UTSouthwestern
Harold C. Simmons
Comprehensive Cancer Center

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Title: A phase1b/2 Clinical Trial of Chemotherapy and the AXL-inhibitor Bemcentinib for Patients With Metastatic Pancreatic Cancer

Principal Investigator(s): Syed Kazmi, M.D.

Version 6: October 1, 2020

NCT Number: NCT03649321

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PROTOCOL NUMBER SCCC-08218

A phase1b/2 clinical trial of chemotherapy and the AXL-inhibitor bemcentinib for patients with metastatic pancreatic cancer

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Study Drug/Treatment: Bemcentinib
Nab-paclitaxel (ABRAXANE®)
Gemcitabine (GEMZAR®)
Cisplatin (Phase 1b)

IND/IDE Number: 141513

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Signature Page

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Amendment/Version #6: October 1, 2020

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

TABLE OF CONTENTS

LIST OF ABBREVIATIONS **1**

STUDY SCHEMA **3**

STUDY SUMMARY **3**

1.0 BACKGROUND AND RATIONALE **6**

1.1 Disease Background 6

1.2 Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities 7

1.3 Other Agents ..... **Error! Bookmark not defined.**

1.4 Rationale 15

1.5 Correlative Studies 16

2.0 STUDY OBJECTIVES **16**

2.1 Primary Objectives 16

2.2 Secondary Objectives 16

2.3 Exploratory Objectives 16

2.4 Endpoints 16

3.0 PATIENT ELIGIBILITY **18**

3.1 Inclusion Criteria 17

3.2 Exclusion Criteria 18

4.0 TREATMENT PLAN **20**

4.1 Phase 1b Treatment Dosage and Administration 20

4.2 Phase 2 Treatment Dosage and Administration 20

4.3 Administration of bemcentinib 21

4.4 Toxicities and Dosing Delays/Dose Modifications 21
4.5 Concomitant Medications/Treatments 28
4.6 Other Modalities and Procedures 28
4.7 Duration of Therapy 29
4.8 Duration of Follow Up 29
4.9 Removal of Subjects from Protocol Therapy 29
4.10 Subject Replacement 29

5.0 STUDY PROCEDURES 30

5.1 Screening/Baseline Procedures 30
5.2 Procedures During Treatment 30
5.3 Follow-up Procedures 33
5.4 Time and Events Table 34
5.5 Removal of Subjects from Study 35

6.0 Measurement of Effect 35

6.1 Antitumor Effect- Solid Tumors 35
6.2 Safety/Tolerability 40

7.0 ADVERSE EVENTS 40

7.1 Experimental Therapy 40
7.2 Adverse Event Monitoring 41
7.3 Steps to Determine If an Adverse Event Requires Expedited Reporting 42
7.4 Stopping Rules 45

8.0 DRUG/TREATMENT INFORMATION 45

8.1 Agent/Treatment - Bemcentinib 45

9.0 CORRELATIVES/SPECIAL STUDIES 46

9.1 Sample Collection Guidelines 46

9.2 Assay Methodology 47

9.3 Specimen Banking 47

10.0 STATISTICAL CONSIDERATIONS 47

10.1 Study Design/Study Endpoints 47

10.2 Sample Size and Accrual 48

10.3 Data Analyses Plans 49

11.0 STUDY MANAGEMENT 49

11.1 Conflict of Interest 49

11.2 Institutional Review Board (IRB) Approval and Consent 49

11.3 Required Documentation 50

11.4 Registration Procedures 50

11.5 Data Management and Monitoring/Auditing 51

11.6 Adherence to the Protocol 51

11.7 Amendments to the Protocol 53

11.8 Record Retention 53

11.9 Obligations of Investigators 53

12.0 REFERENCES 54

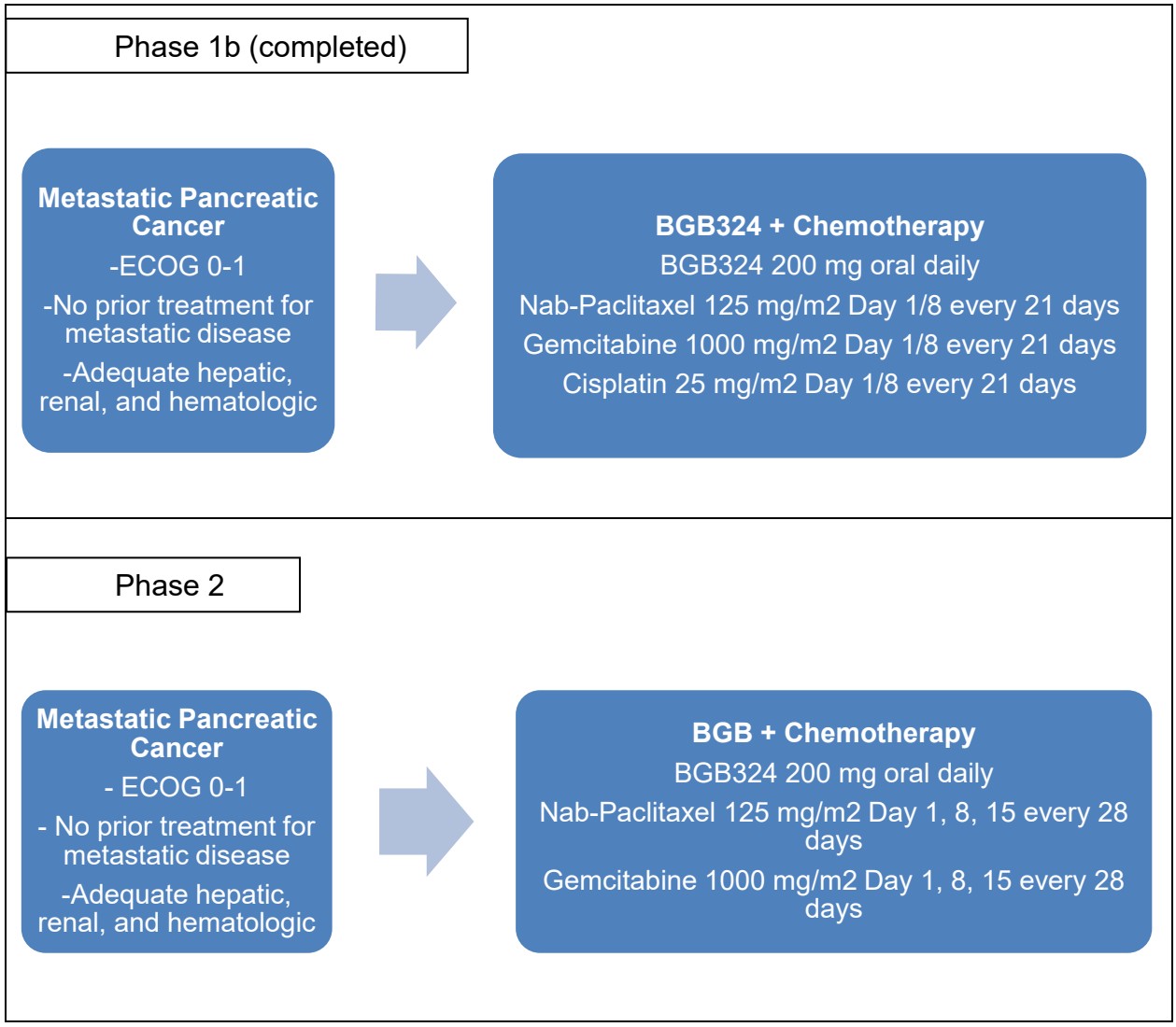
13.0 APPENDICES 55

LIST OF ABBREVIATIONS (EXAMPLES)

AE	Adverse Event
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
Bid	Twice a Day
BP	Blood Pressure
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
COI	Conflict of Interest
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DOT	Disease Oriented Team
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EMT	Epithelial to Mesenchymal Transition
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HR	Heart Rate
HRPP	Human Research Protections Program
IB	Investigator's Brochure
IND	Investigational New Drug
IRB	Institutional Review Board
IV (or iv)	Intravenously
KPS	Karnofsky Performance Status
LD	Longest Diameter
LDH	Lactate Dehydrogenase
MDS	Myelodysplastic Syndrome
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NS	Normal Saline
NSCLC	Non-Small Cell Lung Cancer
NYHA	New York Heart Association

OR	Objective Response
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed Cell Death Receptor
PD-L1	Programmed Death Ligand 1
PDA	Pancreatic Ductal Adenocarcinoma
PDAC	Pancreatic Ductal Adenocarcinoma Cancer
PI	Principal Investigator
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Partial Response
QOL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
RR	Respiratory Rate
RTR	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGPT	Serum Glutamic Pyruvic Transaminase
SMC	Safety Monitoring Committee
TNBC	Triple Negative Breast Cancer
ULN	Upper Limit of Normal
UPIRSO	Unanticipated Problems Involving Risks to Subjects or Others
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	A phase1b/2 clinical trial of chemotherapy and the AXL-inhibitor bemcentinib for patients with metastatic pancreatic cancer
Short Title	Clinical trial of chemotherapy and bemcentinib for metastatic pancreatic cancer
Protocol Number	BGB324
BerGenBio protocol number	BGBIL010
Phase	Phase 1b/2
Methodology	Safety run-in followed by a phase 2 study
Study Duration	30 months
Study Center(s)	2 US sites
Objectives	Determine the overall response rate (ORR) of bemcentinib plus chemotherapy (nab-paclitaxel/gemcitabine) in patients with metastatic pancreatic adenocarcinoma.
Number of Subjects	3-44
Phase 1b/2 Diagnosis and Main Inclusion Criteria	1. Ability to understand and the willingness to sign a written informed consent. 2. Patients must have a histologically or cytologically confirmed pancreatic adenocarcinoma that is metastatic or recurrent. 3. No prior systemic therapy for metastatic disease. a. Prior adjuvant therapy, if completed more than 6 months prior to date of enrollment, is acceptable. b. Radiosensitizing chemotherapy, if completed at least 4 weeks prior to date of enrollment, is acceptable. 4. Measurable disease per RECIST 1.1 criteria. 5. Age 18-70 years 6. ECOG performance status 0 or 1 7. Adequate hematologic, hepatic and renal function as defined in Table 2 8. Adequate contraception as defined in protocol section 3.1. 9. Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except alopecia). If the patient received major surgery or radiation therapy of >30 Gy, they must have recovered from the toxicity and/or complications from the intervention.
Phase 1b Study Product(s), Dose, Route, Regimen	Bemcentinib orally starting Cycle 1 day 2 nab-Paclitaxel intravenously, Day 1 and 8 every 21 days Gemcitabine intravenously, Day 1 and 8 every 21 days Cisplatin intravenously, Day 1 and 8 every 21 days
Phase 2 Study Products, Route, Regimen	Bemcentinib orally starting Cycle 1 day 2 nab-Paclitaxel intravenously, Day 1, 8 and 15 every 28 days Gemcitabine intravenously, Day 1, 8 and 15 every 28 days
Phase 1b/2 Duration of administration	Until progression or intolerable side effects.

Statistical Methodology	To establish safety of the proposed combination, 3 -12 patients will be recruited in Phase1b (safety run in) based on modified 3+3 dose escalation rules. (completed 9/2020) In Phase 2 of the study, 35 patients will be enrolled The proposed scheme is based on Simon's minimax two-stage design for a phase 2 trial using 10% type I error rate and 80% power. For comparisons of 23% (null hypothesis) vs. 40% (alternative hypothesis), 21 patients will be accrued in the first stage. If there are 4 or fewer responses out of 21 patients, the trial will be stopped early for futility. Otherwise, 14 additional patients will be accrued for a total of 35 patients. The null hypothesis will be rejected if 12 or more responses are observed out of 35 patients.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background and Introduction

There is a desperate need to develop agents that specifically and efficaciously treat patients with pancreatic ductal adenocarcinoma cancer (PDAC) that have extremely recalcitrant cancers, and 5-year survival rates of 8%. Unfortunately, PDACs have an ever-increasing incidence and are expected to be the second leading cancer by 2020[1,2]. Current therapies against PDAC lack rationale that exploit cancer-specific targets, are subject to inherent resistance mechanisms, and are ineffective against non-cycling cancer cells. Efficacious treatments for these cancers will require use of agents that cause tumor-specific cell death independent of p53 or oncogenic driver mutations, or apoptotic processes (e.g., caspase-independent), since a majority of these cancers lack functional p53, have activated or mutant tumor driver mutations, and/or have defects in apoptotic pathways that confer growth advantages and drug resistance[3,4].

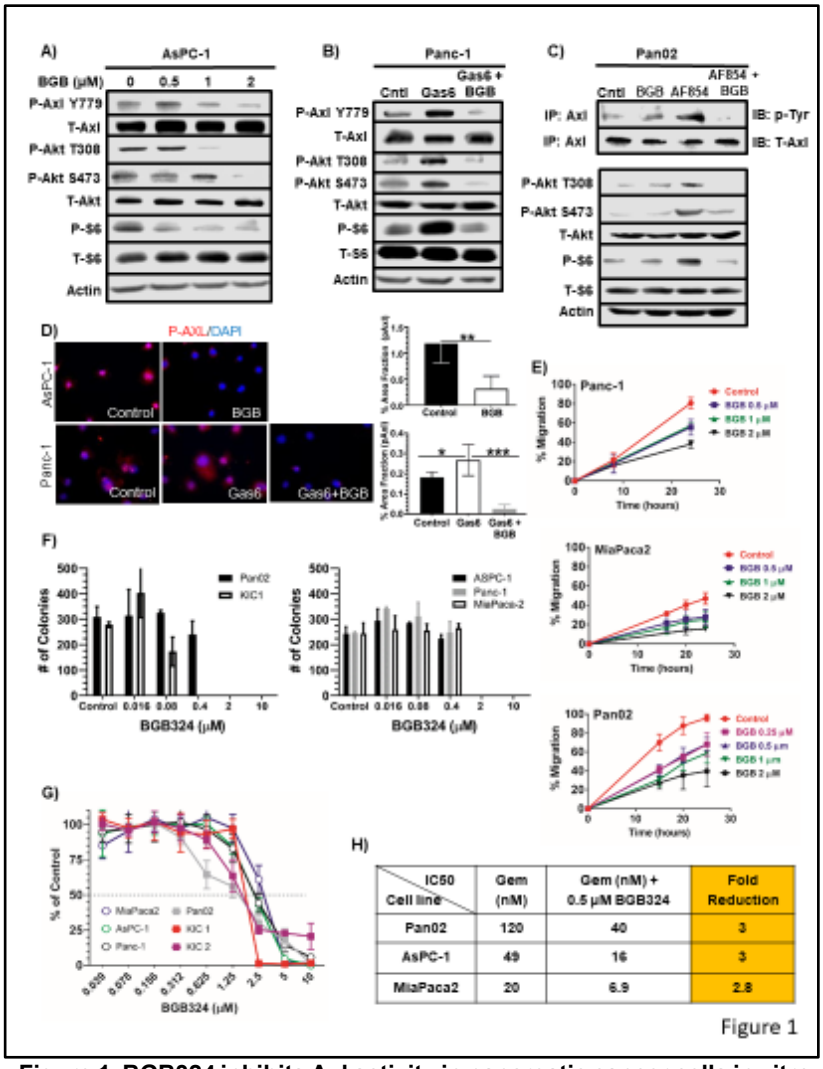
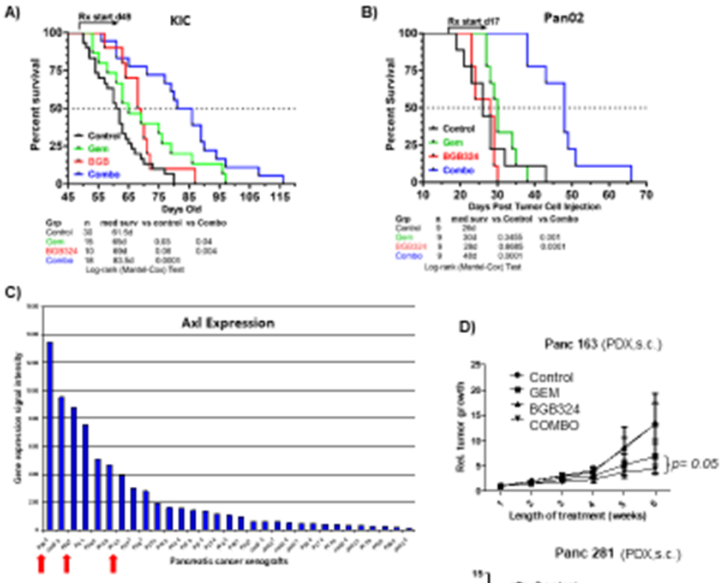


Figure 1. BGB324 inhibits Axl activity in pancreatic cancer cells in vitro.

AXL along with TYRO3 and MER belong to the TAM family of receptor tyrosine kinases (RTKs)[5]. AXL is activated by Growth Arrest-Specific factor 6 (GAS6), binding of which results in AXL dimerization, autophosphorylation and subsequent activation of signaling pathways, such as the PI3K/AKT, Mitogen-Activated Protein Kinase (MAPK), STAT and NF-κB cascades [5]. GAS6-induced AXL signaling promotes adhesion, migration, invasion, pro-inflammatory cytokine production, anti-apoptosis, proliferation and survival of cancer cells[6]. AXL is expressed highly in multiple cancers [5], is linked to metastasis [7,8] poor survival [9,10], and drug resistance[11].

The AXL pathway is relevant in pancreatic cancer as systemic AXL inhibition may enhance the efficacy of cancer therapy through multiple mechanisms. AXL is expressed highly in 70% of resected pancreatic tumors (n=54). AXL expressing tumors were associated with poorer recurrence free and overall survival[12]. Selective AXL pathway inhibition potently block metastasis in several preclinical models of pancreatic cancer. Our group recently demonstrated that pharmacologic inhibition of Gas6 activity impaired pancreatic tumor growth and metastatic spread in an AXL-dependent manner [13]. This is associated with a loss of mesenchymal protein expression, EMT transcription factor expression, decreased tumor proliferation and increased apoptosis[13].



METASTASES	Spleen	Small Intestine	Kidney	Liver	Lung	Lymph nodes
Control (n=7)	7	7	0	7	1	0
GEM (n=6)	6	6	0	2	0	2
BGB324 (n=6)	2	0	0	0	0	0
Combo (n=7)	2	1	0	0	0	0

Figure 2

Figure 2. AXL inhibition in mice with advanced PDA improves survival.

Bemcentinib is a first in class, oral tyrosine kinase inhibitor of the AXL pathway. We investigated the anti-proliferative effect of AXL inhibition by bemcentinib in 6 human and 3 mouse PDAC cell lines in vitro by MTS assay (Fig. 1G). Bemcentinib inhibited cell proliferation in a dose-dependent manner with IC_{50} values ranging from 1-4.0 μM. Notably, bemcentinib reduced the in vitro IC_{50} value of gemcitabine 3-fold in all cell lines (Fig. 1H). In contrast to the relatively modest sensitization of gemcitabine by bemcentinib in vitro, we observed a dramatic effect of this therapeutic combination on overall survival in vivo in mice bearing large advanced PDAC tumors. A genetically engineered mouse model of PDAC (*KIC)* that received saline had a median survival of 61.5 days, while treatment with bemcentinib or gemcitabine only modestly extended the median survival to 65 and 69 days, respectively (*P* value of 0.03 and <0.001 vs. controls). However, combination therapy significantly improved survival to a median of 83.5 days (*P* value < 0.0001 vs. control; *P* value < 0.05 vs. gemcitabine alone) (Fig. 2A).[14]
AXL is also expressed by innate immune cells, including natural killer (NK) cells [15] and tumor-associated macrophages [16], and has been implicated in immune suppression[17]. AXL pathway drives proliferation of *myc* activated pancreatic cancers in preclinical models. Additionally, inhibition of AXL results in antiproliferative activity and suppression of neutrophil infiltration.

1.2 Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities

Bemcentinib is a small molecule, orally bioavailable, highly specific inhibitor of AXL kinase. AXL is a member of the Tyro3, Axl, Mer (TAM) family of receptor tyrosine kinases. AXL receptor overexpression has been detected in a wide range of solid tumours and myeloid leukaemias[18,19].

AXL receptor expression correlates with malignant progression and is an independent predictor of poor patient overall survival in several malignancies including pancreatic[20], prostate[21], lung[22,23], breast[24], colon[25] and AML[26].

Aberrant activation of AXL in tumour cells promotes tumourigenicity, invasiveness, survival and metastasis in a range of cancer types[19] and is a recognised mechanism of acquired resistance to targeted therapeutics *in vitro* and *in vivo*[23,27]. Inhibition of AXL blocks tumor formation, metastasis and reverses drug resistance (e.g. erlotinib) in several experimental cancer models, including TNBC, hormone resistant prostate cancer and adenocarcinoma of the lung[28,24,21,23]. This key role for AXL signaling in malignancy is associated with the Epithelial to Mesenchymal Transition (EMT), a gene regulatory programme governing hundreds of genes, that engenders invasive and stem cell activities during development, wound healing and tissue homeostasis[29,30]. In tumours, EMT produces malignant features that drive drug resistance and metastasis[31,24,27]. Tumour EMT is activated by hypoxia, inflammatory cytokines and chemotherapy and is strongly associated with the development of drug resistance[31,30]. AXL is activated by EMT in tumour cells and AXL signaling is required to maintain EMT-associated metastatic, stem cell and drug resistance traits[32,24,33,23,27]. EMT in tumour cells is linked to immunosuppression via enhanced expression of the PD1/programmed death ligand 1 (PD-L1) axis[34,35]. The importance of AXL signaling in mediating this transformation is becoming increasingly understood.

1.2.1 Summary of Pre-Clinical Activity

Bemcentinib demonstrates potent inhibition of AXL in biochemical and cell-based kinase inhibition assays. The selectivity of bemcentinib for AXL is illustrated in Table 1.

Table 1 Bemcentinib Kinase Selectivity Profile

Kinase	Kinome Scan binding assay (Kd)		KinaseProfiler kinase activity assay (IC50)		BaF3 cell-based kinase activity assay (IC50)	
	nM	fold	nM	fold	nM	fold
Axl	0.4	1	4.6	1	63	1
Tie2	270	680	30	6.4	355	5.5
Ret	73	180	38	8.1	>316	>5
Flt1	400	>1000	40	8.7	>1000	>15
Flt4	460	>1000	41	8.8	>1000	>15
Yes	810	>1000	43	9.2	n/a	n/a

n/a = not applicable

Bemcentinib inhibits the growth and survival of tumor cell lines derived from a range of solid and leukemic tumors.

A modest substrate and time-dependent inhibition of CYP3A4/5 activity by bemcentinib was observed in an *in vitro* study with human liver microsomes.
A comprehensive summary of the pre-clinical activity of bemcentinib is presented in the current version of the Investigator's Brochure (IB).

1.2.2 Non-clinical toxicology of bemcentinib

To support clinical studies with bemcentinib a series of animal toxicology and safety studies, including 28-day repeat dosing studies in rodents and monkeys and a single dose telemetered cardiovascular (CV) safety study in monkeys, have been conducted. Comparisons of the data reported in the rodent and monkey studies indicate that primates are more sensitive to bemcentinib on a per body weight basis.

The results of the repeat dose 28-day study in monkeys identified the liver, reticuloendothelial system and hematopoietic system as target organs. These events were largely thought to be due to macrophage accumulation and were only partially reversible across the planned 16-day recovery period, although this was anticipated to be due to the slow elimination of the compound. Similar findings were identified in mice treated across a range of dose levels with partial recovery noted 16 days later.

In the CV safety study, single oral administration of bemcentinib (7.5 mg/kg – 60 mg/kg) was associated with recoverable, non-adverse decreases in heart rate and corresponding increases in the RR interval durations. Dose-dependent increase in QTc interval was noted at all dose levels; the magnitude of the QTc effect at the highest dose level was 17%, whilst at 7.5 mg/kg and 15 mg/kg, the change generally fell below 10% compared to vehicle control and pre-dose values. These observations were consistent with the previously identified IC_{50} for human ether-à-go-go related gene (hERG) channel inhibition of 0.53 μM bemcentinib.

Bemcentinib was negative in the Ames bacterial mutation assay, suggesting that bemcentinib is not mutagenic. Bemcentinib was also negative in an *in vitro* mammalian cell cytogenetic study in human lymphocytes suggesting that bemcentinib is not clastogenic.

1.2.3 High Dose Steroids and Mouse Model

In an academic model of osteoporosis, bemcentinib was administered in combination with high dose corticosteroids (12.5 mg/kg per day of prednisolone). In this research study, 6 out of 7 mice experienced severe toxicity after five continuous days of combination therapy. Four out of 7 animals died and the other 2 were euthanized for humane reasons. The exact mechanism of this effect is currently under investigation. The mice received very high levels of corticosteroids to induce rapid onset of osteoporosis – on a mg/kg basis, the corticosteroid dose was 20-fold higher than a typical high dose commonly used in clinical practice. Additionally, the dose of bemcentinib used in this model was 50mg/kg which is 6-fold higher than the maximum exposure observed in human clinical studies. Following further investigational toxicology studies, it has been established that effects of steroids are not exacerbated by coadministration of bemcentinib. However, investigators are encouraged to follow their local guidelines for monitoring if a patient requires treatment with high dose steroids.

1.2.4. Pharmacokinetics and Metabolism of bemcentinib

Bemcentinib had moderate to high plasma clearance (33.7, 18.7 and 43.3 mL/min/kg in rats, dogs and monkeys, respectively) i.e. plasma clearance approached hepatic blood flow in these species. Since bemcentinib is sequestered into blood cells, blood clearance will be lower than plasma clearance at least in monkeys (monkeys are currently the only species tested). However, bemcentinib was metabolically stable in vitro suggesting that liver metabolism was unlikely to contribute significantly to the elimination of bemcentinib in vivo.

There was an inhibitory effect of bemcentinib on cytochrome P450 (CYP) 3A4 IC_{50} 1 to 5 micromolar; therefore, there is at least a moderate risk of interactions with co-administered drugs that are CYP3A4 substrates.

1.3 Clinical Studies with bemcentinib

Please refer to the current version of the bemcentinib Investigator's Brochure for further details of the clinical studies with bemcentinib.

At the cut off date of 30th July 2020, one Phase I (Study BGBC001) study has been completed in healthy volunteers and one Phase II study (Study BGBC007) evaluating bemcentinib in combination with pembrolizumab in patients with triple negative breast cancer (TNBC) has been terminated due to pre-defined futility. Four oncology clinical studies are currently active with BerGenBio as the sponsor, with a further 6 Investigator-led clinical studies enrolling patients with advanced cancers. Bemcentinib is being administered as monotherapy and with cytarabine and decitabine in Study BGBC003, with erlotinib in Study BGBC004, and with pembrolizumab in Study BGBC008. Two new studies have also been set up to investigate the use of bemcentinib in the treatment of hospitalized patients with COVID-19 (BGBCIL019 and BGBC020), with one patient enrolled to date in study BGBCIL019.

In addition, seven investigator-led studies are ongoing: BGBIL005 in patients with advanced NSCLC using bemcentinib in combination with docetaxel, BGBIL006 conducted in patients with advanced non-resectable or metastatic melanoma using bemcentinib in combination with pembrolizumab or dabrafenib and trametinib, BGBIL009 in patients with AML or MDS using bemcentinib alone, BGBIL010 in patients with metastatic pancreatic cancer using bemcentinib in combination with nab-paclitaxel, gemcitabine and cisplatin, BGBIL013 in patients with recurrent glioblastoma, BGBIL011, the mesothelioma stratified therapy (MiST) study in patients with relapsed mesothelioma patients in combination with pembrolizumab and BGBIL019, in hospitalized patients with Covid-19.

1.3.1. Safety Summary and reference safety information

The reference safety information below is based on a data cut of active trials on 30 July 2020 as presented in the IB V14.0 dated 14 October 2020. At the time of cut-off, 241 have been treated with bemcentinib in four BerGenBio sponsored clinical studies, enrolling patients with AML, MDS, NSCLC, TNBC,TNIBC and Covid-19 Please refer to the latest edition of the IB for the most up-to-date safety information during the conduct of this clinical study.

In this IB update, acute kidney injury has been added as a new event for the expectedness assessment following treatment with bemcentinib in the Reference Safety Information (RSI). Although acute kidney injury has been added to the RSI on the basis of 2 reported SAEs, there are a number of factors in each clinical presentation that confound and make it unlikely that bemcentinib is associated with the development of acute kidney injury. In all ongoing clinical studies, there are a number of inclusion/exclusion criteria that ensure patients with renal impairment are not enrolled into clinical studies of bemcentinib. Patients enrolled in clinical studies are also monitored closely so early renal impairment can be detected, with these measures including measuring blood creatinine levels, as well as other renal function parameters, clinical chemistry, and urinalysis at each study visit.

Most commonly reported TEAEs in company sponsored studies were diarrhea (49%), nausea (32%) and ECG QT prolongation and fatigue (both 27%). In most cases these events responded well to symptomatic treatment and did not lead to treatment discontinuation or dose reduction. As expected the incidence of infections was higher in

the relapsed/refractory AML/MDS patient group whilst reversible increases in serum creatinine were more frequent in patients with NSCLC.

At the data cut-off date of 30 July 2020, a total of 342 SAEs reports in 147 patients across the four BerGenBio sponsored clinical studies. SAEs in 73 patients being considered related to study treatment. In the Investigator-led studies, 128 SAEs were reported in 71 patients.

Study BGBC003
At the data cut-off date, a total of 72 SAEs were reported in 30 out of 36 patients enrolled in Part A and 101 SAEs were reported in 46 out of 63 patients enrolled in Part B. Twenty-two SAEs in 15 patients in Part A and 33 SAEs in 23 patients in Part B were study treatment-related. The most commonly reported SAEs were febrile neutropenia, pneumonia, sepsis, pyrexia and anaemia.

Study BGBC004
At the data cut-off date, a total of nine patients out of 40 patients enrolled experienced 16 SAEs: two events in one patient in the run-in phase, four events in three patients in Arm A (600 mg/200 mg monotherapy dose), three events in two patients in Arm B, and seven events in three patients in Arm C. Three patients experienced SAEs which were suspected to be related to bemcentinib: one patient in Arm A (one event of transient ischemic attack [Grade 2] and one event of a transient neurologic event [Grade 2]), one patient in Arm B (increased creatine phosphokinase [Grade 3]), and one patient in Arm C (diarrhea [Grade 3]). None of the related SAEs led to discontinuation from the study.

Study BGBC007
At the data cut-off date, a total of 22 patients out of 29 patients enrolled experienced 63 SAEs, with 34 SAEs in 15 patients assessed as related to treatment with bemcentinib. Nineteen SAEs led to dose interruption, four to dose reduction whilst 13 patients withdrew from treatment due to SAEs. Most commonly reported SAEs were pyrexia, dyspnea, liver toxicity/ elevated liver function tests (LFTs), pleural effusion, maculo-papular rash, and febrile neutropenia.

Study BGBC008
At the data cut-off date, a total of 39 patients out of 73 patients enrolled experienced 74 SAEs. A total of 20 SAEs in 12 patients were assessed as related to treatment with bemcentinib and pembrolizumab and 23 SAEs in 15 patients were assessed as related to bemcentinib alone. Most commonly reported SAEs were pneumonia, AST increased, ALT increased, dyspnoea, autoimmune hepatitis, and pyrexia.

1.3.2 Rationale for bemcentinib dose

Daily dosing with 200 mg bemcentinib has been performed in patients with NSCLC and relapsed/refractory AML. Serial specimens of myeloid blasts have been collected from patients with AML. In myeloid blasts samples collected from patients who have completed 21-days of therapy exhibit reduced levels of phospho-Axl, phospho-Akt and phospho-ERK. All of these changes are consistent with inhibition of intracellular signaling pathways which are driven by signaling through Axl. Further evidence of Axl modulation in patients treated at this dose level is evident in the accompanying increase in soluble Axl which is closely related to the average concentration achieved. Increased levels of soluble Axl occurs downsteam of increased sheddase activity following inhibition of intracellular MAPK signalling. These observations suggest that a daily dose of 200 mg bemcentinib has significant impact on inhibiting Axl signalling in patients.

1.3.3 Rationale for chemotherapy selection

Molecular targeted therapies and immune checkpoint inhibitors have revolutionized the treatment of many other solid tumors, such as lung cancer, renal cell carcinoma and melanoma. Chemotherapy remains the standard of care for patients with metastatic pancreatic cancer.[36,37] The combination of gemcitabine, nab-paclitaxel and cisplatin has been shown to have activity in pancreatic cancer in a single arm, pilot clinical trial of 25 patients[38]. By RECIST 1.1 criteria, two patients had complete response (8.3%), 15 partial response (62.5%), 4 stable disease (16.7%), and 3 progressive disease (12.5%). Median time on therapy was 5.5 months, range (1 – 9.5). Most updated median OS was 16.5 months.

Treatment related grade 3 - 4 adverse events included thrombocytopenia 76% (gr 3 = 36%, gr 4 = 40%) with no serious bleeding events, anemia 32% (gr 3 = 32%, gr 4 = 0%), neutropenia 24% (gr 3 = 20%, gr 4 = 4%), infection 20% (gr 3 = 16%, gr 4 = 4%), and diarrhea 16% (gr 3 = 16%, gr 4 = 0%). Peripheral neuropathy ≥ gr 3 was seen in only 1 pt (gr 3 = 4%). Grade 5 AEs were infection (1), cardiac arrest (1), and stroke (1).

Although this was a small study, the high response rates are encouraging and warrant further investigation in pancreatic cancer. Our preclinical data demonstrates synergy with gemcitabine and we would like to build on the triple chemotherapy combination in this clinical trial. Of note, additional clinical trials with this combination are underway for other cancers (cholangiocarcinoma NCT02392637). The adverse events from triple agent chemotherapy are summarized in the Figures 1 and 2.

1.3.4 Rationale for safety run in (Phase 1b)

As highlighted previously, the combination of triple agent chemotherapy with gemcitabine, nab-paclitaxel and cisplatin led to unprecedented tumor response rates in a pilot clinical trial in pancreatic cancer patients[38]. Toxicity in the form of cytopenia was observed. In this clinical trial we propose to add the AXL pathway inhibitor bemcentinib with systemic chemotherapy. Bemcentinib is in clinical trials as monotherapy, in combination with checkpoint inhibitor pembrolizumab, chemotherapy (docetaxel) and the oral tyrosine kinase inhibitor erlotinib. The main toxicity observed with bemcentinib was gastrointestinal disturbance. There were no DLTs and all adverse events were grade 1, except for nausea and vomiting, which were grade 2 (See IB for details). Bemcentinib related cytopenias were not frequently observed. Given the non overlapping toxicities, we anticipate bemcentinib will combine with triple agent chemotherapy (gemcitabine/nab-paclitaxel/cisplatin) without significant additional toxicity.

Adverse Events Grade 3-5

	N = 25 Grade		
Adverse Event Description	*3*	*4*	*5*
Overall	12 (48%)	9 (36%)	3 (12%)
Anemia	8 (32%)		
Febrile neutropenia		1 (4%)	
Cardiac arrest			1 (4%)
Diarrhea	4 (16%)		
Nausea	2 (8%)		
Vomiting	2 (8%)		
Fatigue	1 (4%)		
Fever	2 (8%)		
Anorectal infection	1 (4%)		
Enterocolitis infectious	1 (4%)		
Infections and infestations - acute cryptosporidiosis			1 (4%)
Lung infection	2 (8%)		

Serious Adverse Events All Grades

	N = 25 Grade			
Adverse Event Description	*2*	*3*	*4*	*5*
Overall	1 (4%)	7 (28%)	2 (8%)	3 (12%)
Anemia		1 (4%)		
Cardiac arrest				1 (4%)
Dehydration		2 (8%)		
Diarrhea		1 (4%)		
Epistaxis		1 (4%)		
Febrile neutropenia			1 (4%)	
Fever		2 (8%)		
Acute cryptosporidiosis				1 (4%)
Lung infection		1 (4%)		
Nausea		1 (4%)		
Platelet count decreased		1 (4%)	1 (4%)	
Sepsis			1 (4%)	
Stroke	1 (4%)	1 (4%)		1 (4%)
Vomiting		1 (4%)		

Adverse events have been reviewed by the study Safety Monitoring Committee (SMC) and the SCCC DSMC before enrollment into phase 2 can commence. The SMC is comprised of a representative from each investigational site and a representative of the Sponsor study team. Once safety of combination treatment has been demonstrated, enrollment on the phase 2 2 portion, of the trial will begin.

Treatment will begin at Dose level 1 (Section 4.0) and additional dose levels can be explored based on input from the SMC.

The criteria used to determine if the study will advance to Phase 2 can be referenced in section 10.1 of the protocol.

1.4 Other Agents

1.4.1 Nab-Paclitaxel

NAB-PACLITAXEL for Injectable Suspension (also known as ABI-007, nab-paclitaxel, paclitaxel protein-bound particles for injectable suspension) is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. NAB-PACLITAXEL is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. NAB-PACLITAXEL is free of solvents. The active agent in NAB-PACLITAXEL is paclitaxel.

Indication

In the United States, NAB-PACLITAXEL for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is indicated for the treatment of metastatic PDAC as first-line treatment, in combination with gemcitabine.

Introduction

NAB-PACLITAXEL is a biologically interactive albumin-bound paclitaxel combining a protein with a chemotherapeutic agent in the particle form. This composition provides a novel approach of increasing intra-tumoral concentrations of the drug by a receptor-mediated transport process allowing transcytosis across the endothelial cell. This albumin-specific receptor mediated process involves the binding of albumin to a specific receptor (gp60) on the intraluminal endothelial cell membrane, resulting in activation of a protein (caveolin-1), which initiates an internalization process in the endothelial cell through the formation of caveolae, with transport of the intact albumin-bound chemotherapeutic complex via these caveolae to the underlying tumor interstitium[39]. Other postulated mechanisms of action for the combination of gemcitabine with nab-paclitaxel include downregulation of cytidine deaminase by paclitaxel resulting in higher/sustained concentrations of gemcitabine, macropinocytosis of proteins such as albumin by Ras-transformed cells which would allow for enhanced uptake of paclitaxel loaded albumin nanoparticles into pancreatic cancer tumor cells[40,41].

Preclinical Studies with NAB-PACLITAXEL

Preclinical studies comparing NAB-PACLITAXEL to Taxol® (paclitaxel Cremophor® EL solvent-based, BMS) demonstrated lower toxicities, with an MTD approximately 50% higher for NAB-PACLITAXEL compared to Taxol. At equal doses there was less myelosuppression and improved efficacy in a xenograft tumor model of human mammary adenocarcinoma. At equitoxic doses of paclitaxel, NAB-PACLITAXEL treated groups showed more complete regressions, longer time to recurrence, longer doubling time, and prolonged survival. At equal dose, tumor paclitaxel area under the curve was 33% higher for NAB-

PACLITAXEL versus solvent based paclitaxel, indicating more effective intratumoral accumulation of NAB-PACLITAXEL[42].

Clinical Studies with NAB-PACLITAXEL

A multicenter, multinational, randomized, open-label study was conducted in 861 patients comparing NAB-PACLITAXEL plus gemcitabine versus gemcitabine monotherapy as first-line treatment of metastatic adenocarcinoma of the pancreas. Key eligibility criteria were Karnofsky Performance Status (KPS) ≥70, normal bilirubin level, transaminase levels ≤ 2.5 times the upper limit of normal (ULN) or ≤ 5 times the ULN for patients with liver metastasis, no prior cytotoxic chemotherapy in the adjuvant setting or for metastatic disease, no ongoing active infection requiring systemic therapy, and no history of interstitial lung disease. Patients with rapid decline in KPS (≥10%) or serum albumin (≥20%) during the 14 day screening period prior to study randomization were ineligible.

A total of 861 patients were randomized (1:1) to the NAB-PACLITAXEL/gemcitabine arm (N=431) or to the gemcitabine arm (N=430). Randomization was stratified by geographic region (Australia, Western Europe, Eastern Europe, or North America), KPS (70 to 80 versus 90 to 100), and presence of liver metastasis (yes versus no). Patients randomized to NAB-PACLITAXEL/gemcitabine received NAB-PACLITAXEL 125 mg/m^2 as an intravenous infusion over 30-40 minutes followed by gemcitabine 1000 mg/m^{2}as an intravenous infusion over 30-40 minutes on Days 1, 8, and 15 of each 28-day cycle. Patients randomized to gemcitabine received 1000 mg/m^2 as an intravenous infusion over 30-40 minutes weekly for 7 weeks followed by a 1-week rest period in Cycle 1 then as 1000 mg/m^2 on Days 1, 8 and 15 of each subsequent 28-day cycle. Patients in both arms received treatment until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall survival (OS). Additional outcome measures were progression-free survival (PFS) and overall response rate (ORR), both assessed by independent, central, blinded radiological review using RECIST (version 1.0).

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

The median overall survival of the NAB-PACLITAXEL/gemcitabine group was 8.5 months compared to 6.7 months in the gemcitabine alone group (HR 0.72, p<0.0001). PFS was similarly improved in the combination arm (5.5 vs. 3.7 months, HR 0.69, p<0.0001). Overall response rate by central review was 23% with NAB-PACLITAXEL/gemcitabine and 7% with gemcitabine alone (p<0.0001).

Potential Risks of NAB-PACLITAXEL Toxicities

The most common toxicities reported with NAB-PACLITAXEL when given with gemcitabine in the pancreatic cancer studies include myelosuppression (neutropenia: 73%, thrombocytopenia: 38%), fatigue (59%), peripheral edema (46%), pyrexia (41%), nausea (54%) vomiting (36%), diarrhea (44%), sensory neuropathy (54%), alopecia (50%), arthralgia (11%), myalgia (10%). During post marketing surveillance, rare cases of severe hypersensitivity reactions have occurred.

Further Information See Appendix 2 Nab paclitaxel (Nab-PaclitaxelTM) Prescribing Information (Updated 1/2012) – Accessed via Nab-Paclitaxel Website: http://www.Nab-Paclitaxel.com/docs/Nab-Paclitaxel_PrescribingInformation.pdf

1.4.2 **Gemcitabine**

The most common toxicities reported for gemcitabine include myelosuppression, transient elevations in serum transaminases (approximately 70%), nausea and vomiting (69%), fever (41%), rash (30%), diarrhea (19%), flu syndrome, (19%), infection (16%), alopecia (15%), edema (13%), stomatitis (11%),) neurotoxicity (mild 10%, severe <1%), mild proteinuria and hematuria; Hemolytic Uremia Syndrome (HUS) reported rarely (0.25%), dyspnea (0.2%) and serious pulmonary toxicity (0.06%). Also reported include constipation and pruritus.

Gemcitabine (GemzarTM) Prescribing Information (Updated 09/2017) – Accessed via Gemzar Website: http://pi.lilly.com/us/gemzar.pdf

1.4.3 **Cisplatin – Phase 1b**

The most common toxicities of cisplatin include nephrotoxicity (28-36%; acute renal failure and chronic renal insufficiency), peripheral neuropathy (dose and duration dependent), nausea and vomiting (76% to 100%), myelosuppression (25% to 30%; nadir: day 18-23; recovery: by day 39; mild with moderate doses, mild-to-moderate with high-dose therapy), liver enzymes increased (especially SGOT and bilirubin), ototoxicity (10% to 30%; manifested as high frequency hearing loss; ototoxicity is especially pronounced in children), tissue irritation (extravasation).

Other toxicities (<1%) include alopecia (mild), anaphylactic reaction, arrhythmias, arterial vasospasm (acute), blurred vision, bradycardia, diarrhea, heart block, heart failure, hemolytic anemia (acute), hemolytic uremic syndrome, hypercholesterolemia, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, limb ischemia (acute), mesenteric ischemia (acute), myocardial infarction, myocardial ischemia, mouth sores, neutropenic typhlitis, optic neuritis, orthostatic hypotension, pancreatitis, papilledema, phlebitis, reversible posterior leukoencephalopathy syndrome (RPLS), SIADH, stroke, thrombophlebitis, thrombotic thrombocytopenic purpura.

Cisplatin Prescribing Information (updated 2012) – Accessed via Daily Med (National Library of Medicine) http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=a440f077-46f6-4688-a209- 65bce38d1c92

1.5 Rationale for clinical trial

Bemcentinib inhibits pancreatic cancer proliferation as monotherapy and in combination with gemcitabine through inhibition of the AXL pathway. The combination of nab-paclitaxel/gemcitabine has encouraging signs of clinical activity in patients with metastatic PDAC[38]. We would like to build on this combination in a biomarker driven phase 1b/2 clinical trial of bemcentinib plus chemotherapy for patients with metastatic PDAC.

The chemotherapy regimen for phase 2 will be gemcitabine and nab-paclitaxel combined with bemcentinib. The trial design has been modified from a randomized study of gemcitabine/nab-paclitaxel/cisplatin +/- bemcentinib to a single arm study of gemcitabine/nab-paclitaxel + bemcentinib. This decision was made after discussion with the study investigators and industry collaborator based on the observed clinical activity and tolerance of gemcitabine/nab-paclitaxel/cisplatin with bemcentinib in phase 1b. The

modified, single arm phase 2, design will allow the investigators to assess the addition of bemcentinib to standard of care chemotherapy based on historical control of chemotherapy alone. Single arm phase 2 trials with a response rate end point will allow a preliminary measure of activity which can then be confirmed in a future confirmatory randomized trial. Therefore, the treatment in Phase 2 of the trial will involve nab-paclitaxel/gemcitabine/bemcentinib.

Rationale for Phase 2:
Phase 2 of the trial will allow further assessment of clinical activity and tolerance of therapy

1.6 Correlative Studies

Tissue and blood biomarker assays are proposed with the goal to assess the effect of chemotherapy and bemcentinib on 1) AXL pathway activity in tumor tissue, 2) changes in immune landscape including upregulation of immune cytokines, and immune cell infiltration into the tumor, 3) apoptosis and decreased proliferation of tumor, and 4) to identify predictive biomarkers of response.
Investigators will follow methods previously described[13,14].
Baseline and on treatment blood and tissue collection will be obtained as described in section 5.

Details on sample collection are summarized in the laboratory manual.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 Determine the clinical activity as defined by overall response rate (ORR) of bemcentinib plus chemotherapy (nab-paclitaxel/gemcitabine) in patients with metastatic pancreatic adenocarcinoma.

2.2 Secondary Objectives

2.2.1 Determine clinical activity of bemcentinib plus chemotherapy as defined by complete response rate (CRR), partial response, stable disease, duration of response – overall response/stable disease, median progression free survival (PFS), 1-year and 2-year overall survival (OS) rate.

2.2.2 Determine clinical benefit rate as defined by CR, PR, and SD response rates.

2.2.3 Assess safety and tolerability of bemcentinib plus chemotherapy in patients with metastatic pancreatic adenocarcinoma.

2.3 Exploratory Objectives

2.3.1 Compare the effect of treatment, with chemotherapy alone vs chemotherapy + Axl inhibitor bemcentinib on changes in tissue and blood biomarkers.

2.3.2 Correlate changes in tissue and blood biomarkers with clinical outcomes (ORR).

2.4 Endpoints

Primary End point:
Overall response rate (ORR)

2.4.1 Complete response rate (CRR), partial response, stable disease, duration of response - overall response/stable disease
2.4.2 Clinical benefit response – percent of CR, PR, and SD

2.4.3 Median PFS, 1 year and 2 year overall survival (OS) rate
2.4.4 Safety and tolerability of the combination
2.4.5 Correlate changes in circulating and tissue biomarkers with clinical outcome (ORR)

3.0 SUBJECT ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all inclusion and no exclusion criteria to be registered into the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

1. Ability to understand and the willingness to sign a written informed consent.
2. Patients must have histologically or cytologically confirmed recurrent or metastatic pancreatic adenocarcinoma.
3. No prior systemic therapy for metastatic or recurrent disease.
   -Prior adjuvant therapy, if completed more than 6 months prior to date of enrollment, is acceptable.
   -Radiosensitizing chemotherapy, if completed at least 4 weeks from date of enrollment, is acceptable.
4. Measurable disease per RECIST1.1 criteria
5. Age 18-70 years at the time of enrollment
6. ECOG performance status 0 or 1
7. Have resolution of toxic effect(s) or intervention complication to Grade 1 or less (except alopecia) from any prior chemotherapy, major surgery, or radiation therapy of >30 Gy.
8. Adequate hematologic, hepatic, and renal function as defined per Table 2. All screening labs should be performed within 14 days of date of enrollment.

Table 2

Hemoglobin	≥ 10 g/dL
ANC	≥ 1,500/µL
Platelets	≥ 100,000/µL
Total bilirubin	< 1.5 x institutional ULN
AST (SGOT) & ALT(SGPT)	≤ 2.5 x institutional ULN in patients without known liver metastasis; ≤ 5 x institutional ULN in patients with known liver metastasis
Serum creatinine	≤ 1.5 times ULN, and calculated creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault equation)
INR or PT	International Normalized Ratio (INR) or Prothrombin Time (PT) ≤1.5 times the ULN
Albumin	≥ 3.0 g/dL

9. Female patients of childbearing potential must have a negative pregnancy test (either urine or serum pregnancy test). If the urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:
   - Has not undergone a hysterectomy or bilateral oophorectomy; or
   - Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

10. Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the

duration of study participation, and for ***120*** days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician, or study team member, immediately.

3.2 Exclusion Criteria

1. Is currently participating and receiving study therapy in a first line setting for metastatic or recurrent pancreatic adenocarcinoma.
2. Participated in a study of an investigational agent or used an investigational device within 4 weeks of the first dose of study treatment.
3. Patients with known untreated brain metastases. Patients without known or suspected brain metastases do not require radiologic imaging prior to enrollment.
4. Has a known additional malignancy that is progressing or requires active treatment. *Note: Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.*
5. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, significant pulmonary disease (shortness of breath at rest or mild exertion), or uncontrolled infection or psychiatric illness/social situations that would limit compliance with study requirements.
6. History of the following cardiac conditions:
7. Congestive cardiac failure of >Grade II severity according to the NYHA (defined as symptomatic at less than ordinary levels of activity);
8. Ischemic cardiac event including myocardial infarction within 3 months prior to date of enrollment
9. Uncontrolled cardiac disease, including unstable angina pectoris, uncontrolled hypertension (i.e. sustained systolic BP >160 mmHg or diastolic BP >90 mmHg), cardiac arrhythmia, or need to change medication due to lack of disease control within 6 weeks prior to date of enrollment;
10. History or presence of sustained bradycardia (≤55 BPM), left bundle branch block, cardiac pacemaker or ventricular arrhythmia. Note: Patients with a supraventricular arrhythmia requiring medical treatment, but with a normal ventricular rate are eligible;
11. Known family history or personal history of long QTc syndrome or previous drug-induced QTc prolongation of at least Grade 3 (QTc >500 ms).
12. Abnormal left ventricular ejection fraction (LVEF) on ECHO or MUGA less than <45%.
13. Current treatment with any agent known to cause Torsades de Pointes which cannot be discontinued at least five half-lives or two weeks prior to the first dose of study treatment.
14. Screening 12-lead ECG, in triplicate, with a measurable QTc interval according to Fridericia's correction >450 ms.
15. Known active infection with human immunodeficiency virus (HIV), hepatitis B or C viruses (screening not required, follow institutional practice):
16. Patients who have a history of hepatitis B infection are eligible provided they are hepatitis B surface antigen negative.
17. Patients who have a history of hepatitis C infection are eligible provided they have no evidence of hepatitis C ribonucleic acid using a quantitative polymerase chain reaction assay at least 6 months after completing treatment for hepatitis C infection.
18. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals.
19. Treatment with any medication which is predominantly metabolized by CYP3A4 and has a narrow therapeutic index
20. Major surgery within 4 weeks prior to date of enrollment; excluding skin biopsies and procedures for insertion of central venous access devices.
21. Inability to tolerate oral medication

22. Existing gastrointestinal disease affecting drug absorption such as celiac disease or Crohn's disease, or previous bowel resection which is considered to be clinically significant or could interfere with absorption.
23. Known lactose intolerance
24. Is pregnant or breastfeeding
25. Any significant medical condition lab abnormality, or psychiatric illness, in the opinion of the investigator, that might interfere with the patient's participation in the study or in the evaluation of the study results.
26. Unwillingness or inability to comply with study procedures.

4.0 TREATMENT PLAN

4.1 Phase 1b Treatment Dosage and Administration

REGIMEN DESCRIPTION					
Agent	**Premedications; Precautions**	**Starting Dose**	**Route**	**Schedule**	**Cycle Length**
bemcentinib	Do not eat for at least two hours before and one hour following bemcentinib dose. Take at same time each day.	200 mg	orally	Daily starting on Cycle 1 day 2	3 weeks (21 days)
nab-paclitaxel	Infusion time – 30 min (+/- 5 min)	100 mg/m2	intravenously	Day 1 and 8	
gemcitabine	Infusion time – 30 min (+/- 5 min)	800 mg/m2	intravenously	Day 1 and 8	
cisplatin	Infusion time – 60 min (+/- 5 min)	25 mg/m2	intravenously	Day 1 and 8	

4.2 Phase 2 Treatment Dosage and Administration

REGIMEN DESCRIPTION					
Agent	**Premedications; Precautions**	**Starting Dose**	**Route**	**Schedule**	**Cycle Length**
bemcentinib	Do not eat for at least two hours before and one hour following bemcentinib dose. Take at same time each day.	200 mg	orally	Daily starting on Cycle 1 day 2	4 weeks (28 days)
nab-paclitaxel	Infusion time – 30 min (+/- 5 min)	125 mg/m2	intravenously	Day 1, 8, and 15	
gemcitabine	Infusion time – 30 min (+/- 5 min)	1000 mg/m2	intravenously	Day 1, 8, and 15	

The study drugs will be stored according to package inserts.
Drugs will be administered in the following order with the specified pre-medications and hydration:

Pre-medication:
Phase 1b only Pre cisplatin hydration: 0.9% Sodium Chloride Injection 1000 mL with Mannitol 18.5 grams and Magnesium Sulfate 2 grams IV infusion over 2 hours on days 1 and 8 repeated every 21 days.

Phase 2 Aloxi (palonosetron) 0.25 mg IV, Emend (fosaprepitant) 150 mg IV and dexamethasone 12 mg IV within 30 minutes prior to treatment on days 1, 8, 15 repeated every 28 days. Patients will continue oral antiemetic prophylaxis at home with dexamethasone 4 mg bid for 2 days after chemotherapy.

Phase 1b - Chemotherapy administration:
Nab-paclitaxel 100 mg/m^2 in NS dilute to a total concentration of 5 mg/mL (DO NOT FILTER) over 30 minute IV infusion on days 1 and 8 repeated every 21 days, followed by:
Cisplatin 25mg/m^2 in 500 mL of NS over 60 minute IV infusion on days 1 and 8 repeated every 21 days, followed by:
Gemcitabine 800 mg/m^2 in 500ml over 30 minute IV infusion on days 1 and 8 repeated every 21 days

Phase 2 – Chemotherapy Administration:
Nab-paclitaxel 125mg/m^2 in NS dilute to a total concentration of 5 mg/mL (DO NOT FILTER) over 30 minute IV infusion on days 1, 8, 15 repeated every 28 days, followed by:
Gemcitabine 1000 mg/m^2 in 500ml over 30 minute IV infusion on days 1, 8, 15 repeated every 28 days

Post-hydration
Phase 1b only Post-cisplatin hydration: 0.9% Sodium Chloride Injection 1000 mL IV infusion over 3 hours on days 1 and 8 repeated every 21 days. May start at the same time as the gemcitabine infusion.

(Premedication and drug concentration may be changed to match institutional standard of care)

4.3 Administration of bemcentinib

- Bemcentinib is provided in bottles containing a specified number of capsules per bottle to dispense to patients. Patients will be asked to take the specified number of capsules for their prescribed dose on an empty stomach at a similar time each morning when they wake or more than 2 hours after a light meal, with water. To maintain a fasted state, patients should be told not to eat or drink anything other than water for at least 1 hour after taking the drug.

- At all clinic visits, patients will be asked not to take their bemcentinib dose before coming into the clinic. All samples will be collected pre-dose (for both chemotherapy and bemcentinib) prior to bemcentinib and chemotherapy administration.

4.4 Toxicities and Dosing Delays/Dose Modifications

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table (Section 5.5).
Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Toxicity will be graded according to the NCI CTCAE, Version 5 (which is available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf). For any event which is apparent at baseline, the dose modification will apply according to the corresponding shift in toxicity grade if the investigator feels this is appropriate, (e.g. if a patient has grade 1 asthenia at baseline which increases to grade 2 during treatment, this will be considered as a shift of 1 grade and treated as a grade 1 toxicity for dose modification purposes).

A cycle of therapy may be delayed up to 21 days to allow for weather events, patient's personal emergencies, observation of holidays, or other unforeseen delays that the Investigator deems to be in the best interest of the patient.

For any dose interruptions, re-initiation of therapy may be delayed for a maximum of 21 days to allow recovery from any toxicity. In exceptional cases where subjects are responding or

receiving clinical benefit, re-initiation of therapy after missing > 21 consecutive days of treatment may be done on a case-by-case basis after confirmation with the Principal Investigator and/or Medical Monitor

Treatment related toxicities will be attributed by investigators as:
1) Bemcentinib related,
2) Chemotherapy related or
3) Related to combination of bemcentinib+chemotherapy.

Dose modifications and treatment delays based on observed drug-related toxicity will be performed as described below.

4.4.1 Bemcentinib Dose modifications

If a patient experiences toxicity deemed related to bemcentinib, as defined by probably or definitely related, please follow guidance in Table 3. Tolerability is determined by the PI/ treating Sub-Investigator.

Table 2: Dose modification of bemcentinib for toxicity

Grade (CTCAE)	Recommended Dose Modification
Grade 1	
Any occurrence	Maintain dose at 200mg (no modification)
Grade 2	
Any occurrence	Interrupt treatment until toxicity returns to baseline or Grade 1, then resume bemcentinib at 200mg daily. If the patient develops the same toxicity at Grade 2, please discuss with medical monitor
Grade 3	
Any occurrence	Interrupt treatment until toxicity returns to baseline or Grade 1 Resume bemcentinib at 100 mg daily on Day 1 of subsequent cycle, then titrate up to 200 mg daily . If 200 mg daily dose is not tolerated, reduce the dose to 100 mg daily. If the patient develops the same toxicity at Grade 3, please discuss with medical monitor /PI
Grade 4	
1st occurrence	Discontinue permanently or discuss with medical monitor/PI
Notes: • Dose reduction below 100 mg daily is not possible (a single capsule contains 100 mg bemcentinib) • Patients being considered for dose reduction or permanent discontinuation of bemcentinib may be discussed with the Medical Monitor/PI • Patients are eligible for a 12 week dose delay with bemcentinib. For delays longer than 12 weeks, Medical Monitor/ PI approval is needed	

If after a 21 day delay, bemcentinib-related toxicity has not resolved to Grade ≤ I the patient should be withdrawn from the study, unless the request is made due to rationale mentioned in section 4.3. Once a patient has undergone a dose reduction subsequent escalation is not possible.

In order to reduce the risk of QTc prolongation, all efforts should be made to maintain the patient's serum potassium levels at > 4 mmol/L during treatment with bemcentinib and for 2 weeks following

completion of therapy. Patients with a QTc of ≥ 480 ms should be closely monitored on the clinical trial unit until their QTc falls below 480 ms and their electrolytes should be measured and corrected as necessary.

If a patient experiences QTc prolongation despite normal serum potassium and magnesium levels, bemcentinib dosing should be modified as outlined in Table 4. If a patient experiences ventricular arrhythmia at any time they should be withdrawn from the study.

Table 4: Dose Modification of bemcentinib for QTc Prolongation

QTcF	Recommended bemcentinib Dose Modification
Grade 1 (451-480 ms)	
Any occurrence	No dose modification required
Grade 2 (481-500 ms)	
1st occurrence and 2nd occurrence	Continue dosing and conduct weekly ECGs; i) if QTcF reduces to ≤Grade 1 by 14 days from initial recording, no dose modification is required ii) if QTcF does not reduce to ≤Grade 1 by 14 days from initial recording, dose reduce to 100 mg daily and titrate it to 200mg if possible
3rd and subsequent occurrence	At 3rd occurrence, interrupt bemcentinib dosing for ≤ 14 days and conduct weekly ECGs; i) if QTcF reduces to ≤Grade 1 within 14 days, restart bemcentinib at 100 mg dose and maintain at 100 mg for the remainder of the study ii) if QTcF does not reduce to ≤Grade 1 within 14 days, discontinue treatment permanently or discuss with medical monitor. At any subsequent occurrence, discontinue treatment permanently or discuss with medical monitor.
≥Grade 3 (≥501 ms)	
Any occurrence	For 1st occurrence, interrupt treatment for ≤14 days; - if QTcF reduces to ≤Grade 1, reduce dose by 100 mg daily, discontinue treatment if dose reduction is not possible or discuss with medical monitor - if QTcF does not reduce to ≤Grade 1, discontinue treatment or discuss with medical monitor For 2nd occurrence, discontinue treatment or discuss with medical monitor
Ventricular arrhythmia	
Any occurrence	Discontinue permanently

Notes:
- Serum calcium, magnesium and potassium should be measured per schedule of events while as defined in study procedure whilst receiving bemcentinib;
- Treatment interruption for bemcentinib-related QTcF prolongation is only allowed for 14 days
- Dose reduction below 100 mg daily is not possible (a single capsule contains 100 mg bemcentinib)
- Patients being considered for dose reduction or permanent discontinuation of bemcentinib may be discussed with the Medical Monitor

4.4.2 Chemotherapy dose modifications

Any toxicity associated or possibly associated with gemcitabine and Nab-Paclitaxel treatment may be managed according to standard medical practice.

- A maximum of 21 day treatment delay, from date of intended dose, is permitted to allow recovery of toxicities.
- In the event that patients must have treatment delayed within a cycle, those doses held during a cycle will be skipped and not made up – treatment schedule will not be altered from Q4W design due to skipped dose.
- If chemotherapy is on hold due to treatment related toxicity the treating investigator will determine whether to concurrently hold or continue bemcentinib.
- Dose modifications/delay/cessation of individual drugs (bemcentinib, gemcitabine, Nab-Paclitaxel, or cisplatin) can be done based on the specific toxicity.
- Once a dose of any study drug has been reduced, it should not be increased at a later time.
- Growth factors may be used to treat hematologic toxicity, per institutional standard, and will not constitute a dose reduction.

Table 5: Phase 1b Dose Levels

Dose Level	Nab-Paclitaxel (mg/m2)	Cisplatin (mg/m2)	Gemcitabine (mg/m^2)	Bemcentinib
Baseline	100	25	800	200 mg
- 1	75	25	600	200 mg
- 2	50	25	600	100 mg

Table 6: Phase 2 Dose Levels

Dose Level	Nab-Paclitaxel (mg/m2)	Gemcitabine (mg/m^2)	Bemcentinib
1 - Baseline	125 D1, 8, 15	1000 D1, 8, 15	200 mg
- 1	125 D1, 15	1000 D1, 15	200 mg
- 2	100 D1, 15	800 D1, 15	200 mg
- 3	75 D1, 15	600 D1, 15	100 mg

Hematologic Toxicity

In the event dose modifications are required at the beginning of a cycle or within a cycle due to hematologic toxicities, doses of nab-paclitaxel and gemcitabine may be adjusted as detailed below.

Table 7: Dose Modifications for Day 1 of Each Cycle (Hematologic Toxicity)

ANC		Platelets	Timing
≥ 1,500 cells/mm^3	AND	≥ 100,000/uL	Treat on time
< 1,500 cells/mm^3	OR	< 100,000/uL	Delay by 1 week intervals until recovery

Table 8: Phase 1b/2 Dose Modifications for Day 8, 15 of Each Cycle (Hematologic Toxicity)*

Day 8 Laboratory Results	Nab-Paclitaxel	Cisplatin (Phase 1b only)	Gemcitabine
ANC > 1000 and Platelets ≥ 100,000	100%	100%	100%
ANC 500-1000[a] or Platelets 50,000-99,000	Decrease dose by 1 level (treat on time)	100%	Decrease dose by 1 level (treat on time)
ANC < 500 or Platelets < 50,000	HOLD	HOLD	HOLD
Febrile Neutropenia (Grade 3 or 4)[b]	HOLD. Upon resuming dosing, decrease to next lower dose level and do not re-escalate throughout the rest of treatment.	HOLD	HOLD. Upon resuming dosing, decrease to next lower dose level and do not re-escalate throughout the rest of treatment.
Recurrent Febrile Neutropenia (Grade 3 or 4)	Decrease 2 dose levels from prior and do not re-escalate throughout the rest of treatment.	HOLD	Decrease 2 dose levels from prior and do not re-escalate throughout the rest of treatment.

* See Table 4 for dose reductions guidelines.

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

[b] Febrile neutropenic patients should have their chemotherapy treatment interrupted and the following work up and treatment is recommended: A full sepsis diagnostic work-up should be performed while continuing broad spectrum antibiotics. If cultures are positive, the antibiotic may or may not be changed, depending on the sensitivity profile of the isolated organism. Patients with persisting fever after 3 weeks, despite uninterrupted antibiotic treatment, will discontinue study treatment. Patients can also receive G-CSF, in addition to antibiotic treatment, to hasten the resolution of their febrile neutropenia (following current institutional guidelines). In all cases, blood counts must have returned to non-neutropenic levels before resuming chemotherapy treatment.

Special Instructions Regarding Treatment of Chemotherapy-related Toxicity

Dose modification or delay may occur in the setting of lower Grade toxicity if the treating physician believes that it is in the interest of a subject's safety. Alopecia and nausea and/or vomiting that can be controlled by antiemetics do not require dose modification or interruption. No dose reduction or interruption will be required for anemia as it can be satisfactorily managed by transfusions. Suggested guidance for dose reductions for non-hematologic toxicity are listed below. Nab-Paclitaxel and Gemcitabine and specific exceptions are listed separately below Tables 8 and 9.

Table 9: Guidance for Phase 1b/2 Dose Modifications on Day 1 of Each Cycle (Non-Hematologic Toxicity)*

Toxicity	Nab-Paclitaxel /Gemcitabine dose this cycle
Grade 0-2 toxicity	Same as Day 1 previous cycle (except for Grade 2 cutaneous toxicity where doses of nab-paclitaxel/gemcitabine can be reduced to next lower dose level – see below)
Grade 3 toxicity[a,c]	Decrease nab-paclitaxel/gemcitabine to next lower dose level[a]
Grade 4 toxicity[b]	Off protocol treatment[b]

Dose held in 2 previous consecutive cycles	Decrease nab-paclitaxel/gemcitabine to next lower dose level and continue throughout the rest of treatment

* Except peripheral neuropathy and nephrotoxicity (see section 4.3.2.4)
a If the toxicity only affects neuropathy, then only nab-paclitaxel should be reduced (see below).
b Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement (see below).
c Excluding ≥ Grade 3 electrolyte abnormality that lasts <24 hours to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions.

Table 10: Guidance for Phase 1b/2 Dose Modifications on Day 8 & 15 of Each Cycle (Non-Hematologic Toxicity)

CTC Grade	% of Day 1 Nab-Paclitaxel/Gemcitabine Dose
0-2	100%[a]
3+	Hold treatment until resolution to ≤ Grade 1[b,c]

a Except for cutaneous toxicity (see below).
b Pulmonary embolism (a Grade 4 toxicity in the CTCAE tables) if mild or asymptomatic, will be exempt from this requirement.
c Excluding electrolyte abnormalities per judgment of the physician/investigator.

4.4.2.1 G-CSF Administration

The exact dosage amount and schedule for G-CSF support will be left to the treating physician's discretion. A recommended approach would be to administer G-CSF 5 mcg/kg/day (rounded to the nearest vial size per investigator's standard of care) 24 hours after chemotherapy until recovery to the predetermined neutrophil count.

4.4.2.2 Sensory Neuropathy

nab-paclitaxel treatment should be withheld in patients who experience ≥ Grade 3 peripheral neuropathy. Gemcitabine administration can continue during this period. Patients experiencing peripheral neuropathy that requires a delay in scheduled nab-paclitaxel dosing for ≥ 21 days will discontinue study treatment. The time to resolution to Grade ≤ 2 should be the adverse event duration used for adverse event reporting. In those patients who experience Grade 4 sensory neuropathy, both drugs should be withheld, and treatment resumed at a reduction of 2 dose levels (Dose Level -2) in subsequent cycles after the sensory neuropathy improves to ≤ Grade 2. Note: the investigator may elect to dose modify for Grade 2 sensory neuropathy.

4.4.2.3 Cutaneous Toxicity

Patients who develop Grade 2 or 3 cutaneous toxicity should have their dose reduced to the next lower dose level as per Table 5. If the patient continues to experience these reactions, despite dose reduction, treatment should be discontinued. Patients who develop Grade 4 cutaneous toxicity should have treatment discontinued.

4.4.2.4 Gastrointestinal Toxicity

If Grade 3 mucositis or diarrhea occurs, all 3 study drugs should be withheld until resolution to ≤ Grade 1, then reinstituted at the next lower dose level as per Table 4. Patients who develop Grade 4 mucositis or diarrhea should have treatment discontinued.

4.4.2.5 Pulmonary Embolism

Asymptomatic or clinically mild pulmonary embolism can be treated with low-molecular weight heparin without interruption of therapy. Moderate to severe pulmonary embolism will require permanent discontinuation of treatment.

4.4.2.6 Interstitial Pneumonitis

Pulmonary toxicity has been reported for both gemcitabine and paclitaxel. Epidemiology reports show that gemcitabine monotherapy is weakly associated with lung toxicity. A retrospective review of pooled clinical trial data of 4,448 patients with mixed cancer indications reported an incidence of dyspnea of 0.2% and serious pulmonary toxicity of 0.06%.

During study participation, patients should be carefully monitored for signs and symptoms of pneumonitis (i.e. episodes of transient or repeated dyspnea with unproductive persistent cough or fever) and, if observed, immediate clinical evaluation and timely institution of appropriate management (emphasizing the need for corticosteroids if an infectious process has been ruled out as well as appropriate ventilation and oxygen support when required). Administration of study drugs will be permanently discontinued upon making a diagnosis of interstitial pneumonitis.

Prevention, Surveillance and Management of Interstitial Pneumonitis

During study treatment, episodes of transient or repeated dyspnea with unproductive persistent cough or fever should be paid attention to. Radiographic evaluation with chest X-rays and CT scans (normal or high resolution) may be indicated to look for infiltrates, ground-glass opacities, or honeycombing patterns. Pulse oximetry and pulmonary function tests can show respiratory and ventilation compromise.

Infections should be ruled out with routine immunological/ microbiological methods. Transbronchial lung biopsy is not recommended, given its limited value and risk of pneumothorax and hemorrhage, and should be reserved for cases with unclear etiology.

Study drug administration should be interrupted upon diagnosis of interstitial pneumonitis and patients permanently discontinued from further study drug treatment. After ruling out an infectious etiology, intravenous high-dose corticosteroid therapy and secondary pathogen coverage should be instituted without delay. Patients with an added immunological component may also require immune modulation with azathioprine or cyclophosphamide. Appropriate ventilation and oxygen support should be used when required.

4.4.2.7 Sepsis

Sepsis has been reported in less than 1% patients during Nab-Paclitaxel monotherapy and fatalities attributed to these events have been rare. However, the risk was appreciably higher in patients with advanced or metastatic pancreatic cancer receiving Nab-Paclitaxel in combination with gemcitabine with a rate of 5% in patients with or without neutropenia receiving Nab-Paclitaxel/gemcitabine. Complications due to the underlying pancreatic cancer, especially biliary obstruction, or presence of biliary stent, were identified as significant contributing factors. The increased risk of sepsis in the setting of advanced or metastatic cancer in combination with gemcitabine could be managed with prophylactic antibiotic treatment in febrile patients (regardless of neutrophil count) and dose reduction, and with G-CSF treatment in neutropenic patients. If a patient becomes febrile (regardless of neutrophil count), initiate treatment with broad spectrum antibiotics. For febrile neutropenia, withhold Nab-Paclitaxel and gemcitabine until fever resolves and ANC ≥ 1500, then resume treatment at reduced dose levels.

Prophylaxis Against Sepsis

Due to the incidences of non-neutropenic sepsis, at the first occurrence of fever ≥ 38.5°C (regardless of neutrophil count), institution of ciprofloxacin (500 mg orally, twice daily) or amoxicillin/clavulanate (500 mg orally, 2-3 times daily) in patients with allergy to

fluoroquinolones should be initiated. On their first visit, patients should be provided with enough ciprofloxacin (or the alternative antibiotic) for use at home, and they should be instructed to begin taking it when they first record a temperature of ≥ 38.5 °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 and to be evaluated for sepsis as soon as possible. Hospitalization or evaluation in the emergency room may be required depending on the clinical presentation. If hospitalization is required, this should be reported as a Serious Adverse Event (SAE).

4.4.2.8 Hypersensitivity Reactions

Hypersensitivity reactions rarely occur. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Patients who experience severe hypersensitivity reactions to Nab-Paclitaxel should not be re-challenged. It is not recommended to administer Nab-Paclitaxel to patients with prior hypersensitivity to a taxane.

Nab-Paclitaxel Premedication

Patients do not require premedication prior to Nab-Paclitaxel administration, as hypersensitivity reactions are rare. Although the solubilizing agents Cremophor® EL and Tween® 80 have long been implicated in adverse events including hypersensitivity reactions due to their detergent-like nature and known ability to induce histamine release[43], the administration of solvent-based taxanes (Taxol® and Taxotere®) requires premedication with corticosteroids and histamine receptor blocking agents to prevent the occurrence of hypersensitivity reactions. However, the hypersensitizing role of the taxane molecules themselves cannot be ruled out.

In the unlikely event of a mild hypersensitivity reaction, premedication may be administered using the premedication regimen the institution typically uses for solvent based paclitaxel. In the rare event of a severe hypersensitivity reaction, discontinue Nab-Paclitaxel.

Concomitant Medications

Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator. Erythropoietin and G-CSF may be administered at the discretion of the investigator, consistent with institutional guidelines.

4.5 Concomitant Medications/Treatments

Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator.
Erythropoietin and G-CSF may be administered at the discretion of the investigator, consistent with institutional guidelines.
Concurrent treatment with any agent known to cause Torsade de Points is an exclusion criterion for the study.

4.6 Other Modalities or Procedures

Blood and tissue specimens will be collected, for analysis of pharmacodynamic endpoints of therapy.
Detailed procedures for the collection, processing, storage, and shipment of the samples will be provided in the Study Laboratory Manual.

Tissue collection:

Baseline tissue collection: Baseline tissue specimen should be requested/collected as specified in the lab manual(tissue block is preferred). Repeat biopsy is not required at baseline, archival tissue is sufficient.

On treatment tissue: The on-treatment tissue collection should be performed, if feasible, during Cycle 2 or Cycle 3 in patients who consent to tissue collection.

- The most accessible tumor disease site (preferably not a target lesion), as determined by investigator, will be biopsied.
- Up to 3 X Core needle biopsy will be preferred when clinically possible.

Blood
Refer to lab manual for details

Baseline sample Cycle 1 Day 1: Baseline sample should be collected prior to treatment.

On treatment samples: On treatment blood samples will be collected pre-dose on the following days:

1. Cycle 1 Day 2
2. Cycle 1 Day 4
3. Cycle 1 Day 8
4. Cycle 1 Day 11
5. Cycle 1 Day 15
6. Cycle 2 Day 1
7. Cycle 2 Day 8
8. Cycle 2 Day 15
9. Day 1 of each subsequent cycle
10. At the time of disease progression or End of Study visit, whichever comes first.

4.7 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the subject unacceptable for further treatment in the judgment of the investigator

4.8 Duration of Follow Up

After completion of treatment, for any reason, subjects will be followed until death, lost to follow-up, or withdraw of consent for long term follow-up.

4.9 Removal of Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 5.6 apply. Notify the UTSW Principal Investigator and document the reason for study removal and the date the subject was removed in the Case Report Form. The subject should be followed-up per protocol.

4.10 Subject Replacement

Phase 1b: Patients in safety run-in phase should be followed for at least 3 weeks (Cycle 1). Patients who are withdrawn prior to the 3 week monitoring in the run-in phase will be replaced to allow the stated number of patients to be observed for safety.

Phase 2: Patients in safety run-in phase should be followed for at least 4 weeks (Cycle 1). Patients who are withdrawn prior to the 4 week monitoring in the run-in phase for any reason other than DLT will be replaced to allow the stated number of patients to be observed for safety.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed solely for the purpose of this research study will be done only after obtaining informed consent. However, assessments performed for routine care of the patient may be used for baseline values even if completed before informed consent was obtained.

All screening procedures must be performed within **21 days** prior to date of enrollment, with the exception of laboratory assessments. The screening procedures include:

- Informed Consent
- Medical history
- ECOG Performance Status
- Inclusion / exclusion criteria
- Vital Signs
- Physical examination
- Concomitant medication notation
- Tumor Measurements per RECIST 1.1
- Hematology: CBC with differential and platelet count
- Serum chemistries: glucose, creatinine, BUN, total bilirubin, AST, ALT, alkaline phosphatase albumin, LDH, total protein, and electrolytes (sodium, potassium, phosphorus, chloride, C02, magnesium, calcium). In patients with known Gilbert's syndrome, it is recommended to perform a direct bilirubin and indirect bilirubin. Calculate creatinine clearance.
- CA 19-9
- CPK
- Pregnancy test (either urine or serum pregnancy test) within 72 hours prior to the first dose of study treatment. If the urine pregnancy test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
- EKG - triplicate 12-lead EKGs must be taken less than 5 minutes apart with the patient having rested for at least 10 minutes in the supine position prior to assessment
- ECHO or MUGA
- Archival Tissue for correlative analysis. Baseline tissue specimen should be requested/collected as specified in the lab manual (tissue block is preferred). Repeat biopsy is not required at baseline, archival tissue is sufficient. Confirmation or presence of archival tumor tissue is not mandatory for eligibility.

5.2 Procedures During Treatment (Cycle is 28 days)

Day 1

- Inclusion/exclusion review (Cycle 1 only)
- Physical exam
- Vital Signs
- Measurement of weight (kg) and BSA calculation prior to dosing
- ECOG Performance Status
- Hematology
- Serum chemistries
- Blood for correlative analysis
- CA 19-9 (C3 and every subsequent odd cycle Day 1)
- CPK (C3 and every subsequent odd cycle Day 1
- EKG (not Cycle 1)
- Pregnancy Test
- Adverse Events (AEs) using the NCI CTCAE 5.0
- Concomitant medication notation
- Chemotherapy administration
- PK testing (5ml at cycles 2, 3 and 4 only) – 1st 15 patients only.
- Tumor measurements per RECIST 1.1 (before C3 and prior to every odd cycle)
- Optional Tissue biopsy for correlative analysis. The on-treatment tissue collection should be performed during Cycle 2 or Cycle 3 in patients who consent to tissue collection

Day 2 (Only cycle 1 for patients receiving bemcentinib

- Vital Signs
- Hematology
- EKG
- Blood for correlative analysis
- AEs using the NCI CTCAE 5.0
- Concomitant medication notation
- Start bemcentinib dosing

Day 4 (Only cycle 1 for patients receiving bemcentinib)

- Vital Signs
- EKG
- Hematology
- Blood for correlative analysis
- AEs using the NCI CTCAE 5.0
- PK testing 1st 15 patients only
- Concomitant medication notation
- Bemcentinib dosing

Day 8 of each cycle

- Vital Signs
- Hematology

- Serum chemistries
- Blood for correlative analysis (Cycle 1 and 2 only)
- AEs using the NCI CTCAE 5.0
- PK testing (Cycle 1 only) 1st 15 patients only
- EKG bemcentinib patients only
- Concomitant medication notation
- Chemotherapy administration
- Bemcentinib dosing

Day 11 (Only cycle 1 for patients receiving bemcentinib)

- Vital Signs
- EKG
- AEs using NCI CTCAE 5.0
- PK testing 1st 15 patients only
- Concomitant medication notation
- Bemcentinib dosing

Day 15 of each cycle

- Vital Signs
- Hematology
- Serum chemistries
- Blood for correlative analysis (Cycle 1 and 2 only)
- AEs using the NCI CTCAE 5.0
- PK testing (Cycle 1 only) 1st 15 patients only
- EKG bemcentinib patients only
- Concomitant medication notation
- Chemotherapy administration
- Bemcentinib dosing

Day 18 (Only cycle 1 for patients receiving bemcentinib)

- Vital Signs
- EKG
- AEs using the NCI CTCAE 5.0
- Concomitant medication notation
- Bemcentinib dosing

Off Treatment Visit (30 days after last dose – any drug)

- Physical Exam
- Measurement of weight (kg) and BSA calculation
- Vital signs
- ECOG Performance status
- Hematology
- Serum chemistries
- CA 19-9
- CPK

- EKG (only for patients that received bemcentinib)
- Blood for correlative analysis
- AEs using the NCI CTCAE 5.0
- Concomitant medication notation

5.3 Follow-up Procedures

- If treatment related toxicities occur, the subject will be followed every month (+/- 7 days), from off treatment visit date, after completion of (or early withdrawal from) study treatment until resolution
- If no treatment related toxicities occur, the subject will be followed for survival end points every 3 months (+/-7 days), from off treatment visit date. This may be done through medical record review or phone call.

Schedule of Events	Screening	C1D1	C1D2 & C1D4	C1 D8	C1 D11	C1 D15	C1 D18	C2+ D1[i]	C2+ D8[i]	C2+ D15[i]	Off -Tx	Long Term FU
Informed Consent	X											
Medical History	X											
Performance Status	X	X						X			X	
Inclusion / exclusion criteria	X	X review										
Vital Signs[a]	X	X	X	X	X	X	X	X	X	X	X	
Weight and BSA Calculation	X	X						X			X	
Physical examination[b]	X	X						X			X	
Adverse events		X	X	X	X	X	X	X	X	X	X	
Tumor Measurements	X							X before C3, etc.				
Hematology[c]	X	X	X	X		X		X	X	X	X	
Serum Chemistry[c]	X	X		X		X		X	X	X	X	
Tumor Marker CA19-9	X							X C3, etc.			X	
CPK	X							X C3, etc.			X	
Pregnancy test[d]	X	X						X				
PK testing[e]		X	X	X	X	X		X C2, 3 & 4 only				
EKG[f]	X		X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	X[f]	
ECHO or MUGA	X							X[g]			X[g]	
Blood for Correlative analysis[j]		X	X	X		X		X[j]	X[h]	X	X	
Archived Tissue for Correlative analysis	X											
Optional: Tissue biopsy								X (once) Cycle 2 or 3				
Chemotherapy dosing		X		X		X		X	X	X		
Bemcentinib dosing[j]			X	X	X	X	X	X	X	X		
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	

Survival Status												X

a Vital signs include BP, HR, RR, temperature. Height is only required at screening.
b Full physical examination includes neuropathy assessment at screening, C1D1, and end of study.
c See sections 5.1 for full listing of required labs
d Only for women of childbearing potential
e PK samples will be taken for the first 15 patients.
f For the screening, triplicate 12-lead EKGs must be taken less than 5 minutes apart with the patient having rested for at least 10 minutes in the supine position prior to assessment. All subsequent assessments are single ECGs unless QTc prologation is observed, then triplicate ECGs will be required. If a patient has bemcentinib interrupted for 14 days or more for toxicity, an ECG will be conducted twice weekly for the following 2 weeks once a patient restarts daily dosing. If patient is permanently discontinued from bemcentinib, with no residual cardiovascular related toxicities, ECGs can be discontinued until off treatment visit.
g ECHO or MUGA as clinically indicated
h Collect only at Cycle 2
i +/- 3 day window for subsequent cycles to account for holidays. Patient may be treated before a test is resulted provided the following is met: 1) test is drawn and pending, 2) investigator deems safety of the patient will not be effected, and 3) all protocol specified treatment parameters are met.
j Please refer to lab manual for additional collection details. No longer required if bemecentinib is permanently discontinued.

5.5 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

- Subject voluntarily withdraws from treatment (follow-up permitted);
- Subject withdraws consent (termination of treatment and follow-up);
- Subject is unable to comply with protocol requirements;
- Subject demonstrates disease progression (unless continued treatment with study drug/treatment is deemed appropriate at the discretion of the investigator and approval by PI);
- Subject experiences toxicity that makes continuation in the protocol unsafe;
- Treating physician judges continuation on the study would not be in the subject's best interest;
- Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);
- Lost to follow-up, only after 3 documented attempts, he or she can be deemed lost to follow-up.

6.0 MEASUREMENT OF EFFECT

6.1 Antitumor Effect-Solid Tumors

Response and progression will be evaluated in this study using the new international RECIST criteria (version 1.1, 2009) proposed by the RECIST committee[44]. All patients who have measurable disease according to the RECIST criteria and who have their disease re-evaluated will be evaluable for response. For the purposes of this study, patients should be reevaluated for response approximately every 3 cycles. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term

"evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

6.1.1 Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with study therapy.

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

6.1.2 Disease Parameters

Measurable Disease:
Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT or MRI) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease.
All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI). For bone and cystic lesions please refer to the RECIST criteria (version 1.1, 2009).

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Target lesions.
A maximum of 2 lesions per organ and 5 lesions in total should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the diameters for all target lesions (longest for non-nodal lesions, short axis for nodal lesions) will be calculated and reported as the baseline sum diameters (LD). The baseline sum diameters will be used as reference by which to characterize the objective tumor response.

Non-target lesions.
All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. "multiple enlarged pelvic lymph nodes" or "multiple liver metastases"). Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.1.3 Methods for Evaluation of Measurable Disease

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

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

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and Magnetic Resonance Imaging. Conventional CT and MRI should be performed to obtain images of 5 mm or less slice thickness.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., 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.

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target and non-target lesions including normalization of elevated tumor marker level. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. All non-target lymph nodes must be non-pathological in size (< 10 mm short axis). Complete response must be confirmed at a second tumor assessment not less than 4 weeks apart from the assessment at which CR was observed.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. Partial response must be confirmed at a second tumor assessment not less than 4 weeks apart from the assessment at which PR was observed.

Progressive Disease (PD):
At least a 20% increase (and an absolute increase of at least 5 mm) in the sum of LD of measured lesions taking as references the smallest sum LD recorded since the treatment started. Appearance of new lesions will also constitute PD. In exceptional circumstances, unequivocal progression of non-target lesions may be accepted as evidence of disease progression.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Non-CR/Non-PD: Persistence of 1 or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

(Non-CR/Non-PD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the study chair.

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

6.1.5 Time point evaluation

At each protocol specified time point, a response assessment occurs. Table 9 provides a summary of this for patients who have measurable disease at baseline. Table 10 provides a summary of this for patients with non-measurable (therefore non-target) disease.

Table 11: Response for Measurable Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires
CR	CR	No	CR	≥ 4 weeks Confirmation
CR	Non-CR/Non-PD	No	PR	≥ 4 weeks Confirmation
CR	Not evaluated	No	PR	
PR	Non-PD or not all evaluated	No	PR	
SD	Non-PD or not all evaluated	No	SD	Documented at least once ≥ 6 weeks from baseline
Not All Evaluated	Non-PD	No	NE	NE
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. NE = inevaluable Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 12: Response for Non-measurable Disease

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
NE = inevaluable a ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.		

6.1.6 Evaluation of Best Overall Response

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

Table 13: Response Assignment

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

NE = inevaluable. If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact, the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment.

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

6.1.7 Duration of Response

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

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

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

6.1.8 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

6.2 Safety/tolerability

Analyses will be performed for all subjects having received at least one dose of study therapy. The study will use the CTCAE version 5.0 for reporting of non-hematologic adverse events (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40) and modified criteria for hematologic adverse events (Appendix #/letter).

7.0 ADVERSE EVENTS

7.1 Experimental Therapy

For the most recent safety update (in drug studies), please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

7.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, **will begin after the 1st dose of study drug** and are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event while on study or until 30 days post last dose, regardless of its relationship to study therapy, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- there is a satisfactory explanation other than the study therapy for the changes observed; or
- death.

7.2.1 Definitions

Adverse Events will be reported as indicated by the appropriate following table (see below).

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporally associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

OHRP and UTSW HRPP define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization[1,2] or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or

- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is, by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring ≥24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

[2] NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

7.2.2 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The phrase "unanticipated problems involving risks to subjects or others" is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

AND

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

7.2.3 Steps to Determine If a Serious Adverse Event Requires Expedited Reporting to the SCCC DSMC

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

Step 3: Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *may NOT be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported as indicated in the sections below.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the treatment. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol (if applicable);
- the drug package insert (if applicable);
- the current Investigator's Brochure (if applicable)
- the Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities section of this protocol

7.2.4 Reporting SAEs and UPIRSOs to the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC)

SAEs and UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs occurring during the protocol-specified monitoring period and all UPIRSOs should be submitted to the SCCC DSMC within 5 business days of the study team members awareness of the event(s). In addition, for participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events or unanticipated problems.

The UTSW study PI is responsible for ensuring SAEs/UPIRSOs are submitted to the SCCC DSMC Coordinator. This may be facilitated by the IIT project manager, study team, sub-site or other designee. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE or UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if

further action is required. *(See Appendix III of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized).*

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Comprehensive Cancer Center, the IIT Project Manager or designee ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all SAEs and UPIRSOs upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Telephone reports to: Muhammad Beg, MD 214-648-7029 Ellen Siglinsky-Clinical Research Manager 214-648-7031
Written reports to: Muhammad Beg, MD c/o GI Clinical Research Manager 5323 Harry Hines Blvd, NB2.418 Dallas, Texas 75390 Fax: 214-648-1906 UTSW SCCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-7084 or deliver to NB2.300 Email: GlobalSAEInbox@Chiltern.com UTSW Investigator Initiated Trial (IIT) Team Email: SCCC-IIT@UTSouthwestern.edu UTSW Institutional Review Board (IRB) Submit a Reportable Event via eIRB with a copy of the final sponsor report as attached supporting documentation

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or

recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

For purposes of this policy, UPIRSOs include unanticipated adverse device effects (UADEs) and death or serious injury related to a humanitarian use device (HUD).

UPIRSOs must be promptly reported to the UTSW HRPP within 5 working days of study team awareness.

For research relying on a non-UT Southwestern IRB (external, central, or single IRB):

Investigators relying on an external IRB who are conducting research on behalf of UT Southwestern or its affiliates are responsible for submitting **LOCAL** UPIRSOs to the UT Southwestern IRB within 5 working days of study team awareness. Investigators must report to their relying IRB according to the relying IRB's policy. In addition, the external IRB's responses or determinations on these local events must be submitted to the UT Southwestern IRB within 10 working days of receipt.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/hrpp/quality-assurance/

7.4 Stopping Rules

The study can be stopped early based on the following critiera:

- Per PI or sponsor discretion
- DSMC recommendation
- Futility analysis as detailed in section 10.2.

8.0 DRUG/TREATMENT INFORMATION

Gemcitabine: See standard prescribing information
Nab-paclitaxel: See standard prescribing information
Cisplatin (Phase 1b): See standard prescribing information

8.1 Agent bemcentinib

- Other names for the drug(s): BGB324, R428
- Classification - type of agent: Kinase inhibitor
- Mode of action: Inhibitor of Axl kinase
- Storage and stability: bemcentinib capsules should be stored at or below 25°C in white round polyethylene bottles
- Protocol dose: 200mg daily
- Preparation: Capsules of 100mg bemcentinib
- Route of administration for this study: Oral

- Incompatibilities: Concurrent treatment with any agent known to cause Torsade de Points is an exclusion criterion for the study.
- Continuous treatment with more than 40mg prednisolone (or equivalent dose of systemic corticosteroid) is prohibited throughout the trial.
- Treatment with any medication which is predominantly metabolized by CYP3A4 and has a narrow therapeutic index is an exclusion criterion for the study.
- Availability: Provided by BerGenBio free of charge
- Side effects: Adverse Drug Reactions occurring in ≥10% of patients are diarrhea, nausea, vomiting and electrocardiogram QT prolongation. Please refer to the current Investigator's Brochure for further details.
- Nursing implications: EKG monitoring

8.1.1 Return and Retention of Study Drug

Institutional pharmacy standard operating procedures will be followed for retention, storage, and destruction of study drug.

8.1.2 IP Compliance

IP will be dispensed with a paper pill diary and instructions on how to complete and record each dosage.

9.0 CORRELATIVES/SPECIAL STUDIES

Tissue and blood biomarker assays are proposed with the goal to assess the effect of combination chemotherapy and bemcentinib on 1) AXL pathway activity in tumor tissue, 2) changes in immune landscape including upregulation of immune cytokines, and immune cell infiltration into the tumor, 3) apoptosis and decreased proliferation of tumor, and 4) to identify predictive biomarkers of response.

Please see Laboratory Manual for details on blood and tissue collection guidelines. All shipments and questions should be directed to the following:

Attn: Dr. Farjana Fattah
Biomarker Research Core (BRC) Laboratory
Simmons Comprehensive Cancer Center
6001 Forest Park Rd, ND2.136
Dallas, TX 75390
Phone: (214) 645-6430
Back-Up Phone: (214) 648-4673
Fax: (214) 645-6347

9.1 Sample Collection Guidelines

Samples will be collected at the time points listed in section 5 of this protocol.

For details on sample collection and processing please refer to Laboratory Manual.

9.2 Assay Methodology

Samples will be stored at each investigators' facility until requested by UTSW Coordinating Center. Batched analysis will be performed on study samples. A committee comprised of study investigators will determine the final correlative analysis plan.

9.3 Specimen Banking

Subject samples collected for this study will be retained at UT Southwestern. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the subject, best efforts will be made to stop any additional studies and to destroy the specimens.

Muhammad Shaalan Beg, MD will be responsible for reviewing and approving requests for clinical specimen from potential research collaborators outside of the University of Texas Southwestern Medical Center. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimen will be the property of the University of Texas Southwestern Medical Center for publication and any licensing agreement will be strictly adhered to.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

Phase 1b of the clinical trial is a safety run-in to establish safety of the combination of bemcentinib and chemotherapy (gemcitabine/nab-paclitaxel/cisplatin) (Enrollment Completed 9/2020)

Phase 2 is a open label, clinical trial of chemotherapy (gemcitabine/nab-paclitaxel) with bemcentinib.

The primary end point is overall response rate.

Phase 1b: Safety run in (enrollment completed 9/2020)
A modified 3+3 design will be used to determine the dose of bemcentinib for the randomized, Phase 2, of the study.

In the safety run in, three patients will be enrolled to Dose level 1.

- If none of the first 3 evaluable patients in a dose cohort experiences a DLT within the DLT evaluation interval, then the randomized portion (Phase 2 of the trial will begin.
- If at least 1 of the first 3 evaluable patients in a cohort experiences a DLT within the DLT evaluation interval, then 3 additional patients will be treated at that dose level.
    - If no more than 1 of the first 6 evaluable patients experiences a DLT during the DLT evaluation interval, then the Phase 2 of trial will begin.
    - If 2 or more of the first 6 evaluable patients in a cohort experience a DLT, that dose level has exceeded the MTD and a lower dose level will be explored.

PI may investigate additional starting dose levels as defined in table 5 in the protocol. If additional doses outside of the protocol are needed, then a modification to the protocol may be considered. The study safety committee (comprising co-investigators and other site PIs) and the DSMC chair may be consulted as needed.

Dose limiting toxicity (DLT)
Any patient who receives treatment on this protocol will be evaluable for toxicity. DLT will be defined by the occurrence of any of the following toxicities in patients of the trial which are possibly or probably related to study treatment, during cycle 1 only, as defined by CTCAE version 5.0

- Any nonhematologic grade 3 or 4 toxicity except alopecia
- Grade ≥ 3 diarrhea, vomiting, or nausea that persists for > 3 days despite optimal supportive care
- Any Grade 4 or 5 treatment related toxicity that is *at least possibly related* to treatment Grade 4 neutropenia lasting more than 5 days or febrile neutropenia
- Platelets <25,000 uL with significant bleeding
- Grade ≥ 3 Anemia lasting for more than 5 days
- Any drug-related liver function test (LFT) abnormality that meets the following criteria:

If a subject has a baseline AST or ALT within normal limits:
1. AST or ALT > 5-8x ULN for > 2 weeks
2. AST or ALT > 8x ULN, irrespective of duration
3. Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN

If a subject has a baseline AST or ALT within Grade 1 or 2 toxicity range:
1. AST or ALT > 10x ULN for > 2 weeks
2. AST or ALT > 15x ULN, irrespective of duration
3. Total bilirubin > 5x ULN
4. Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN

10.2 Sample Size and Accrual

Sample size: The total sample size of this study (Phase 1b and Phase 2) will be between 3 and 44 patients.

Phase 1b (enrollment completed 9/2020): will comprise a safety run-in for the first 3-12 patients treated with bemcentinib plus nab-paclitaxel/gemcitabine/cisplatin.

Sample size of Phase 1b will be determined by safety criteria as detailed above. Adverse event (safety) data will be reviewed by the Safety Monitoring Committee (SMC) before enrolment into Phase 2 can commence. The SMC will be comprised of a representative from each actively-recruiting investigational site and a representative of the Sponsor study team. Once safety of combination treatment has been demonstrated, enrollment on Phase 2 portion, of the trial will begin.

Phase 2: Patients will be treated with bemcentinib plus nab-paclitaxel/gemcitabine. Only patients that successfully complete the 1st imaging assessment will be considered evaluable for efficacy. Non-evaluable patients will be replaced.
In Phase 2 of the study, 32 patients will be enrolled. The proposed scheme is based on Simon's minimax two-stage design for a phase 2 trial using 10% type I error rate and 80% power.
For comparisons of 23% (null hypothesis) vs. 40% (alternative hypothesis), 21 patients will be accrued in the first stage.

If there are 4 or fewer responses out of 21 patients, the trial will be stopped early for futility.
Otherwise, 11 additional patients will be accrued for a total of 32 patients.
The null hypothesis will be rejected if 10 or more responses are observed out of 32 patients.

Interim Safety analysis: A preplanned interim safety analysis has been perfomed after 6 patients have completed the DLT period in the revised Phase 1b. For additional paitnets the study team will analyze the presence of grade 3 or higher treatment-related toxicity. If 3 or more of the first 6 patients treated in Phase 2 have grade 3 of higher treatment toxicity a lower starting dose of therapy (as detailed in Table 5) will be considered.

10.3 Data Analyses

Statistical analysis: The overall response rate (ORR) and complete response (CR) rate are defined as the proportions of subjects with CR and objective response (OR), respectively. The efficacy endpoints CR and OR will be analyzed by estimating the CR and ORR and its 95% CI with the exact binomial method. The analyses of ORR will be performed on the Response Evaluable Population. ORR is defined as the proportion of patients with CR+partial response as their best clinical response.

The generalized estimating equation approach will be performed to see if there is an association between biomarker expression including, tissue axl expression, circulating multiplex assay (sAXL, gas 6), myc amplification status at baseline and clinical activity. If such an association exists, secondary analyses for efficacy endpoints will be conducted in “biomarker positive” and “biomarker negative” subpopulation determined by the cutoff points.

Progression-free survival and overall survival will be estimated using Kaplan-Meier method and the corresponding 95% confidence interval will be estimated using Greenwood’s formula.

Clinical Benefit rate (CBR) will be calculated as a sum of the proportion of patients with CR+PR + Stable disease at week 8, week 12, week 24 and week 52.

All patients will be evaluable for toxicity assessment. The number and percentage of subjects reporting treatment-emergent AEs will be summarized overall and by the worst CTCAE grade, system organ class, and preferred term. Similarly, the number and percentage of subjects reporting treatment-emergent SAEs and treatment-emergent AE/SAEs considered related to investigational product will be summarized.

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

11.3 Required Documentation (for multi-site studies)

Before the study can be initiated at any sub-site, the following documentation must be provided to the UTSW Research Manager.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list or Federal-wide Assurance letter
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: This is required if UT Southwestern holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A copy of the IRB-approved consent form
- Protocol Signature Page
- Acknowledgement for bemcentinib Investigator's Brochure (IB)
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Signed site-specific monitoring plan
- Executed clinical research contract

11.4 Registration Procedures

All subjects must be registered with the multi-site IIT team at UTSW before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the multi-site IIT team at UTSW. To register a subject, email SCCC-IIT@UTSouthwestern.edu and Kelly Kyle at Kelly.Kyle@UTSouthwestern.edu Monday through Friday, 9:00AM-5:00PM.

Each site will be given a number beginning with 01. New subjects at each site will receive a number upon study consent such that the first subject consented is numbered 001, the second subject consented receives the number 002, etc. In practice, the first subject at the first site will be numbered 01-001, the first subject at the second site will be 02-001, This number will not change upon confirmation of eligibility and enrollment or screen failure.

Each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration/randomization code according to the numbering schema outlined above, which should then be entered as the patient study id in Velos upon updating the status to enrolled.

11.5 Data Management and Monitoring/Auditing

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for SCCC Investigator Initiated Trials. REDCap will be used for electronic case

report forms in accordance with Simmons Comprehensive Cancer Center requirements, as appropriate for the project

In order to facilitate remote source to case report form verification, the Simmons Comprehensive Cancer Center study team will require other institutions participating in this trial as sub-sites to enter data into the selected EDC system and upload selected de-identified source materials when instructed.

Trial monitoring will be conducted according to the study specific monitoring plan. For guidance on creating a monitoring plan, refer to the UTSW SCCC IIT Management Manual.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The Quality Assurance Coordinator (QAC) works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

11.6 Adherence to the Protocol

Except for an emergency situation, in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.6.1 Exceptions (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:

- intentional on part of the investigator; or
- in the investigator's control; or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)

  ➢ **Reporting requirement***: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation. For eligibility waivers, studies which utilize the SCCC-DSMC as the DSMC of record must also obtain approval from the DSMC prior to submitting to IRB for approval.

11.6.2 Emergency Deviations: include any departure from IRB-approved research that is necessary to:

- avoid immediate apparent harm, or
- protect the life or physical well-being of subjects or others

  ➢ **Reporting requirement***: Emergency deviations must be promptly

reported to the IRB within 5 working days of occurrence.

11.6.3 Serious Noncompliance (formerly called **major deviations** or **violations**): include any departure from IRB-approved research that:

- Increase risk of harm to subjects; and/or
  adversely affects the rights, safety, or welfare of subjects (any of which may also be an unanticipated problem); and/or
- adversely affects the integrity of the data and research (i.e., substantially compromises the integrity, reliability, or validity of the research)

  ➢ **Reporting requirement***: Serious Noncompliance must be promptly reported to the IRB within 5 working days of discovery.

11.6.4 Continuing Noncompliance: includes a pattern of repeated noncompliance (in or more protocols simultaneously, or over a period of time) which continues **after** initial discovery, including inadequate efforts to take or implement corrective or preventive action within a reasonable time frame.

➢ **Reporting requirement***: Continuing Noncompliance must be promptly reported to the IRB within 5 working days of discovery.

11.6.5 Noncompliance (that is neither serious nor continuing; formerly called minor deviations) any departure from IRB-approved research that:

- Does not meet the definition of serious noncompliance or continuing noncompliance

  ➢ **Reporting requirement***: Noncompliance that is neither serious nor continuing should be tracked and summarized the next IRB continuing review, or the notice of study closure- whichever comes first..

*Reporting Requirements reflect UTSW HRPP/IRB guidelines; participating sites should follow the reporting guidelines for their IRB of record

11.7 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

11.8 Record Retention

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

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

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with

a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted, and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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13.0 APPENDICES

Appendix 1
Examples of CYP3A4 substrates are provided below. A further source of information on CYP3A4 substrates can be found at The University of Washington Metabolism and Transport Drug Interaction Database (see www.druginteractioninfo.org).

University of Indiana CYP3A4, 5, 7 P450 Drug Interactions Abbreviated "Clinically Relevant" Table of Substrates

Macrolide antibiotics:	**HIV Antivirals:**	**HMG CoA Reductase Inhibitors:**
clarithromycin	indinavir	atorvastatin
erythromycin (not 3A5)	ritonavir	lovastatin
NOT azithromycin	saquinavir	NOT pravastatin
telithromycin	nevirapine	NOT rosuvastatin
		simvastatin
Anti-arrhythmics:	**Prokinetics:**	
quinidine→3-OH	cisapride	**Others:**
		alfentanyl
Benzodiazepines:	**Antihistamines:**	aripiprazole
alprazolam	astemizole	boceprevir
diazepam→3OH	chlorpheniramine	buspirone
midazolam		carbamazepine
triazolam	**Calcium Channel Blockers:**	gleevec
	amlodipine	haloperidol
Immune Modulators:	diltiazem	pimozide
cyclosporine	felodipine	quinine
tacrolimus (FK506)	nifedipine	tamoxifen
sirolimus	nisoldipine	telaprevir
	nitrendipine	trazodone
PDE-5 Inhibitors:	verapamil	vincristine
sildenafil		
tadalafil		
vardenafil		

Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "/clinpharm/ddis/clinical-table/" Accessed 20 October 2016.

Pharmacy Times published List of CYP3A4 Substrates

Alfentanil (Alfenta)	Docetaxel (Taxotere)	Ketoconazole (Nizoral)	Quinine
Alfuzosin (Uroxatral)	Donepezil (Aricept)	Lapatinib (Tykerb)	Ranolazine (Ranexa)

Almotriptan (Axert)	Doxorubicin (Adriamycin)	Levomethadyl (Orlaam)	Repaglinide (Prandin)
Alprazolam (Xanax)	Droperidol	Loperamide (Imodium)	Rifabutin (Rimactane)
Amiodarone (Cordarone)	Dutasteride (Avodart)	Lopinavir (Kaletra)	Ritonavir (Norvir)
Amlodipine (Norvasc)	Ebastine (Kestine)	Loratadine (Claritin)	Saquinavir (Invirase)
Aprepitant (Emend)	Efavirenz (Sustiva)	Lovastatin (Mevacor)	Sibutramine (Meridia)
Atazanavir (Reyataz)	Eletriptan (Relpax)	Maraviroc (Selzentry)	Sildenafil (Viagra)
Atorvastatin (Lipitor)	Eplerenone (Inspra)	Mefloquine (Lariam)	Simvastatin (Zocor)
Bepridil (Vascor)	Ergotamine (Ergomar)	Methylprednisolone	Sirolimus (Rapamune)
Bexarotene (Targretin)	Erlotinib (Tarceva)	Midazolam (Versed)	Solifenacin (Vesicare)
Bosentan (Tracleer)	Erythromycin	Mifepristone (Mifeprex)	Sufentanil (Sufenta)
Bromocriptine (Parlodel)	Estazolam (ProSom)	Modafinil (Provigil)	Sunitinib (Sutent)
Budesonide (Entocort)	Eszopiclone (Lunesta)	Nefazodone	Tacrolimus (Prograf)
Buprenorphine (Subutex)	Ethinyl Estradiol	Nevirapine (Viramune)	Tadalafil (Cialis)
Bupropion (Zyban, Wellbutrin, Voxra)	Ethosuximide (Zarontin)	Nicardipine (Cardene)	Tamoxifen (Nolvadex)
Carbamazepine (eg, Tegretol)	Etoposide (Vepesid)	Nifedipine (Adalat)	Tamsulosin (Flomax)
Cevimeline (Evoxac)	Exemestane (Aromasin)	Nimodipine (Nimotop)	Teniposide (Vumon)
Cilostazol (Pletal)	Felodipine (Plendil)	Nisoldipine (Sular)	Testosterone
Cisapride (Propulsid)	Fentanyl (Sublimaze)	Nitrendipine (Baypress)	Tiagabine (Gabitril)
Clarithromycin (Biaxin)	Finasteride (Proscar)	Oxybutynin (Ditropan)	Tinidazole (Tindamax)
Clonazepam (Klonopin)	Flurazepam (Dalmane)	Oxycodone (Percodan)	Tipranavir (Aptivus)
Clopidogrel (Plavix)	Fosamprenavir (Lexiva)	Paclitaxel (Taxol)	Topiramate (Topamax)
Colchicine	Galantamine (Reminyl)	Paricalcitol (Zemplar)	Triazolam (Halcion)
Cyclophosphamide (Cytoxan)	Gefitinib (Iressa)	Pimozide (Orap)	Vardenafil (Levitra)
Cyclosporine (Neoral)	Granisetron (Kytril)	Pioglitazone	Verapamil (Calan)
Dapsone (Avlosulfon)	Halofantrine (Halfan)	Praziquantel (Biltricide)	Vinblastine (Velbane)
Darunavir (Prezista)	Ifosfamide (Ifex)	Prednisolone	Vincristine (Oncovin)
Dasatinib (Sprycel)	Imatinib (Gleevec)	Prednisone	Ziprasidone (Geodon)
Delavirdine (Rescriptor)	Indinavir (Crixivan)	Propoxyphene (Darvon)	Zolpidem (Ambien)
Dexamethasone (Decadron)	Irinotecan (Camptosar)	Quazepam (Doral)	Zonisamide (Zonegran)
Dihydroergotamine	Isradipine (DynaCirc)	Quetiapine (Seroquel)	Zopiclone (Imovane)

Diltiazem (Cardizem)	Itraconazole (Sporanox)	Quinacrine	
Disopyramide (Norpace)	Ixabepilone (Ixempra)	Quinidine	

CYP3A4 Substrates obtained from: Pharmacy Times 'Get to Know an Enzyme: CYP3A4'. John R. Horn, PharmD, FCCP, and Philip D. Hansten, PharmD. Published Online: Monday, September 1, 2008

Appendix 2

2C8 SUBSTRATES:

AMODIAQUINE

CERIVASTATIN

PACLITAXEL

REPAGLINIDE

SORAFENIB

TORSEMIDE

2C8 INHIBITORS:

GEMFIBROZIL

GLITAZONES (thiazolidinediones)

MONTELUKAST

QUERCETIN

TRIMETHOPRIM

2C8 INDUCERS:

RIFAMPICIN

Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). "https://drug-interactions.medicine.iu.edu" Accessed 29 October 2018.