clinical rationale for the development of BBI-608 can be found in the Investigator Brochure.

2.3.2 Safety Profile

The predominant adverse drug reactions (ADRs) associated with BBI-608 are gastrointestinal in nature. BBI-608 appears to irritate the gastrointestinal epithelium, which can result in diarrhea, abdominal pain, nausea, vomiting, and decreased appetite (anorexia). Fatigue is also reported.

These ADRs are predominantly mild (grade 1 or grade 2), but can be severe (grade 3). Gastrointestinal or other ADRs that are grade 4 in severity are rare (<1%). However, even mild or moderate events, if persistent, can result in dehydration; which, if severe, can lead to other events such as hypovolemia, hypotension, electrolyte abnormalities, and increased serum creatinine/acute kidney injury. Other sequelae such as dizziness or falls could also occur.

The common ADRs for BBI-608 are shown in **Table 1** below. The table shows two sets of frequencies or rates. The first set (3rd column) is the range of rates reported for each event as a non-serious occurrence across the clinical trials. Different rates are observed in each trial because of different study populations and the different combination therapeutics involved. The second set of rates (4th column) is the overall frequency in which the event is reported as a serious adverse drug reaction.

Table 1: Frequency of Common Adverse Drug Reactions

System Organ Class (SOC)	Preferred Term (PT)	Event Rates (Range)[¥] *Non-serious*	Serious Event Rate[¥]
Gastrointestinal disorders	Diarrhoea	60 – 80%	3.2%
	Vomiting	20 – 30%	1.4%
	Nausea	30 – 50%	1.1%
	Abdominal pain	20 – 40%	0.7%
General disorders	Fatigue	25 – 40%	0.5%
	Asthenia	5 – 10%	0.3%
Metabolism and nutrition disorders	Decreased appetite	30 – 50%	0.1%
	Dehydration	10 – 15%	1.6%
	Electrolyte disorders*	5 – 10%	0.2%
Renal and urinary disorders	Acute kidney injury*	1 – 2%	0.5%
Vascular disorders	Hypotension*	1 – 2%	0.1%

*Event can occur secondary to dehydration or fluid loss as the result of nausea, vomiting, diarrhea, abdominal pain, decreased appetite, or a combination of these events.
[¥]The ranges presented are the event rates observed across different trials that involve different populations and different combination therapeutics, out of ~2500 exposed patients.

Refer to the current version of the Investigator's Brochure for more comprehensive safety data.

2.3.3 BBI-608 for Pancreatic Cancer

The BBI608-118 (aka BBI608-201PANC) study was initiated to evaluate BBI-608 in combination with standard chemotherapy for advanced PDAC. The primary objectives of the study included determination of the safety, tolerability, pharmacokinetic characteristics, and recommended phase II dose (RP2D) of BBI-608 in combination with each of the backbone regimens. Secondary objectives included evaluation of preliminary anti-tumor activity. The study has completed accrual and analysis is ongoing.

Patients with PDAC were eligible if they were appropriate to receive treatment with one of several standard regimens for advanced pancreatic cancer: albumin-bound paclitaxel (nab-paclitaxel) plus gemcitabine, FOLFIRINOX, liposomal irinotecan (Onivyde [MM-398]) plus 5FU/Leucovorin, or FOLFIRI. The trial was not randomized and a treatment arm was selected by investigators based on the specific clinical context for each patient.

Once enrolled, patients received twice daily administration of BBI-608 in combination with a standard chemotherapeutic backbone as set forth above. RP2D was determined to be 240 mg BID (480 mg total daily) for all combination arms.

In the BBI-608 in combination with gemcitabine plus nab-paclitaxel study arm, patients received gemcitabine 1000 mg/m^2 intravenously plus nab-paclitaxel 125 mg/m^2 intravenously on days 1, 8, and 15 of a 28-day study cycle. Dose adjustment of either BBI-608 or gemcitabine/nab-paclitaxel (either agent) was permitted in the event of toxicity.

Out of 71 patients enrolled, a total of 66 patients had not previously received BBI-608. A majority of these patients had not received any systemic therapy, with approximately 25% having received adjuvant therapy with recurrence at less than 6 months of the last adjuvant dose.

As of September 1, 2017, 64 out of the 66 patients enrolled had protocol treatment dose-administration confirmed in the study database. These 64 patients were included in an analysis of safety and efficacy. Objective response per RECIST 1.1 was observed in 31 (48%) of patients, including 2 (3%) with complete response (CR) and 29 (45%) with partial response (PR). An additional 19 (30%) patients had

stable disease (SD), and the disease control rate (DCR, proportion with CR, PR, or SD per RECIST 1.1) was 78%. There were 39 (61%) patients with a progression event and 43 (67%) patients who died, with a median progression-free survival (mPFS) of 7.4 months and a median overall survival (mOS) of 10.9 months.

Adverse events (AEs) in the clinical database as of September 1st, 2017 and observed in at least 10% of study patients are presented in Table 2 below. Updated clinical data from this trial, if available, can be found in the IB.

Table 2: BBI608-118 Adverse Events - BBI-608 + Gemcitabine/nab-Paclitaxel (n = 64*)

Treatment emergent adverse events in ≥10% of patients
Worst grade reported, data extract: 01SEP2017

System Organ Class	Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
		n	%	N	%	n	%	n	%	N	%	n	%
Gastrointestinal	Diarrhoea	31	48.4	11	17.2	4	6.3	1	1.6	0	0	47	73.4
	Nausea	19	29.7	10	15.6	1	1.6	0	0	0	0	30	46.9
	Abdominal pain	12	18.8	10	15.6	3	4.7	0	0	1	1.6	26	40.6
	Vomiting	10	15.6	9	14.1	1	1.6	1	1.6	0	0	21	32.8
	Constipation	4	6.3	5	7.8	1	1.6	0	0	0	0	10	15.6
	Dyspepsia	5	7.8	2	3.1	0	0	0	0	0	0	7	10.9
General, administration site	Fatigue	18	28.1	14	21.9	12	18.8	0	0	0	0	44	68.8
	Oedema peripheral	19	29.7	5	7.8	3	4.7	0	0	0	0	27	42.2
	Pyrexia	17	26.6	2	3.1	2	3.1	1	1.6	0	0	22	34.4
	Mucosal inflammation	5	7.8	2	3.1	0	0	0	0	0	0	7	10.9
Metabolism and nutrition	Decreased appetite	11	17.2	10	15.6	0	0	0	0	0	0	21	32.8
	Hypokalaemia	4	6.3	4	6.3	4	6.3	0	0	0	0	12	18.8
	Dehydration	1	1.6	8	12.5	2	3.1	0	0	0	0	11	17.2
	Hyponatraemia	4	6.3	1	1.6	3	4.7	0	0	0	0	8	12.5
Nervous system	Neuropathy peripheral	15	23.4	6	9.4	4	6.3	0	0	0	0	25	39.1
	Dysgeusia	8	12.5	0	0	0	0	0	0	0	0	8	12.5
	Headache	7	10.9	0	0	0	0	0	0	0	0	7	10.9
Respiratory	Dyspnoea	6	9.4	4	6.3	3	4.7	0	0	0	0	13	20.3
	Cough	7	10.9	1	1.6	0	0	0	0	0	0	8	12.5
Skin and subcutaneous tissue	Alopecia	6	9.4	15	23.4	0	0	0	0	0	0	21	32.8
	Rash	11	17.2	2	3.1	0	0	0	0	0	0	13	20.3
Blood and lymphatic system	Neutropenia	1	1.6	0	0	13	20.3	4	6.3	0	0	18	28.1
	Anaemia	1	1.6	6	9.4	8	12.5	0	0	0	0	15	23.4
	Thrombocytopenia	4	6.3	1	1.6	6	9.4	0	0	0	0	11	17.2
Investigations	Weight decreased	6	9.4	5	7.8	0	0	0	0	0	0	11	17.2
	Neutrophil count ↓	3	4.7	1	1.6	0	0	3	4.7	0	0	7	10.9
Musculoskeletal	Pain in extremity	5	7.8	2	3.1	1	1.6	0	0	0	0	8	12.5
Psychiatric	Depression	4	6.3	3	4.7	0	0	0	0	0	0	7	10.9
Renal and urinary	Chromaturia	8	12.5	0	0	0	0	0	0	0	0	8	12.5

*Protocol therapy administration records were not available as of data extract for 2 of the 66 cohort patients.

Refer to the current version of the Investigator's Brochure for more comprehensive safety data.

2.4 SUMMARY

BBI-608 at a dose of 240 mg BID (480 mg total daily) combined with a standard regimen of gemcitabine and nab-paclitaxel was tolerated in patients with advanced pancreatic cancer. The clinical activity observed in the BBI608-118 (BBI608-201PANC) study, paired with the unmet medical need for additional effective therapies in pancreatic cancer, provides a rationale for further clinical investigation. CanStem111P is designed to evaluate the role of BBI-608 in combination with nab-paclitaxel and gemcitabine as frontline therapy for metastatic PDAC.

3.0 TRIAL DESIGN

This is an international multi-center, prospective, open label, randomized phase III trial of BBI-608 plus nab-paclitaxel with gemcitabine (Arm 1) *versus* nab-paclitaxel with gemcitabine (Arm 2) in adult patients with metastatic pancreatic adenocarcinoma.

Following the interim analysis, the trial will continue with patients who have not yet achieved the primary study endpoint (death), and with patients currently on protocol therapy and who may receive BBI-608 and/or gemcitabine and/or nab-paclitaxel on study based on the clinical judgement of the investigator that this is in the patient's best interest, provided the patient is fully informed, in agreement and has provided consent. Patients will receive protocol treatment until any of the discontinuation criteria are met or until February 28th, 2020, whichever occurs first. The protocol will continue to be followed for all endpoints until study completion.

3.1 STRATIFICATION

At randomization, patients will be stratified by:

1. Geographical region (North America/Western Europe/Australia vs. Japan/Korea vs. Rest of the World)
2. ECOG performance status (ECOG 0 *vs* ECOG 1)
3. Presence of liver metastases (yes *vs* no)

3.2 RANDOMIZATION

Patients will be randomized to the study according to a 1:1 ratio using a permuted block randomization procedure to receive one of the following 2 treatments:

1. Arm 1: BBI-608 plus nab-paclitaxel with gemcitabine
2. Arm 2: nab-paclitaxel with gemcitabine

Total planned sample size for this study is 1132 patients.

Patients will be randomized to one of the following two arms:

Arm	Study Treatment		
	Agent(s)	Dose and Route	Duration
1	BBI-608	240 mg orally two times daily[1,2]	Patients may continue to receive protocol therapy as long as they have not experienced any adverse events requiring permanent discontinuation of study medication and have not demonstrated disease progression based on RECIST 1.1 criteria.[4,5]
	Nab-paclitaxel with gemcitabine	Nab-Paclitaxel 125 mg/m^2 IV and Gemcitabine 1000 mg/m^2 IV, on Days 1, 8 and 15[3]	
2	Nab-paclitaxel with gemcitabine	Nab-Paclitaxel 125 mg/m^2 IV and Gemcitabine 1000 mg/m^2 IV,	

		on Days 1, 8 and 15[3]	

[1] BBI-608 should be taken one hour before or two hours after a meal, two times daily, with approximately 12 hours between doses. BBI-608 administration will begin 2 days prior to the backbone chemotherapy infusion on Day 1 of Cycle 1. These two days are referred to as *Run-in Day 1 and Run-in Day 2*. The Run-in period may be extended by up to 3 additional calendar days. Run-in Day 1 should occur within 2 calendar days of patient randomization.

[2] Patients should be encouraged to maintain sufficient fluid intake while on protocol treatment, such as taking BBI-608 with approximately 250 mL of fluid over the course of 30 minutes after the dose.

[3] Nab-paclitaxel 125 mg/m^2 will be administered intravenously over approximately 30 minutes starting on Day 1 of Cycle 1, at least 2 hours after the first daily dose of BBI-608. Gemcitabine 1000 mg/m^2 will be administered intravenously over approximately 30-60 minutes immediately following nab-paclitaxel infusion. The infusions will repeat on Days 1, 8 and 15 of every 28-day cycle.

[4] If nab-paclitaxel and/or gemcitabine is/are discontinued due to toxicity, BBI-608 may be continued as monotherapy until another criterion for stopping treatment is met with the Sponsor's approval, if it is believed to be in the patient's interest by the investigator and patient, and with the patient's informed consent. If BBI-608 is discontinued due to toxicity, nab-paclitaxel and gemcitabine may be continued until another criterion for stopping treatment is met.

[5] If at the time of disease progression based on RECIST 1.1 criteria on nab-paclitaxel and gemcitabine with BBI-608, the patient has not experienced any adverse events requiring permanent discontinuation of BBI-608, the patient is not a candidate for second-line chemotherapy, it is believed to be in the patient's best interest by the investigator and patient, and with the patient's informed consent, BBI-608 may be continued in monotherapy following discontinuation of nab-paclitaxel and gemcitabine with the Sponsor's approval.

3.3 INCLUSION OF WOMEN AND MINORITIES

Patients enrolled in this study will be representative of the mix of genders, races and ethnicities seen in the general population of patients with PDAC. The effect of the intervention under investigation will be analyzed in gender, racial and ethnic subgroups, with recognition of the potentially limited statistical power of this analysis.

3.4 PHARMACEUTICAL DATA

3.4.1 BBI-608

Supplied: BBI-608 is supplied in 80 mg strength capsules.

Stability: Initial product use dating is 24 months from the date of manufacture and can be extended to a maximum of 5 years from date of manufacture assuming acceptable results at re-assay time-point testing.

Storage: BBI-608 capsules should be stored in a tightly closed container at a temperature between 15 to 25ºC (59 °F to 77 °F).

Route of Administration: Oral: Patients should take BBI-608 twice daily, approximately one hour prior to or two hours after meals, with the first dose given in the morning and the second dose given approximately 12 hours later (ideally between 10 and 14 hours from the previous dose).

3.4.2 Nab-Paclitaxel and Gemcitabine

Please refer to the nab-paclitaxel and gemcitabine Product Labels for product description, stability information, storage instructions, and route of administration.

4.0 STUDY POPULATION

The trial population will consist of subjects with metastatic histologically or cytologically confirmed PDAC. Subjects will not have received systemic chemotherapy for their metastatic PDAC.

4.1 INCLUSION CRITERIA

Questions about eligibility criteria should be addressed prior to randomization.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases.

Eligibility criteria will be verified by the sponsor and/or sponsor designee prior to patient randomization.

Patients must fulfill all of the following criteria to be eligible for admission to the study:

4.1.1 Written, signed consent for trial participation must be obtained from the patient appropriately in accordance with applicable ICH guidelines and local and regulatory requirements prior to the performance of any study specific procedure.

4.1.2 Must have histologically or cytologically confirmed advanced PDAC that is metastatic. The definitive diagnosis of metastatic PDAC will be made by integrating the histopathological data within the context of the clinical and radiographic data. Patients with islet cell neoplasms are excluded.

4.1.3 Must not have previously received chemotherapy or any investigational agent for the treatment of PDAC.

- A fluoropyrimidine or gemcitabine administered as a radiation sensitizer in the adjuvant setting is allowed for as long as last dose was administered > 6 months prior to randomization and no lingering toxicities are present.

4.1.4 Nab-paclitaxel with gemcitabine therapy is appropriate for the patient and recommended by the Investigator.

4.1.5 Patient has one or more metastatic tumors evaluable by CT scan with contrast (or MRI, if patient is allergic to CT contrast media) per RECIST 1.1. Imaging investigations including CT/MRI of chest/abdomen/pelvis or other scans as necessary to document all sites of disease must be performed within 14 days prior to randomization. Qualifying scans performed as part of standard of care prior to patient signature of the study informed consent will be acceptable as baseline scanning as long as scanning is performed $\leq$ 14 days prior to randomization.

4.1.6 Must have ECOG Performance Status of 0 or 1, assessed within 14 days prior to randomization. Two observers qualified to perform assessment of the performance status will be required to perform this assessment. If discrepant, the one with the most deteriorated performance status will be considered true.

- Patients must not require any help with activities of daily living (ADLs), including eating, dressing, washing or using the toilet.
- Patients must not need to stay in bed or chair for 50% or more of waking hours.
- Patients with factors that limit accurate assessment of performance status will not be eligible for the study. This includes but is not limited to patients with pre-existing conditions preventing them from full mobility (including but not limited to spinal or orthopedic conditions, amputees, morbid obesity defined by BMI > 40).

4.1.7 Must have life-expectancy of > 12 weeks.

4.1.8 Must be ≥ 18 years of age.

- Due to increased risk of sepsis in patients >80 years old, candidate patients in this age group should be thoroughly evaluated prior to study randomization to ensure they are fit to receive chemotherapy. In addition to all of the inclusion/exclusion criteria listed, clinical judgment should be used regarding patients' susceptibility to infection (including but not limited to presence of ascites or diabetes mellitus increasing risk of infection). Furthermore, the expected stability of their performance status while receiving repeat weekly chemotherapy cycles should be given special attention. Patients in this age group should not be randomized on the study should there be any hesitation on any of these considerations.

4.1.9 *For male or female patients of child producing potential:* Must agree to use contraception or take measures to avoid pregnancy during the study and for 180 days after the final dose of nab-paclitaxel and gemcitabine or for 30 days for female patients and for 90 days for male patients, after the final BBI-608 dose if nab-paclitaxel and gemcitabine were not administered.

Adequate contraception is defined as follows:

1. Complete true abstinence: when this is in line with the preferred and usual lifestyle of the subject.
2. Consistent and correct use of one of the following methods of birth control:
   a. male partner who is sterile prior to the female subjects entry into the study and is the sole sexual partner for that female subject; or
   b. implants of levonorgesterol; or
   c. injectable progestagen; or
   d. any intrauterine device (IUD) with a documented failure rate of less than 1% per year; or
   e. any intrauterine hormone-releasing system (IUS) with a documented failure rate of less than 1% per year; or
   f. oral contraceptive pill (either combined or progesterone only); or
   g. one barrier method, for example diaphragm with spermicide or condom with spermicide in combination with either implants of levonorgesterol or injectable progestagen, any intrauterine device (IUD) or intrauterine hormone-releasing system (IUS) with a documented failure rate of less than 1% per year, or oral contraceptive pill (either combined or progesterone only).

4.1.10 Women of child bearing potential (WOCBP) must have a negative serum or urine pregnancy test within 3 days prior to randomization. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of human chorionic gonadotropin (HCG).

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhoea > 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL). Even women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g. vasectomy), should be considered to be of child bearing potential.

4.1.11 Patient has adequate biological parameters as demonstrated by the following blood counts at baseline (obtained ≤ 14 days prior to randomization; laboratory testing performed as part of standard of care prior to patient signature of informed consent for the study will be acceptable as baseline laboratory work as long as testing is performed ≤ 14 days prior to randomization):

- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
- Platelet count > 100,000/mm^3 (100 x 10^9/L). Must not have required transfusion of platelets within 1 week of baseline platelet count assessment.
- Hemoglobin (Hgb) ≥ 9 g/dL. Must not have required transfusion of red blood cells within 1 week of baseline Hgb assessment.

4.1.12 Patient has the following blood chemistry levels at baseline (obtained ≤ 14 days prior to randomization; laboratory testing performed as part of standard of care prior to patient signature of informed consent for the study will be acceptable as baseline laboratory work as long as testing is performed ≤ 14 days prior to randomization):

- AST (SGOT) and ALT (SGPT) ≤ 2.5 × institutional upper limit of normal (ULN) [≤ 5 × ULN in presence of liver metastases]
- Total bilirubin ≤ 1.5 x institutional ULN. If total bilirubin is > ULN and ≤ 1.5 x ULN, it must be non-rising for at least 7 days.
- Serum creatinine within normal limits or calculated clearance > 60 mL/min/1.73 m^2 for patients with serum creatinine levels above or below the institutional normal value. If using creatinine clearance, actual body weight should be used for calculating creatinine clearance (eg. Using the Cockroft-Gault formula). For patients with a Body Mass Index (BMI) > 30 kg/m^2, lean body weight should be used instead.

4.1.13 Patient not on anticoagulation has acceptable coagulation studies (obtained ≤ 14 days prior to randomization; laboratory testing performed as part of standard of care prior to patient signature of informed consent for the study will be acceptable as baseline laboratory work as long as testing is performed ≤ 14 days prior to randomization) as demonstrated by prothrombin time (PT) and partial thromboplastin time (PTT) below or within normal limits (+15%).

- Patients on anticoagulation must have coagulation values within the therapeutic range appropriate for the anti-coagulation indication.

4.1.14 Patient has no clinically significant abnormalities on urinalysis results (obtained ≤ 14 days prior to randomization; laboratory testing performed as part of standard of care prior to patient signature of informed consent for the study will be acceptable as baseline laboratory work as long as testing is performed ≤ 14 days prior to randomization).

4.1.15 Patient must have adequate nutritional status with Body Mass Index (BMI) ≥ 18 kg/m^2 and body weight of > 40 kg with serum albumin ≥ 3 g/dL.

4.1.16 Baseline laboratory evaluations must be done within 14 days prior to randomization and some must be repeated ≤ 72 hours prior to randomization, as listed in Section 5.0.

4.1.17 Patients requiring biliary stent placement must have biliary stent placed ≥ 7 days prior to screening.

4.1.18 Pain symptoms should be stable (of tolerable Grade 2 or less).

4.1.19 Only patients with available archival tumor tissue must consent to provision of, and Investigator(s) must confirm access to and agree to submit a representative formalin fixed paraffin block of tumor tissue in order that the specific correlative marker assays proscribed in Section 13.6 (Correlative Studies) of this protocol may be conducted. Submission of the tissue does not have to occur prior to randomization. Where local center regulations prohibit submission of blocks of tumor tissue, two 2 mm cores of tumor from the block and 5-20 unstained slides of whole sections of representative tumor tissue are preferred. Where it is not possible to obtain two 2 mm cores of tumor from the block, 5-20 unstained slides of representative tumor tissue are also acceptable.

- Where no previously resected or biopsied tumor tissue exists or is available, on the approval of the Sponsor/designated CRO, the patient may still be considered eligible for the study.

4.1.20 Patient must consent to provision of a sample of blood in order that the specific correlative marker assays proscribed in Section 13.6 (Correlative Studies) may be conducted.

4.1.21 Patients must be accessible for treatment and follow-up. Patients registered on this trial must receive protocol treatment and be followed at the participating center. This implies there must be reasonable geographical limits placed on patients being considered for this trial. Investigators must ensure that the patients randomized on this trial will be available for complete documentation of the treatment, response assessment, adverse events, and follow-up.

4.1.22 Protocol treatment is to begin within 2 calendar days of patient randomization for patients randomized to Arm 1. Patients randomized to Arm 2 must begin protocol treatment within 7 calendar days of randomization.

4.1.23 The patient is not receiving therapy in a concurrent clinical study and the patient agrees not to participate in other interventional clinical studies during their participation in this trial while on study treatment. Patients participating in surveys or observational studies are eligible to participate in this study.

4.2 EXCLUSION CRITERIA

Patients who fulfill any of the following criteria are not eligible for admission to the study:

4.2.1 Patients with no evidence of metastatic disease as well as patients with a local recurrence following surgical resection of primary lesion.

4.2.2 Patient has experienced a decline in ECOG performance status between Baseline visit and

within 72 hours prior to randomization.

4.2.3 Patient has a ≥ 20% decrease in serum albumin level between Baseline visit and within 72 hours prior to randomization.

4.2.4 Patient has a ≥ 10% decrease in weight between Baseline visit and within 72 hours prior to randomization.

4.2.5 Any prior anti-cancer chemotherapy, biologic or investigational therapy for PDAC.
a. Patients receiving immunotherapy for non-cancer related treatment within ≤ 4 weeks of first planned dose of study treatment will be excluded.
b. A fluoropyrimidine or gemcitabine administered as a radiation sensitizer in the adjuvant setting is allowed for as long as last dose was administered > 6 months prior to randomization.

4.2.6 Major surgery within 4 weeks prior to randomization.

4.2.7 Any known brain or leptomeningeal metastases are excluded, even if treated.

4.2.8 Patients with clinically significant ascites or pleural effusions.

4.2.9 Women who are pregnant or breastfeeding. Women should not breastfeed while taking study treatment and for 4 weeks after the last dose of BBI-608 or while undergoing treatment with nab-paclitaxel and gemcitabine and for 180 days after the last dose of nab-paclitaxel and gemcitabine.

4.2.10 Gastrointestinal disorder(s) which, in the opinion of the Principal Investigator, would significantly impede the absorption of an oral agent (e.g. active Crohn's disease, ulcerative colitis, extensive gastric and small intestine resection).

4.2.11 Unable or unwilling to swallow BBI-608 capsules daily.

4.2.12 Uncontrolled inter-current illness including, but not limited to, ongoing or active infection, clinically significant non-healing or healing wounds, symptomatic congestive heart failure, unstable angina pectoris, clinically significant cardiac arrhythmia, significant pulmonary disease (shortness of breath at rest or mild exertion), uncontrolled infection or psychiatric illness/social situations that would limit compliance with study requirements.

a. History of cardiac disease: congestive heart failure (CHF) > NYHA Class II; active coronary artery disease, myocardial infarction or coronary stenting within 6 months prior to randomization; unevaluated new onset angina within 3 months or unstable angina (angina symptoms at rest) or cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted).

b. Current uncontrolled hypertension (systolic blood pressure [BP] > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management) as well as prior history of hypertensive crisis or hypertensive encephalopathy.

c. Significant vascular disease (e.g., aortic aneurysm, aortic dissection, symptomatic peripheral vascular disease including claudication, Leo Buerger's disease). Treated peripheral vascular disease that is stable for at least 6 months is allowed.

d. Evidence of bleeding diathesis or clinically significant coagulopathy.

e. Major surgical procedure (including open biopsy, significant traumatic injury, etc.) within 28 days, or anticipation of the need for major surgical procedure during the course of the study as well as minor surgical procedure (excluding placement of a vascular access device or bone marrow biopsy) within 7 days prior to randomization.

f. Patients with clinically significant abnormalities on urinalysis at ≤ 14 days prior to randomization.

g. History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 6 months prior to randomization.

h. Ongoing serious, non-healing wound, ulcer, or bone fracture.

i. Known infection with Human Immunodeficiency Virus (HIV), and/or active infection with hepatitis B, or hepatitis C.

j. History of interstitial lung disease, history of slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies.

k. History of hemolytic-uremic syndrome.

l. History of connective tissue disorders (eg, lupus, scleroderma, arteritis nodosa).

m. Serious medical risk factors involving any of the major organ systems, or serious psychiatric disorders that could compromise the patient's safety or the study data integrity.

4.2.13 Known hypersensitivity to gemcitabine, taxanes or any of their excipients, or the patient exhibits any of the events outlined in the Contraindications or Special Warnings and Precautions sections of the product or comparator SmPC or Prescribing Information. Possible hypersensitivity to BBI-608 or one of the excipients which include the azo dyes sunset yellow and allura red.

4.2.14 Neurosensory neuropathy ≥ grade 2 at baseline.

4.2.15 Uncontrolled chronic diarrhea ≥ grade 2 at baseline.

4.2.16 Patients being treated with Warfarin.

4.2.17 Patients with active, uncontrolled bacterial, viral or fungal infection(s) requiring systemic therapy

4.2.18 Patients with a history of other malignancies except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumors curatively treated by surgery alone or surgery plus radiotherapy with no evidence of disease continuously for ≥ 5 years.

4.2.19 Any active disease condition which would render the protocol treatment dangerous or impair the ability of the patient to receive protocol therapy.

4.2.20 Any condition (e.g. psychological, geographical, etc.) that does not permit compliance with the protocol, including patients with history of poor compliance or history of drug/alcohol abuse, or excessive alcohol beverage consumption that would interfere with the ability to

comply with the study protocol. Patients planning to take a vacation for 14 or more consecutive days during the course of the study are ineligible.

5.0 PRE-RANDOMIZATION (BASELINE) SCHEDULE OF EVENTS (SEE APPENDICES I AND II)

Baseline evaluations will be performed for all patients to determine study eligibility. These evaluations must be obtained ≤ 14 days prior to randomization.

Repeat of screening laboratory tests will be allowed only in the event of a laboratory error or for patients who halted screening previously without having failed any of the screening tests/evaluations or inclusion criteria for this study. Otherwise, re-screening will not be allowed.

Any questions regarding patient eligibility should be directed to Sponsor or other Sponsor-nominated designee for written approval.

Additional testing will be repeated ≤ 72 hours prior to randomization: ECOG performance status (PS), vital signs, weight, concurrent medication list and serum albumin will be repeated at ≤ 72 hours prior to randomization after first being performed as part of Baseline testing. Total bilirubin will be repeated ≤ 72 hours prior to randomization for patients with total bilirubin > 1 and ≤ 1.5 x ULN at Baseline testing with at least 7 days between Baseline and repeat assessments.

All appropriate eCRF pages must be completed for patients prior to obtaining pre-randomization approval and following completion of additional testing at ≤ 72 hours prior to randomization, in accordance with the eCRF completion guidelines and the Eligibility Verification Procedure Flow Chart.

Investigations		Timing of Baseline Evaluation prior to randomization	Additional Testing at ≤ 72 hrs prior to randomization[3]
Informed Consent[1]	• Signature	≤ 14 days	
Patient History and Evaluation including:	• All known prior medical and therapeutic history[2] • Physical examination[11, 14] • Vital signs[5,11] • Height, weight[12], ECOG performance status[11] • Concurrent medication list[11]	≤ 14 days	• ECOG performance status • Vital signs[5] • Weight • Concurrent medication list[4]
Hematology	• CBC + 5-part differential • Platelet count	≤ 14 days[11]	-
Biochemistry	• Creatinine[6], Total Bilirubin, AST, ALT, Alkaline Phosphatase, LDH, Albumin, Sodium, Potassium, Magnesium, Phosphate, BUN (blood urea nitrogen)	≤ 14 days[11]	• Serum Albumin • Total Bilirubin[12,13]
Urinalysis	• Dipstick (including protein, specific gravity, glucose and blood)	≤ 14 days[11]	-
Coagulation	• PT • PTT	≤ 14 days[11]	-
Tumor Marker	• CA 19-9	≤ 14 days[11]	-
Cardiac Assessment	• ECG (12 lead)	≤ 14 days[11]	-
Radiology & Imaging[7]	• CT/MRI scan of chest/abdomen/pelvis with tumor measurement and evaluation by RECIST 1.1 criteria	≤ 14 days	-
Correlative Studies	• Submission of representative diagnostic tumor tissue[8]	On request	-
	• Blood sample collection[8]	≤ 14 days	-

Other Investigations	• Serum or urine pregnancy test[9]	≤ 3 days	-
Adverse Events[10]	• Baseline adverse event evaluation (to document residual adverse event from previous therapy and baseline symptoms)	≤ 14 days	-
Quality of Life	• EORTC QLQ-C30	≤ 14 days	-

[1] Study participants will undergo signature of informed consent prior to randomization.
[2] Medical history must include date of diagnosis including histological or cytological documentation of malignancy.
[3] Patient will be excluded from participation if any of the following occurs at ≤ 72 hours prior to randomization: increase in ECOG PS (two observers will be required to assess KPS on each occasion and if discrepant, the one with the most deteriorated performance status will be considered true), weight loss of ≥10% from baseline testing, ≥ 20% decrease in serum albumin from baseline testing, or in the event of a clinically-significant change in vital signs.
[4] Any anesthesia procedures, such as spinal block or other injections administered for pain control following Baseline Evaluation will be reported at ≤ 72 hours prior to randomization.
[5] Vital signs include temperature, heart rate, blood pressure, respiratory rate and O_2 saturation on room air.
[6] Baseline creatinine or creatinine clearance may be used to demonstrate eligibility as per section 4.1.
[7] Standard tumor measurement procedures will be followed to assess response to therapy. The same method of assessment and the same technique should be used to identify and report each lesion at baseline and at reassessment. Qualifying scans performed as part of standard of care prior to patient signature of the study informed consent will be acceptable as baseline scanning as long as scanning is performed ≤ 14 days prior to randomization. Should clinical or radiologic progression occur from the time of baseline imaging prior to randomization, a new baseline scan will need to be obtained prior to randomization.
[8] Details for collection, processing, storing and shipping these samples will be provided in a separate laboratory procedure manual.
[9] In women of childbearing potential only. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG.
[10] Adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix IV).
[11] Laboratory testing performed as part of standard of care prior to patient signature of the study consent will be acceptable as baseline labwork as long as testing is performed ≤ 14 days prior to randomization. If required laboratory tests cannot be performed within indicated timelines due to technical reasons, lab retest and prolongation of the screening period for 3 working days is allowed.
[12] Total bilirubin assessment at ≤ 72 hours prior to randomization will be performed only for patients who had total bilirubin of > 1 and ≤ 1.5 x ULN at baseline measurement. Patients with total bilirubin ≤ 1 ULN at baseline measurement will not require repeat total bilirubin measurement at ≤ 72 hours prior to randomization.
[13] At least 7 days must pass between Baseline and ≤ 72 hour measurements of total bilirubin for patients with baseline total bilirubin measurement of > 1 and ≤ 1.5 x ULN.
[14] A physical exam should include general appearance, HEENT (head, eyes, ears, nose), dermatological, respiratory, cardiovascular/circulatory, abdomen, lymphatic, genitourinary, musculoskeletal, and neurological assessments.

6.0 ENTRY/RANDOMIZATION PROCEDURES

6.1 ENTRY PROCEDURES

Repeat of screening laboratory testing will be allowed only in case of laboratory error. Otherwise, re-screening will not be allowed for patients who screen fail during initial screening procedures. Following Sponsor approval of patient eligibility pre-randomization, patients will be randomized. All randomizations will be done through the randomization and trial supply management (RTSM) system. Complete details regarding obtaining a password, accessing the system and registering/randomizing patients will be provided at the time of study activation.

All patients screened for the study by the participating treatment center will be assigned a subject screening number and all eligible patients enrolled on the study will be assigned an additional subject randomization number; these must be used on all documentation and correspondence.

The following information will be required:

- patient's date of birth (as allowed by local regulations) and age
- patient's initials (as allowed by local regulations)
- confirmation of the requirements listed in sections 4.1 and 4.2
- stratification factors

6.2 STRATIFICATION

The permuted block randomization procedure will balance between treatment arms within each of the following stratification factors:

- Geographical region (North America/Western Europe/Australia vs. Japan/Korea vs. Rest of the World)
- ECOG performance status (0 *vs.* 1)
- Presence of liver metastases (yes *vs.* no)

6.3 RANDOMIZATION

Patients will be randomized 1:1 between the two treatment arms and the randomization will be provided electronically (via RTSM).

Note: The validity of results of the trial depends on the authenticity of, and the follow-up of, all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis, unless the participant withdraws from the trial and requests that data collection/submission cease from the point in time of withdrawal.

All eligible patients randomized to the trial will be followed by the coordinating center. It is the responsibility of the physician investigator to have full satisfaction in that the patient is indeed eligible before requesting randomization.

All randomized patients are to be followed until death or until the study sponsor or sponsor's designee inform sites that further follow-up is no longer required.

7.0 PROTOCOL TREATMENT

7.1 TREATMENT PLAN

Protocol treatment is to begin within 2 calendar days of patient randomization for patients randomized to Arm 1. Patients randomized to Arm 2 must begin protocol treatment within 7 calendar days of randomization.

Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment will be permitted for all patients on this trial. Details of interventions (e.g. medications such as antibiotics, analgesics, antihistamines, steroids, G-CSF, erythropoietin), procedures (e.g. paracentesis, thoracentesis), or blood products (e.g. blood cells, platelets, or fresh frozen plasma transfusions) should be recorded on the case report forms.

Patients may continue to receive assigned protocol therapy until any of the discontinuation criteria are met or until February 28th, 2020, when the study is planned for completion, whichever occurs first.

7.2 DRUG ADMINISTRATION

One treatment cycle is defined as 4 weeks (28 days) with BBI-608 administered continuously, and nab-paclitaxel with gemcitabine administered weekly for 3 consecutive weeks with the fourth week off. BBI-608 administration will begin 2 days prior to the first nab-paclitaxel and gemcitabine infusion administered on Day 1 of Cycle 1. These two days are referred to as *Run-In Day 1* and *Run-In Day 2*. The *Run-in* period may be extended by up to 3 additional calendar days. In case of gastrointestinal toxicity secondary to BBI-608, administration of nab-paclitaxel with gemcitabine may be delayed for as long as necessary until resolution of symptoms.

Arm	Agent(s)	Dose and Route	Duration
1	BBI-608	240 mg orally two times daily[1,2]	Patients may continue to receive protocol therapy as long as they have not experienced any adverse events requiring permanent discontinuation of study medication and have not demonstrated disease progression based on RECIST 1.1 criteria. [4,5]
	Gemcitabine +nab-Paclitaxel	Nab-Paclitaxel 125 mg/m^2 IV and Gemcitabine 1000 mg/m^2 IV, on Days 1, 8 and 15[3]	
2	Gemcitabine +nab-Paclitaxel	Nab-Paclitaxel 125 mg/m^2 IV and Gemcitabine 1000 mg/m^2 IV, on Days 1, 8 and 15[3]	

[1] BBI-608 should be taken one hour before or two hours after a meal, two times daily, with approximately 12 hours between doses. BBI-608 administration will begin 2 days prior to the nab-paclitaxel and gemcitabine infusions on day 1 of cycle 1. These two days are referred to as *Run-in Day 1* and *Run-in Day 2* (*run-in* period may be extended by up to 3 additional calendar days). Run-in Day 1 should occur within 2 calendar days of patient randomization for patients randomized to Arm 1. Patients randomized to Arm 2 must begin protocol treatment within 7 calendar days of randomization. In case of gastrointestinal toxicity secondary to BBI-608, administration of nab-paclitaxel and/or gemcitabine may be delayed for as long as necessary until resolution of symptoms.

[2] Patients should be encouraged to maintain sufficient fluid intake while on protocol treatment, such as taking BBI-608 with approximately 250 mL of fluid over the course of 30 minutes after the dose.

[3] Nab-paclitaxel 125 mg/m^2 will be administered intravenously over approximately 30 minutes starting on Day 1 of Cycle 1, at least 2 hours after the first daily dose of BBI-608. Gemcitabine 1000 mg/m^2 will be administered

intravenously over approximately 30-60 minutes immediately following nab-paclitaxel infusion. The infusions will repeat on Days 1, 8 and 15 of every 28-day cycle.

[4] If either nab-paclitaxel and/or gemcitabine is discontinued due to toxicity, BBI-608 may be continued as monotherapy until another criterion for stopping treatment is met with the Sponsor's approval, if it is believed to be in the patient's best interest by the investigator and patient, and with the patient's informed consent. If BBI-608 is discontinued due to toxicity, nab-paclitaxel and/or gemcitabine may be continued until another criterion for stopping treatment is met.

[5] If at the time of disease progression based on RECIST 1.1 criteria on nab-paclitaxel and gemcitabine with BBI-608, the patient has not experienced any adverse events requiring permanent discontinuation of BBI-608,the patient is not a candidate for second-line chemotherapy, it is believed to be in the patient's best interest by the investigator and patient, and with the patient's informed consent, BBI-608 may be continued in monotherapy following discontinuation of nab-paclitaxel and gemcitabine with the Sponsor's approval.

Patients will receive BBI-608 two times daily, approximately one hour prior to or two hours after meals, with the first dose given in the morning and the second dose given approximately 12 hours later.

Detailed instructions for the preparation, premedication, and administration of nab-paclitaxel with gemcitabine are provided in the Product Labels approved by US FDA and/or Summary of Product Characteristics. Nab-paclitaxel 125 mg/m^2 will be administered intravenously over approximately 30 minutes starting on Day 1 of Cycle 1, following the first dose of BBI-608. Gemcitabine 1000 mg/m^2 will be administered intravenously over approximately 30-60 minutes immediately following nab-paclitaxel infusion. The infusions will repeat on Day 1, 8 and 15 of every 28-day cycle. In case of toxicity, dose adjustment is permitted.

If either gemcitabine and/or nab-paclitaxel is/are permanently discontinued due to toxicity, BBI-608 may be continued as monotherapy until another criterion for stopping treatment is met with the Sponsor's approval, it is believed to be in the patient's best interest by the investigator and patient, and with the patient's informed consent. If BBI-608 is permanently discontinued due to toxicity, nab-paclitaxel with gemcitabine may be continued until another criterion for stopping treatment is met.

Handling instructions for BBI-608 will be provided to all sites. Investigators may refer to the Investigator Brochure for detailed instructions.

Drug Dosing Schedule

Week[1]	1	2	3	4	5	6	7	8
nab-Paclitaxel/Gemcitabine	Cycle 1				Cycle 2 and Beyond			
	X	X	X		X	X	X	
BBI-608[2]	Cycle 1				Cycle 2 and Beyond			
	X	X	X	X	X	X	X	X

[1] Nab-Paclitaxel/Gemcitabine weekly dosing is scheduled once weekly for 3 consecutive weeks with forth week off.

[2] BBI-608 dosing is scheduled twice daily continuously throughout the study.

7.3 ADVERSE EVENT PROPHYLAXIS

7.3.1 BBI-608

Gastrointestinal Prophylaxis

The major adverse events associated with the use of BBI-608 are gastrointestinal events (nausea, diarrhea, and abdominal cramping) and fatigue. Fatigue is often secondary to gastrointestinal events. There is no hematologic toxicity associated with BBI-608. We strongly recommend that pre-existing laxative bowel regimens, such as stool softeners, be held starting the day prior to first dose of study treatment and may be resumed in cases of no bowel movement during the first 2 days of protocol treatment. Fiber supplementation may be continued. Additionally, prophylactic anti-diarrheal medications, such as Loperamide and/or Diphenoxylate/Atropine, starting 1 day prior to start of BBI-608 are strongly recommended for all patients without history of constipation (just prior to randomization) for the first 4 weeks of study treatment with BBI-608. Antidiarrheal prophylaxis should be held if constipation develops. Details regarding the use of prophylactic medication for the management of common BBI-608 related gastrointestinal adverse events are specified in the supplementary Adverse Event Management handout as well as in the Pharmacy Manual.

No hematologic toxicity related to BBI-608 treatment has been observed.

BBI-608 Pre-Medication Recommendations:

Category	*Specific Measures*	*Start*	*End*
Anti-Diarrheal	Loperamide 4 mg BID or Diphenoxylate/Atropine 5 mg BID	24 hours prior to the first dose of BBI608 on Run-In Day 1	Stop anti-diarrheal if there are no bowel movements during the first 2 days of administration of BBI-608. Should be continued for the first 4 weeks of treatment with BBI-608. Can be continued and/or modified at the discretion of the treating investigator
Anti-Emetic	Ondansetron 8 mg once or Other anti-emetic (5HT3-antagonist preferred)	Approx. 1 hour prior to the first dose of BBI608 on Run-In Day 1	Should be continued for the first 4 weeks of treatment with BBI-608. May be continued and/or modified at discretion of treating investigator

7.3.2 Nab-Paclitaxel and Gemcitabine

Anti-Emetic Prophylaxis
Initial antiemetic prophylaxis is strongly recommended with a 5HT3 agent (PO or IV) in combination with dexamethasone 8 or 10 mg (PO or IV) prior to administration of Gemcitabine. Dexamethasone may be continued at the dose of 4 mg twice daily or three times daily for 3-4 days at the Investigator's discretion. If a patient experiences nausea and/or vomiting following the first dose, Institutional guidelines and Investigator's recommendations should be followed for breakthrough antiemetic management.

Hematopoietic Support Administration
G-CSF support may be given according to Institutional standards for the treatment of neutropenia and/or thrombocytopenia, neutropenic fever or infections associated with neutropenia and for the prevention of febrile neutropenia in patients with an ANC < 500 cells/ml. Patients not experiencing resolution of neutropenia within 21 days, despite uninterrupted granulocyte stimulating factor treatment, will discontinue study treatment. Erythropoietin may be administered at the discretion of the Investigator, consistent with Institutional guidelines.

Sepsis Prophylaxis
At the first occurrence of fever ≥ 38.5 ^{0}C, patients should be instructed to immediately contact their physician. Prophylactic institution of broad-spectrum antibiotics (such as amoxicillin/clavulanate 500 mg PO 2-3 times daily) should be considered for febrile patients at the Investigator discretion and/or as per Institutional standards. On day of randomization, patients should be provided with enough antibiotic for use at home, and they should be instructed to begin taking it when they first record a temperature of ≥ 38.5 ^{0}C (or if they feel they are developing a fever and a thermometer is not available). They should also immediately contact their physician for guidance on where to go for blood counts to be evaluated for sepsis as soon as possible. Hospitalization or evaluation in the emergency room may be required depending on their clinical presentation. Administration of prophylactic antibiotics to otherwise uncomplicated patients with biliary stents will be at the discretion of the Investigator. Biliary stents should be monitored closely to determine need for replacement.

Due to increased risk of sepsis in patients >80 years old, candidate patients in this age group should be carefully followed clinically throughout study treatment. This patient population will also be carefully monitored by the independent DSMB.

7.4 BBI-608 DOSE MODIFICATION

The major adverse events associated with the use of BBI-608 are gastrointestinal events (nausea, diarrhea, and abdominal cramping) and fatigue. Fatigue is often secondary to gastrointestinal events. There is no hematologic toxicity associated with BBI-608. We recommend that pre-exiting laxative bowel regimens, such as stool softeners, be held starting the day prior to first dose of BBI-608 treatment and may be resumed in cases of no bowel movement during the first 2 days of BBI-608 treatment. Fiber supplementation may be continued. Additionally, prophylactic anti-diarrheal medications, such as Loperamide and/or Diphenoxylate/Atropine, starting 1 day prior to start of BBI-608 are strongly recommended for all patients treated with BBI-608.

The guidelines that follow outline dosing modifications and recommended interventions should the above adverse events occur.

Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (see Appendix IV). If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

BBI-608 Dose Modification Recommendations For Gastrointestinal Adverse Events:

Suspected BBI-608 -Related Adverse Event	Investigator Action
Grade 1 or tolerable Grade 2 Symptoms	Patient should remain at current dose. Attempt pharmacologic measures to minimize symptoms (see symptom specific treatment table below).
Intolerable Grade 2 Symptoms	If intolerable symptoms persist despite optimized medical management, dose reduction and sufficient oral hydration are recommended. A dose interruption of ½ to 3 days prior to reduction can also be considered. Dosing should be reduced to the next Modification Level on the *dose modification table*. Pharmacologic symptom support and/or prophylaxis should be maintained.

	After a dose reduction, AM and PM doses may be increased in 80 mg increments every 3-7 days as tolerated.*, **
Grade 3 or 4 Symptoms	A dose interruption of ½ to 3 days is recommended until symptoms are reduced to ≤ tolerable grade 2. Dosing should be reduced to the next Modification Level on the *dose modification table*. Pharmacologic symptom support and/or prophylaxis should be maintained. After a dose reduction, AM and PM doses may be increased in 80 mg increments every 3-7 days as tolerated.*, **
* If, during the course of re-escalation, a dosing regimen is not tolerated despite optimized medical management, dosing should return to the highest previously tolerated dosing regimen. ** Asymmetry between AM and PM dose is allowed during re-escalation (e.g. 160 mg AM/240 mg PM).	

BBI-608 Dose Modification Table:

Dose Level	Dose
Full dose	240 mg twice daily (q12h)
Modification Level-1	80 mg twice daily (q12h), up-titrate as tolerated**
Modification Level-2	80 mg once daily*, up-titrate as tolerated**
* If 80 mg once daily is not tolerated, a dose interruption of 1-3 days followed by re-challenge at 80 mg once daily is recommended. ** Morning and evening doses can be increased in 80 mg increments every 3-7 days or slower as tolerated, up to 240 mg two times daily.	

Recommended symptom-specific supportive treatment for common BBI-608-related adverse events is as follows (unless contraindicated). Prophylactic anti-diarrheal medications, such as Imodium and/or lomotil, starting 1 day prior to start of BBI-608 are strongly recommended for all patients:

BBI-608 GI Toxicity/Adverse Event Supportive Treatment:

Diarrhea & Abdominal Cramping	Nausea, Vomiting, or Anorexia
Dicyclomine *(e.g., Bentyl)*: Recommended when the predominant issue is cramping or abdominal pain	**1st line:** 5HT3-inhibitors *(Ondansetron, Palonosetron, Granisetron)*
Diphenoxylate/atropine *(Lomotil)* **Loperamide** *(Imodium)* These agents may be also be useful in combination	**2nd line:** Dexamethasone *(Decadron)*, ideally in combination with a 5HT3-inhibitor. Short term use can be very effective
Systemic opioids (e.g. *Dilaudid, Codeine*): have been found effective in reducing abdominal pain and watery diarrhea	**Other agents**: anti-histamines, benzodiazepines, proton pump inhibitors/H2 antagonists, dopamine antagonists, and cannabinoids
Hyoscine *(Buscopan, Scopolamine, Levsin)*: Anti-spasmodic agents helpful for abdominal cramping	

Budesonide (*Entocort EC*): Corticosteroid with limited systemic absorption; 9 mg once daily for 8 to 12 weeks	

Details regarding the use of supportive medication for the management of common BBI-608-related adverse events are specified in the supplementary Adverse Event Management handout as well as in the Pharmacy Manual.

7.4.1 Hematologic Adverse Events

No hematologic toxicity related to BBI-608 treatment has been observed. Should a study subject experience a Grade 1 or 2 hematologic adverse event, dosing may continue while an alternate explanation is sought and/or a therapeutic intervention is undertaken.

In the unlikely event of a Grade 3 or 4 hematologic adverse event, continued dosing will be at the discretion of the study Investigator. Since a Grade 3 or 4 hematologic event attributed to BBI-608 has not been reported, a prompt evaluation for an alternate explanation is strongly recommended.

7.4.2 Non-Hematologic (Gastrointestinal) Adverse Events

The dose modifications above should be followed in the occurrence of gastrointestinal adverse events or in the event of their sequelae. BBI-608 dose modification should not be followed for non-gastrointestinal events as they are not expected with use of BBI-608. Toxic effects will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (Appendix IV).

7.4.3 Other Situations

Change in Urine Color and Odor: Occasionally, subjects have reported an orange-brown color change to their urine. Rarely, subjects also report a new odor to their urine. All subjects should be made aware of the possibility of these effects. Dosing can be continued in the presence of these events.

7.5 NAB-PACLITAXEL AND GEMCITABINE DOSE MODIFICATION

Dose modifications for hematologic and non-hematologic toxicities (using NCI CTCAE Version 4.0) expected from nab-paclitaxel with gemcitabine should be performed according to the recommendations outlined below. Dose modifications for non-gastrointestinal toxicities expected from nab-paclitaxel with gemcitabine may also follow institutional guidelines. There will no dose reductions or adjustments for lymphopenia or alopecia. Dose level modifications of nab-paclitaxel and gemcitabine will occur at two dose levels. Any toxicity requiring dose level modification beyond the second dose modification warrants treatment discontinuation. Any further dose modification may be allowed in line with clinical practice per Sponsor and Investigator agreement..

When a dose reduction is required, no dose reescalation will be permitted for the duration of study treatment (with exception for hematologic toxicity on Day 15 when re-escalation with G-CSF support is permitted following a dose reduction on Day 8 of the same cycle).

Nab-Paclitaxel and Gemcitabine Dose Modification Table:

Dose Level	Nab-Paclitaxel (mg/m^2)[1]	Gemcitabine (mg/m^2)[1]
Starting Dose	125	1000

Modification Dose Level 1	100	800
Modification Dose Level 2[2]	75	600

[1] Dose reductions may or may not be concomitant. Please refer to specific hematologic and other toxicity modification recommendations outlined below.
[2] A maximum of 2 dose level reductions is allowed.

7.5.1 Hematologic Toxicity

Prior to each dose of nab-paclitaxel with gemcitabine, the ANC and platelet count should be evaluated. Dose modifications for hematologic toxicities expected from nab-paclitaxel with gemcitabine should be performed depending to their occurrence within a given cycle and according to the following Product label recommendations:

Cycle Day	**ANC (cells/mm^3)**		**Platelet Count (cells/mm^3)**	**Gemcitabine Dosing[1,2]**	**nab-Paclitaxel Dosing[1,2]**
1	< 1500	Or	< 100,000	Delay dosing by 1 week intervals until recovery	Delay dosing by 1 week intervals until recovery
8	500 to 1000	Or	50,000 to < 75,000	Reduce dosing by 1 Dose Level and treat on time	Reduce dosing by 1 Dose Level and treat on time
	< 500	Or	< 50,000	Hold dosing	Hold dosing
Day 15: IF Day 8 doses were unmodified:					
	500 to 1000	Or	50,000 to < 75,000	Treat on time with Full Dose Level and give G-CSF[3]	Treat on time with Full Dose Level and give G-CSF[3]
	< 500	Or	< 50,000	Hold dosing and give G-CSF[3]	Hold dosing and give G-CSF[3]
Day 15: IF Day 8 doses were reduced:					
	> 1000	Or	≥ 75,000	Return to Previous Dose Level, treat on time and give G-CSF[3]	Return to Previous Dose Level, treat on time and give G-CSF[3]
	500 to 1000	Or	50,000 to < 75,000	Treat on time with same Dose Level as Day 8 and give G-CSF[3]	Treat on time with same Dose Level as Day 8 and give G-CSF[3]
	< 500	Or	< 50,000	Hold dosing and give G-CSF[3]	Hold dosing and give G-CSF[3]
Day 15: IF Day 8 doses were held:					
	> 1000	Or	≥ 75,000	Decrease Day 1 Dose by 1 Level, treat on time and give G-CSF[3]	Decrease Day 1 Dose by 1 Level, treat on time and give G-CSF[3]
	500 to 1000	Or	50,000 to < 75,000	Decrease Day 1 Dose by 2 Levels, treat on time and give G-CSF[3]	Decrease Day 1 Dose by 2 Levels, treat on time and give G-CSF[3]
	< 500	Or	< 50,000	Hold dosing and give G-CSF[3]	Hold dosing and give G-CSF[3]
Grade 3-4 Febrile Neutropenia at any point in the cycle (defined as temperature ≥ 101 °F with a neutrophil count of ≤ 1000 cells/ml)[4]				Hold dosing until fever resolution and ANC > 1500 and resume at next lower dose level and do not re-escalate throughout the rest of treatment.	Hold dosing until fever resolution and ANC > 1500 and resume at next lower dose level and do not re-escalate throughout the rest of treatment.
Recurrent Grade 3-4 Febrile Neutropenia at any point in the cycle[5]				Decrease dosing 2 Dose Levels (to 600 mg/m^2) and do not re-escalate throughout the rest of treatment.	Decrease dosing to next lower Dose Level and do not re-escalate throughout the rest of treatment.

[1] Once a dose of any drug is decreased for toxicity, re-escalation is not permitted (with exception of hematologic toxicity on Day 15 when re-escalation with G-CSF support is permitted following a dose reduction on Day 8 of the same cycle).
[2] Dose level reductions should be performed as shown in the dose modification table above.
[3] G-CSF administration is optional if only platelet count meets G-CSF administration criterion and ANC count is above threshold.

[4] Febrile patients (regardless of neutrophil count) should have a full sepsis diagnostic work-up while continuing broad spectrum antibiotics. Patients with persisting fever after 3 weeks, despite uninterrupted antibiotic treatment, will discontinue study treatment. Febrile neutropenic patients may also receive G-CSF to hasten the resolution of their febrile neutropenia (following Institutional guidelines and Investigator judgment). In all cases blood counts must return to baseline before resuming chemotherapy treatment.

[5] If patients do not experience resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, study treatment will be discontinued.

7.5.2 Other Non-Hematologic Toxicities

Dose modification for other toxicities specified below expected from nab-paclitaxel with gemcitabine regimen occurring ON DAY 1 of any cycle or WITHIN a cycle should be performed according to the following recommendations:

Other Adverse Event	Occurrence ON DAY 1 of Each Cycle	Occurrence WITHIN a Cycle
Grade 0, 1 or 2 toxicity including Grade 3 alopecia and Grade 3 nausea/vomiting[1]	Same as Day 1 of previous cycle except for Grade 2 cutaneous toxicity.[2]	Same as Day 1 of the ongoing cycle except for Grade 2 cutaneous toxicity.[2]
Grade 3 Toxicity (except for Grade 3 nausea/vomiting/diarrhea/mucositis, alopecia, cutaneous toxicity and neuropathy)[1,2,3,5]	Decrease dose of both nab-paclitaxel and gemcitabine to the next lower Dose Level.	Hold either nab-paclitaxel and/or gemcitabine until resolution of toxicity to ≤ Grade 1. Then resume treatment with both drugs at the next lower Dose Level.
Grade 4 Toxicity[1,2,3,4,5] (except for Grade 4 diarrhea/mucositis, pulmonary embolism, cutaneous toxicity and neuropathy)	Hold either nab-paclitaxel and/or gemcitabine depending on the type of non-hematologic toxicity and the judgment of the Physician/Investigator. Treatment discontinuation depending on the judgment of the Investigator.	
Dose Held in 2 Previous Consecutive Cycles	Decrease gemcitabine dose to next lower Dose Level and continue throughout the rest of treatment	
Grade 3-4 Diarrhea/Mucositis[5]	Hold dosing with both nab-paclitaxel and gemcitabine until improvement to ≤ Grade 1 and resume both nab-paclitaxel and gemcitabine at next lower Dose Level.	
Interstitial Pneumonitis (any Grade)	Discontinue study treatment.	

[1] For treatment of Grade 3-4 nausea/vomiting, Initial antiemetic prophylaxis is recommended with a 5HT3 agent (PO or IV) in combination with dexamethasone 8 or 10 mg (PO or IV) prior to administration of gemcitabine to be continued at 4 mg BID or TID for 3-4 days at the Investigator's discretion. Institutional guidelines and Investigator's recommendations should be followed for breakthrough antiemetic management. BBI-608 dosing modification as outlined in Section 7.4 may be appropriate depending on the judgment of the Investigator.

[2] Grade 2 or 3 cutaneous toxicity on Day 1 of any cycle requires reduction of both nab-paclitaxel and gemcitabine to the next lower Dose Level. If Grade 2-3 cutaneous toxicity recurs despite dose reduction, treatment should be discontinued.

[3] For Grade ≥ 3 neuropathy, nab-paclitaxel treatment should be held and gemcitabine may be continued. Nab-paclitaxel treatment may be resumed at next lower level if neuropathy improves to ≤ Grade 1. Discontinuation of treatment with nab-paclitaxel is recommended in cases of peripheral neuropathy resulting in > 21 day delay in nab-paclitaxel administration unless not deemed appropriate in the judgment of the Investigator.

[4] Except for mild or asymptomatic pulmonary embolism treated with low-molecular-weight heparin without interruption of therapy. Moderate to severe pulmonary embolism will require permanent discontinuation of treatment.

[5] For initial treatment of Grade 3-4 diarrhea/mucositis BBI-608 dosing modification may be initiated as per Section 7.4 prior to modification of backbone chemotherapy dosing.

When laboratory parameters or adverse events indicate that either or both nab-paclitaxel and/or gemcitabine infusions should be delayed, the infusions scheduled for that day are not given. The infusions will be considered skipped and not made up. The next infusion will be administered on the following scheduled infusion day if the toxicity is resolved to an acceptable level. Laboratory parameters should be evaluated prior to the next scheduled infusion and actions taken according to the protocol parameters.

If toxicity is thought by the Investigator to be related to both BBI-608 and nab-paclitaxel and

gemcitabine, then the dose modification rules for both treatment regimens should be followed.

If either gemcitabine and/or nab-paclitaxel is/are held or discontinued for toxicities solely related to gemcitabine and/or nab-paclitaxel, BBI-608 therapy may be continued until another discontinuation criterion for stopping therapy is met with the Sponsor's approval, if it is believed to be in the patient's best interest by the investigator and patient, and with the patient's informed consent.

If BBI-608 is permanently discontinued due to toxicity, nab-paclitaxel and gemcitabine therapy may be continued until another discontinuation criterion for stopping therapy is met.

7.6 BLINDING/UNBLINDING

This is an open label study. The primary endpoint of this study is overall survival, the assessment of which is unlikely to be impacted by the open-label nature of the study.

However, to comply with ICH E6 (R2) Guideline for Good Clinical Practice (2016) recommending the blinded review of planned analyses [http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf], and to minimize the risk of any potential bias in the interim and final analyses, a blinding plan was implemented by the Sponsor and by the CRO to maximize the integrity of the study. The Sponsor blinding plan outlines the internal communication processes, data access levels, and firewalls that will be utilized to achieve study blinding internally.

7.7 PATIENT MONITORING

For the duration that patients are on study therapy, adverse event monitoring will be done continuously. Patients will be evaluated for adverse events at each visit, and are to be instructed to call their physician to report any adverse events between visits.

7.8 CONCOMITANT MEDICATIONS/PROCEDURES

7.8.1 Permitted Treatments

All information regarding concomitant treatments (medications or procedures) must be recorded on the patient's CRF (including the name of the medication or procedure and duration of treatment).

Palliative and supportive care is permitted for disease-related symptoms for all patients.

All palliative and supportive care measures may be administered to patients in any study arm at the Investigator's discretion. Incident palliative radiotherapy is permitted in any study arm while on study, but requirement of radiation to the target lesion(s) will qualify the patient as having disease progression.

Overall, CYP isoenzymes have an insignificant role in the biotransformation of BBI-608. The CYP P450 isoform 1A2 is the predominant isoform involved in the drug's metabolism. Although the following drugs are permitted while on study treatment, all reasonable measures should be done to avoid use of drugs that are strong inhibitors of CYP1A2 unless there is medical necessity for their use.

Strong CYP1A2 inhibitors include:

- Ciprofloxacin and other fluoroquinolones
- Fluvoxamine
- Enoxacin
- Zafirlukast

Investigators may refer to the Investigator Brochure for additional information.

Patients who require use of concomitant medications metabolized by the CYP1A2, 2D6, 2C19, 3A4 and 2C9 enzymes should be monitored, as per drug product label, as use of BBI-608 can inhibit the abovementioned CYP enzymes leading to increased drug concentrations of the enzyme metabolites.

In addition, nab-paclitaxel is metabolized by CYP2C8 and CYP3A4; caution should be exercised when administering with drugs which are CYP2C8 or CYP3A4 inducers or inhibitors, e.g. amiodarone, cyclosporine, grapefruit juice, simvastatin etc.

7.8.2 Non-Permitted Treatments

Concurrent chemotherapy, hormonal therapy (except corticosteroids), immunotherapy, biologic therapy OR other experimental agents should not be given to study patients while on protocol treatment.

7.9 DURATION OF THERAPY

Patients may continue to receive protocol therapy as long as they have not experienced any adverse events requiring permanent discontinuation of protocol treatment, have not demonstrated disease progression based on RECIST 1.1 criteria, it is believed to be in the patient's best interest by the investigator and patient, or until February 28th, 2020, whichever occurs first. For details concerning toxicity, please consult sections 7.3, 7.4 and 7.5. For a complete list of general criteria for stopping study treatment, please see section 11.0.

Following disease progression based on RECIST 1.1 criteria, patients will permanently discontinue treatment with nab-paclitaxel and gemcitabine, but may continue BBI-608 treatment with the Sponsor's approval for as long as in the opinion of the investigator and patient that it is believed to be in the patient's best interest and with the patient's informed consent, until February 28th, 2020 or the following requirements are met:

1. Patient does not demonstrate a clinically apparent decline in performance status.
2. Patient does not demonstrate clinically significant worsening of disease related symptoms.
3. Patient does not have any new radiographic findings to warrant emergent intervention to prevent morbidity (for example, impending cord compression).
4. Patient demonstrates a tolerable toxicity profile with BBI-608 administration.

7.10 PATIENT COMPLIANCE

Treatment compliance for BBI-608 is defined as the ratio, expressed as a percentage, of the number of BBI-608 capsules taken by a patient over the course of a time interval to the number of capsules

intended to be taken over that same time interval.

Treatment compliance for nab-paclitaxel with gemcitabine is defined as the ratio, expressed as a percentage, of the amount of each of the component drugs administered to a patient (milligrams/m^2) over the course of a time interval to amount of the component IV drug intended to be administered over that same time interval.

Treatment compliance in all study arms will be monitored by drug accountability, as well as the monitoring of patient-reported compliance.

8.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

Evaluations will be performed at different intervals throughout the study. If dose delays occur for any reason on the study, other study assessments, including assessment by physician and QoL questionnaires, will not be delayed, but should continue at the time indicated from randomization.

8.1 EVALUATION DURING PROTOCOL TREATMENT

Investigations		Timing
Patient history and Evaluation	• Physical examination • Vital signs (temperature, heart rate, respiratory rate, blood pressure, O_2 saturation on room air) • ECOG Performance status • Concurrent medication list • Weight	Day 1 of every 28 day study cycle, starting with Cycle 2 (+/-3 days) or within 72 hours prior to each nab-paclitaxel with gemcitabine infusion
Hematology	• CBC + differential, Platelet count	Days 1, 8 and 15 of every 28 day study cycle starting with Cycle 1 (+/-3 days) (Hematology investigations should be performed within 72 hours prior to Day 1 of each study cycle, or within 72 hours prior to each nab-paclitaxel with gemcitabine infusion)
Biochemistry	• Creatinine, Total Bilirubin, AST, ALT, Alkaline Phosphatase, LDH, Albumin, Sodium, Potassium, Magnesium, Phosphate, BUN (blood urea nitrogen)	Day 1 of every 28 day study cycle, starting with Cycle 1 (+/-3 days) (Biochemistry and Urinalysis investigations should be performed within 72 hours prior to Day 1 of each study cycle, or within 72 hours prior to first nab-paclitaxel with gemcitabine infusion of each cycle)
Urinalysis	• Dipstick (including protein, specific gravity, glucose and blood)	
Other Investigations	• Serum or urine pregnancy test [1]	Day 1 of every 28 day study cycle, starting with Cycle 2 (+/-3 days)
Adverse Events [2]	• Adverse Event evaluation must be done at each study visit	Days 1, 8 and 15 of every 28 day study cycle
	• Adverse Event evaluation by phone	On *Run-in Day 2*
Serious Adverse Events [3]	Serious Adverse Event evaluation will be done from the time of informed consent signature and for 30 days following the last dose of protocol therapy.	

Cardiology Assessment	• ECG	Within 2 hours of completion of nab-paclitaxel with gemcitabine infusion on first day of nab-paclitaxel with gemcitabine treatment and as clinically indicated thereafter
Radiology & Imaging	• CT/MRI scan as per baseline assessment with tumor measurement and evaluation by RECIST 1.1 criteria [4, 5]	Every 8 weeks (every 56 days) after randomization[4, 5] (+/-5 days)
Correlative Studies	• Submission of blood samples [6]	At 4 weeks after Cycle 1 Day 1 (+/-3 days)
Sparse PK Collection	• Submission of blood samples to central lab [6]	At Days 8 and 15 of Cycle 1, and at Day 1 of Cycle 2 (corresponding to the 2nd, 3rd and 4th nab-paclitaxel with gemcitabine infusion days)
Quality of Life	• EORTC QLQ-C30[7]	At 4, 8, 12, 16 and 24 weeks after Cycle 1 Day 1 (+/- 3 days)
Nab-paclitaxel with gemcitabine Administration	• IV nab-paclitaxel with gemcitabine infusion	Days 1, 8 and 15 of every 4 week (28 day) study cycle, starting with Cycle 1 (+/-3 days)

[1] In women of childbearing potential only a negative pregnancy test must be demonstrated every 4 weeks until 4 weeks after the administration of the final dose of protocol therapy. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG.

[2] Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix IV). Adverse event assessment by phone on *Run-in day 2* is only applicable to patients receiving BBI-608.

[3] Serious adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix IV).

[4] The same method of assessment and the same technique should be used to identify and report each lesion at baseline and at reassessment during treatment. Tumor evaluations will continue until progressive disease is documented (as described in section 9.0). For patients who remain on protocol therapy after objective disease progression has been documented, no further imaging assessments are mandated, but where these occur as a component of care, tumor measurements and assessment must be reported.

[5] Copies of imaging assessments may be requested.

[6] Details for collection, processing, storing and shipping these samples will be provided in a separate procedure manual.

[7] To be completed in clinic. Questionnaires should be completed prior to any interactions with clinical team to avoid any influence.

8.2 EVALUATION AFTER PERMANENT PROTOCOL TREATMENT DISCONTINUATION

Investigations		Timing
Patient History and Evaluation	• Physical Examination • Vital signs (temperature, heart rate, respiratory rate, blood pressure, O_2 saturation on room air) • Weight + ECOG Performance status • Subsequent cancer therapy[1] • Concurrent medication list	At the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days. (+/- 3 days)
Adverse Events [2]	• Adverse Event evaluation[2]	
Serious Adverse Events [3]	Serious Adverse Event evaluation will be done from the time of informed consent signature and for 30 days following the last dose of protocol therapy.	
Overall Survival	• Assess for survival of patient [4]	Starting at the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days, every 4 weeks thereafter for 6 months, then every 3 months thereafter. (+/- 7 days)
Other Investigations	• Serum or urine pregnancy test [5]	At the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days (+/- 3 days)
Hematology	• CBC + differential, Platelet count	
Biochemistry	• Creatinine, Total Bilirubin, AST, ALT, Alkaline Phosphatase, LDH, Albumin, Sodium, Potassium, Magnesium, Phosphate, BUN (blood urea nitrogen)	
Urinalysis	• Dipstick (including protein, specific gravity, glucose and blood)	
Cardiology Assessment	• ECG	At the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days (+/- 3 days)
Radiology & Imaging	• CT/MRI scan as per baseline assessment with tumor measurement and evaluation by RECIST 1.1 criteria [6]	Every 8 weeks (56 days) after randomization until objective disease progression is documented.[6] (+/- 5 days)
Correlative studies	• Submission of blood samples[7]	At first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days (+/- 3 days)
Quality of Life	• EORTC QLQ-C30[8]	At first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days (+/- 3 days)

[1] After permanent protocol treatment discontinuation of nab-paclitaxel and gemcitabine and BBI-608, Physical examination, vital signs, ECOG status and subsequent cancer treatment will be recorded at the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days (+/- 3 days). Subsequent cancer treatment will be captured until end of study.

[2] Adverse events related to protocol treatment will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix IV). Adverse events relevant to cancer or to subsequent cancer treatments will not be captured. Attribution of adverse events will continue to be recorded following treatment discontinuation.

[3] Serious adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix IV).

[4] Post permanent study treatment discontinuation, overall survival status will be monitored on a monthly basis for 6 months and then every 3 months thereafter until death, the study closes or 3 years have elapsed since subject discontinuation from treatment. In the event that patient is unable to attend clinic, post-progression follow-up may be by means of telephone contact.

[5] In women of childbearing potential only. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG.

[6] The same method of assessment and the same technique should be used to identify and report each lesion at baseline and at reassessment during treatment. Tumor evaluations will continue until progressive disease is documented (as described in section 9.0). If a patient discontinues protocol treatment for a reason other than objective progression, every effort should be made to obtain this assessment on the same schedule until progression is observed. It is recommended that subsequent therapy not be instituted until disease progression is documented. If a patient starts a new anti-cancer therapy prior to disease progression, then repeat imaging and tumor response assessments should be discontinued.

[7] Details for collection, processing, storing and shipping these samples will be provided in a separate procedure manual. The samples will be collected only if the patient discontinues protocol treatment prior to 4 weeks of therapy with nab-paclitaxel with gemcitabine with or without BBI-608.

[8] To be completed in clinic. Questionnaires should be completed prior to any interactions with clinical team to avoid any influence. Questionnaire will be collected in the post-treatment discontinuation period only if the patient discontinues nab-paclitaxel and gemcitabine with or without BBI-608 protocol treatment prior to 24 weeks of therapy and has an ECOG PS of less than 4 and has not been hospitalized for end of life care.

9.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

9.1 DEFINITIONS

9.1.1 Evaluable for Adverse Events

All patients who have received at least one dose of study drug (BBI-608 or Nab-Paclitaxel or Gemcitabine) will be evaluable for adverse events from the time of their first dose.

9.1.2 Evaluable for OS

All randomized patients will be included in the analysis of OS, which is defined as the time interval between the date of randomization and the date of death from any cause. Patients who are still alive at the time of the final analysis, or who have become lost to follow-up will be censored at their last date known to be alive.

9.1.3 Evaluable for PFS

All randomized patients will be included in the analysis of PFS, which is defined as the time interval between the date of randomization and the date of objective disease progression or death, whichever comes first. If neither event has been observed, then the patient will be censored at the date of the last tumor assessment.

Disease progression is defined as objective progression per RECIST 1.1 *(Eisenhauer, 2009)*. It is required to perform, whenever possible, a radiological confirmation of the clinical suspicion of tumor progression. In the situation where there is clinical suspicion of progression but objective progression cannot be determined per RECIST 1.1, disease is defined as clinical deterioration without objective evidence of progression.

The date of disease progression is defined as the date when the criteria for objective progression are first met.

9.1.4 Evaluable for DCR

Patients who have measurable disease by RECIST 1.1 at randomization will be included in the analysis of DCR which is defined as a composite of Stable Disease, Partial Response and Complete Response as classified according to the definitions set out below *(Eisenhauer, 2009)*. For patients who discontinue protocol therapy prior to their first objective assessment of response, it is imperative that an objective response assessment be undertaken as close to the protocol specified schedule as possible.

9.1.5 Evaluable for ORR

Patients with measurable disease by RECIST 1.1 at randomization will be included in the analysis of ORR which is defined as a composite of Partial Response and Complete Response as classified according to the definitions set out below *(Eisenhauer, 2009).* For patients who discontinue protocol therapy prior to their first objective assessment of response, it is imperative that an objective response assessment be undertaken as close to the protocol specified schedule as possible.

9.1.6 Evaluable for QoL Assessment

All patients who have completed the baseline quality of life questionnaire and at least one other QoL questionnaire are evaluable.

9.2 RESPONSE AND EVALUATION ENDPOINTS

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST committee.

9.2.1 Measurable Disease

Measurable *tumor lesions* are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray and as ≥ 10 mm with CT scan, or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

9.2.2 Non-Measurable Disease

All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

9.2.3 Target Lesions

When more than one measurable tumor lesion is present at baseline all lesions up to *a maximum of 5 lesions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the *short* axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed (see 10.2.4). At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

9.2.4 Non-Target Lesions

All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

9.2.5 Response

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of *target* and *non-target*. Pathological lymph nodes must have short axis measures < 10 mm (Note: continue to record the measurement even if < 10 mm and considered CR). Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases *(Eisenhauer, 2009)*) before CR can be accepted.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non-target lesions must be non-PD.

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

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). For patients with on-study tumor assessments with questionable findings of new lesions, such as cases where it is possible that the lesions were present at baseline imaging albeit less visible, the patient may continue treatment (if patient is clinically doing well) for an additional 4-8 weeks, until the next scan which will either confirm presence of a new lesion finding or exclude it. In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment or where the tumor burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Table 2: Integration of Target, non-Target and New Lesions into Response Assessment

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
Target Lesions ± Non Target Lesions				
CR	CR	No	CR	Tumor nodes < 10mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	Documentation at least once ≥ 6 wks. from baseline
Not all evaluated	Non-PD	No	NE	

PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non-Target Lesions ONLY				
N/A	CR	No	CR	Tumor nodes < 10mm
N/A	Non-CR/non-PD	No	Non-CR/non-PD	
N/A	Not all evaluated	No	NE	
N/A	Unequivocal PD	Any	PD	
N/A	Any	Yes	PD	
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without radiological progression having been observed at that time should be reported as "symptomatic deterioration". This is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.				

9.3 RESPONSE DURATION

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

9.4 STABLE DISEASE DURATION

Stable disease duration will be measured from the time of randomization until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

9.5 METHODS OF MEASUREMENT

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

Additionally, for optimal tumor assessment scanning options are listed below in the decreasing order of preference:

Order of Preference	Scanning Option
1	Chest-Abdomen-Pelvis CT with oral and I.V. contrast
2	Chest CT without I.V. contrast PLUS MRI Abdomen-Pelvis with oral and I.V. contrast[1]
3	Chest-Abdomen-Pelvis CT with oral contrast[2]

[1] If Iodine contrast media is medically contraindicated.

[2] If Iodine contrast media is medically contraindicated and MRI cannot be performed.

9.5.1 Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm as assessed using callipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

9.5.2 Chest X-ray

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

9.5.3 CT/MRI

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Other specialized imaging or other techniques may also be appropriate for individual case *(Eisenhauer, 2009)*. For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

9.5.4 Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

9.5.5 Endoscopy/Laparoscopy

The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

9.5.6 Histology

These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

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.

10.0 SERIOUS ADVERSE EVENT REPORTING

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for Adverse Event (AE) and Serious Adverse Event (SAE) reporting (version can be found in Appendix IV).

All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. All SAEs must be reported to the Sponsor within 24 hours (Section 10.2).

10.1 DEFINITION OF A PROTOCOL REPORTABLE SERIOUS ADVERSE EVENT

All serious adverse events must be reported in an expedited manner (see Section 10.2 for reporting instructions). These include events occurring from the time the patient signs informed consent until 30 days after last protocol treatment administration. Determination of relationship between the event and study drug should be made by a qualified physician Investigator.

A serious adverse event (SAE) is any adverse event that at any dose:

- results in death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration);
- results in persistent or significant disability or incapacity;
- is a congenital anomaly/birth defect.
- is an important medical event.

Note: clinically significant test results should be recorded on the AE CRF using the appropriate CTCAE description and grading scale.

10.2 SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS

SAE reporting will commence following the signature of the informed consent and continue for 30 days following the last dose of BBI-608 and/or Nab-Paclitaxel and/or Gemcitabine. Any SAE occurring following patient signature of informed consent and prior to patient randomization must be submitted to the Sponsor/Sponsor Designee for review and confirmation of randomization eligibility prior to patient randomization and/or study drug administration, even if the patient completely recovered from the SAE. Additionally, any SAE occurring at any time following administration of the final dose of protocol treatment that is suspected to be related to study treatment must be reported.

All SAEs must be reported using the SAE Report Form for this trial.

Within 24 hours: Submit Initial Serious Adverse Event Report

Within 7 days: Submit Follow-up Serious Adverse Event Report updated with as much detail as possible.

Detailed instructions for the submission of SAE Reports will be provided separately.

10.3 PROCEDURES IN CASE OF AN OVERDOSE

Use of BBI-608 in doses in excess of that specified in the protocol should be reported in the following manner:

If an adverse event(s) is associated with ("results from") the overdose of BBI-608, the overdose and adverse event are reported on the SAE Report Form, even if no other criteria for serious are met. The SAE Report Form should be submitted within 24 hours. The overdose should also be recorded on the relevant AE form in the eCRF using the term "accidental or intentional overdose with adverse effect."

If the overdose of BBI-608 is not associated with an adverse event, the overdose is reported as a non-serious AE, on the relevant AE form in the eCRF within 24 hours, using the event term "accidental or intentional overdose without adverse effect." The Clinical Research Associate responsible for the investigational center should also be notified of the event within 24 hours.

Investigators/site personnel are to consult the local, approved product labels for nab-paclitaxel with gemcitabine treatment regimen for guidance on the definition of an overdose of these agents as well as for guidance on reporting of any AE or SAE associated with overdose of either nab-paclitaxel or gemcitabine. Overdose of either nab-paclitaxel or gemcitabine should also be reported to the Sponsor in accordance with overdose reporting guidelines above.

10.4 OTHER PROTOCOL REPORTABLE EVENTS – PREGNANCY/EXPOSURE REPORTING

WOCBP may be enrolled in this clinical trial. WOCBP are defined as women who have had a menstrual period during the last year and have not had a hysterectomy. Precautions are required to be taken to prevent pregnancy during the clinical trial when the research population includes WOCBP. This includes pregnancy testing, use of effective methods of birth control, and pregnancy as an exclusion factor. The trial sample informed consent form includes *the potential for unidentified risks to the embryo/fetus.* It also includes general information on pregnancy prevention and the required minimum period during which birth control must be utilized.

10.4.1 Pregnancy Prevention

WOCBP and males who are enrolled in the trial must be informed of the requirement to use contraception as outlined in the eligibility criteria (Sections 4.1 and 4.2). Investigators are advised to inform the female partners of male participants when appropriate and compliant with local policy.

A highly effective method of birth control is defined as those which result in a failure rate of <1% per year when used consistently and correctly.

10.4.2 Pregnancy Occurring in WOCBP Exposed to Study Agent

Any female participant who becomes pregnant during the course of the trial should be instructed to

stop taking study medication immediately.

The Investigator should provide counselling and discuss the risks and possible side effects to the embryo/fetus from BBI-608 and nab-paclitaxel with gemcitabine. Monitoring should continue until conclusion of the pregnancy. The same should occur for female partners of a male participant, or any female exposed to BBI-608 when appropriate and compliant with local policy.

10.4.3 Pregnancy/Exposure Reporting

The Investigator is required to report to the sponsor any pregnancy where the embryo/fetus could have been exposed to BBI-608. This means pregnancies occurring in female participants, female partners of male participants, or females exposed through direct contact with the agent during their pregnancy (for example, environmental exposure involving direct contact with the agent). Pregnancies occurring until 30 days in female patients and until 90 days in partners of male patients, after the completion of BBI-608 must also be reported. Pregnancies occurring until 180 days in female patients and until 180 days in partners of male patients, after the completion of nab-paclitaxel and/or gemcitabine must also be reported.

The Investigator is required to inform the Sponsor within 24 hours of learning of the pregnancy using the SAE reporting form appropriate for the trial as indicated above. In the Adverse Event column please enter the following: “pregnancy, puerperium and perinatal conditions – other, specify” (fetal exposure). Please note that the patient identification number must correspond to the participant in the main trial. Specifically, in the case of pregnancy in the female partner of a male participant, the male participant’s patient identification number should be used for reporting purposes.

The SAE form must be updated to reflect the outcome of the pregnancy. For example:

- “pregnancy, puerperium and perinatal conditions – other, specify” (normal live birth),
- “pregnancy, puerperium and perinatal conditions – other, specify” (therapeutic abortion), or
- another term under "pregnancy, puerperium and perinatal conditions" as applicable.

Information on the medical history of the parents that may relate to assessing any potential fetal outcomes is requested, *as is information on the health of the newborn*. The narrative section of the SAE form should be used to communicate all relevant information pertaining to the pregnancy.

10.5 RESPONSIBILITY FOR REPORTING SERIOUS ADVERSE EVENTS TO REGULATORY AGENCIES

Boston Biomedical, or the delegated CRO, will provide expedited reports of SAEs to FDA and other applicable regulatory authorities, for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are related to treatment BBI-608 (suspected unexpected serious adverse reaction [SUSAR]):

- **Unexpected** adverse events are those which are not consistent in either nature or severity with the reference safety information contained in the Investigator’s Brochure
- Adverse events considered **related to protocol treatment** are those events which have a reasonable possibility of being related to BBI-608.

Boston Biomedical will determine which SAEs meet the criteria for regulatory reporting.

10.6 REPORTING SAFETY REPORTS TO INVESTIGATORS

Boston Biomedical, or the delegated CRO, will notify Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial and Safety Updates (SUs) from other clinical trials) that are reportable to regulatory authorities. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment.

11.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING ALL STUDY TREATMENT

11.1 CRITERIA FOR DISCONTINUING PROTOCOL TREATMENT

Patients should stop protocol treatment in the following instances:

- Progressive Disease (see section 9.2.5)
- Pregnancy
- Intercurrent illness which would, in the judgement of the Investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy
- Unacceptable toxicity
- Request by the patient

If a patient discontinues protocol treatment for objective progression on nab-paclitaxel and gemcitabine with BBI-608 (Arm 1), the patient together with their investigator, may elect to continue treatment with BBI-608 in monotherapy with the Sponsor's approval, provided no discontinuation criterion involving BBI-608-related adverse events is met, it is believed to be in the patient's best interest by the investigator and patient, and with the patient's informed consent.

If a patient permanently discontinues protocol treatment for a reason other than objective progression, every effort should be made to obtain tumor evaluations on the same schedule until progression is observed.

Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

11.2 DURATION OF PROTOCOL TREATMENT

Patients may continue to receive protocol treatment as long as they have not experienced any adverse events requiring permanent discontinuation of study medication and have not demonstrated disease progression based on RECIST criteria, if it is believed to be in the patient's best interest or until February 28th, 2020, when the study is planned for completion, whichever occurs first.

There will be no cross-over to BBI-608-containing study arm in combination with nab-paclitaxel and gemcitabine (Arm 1) from the nab-paclitaxel and gemcitabine only study arm (Arm 2) and vice versa.

11.3 THERAPY AFTER PROTOCOL TREATMENT IS PERMANENTLY DISCONTINUED

Treatment after all protocol therapy has been permanently discontinued is at the discretion of the Investigator. Information on post-study anti-cancer treatment will be collected in this study.

11.4 FOLLOW-UP OFF PROTOCOL TREATMENT

Follow-up will continue after treatment completion according to the plan described in the protocol (see Section 8.2). Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients permanently discontinue protocol treatment prematurely and/or no longer attend the participating institution.

12.0 CENTRAL REVIEW PROCEDURES, TISSUE COLLECTION, AND CORRELATIVE STUDIES

12.1 CENTRAL RADIOLOGY REVIEW

There will be no central radiology review for this study.

12.2 CENTRAL PATHOLOGY REVIEW

There will be no central pathology review for this study.

12.3 TISSUE COLLECTION

Protocol-Mandated Correlative Studies:

The submission of a representative diagnostic tumor tissue and of a blood sample for correlative studies defined in Section 13.6 (Correlative Studies) is mandatory for participation in this trial (although submission of the tissue does not have to occur prior to randomization). Where local center regulations prohibit submission of blocks of tumor tissue, two 2 mm cores of tumor from the block and 5-20 unstained slides of representative tumor tissue are requested. Where 2 mm cores of tumor from the block are unavailable, 5-20 unstained slides of representative tumor tissue are requested. Where no previously resected or biopsied tumor tissue exists, on the approval of the Sponsor/designated CRO, the patient may still be considered eligible for the study.

After patient consent, blood sample and paraffin tumor blocks will be the preferred tissue material to collect. If tumor blocks are unavailable, then two 2 mm cores of tumor from the block and 5-20 specimen slides are preferred. If two 2 mm cores of tumor from the block are unavailable, 5-20 specimen slides will be acceptable. If, at any time, the submitting hospital requires the block to be returned for medical or legal concerns, it will be returned by courier on request.

Samples will be used for research purposes only and will not be sold. Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of randomization to the trial. Material issued to researchers will be anonymous and only identified by a coded number.

Testing for hereditary genetic defects predisposing to malignant disease will not be carried out without the expressed consent of the patient.

All patients on whom a blood sample and/or diagnostic tumor block is collected will be aware of this retrieval and will have given their consent.

12.4 SPARSE PHARMACOKINETIC PLASMA SAMPLE COLLECTION – NAB-PACLITAXEL WITH GEMCITABINE AND BBI-608 (ARM 1 ONLY)

Plasma samples for sparse pharmacokinetics (PK) analysis will be obtained from all patients randomized to nab-paclitaxel with gemcitabine and BBI-608 study arm (Arm 1) at the study visits occurring on Days 8 and 15 of Cycle 1, and Day 1 of Cycle 2 (corresponding to nab-paclitaxel with

gemcitabine infusion days). Patients randomized to nab-paclitaxel and gemcitabine arm alone (Arm 2) will not undergo collection of blood for sparse PK analysis.

Day 8 (Cycle 1) Study Visit:
The Day 8 (Cycle 1) visit should be scheduled prior to 10 AM. On the day of this visit, patients should be instructed to wait to take their first daily dose of BBI-608 until they arrive in clinic. After arrival in the clinic, but approximately 5 minutes prior to administration of the first daily dose of BBI-608, a plasma sample will be obtained. Nab-paclitaxel infusion will be started approximately 2 hours after BBI-608 administration. A second plasma sample will be obtained within 60-180 minutes after the start of nab-paclitaxel infusion. A third plasma sample will be obtained within 240-480 minutes after the start of nab-paclitaxel infusion.

Day 15 (Cycle 1) Study Visit:
The Day 15 (Cycle 1) visit should be scheduled prior to 10 AM. On the day of this visit, patients should be instructed to take their first daily dose of BBI-608 until they arrive in clinic. After arrival in the clinic, but approximately 5 minutes prior to administration of the first daily dose of BBI-608, a plasma sample will be obtained. Nab-paclitaxel infusion will be started approximately 2 hours after BBI-608 administration. A second plasma sample will be obtained within 60-180 minutes after the start of nab-paclitaxel infusion. A third plasma sample will be obtained within 240-480 minutes after the start of nab-paclitaxel infusion.

Day 1 (Cycle 2) Study Visit:
The Day 1 (Cycle 2) visit should be scheduled prior to 10 AM. On the day of this visit, patients should be instructed to wait to take their first daily dose of BBI-608 until they arrive in clinic. After arrival in the clinic, but approximately 5 minutes prior to administration of the first daily dose of BBI-608, a plasma sample will be obtained. Nab-paclitaxel infusion will be started approximately 2 hours after BBI-608 administration. A second plasma sample will be obtained within 60-180 minutes after the start of nab-paclitaxel infusion. A third plasma sample will be obtained within 240-480 minutes after the start of nab-paclitaxel infusion.

For all days during which a plasma sample is obtained for PK analysis, the precise time of all doses of BBI-608 (on the day of sampling and the day prior), the precise time of the initiation of nab-paclitaxel and gemcitabine administration, and the precise time of all PK sampling must be captured.

Samples will be processed, stored and shipped according to the instructions provided in the separate Sparse PK sampling laboratory manual for this study.

13.0 STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

13.1 OBJECTIVES AND DESIGN

The primary objective of this study is to assess the effect of orally administered BBI-608 plus weekly nab-paclitaxel with gemcitabine (Arm 1), in comparison to weekly nab-paclitaxel with gemcitabine (Arm 2) on the Overall Survival (OS) in patients with metastatic PDAC.

Key secondary objectives for this study include comparisons of PFS in the general population, DCR in the general population and ORR in the general population. Other secondary objectives include Adverse Events and Quality of Life Assessment in the general population between the two treatment arms.

This is a multi-center, prospective, open-label, randomized Phase III trial. Patients will be randomized to receive either BBI-608 plus weekly nab-paclitaxel with gemcitabine, or weekly nab-paclitaxel with gemcitabine in a 1:1 ratio and will be stratified by geographical region (North America/Western Europe/Australia vs. Japan/Korea vs. Rest of the World), ECOG performance status (ECOG 0 versus ECOG 1), and presence of liver metastases (yes versus no).

13.2 STUDY ENDPOINTS AND ANALYSIS

13.2.1 Primary Endpoint

OS in the General Study Population

Unless otherwise specified, all efficacy analyses will be based on the Primary Analysis Set, which includes all randomized patients. Patients will be analyzed as randomized. As a sensitivity analysis, the Per Protocol population will also be analyzed for key efficacy endpoints.

Overall Survival in the general study population, the primary endpoint of this study, is defined as the time from randomization to death from any cause. Patients who are alive at the time of the final analysis or who have become lost to follow-up will be censored at their last date known to be alive. Patients will be analyzed in the arm to which they are randomized regardless of the treatment they received (intent-to-treat analysis). The survival experience of patients in both treatment groups will be summarized by the Kaplan-Meier method and compared primarily by a stratified log-rank test adjusting for stratification variables at randomization.

Sensitivity analyses based on stratified Cox proportional hazards model will also be performed. These sensitivity analyses are not included in the multiplicity adjustment for secondary outcomes detailed below and, as such, do not control for type I error. Geographical region (North America/Western Europe/Australia vs. Japan/Korea vs. Rest of the World), ECOG performance status (ECOG 0 *versus* ECOG 1), and presence of liver metastases (yes *versus* no) will be the stratification factors to define

the stratified Cox proportional hazards model.

Subgroup analysis and the corresponding forest plot analysis may be performed using the stratification factors mentioned above as well as the following factors:

- Primary tumor location (head *versus* other)
- Level of CA19-9 (normal *versus* <59 x ULN *versus* ≥59 x ULN)
- Age (< 65 *versus* ≥ 65)
- Sex (male *versus* female)
- Number of metastatic sites at baseline (1 *versus* ≥ 2)
- Race (white, black, Asian, other)
- Country (Canada, USA, Europe, others)

13.2.2 Key Secondary Endpoints

The following secondary outcomes will be assessed.

PFS in the General Study Population
PFS in the general study population is defined as the time from randomization to the first objective documentation of disease progression or death due to any cause. If a patient has not progressed or died at the time of final analysis, PFS will be censored on the date of the last tumor assessment. This includes patients who are lost to follow-up or have withdrawn consent.

DCR in the General Study Population
DCR is defined as the proportion of patients with a documented complete response, partial response, and stable disease (CR + PR + SD) based on RECIST 1.1. The primary estimate of DCR will be based on patients with measurable disease by RECIST 1.1 at randomization.

ORR in the General Study Population
ORR is defined as the proportion of patients with a documented complete response and partial response (CR + PR) based on RECIST 1.1. The primary estimate for ORR will be based on patients with measurable disease by RECIST 1.1 at randomization.

13.2.3 Other Secondary Endpoints

Safety Analysis
All patients who have received at least one dose of study drug will be included in the safety analysis. The incidence of adverse events will be summarized by type of adverse event and severity using the NCI Common Terminology Criteria for Adverse Events Version 4.0. A Fisher's exact test may be used to compare adverse events between the two arms.

QoL Analysis
The QoL of patients will be assessed using EORTC QLQ-30 while the patient remains on BBI-608 as per Section 8.1. The EORTC QLQ-30 is a self-administered cancer specific questionnaire with multi-dimensional scales. It consists of both multi-item scales and single item measures, including five functional domains, a global quality of life domain, three symptom domains, and six single items. Scoring of the EORTC QLQ-30 data will be completed following the procedures recommended by the

EORTC Study Group on Quality of Life. For each domain or single item measure a linear transformation will be applied to standardize the raw score to range between 0 and 100. The quality of life data will be analyzed to look for statistically and clinically significant differences between the BBI-608 plus nab-paclitaxel with gemcitabine *versus* nab-paclitaxel with gemcitabine groups. Questionnaire compliance rates will be ascertained for each group at each measurement time point. Mean baseline scores for each subscale and summary scores will be calculated.

The endpoints in QoL analysis are the mean EORTC QLQ-C30 QoL change scores from baseline at time 2 (~8 weeks from Cycle 1 Day 1) and time 4 (~16 weeks from Cycle 1 Day 1) for the physical function and global health status/quality of life subscale scores. Wilcoxon tests will be used to compare the difference at each of these two time points between two treatment arms for each of these two subscales. The proportion of patients in either arm with at least a minimum of 10 unit(s) deterioration in change scores at both 8 and 16 weeks from Cycle 1 Day 1 will be compared by means of Fisher's exact test.

13.2.4 Exploratory Endpoints

OS in the Predefined Biomarker-positive Population
OS in the general predefined biomarker-positive population is defined as the time from randomization to death due to any cause. If a patient has not died at the time of final analysis, OS will be censored on the date of the last follow up assessment. This includes patients who are lost to follow-up or have withdrawn consent.

PFS in the Predefined Biomarker-positive Population
PFS in the predefined biomarker-positive population is defined as the time from randomization to the first objective documentation of disease progression or death due to any cause. If a patient has not progressed or died at the time of final analysis, PFS will be censored on the date of the last tumor assessment. This includes patients who are lost to follow-up or have withdrawn consent.

ORR and DCR in the Predefined Biomarker-positive Population
ORR in the predefined biomarker-positive population is defined as the proportion of patients with a documented complete response and partial response (CR + PR) based on RECIST 1.1. The primary estimate for ORR will be based on patients with measurable disease by RECIST 1.1 at randomization. DCR in the predefined biomarker-positive population is defined as the proportion of patients with a documented complete response, partial response, and stable disease (CR + PR + SD) based on RECIST 1.1. The primary estimate of DCR will be based on patients with measurable disease by RECIST 1.1 at randomization.

13.3 SAMPLE SIZE AND DURATION OF STUDY

The primary study endpoint for all patients on the study is OS.

The study is designed to have a power of 90% and a one-sided alpha of 2.5% to detect a 20% reduction in the continuous risk of death (HR 0.80, which corresponds to an increase of median survival from 8.5 to 10.63 months) in the Intention to Treat (ITT) general study population. The 864th event will trigger the final analysis. It is estimated that 864 events will be required to detect a 20% reduction in the risk of death which would be observed by randomizing 1132 patients over 24 months with patient follow up for an additional 12 months, for total study duration of 36 months. It is anticipated that up to 5% dropout rate will occur for the entire study.

The overall power of the study will be approximately 90% after the multiplicity control procedure is considered.

When the required number of events for the primary endpoint has been reached, all randomized patients still alive will continue study follow up through to their deaths.

13.4 SAFETY MONITORING

Adverse events will be monitored on an on-going basis by central review.

13.5 INTERIM ANALYSIS

Prior to this amendment, there was one interim analysis presented to the independent DSMB. Additionally, DSMB reviewed safety data during conduct of the study. The role and responsibility of the DSMB are defined in a separate Charter.

The interim analysis involved a stratified log-rank test. Nominal p-values were based on the Lan-DeMets error spending function using an O'Brien-Fleming stopping boundary in order to preserve the overall one-sided alpha level of 0.025.

The interim analysis was performed when approximately 432 deaths (50% of the required events) were observed. The interim analysis was for futility only, with the futility boundary set at HR $\geq$ 1. Safety data and primary analysis based on approximately 432 events were presented to the DSMB on June 24th, 2019. The DSMB reviewed the results on July 1st, 2019. Based on the recommendation of the DSMB, the Sponsor informed investigators on July 2nd, 2019 that the study would be discontinued due to futility. For patients enrolled to Arm 1, the Sponsor advised that patients stop treatment with BBI-608 but given that no safety concerns were identified by the DSMB, in cases in which a patient appears to be deriving benefit from BBI-608 in the opinion of the investigator and with the patient's informed consent, continuation of protocol therapy was permitted. Patients enrolled to Arm 2 were given the option to continue receiving standard of care therapy within the study.

Patients may continue to receive protocol therapy until a discontinuation criterion is met, if believed to be in the patient's best interest by the investigator and patient, and with the patient's informed consent, or until February 28th, 2020, whichever occurs first.

At study completion, analysis will be conducted for primary endpoint of OS as outlined in Section 13. Additionally, all secondary and exploratory analyses will be performed as outlined in the protocol.

13.6 CORRELATIVE STUDIES

The correlative science component of the CanStem111P trial will include tumor and blood based assays to identify biomarkers of benefit from BBI-608 therapy, as well as biomarkers of BBI-608 resistance. The purpose of these studies is to explore the possible relationship between biomarkers and disease response. The research aims to validate molecular markers such as genes (DNA) and gene products (mRNA or proteins), with measurements of their sequence, post translation modifications or

degree of expression, that can guide the use of appropriate therapeutic treatment regimens. The ultimate goal of identifying molecular markers is to improve subject responses and other measures of clinical benefit by matching an individual subject's tumor diagnostic profile with an anticancer agent that has demonstrated a therapeutic advantage in subjects with a similar diagnostic profile. If such a marker can be identified, the samples and results may also aid in the development of diagnostic devices.

Using data from this and other trials, the relationship between a number of molecular markers associated with the STAT3, β-catenin and other related pathways, and the clinical outcomes with BBI-608 therapy may be explored. Multiple molecular markers in a paraffin-embedded tumor tissue sample can be determined by analyzing RNA and protein in the tissue sample.

In addition to analysis of potential biomarkers of benefit from BBI-608 therapy, an analysis of markers of resistance to BBI-608 will be conducted using blood samples drawn at baseline as well at 4 weeks post initiation of therapy. This analysis may involve SNPs, CYPS, and metabolomics.

Paraffin-embedded tumor specimens, or cores (two 2 mm cores of tumor from the block) and 5-20 unstained slides obtained from paraffin embedded specimens will be required. Where it is not possible to obtain two 2 mm cores of tumor from the block, 5-20 unstained slides of representative tumor tissue are also acceptable. Patients who do not have available archival tissue may enroll on the study with permission of the Sponsor/CRO.

Blood samples will be collected prior to dosing with BBI-608 and then at week 4 while on BBI-608 in combination with nab-paclitaxel and gemcitabine.

The following analysis will be performed to investigate the relationship between endpoints and biomarker levels (e.g. phospho-STAT3, etc):

For each biomarker, Cox Proportional Hazards model will be used to model the relationship between Overall Survival, Progression-Free Survival and duration of response with baseline value of the biomarker. The model will also include assigned treatment, interaction between treatment and biomarker, and will be stratified by baseline ECOG performance status.

For biomarkers with post-baseline measurements, similar analysis will be done with change from baseline of a biomarker as a covariate, for both time points. An additional model that includes prognostic factors may be investigated.

The relationship between the endpoint and binary biomarkers (e.g. baseline phospho-STAT3 status, ß-catenin, etc) will be also examined using the log-rank test, stratified by treatment and baseline ECOG performance status. Subgroup analysis by the status of the binary biomarker may also be performed. The Kaplan-Meier method will be used to describe overall survival, progression-free survival and duration of response by the status of the biomarker (e.g. phospho-STAT3-high vs. phospho-STAT3-low) and by treatment group.

The relationships between the binary response variable (e.g. objective response, DCR) with baseline values of biomarkers as well as with their change from baseline and at week 4 time point during treatment with nab-paclitaxel and gemcitabine with or without BBI-608 will be investigated using logistic regression that includes assigned treatment and biomarker value and treatment-by-biomarker interaction, stratified by baseline ECOG performance status. An additional model that includes prognostic factors may be investigated. The relationship between response and binary biomarkers (e.g.

baseline phospho-STAT3 status or STAT3 status) will also be examined using the CMH test, stratified by treatment and baseline ECOG performance status. Subgroup analysis by the status of the binary biomarker may also be performed.

Exploratory analyses, in addition to those described in this section, such as alternative modeling approaches and analyses of other biomarkers are expected and may be performed. All analyses described in this section are based on availability of data.

13.7 SPARSE PHARMACOKINETIC ANALYSIS

Exploratory analyses will be performed on the bioanalytic data obtained from sparse plasma sampling in order to characterize the population pharmacokinetics of BBI-608. Demographic and pathophysiologic factors that affect plasma concentration of BBI-608 and nab-paclitaxel with gemcitabine in this population of patients with metastatic PDAC will be examined. The exposure-response relationship between clinical and safety endpoints and BBI-608/nab-paclitaxel with gemcitabine exposure will also be examined.

14.0 PUBLICATION

Boston Biomedical, Inc. acknowledges that the Investigator(s) have certain professional responsibilities to report to the scientific community on findings in clinical investigations they conduct. A Principal Investigator shall have the right to publish the results of research performed under this protocol; provided, such publication does not disclose any Confidential Information or trade secrets of Boston Biomedical (other than the Clinical Results).

If the Study is conducted as part of a multi-center protocol, Principal Investigator at each institution agrees not to independently publish their findings except as part of an overall multi-center publication. No other publication is allowed before the primary peer-reviewed scientific publication

The primary author agrees to, prior to submitting a manuscript, abstract, or any other written or oral presentation describing the Results for publication or presentation, forward to Boston Biomedical a copy of the item to be submitted for publication or presentation no less than forty-five (45) days prior to their submission. Upon reasonable request by Boston Biomedical, the primary author agrees to withhold such publication an additional 30 days to permit the preparation and filing of related patent applications. In addition, Boston Biomedical shall have the right to require the primary author to delete from any publication or presentation any Confidential Information (other than the Clinical Results) of Boston Biomedical's and to require that any publication or presentation concerning the Study acknowledge the Sponsor's support.

15.0 RESEARCH OUTSIDE THE TERMS OF THIS PROTOCOL

Boston Biomedical has a legal responsibility to report fully to the regulatory authorities all the results of administration of its investigational drugs.

No investigative procedures other than those described in this protocol shall be undertaken on subjects enrolled in this study (unless required for the care of the subject), without the agreement of the IRB/Ethics Committee and Boston Biomedical. The nature and results of any such procedures must be recorded and reported by a method agreed between Boston Biomedical and the Investigator. The consent of the subjects must be obtained before any such procedures are undertaken.

The investigative drug provided to the Investigator for use under this protocol may not be used for any other purpose, including another study, compassionate use, or personal use.

16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

16.1 REGULATORY CONSIDERATIONS

All institutions must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

The conduct of this trial must comply with local laws and national regulations [e.g. in the United States of America with applicable US FDA Regulations; in Canada with Division 5 of the Canadian Regulations Respecting Food and Drugs (Food and Drugs Act)] relevant to the use of new therapeutic agents in the country of conduct.

16.2 INCLUSIVITY IN RESEARCH

Individuals must not be excluded from participation in clinical trials on the basis of attributes such as culture, religion, race, national or ethnic origin, colour, mental or physical disability (except incapacity), sexual orientation, sex/gender, occupation, ethnicity, income, or criminal record, unless there is a valid reason (i.e. safety) for the exclusion.

In accordance with the Declaration of Helsinki and the Tri-Council Policy Statement (TCPS), vulnerable persons or groups will not be automatically excluded from a clinical trial (except for incompetent persons) if participation in the trial may benefit the patient or a group to which the person belongs.

However, extra protections may be necessary for vulnerable persons or groups. It is the responsibility of the local Investigator and Institutional Review Board (IRB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and IRB should provide special protections for those who are vulnerable to abuse, exploitation or discrimination. As vulnerable populations may be susceptible to coercion or undue influence, it is especially important that informed consent be obtained appropriately.

Centers are expected to ensure compliance with local IRB or institutional policy regarding participation of vulnerable persons/groups. It is the center's responsibility to ensure compliance with all local SOPs.

Persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited to this study. It is the responsibility of the local Investigator to determine the subject's competency, in accordance with applicable local policies and in conjunction with the local IRB (if applicable).

Subjects who were competent at the time of enrollment in the clinical trial but become incompetent during their participation do not automatically have to be removed from the study. When re-consent of the patient is required, Investigators must follow applicable local policies when determining if it is acceptable for a substitute decision maker to be used. The Sponsor will accept re-consent from a substitute decision maker. If this patient subsequently regains capacity, the patient should be re-consented as a condition of continuing participation.

16.3 OBTAINING INFORMED CONSENT

Informed consent will be obtained for each participant/potential participant in this trial, in accordance with ICH-GCP section 4.8. The center is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, the Sponsor may require that participants/potential participants be informed of any new information may impact a participant's/potential participant's willingness to participate in the study.

Based upon applicable guidelines and regulations (Declaration of Helsinki, ICH-GCP), a participating Investigator (as defined on the participants list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. The Sponsor recognizes that in many centers other personnel (as designated on the participants list) also play an important role in this process. In accordance with GCP 4.8.5, it is acceptable for the Principal Investigator to delegate the responsibility for conducting the consent discussion.

The Sponsor requires that each participant sign a consent form prior to their enrolment in the study to document his/her willingness to take part. The Sponsor may also require, as indicated above, that participants/potential participants be informed of new information if it becomes available during the course of the study. In conjunction with GCP 4.8.2, the communication of this information should be documented.

The Sponsor allows the use of translators in obtaining informed consent. Provision of translators is the responsibility of the local center. Centers should follow applicable local policies when procuring or using a translator for the purpose of obtaining informed consent to participate in a clinical trial.

In accordance with ICH-GCP 4.8.9, if a subject is unable to read, then informed consent may be obtained by having the consent form read and explained to the subject. This process must be thoroughly documented.

16.3.1 Obtaining Consent for Pregnancy/Exposure Reporting

Information from and/or about the subject (i.e. the pregnant female, the newborn infant, male partner) should not be collected about or from them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about or from them. If the pregnant female is not a participant in the main trial, consent should be obtained via use of the *exposure/*pregnancy follow-up consent form.

In the case of information collected about a newborn, consent should be provided by the legal guardian. In cases where the legal guardian is the participant in the main trial, consent is obtained via the main consent. If the legal guardian is not the trial participant, consent should be obtained via the exposure/pregnancy follow-up consent.

Participants will not be withdrawn from the main trial as a result of refusing or withdrawing permission to provide information related to the pregnancy*/exposure*. Similarly, male participants will not be withdrawn from the main study should their partner refuse/withdraw permission.

16.4 DISCONTINUATION OF THE TRIAL

The study is planned for completion on February 28th, 2020, at which time the Sponsor will cease provision of protocol treatment.

If this trial is discontinued for any reason by the Sponsor prior to February 28th, 2020, all centers will be notified in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of patients participating on the trial or other persons, the Sponsor will provide this information to centers as well.

If this trial is discontinued at any time by the center (prior to closure of the trial by the Sponsor), it is the responsibility of the Principal Investigator to notify the Sponsor of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the Sponsor or locally by the center, it is the responsibility of the Principal Investigator to notify the local Institutional Review Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

Following trial closure after demonstrating overall survival benefit, and until the time that BBI-608 is commercially available, all patients randomized on the trial may have an opportunity to receive treatment with BBI-608; provided, that the Principal Investigator has determined that such continued treatment would be in the best interest of the patient, and subject to approval by the applicable regulatory authorities. This will be done via a new, open label extension study, or in another manner as determined by the Sponsor, requiring additional regulatory approval.

16.5 RETENTION OF PATIENT RECORDS AND STUDY FILES

All essential documents must be maintained in accordance with ICH-GCP.

The Principal Investigator must ensure compliance with GCP Guideline from every person involved in the conduct of the clinical trial at the site.

Essential documents must be retained for 25 years following the completion of the trial at the center (25 years post final analysis, last data collected, or closure notification to IRB, whichever is later), or until notified by the Sponsor that documents no longer need to be retained.

In accordance with GCP 4.9.7, upon request by the monitor, auditor, IRB or regulatory authority, the Investigator/institution must make all required trial-related records available for direct access.

The Sponsor will inform the Investigator/Institution as to when the essential documents no longer need to be retained.

16.6 ON-SITE MONITORING/AUDITING

In addition to the routine review of case report forms and supporting documents sent to the central office, site monitoring will be conducted at participating centers in the course of the study as part of the overall quality assurance programme. The monitors/auditors will require access to patient medical records to verify the data, as well as pharmacy, essential document binders, standard operating

procedures (including electronic information) and ethics documentation.

At any time, your site may be subject to an inspection by a regulatory agency such as the Health Canada Inspectorate or the FDA. Your site may also be subject to an audit by the Sponsor.

16.7 CASE REPORT FORMS

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection. Details for accessing the EDC system and completing the on-line Case Report Forms will be provided separately.

REFERENCES

Cancer Stem Cell, special issue: June 10 special issue of Journal of Clinical Oncology [J Clin Oncol. 2008 26(17)].

Akira, S. (1999). Functional Roles of STAT Family Proteins: Lessons from Knockout Mice. *Stem Cells*, *17*(3), 138-146.

Al-Hajj, M., & Clarke, M. (2004). Self-renewal and solid tumor stem cells. *Oncogene*, *23*(43), 7274-7282.
Blazer, M., Wu, C., Goldberg, R., Phillips, G., Schmidt, C., & Muscarella, P. et al. (2014). Neoadjuvant Modified (m) FOLFIRINOX for Locally Advanced Unresectable (LAPC) and Borderline Resectable (BRPC) Adenocarcinoma of the Pancreas. *Annals of Surgical Oncology*.

Arpin, C. C., Mac, S., Jiang, Y., Cheng, H., Grimard, M., Page, B. D., ... & Rosa, D. A. (2016). Applying Small Molecule Signal Transducer and Activator of Trancription-3 (STAT3) Protein Inhibitors as Pancreatic Cancer Therapeutics. *Molecular Cancer Therapeutics*, molcanther-0003.

Boman, B., & Wicha, M. (2008). Cancer Stem Cells: A Step Toward the Cure. *Journal of Clinical Oncology*, *26*(17), 2795-2799.

Chen LT, Von Hoff DD, Li CP, et al. (2015). Expanded analyses of NAPOLI-1: Phase 3 study of MM-398 (nal-IRI), with or without 5-fluorouracil and leucovorin, versus 5-fluorouracil and leucovorin, in metastatic pancreatic cancer (mPAC) previously treated with gemcitabine-based therapy. *Journal of Clinical Oncology, 33, suppl 3, abstr 234.*

Cho, R., & Clarke, M. (2008). Recent advances in cancer stem cells. *Current Opinion in Genetics & Development*, *18*(1), 48-53.

Clevers, H. (2011). The cancer stem cell: premises, promises and challenges. *Nature Medicine*, 313-319.

Conroy, T., Desseigne, F., Ychou, M., Bouche, O., Guimbaud, R., & Becouarn, Y. et al. (2011). FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. *New England Journal of Medicine*, *364*(19), 1817-1825.

Corbo, V., Tortora, G., & Scarpa, A. (2012). Molecular pathology of pancreatic cancer: from bench-to-bedside translation. *Current Drug Targets*,*13*(6), 744-752.

Corcoran, R. B., Contino, G., Deshpande, V., Tzatsos, A., Conrad, C., Benes, C. H., ... & Bardeesy, N. (2011). STAT3 plays a critical role in KRAS-induced pancreatic tumorigenesis. *Cancer Research*, *71*(14), 5020-5029.

Davis, J., Pandalai, P., Ripley, R., Langan, R., & Avital, I. (2012). Expanding Surgical Treatment of Pancreatic Cancer. *Pancreas*, *41*(5), 678-684.

Denley, S., Jamieson, N., McCall, P., Oien, K., Morton, J., & Carter, C. et al. (2013). Activation of the IL-6R/Jak/Stat Pathway is Associated with a Poor Outcome in Resected Pancreatic Ductal Adenocarcinoma. *Journal of Gastrointestinal Surgery*, *17*(5), 887-898.

Eisenhauer, E., Therasse, P., Bogaerts, J., Schwartz, L., Sargent, D., & Ford, R. et al. (2009). New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *European Journal of Cancer*, *45*(2), 228-247.

Fofaria, N. M., & Srivastava, S. K. (2014). STAT3 induces anoikis resistance, promotes cell invasion and metastatic potential in pancreatic cancer cells. *Carcinogenesis*, bgu233.

Fukuda, A., Wang, S., Morris, J., Folias, A., Liou, A., & Kim, G. et al. (2011). Stat3 and MMP7 Contribute to Pancreatic Ductal Adenocarcinoma Initiation and Progression. *Cancer Cell*, *19*(4), 441-455.

Goldstein D, El Maraghi RH et al. (2014). Updated survival from a randomized phase III trial (MPACT) of nab-Paclitaxel plus gemcitabine versus gemcitabine alone for patients (pts) with metastatic adenocarcinoma of the pancreas. *Journal of Clinical Oncology, 32, suppl 3, abstr 178.*

Gupta, P., Chaffer, C., & Weinberg, R. (2009). Cancer stem cells: mirage or reality?. *Nature Medicine*, *15*(9), 1010-1012.

Gupta, P., Fillmore, C., Jiang, G., Shapira, S., Tao, K., Kuperwasser, C., & Lander, E. (2011). Stochastic State Transitions Give Rise to Phenotypic Equilibrium in Populations of Cancer Cells. *Cell*, *147*(5), 1197.

Hanahan, D., & Weinberg, R. (2011). Hallmarks of Cancer: The Next Generation. *Cell*, *144*(5), 646-674.

Hermann, P., Huber, S., Herrler, T., Aicher, A., Ellwart, J., & Guba, M. et al. (2007). Distinct Populations of Cancer Stem Cells Determine Tumor Growth and Metastatic Activity in Human Pancreatic Cancer. *Cell Stem Cell*, *1*(3), 313-323.

Hidalgo, M. (2010). Pancreatic Cancer. *New England Journal of Medicine*, *362*(17), 1605-1617.

Hochberg, Y. (1988). A Sharper Bonferroni Procedure for Multiple Tests of Significance. *Biometrika*, *75*(4), 800.

Holland, S., DeLeo, F., Elloumi, H., Hsu, A., Uzel, G., & Brodsky, N. et al. (2007). STAT3 Mutations in the Hyper-IgE Syndrome. *New England Journal of Medicine*, *357*(16), 1608-1619.

Hong, S., Wen, J., Bang, S., Park, S., & Song, S. (2009). CD44-positive cells are responsible for gemcitabine resistance in pancreatic cancer cells. *International Journal of Cancer*, *125*(10), 2323-2331.

Ibrahem, S., Al-Ghamdi, S., Baloch, K., Muhammad, B., Fadhil, W., Jackson, D., ... & Ilyas, M. (2014). STAT3 paradoxically stimulates β-catenin expression but inhibits β-catenin function. *International Journal of Experimental Pathology*, *95*(6), 392-400.

Kawada, M., Seno, H., Uenoyama, Y., Sawabu, T., Kanda, N., & Fukui, H. et al. (2006). Signal Transducers and Activators of Transcription 3 Activation Is Involved in Nuclear Accumulation of Â -Catenin in Colorectal Cancer. *Cancer Research*, *66*(6), 2913-2917.

Klimstra, D. (2007). Nonductal neoplasms of the pancreas. *Mod Pathol*, *20*(1s), S94-S112.

Lee, C., Dosch, J., & Simeone, D. (2008). Pancreatic Cancer Stem Cells. *Journal of Clinical Oncology*, *26*(17), 2806-2812.

Lesina, M., Kurkowski, M., Ludes, K., Rose-John, S., Treiber, M., & Kloppel, G. et al. (2011). Stat3/Socs3 Activation by IL-6 Transsignaling Promotes Progression of Pancreatic Intraepithelial Neoplasia and Development of Pancreatic Cancer. *Cancer Cell*, *19*(4), 456-469.

Li, C., Heidt, D., Dalerba, P., Burant, C., Zhang, L., & Adsay, V. et al. (2007). Identification of Pancreatic Cancer Stem Cells. *Cancer Research*, *67*(3), 1030-1037.
Maeda, S., Shinchi, H., Kurahara, H., Mataki, Y., Maemura, K., & Sato, M. et al. (2008). CD133 expression is correlated with lymph node metastasis and vascular endothelial growth factor-C expression in pancreatic cancer. *Br J Cancer*, *98*(8), 1389-1397.

Li, Y.Z., Rogoff, H.A., Keates, S., Gao, Y., Murikipudi, S., Mikule, K., Leggett, D., Li, W., Pardee, A.B., Li, C.J. (2015) *PNAS*, 112(6), 1839-1844.

Mahaseth, H., Brutcher, E., Kauh, J., Hawk, N., Kim, S., & Chen, Z. et al. (2013). Modified FOLFIRINOX Regimen With Improved Safety and Maintained Efficacy in Pancreatic Adenocarcinoma. *Pancreas*, *42*(8), 1311-1315.

Maurer, W., Bretz, F. (2013). Multiple testing in group sequential trials using graphical approaches. *Statistics in Biopharmaceutical Research*, 5, 311-320.

Niwa, H., Burdon, T., Chambers, I., & Smith, A. (1998). Self-renewal of pluripotent embryonic stem cells is mediated via activation of STAT3. *Genes & Development*, *12*(13), 2048-2060.

Ohara, Y., Oda, T., Sugano, M., Hashimoto, S., Enomoto, T., & Yamada, K. et al. (2013). Histological and prognostic importance of CD44+/CD24+/EpCAM+ expression in clinical pancreatic cancer. *Cancer Science*, *104*(8), 1127-1134.

Ponti, D. (2005). Isolation and In vitro Propagation of Tumorigenic Breast Cancer Cells with Stem/Progenitor Cell Properties. *Cancer Research*, *65*(13), 5506-5511.

Pramanik, K. C., Fofaria, N. M., Gupta, P., Ranjan, A., Kim, S. H., & Srivastava, S. K. (2015). Inhibition of β-catenin signaling suppresses pancreatic tumor growth by disrupting nuclear β-catenin/TCF-1 complex: critical role of STAT-3. *Oncotarget*, *6*(13), 11561.

Rasheed, Z., & Matsui, W. (2012). Biological and clinical relevance of stem cells in pancreatic adenocarcinoma. *Journal of Gastroenterology And Hepatology*, *27*, 15-18.

Scholz, A., Heinze, S., Detjen, K., Peters, M., Welzel, M., & Hauff, P. et al. (2003). Activated signal transducer and activator of transcription 3 (STAT3) supports the malignant phenotype of human pancreatic cancer. *Gastroenterology*, *125*(3), 891-905.

Shah, A., Summy, J., Zhang, J., Park, S., Parikh, N., & Gallick, G. (2007). Development and Characterization of Gemcitabine-Resistant Pancreatic Tumor Cells. *Annals of Surgical Oncology*, *14*(12), 3629-3637.

Shahda, S., El-Rayes, B., O'Neil, B., Starodub, A., Hanna, W., & Borodyansky, L. et al. (2016). A Phase Ib study of Cancer Stem Cell (CSC) Pathway inhibitor BBI-608 in combination with Nab-paclitaxel and gemcitabine (nab-PTX) in patients (pts) with metastatic pancreatic ductal adenocarcinoma (mPDAC). *Journal of Clinical Oncology*.

Siegel, R., Naishadham, D., & Jemal, A. (2013). Cancer statistics, 2013. *CA: A Cancer Journal for Clinicians*, *63*(1), 11-30.

Singh, S., Srivastava, S., Bhardwaj, A., Owen, L., & Singh, A. (2010). CXCL12-CXCR4 signalling axis

confers gemcitabine resistance to pancreatic cancer cells: a novel target for therapy. *Br J Cancer*, *103*(11), 1671-1679.

Venkatasubbarao, K., Peterson, L., Zhao, S., Hill, P., Cao, L., & Zhou, Q. et al. (2013). Inhibiting signal transducer and activator of transcription-3 increases response to gemcitabine and delays progression of pancreatic cancer. *Molecular Cancer*, *12*(1), 104.

Von Hoff, D., Ervin, T., Arena, F., Chiorean, E., Infante, J., & Moore, M. et al. (2013). Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine. *New England Journal of Medicine*, *369*(18), 1691-1703.

Von Hoff, D., Ramanathan, R.K., Borad, M.J., Laheru, D.A., Smith, L.S., Wood, T.E., et al. (2011). Gemcitabine plus nab-Paclitaxel is an active regimen in patients with advanced pancreatic cancer: a Phase I/II trial. *Journal of Clinical Oncology,* 29(34), 4548-4554.

White, B., Chien, A., & Dawson, D. (2012). Dysregulation of Wnt/β-Catenin Signaling in Gastrointestinal Cancers. *Gastroenterology*, *142*(2), 219-232.

Winter, J., Cameron, J., Campbell, K., Arnold, M., Chang, D., & Coleman, J. et al. (2006). 1423 Pancreaticoduodenectomies for Pancreatic Cancer: A Single-Institution Experience. *Journal of Gastrointestinal Surgery*, *10*(9), 1199-1211.

Zhang, Y., Morris, J., Yan, W., Schofield, H., Gurney, A., & Simeone, D. et al. (2013). Canonical Wnt Signaling Is Required for Pancreatic Carcinogenesis. *Cancer Research*, *73*(15), 4909-4922.

APPENDIX I - PATIENT EVALUATION FLOW SHEET: ARM 1 (TREATMENT WITH NAB-PACLITAXEL AND GEMCITABINE WITH BBI-608)

Tests & Procedures	Pre-Randomization (Baseline)		During Protocol Treatment								After Permanent Treatment Discontinuation	
Day			Run-In		Cycle 1			Cycle 2 & Beyond				
			1	2	1	8	15	1	8	15		
Timing & Window	≤14 days prior to randomization	≤3 days prior to randomization	To begin ≤2 days after randomization[15] Can be extended up to 3 days		+/- 3 days						4 weeks post protocol treatment (+/- 7 days)	Every 4 weeks for the first 6 months, then every 3 months thereafter (+/- 7 days)
Informed Consent	X											
Prior Medical and Therapeutic History[2]	X											
Physical Examination	X[7]							X			X	
Vital Signs (temperature, heart rate, blood pressure, respiratory rate, O_2 saturation on room air)	X[7]	X						X			X	
Height	X[7]											
Weight	X[7]	X						X			X	
ECOG Performance Status	X[7]	X						X			X	
Concurrent Medication List	X	X[3]						X			X	
Adverse Event Assessment[4]	X			X[5]	X	X	X	X	X	X	X	X
Hematology[9, 10]	X[7]				X	X	X	X	X	X	X	
Biochemistry[6, 10]	X[7]				X			X			X	
Total Bilirubin[10]	X[7]	X			X			X			X	
Albumin[10]	X[7]	X			X			X			X	
Urinalysis [10]	X[7]				X			X			X	
Coagulation (PT + PTT)	X[7]											
Tumor marker (CA 19-9)	X[7]											
Pregnancy test, serum or urine (if applicable)[7,8]		X						X			X	
ECG (12-lead)	X[7]				X						X	
Radiology & Imaging[11]	X		Every 8 weeks (56 days) +/- 5 days from randomization until progressive disease is documented									
Submission of representative block of diagnostic tumor tissue	Upon request after randomization											
Blood collection for correlative studies	X							X[12]			X[12]	
Blood collection for sparse PK analysis						X	X	X[12]				
Quality of Life Assessment (EORTC QLQ-C30)[13]	X							X			X[14]	
Begin BBI-608 Administration[15]			X									
Dispense BBI-608[16]					X			X				
Gemcitabine with Nab-Paclitaxel Infusion[17]					X	X	X	X	X	X		
Subsequent Cancer Therapy[18]											X	X
Assessment for survival of patient[19]											X	X

1 Patient will be excluded from participation if any of the following occurs at ≤ 72 hours prior to randomization: increase in ECOG PS (two observers will be required to assess performance status on each occasion and if discrepant, the one with the highest deterioration of performance will be considered true), weight loss of ≥10% from baseline testing, ≥ 20% decrease in serum albumin from baseline testing, or clinically significant change in vital signs.

2 Medical history must include date of diagnosis including histological or cytological documentation of malignancy.

3 Any anesthesia procedures, such as spinal block or other injections administered for pain control following Baseline Evaluation will be reported at ≤ 72 hours prior to randomization.

4 Adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix IV). Following permanent protocol treatment discontinuation, patients will be assessed for any protocol treatment related adverse events every 8 weeks, starting with the 4 week post-protocol treatment discontinuation visit.

5 Adverse event assessment by phone should be performed on *Run-In Day 2*.

6 Baseline creatinine or creatinine clearance may be used to demonstrate eligibility.

7 If required laboratory tests cannot be performed prior to randomization within indicated timelines due to technical reasons, lab retest and prolongation of the screening period for 3 working days is allowed. Laboratory testing performed as part of

standard of care prior to patient signature of the informed consent for the study will be acceptable as baseline labwork as long as testing is performed ≤ 14 days prior to randomization.

8 In women of childbearing potential only. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG.

9 Hematology should be done within 72 hours prior to nab-paclitaxel + gemcitabine administration. Laboratory testing performed as part of standard of care prior to patient signature of the informed consent for the study will be acceptable as baseline labwork as long as testing is performed ≤ 14 days prior to randomization.

10 Laboratory investigations should be performed within 72 hours prior to Day 1 of each Cycle of protocol treatment. Laboratory testing performed as part of standard of care prior to patient signature of the informed consent for the study will be acceptable as baseline labwork as long as testing is performed ≤ 14 days prior to randomization. Total bilirubin will need to be repeated at ≤72 hours prior to randomization only for patients with Baseline total bilirubin >1 and ≤1.5 x ULN.

11 Standard tumor measurement procedures will be followed to assess response to therapy. The same method of assessment and the same technique should be used to identify and report each lesion at baseline and at reassessment during treatment. Tumor evaluations will continue until progressive disease is documented. For patients who remain on protocol therapy after objective disease progression has been documented, no further imaging assessments are mandated, but where these occur as a component of care, tumor measurements and assessment must be reported. Tumor assessments should be obtained within +/- 5 days of protocol specified schedule. Qualifying scans performed as part of standard of care prior to patient signature of the study informed consent will be acceptable as baseline scanning as long as scanning is performed ≤ 14 days prior to randomization.

12 Sample will be collected 4 weeks after Day 1 Cycle 1 and will not be performed beyond Cycle 2. A sample will be collected following protocol treatment discontinuation if discontinuation occurs prior to 4 weeks of therapy.

13 To be completed in clinic. Questionnaires should be completed at baseline and at 4, 8, 12, 16 and 24 weeks from Cycle 1 Day 1 for as long as patient remains on protocol therapy or until deterioration to ECOG PS 4 or hospitalization for end of life care.

14 EORTC QLQ-C30 questionnaire will be collected in the post-protocol discontinuation period only if the patient discontinues protocol treatment prior to 24 weeks of therapy and has an ECOG PS of less than 4 and has not been hospitalized for end of life care.

15 BBI-608 administration will begin 2 days prior to the nab-paclitaxel+gemcitabine infusion on Day 1 of Cycle 1. These two days are referred to as *Run-in Day* and *Run-in Day 2*. *Run-in Day 1* should occur within 2 calendar days of patient randomization. The *run-in* period may be extended by up to 3 additional calendar days.

16 Patients continuing on BBI-608 monotherapy post disease progression on nab-paclitaxel and gemcitabine will maintain the same schedule of events, except no longer have visits or bloodwork or AE assessment on Day 8 or Day 15 of the cycle following treatment discontinuation of nab-paclitaxel and gemcitabine.

17 Nab-paclitaxel with gemcitabine administration should proceed according to institutional standard practice (with respect to pre-treatment laboratory evaluation, clinical assessment, pre-medication, and monitoring during and after infusion).

18 Subsequent cancer treatment will be captured until end of study.

19 After the first visit at which the patient has been off protocol treatment (BBI-608 and nab-paclitaxel with gemcitabine) for 4 weeks, monitored on a monthly basis for 6 months and then every 3 months thereafter until death, the study closes or 3 years have elapsed since subject discontinuation from treatment. In the event that patient is unable to attend clinic, post-progression follow-up may be by means of telephone contact.

APPENDIX II - PATIENT EVALUATION FLOW SHEET: ARM 2 (TREATMENT WITH NAB PACLITAXEL AND GEMCITABINE)

Tests & Procedures	Pre-Randomization (Baseline)		During Protocol Treatment						After Permanent Treatment Discontinuation	
Day			Cycle 1			Cycle 2 & Beyond				
			1	8	15	1	8	15		
Timing & Window	≤14 days prior to randomization	≤3 days prior to randomization[1]	C1D1 to begin ≤4 days after randomization +/- 3 days						4 weeks post protocol treatment (+/- 7 days)	Every 4 weeks for the first 6 months, then every 3 months thereafter (+/- 7 days)
Informed Consent	X									
Prior Medical and Therapeutic History[2]	X									
Physical Examination	X[6]					X			X	
Vital Signs (temperature, heart rate, blood pressure, respiratory rate, O_2 saturation on room air)	X[6]	X				X			X	
Height	X[6]									
Weight	X[6]	X				X			X	
ECOG Performance Status	X[6]	X				X			X	
Concurrent Medication List	X	X[3]				X			X	
Adverse Event Assessment[4]	X		X	X	X	X	X	X	X	X
Hematology[8, 9]	X[6]		X	X	X	X	X	X	X	
Biochemistry[5,9]	X[6]		X			X			X	
Total Bilirubin[9]	X[7]	X	X			X			X	
Albumin[9]	X[6]	X	X			X			X	
Urinalysis[9]	X[6]		X			X			X	
Coagulation (PT + PTT)	X[6]									
Tumor marker (CA 19-9)	X[6]									
Pregnancy test, serum or urine (if applicable)[6,7]		X				X			X	
ECG (12-lead)	X[6]		X						X	
Radiology & Imaging[10]	X		Every 8 weeks (56 days) +/- 5 days from randomization until progressive disease is documented							
Submission of representative block of diagnostic tumor tissue	Upon request after randomization									
Blood collection for correlative studies	X					X[11]			X[11]	
Quality of Life Assessment (EORTC QLQ-C30)[12]	X					X			X[13]	
Gemcitabine with Nab-Paclitaxel Infusion[14]			X	X	X	X	X	X		
Subsequent Cancer Therapy[15]									X	X
Assessment for survival of patient[16]									X	X

1 Patient will be excluded from participation if any of the following occurs at ≤ 72 hours prior to randomization: increase in ECOG PS (two observers will be required to assess performance status on each occasion and if discrepant, the one with the highest deterioration of performance will be considered true), weight loss of ≥10% from baseline testing, ≥ 20% decrease in serum albumin from baseline testing, or clinically significant change in vital signs.
2 Medical history must include date of diagnosis including histological or cytological documentation of malignancy.
3 Any anesthesia procedures, such as spinal block or other injections administered for pain control following Baseline Evaluation will be reported at ≤ 72 hours prior to randomization.
4 Adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix IV). Following permanent protocol treatment discontinuation, patients will be assessed for any protocol treatment related adverse events every 8 weeks, starting with the 4 week post-protocol treatment discontinuation visit.

5 Baseline creatinine or creatinine clearance may be used to demonstrate eligibility.
6 If required laboratory tests cannot be performed prior to randomization within indicated timelines due to technical reasons, lab retest and prolongation of the screening period for 3 working days is allowed. Laboratory testing performed as part of standard of care prior to patient signature of the informed consent for the study will be acceptable as baseline labwork as long as testing is performed ≤ 14 days prior to randomization.
7 In women of childbearing potential only. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG.
8 Hematology should be done within 72 hours prior to nab-paclitaxel + gemcitabine administration. Laboratory testing performed as part of standard of care prior to patient signature of the informed consent for the study will be acceptable as baseline labwork as long as testing is performed ≤ 14 days prior to randomization.
9 Laboratory investigations should be performed within 72 hours prior to Day 1 of each Cycle of protocol treatment. Laboratory testing performed as part of standard of care prior to patient signature of the informed consent for the study will be acceptable as baseline labwork as long as testing is performed ≤ 14 days prior to randomization. Total bilirubin will need to be repeated at ≤72 hours prior to randomization only for patients with Baseline total bilirubin ≥1 and ≤1.5 x ULN.
10 Standard tumor measurement procedures will be followed to assess response to therapy. The same method of assessment and the same technique should be used to identify and report each lesion at baseline and at reassessment during treatment. Tumor evaluations will continue until progressive disease is documented. For patients who remain on protocol therapy after objective disease progression has been documented, no further imaging assessments are mandated, but where these occur as a component of care, tumor measurements and assessment must be reported. Tumor assessments should be obtained within +/- 5 days of protocol specified schedule. Qualifying scans performed as part of standard of care prior to patient signature of the study informed consent will be acceptable as baseline scanning as long as scanning is performed ≤ 14 days prior to randomization.
11 Sample will be collected 4 weeks after Day 1 Cycle 1 and will not be performed beyond Cycle 2. A sample will be collected following protocol treatment discontinuation if discontinuation occurs prior to 4 weeks of therapy.
12 To be completed in clinic. Questionnaires should be completed at baseline and at 4, 8, 12, 16 and 24 weeks from Cycle 1 Day 1 for as long as patient remains on protocol therapy or until deterioration to ECOG PS 4 or hospitalization for end of life care.
13 EORTC QLQ-C30 questionnaire will be collected in the post-protocol discontinuation period only if the patient discontinues protocol treatment prior to 24 weeks of therapy and has an ECOG PS of less than 4 and has not been hospitalized for end of life care.
14 Nab-paclitaxel with gemcitabine administration should begin within 7 calendar days of randomization and proceed according to institutional standard practice (with respect to pre-treatment laboratory evaluation, clinical assessment, pre-medication, and monitoring during and after infusion).
15 Subsequent cancer treatment will be captured until end of study.
16 After the first visit at which the patient has been off protocol treatment (nab-paclitaxel with gemcitabine) for 4 weeks, monitored on a monthly basis for 6 months and then every 3 months thereafter until death, the study closes or 3 years have elapsed since subject discontinuation from treatment. In the event that patient is unable to attend clinic, post-progression follow-up may be by means of telephone contact.

APPENDIX III - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX IV - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:
(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

APPENDIX V - QUALITY OF LIFE ASSESSMENT

Introduction

The assumption that control of symptoms will automatically improve quality of life is probably true but hasn't yet been tested, especially in determining how certain symptoms may or may not affect quality of life. Current literature reveals interesting things; two in particular are:

- additional and useful information may be obtained from quality of life measurements
- a growing consensus that the goal of medical care today for most patients is the preservation of function and well-being in everyday life

We have reached the stage where the collection of information about psychological distress, social disruption, emotional trauma and painful side-effects is not only necessary but a routine component in many protocols.

Quality of life data can be used in a variety of ways:

- to try to achieve the best possible outcome for patients
- to evaluate the extent of change in the quality of life of an individual or group across time
- to evaluate new treatments and technologies
- to support approval of new drug applications
- to try to provide the best value for health care dollars
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of not only drugs but also new therapies or methods of delivery will most likely be based on a combination of quality of life, survival, response, and adverse event data.

Instructions for Administration of a Quality of Life Questionnaire.

The instructions below are intended as a guide for the administration of the Quality of Life questionnaire.

1. Preamble

Quality of life data are collected for research purposes, and will usually not be used for the patient's individual medical care. The assessment is in the form of a self-report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

The usual scheduled times to obtain the questionnaires are as follows:

- pre-randomization or pre-registration (baseline)
- during treatment
- during follow-up

The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

If a particular question has not been answered, please document the reason(s) in the appropriate space on the

questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pre-Treatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g.: psychological distress, social disruption, side-effects, et cetera.

Study staff should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The quality of life questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, s/he should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

The quality of life questionnaire should be given to the patient before being seen by the doctor, for as long as the patient continues on Protocol therapy, as required by the schedule at approximately:
4, 8, 12, 16 and 24 weeks or until deterioration to ECOG PS 4 or hospitalization for end of life care
the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days (+/- 3 days) if study therapy discontinuation occurred prior to 24 weeks and until deterioration to ECOG PS 4 or hospitalization for end of life care

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how quality of life is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If . . .

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one:

If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

This box to be completed by the clinical research coordinator: Study ID #: _____ Pt. Initials: ____ ____ ____

European Organization for Research and Treatment of Cancer (EORTC)

Quality of Life Questionnaire

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.

	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 a 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

This box to be completed by the clinical research coordinator: Study ID #: _____ Pt. Initials: ____ ____ ____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
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

This box to be completed by the clinical research coordinator: Study ID #: _____ Pt. Initials: ____ ____ ____

During the past week:	Not **At All**	A **Little**	Quite **a Bit**	Very **Much**
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

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank you.