BPM31510IV-05

A Phase 2 Study of BPM31510 ([redacted]) Nanosuspension Injection Administered Intravenously with Gemcitabine as 2nd/3rdline therapy in Advanced Pancreatic Cancer Patients

BERG PROTOCOL NUMBER:	BPM31510IV-05
PCRT PROTOCOL NUMBER:	PCRT 15-002
TRIAL DRUG:	BPM31510 ([redacted] Nanosuspension Injection
IND NUMBER:	108,093
EudraCT Number:	2017-001470- 42
SPONSOR:	BERG LLC 500 Old Connecticut Path Building B Framingham, MA 01701

ORIGINAL DATE:	20 November 2015
AMENDMENT 1:	01 April 2016
AMENDMENT 2:	20 April 2016
AMENDMENT 3:	03 October 2016
AMENDMENT 4:	27 January 2017
AMENDMENT 5:	16 June 2017
AMENDMENT 6:	19 August 2017
AMENDMENT 6.1	05 January 2018 (UK Version only)
AMENDMENT 7:	25 August 2018

Clinical Trial Protocol Statement of Compliance

This clinical trial shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (GCP)
- Ethical principles that have their origins in the Declaration of Helsinki
- Food and Drug Administration (FDA) Code of Federal Regulation (CFR):
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Patients**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**
  - Annex 1 of Directive 2001/83/EC
  - European Union (EU) clinical-trial legislation (Directive 2001/20/EC)
  - Clinical Trial Regulation (EU No 536/2014)

As the Principal Investigator (PI), I understand that my signature on the protocol constitutes my agreement and understanding of PI responsibilities to conduct the clinical trial in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

As the Sponsor Representative, I understand that my signature constitutes agreement and understanding of acceptance of the defined and contracted Sponsor responsibilities to the CRO and the PI as defined by the protocol, applicable clinical trial agreements (CTA), and/or business contracts, but does not in any capacity relieve me of my responsibilities as the Sponsor. Additionally, my signature constitutes my understanding and agreement that any changes to the protocol, CTA, or contracts shall be implemented timely with my review and approval prior to implementation.

Clinical Trial Protocol Approval Page

A Phase 2 Study of BPM31510 ( ) Nanosuspension Injection Administered Intravenously with Gemcitabine as 2nd /3rd line therapy in Advanced Pancreatic Cancer Patients

BERG Protocol Number:	BPM31510IV-05
PCRT Protocol Number:	PCRT 15-002
Trial Drug:	BPM31510 (Nanosuspension Injection
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BERG CMO Name **BERG Chief Medical Officer** **Date**

BERG CSO Name **BERG Clinical and Scientific Operations** **Date**

Lead /Principal Investigator Name **Principal Investigator Signature** **Date**

Clinical Trial Protocol Acceptance Form

A Phase 2 Study of BPM31510 ([redacted] Nanosuspension Injection Administered Intravenously with Gemcitabine as 2nd /3rd line therapy in Advanced Pancreatic Cancer Patients

BERG Protocol Number:	BPM31510IV-05
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Principal Investigator Name **Principal Investigator Signature** **Date**

CLINICAL PROTOCOL BPM31510IV-05 SYNOPSIS

Title of Trial:	**A Phase 2 Study of BPM31510 ([redacted]) Nanosuspension Injection Administered Intravenously with Gemcitabine as 2nd /3rd line therapy in Advanced Pancreatic Cancer Patients**	
BERG Protocol Number:	BPM31510IV-05	
Sponsor:	BERG LLC 500 Old Connecticut Path Building B Framingham, MA 01701 USA	
Trial Duration:	The duration of the trial is 36 months.	**Phase of Trial:** 2
Trial Population and Trial Centers:	The trial population is advanced pancreatic cancer patients who have received no more than 2 previous chemotherapy regimens. This is a multicenter trial to be conducted at up to 20 sites in the U.S. & Europe	
Objectives:	**Primary:** Primary Objectives: Evaluate the Overall Response Rate in patients treated with the combination of BPM31510 with gemcitabine Secondary Objectives: Evaluate Overall Survival; Evaluate Progression-Free Survival overall and at around 10 weeks (equal to 2 cycles of treatment; cycle 1 = 6 weeks + cycle 2 = 4 weeks); Evaluate Time to Progression (TTP); Evaluate Tumor Response using Adaptive Molecular Responses (epi-genomic analysis (SNP or X-ome technology)) Determine the toxicity profile of BPM31510 in combination with gemcitabine when administered as a 144-hour (two 72-hr) intravenous (IV) infusion in patients with advanced pancreatic cancer. Evaluate change in CA 19-9 levels. Evaluate changes in patient reported Quality of Life at the end of Cycle 2, and at End of Study or early termination Primary Endpoint: Overall Response Rate. A two-stage design will be used such that if one of the initial ten enrolled patients experiences a tumor response of Partial Response (PR) or better, based on RECIST 1.1 criteria, after 2 cycles of treatment, then the study will be expanded to enroll an additional 15 patients for a total of 25 evaluable patients. In the absence of at least one CR or PR, if at least 3 patients experience stable disease the Sponsor can choose to enroll the additional 15 patients into the expansion stage. Secondary Endpoints Efficacy: Best response, disease control rate (CR+PR+SD), Duration of Response, Overall Survival, Progression-Free Survival (PFS), Time to Progression, and CA 19-9 level change. Quality of Life: FACT-HEP self-administered patient questionnaire Safety: Laboratory results, adverse events, vital signs, concomitant medications, concomitant procedures and ECG.	

Objectives (cont'd):	**<u>Exploratory:</u>** The exploratory objectives are: • To evaluate the effects of BPM31510 on shifting tumors to aerobic respiration by 18-FDG-PET imaging. • Tumor, plasma and urine samples will be assayed for levels of markers of BPM31510 activity using (but not limited to): o genomic (e.g. microarray, SAGE, northern blotting, gene expression), proteomic (e.g., LC/MS based analysis, 2DE-MS, MALDI TOF, antibody array, ELISA, immunohistochemistry, tissue microarray, flow cytometry, western blotting), o metabolomics (e.g., global analysis of metabolites in biological samples; identification of specific markers of energy metabolism e.g., pyruvate, lactate), o lipidomics (e.g., global analysis of lipid classes; identification of specific lipids e.g., derivatives of palmitate, linoleic acid, arachidonic acid). The objective of this integrative approach is to stratify patient populations based on phenotypic or molecular profiles for therapeutic benefit. This includes assessing the patient's biofluid as well as the tumor for markers of positive, stable or negative outcome allowing for guidance of selection of participants in future cohorts.

Trial Design:	This is a Phase 2 multicenter, open-label, non-randomized study to examine the safety and effectiveness of BPM31510 administered over 144-hours (two 72-hour 110mg/Kg doses) continuous intravenous (IV) infusion in combination with gemcitabine in advanced pancreatic cancer patients as 2nd / 3rd line therapy. [redacted] Toxicity will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.02). Assessments of the antitumor activity of the combination will be performed at the end of Cycle 2 and every 2 cycles thereafter using standard techniques such as computerized tomography (CT) or magnetic resonance imaging (MRI) for patients with measurable disease. Response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix E:RECIST Response Criteria for Solid Tumors). Patients who experience no unacceptable toxicity or disease progression, may receive additional 28-day cycles for up to 1 year. Patients will continue BPM31510 in combination with gemcitabine, for a maximum of 12 cycles in the absence of intolerable toxicity and progression. If gemcitabine is discontinued due to chemotherapy-related toxicity, patients may continue to receive BPM31510 as monotherapy. Patients who experience disease progression but are, in the opinion of the investigator, receiving clinical benefit may continue BPM31510 as a monotherapy or in combination with gemcitabine pending approval from the Sponsor.
Efficacy Assessments	Efficacy measures will include: Overall Survival (OS) Overall Response Rate (ORR) Best Response Duration of Response Progression Free Survival (PFS) Clinical Benefit Rate (SD+PR+CR) CA 19-9 level change Quality of Life changes (FACT-Hep)

Safety Assessments	Safety measures will include: AEs Hematology, clinical chemistry, and urinalysis Physical examination and vital signs Concomitant medications/procedures 12-lead ECGs ECOG Performance Status Dose Modifications of protocol-specified treatment
Exploratory Assessments	• Assessment of tumor metabolic activity (18-FDG-PET/CT) will be done ≤ 14 calendar days prior to starting treatment with BPM31510 and repeated after the completion of Cycle 2, and then after every 2 Cycles (Cycle 4, 6, 8, …). The PET scan will be performed to assess the effects of BPM31510 on the shifting tumors to aerobic respiration. • Plasma and urine samples will be assayed for levels of markers of BPM31510 activity using (but not limited to): o genomic (e.g. microarray, SAGE, northern blotting, gene expression), proteomic (e.g., LC/MS based analysis, 2DE-MS, MALDI TOF, antibody array, ELISA, immunohistochemistry, tissue microarray, flow cytometry, western blotting), o metabolomics (e.g., global analysis of metabolites in biological samples; identification of specific markers of energy metabolism e.g., pyruvate, lactate), o lipidomics (e.g., global analysis of lipid classes; identification of specific lipids e.g., derivatives of palmitate, linoleic acid, arachidonic acid). The objective of this integrative approach is to stratify patient populations based on phenotypic or molecular profiles for therapeutic benefit. This includes assessing the patient's biofluid as well as the tumor for markers of positive, stable or negative outcome allowing for guidance of selection of participants in future cohorts. These exploratory data will be correlated with the secondary endpoints of PFS and TTP.
Number of Patients:	This study will occur in two parts. Part 1 of the study will enroll ten evaluable (10) patients in the BPM31510 plus gemcitabine (combination therapy arm). If at least one of ten patients treated experiences a Complete Response (CR) or Partial Response (PR), based on RECIST 1.1 criteria, after 2 cycles of treatment, then Part 2 of the study will enroll an additional 15 patients for a total of 25 evaluable patients. In the absence of at least one CR or PR if at least 3 patients experience stable disease, the Sponsor can choose to enroll 15 additional patients into the expansion stage. Patients who fail to complete at least 2 cycles of therapy will be replaced until a maximum of 25 evaluable patients have been treated.

Trial Drugs, Dose, and Mode of Administration:	BPM31510 Nanosuspension Injection (40 mg/mL) will be administered IV over 144 hours (two 72-hour 110 mg/Kg doses). Each patient will receive 2 consecutive 72-hour infusions per week (Tuesday-Friday and Friday-Monday). The dose for BPM31501 is 110 mg/Kg. Patients will also be treated with gemcitabine IV once weekly (starting at week 3) at a starting dose of 1000 mg/m^2. [redacted]
Duration of Therapy	Patients may continue treatment for up to 12 cycles within their assigned treatment in the absence of progressive disease, unacceptable toxicity, or until any of the discontinuation criteria listed in Section 3.4 are met. Patients evaluated as having gemcitabine toxicity or disease progression may remain on monotherapy at the investigator's discretion if experiencing clinical benefit and after consultation with the sponsor.
Trial Drug Supply:	Clinical trial supplies of BPM31510 will be provided by BERG LLC. The chemotherapy agent gemcitabine is commercially available and will be provided through commercial sources.

Inclusion Criteria:	Patients must meet the following criteria in order to be included in the clinical trial: 1. The patient has a histologically or cytologically confirmed metastatic pancreatic adenocarcinoma. 2. The patient has received at least one, but no more than 2, prior standard or experimental therapies for metastatic pancreatic cancer*. If the patient has had prior gemcitabine treatment, the last date of gemcitabine administration should be ≥ 28 days prior to receiving study treatment. All patients who have previously received gemcitabine should be discussed with the medical monitor during screening . 3. The patient is at least 18 years old. 4. The patient has an ECOG [redacted] 5. Measurable tumor lesions according to RECIST 1.1 criteria [redacted] 6. In the opinion of the Investigator, the patient has a life expectancy of > 3 months. 7. Sexually active patients and their partners agree to use an accepted method of contraception during the course of the study [redacted] 8. Female patients of childbearing potential must have a negative pregnancy test within 1 week prior to beginning study treatment. 9. The patient has adequate organ and marrow function as follows: • ANC ≥ 1500 mm^3, platelets ≥ 100,000/mm^3, hemoglobin ≥ 9 g/dL, • serum creatinine ≤upper limit of normal (ULN) or calculated creatinine clearance > 50 ml/min; 10. Total bilirubin ≤ 1.5 X ULN (unless related to Gilbert's Syndrome); alanine aminotransferase (ALT), aspartate transaminase (AST) ≤ 2.5 times the upper limit of normal (ULN) if no liver involvement or ≤ 5 times the upper limit of normal with liver involvement. 11. The patient has serum electrolytes (including calcium, magnesium, phosphorous, sodium and potassium) within normal limits (supplementation to maintain normal electrolytes is allowed). 12. The patient has adequate coagulation: prothrombin time (PT) and an International Normalized Ratio (INR), and partial thromboplastin time (PTT) ≤ 1.5 times the upper limit of normal (ULN), 13. In the opinion of the Investigator, the patient is capable of understanding and complying with the protocol and has signed the informed consent document. *For the purposes of this study, patients who have received at least one, but no more than 2, prior standard therapies for locally advanced pancreatic cancer and then transition to a diagnosis of metastatic pancreatic cancer ≤ 6 months post therapy may count the treatment for locally advanced cancer as 1st line treatment for metastatic cancer.

Exclusion Criteria:	The patient will be excluded from study participation if any of the following criteria are met: 1. The patient has uncontrolled intercurrent illness including, but not limited to uncontrolled infection, symptomatic congestive heart failure (NYHA class III and IV), uncontrolled cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements [redacted] 2. The patient has active heart disease including myocardial infarction within previous 3 months, symptomatic coronary artery disease, arrhythmias not controlled by medication, unstable angina pectoris, or uncontrolled congestive heart failure (NYHA class III and IV) [redacted] 3. The patient has received chemotherapy within 2 weeks or radiotherapy within 4 weeks or has received nitrosoureas or mitomycin C within 6 weeks prior to the first dose of study drug. The patient must have recovered from treatment related toxicities to Grade 1 or less (other than alopecia). 4. Patients previously treated with gemcitabine: who discontinued gemcitabine due to toxicity in the first 6 weeks of prior treatment or is/was unable to tolerate a dose of 800 mg/m2 weekly at any point due to toxicity. 5. The patient has received radiation to ≥ 25% of his or her bone marrow within 4 weeks of the first dose of study drug. 6. The patient has received an investigational drug within 30 days of the first dose of study drug. 7. Evidence of central nervous system (CNS) metastasis (negative imaging study, if clinically indicated, within 4 weeks of Screening Visit). 8. History of other malignancies (except adequately treated Stage 1 cancer, cured basal cell carcinoma, superficial bladder cancer, breast ductal carcinoma *in situ* (DCIS) without invasive component, or carcinoma *in situ* of the cervix) unless documented free of cancer for ≥5 years. 9. The patient has not recovered to grade ≤ 1 from adverse events (AEs) due to investigational drugs or other medications, which were administered more than 4 weeks prior to the first dose of study drug. 10. The patient is pregnant or lactating. 11. The patient is known to be positive for the human immunodeficiency virus (HIV). The effect of BPM31510 on HIV medications is unknown. Note: HIV testing is not required for eligibility, but if performed previously and was positive, the patient is ineligible for the study.

Exclusion Criteria (cont'd):	12. The patient has an inability or unwillingness to abide by the study protocol or cooperate fully with the Investigator or designee. 13. The patient is receiving digoxin, digitoxin, lanatoside C or any type of digitalis alkaloids. 14. The patient has uncontrolled or severe coagulopathies or a history of clinically significant bleeding within the past 6 months, such as hemoptysis, epistaxis, hematochezia, hematuria, or gastrointestinal bleeding. 15. The patient has a known predisposition for bleeding such as von Willebrand's disease or other such condition. 16. The patient requires therapeutic doses of any anticoagulant, including LMWH. Concomitant use of warfarin, even at prophylactic doses, is prohibited.
Statistical Methodology:	This phase 2 trial will examine the safety and efficacy of BPM31510 as a combination therapy with gemcitabine in advanced pancreatic cancer patients as $2^{nd}/3^{rd}$ line therapy. The primary safety endpoint is to determine the safety of BPM31510 as a combination therapy in this patient population. The primary efficacy endpoint is overall response rate. This study will occur in two parts. Part 1 of the study will enroll ten (10) evaluable patients. If at least one of ten evaluable patients treated experience a Complete Response (CR) or Partial Response (PR), based on RECIST 1.1 criteria, after 2 cycles of treatment, then Part 2 of the study will enroll an additional 15 patients for a total of 25 evaluable patients. In the absence of at least one CR or PR, if at least 3 patients experience stable disease the Sponsor can choose to enroll the additional 15 patients into the expansion stage. Toxicity grading will be defined using CTCAE v4.02. Response rates will be summarized using frequency table techniques; exact 95% confidence intervals may be generated. Safety observations and measurements including study drug exposure, adverse events, laboratory data, vital signs, and ECOG performance status will be summarized using descriptive statistics (number of patients, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequency and percentages for discrete variables. Adverse events and serious adverse events will be tabulated by system organ class and preferred terms and coded using MedDRA version 19.0 (or most current version). Laboratory test results will be summarized using values observed at each visit and shift from baseline values. Exploratory data will be collected on all patients to correlate with PD data and response. The objective of this integrative approach is to stratify patient populations based on phenotypic and/or molecular profiles for therapeutic benefit and outcomes. This includes assessing the patient's biofluid as well as the tumor for markers of positive, stable or negative outcome allowing for guidance of selection of participants in future cohorts.

CLINICAL TRIAL BPM31510IV-05 CONTACT INFORMATION:

BERG Contact Information:	BERG LLC 500 Old Connecticut Path Building B Framingham, MA 01701
Principal Investigator /Coordinating Investigator:	[redacted]
Medical Monitor:	[redacted]
Safety Surveillance / Pharmacovigilance [redacted]	[redacted]
BERG Clinical Operations	[redacted]
BERG Clinical Operations	[redacted]

LIST OF ABBREVIATIONS

AE	adverse event
ALT (SGPT)	alanine aminotransferase
ALP	alkaline phosphatase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time (commonly interchanged with PTT)
AST (SGOT)	aspartate aminotransferase
ATP	adenosine triphosphate
$AUC_{0\text{-}24hr}$	area under the concentration-time curve from time 0 to 24 hrs.
BPM	BERG Molecule
BUN	blood urea nitrogen
BWFI	Bacteriostatic Water for Injection
CA	Competent Authorities
CBC	complete blood count
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CHF	congestive heart failure
CL	Clearance
C_{max}	maximum concentration
CMP	comprehensive metabolic profile
CNS	central nervous system
CP	Cyclophosphamide
CR	complete response
[redacted]	[redacted]
CRC	Cohort Review Committee
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive protein
CSF	colony-stimulating factor
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
EC	Ethics Committee
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ED_{50}	dose required for 50% tumor inhibition
EDC	Electronic Data Capture (system)
FACT-HEP 8.0	Functional Assessment of Cancer Therapy – HEP 8.0
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal

GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
ICH	International Conference on Harmonization
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board (or EC)
IV	intravenous(ly)
LMWH	Low molecular weight heparin
LV	Leucovorin
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NYHA	New York Heart Association
ORR	Overall Response Rate
PD	Pharmacodynamic
PD	progressive disease
PDA	pancreatic ductal adenocarcinoma
PET	Positron Emission Tomography
PFS	progression free survival
PHI	protected health information
PK	Pharmacokinetic
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time (commonly interchanged with aPTT)
PVC	polyvinyl chloride
RECIST	Response Evaluation Criteria in Solid Tumors (v1.1)
RNA	ribonucleic acid
QA	quality assurance
SAE	serious adverse event
SUV	standard uptake value (for PET scans)
$t_{1/2}$	half-life
t_{max}	time to maximum concentration
TTP	time to progression
ULN	Upper Limit of Normal
Vd	volume of distribution
VEGF	vascular endothelial growth factor
WBC	white blood cell

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1 INTRODUCTION

1.1 Background

Pancreatic cancer continues to be a highly lethal disease with an overall 5-year survival of only 7%. Since 2004, the incidence of pancreatic cancer has been increasing by 1.5% per year and it is estimated that there will be 48,960 new cases diagnosed in the United States in 2015, with 40,560 expected deaths. Pancreatic cancer is the fourth most common cause of cancer-related deaths in both men and women, and the incidence is about equal in both sexes (ACS 2015). Of all types of pancreatic cancers, pancreatic ductal adenocarcinoma (PDA) is by far the most common, representing 80% of cases ([redacted]

Due to lack of adequate screening techniques, greater than 80% of patients at the time of diagnosis present with unresectable, advanced disease. Standard treatment options for inoperable patients with locally advanced and metastatic PDA have been quite limited. Gemcitabine monotherapy, approved by the FDA in 1996, demonstrated a median survival of 5.7 months [redacted] and has been the mainstay in treating patients with PDA. The first combination regimen to demonstrate any survival benefit compared with gemcitabine alone was gemcitabine plus erlotinib, with median survival of 6.24 months versus 5.91 months for single agent gemcitabine ([redacted]

A meta-analysis of randomized trials by Heinemann and colleagues showed that patients with advanced pancreatic cancer and a good performance status may benefit from combination chemotherapy with gemcitabine plus a platinum agent or a fluoropyrimidine ([redacted] Multiple combination regimens are being utilized.

Recently, the regimen of 5-fluorouracil/leucovorin/irinotecan/oxaliplatin (FOLFIRINOX) compared with gemcitabine demonstrated improvement in both progression-free survival (6.4 vs. 3.3 months) and overall survival (11.1 vs. 6.8 months) for patients with a good performance status. FOLFIRINOX, however, is associated with substantial grade 3 and 4 toxicities, including diarrhea, nausea, vomiting, fatigue, neutropenia and febrile neutropenia, and cannot be given to patients >76 years of age or in some cases patients with head of the pancreas tumors ([redacted]

Current treatment regimens for advanced PDA although offering modest improvements in progression-free survival (PFS) and overall survival (OS), are clearly inadequate in achieving long term survival in these patients. Additional treatment strategies are desperately needed.

BERG, LLC (BERG) is developing Sterile BPM31510 ([redacted] Nanosuspension Injection for the treatment of advanced malignancies. The active ingredient in the BPM31510 injectable formulation [redacted]

BPM31510 inhibits multiple metabolic pathways, and thus interferes with multiple cellular processes simultaneously. In vitro studies demonstrated a selective apoptosis response [redacted] in over 30 cancer cell lines with no toxicity to normal cells. [redacted] inhibited growth of melanoma, breast, prostate, liver, and bone cancer cell lines in culture [Narain 2004a,b, Persaud 2005]. The mechanism of action [redacted] involves the stimulation of the mitochondrial, pro-

apoptotic bcl-2 proteins that cause death in oncotic cells with no change to normal fibroblasts, melanocytes and keratinocytes [Narain 2004b, 2006b, 2008; Persaud 2008, 2009].

1.2 BPM31510 Nonclinical Pharmacology Studies

Nonclinical studies conducted at the University of Miami demonstrated significant in vivo inhibition of tumor growth with BPM31510 in mouse xenograft models. In efficacy studies, BPM31510 had significant effects on survival and health against pancreatic, lung, liver, and central nervous system (CNS) tumors. At 0.5 to 50 mg/kg, a dose-related improvement in mortality was observed in mice injected with pancreatic tumor cells (MiaPACA2). Survival and improved health was significantly increased at doses ≥5 mg/kg. Co-administration with doxorubicin resulted in a significant improvement in survival as well as the number of animals free of tumors [data on file].

A dose-related increase in survival (0.5 to 50 mg/kg/day) compared to untreated controls was seen in rat xenograft models of various cancers including chloromas of lung and liver. These studies included BPM 31510 alone or in combination with chemotherapy agents (data on file) that resulted in synergies in improving overall survival times of the treated cohort compared to untreated controls.

1.2.1 [redacted]

[redacted]

1.3 BPM31510 Toxicology Studies

Single Dose Toxicity Studies

Toxicity associated with single IV doses of BPM31510 was characterized in range-finding studies in rats and dogs. Findings included dose-dependent changes in clinical signs, clinical

pathology parameters reflective of effects on kidney, liver and hematopoietic tissues, and histopathological findings primarily in lymphoid and GI tract tissues. Phlebitis at the injection site (non-diluted formulation was administered), fluid in thoracic cavity and discolored internal gastrointestinal tract were observed in rats.

No histopathological changes associated with BPM31510 administration were observed at the highest non-lethal doses in rats and dogs in these studies. Toxicokinetic analysis showed a slightly greater than dose proportional increase in the C_{max} and $AUC_{0\text{-}24h}$ with increasing IV doses. There were no apparent gender-related differences in the PK of BPM31510.

Repeat-Dose Toxicity Studies

Good Laboratory Practice (GLP)-compliant 28-day repeat dose studies were conducted in rats and dogs, and a non-GLP study was performed in cynomolgus monkeys. In these studies BPM31510 was administered undiluted IV every other day (3 times per week) for 28 days. Findings included dose-dependent changes in clinical pathology parameters of the liver, kidney, organ weights, and tissue histomorphologic appearance of the liver. Safety signals included transient decreases in complete blood cell (CBC) and white blood cell (WBC) counts, phlebitis, diarrhea, minimal multifocal hepatocellular degeneration and necrosis with associated minimal reactive hepatitis (1 of 12 monkeys dosed with active BPM31510 product) and nephrotoxicity. There were no effects on electrocardiograms (ECG) in dogs, and no adverse clinical findings in the central nervous or respiratory systems of rats and dogs.

Toxicokinetic evaluations in rats and dogs showed C_{max} and $AUC_{0\text{-}t}$ increased with dose; there were no apparent gender difference in the PK of BPM31510 in the 28-day studies.

[redacted]

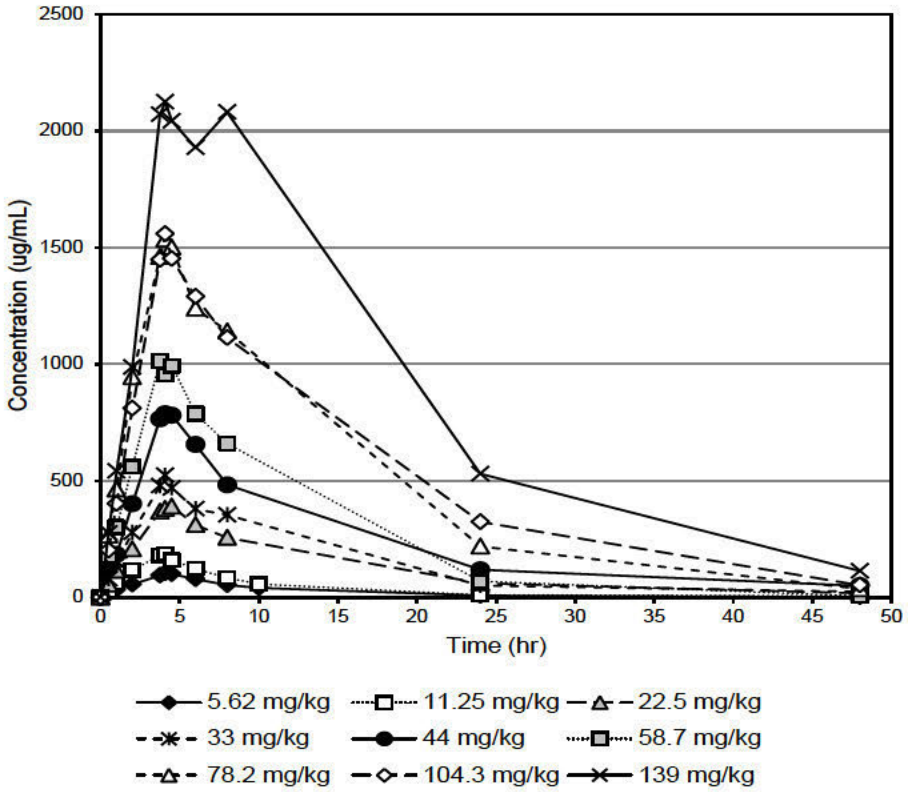
1.4 BPM31510-IV First-in-Human Phase 1 Study in Solid Tumors (CTL0510) – Four Hour Infusion Study

The first-in-human Phase 1 study with BPM31510 was conducted in 50 patients with advanced solid tumors. The objectives were to assess the safety, maximum tolerated dose, PK, and PD of BPM31510 [redacted] Plasma concentration profiles and PK parameters were determined from blood samples collected pre-dose and at intervals to 48 hours post-dose.

Evaluation of the PK parameters indicated linear or close to linear dose-proportionality with the 4-hour infusion schedule. As shown in **Figure 1** the curves are similar for all doses. There was some evidence of non-linearity at the lowest dose levels. However, for doses of 22.5 mg/kg or higher, dose-proportionality appeared linear.

T_{max} and C_{max} were generally associated with the end of the infusion. The $t_{1/2}$ ranged from 2.18 to 18.0 hours, with little or no dependence of $t_{1/2}$ on dose. Considering all dose groups, there was no apparent accumulation with increasing duration of dosing.

Figure 1: BPM31510 Plasma Concentrations on the 4-Hr Schedule (Study CTL0510)



- The majority of AEs during the study were CTCAE grade 1 or 2, with the most common non-laboratory AEs (all causalities combined) being fatigue; nausea; dyspnea; abdominal pain, fever, tachycardia, vomiting, anorexia, and diarrhea. Of these, AEs related to BPM31510 included fatigue (24%), headache (10%), nausea (8%), fever (8%), chills (6%) and arthritis (4%).

  The most common laboratory AEs (all causalities combined) were: anemia (98%), hyperglycemia (88%), PTT prolonged (82%), INR increased (76%); hypoalbuminemia (70%), AST increased (66%), alkaline phosphatase increased (62%), platelet count decreased (58%), and hypocalcemia (42%). Of these laboratory AEs, those judged to be BPM31510-related included PTT prolonged (80%), platelet count decreased (14%), AST increased (8%), and alkaline phosphatase increased (2%). In addition, 38 patients experienced abnormal INR values, and in 34 of these patients (68%) the increased INR was considered related to BPM31510. Increased INR was clinically significant in 14 of the patients, having increased to grade 3 or caused a bleeding event. When Vitamin K was administered, all INRs decreased to grade 1 or resolved. Seven of the 14 patients with clinically significant increased INR had a medical history of bleeding events or increased coagulopathy prior to the study.

  Although no DLTs were identified with the 4-hour infusion schedule, 2 patients had serious bleeding events associated with increased INR at the 104.3 mg/kg dose level. One of these SAEs resulted in the patient's death due to hemothorax. Upon review of both cases, the Sponsor placed the study on clinical hold and implemented strategies to monitor and mitigate coagulopathies associated with BPM31510 in all protocols.

Twenty patients died due to disease progression or intercurrent illness. Four patients discontinued treatment due to AEs reported as unrelated to treatment: grade 2 infection at the tumor site (1), grade 3 thrombocytopenia (2), and grade 4 AST increased (1). Three patients were actively being treated at the time of the study hold: 2 patients at the 104.3 mg/kg dose level and 1 patient had received 2 doses at the 139 mg/kg dose level.

Two SAEs were reported as possibly related to BPM31510: grade 3 APTT prolonged and grade 3 hematuria. No clinically significant changes in vital signs or physical examination findings were observed.

The best response to BPM31510 was stable disease in 23 of 50 patients (46%), One patient with a sarcoma had a partial response, and 15 patients (30%) had progressive disease.

Please refer to the BPM31510 Investigator Brochure for further detail on relevant studies. The reference document for determination of expectedness of adverse events is the Investigator Brochure.

BPM31510-IV Phase I study in Solid Tumors - A 144-hour continuous infusion study

The second trial is a Phase 1a/b multicenter, open-label, non-randomized, dose-escalation study to examine the dose limiting toxicities (DLT) of BPM31510 administered as a 144-hour continuous intravenous (IV) infusion as monotherapy (treatment Arm 1) and in combination with chemotherapy consisting of gemcitabine, docetaxel, or 5FU (treatment Arm 2) in patients with solid tumors. In the Phase 1a portion of the trial, patients who meet eligibility parameters receive 2 consecutive 72-hour infusions of BPM31510 twice weekly on Tuesday and Friday (i.e., Days 1, 4, 8, 11, 15, 18, 22, and 25), essentially receiving BPM31510 treatment for 144 (72-hr x2) hours per week of each 28-day cycle.

In the current open Phase I trial using BPM31510 in combination with gemcitabine for patients with solid tumors, 52 patients have been treated (31 with BPM31510 alone and 21 patients with BPM31510 in combination with gemcitabine. Monotherapy dose levels are 66mg/kg, 88mg/kg, 110mg/kg, 137mg/kg and 171mg/kg. BPM31510 dose levels in combination with gemcitabine are 50mg/kg, 66mg/kg, 88mg/kg, 110mg/kg, 137mg/kg and 171mg/kg. All combination therapy patients received a gemcitabine dose of 1000 mg/m² IV infusion.

The number of patients treated in each group to date is in table below;

As of 01 Apr 2016, 1134 adverse events have been reported; 401 events were reported in monotherapy patients and 733 events reported in BPM31510 / Gemcitabine combination therapy patients.

75 events reported in 38 (73%) of the 52 patients (12 combo therapy and 26 monotherapy) were reported as serious. Of the serious adverse events, 27 were not related, 1 was definitely related (APTT prolongation), and 1 was probably related (AST elevation), 8 were possibly related (anemia, thrombocytopenia, dysphagia with fatigue and weakness, nausea and vomiting, AST elevation, venous thrombosis, and ANC decreased) and 10 were unlikely related. There were no severe or serious events reported in more than one patient, in either arm, which were judged to be life threatening or resulted in death. No deaths occurred within 30 days of treatment were reported in this study to date.

Table 2: Reported Serious Adverse Events

Treatment Arm	Definitely Related	Probably Related	Possibly Related	Unlikely Related	Unrelated
BMP31510 Monotherapy (n=31)	1	1	5	28	22
BPM31510 / Gemcitabine Combination therapy (n=21)	0	0	3	10	5
Totals (n=52)	1	1	8	38	27

A total of 595 events were identified as at least possibly related by the investigator. Of these, 375 (63%) were reported as mild, 161 (27%) moderate, 48 (8%) severe, and 11 (2%) life threatening.

Table 3: Adverse Events that occur with a frequency of ≥7%.

Event	Grade	#Occurrences/percent BPM31510 Monotherapy	Occurrences/percent BPM31510 / Gemcitabine
Elevated INR	**Grade 1 & 2**	**38 (24%)**	**74 (43%)**
Elevated APTT	**Grade 1, 2 & 3**	**34 (21%)**	**66 (43%)**
Anemia	**Grade 2,3 & 4***	**32 (18%)**	**74 (39%)**

*Grade 4 anemia recovered with sequelae after blood transfusion

The majority of AEs (95%) reported during the study were CTCAE Grade 1 or 2, with the most common non-laboratory AEs (all causalities combined) being fatigue; nausea; dyspnea; abdominal pain, fever, vomiting, anorexia, edema, constipation, pleural effusion anxiety and arthralgia. The most common related adverse events that were identified as possibly, probably, or definitely related to the study drug are thrombocytopenia, anemia, elevated PT/PTT/INR and elevated LFT/AST/ALT/LDH. The majority of the events resolved with treatment.

The most common laboratory AEs experienced by patients in both arms (all causalities combined) were: INR elevated (7%), anemia (7%), PTT prolonged (7%), PT prolonged (6%), thrombocytopenia 5(%), and AST increased (4%).

Of these laboratory AEs, those judged to be BPM31510-related included INR elevated (16%), PTT prolonged (13%), PT prolonged (13%), anemia (9%, platelet count decreased (9%), AST increased (4%), and hypertriglyceridemia (4%).

In all 67 patients' experienced abnormal INR values. In 23 of these patients (34%) the increased INR was considered related to BPM31510 alone while in the 42 patients (63%) enrolled in the combo-therapy arm the increased INR was considered related.

Increased INR was clinically significant in 1 of the monotherapy patients having increased to grade 3 or caused a bleeding event. When Vitamin K was administered, all INRs decreased to grade 1 or resolved.

Six patients (4 monotherapy and 2 combination therapy) died due to disease progression or intercurrent illness. None of the deaths occurred within 30 days of treatment and none of the deaths were deemed related to BPM31510.

1.4.1 [redacted]

[redacted]

a continuous infusion over a 48 hours period with a total of two 48 hour infusion over a duration [redacted]

[redacted]

In all cancer cell lines tested as described in the Figure 2 below, decrease in cell viability in response to BPM31510 was evident as early as 24 hours and increased progressively between 48 and 72 hours. There was a consistent decrease in cell viability in the cancer cell lines tested independent of the mutational status. In each of the cell lines, extent of BPM31510 effect on cell viability was associated with duration of exposure, with some cell lines exhibiting higher sensitivity at 48 hours times while in other cancer cell lines decrease in cell viability was observed at 72 hours. This data suggest that duration of exposure, an indirect measure of drug-cell contact is an important and critical component of BPM31510 effect on viability of cancer cells of different lineage. In an effort to extend these finding in the preclinical animal models, several studies were undertaken wherein different dosing regimens were tested to determine correlates to the dose (concentration in mg/kg body weight) and dosing regimen and its association to overall clinical presentation and outcomes.

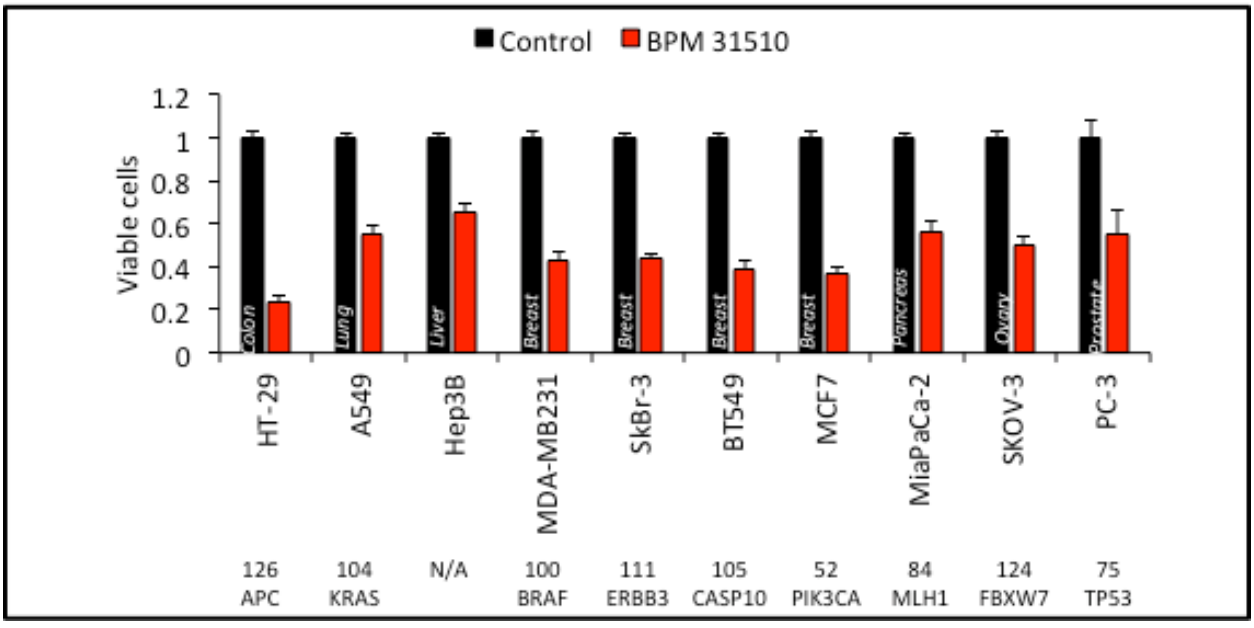


Figure 2: Effect of BPM31510 on viability of cancer cells lines. Each of the cell lines was treated with a fixed dose (100μM) of BPM31510 and cell viability measured between 24 and 72 hours duration. The data represents cell viability in the absence and presence of BPM31510 at 48 or 72 hours exposures.

Note: All treatments had readouts at 24, 48 and 72h cell viability. The figure describes maximal responses in each of cell line that was observed – in cell lines described in figure, this was either at 48 or 72 hour.

The Table below describes a study investigating three different dosing regimens for BPM31510 in a pancreatic cancer xenograph model established using human derived MIA-PACA-2 cell lines introduced into the pancreas of hairless nude mice.

Table 4: BPM31510 in a pancreatic cancer xenograph model

	Regimen 1	Regimen 2	Regimen 3
BPM 31510	**Once/Daily** 50 mg/kg	**Twice/Daily** 50 mg/kg	**Thrice/Daily** 50 or 75 mg/kg
Gemcitabine	Once/Week 150 mg/kg (Day 7, 14 & 21)/28 Day Cycle	Once/Week 150 mg/kg (Day 7, 14 & 21)/28 Day Cycle	Once/Week 150 mg/kg (Day 7, 14 & 21)/28 Day Cycle
Gemcitabine + BPM 31510	**Gemcitabine** Once/Week 150 mg/kg (Day 7, 14 & 21)/28 Day Cycle + **BPM 31510 Once/Daily** 50 mg/kg	**Gemcitabine** Once/Week 150 mg/kg (Day 7, 14 & 21)/28 Day Cycle + **BPM 31510 Twice/Daily** 50 mg/kg	**Gemcitabine** Once/Week 150 mg/kg (Day 7, 14 & 21)/28 Day Cycle + **BPM 31510 Thrice/Daily** 50 or 75 mg/kg

Effect of BPM31510 alone or in combination with gemcitabine on total survival in preclinical animal model of pancreatic cancer. The table describes the three regimens utilized for the study which included once/daily, twice/daily or thrice/daily dosing of BPM31510 either 50 mg/kg body weight (Regimen 1 & Regimen 20) and inclusion of 75 mg/kg body weight in Regimen 3 alone or in combination with a fixed dose gemcitabine (150 mg/kg body weight).

Each group of animals received chemotherapeutic treatment for a minimum of three cycles and was maintained to determine outcomes.

In each of the cohorts tested, BPM31510 alone was associated with increase in survival of animals compared to untreated or treated with chemotherapy alone (Figure 3 below). Of interest is the observation that BPM31510 when added to gemcitabine chemotherapy had an additive effect, with better results observed than for either BPM31510 or chemotherapy alone.

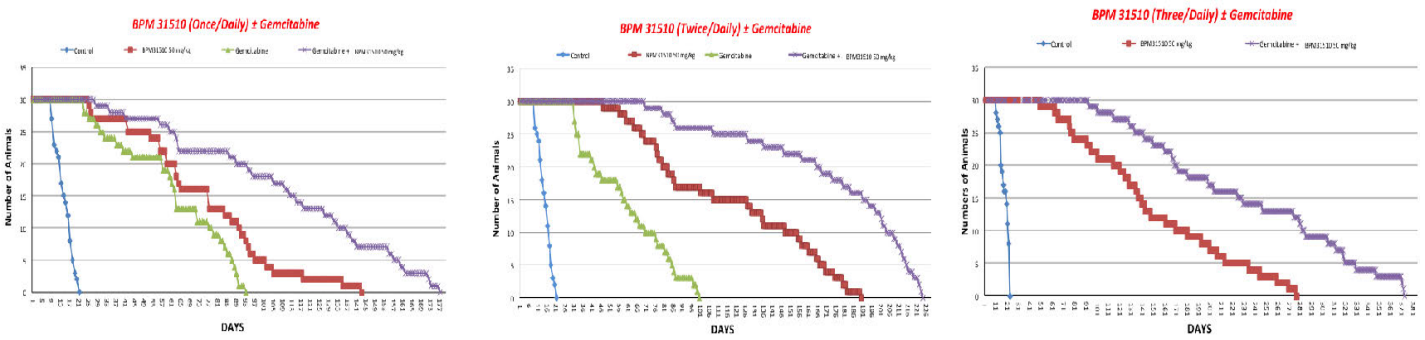


Figure 3: Effect of gemcitabine, BPM31510 (50 mg/kg body weight dose) and combination of gemcitabine + BPM31510 on survival in pancreatic cancer model. The panel of figures above describes survival profiles of animals treated with once/daily BPM31510 (left figure), or the same total daily dose of BPM31510 divided for twice/daily dosing (middle figure) or thrice/daily dosing (right figure) of BPM31510 alone or in combination with gemcitabine. The left and middle figures additionally provide the survival profiles of animals treated with gemcitabine alone, as comparison control for the animals treated with BPM31510 monotherapy or combination therapy of BPM31510 with gemcitabine.

The Figure above provides evidence that increasing doses of BPM31510 from once/daily dosing to three times per day was associated with significant improvement in duration of survival along with decrease in tumor size and histopathology. This observation suggests that the 50 mg/kg body weight dose of BPM31510 distributed over 24 hour duration in three separate dosing regimen is associated with significant improvement compared to administration of identical dose as a single once/daily administration. Thus, the improvement in and maintenance of animals administered 50 mg/kg dose of BPM31510 in multiple bolus may be due to a relatively constant level of BPM31510 in the blood for longer duration that can be potentially achieved compared to a single daily administration.

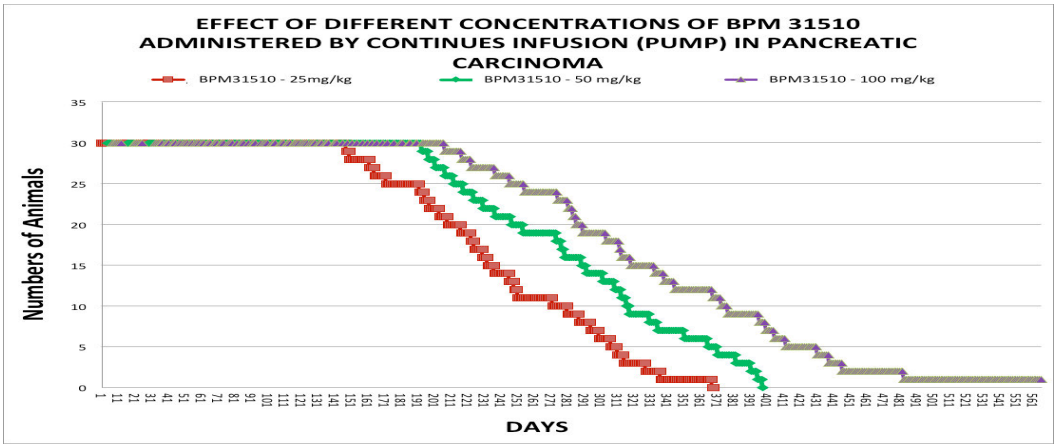


Figure 4: Effect of continuous infusion of increasing concentrations of BPM31510 on the duration of survival of animal model of pancreatic cancer. An infusion pump was surgically installed in the animals to facilitate continuous infusion of BPM31510 at dose of 25 mg/kg, 50 mg/kg and 100 mg/kg body weight per day respectively.

A continuous infusion protocol was implemented to determine the effect of constant BPM31510 administration on endpoints in animal model of cancer. The Figure above describes the effect of continuous infusion of increasing concentrations of BPM31510 on duration of survival in an animal model of pancreatic cancer.

Continuous infusion of BPM31510 at a dose of 25 mg/kg body weight per day was associated with increase in duration of survival compared to the animal cohort administered 50 mg/kg body weight in three divided doses. Thus, continuous infusion of BPM31510 administration at the 25 mg/kg body weight dose over a 24 hour duration was associated with better survival compared to administration of the aforementioned regimen.

The observed improvement in animal cohorts administered BPM31510 as a continuous infusion is recapitulated in other animal models of cancer. Figure 4 describes the duration of survival in prostate cancer model of animals administered BPM31510 using two treatment regimen. The cohorts treated with BPM31510 administered 75 mg/kg body weight distributed over 24 hours demonstrated overall significantly positive results. In contrast, the animal cohorts administered BPM31510 at the same dose as a continuous infusion demonstrated an even greater positive effect when compared to the multiple bolus regimen.

In summary, the data presented provides support that both dose and dosing schedule are potentially critical parameters associated with survival outcomes in preclinical model of cancer tested. Increased dose of BPM31510 is associated with significant improvement in duration of survival in the animal models. Furthermore, the data presented provide evidence that continuous infusion of BPM31510 is associated with significant improvement in the overall endpoints in a cancer model. Thus, the ability to maintain a higher relatively constant blood concentration of BPM31510 that can potentially be achieved using a continuous infusion protocol appears to be an important determinant in the improvement of overall survival and slowing of clinical deterioration effects in this cancer model.

1.5 In Vitro Data Supporting the Combination of BPM31510 & Chemotherapy

The combination of chemotherapeutic agents in the treatment of cancers is supported by the rationale that a mixture of agents with differing mechanisms of action (and dose limiting toxicities) provides a broader range of cytotoxic coverage to the heterogeneous population of cancer cells and minimizes the incidence of drug resistance in cancer. The mechanisms of action of chemotherapeutic agents in eliciting anti-cancer effects converge on their individual or combined abilities to activate the process of apoptosis.

Significant progress has been made toward understanding the mechanism(s) influencing life/death pathways and the centrality of mitochondria and metabolic regulatory networks in dictating survival outcomes. The role of the Bcl-2 family of proteins in regulating the survival/death balance is well understood and has been investigated for utility in the clinics. Recently, Davids and Letai (2012) suggested that chemotherapeutic agents "push" cancer cells towards the commitment of apoptosis, the extent of the "push" beyond a threshold is essential for commitment to the apoptotic process. Since the apoptotic process is governed at the level of the mitochondria, a "mitochondrial priming" event should increase the sensitivity of cancer cells to the cytotoxic potential of chemotherapeutic agents (Chonghaile 2011). BPM31510 influences the metabolic network in cancer cells, effecting a shift from glycolysis to mitochondrial oxidative phosphorylation and re-educating cancer cells to undergo apoptosis. In addition, the central role of [redacted] in arbitrating

mitochondrial-centric bioenergetics network is indicative of its potential utility in "priming" the cancer cells to the cytotoxic effects of chemotherapy agents.

Experiments were designed to characterize (a) the effect of combining BPM31510 with chemotherapy agents on the cytotoxic response in cancer cell lines and (b) the effect of pre-treatment of cancer cells with BPM31510 followed by combination with chemotherapy agents on the sensitivity of cancer cells to the cytotoxic effects of chemotherapy agents. The data presented below indicate that pretreatment with BPM31510 alone and in combination with gemcitabine, 5-FU or docetaxel is associated with an increase in the cytotoxic potential compared to chemotherapy treatment alone, suggesting the utility of BPM31510 in effectuating "priming" of certain cancer cells to the cytotoxic effects of standard of care chemotherapy agents. The cancer cell lines used in the experiments are shown in the following table.

Table 5: The cancer cell lines used in the experiments

	Chemotherapeutic Agents		
Cell Description	**Gemcitabine**	**Docetaxel**	**5-FU**
Pancreatic Cancer	Mia-PaCa2		Mia-PaCa2
Prostate Cancer		PC3	
Lung Cancer	A549	A549	
Breast Cancer			SK-Br3
Breast Cancer			MDA231
Colorectal Cancer			HT-29

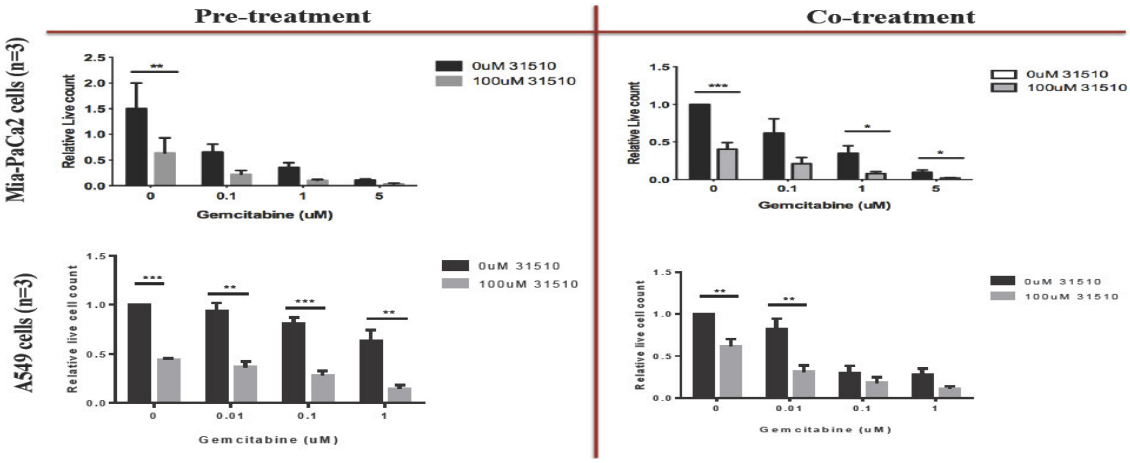
In the pretreatment protocol, cancer cells were pretreated with BPM31510 (100 µM) alone for 6 hours. This was followed by exposure to BPM31510 (100 µM) in combination with increasing doses of the chemotherapy agent. The concentrations of chemotherapy agents were empirically established using dose-response experiments prior to implementation of this protocol.

For all cell lines tested, the combination phase of treatment was 48 hours. The summary below provides data specific to the effect of BPM31510 alone or in combination for testing on the pancreatic cancer model, using the MiaPaCa-2 cultured cell line and either gemcitabine or 5-FU. The data presented in Figures 2 and 3 represent examples of the cytotoxic response in cancer cell lines that were pretreated with BPM31510 (100 µM) for 6 hours (left panels) followed by the combination of BPM31510 (100 µM) with gemcitabine, 5-FU or docetaxel for 48 hours. The right panels of each figure represent cytotoxic response in cancer cells treated with the combination of BPM31510 (100 µM) with chemotherapy agents for 48 hours (no pretreatment). Data is expressed in terms of relative live cell counts determined using trypan blue exclusion as criteria for cell viability determination and compared to total cell counts (Stoddard 2011).

Cancer cell lines treated with 100 μM BPM31510 were associated with decreases in relative live cell counts (i.e., cytotoxic response) reaching variable levels of significance ($p<0.05$ or greater) compared to the respective chemotherapeutic agent alone (Figure 2 and 3). Pretreatment of cancer cells with BPM31510 (100 μM) was associated with a dose-dependent cytotoxic response at lower doses of chemotherapy, particularly in pancreatic and lung cancer treated with gemcitabine (Figure 2) or 5-FU (Figure 3). In the rest of the pretreatment groups, the cytotoxic response elicited by BPM31510 appeared to be maximal with no additive effect observed in the presence of increasing concentrations of chemotherapy agent e.g., colorectal cancer treated with 5-FU (Figure 3). In a few instances, a particular chemotherapy treatment in a particular cancer cell line required significant dose escalations to observe dose response. However, introduction of 100 μM BPM31510 (as combination) produced a cytotoxic response at very low dose spectrum of chemotherapy, hence the lack of dose dependence e.g., in colorectal cancer co-treatment panel (Figure 3). The addition of BPM31510 produced a cytotoxic response in the presence of 0.1 μM 5-FU that was almost equipotent to that observed with 1μM 5-FU, although 5-FU by itself did not show much difference at eliciting a cytotoxic response between the 2 doses.

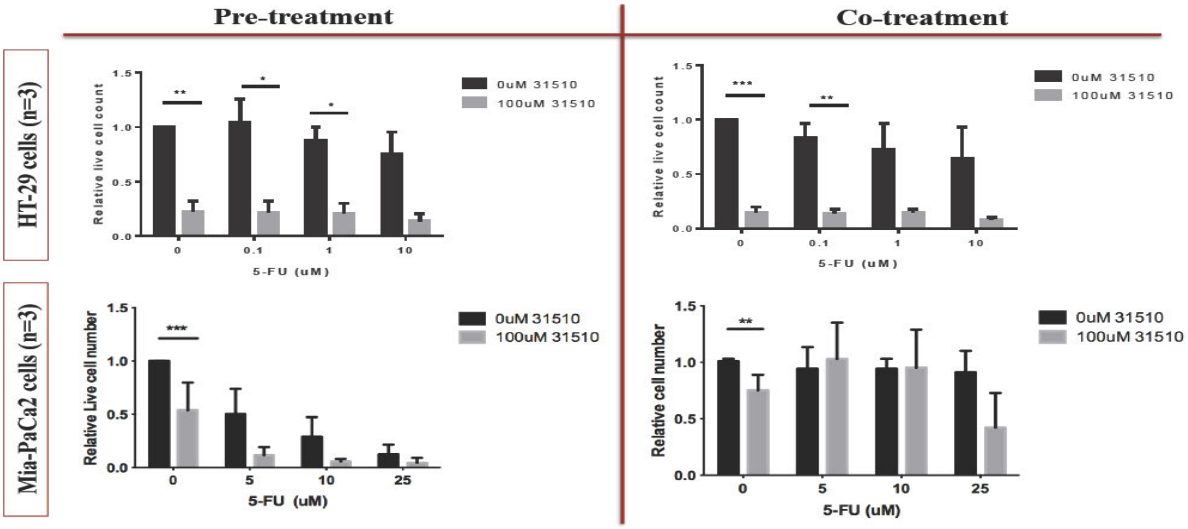
In the combination treatment regimen, pancreatic cancer treated with BPM31510/5-FU combination demonstrated variability in cytotoxic response. In contrast, pancreatic cancer cells exhibited a dose-dependent decrease in live cell count treated with a combination of BPM31510/gemcitabine. Similarly, lung cancer treated with BPM31510 in combination with gemcitabine (Figure 5) demonstrated a trend towards dose-dependent decrease in live cell counts reaching variable levels of significance ($p < 0.05$ or greater) at specific doses compared to chemotherapy alone. Similar to observations in the pretreatment group, the cytotoxic response elicited by BPM31510 appeared to be maximal with no additive effect observed in the presence of increasing concentrations of chemotherapy agent e.g., colorectal cancer treated with 5-FU (Figure 6). Overall, data suggests that pretreatment with BPM31510 and/or the combination of BPM31510 with chemotherapy improves cytotoxicity with low doses of chemotherapy agent in most cancer cell lines, the extent of differential response in pretreatment or combination groups reaching variable significance of $p < 0.05$ or greater depending on cell line, treatment protocol and dose.

Figure 5: Effect of BPM31510 Alone or in Combination with Gemcitabine in Pancreatic and Lung Cancer Cells



(* P<0.05; ** P<0.01; *** P<0.001)

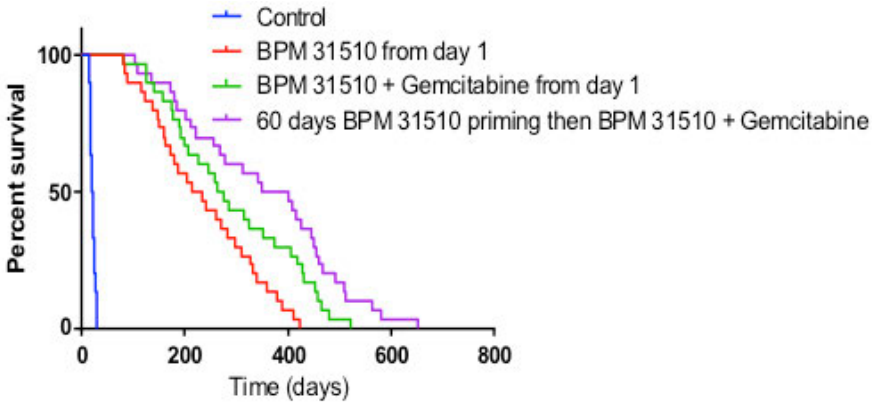
Figure 6: Effect of BPM31510 Alone or in Combination with 5-FU in Colorectal and Pancreatic Cancer Cells



(* P<0.05; ** P<0.01; *** P<0.001)

1.6 Sensitization of pancreatic cancer by BPM31510 pretreatment

The efficacy of BPM31510 continuous infusion for 60 days followed by treatment with gemcitabine in pancreatic cancer xenograft model was compared to treatment regimens of BPM31510 alone or BPM31510 – gemcitabine combination therapy initiated Day1.



BPM 31510: 100 mg/kg/day continuous infusion pump
Gemcitabine 150 mg/kg IV, 1X per week on day 7, 14, and 21 per 28 day cycle
N=30 mice/group

	Median survival (days)
Control	20.5
BPM 31510 from day 1	224
BPM 31510 + Gemcitabine from day 1	270
60 days BPM 31510 priming then BPM 31510 + Gemcitabine	375

Figure 7: Effect of BPM31510 alone, in combination with gemcitabine therapy initiated Day 1 and BPM31510 treatment for 60 days as continuous infusion followed by combination with gemcitabine in pancreatic cancer xenograft model.

Continuous infusion of BPM31510 alone or in combination with gemcitabine was associated with increase in duration of survival in pancreatic cancer xenograft mice model. Interestingly, a 60 day treatment of BPM31510 as a single agent followed by incorporation of gemcitabine as a combination cytotoxic chemotherapy agent was associated with improvement in duration of survival (Figure 7above). The data suggests that extended infusion of BPM31510 (the duration in this study is almost equivalent to two cycles of monotherapy in the clinical trial) followed by gemcitabine improves duration of survival.

The preclinical animal data along with *in vitro* demonstration that BPM31510 and gemcitabine induce activation of apoptotic pathways in MIA-PACA2 cells by two independent mechanisms that convergence at the mitochondria in a synergistic manner suggests that the observed improvement in duration of survival in the 60 day BPM31510 treatment followed by gemcitabine is suggestive of sensitization and mechanism based synergy.

1.7 Dose Selection for BPM31510 & Chemotherapy

Results from the on-going BPM31510IV-04 Phase 1 clinical study, started in 2013, have demonstrated the safety of BPM31510 up to a dose of 110 mg/kg IV when given in combination with gemcitabine and up to 171 mg/kg when given as monotherapy. Furthermore, data from preclinical studies in xenograft models for pancreatic cancer suggest that higher doses of BPM31510 alone or in combination with gemcitabine was associated with improved duration of survival. The combination of safety (observed in human trials) and efficacy (observed in preclinical studies) results encouraged the Sponsor to perform further clinical studies and to explore efficacy of IV BPM31510 alone and in combination with gemcitabine in the treatment of advanced pancreatic cancer.

Additional information about the product, including pharmacology, toxicology, and prior human use experience is contained in the Investigator's Brochure (IB). All combination therapy patients will receive a gemcitabine dose of 1000 mg/m² IV infusion which is the recommended starting dosage for patients being treated for recurring pancreatic cancer.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To evaluate the Overall Response Rate in patients treated with the combination of BPM31510 with gemcitabine.

2.2 Secondary Objectives

The secondary objectives of this study are:

- Evaluate Overall Survival;
- Evaluate Progression-Free Survival—overall and at around 10 weeks [redacted]
- Evaluate Time to Progression (TTP);
- Evaluate Tumor Response using Adaptive Molecular Responses (epi-genomic analysis (SNP or X-ome technology));
- Determine the toxicity profile of BPM31510 in combination with gemcitabine when administered as a 144-hour (two 72-hr) intravenous (IV) infusion in patients with advanced pancreatic cancer.
- Evaluate Change in CA 19-9 levels.
- Evaluate changes in patient reported Quality of Life using the validated FACT-HEP patient-reported outcomes instrument specific for patients with hepatobiliary and pancreatic cancers at the end of Cycle 2 and at End of Study or Early Termination

2.3 Exploratory Objectives

The exploratory objectives of this trial are:

- To evaluate the effects of BPM31510 on shifting tumors to aerobic respiration by PET imaging.
- Plasma and urine samples will be assayed for levels of markers of BPM31510 activity using (but not limited to):
    - genomic (e.g. microarray, SAGE, northern blotting, gene expression), proteomic (e.g., LC/MS based analysis, 2DE-MS, MALDI TOF, antibody array, ELISA, immunohistochemistry, tissue microarray, flow cytometry, Western blotting),
    - metabolomics (e.g., global analysis of metabolites in biological samples; identification of specific markers of energy metabolism e.g., pyruvate, lactate),
    - lipidomics (e.g., global analysis of lipid classes; identification of specific lipids e.g., derivatives of palmitate, linoleic acid, arachidonic acid).

The objective of this integrative approach is to stratify patient populations based on phenotypic or molecular profiles, with the aim of correlating these profiles with patient outcomes to facilitate prediction of therapeutic benefit to aid in future patient selection. This includes

assessing the patient's biofluid as well as the tumor for markers of positive, stable or negative outcome allowing for guidance of selection of participants in future cohorts.

3 STUDY POPULATION

3.1 Number of Patients

This study will occur in two parts. Part 1 of the study will enroll ten (10) evaluable patients. If at least one of ten patients treated experiences a Complete Response (CR) or Partial Response (PR), based on RECIST v1.1 criteria, after 2 cycles of treatment, then Part 2 of the study will enroll an additional 15 patients for a total of 25 evaluable patients. In the absence of at least one CR or PR, if at least 3 patients experience stable disease following the first 2 cycles of treatment the Sponsor can choose to enroll the additional 15 patients into the expansion stage.

3.2 Inclusion Criteria

Patients must meet the following criteria in order to be included in the clinical trial:

1. The patient has a histologically or cytologically confirmed metastatic pancreatic adenocarcinoma.
2. The patient has received at least one but no more than 2 prior, standard or experimental therapies for metastatic pancreatic cancer*. If the patient has had prior gemcitabine treatment, the last date of gemcitabine administration-should be ≥ 28 days prior to receiving study treatment. All patients who have previously received gemcitabine should be discussed with the medical monitor during screening.

3. The patient is at least 18 years old.
4. The patient has an ECOG performance status 0 - 1 [redacted]
5. Measurable tumor lesions according to RECIST 1.1 criteria [redacted]
6. In the opinion of the Investigator, the patient has a life expectancy of > 3 months.
7. Sexually active patients and their partners agree to use an accepted method of contraception during the course of the study [redacted]
8. Female patients of childbearing potential must have a negative pregnancy test within 1 week prior to beginning study treatment.
9. The patient has adequate organ and marrow function as follows:
   ANC ≥ 1500 mm^3, platelets ≥ 100,000/mm^3, hemoglobin ≥ 9 g/dL, serum creatinine ≤ULN or calculated creatinine clearance > 50 ml/min;
10. Total bilirubin ≤ 1.5 X ULN (unless related to Gilbert's Syndrome); alanine aminotransferase (ALT), aspartate transaminase (AST) ≤ 2.5 times the upper limit of normal if no liver involvement or ≤ 5 times the upper limit of normal with liver involvement.
11. The patient has serum electrolytes (including calcium, magnesium, phosphorous, sodium and potassium) within normal limits (supplementation to maintain normal electrolytes is allowed).

12. The patient has adequate coagulation: prothrombin time (PT) and an International Normalized Ratio (INR), and partial thromboplastin time (PTT) ≤ 1.5 times the upper limit of normal.
13. In the opinion of the Investigator, the patient is capable of understanding and complying with the protocol and has signed the informed consent document.

*For the purposes of this study, patients who have received at least one, but no more than 2, prior standard therapies for locally advanced pancreatic cancer and then transition to a diagnosis of metastatic pancreatic cancer ≤ 6 months post therapy may count the treatment for locally advanced cancer as 1st line treatment for metastatic cancer.

3.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from trial entry:

1. The patient has uncontrolled intercurrent illness including, but not limited to uncontrolled infection, symptomatic congestive heart failure (NYHA class III and IV), uncontrolled cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance [redacted].
2. The patient has active heart disease including myocardial infarction within previous 3 months, symptomatic coronary artery disease, arrhythmias not controlled by medication, unstable angina pectoris, or uncontrolled congestive heart failure (NYHA class III and IV) [redacted]
3. The patient has received chemotherapy within 2 weeks or radiotherapy within 4 weeks or has received nitrosoureas or mitomycin C within 6 weeks prior to the first dose of study drug. The patient must have recovered from treatment related toxicities to Grade 1 or less (other than alopecia).
4. Patients previously treated with gemcitabine: who discontinued gemcitabine due to toxicity in the first 6 weeks of prior treatment or is/was unable to tolerate a dose of 800 mg/m^2 weekly at any point due to toxicity are not eligible
5. The patient has received radiation to ≥ 25% of his or her bone marrow within 4 weeks of the first dose of study drug.
6. The patient has received an investigational drug within 30 days of the first dose of study drug.
7. Evidence of central nervous system (CNS) metastasis (negative imaging study, if clinically indicated, within 4 weeks of Screening Visit).
8. History of other malignancies (except adequately treated Stage 1 cancer, cured basal cell carcinoma, superficial bladder cancer, breast ductal carcinoma *in situ* (DCIS) without invasive component, or carcinoma *in situ* of the cervix) unless documented free of cancer for ≥5 years.

9. The patient has not recovered to Grade ≤ 1 from adverse events (AEs) due to investigational drugs or other medications, which were administered more than 4 weeks prior to the first dose of study drug.
10. The patient is pregnant or lactating.
11. The patient is known to be positive for the human immunodeficiency virus (HIV). The effect of BPM31510 on HIV medications is unknown. Note: HIV testing is not required for eligibility, but if performed previously and was positive, the patient is ineligible for the study.
12. The patient has an inability or unwillingness to abide by the study protocol or cooperate fully with the Investigator or designee.
13. The patient is receiving digoxin, digitoxin, lanatoside C or any type of digitalis alkaloid.
14. The patient has uncontrolled or severe coagulopathies or a history of clinically significant bleeding within the past 6 months, such as hemoptysis, epistaxis, hematochezia, hematuria, or gastrointestinal bleeding.
15. The patient has a known predisposition for bleeding such as von Willebrand's disease or other such condition.
16. The patient requires therapeutic doses of any anticoagulant, including LMWH. Concomitant use of warfarin, even at prophylactic doses, is prohibited.

3.4 Discontinuation from Trial Treatment

Permanently discontinue BPM31510 treatment if any of the following conditions are met:

- Documented progressive disease*
- Occurrence of a ≥ grade 2 INR increased associated with clinically significant bleeding, or with no bleeding but does not normalize with Vitamin K, cryoprecipitate or fresh frozen plasma within 7 calendar days.
- Occurrence of a second asymptomatic grade 3 INR.
- Grade 3 PTT abnormalities (with or without bleeding) or ≥ grade 2 elevations in PTT with clinically significant bleeding.
- Treatment delay of greater than 14 calendar days (without sponsor approval).
- Patient withdrawal of consent for study participation at any time.
- Withdrawal of a patient at the Investigator's discretion for any reason that the Investigator believes continuation of study drug therapy would not be in the patient's best interest. The reason for the patient's discontinuation must be recorded on the Case Report Form (CRF).
- An intercurrent illness which, in the opinion of the Investigator, would prevent completion of study-related evaluations.
- Pregnancy ([redacted]
- Patient noncompliance with study or follow-up procedures.
- Termination of the study by BERG.
- The patient exhibits signs of anaphylaxis.

*Patients who experience disease progression but are, in the opinion of the investigator, receiving clinical benefit may continue BPM31510 as a monotherapy or in combination with gemcitabine or as a monotherapy with approval from the Sponsor.

The study may be terminated at any time by the Sponsor for safety concerns or if in the Sponsor's judgement there are no further benefits to be expected from the study. In such a case, the Sponsor or delegate will inform the study investigators, institutions, and all Regulatory Authorities. The study can also be terminated by the Regulatory Authority for any reason.

An excessive rate of patient withdrawals can render the study uninterpretable; therefore, every reasonable effort will be made to keep the patient in the study. Patients that are withdrawn for any reason prior to completing at least 2 cycles of treatment will be replaced until no more than 25 evaluable patients have been treated under this protocol.

If a patient is withdrawn from treatment, the Investigator will make every effort to complete all final evaluations and laboratory tests required by the protocol. The reason(s) for study termination must be clearly documented on the CRF.

After withdrawal from protocol treatment, patients must be followed for AEs for 30 calendar days after their last dose of BPM31510. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the Investigator, these values are not likely to improve because of the underlying disease. In this case, the Investigators must record his or her reasoning for this decision in the patients' medical records and as a comment on the CRF.

All patients who have CTCAE grade 3 or 4 laboratory abnormalities at the time of treatment discontinuation must be followed until the laboratory values have returned to grade 1 or 2 unless in the opinion of the Investigator it is not likely that these values are to improve because of the underlying disease. In this case, the Investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment on the CRF.

3.4.1 Pregnancy

During the course of the trial, all female patients of childbearing potential (definitions listed in [redacted] must contact the treating Investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating Investigator).

If an Investigator suspects that a patient may be pregnant prior to administration of BPM31510, BPM31510 must be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the patient must not receive any BPM31510, and must be discontinued from the trial.

If an Investigator suspects that a patient may be pregnant after the patient has been receiving BPM31510, BPM31510 must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, BPM31510 must be immediately and permanently stopped, the patient must be discontinued from the trial, and the Investigator must notify the BERG study chair as soon as possible. If a patient becomes pregnant while enrolled in the trial, a

Pregnancy Form (a paper report form, not available within the Electronic Data Capture (EDC) system should be completed [redacted]

4 STUDY REGISTRATION

Human protection committee approval of this protocol and consent form is required. Eligible patients who wish to participate in the trial must provide informed consent prior to enrollment. Informed consent for this trial includes education about the procedures to be followed, the experimental nature of the treatment, as well as the potential benefits, alternatives, side-effects, risks and discomforts of treatment.

The sample size of this study will be a maximum of 25 evaluable patients. This study will occur in two parts. Part 1 of the study will enroll 10 evaluable patients.. If a response of Complete Response (CR) or Partial Response (PR) is not observed in the first 10 patients two cycles of treatment, enrollment may be terminated. If at least one response of CR or PR is observed in the first 10 patients after two cycles of treatment, Part 2 of the study will enroll an additional 15 patients for a total of 25 patients. In the absence of at least one CR or PR, if at least three patients experience stable disease, the Sponsor can choose to enroll the additional 15 patients into the expansion stage.

Both Screening and Enrollment Registration is via the study EDC system and must occur prior to the initiation of protocol therapy. The Screening Registration will consist of submitting relevant information collected on the study specific eCRF pages to verify the patient's eligibility. Once these forms are complete, the site's Principal Investigator will review the data for eligibility determination and assign a treatment regimen to the patient.

Patients registered to screening into the EDC system will be automatically assigned a unique Patient ID number, comprised of the four-digit site number and a unique four-digit sequential number per site. Investigators will be able to view the total number of patients that are currently enrolled in each arm in the EDC system. In addition, the Sponsor will require Investigational sites to provide information on the eligibility of the patient to a specific treatment arm prior to registering patients in enrollment in the EDC system. The Sponsor will provide written confirmation to the Investigator that the patient enrollment to arm requested by the Investigational site is allowable and the arm of the study has not met capacity.

Once the eligibility for the patient is confirmed, the Patient ID number will follow the patient's treatments and outcomes throughout the trial. If the patient is a screen failure, the specific Patient ID number assigned to this subject will not be used again in the study.

5 STUDY DESIGN

This is a Phase 2 multicenter, open-label, non-randomized study to examine the safety and effectiveness of BPM31510 administered in combination with gemcitabine as a 144-hour (two 72-hour) continuous intravenous (IV) infusion in advanced pancreatic cancer patients as 2^{nd}/ 3^{rd} line therapy.

This study will occur in two parts. Part 1 of the study will enroll ten (10) evaluable patients If at least one of ten patients treated experiences a Complete Response (CR) or Partial Response (PR), based on RECIST 1.1 criteria, after 2 cycles of treatment, then Part 2 of the study will enroll an additional 15 patients for a total of 25 patients. In the absence of at least one CR or PR, if at least 3 patients experience stable disease following the first two treatment cycles the Sponsor can choose to enroll the additional 15 patients.

This study is multinational.

Cycle 1 is 6 weeks in duration with BPM31510 administered twice weekly on Tuesdays and Fridays for 6 weeks. Each 110 mg/Kg dose is administered over 72-hours. Patients will also be treated with gemcitabine administered on Mondays, on Days 21, 28 and 35.

Cycles 2-12 are 4 weeks in duration with BPM31510 administered twice weekly on Tuesdays and Fridays for 4 weeks. Patients will be treated with gemcitabine administered on Mondays, Days 7, 14 and 21 of each cycle. Toxicity will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4.02). Safety oversight will be provided by the Medical Monitor

Assessments of the antitumor activity of BPM31510 will be performed at the end of Cycle 2 and every 2 cycles thereafter using standard techniques such as computerized tomography (CT) or magnetic resonance imaging (MRI) for patients with measurable disease. Response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [redacted] Patients who experience no unacceptable toxicity or disease progression, may continue to receive additional 28-day cycles for up to 1 year.

Patients will continue to receive BPM31510 in combination with gemcitabine, for a maximum of 12 cycles in the absence of intolerable toxicity and progression. If gemcitabine is discontinued due to chemotherapy-related toxicity, patients may continue to receive BPM31510 as monotherapy if, in the opinion of the investigator, the patient may continue to receive clinical benefit from continuing use of study drug.

An 18-fluorodeoxyglucose (18-FDG) PET scan will be performed ≤ 14 days prior to starting treatment, at the end of Week 2 and then again after 10 weeks of treatment (end of treatment cycle 2) and then after every additional 2 cycles of completed treatment. This exploratory data will be correlated with the secondary endpoints of PFS and TTP.

6 ADMINISTRATION OF TREATMENT

6.1 Combination BPM31510 and gemcitabine

BPM31510 Nanosuspension Injection (40 mg/mL) will be administered IV over 144 hours; each patient will receive 2 consecutive 72-hour infusions (of 110 mg/Kg) per week (Tuesday-Friday and Friday-Monday). Patients will be subsequently treated with gemcitabine IV once weekly at a starting dose of 1000 mg/m^2, as outlined below, starting 3 weeks after initiation of treatment with BPM31510.

Cycle 1 of therapy is 6 weeks in duration for patients with BPM31510 administered twice weekly on Tuesdays and Fridays for 6 weeks. Patients will be treated with gemcitabine administered on Mondays, Days 21, 28 and 35 during the first treatment cycle.

Response will be assessed after Cycle 2 (10 weeks) and patients who continue onto Cycles 3-12 will be assessed every 2 cycles (8 weeks). Cycles 2-12 are 4 weeks in duration with BPM31510 administered twice weekly on Tuesdays and Fridays for 4 weeks and gemcitabine administered on Mondays, Days 7, 14 and 21 of each treatment cycle.

Alternate dosing schedules are allowed with pre-approval from the study sponsor. For patients receiving an alternate dosing schedule, the gemcitabine chemotherapy treatment will be given after the completion of the sixth infusion (three weeks following initiation of BPM31510 treatment).

If the gemcitabine component of combination therapy is discontinued due to chemotherapy-related toxicity, patients may continue to receive BPM31510 as monotherapy at the investigator's discretion.

6.2 Duration of Therapy

Patients who experience no unacceptable toxicity or disease progression while on BPM31510 for 2 cycles of therapy (10 weeks) may receive additional 28-day cycles of their current treatment for up to 1 year (12 cycles) or until any of the discontinuation criteria listed in [redacted] are met.

Patients who experience disease progression but are, in the opinion of the investigator, receiving clinical benefit may continue BPM31510 as a monotherapy or in combination with gemcitabine with approval from the Sponsor.

6.3 End of Study

The study will end at the conclusion of the enrollment period plus a 12-month follow up period for all patients, or until the last patient enrolled in the study has finished the study, has withdrawn, or expired, whichever occurs first.

6.4 Concomitant Medications and Supportive Care

Supportive measures including analgesics, blood transfusions, and antimicrobials are permitted throughout the trial.

Prophylactic Vitamin K will be given to all patients prior to the beginning of every week of therapy, unless contraindicated as determined by the Investigator. Additional Vitamin K (oral, IM, IV), cryoprecipitate or fresh frozen plasma is to be administered, at the investigators discretion, if the patient has a ≥ grade 2 INR value.

Several other types of therapy may be allowed or prohibited as specified below.

6.4.1 Granulocyte Colony-Stimulating Factors

Prophylactic use of colony stimulating factors is permitted. Hematopoietic colony stimulating factors are allowed to treat cytopenias at the discretion of the Investigator.

6.4.2 Other Cancer Treatments

Therapeutic administration of anticancer therapies including radiation, biologics, or other investigational cytotoxic agents is not permitted without Sponsor's prior approval.

Palliative radiotherapy is permitted with the Sponsor's prior approval.

6.4.3 Other Prohibited Medications

The following medications may not be taken concomitantly with BPM31510:

- Digoxin, digitoxin, lanatoside C or any type of digitalis alkaloids.
- Systemic use of anticoagulants, including LMWH. Concomitant use of warfarin, even at prophylactic doses, is prohibited. Use of heparin for the purposes of line preparation / flushing is allowed.

7 DOSING AND DOSE MODIFICATIONS

7.1 Calculation of BPM31510 Dose

The calculation of the dose of BPM31510 should be based on the patient's weight in kilograms. For obese patients with a Body Mass Index > 30, the dose should be calculated using the

patient's Adjusted Body Weight [redacted]

7.2 Infusion Rate and Loading Dose of BPM31510

For the first dose of each week, a loading dose (approximately 8.2 % of the total volume) will be infused over 1 hour with the remainder of the dose volume infused over approximately 71 hours as indicated. Patients will be monitored closely during the loading dose procedures and during the transition to ambulatory infusion while at the research site. Per protocol section 7.6, Interruption of BPM31510 due to Hemodynamic Instability; patients will undergo study evaluations including AE and vital sign assessments to evaluate the patient's tolerance for BPM31510 and for the treatment administration process. Upon successful infusion of the loading dose, the remainder of the 72-hour infusion will be completed on an outpatient basis.

If the patient exhibits signs of hemodynamic instability at any time during the BPM31510 infusion (loading dose or ambulatory infusion), the infusion will be stopped and the patient's vital signs monitored closely. If hemodynamic instability does not resolve within 2 hours, the infusion will not be restarted. Patients should be directed to report signs and symptoms indicative of vital sign changes to their research site should they become aware of any of these signs and symptoms. The study site should take the appropriate steps for follow up.

If the patient's vital signs stabilize within 2 hours, the infusion can be restarted at ½ the rate and vital signs will be monitored every 10-15 minutes for at least 30 minutes before increasing the administration rate. Vital signs will then be monitored every 10-15 minutes for at least 30 minutes before discharging the patient.

Patients will be instructed on potential signs and symptoms commonly associated with hemodynamic instability and will be directed to contact their research site or contact emergency services as required.

If the pump cannot be programmed to administer the total volume of BPM31510 over 71 hours exactly on the first dose of each week or 72 hours exactly on the second dose of each week, please be sure to document the change in duration on the dosing log eCRF and collect PD specimens based on the **end of infusion time**.

7.3 Missed Doses during Cycle 1

The dose of BPM31510, defined as 110 mg/Kg over a 72-hour infusion, may be interrupted due to BPM31510 related clinically significant toxicity. BPM31510 dose reductions are not allowed. No more than 3 doses (in total) may be missed during Cycle 1 unless approved by Sponsor. Removal from the study will be at the Investigator's discretion based on whether the subject is experiencing clinical benefit from treatment or it is in the best interest of the subject to continue study treatment.

Doses that are missed will not be made-up. If the first dose of the week is missed or held, the second dose will still be given over 72 hours with no loading dose.

7.4 Dose Reduction during Cycles 2-12

Hematologic Toxicity

The Baseline Laboratory Requirements are ANC ≥ 1500 mm^3, platelets ≥ 50,000/mm^3, hemoglobin ≥ 9 g/dL and INR ≤ 1.5 X UNL. Hematology and chemistry should be assessed weekly and coagulation labs should be repeated within 24-72 hours prior to initiation of each dose. BPM31510 must be held for any grade 3 or 4 hematologic toxicity that is at least possibly drug-related. Any grade 3 or 4 hematologic toxicity must return to a grade 1 or be resolved with the exception of INR which must be ≤ 1.5 X UNL prior to continuing administration of BPM31510.

To monitor and mitigate BPM31510-associated coagulopathies, PT, PTT, INR and platelet counts must be assessed prior to administering each dose of BPM31510. Prophylactic Vitamin K will be given to all patients prior to the beginning of every week of therapy, unless contraindicated as determined by the Investigator. Vitamin K formulation, dosing and frequency of dosing is at the Investigators discretion. Additional Vitamin K should be given as needed. An INR value of ≥ grade 2 requires immediate treatment with Vitamin K, cryoprecipitate or fresh frozen plasma as clinically indicated. Any AE must decrease to ≤ grade 1 and the INR must be ≤ 1.5 X UNL before resuming BPM31510 treatment.

If a second adverse event of ≥ grade 3 INR elevations occurs, permanently discontinue BPM31510.

[redacted]

Non-Hematologic Toxicity

A grade 3 or 4 non-hematologic toxicity that is at least possibly drug-related must return to grade 1 or resolve prior to continuing administration of BPM31510. Grade 3 fasting lipid abnormalities are an exception in the absence of clinical signs or symptoms. BPM31510 causes a false positive fasting lipid elevation. Abnormal fasting lipid profiles should be monitored closely, however BPM31510 may continue in the absence of clinical signs or symptoms.

7.4.1 Guidelines for Holding BPM31510 Doses

Dose modification based on type of toxicity (hematologic vs non-hematologic) and grade is provided to guide BPM31510 dosing decisions. Note that the protocol provides for holding or discontinuation of BPM31510, but no dose reductions of BPM31510 are permitted.

Cycle	All Cycles			
Type	Hematologic		Non-Hematologic	
Grade	1 or 2	3 or 4	1 or 2	3 or 4
BPM31510	Continue with the exception of INR< PT, PTT which must be less than or equal to 1.5X ULN*	Hold dose, & may resume at same dose upon AE decrease to grade 1 or resolved, with the exception of INR which must be within or below normal range*	Continue	Hold dose, & may resume upon AE decrease to grade 1 or resolved**

*Normal range is defined as elevated INR must be $\leq$ 1.5 X UNL before resuming treatment.
**Grade 3 fasting lipid abnormalities are an exception in the absence of clinical signs/symptoms.

7.4.2 Guidelines for Dose Modification for Chemotherapy-Specific Toxicity

For toxicities that are likely to be due to gemcitabine, reduction of gemcitabine dose will be permitted. The dose reduction of gemcitabine will be step-wise, to the next lowest dose, as delineated below. Toxicities requiring dose reductions should be documented as adverse events.

Note: Patients may continue to receive BPM31510 as monotherapy if the gemcitabine component of combination therapy is discontinued due to toxicity.

Gemcitabine: Gemcitabine dose levels are 600 mg/m^2, 800 mg/m^2, and 1000 mg/m^2.

Toxicity	ANC (x 10^6/L)	Platelet count (x 10^6/L)	Management
Myelosuppression	$\geq$ 1000	and $\geq$ 75,000	OK to treat.
	500-999	or 50,000-75,000	Hold chemotherapy. Resume if ANC $\geq$ 1000 and PLT $\geq$ 75,000 at 1 dose level reduction to 800 mg/m^2. One further reduction to 600 mg/m^2 may be taken.
	< 500	or < 50,000	Discontinue further gemcitabine.

7.5 Dosing Delays during Cycles 2-12

If the criteria for managing toxicity [redacted] are not met, BPM31510 treatment may be delayed for a maximum of 2 weeks during Cycles 2-12. The patient may resume treatment if treatment is held for less than 2 weeks. No more than 2 weeks may be skipped within a cycle. If treatment cannot be given after a 2-week delay, the patient will be removed from the study and followed for 30 days from the date of the last dose, unless otherwise approved by Sponsor

7.6 Interruption of BPM31510 Due to Hemodynamic Instability

Patients will receive a loading dose of approximately 8.2% (of the total 72 hour dose). The loading dose will be infused over a 1-hour period while the patient is at the research facility. They will undergo study evaluations including AE evaluations and vital sign assessment to

evaluate the patient's tolerance for BPM31510 and for the treatment administration process. Upon successful infusion of the loading dose, the remainder of the 72 hour infusion will be completed on an outpatient basis.

If the patient exhibits signs of hemodynamic instability at any time during the BPM31510 infusion (loading dose or ambulatory infusion), the infusion will be stopped and the patient's vital signs monitored closely. If hemodynamic instability does not resolve within 2 hours, the infusion should not be restarted.

If the patient's vital signs stabilize within 2 hours, the infusion can be restarted at ½ the rate and vital signs will be monitored every 10-15 minutes for at least 30 minutes before increasing the administration rate. Vital signs will then be monitored every 10-15 minutes for at least 30 minutes before discharging the patient.

Patients will be instructed on potential signs and symptoms commonly associated with hemodynamic instability and will be directed to contact their research site or contact emergency services as required.

7.7 Dose Interruption Due to Infusion Pump Malfunction Outside of the Clinic

Study drug administration will be started and completed only at research / treatment facilities authorized by BERG, LLC on the completed Enrollment Authorization Form. Once the infusion has started, patients will continue study drug administration via ambulatory pump. Use of ambulatory pump allows patients to continue infusion at home and to have mobility in completing daily activities with limited restrictions. The ambulatory pumps being used are validated for, and marketed in the EU and US for this purpose. Patients will return to their research /treatment facility 1-2 hours before infusion end to complete the infusion and to have study procedures (including vital sign and AE assessments) completed per protocol.

If problems are encountered during infusion of BPM31510 outside of the clinic, the following steps should be taken:

- If a malfunction occurs after clinic hours, the patient should turn the pump off and call the helpline phone number listed on the pump.
- If the pump cannot be restarted with the assistance of the helpline, the patient should return to the outpatient clinic the following day.
- The clinic staff will determine the length of time the infusion was stopped by calculating the volume of BPM31510 remaining in the cassette/bag, the start time of the infusion, and infusion rate on the pump. The dosing interruption will be captured on the dose eCRF as a pump malfunction and the delay will be recorded.
- If the clinic staff is able to resume the infusion after a delay, this information will be captured. Data regarding the exact amount infused, the duration of any stoppage, and the volume remaining in the cassette at the time the infusion was discontinued will be recorded on the eCRF.

- If the infusion cannot be resumed, the volume of drug left in the cassette/IV bag should be recorded. The remainder of the dose will not be made up by extending the number of days of therapy.
- If the first dose of the week is missed or held, the second dose will still be given over 72 hours with no loading dose.

[redacted]

8 STUDY TREATMENT

8.1 Overview

This study will be conducted in an outpatient setting. The main time periods during the trial are: Screening, Cycle 1, Cycles 2-12, and End of Treatment/Follow-up.

All patients should have assessments at the times specified in the sections below. [redacted] As a general rule, all required visits should occur within ± 3 days, and lab tests and vital signs within ± 30 minutes of the protocol-specified time point, unless otherwise noted. Abnormal labs may be repeated more often than as outlined below at the Investigator's discretion. If the patient experiences toxicity, study treatment can be postponed at the Investigator's discretion, if clinically necessary. If the toxicity does not recover to grade 1 (if toxicity is considered related to study drug) after 2 weeks, the patient will be withdrawn from the study.

The assessment schedule assumes dosing on a Tuesday for the first dose of each week and on Friday for the second dose. Alternate dosing schedules, Monday / Thursday, may be allowed with sponsor pre-approval only.

8.2 Screening

Screening assessments that are standard practice will be collected, reviewed, and will be used by the site PI or designee to determine eligibility prior to obtaining informed consent. Any special or protocol-specific assessments will be performed after informed consent is obtained.

Informed consent may be obtained up to 28 days prior to initiation of treatment. Scans to document measurable or evaluable disease should be performed ≤ 28 days prior to initiation of treatment. Exceptions may be allowed to imaging window with sponsor approval.

Patients will initially undergo a Screening evaluation to determine study eligibility at a maximum of ≤14 days (excepting scans to document measurable or evaluable disease as noted above) prior to the first day of treatment on Cycle 1 Day 1.

Assessments to be performed ≤ 14 days prior to the first day of study treatment:

- Demographics.
- Medical and cancer history.
- Urinalysis
- Tumor assessment (scans ≤ 28 days prior to the first study drug dose; if determined with tumor markers or by clinical observations during a physical examination, assessments must be done ≤ 24-72 hours prior to the first dose).
- 18-FDG-PET scan (≤ 14 calendar days of first BPM31510 dose).
- Concomitant medications, including previous cancer treatments

If the urinalysis, Tumor Assessment, or concomitant medication evaluations are performed more than 14 days prior to the first dose of BPM31510, these evaluations should be repeated on Cycle 1, Day 1 prior to administration of study drug.

Assessments to be performed ≤ 7 calendar days prior to the first day of study treatment are listed below. If any of these assessments are performed more than 7 calendar days prior to the first dose of BPM 31510, they should be repeated on Cycle 1, Day 1 prior to administration of study drug:

- Physical examination.
- Weight.
- Height (does not have to be repeated if >7 days before C1D1 of treatment).
- Vital signs (5-minute sitting blood pressure, pulse, respiratory rate, oral temperature).
- ECOG performance status [redacted]
- FACT-HEP survey administered and completed by patient.
- Pregnancy test (urine or serum) in women of childbearing potential [redacted] Guidelines Regarding Women of Childbearing Potential).
- Hematology [redacted]
- PT/PTT/INR and platelets*
- Serum chemistry panel, including CMP and serum lipids (Table 6)
- C - reactive protein.
- Vitamin K levels*These assessment results must meet the Inclusion Criteria prior to Cycle 1 Day 1 dosing.

8.3 Treatment Period

8.3.1 Cycle 1 (Cycle = 6 weeks)

Safety assessments will be performed prior to administration of each dose of BPM31510. Prophylactic Vitamin K will be given to all patients prior to the beginning of each week of therapy, unless contraindicated as determined by the Investigator. Vital signs will be assessed prior to each dose in Cycles 1-12.

The following assessments will be performed during Cycle 1 (within ± 3 days unless noted otherwise):

- ***Day 1****:* Physical examination and weight.
- ***Day 1:*** ECG pre-dose and at 24 hours post start of infusion (90% of C_{max}).
- ***Day 1****:* CA 19-9 value (or CEA or CA 125 if patient does not express CA 19-9).
- ***Days 1, 8, 15, 22, 29, 36 and 39****:* Vital signs prior to each dose, 1 hour post start of infusion and prior to discharge *(unless discharge is ≤30 minutes from 1-hr post vital sign collection)*. Prior to discharge, the patient will receive instructions to call the research site if they have any signs or symptoms related to potential vital sign changes (shortness of breath, racing heartbeat, dizziness, skin flushing, chills, fever, etc.) or any other side effects they may experience during or after study drug administration. Concomitant Medications are reviewed. Assess for Adverse Events prior to start of infusion and before patient is discharged. Hematology, serum chemistry panel [including CMP and serum lipids], PT/PTT/INR, platelets and urinalysis ≤ 24-72 hours prior to each week's first dose on Tuesday. Patients should not be dosed until those are within normal limits (with the exception of PT/PTT/INR which must be ≤ 1.5X ULN,

or have returned to grade 1 or resolved from previous elevations. Patients will be provided with instructions on reporting of adverse events to site personnel during and following study drug administration.

- ***Day 1:*** Pharmacodynamic samples (PD Blood and Urine are collected pre-dose
- ***Day 2:*** PD Blood & Urine are collected (24 hours after dose start). Vital signs (5-minute sitting blood pressure, pulse, respiratory rate, oral temperature) are assessed and adverse events are collected.
- ***Day 4, 11, and 18:*** PD Blood and Urine samples collected EOI (between the two infusions)
- ***Days 8, 15, 22, 29 and 36:*** PD Blood and Urine samples are collected pre-dose (within 30 mins prior to **start** of new infusion)
- ***Day 25****:* C-Reactive Protein
- ***Days 4, 11, 18, 25, 32, 39****:* Vital signs prior to each dose and 1 hour post start of infusion or prior to discharge, whichever comes first. Assess for Adverse Events prior to start of infusion and before patient is discharged. Prior to discharge, the patient will receive instructions to call the research site if they have any signs or symptoms related to potential vital sign changes (shortness of breath, racing heartbeat, dizziness, skin flushing, chills, fever, etc.) or any other side effects they may experience during or after study drug administration. PT/PTT/INR and platelets ≤ 24-72 hours prior to each dose. Note: laboratory assessment of PT/PTT/INR and platelets can be conducted Monday for the Tuesday dose, but must be conducted on Friday before the dose is administered. Patients should not be dosed until INR and PTT are within ≤ 1.5X ULN.
- ***End of Week 2***: 18-FDG-PET scan (between Day 10- and prior to dosing on day15)
- ***Days 21, 28, and 35*** Gemcitabine dosing days (Mondays). Vital signs prior to each dose, 1-hr post start of infusion and prior to discharge. Assess for Adverse Events prior to start of infusion and before patient is discharged.
- ***Day 21:*** ECG before patient is discharged.
- ***As needed:*** Laboratory testing for any ≥ grade 2 prolonged INR to determine the underlying cause. The workup should include: LFTs, levels of vitamin-K dependent coagulation factors (II, VII, IX, X), Protein C, and Protein S. If ≥ grade 2 INR is not corrected following administration of Vitamin K, additional tests such as mixing studies, fibrinogen level, D-dimer and fibrin split products should be performed. Additional coagulation testing does not need to be completed more than once per patient.

8.3.2 Cycles 2-12 (Cycle = 4 weeks)

- ***Day 1****:* Physical examination, weight, CA 19-9 Value, ECOG performance status [redacted] and pregnancy test (urine or serum) in women of childbearing potential (within 24-72 hours prior to Day 1). [redacted]

- ***Days 1, 8, 15, and 22****:* Adverse Events and Concomitant Medications reviewed. Assess for Adverse Events prior to start of infusion and before patient is discharged. Hematology, serum chemistry panel [including CMP and serum lipids], PT/PTT/INR, platelets and urinalysis ≤ 24-72 hours prior to each Tuesday dose. Patients should not be dosed until those are within normal limits or have returned to grade 1 or resolved from previous elevations with the exception of PT/PTT/INR which must be ≤ 1.5 X UNL.
- ***Day 25:*** C-Reactive Protein
- ***Days 1, 4, 8, 11, 15, 18, 22, and 25****:* Vital signs prior to each dose, 1-hr post start of infusion and prior to discharge *(unless discharge is ≤30 minutes from 1-hr post vital sign collection)*. Prior to discharge, the patient will receive instructions to call the research site if they have any signs or symptoms related to potential vital sign changes (shortness of breath, racing heartbeat, dizziness, skin flushing, chills, fever, etc.) or any other side effects they may experience during or after study drug administration. Assess for Adverse Events prior to start of infusion and before patient is discharged. PT/PTT/INR and platelets ≤ 24-72 hours prior to each dose. Note: laboratory assessment of PT/PTT/INR and platelets can be conducted Monday for the Tuesday dose, but must be conducted on Friday before the dose is administered. Patients should not be dosed until INR is within or below normal limits from previous elevations.
- ***End of Week 10:*** 18-FDG PET scan **and** FACT-HEP questionnaire completed by patient.
- ***End of Cycle 2 and every 2 cycles thereafter*****:** Tumor response assessment [redacted] and ECG if clinically indicated.
- ***Days 1and 15:*** PD Blood and Urine samples are collected pre-dose (within 30 mins prior to **start** of new infusion).
- ***Day 28***: PD Blood and Urine samples are collected EOI
- ***Days 7, 14 and 21:*** Gemcitabine dosing days (Mondays). Assessment of vital signs prior to each dose, 1-hr post start of infusion and prior to discharge. Assess for Adverse Events prior to start of infusion and before patient is discharged.
- ***As needed:*** Laboratory testing for any ≥ grade 2 prolonged INR to determine the underlying cause. The workup should include: LFTs, levels of vitamin-K dependent coagulation factors (II, VII, IX, X), Protein C, and Protein S. If ≥ grade 2 INR is not corrected following administration of Vitamin K, cryoprecipitate or fresh frozen plasma, additional tests such as mixing studies, fibrinogen level, D-dimer and fibrin split products should be performed. Additional coagulation testing does not need to be completed more than once per patient.

8.4 Unscheduled Visits

If additional Unscheduled Visits are required, the following evaluations will be performed at the discretion of the Investigator:

- Physical examination
- Weight
- Vital signs (5-minute sitting blood pressure, pulse, respiratory rate, oral temperature)
- ECOG performance status [redacted]
- Hematology (Table 6)
- PT/PTT/INR and platelets.
- Serum chemistry panel (including CMP and serum lipids) (Table 6)
- C-Reactive Protein (optional, only in patients with a history of CHF or chronic inflammatory conditions such as arthritis and psoriasis)
- Urinalysis (Table 6)
- Laboratory testing as needed for any patient who develops ≥ grade 2 prolonged INR to determine the underlying cause. The workup should include: LFTs, levels of Vitamin-K dependent coagulation factors (II, VII, IX, X), Protein C, and Protein S. If ≥ grade 2 INR is not corrected following administration of Vitamin K, additional tests such as mixing studies, fibrinogen level, D-dimer and fibrin split products should be performed. Additional coagulation testing does not need to be completed more than once per patient.
- Concomitant medications
- Adverse events

8.5 End of Treatment/Early Termination (prior to completing Cycles 1 & 2)

End of Treatment assessments [redacted] Therapy) will be performed within 30 days after the last dose of BPM31510 on the basis of completion of the planned trial treatment period, disease progression, or for any of the reasons [redacted]. After withdrawal from or completion of protocol treatment, patients must be followed for adverse events for at least 30 calendar days, and follow Serious Adverse Events until resolution or stabilization, after the last dose of trial drug, unless unlikely to further improve based on underlying disease in the opinion of the Investigator.

The Investigator must make every effort to complete all End-of-Treatment assessments as follows:

- Physical examination
- Weight
- Vital signs (5-minute sitting blood pressure, pulse, respiratory rate, oral temperature)
- CA 19-9 value (or CEA or CA 125 if patient does not express CA 19-9)
- ECG
- ECOG performance status (Appendix A:ECOG Performance Status Criteria)
- FACT-HEP questionnaire completed by patient.
- Hematology (Table 6)
- PT/PTT/INR and platelets
- Serum chemistry panel (including CMP and serum lipids) (Table 6)

- C - reactive protein.
- Urinalysis
- Tumor assessment
- Concomitant medications
- Adverse events

All patients who are treated under this protocol, and who come off study for any reason (i.e. disease progression, start a new therapy, other) will be followed for survival every 3 months for a minimum of 12 months, or until the study closes, whichever occurs first. Sites are expected to attempt to contact the patient, or caregiver to obtain patient status. On site visits are not required.

At least 3 attempts should be made to contact patients who early term or fail to complete the clinical study. The patient should be documented via EDC as "lost to follow-up" if all attempts fail. Contact attempts should be documented in the patients study file.

8.6 Laboratory Assessments

Local laboratories will perform all laboratory tests and results and lab normal reference range for each test will be provided to the Investigator for entry into the eCRF. Blood and urine samples for hematology, coagulation, serum chemistry, and urinalysis will be prepared for analysis using standard procedures. Laboratory panels are defined in Table 6. Vitamin K and advanced coagulation testing (for Grade 2 increases in INR) may be performed through local laboratory or through the central laboratory contracted by the Sponsor to provide this service.

Table 6: Laboratory Panels

Hematology	CBC with differential, platelets
Coagulation	PT/PTT/INR (Screening only: Vitamin K)
Serum Chemistry	Albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN), calcium, carbon dioxide, chloride, creatinine, gamma-glutamyl transferase (GGT), glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, total protein, serum magnesium, cholesterol, triglycerides
Urinalysis	Appearance, color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and occult blood (microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive)
Laboratory work-up for any ≥ grade 2 INR	LFTs, levels of Vitamin-K dependent coagulation factors (II, VII, IX, X), Protein C, and Protein S. If ≥ grade 2 INR is not corrected following administration of Vitamin K, cryoprecipitate or fresh frozen plasma, additional tests such as mixing studies, fibrinogen level, D-dimer and fibrin split products should be performed. Additional coagulation testing does not need to be completed more than once per patient.

Abnormalities in clinical laboratory tests that are considered clinically significant by the Investigator will be recorded on the AE CRF page. If values meet criteria defining them as serious, they must be reported as serious adverse events (SAEs) [redacted] Special Instructions Regarding Coagulation Assessments Prior to Each BPM31510 Dose

- Prophylactic Vitamin K will be given to all patients prior to the beginning of each week of therapy, unless contraindicated as determined by the Investigator. Additional Vitamin K may be given as needed and at the Investigator's discretion.
- Prior to administering each dose of BPM31510, the PT/PTT, INR and platelet count must be assessed and any clinically significant abnormal result reported to both the primary Investigator and BERG.
- BPM31510 may be administered if the INR, PT, and PTT are ≤ 1.5 times the upper limit of normal and the platelet count is ≥ 50,000/mm^3.
- Any PTT or INR value ≥ grade 2 requires immediate treatment with Vitamin K (oral, IV, IM, or SC), cryoprecipitate or fresh frozen plasma as clinically indicated and BPM31510 will be held until the abnormal lab returns to normal limits (≤ 1.5 x UNL) from previous elevations.
- Patients who develop ≥ grade 2 INR any time during the study should undergo laboratory testing to determine the underlying cause. The workup should include: LFTs, levels of Vitamin K-dependent coagulation factors (II, VII, IX, X), Protein C, and Protein S. If the ≥ grade 2 INR is not corrected following administration of Vitamin K, cryoprecipitate or fresh frozen plasma, as noted above, additional tests such as mixing studies, fibrinogen level, D-dimer and fibrin split products should be performed. Additional coagulation testing does not need to be completed more than once per patient.

8.7 Pharmacodynamic Assessments

8.7.1 Blood Samples for Pharmacodynamic Analysis

Blood samples will be collected during BPM31510 therapy, according to the schedule in Table 7. If the pump cannot be programmed to administer the total volume of BPM31510 over 72 hours exactly, please be sure to document the start and end of infusion times on the dosing log eCRF and collect PD specimens based on the **end of infusion time**.

Detailed preparation, storage, and shipping instructions for PD samples are provided in the Study Laboratory Manual.

Blood samples will be assayed for levels of PD markers of BPM31510 activity using the techniques described in Section 11.6.5. The analyses are essential based on nonclinical data demonstrating the ability of BPM31510 to influence gene, protein, metabolite and lipid anabolic and catabolic pathways including but not limited to areas of apoptosis, angiogenesis, cell cycle regulation, bioenergetics, metabolism, lipid homeostasis, and serum proteins.

All samples will be discarded after the studies are complete and will not be stored for future genetic analysis.

[redacted]

8.7.3 Urine Samples for Pharmacodynamic Analysis

Urine specimens collected for PD analyses will be assayed for markers of BPM31510 activity using (but not limited to) genomic (e.g., microarray, SAGE, northern blotting, gene expression, SNP), proteomic/peptidomic (e.g., LC/MS based analysis, 2DEMS, MALDI TOF, antibody

array, ELISA, western blotting), metabolomics (e.g., global analysis of metabolites in biological samples; identification of specific markers of energy metabolism e.g., pyruvate, lactate), lipidomics (e.g., global analysis of lipid classes; identification of specific lipids e.g., derivatives of palmitate, linoleic acid, arachidonic acid).

The analyses are essential based on in vitro and nonclinical data demonstrating the ability of BPM31510 to influence gene, protein, metabolite and lipid anabolic and catabolic pathways including, but not limited to, areas of apoptosis, angiogenesis, cell cycle regulation, bioenergetics, metabolism, lipid homeostasis, and serum proteins. All samples will be discarded after the studies are completed and will not be stored for future genetic analysis.

Spot samples for urine PD will be collected at the times shown in Table 7, Schedule of Blood and Urine Samples for Pharmacodynamics, in Section 8.7.1 above.

Detailed preparation, storage, and shipping instructions for PD urine samples are provided in the Study Laboratory Manual.

9 IDENTIFICATION OF STUDY TREATMENTS

9.1 BPM31510

[redacted]

9.2 Gemcitabine

Gemcitabine for injection, USP is a nucleoside metabolic inhibitor that exhibits antitumor activity. The clinical formulation supplied is the commercially available, sterile form for intravenous use only. Vials contain either 200 mg or 1 g of gemcitabine HC1 (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment. Gemcitabine is a commercially available product and is being used for the indication for which it has been labeled. For the purposes of this study gemcitabine is considered investigational.

Please refer to the Package Insert/SmPC for detailed information on the properties of gemcitabine drug product and Section 12 Safety Reporting and Analyses for the reporting of adverse events and product complaints.

9.3 Labeling, Packaging and Supply of Study Treatments

9.3.1 BPM31510

BERG will provide the Investigator with an adequate supply of BPM31510 Nanosuspension Injection. BPM31510 will be supplied [redacted]

Table 10: Composition of Sterile BPM31510 Nanosuspension Injection (40 mg/mL)

Ingredient	Vial Volume	Concentration	API Theoretical Quantity per vial
BPM31510	100 mL	40 mg/mL	4000 mg

The labeling and packaging of BPM31510 will be in accordance with Good Manufacturing Practice (GMP) Annex 13 and any other local applicable regulatory requirements. The immediate packaging will also contain a statement to conform with FDA Investigational New Drug (IND) requirements as follows: *Caution: New Drug - Limited by Federal (or United States) law to investigational use or the statement "for clinical trial use only" to meet the requirements for use under the Investigational Medicinal Product Dossier IMPD submitted in European Union Member States*

BPM31510 is an investigational new drug. Accordingly, all drug handling and disposal procedures for investigational drugs should be performed by qualified personnel as documented by the American Hospital Formulary Service (AHFS) or other recognized formulary requirements.

[redacted]

Inventory of the investigational drug supplies must be performed according to applicable state and federal regulations. BERG or its representatives must be granted access on reasonable request to check drug storage, dispensing procedures and accountability records.

9.3.2 Gemcitabine

Gemcitabine is a commercially available product and is being used for the indication for which it has been labeled. Gemcitabine for this study and will be provided by the clinical site or by the Sponsor per clinical trial agreement. For the purposes of this study, Gemcitabine is considered investigational.

Storage conditions for these chemotherapy agents are provided in the gemcitabine Package Insert/SmPC. The expiration date on the label of each drug product must not be exceeded.

Please refer to the Package Insert/SmPC for detailed information on the properties of gemcitabine drug product and Section 12.0 Safety Reporting and Analyses for the reporting of adverse events and product complaints.

Inventory of the investigational drug supplies must be performed according to applicable local regulations. BERG or its representatives must be granted access on reasonable request to check drug storage, dispensing procedures and accountability records.

9.4 Preparation and Administration of Study Treatments

9.4.1 BPM31510

BPM31510 Nanosuspension Injection (40 mg/mL) will be administered IV over 144 hours (two 72 hour 110 mg/Kg doses). Doses will be prepared and administered at the clinical site. The volume of each dose will be based on the patient's weight in kilograms.

Instructions for preparing undiluted BPM31510 drug product for administration as a single 72-hour continuous infusion are as follows (see also storage and administration instructions with drug product and infusion sets).

Note: [redacted]

10. [redacted]

Table 11: [redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[a] PVC, [redacted]

Gemcitabine is to be administered in accordance with the terms of its marketing authorization. Please refer to the respective Package Insert/SmPC for detailed information on how to prepare and administer gemcitabine.

9.5 Accountability of Study Treatments

9.5.1 BPM31510

The Investigator (or designee) is responsible for accountability of all used and unused trial drug supplies at the site.

BERG or contracted CRO monitors will verify receipt of investigational product at the site during monitoring visits and will conduct an inventory of remaining clinical trial supplies at the site close-out visit. All trial drug inventories must be made available for inspection by the monitor, BERG, or representatives, and regulatory agency inspectors upon request.

At the end of the trial, should the return of supplies be requested by the Sponsor, a Return Drug Form will be completed by the site and will accompany the clinical trial supplies that are

returned to BERG (or designee). Clinical trial supplies may be destroyed on-site when prior approval has been granted by BERG or its representative.

9.5.2 Gemcitabine

There are no protocol requirements for accountability of gemcitabine other than those required by the policies and procedures of the study site. Lot numbers for gemcitabine administered to patients in this study will be recorded in the study EDC system.

9.6 Precautions and Risks Associated with Study Treatments

9.6.1 BPM31510

In animals receiving lethal doses of BPM31510, toxicity was rapid in onset (within 15 minutes). In the event of clinical toxicity during infusion, stop the infusion and take appropriate resuscitative measures.

To monitor and mitigate BPM31510-associated coagulopathies, the PT, PTT, INR and platelet count must be assessed prior to each dose of BPM31510. Prophylactic Vitamin K will be given to all patients prior to the beginning of each week of therapy, unless contraindicated as determined by the Investigator. An INR ≥ grade 2 requires immediate treatment with Vitamin K as clinically required. An abnormal INR, PTT, and PT must return to normal (≤ 1.5 X UNL) and platelets must be ≥ 50,000/mm3 prior to treating with BPM31510. Additional Vitamin K should be administered as needed when PT/PTT/INR are abnormal.

[redacted]

9.6.2 Gemcitabine

Refer to the Package Insert/SmPC for detailed information on the risks associated with the use of gemcitabine. The following adverse effects have been reported:

Hematologic: myelosuppression (dose-limiting); anemia, leukopenia, thrombocytopenia; infections (common); sepsis (rare); petechiae; hemorrhage (mild)

Gastrointestinal: nausea and vomiting (common); diarrhea; stomatitis

Hepatic: transient elevations of serum transaminases (common); hepatotoxicity including liver failure and death (rare)

Renal: proteinuria and hematuria (mild, common); Hemolytic Uremic Syndrome (HUS) (rare, serious); elevated serum creatinine or BUN

Skin: rash (common); pruritus; alopecia (common)

Pulmonary: dyspnea, bronchospasm (occasional, serious)

Flu-like Symptoms: fever (common); asthenia, anorexia, headache, cough, chills, and myalgia (common); insomnia, rhinitis, sweating, and malaise (infrequent)

Neurotoxicity: paresthesias (mild, common); severe paresthesias (rare)

Allergic: bronchospasm (rare); anaphylactoid reaction (rare)

Cardiovascular: myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension (rare); edema, peripheral edema (common); generalized edema (rare).

Hepatic Toxicity, Drug-induced liver injury, including liver failure and death, has been reported in patients receiving Gemcitabine alone or in combination with other potentially hepatotoxic drugs. Administration of Gemcitabine in patients with concurrent liver metastases or a pre-existing medical history of hepatitis, alcoholism, or liver cirrhosis can lead to exacerbation of the underlying hepatic insufficiency. Investigators should assess hepatic function prior to initiation of Gemcitabine and periodically during treatment. Discontinue Gemcitabine in patients that develop liver toxicity and/or severe liver injury.

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10 RESPONSE EVALUATIONS AND MEASUREMENTS

For tumor response imaging assessments, and to enable reliable serial measurement of tumor dimensions required by RECIST v1.1 criteria, CT scans of the chest, abdomen, pelvis, and any other sites of known disease with and without intravenous contrast should be obtained at each time point on a dedicated diagnostic CT scanner, unless IV contrast is contraindicated due to renal insufficiency or contrast allergy despite premedication, in which case an alternate imaging method such as MRI may be discussed with Sponsor. When 18-FDG-PET for metabolic response assessment and CT imaging for tumor response are planned for the same time point, a combined PET/CT scan can suffice also for RECIST target lesion response assessment, only provided the CT component of the PET/CT scanner is a dedicated diagnostic quality CT scanner, and the CT scan obtained with and without contrast, thereby providing accurate target lesion dimensions and definition of non-target and new lesions, which lower-resolution CT components used for simple anatomic localization and attenuation cannot provide. For assessing serial changes in tumor uptake of 18-fluorodeoxyglucose, the employed PET scan technique (and preferably same scanner) should be used for each PET scan, to facilitate serial comparison of tumor 18-FDG standard uptake values (SUVs).

Response and progression will be evaluated in this trial using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al. 2009). Lesions that are either measurable or non-measurable will be recorded and measured or assessed at study baseline, and serially followed thereafter at all imaging time points, using the criteria provided below. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy. The same assessment method should be used to assess a lesion pre-treatment, during, and post-treatment.

10.1 [redacted]

[redacted]

Non-Measurable Disease:	All other lesions, including small lesions (longest diameter <10 mm or [redacted]
[redacted]	[redacted]
[redacted]	[redacted]

10.1.1 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment, as per protocol screening requirements.

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

Clinical Lesions:	Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
Chest X-ray:	Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
Conventional CT and MRI:	CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness, contiguously. Spiral CT scan should be performed using a 5-mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound:	When the primary trial endpoint is objective response, ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound may also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
Endoscopy and Laparoscopy:	Use of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Therefore, use of these techniques for objective tumor response should be restricted to validation purposes in specialized centers. Such techniques can be useful in confirming complete pathological response when biopsies are obtained.
Tumor Markers:	Tumor markers alone cannot be used to assess response. If markers are initially above the upper limit of normal, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
Cytology and Histology:	Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

10.1.2 Response Criteria

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions.
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest (nadir) sum LD since the treatment started.
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest (nadir) sum since the treatment started, or the appearance of one or more new lesions. Requires not only 20% increase, but absolute increase of a minimum of 5 mm over sum.

Evaluation of Non-Target Lesions

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

Evaluation of Best Overall Response

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

Per RECIST, confirmation of response (by repeat scans after 4 weeks or as specified in the protocol) is required for this study in which response rate is the primary endpoint.

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

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

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

11 STATISTICAL CONSIDERATIONS

11.1 Overview

This is a Phase 2 multicenter, open-label, non-randomized study to examine the safety and efficacy of BPM31510 with gemcitabine in advanced pancreatic cancer patients as 2nd /3rd line therapy.

Data will be summarized by treatment arm using descriptive statistics (number of patients, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequency and percentages for discrete variables. Exact 95% confidence intervals may be generated using the Clopper-Pearson method for selected efficacy, safety and exploratory variables. Time-to-event endpoints will be assessed using the Kaplan-Meier method [redacted] Medians and proportions event-free at specified time points will be estimated using the Kaplan and Meier method; 95% confidence intervals for median PFS and OS may be generated using the Brookmeyer-Crowley method.

Additional details regarding statistical analyses will be described in the Statistical Analysis Plan (SAP).

11.2 Sample Size Considerations

[redacted]

11.3 Study Populations

The Safety Population will consist of all patients treated with at least one dose of BPM31501 or gemcitabine. The Efficacy Population will consist of all patients who complete at least one cycle of therapy.

11.4 Study Design

[redacted]

11.5 Efficacy Analysis

Assessments based on response will include best response, objective response rate (ORR: CR+PR), disease control rate (DCR: CR+PR+SD), Progression-Free Survival (PFS) and Time to Progression (TTP). Patients without a post-baseline tumor assessment will be analyzed as non-responders in the analysis of ORR and DCR.

11.6 Overall Tumor Response

Objective responses will be evaluated using the Response Evaluation Criteria In Solid Tumors 1.1 (RECIST 1.1). Changes (i.e. improvements) in tumor measurements from baseline values will be assigned a status of CR or PR or SD. Objective response measurements will comprise the sum of CR plus PR. The overall response rate (CR+PR), the disease control rate (CR+PR+SD) as

well as the rates for the individual categories of response (i.e. CR, PR, SD, and PD), will be analyzed. When a CR or PR is documented, a confirmatory CT or PET scan will be obtained per RECIST guidelines.

11.6.1 Progression Free Survival

Progression-free survival (PFS) is defined as the number of days from the first dose of study drug to the first documentation of progression or death due to any cause. Patients who remain alive without progression will be censored for PFS at the date of their last tumor assessment.

11.6.2 Time to Progression

Time to Progression (TTP) is defined as the number of days from the first dose of study drug to the first documentation of progression. Patients without progression will be censored for PFS at the date of their last tumor assessment.

11.6.3 Overall Survival

Overall survival is defined as the number of days from the first dose of study drug to the date of death due to any cause. Patients alive at the time of analysis will be censored at the date of last contact.

11.6.4 Overall changes in patient reported quality of life

Patient-reported outcomes for quality of life (QOL) measures will be assessed using the self-administered Functional Assessment of Cancer Therapy validated patient questionnaire tailored for patients with hepatobiliary and pancreatic cancers, FACT-HEP, which asks patients to consider, rate, and score their treatment- and disease-related symptoms and general quality of life across a spectrum of categories. Changes in QOL scores from baseline values during treatment and follow-up will be assessed. Patient entered scores for each questionnaire item will be summed for each category, multiplied by the number of items, and divided by the number of items answered in the category, according to the instructions provided. The overall quality of life score will comprise the sum of values for each category (Physical, Social, Emotional and Functional Well-being and Additional Concerns specific to Pancreatic Cancer patients). Overall QOL and categorical assessment changes will be analyzed.

11.6.5 Evaluation of Exploratory PD Parameters

Blood samples will be collected for PD during BPM31510 treatment. PET scans performed will be evaluated for the Warburg effect by BPM31510 in the tumors.

Exploratory PD analyses will be performed on blood and urine samples and assayed for markers of BPM31510 activity using (but not limited to) genomic (e.g., microarray, SAGE, northern blotting, gene expression), proteomic (e.g., LC/MS based analysis, 2DEMS, MALDI TOF, antibody array, ELISA, immunohistochemistry, flow cytometry, western blotting), metabolomics (e.g., global analysis of metabolites in biological samples; identification of specific markers of energy metabolism e.g., pyruvate, lactate), lipidomics (e.g., global analysis of lipid classes; identification of specific lipids e.g., derivatives of palmitate, linoleic acid, arachidonic acid).

The exploratory endpoints are defined by molecular characteristics of patient populations that demonstrate predictive power in associating a profile of response, stable design, or lack of efficacy to guide clinical decision making.

11.7 Planned Interim Analyses

No formal interim analysis is planned excepting for the analysis of the first 10 evaluable patients enrolled as described above. These separate analyses will be triggered as soon as the last patient to be enrolled (of the ten) has completed the first two treatment cycles.

11.8 Replacement of Patients

Patients who are enrolled into the study, but fail to receive at least two cycles (10 weeks) of BPM31510 will be replaced.

11.9 Data and Safety Monitoring Board

The trial will not utilize the services of a Data and Safety Monitoring Board.

11.10 Steering Committee

The trial will not utilize the services of a Steering Committee.

12 SAFETY REPORTING AND ANALYSES

12.1 Safety Review

All patients who receive any amount of BPM31510 or gemcitabine will be included in the safety analyses, which will be based on the following:

- The incidence, severity, duration, causality, seriousness, and type of AEs, changes in the patient's physical examination, vital signs, and clinical laboratory results.
- The incidence of death.
- Use of concomitant medications.

12.2 Safety Analyses

Safety assessments will consist of monitoring and recording protocol-defined adverse events (AEs) and serious adverse events (SAEs); measurement of protocol-specified hematology, coagulation, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the trial drug. Selected laboratory measurements will be graded using CTCAE criteria. Adverse Events will be coded using MedDRA 19.0 or version specified by the study safety management plan.

12.3 Adverse Events

The Investigator is responsible for recognizing and reporting serious adverse events promptly to BERG, LLC and/or its Pharmacovigilance (PV) service provider. If not delegated to another entity, it is BERG's responsibility to report relevant SAEs to the applicable local, national, or international regulatory body.

12.3.1 Definitions of Adverse Events

Adverse Event (AE): Any untoward medical occurrence or deterioration of a pre-existing medical condition in a patient or clinical investigation subject following or during exposure to an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the medicinal product is BPM31510 and its combination with gemcitabine.

An undesirable medical condition can include symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver), or the abnormal results of an investigation (e.g., laboratory findings).

The criteria for identifying AEs are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease.
- Any deterioration in non-protocol-required measurements of laboratory value or other clinical test (e.g., ECG or X-ray) that results in symptoms, requires treatment, results in a change in study drug treatment, or discontinuation from study drug.
- Recurrence of an intermittent medical condition (e.g., headache) not present at Baseline.

12.3.2 Assessing Severity of Adverse Events

The NCI CTCAE v4.02 will be used to assign the following severity scale to AEs.

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe
- Grade 4 = Life Threatening
- Grade 5 = Death

AEs that are not defined in the NCI CTCAE should be evaluated for severity according to the following scale:

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe

In addition, all AEs reported using the NCI CTCAE classification and graded as 4 or 5 are to be considered serious.

The criteria for assessing severity are different than those used for seriousness.

12.3.3 Assessing Relationship to Trial Treatment

Items to be considered when assessing the relationship of an AE to BPM31510 or gemcitabine therapy are:

- Temporal relationship of the onset of the event to the initiation of the study treatment.

- The course of the event, considering especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable.
- Whether the event is known to be associated with the study treatment, or with other similar treatments.
- The presence of risk factors in the study patient known to increase the occurrence of the event.
- The presence of non-study treatment related factors which are known to be associated with the occurrence of the event.

12.3.4 Classification of Causality

Causality is a determination of whether there is a reasonable possibility that the study drug may have caused or contributed to an adverse event. It includes assessing temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying diseases, and the presence (or absence) of one or more likely causes.

The Investigator will give his or her opinion as to the relationship of the adverse event to trial drug treatment (i.e., whether the event is related or unrelated to trial drug administration). The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all patients enrolled on the trial.

The Investigator must attempt to determine whether an adverse event is in some way related to the use of the study drug. This relationship should be described as follows:

Not Related: A causal relationship between the study treatment and the AE is not a reasonable possibility. **Related:** A causal relationship between the study treatment and the AE is a reasonable possibility. The Investigator must further qualify the degree of certainty of relatedness as follows:

Unlikely: The event is clearly due to causes distinct from the use of the study drug, such as a documented pre-existing condition, the effect of a concomitant medication, or a new condition that, based on the pathophysiology of the condition and the pharmacology of the study drug, is unlikely to be related to the use of the study drug.

Possible: The event follows a reasonable temporal sequence from administration of the study drug or the event follows a known response pattern to the study drug, *but* the event could have been produced by a concomitant medication or an intercurrent medical condition which, based on the pathophysiology of the condition and the pharmacology of the study drug, is unlikely to be related to the use of the study drug.

Probable: The event follows a reasonable temporal sequence from administration of the study drug, and the event follows a known response pattern to the study drug, and the event cannot be reasonably explained by an intercurrent medical condition, *or* the event cannot be the effect of a concomitant medication.

Definite: The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug, and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug.

Unknown: Based on the evidence available, causality cannot be ascribed.

12.3.5 Recording of Adverse Events

All adverse events (AEs) of any patient enrolled in the trial will be reported in the electronic case report form (eCRF). All AEs, regardless of relationship to study drug or procedure, should be collected beginning at patient consent and continue through thirty days after the last dose of study drug. Patients with AEs that are ongoing at the patient's last study visit must be followed until resolution or for 30 days after the patient's last dose of study drug, whichever comes first. AEs should be reported as SAEs if they become serious and fit the criteria for SAEs. AEs that cause interruption or discontinuation of investigational product, or AEs that are present at the end of their participation in the study must be followed until resolution or for 30 days after the patient's last dose of study drug, whichever comes first. Such patients should receive post-treatment follow-up as appropriate.

If the adverse event is serious, it should be immediately entered into the eCRF, by first entering it into the Adverse Events eCRF and then completing the SAE report form, which should be signed by the PI or authorized designee. Upon completion, the Medical Monitor will be notified by email to review.

12.3.6 Abnormal Laboratory Values and Vital Signs

The reporting of abnormalities of vital signs as adverse events should be avoided. Abnormalities of vital signs should not be reported unless any criterion for an SAE is fulfilled, the vital signs abnormalities cause the patient to discontinue trial treatment, requires a medical intervention (e.g., IV fluid administration for hypotension) or they are determined by the investigator to be clinically significant and which does not rise to the level of fulfilling SAE criteria or the Investigator decides that the abnormality should be reported as an AE.

A laboratory result should be considered by the Investigator to be an adverse event if it:

- Is any grade 3 or 4 laboratory abnormality or any clinically significant grade 1 or 2 hematology or biochemistry laboratory value.
- Results in the withdrawal of study treatment.
- Results in withholding of study treatment pending some investigational outcome.
- Results in the initiation of an intervention (e.g., potassium supplement for hypokalemia).
- Increases in severity compared to Baseline by ≥ 2 NCI grades, with the exception of lymphocytes, albumin, cholesterol, glucose, and electrolytes. For these tests, a change of ≥ 2 grades will be evaluated by the Investigator to determine if they are of clinical significance and if so, will be considered an adverse event.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant CRF or EDC.

12.3.7 Handling of Adverse Events

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

12.4 Serious Adverse Events

12.4.1 Definitions of Serious Adverse Events

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

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or the Sponsor, it results in any of the following outcomes:

- Death (NOTE: death due to disease progression is a study outcome endpoint, will be recorded on the CRF, and does not need to be reported as an SAE).
- A life-threatening adverse drug experience—any adverse experience that placed the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Requires at least a 24-hour inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the previous definition, should also be regarded as serious adverse events. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

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

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility
- Planned hospitalizations required by the protocol
- Hospitalization for administration of study drug or insertion of access for administration of study drug

Hospitalization during the trial for a pre-planned surgical or medical procedure (one which was planned prior to entry in the trial), does not require reporting as a serious adverse event to BERG Safety Department or designee.

12.4.2 Serious Adverse Event Reporting by Investigator

It is the responsibility of the PI and the research teams to ensure serious adverse events are reported according to the Code of Federal Regulations, ICH Good Clinical Practices, the protocol guidelines, the Sponsor's guidelines, and Institutional Review Board/EC policy.

12.4.3 Reporting SAEs to BERG (or designee)

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

Adverse events may occur and must be reported any time they occur from patient consent through the 30-day follow-up period after the last trial treatment. Adverse events classified by the treating Investigator as serious require expeditious handling and reporting to the study pharmacovigilance service provider in order to comply with regulatory requirements. [redacted] the pharmacovigilance service provider) will be notified of all SAEs, regardless of

causality, within 24-hours of the first knowledge of the event by the treating physician or research personnel.

When the adverse event is serious, it should be immediately entered into the Adverse Events eCRF, and then the SAE report form should be completed and signed by the PI or designee. Upon completion of the SAE report form, [redacted] within 24-hours of becoming aware of the event, for initial review and classification. Additional details on SAE reporting can be found in the BPM31510IV-05 Safety Manual provide to your site.

- **All life-threatening or fatal events** that are unexpected and related to the study drug must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Sponsor.
- **An Unexpected Adverse Event** is one that is not listed in the current Clinical Investigator Brochure (CIB)/Package Insert or that differs from the event mentioned in the CIB/Package Insert because of greater severity or specificity.
- **All SAEs and medically confirmed deaths** (regardless of causality assessment) occurring on trial treatment or within 30 days of last trial treatment must be reported to BERG's pharmacovigilance service provider as SAEs using the SAE report form and followed until resolution (with autopsy report if applicable). (NOTE: death due to disease progression is a study outcome endpoint, will be recorded on the CRF, and does not need to be reported as an SAE).
- Deaths occurring within 30 days after last trial treatment that are deemed 'possibly', 'probably' or 'definitely' related to BPM31510 must be reported as SAEs on the SAE report form (with an autopsy report if available).
- Deaths occurring within 30 days after last trial treatment and not attributed to trial treatment (e.g., disease progression) need not be reported as SAEs, but simply captured on the appropriate eCRF.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to BERG. This may include the development of a secondary malignancy.
- **NOTE:** SAEs occurring in patients registered to the trial but not receiving study drug (i.e., occurring before protocol treatment) **do not** require reporting.

To report an SAE, the SAE eCRF should be completed with the necessary information after the AE eCRF is completed in the EDC. Additional eCRF pages that need to be completed and are required for SAE reporting include those that collect:

- Adverse Event
- Study drug (BPM31510) and gemcitabine dosing and administration
- Concomitant Medications
- Demographics
- Baseline Abnormalities/Medical History

The site PI/Coordinator will submit the SAE using the SAE Report Form. Once received by [redacted] the Medical Monitor, BERG and the CRO Project Managers will be notified via e-mail. The site coordinator/PI must complete the AE eCRF and SAE Report Form within 24-hours after the site becoming aware of the SAE.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported as soon as it is available using the same reporting system; these reports should be submitted using the SAE Report Form. The detailed SAE reporting process will be provided to the sites in the Safety Manual.

[redacted]

12.4.4 Reporting SAEs to IRBs/ECs

All events occurring during the conduct of a protocol and meeting the definition of an SAE must be reported to the IRB/EC in accordance with the site's IRB/EC standard operating procedures and timeframes. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the Sponsor regardless of attribution within 24 hours of knowledge of the event.

12.4.5 BERG SAE Reporting Requirements

Berg must inform Investigators and regulatory authorities, including the FDA and EMA, of reportable events in compliance with applicable regulatory requirements on an expedited basis (i.e., within specific timeframes). For this reason, it is imperative that investigational sites provide complete SAE information in the manner described above.

BERG is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating Investigators, in accordance with ICH guidelines, FDA regulations (21 CFR 312.32), ICH E2A Clinical Safety Data Management and/or local regulatory requirements.

BERG or designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of trial drugs to the regulatory agencies via telephone, on-line or by fax within 7 calendar days after being notified of the event. BERG will report all related but unexpected SAEs including non-death/non-life-threatening related but unexpected SAEs associated with the use trial medications to the appropriate authorities (according to local

guidelines), Investigators, and central IRBs/IECs (except in the United States where Investigators are responsible for reporting to their IRBs per local requirements) by a written safety report within 15 calendar days of notification.

12.5 Recording of Adverse Events and Serious Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the SAE Report Forms and AE CRF. Avoid colloquialisms and abbreviations.

All AEs, including those that meet SAE reporting criteria, should be recorded on the AE CRF; AEs that meet the definition of an SAE should additionally be reported following the procedures [redacted]

12.5.1 Diagnosis vs. Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE CRF). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

12.5.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE CRF. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE CRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE CRF.

12.5.3 Abnormal Laboratory Values and Vital Signs

Any grade 3 or 4 laboratory abnormality or any clinically significant grade 1 or 2 hematology or biochemistry laboratory value should be recorded as an AE. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant CRF/ EDC. If the laboratory value or vital sign abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE CRF.

12.5.4 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the Investigator solely to progression of cancer will be recorded on the "Trial Discontinuation" CRF. All other on-trial deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the BERG or designee.

When recording a serious adverse event with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE Report Form and Adverse Event page of the CRF/EDC system. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the CRF or Adverse Event page of the EDC system. During post-trial survival follow-up, deaths attributed to progression of cancer will be recorded only on the "After Progressive Disease Follow-Up" CRF.

12.5.5 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of more than 24 hours or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE [redacted]

12.5.6 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the trial. Such conditions should be recorded on the Medical History CRF. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the trial. When recording such events on an SAE Report Form and/or AE CRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

12.5.7 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

If a patient becomes pregnant while enrolled in the trial, a Pregnancy Form (a paper report form) should be completed and faxed to [redacted] Pharmacovigilance department or designee. The pharmacovigilance department should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to the BERG Clinical Operations or designee.

Congenital anomalies/birth defects always meet SAE criteria and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

12.5.8 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria [redacted] New primary cancers are those that are not the primary reason for the administration of the clinical trial treatment and have developed

after the inclusion of the patient into the trial. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE as they are considered to be disease progression.

12.5.9 Lack of Efficacy

When there is deterioration in the condition for which the clinical trial treatment is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or reporting physician considers the trial treatment contributed to the deterioration of the condition, the deterioration should be considered lack of efficacy and not an AE.

12.5.10 BPM31510 Overdose

Symptomatic and non-symptomatic overdose must be reported in the CRF. Any accidental or intentional overdose with the trial treatment that is symptomatic, even if not fulfilling a serious criterion, is to be reported to [redacted] Pharma's Pharmacovigilance department or designee immediately (within 1 working day) using the appropriate AE eCRF pages, and following the same process described for SAE reporting [redacted] if the overdose is symptomatic.

An overdose is defined as any dose that exceeds the dosage or frequency prescribed by the protocol. For information on how to manage an overdose of BPM31510, see the Investigator Brochure.

12.6 Protocol-Defined Events of Special Interest

Protocol-defined events of special interest related to the safety profile of BPM31510 should be reported expeditiously to the Sponsor [redacted] These events include the following:

- Increased PT/PTT/INR
- Bleeding events
- ≥ Grade 3 increased LFTs considered related to BPM31510.

12.7 Monitoring Plan

Site monitoring shall be conducted to ensure the human patient protection, trial procedures, laboratory, investigational product administration, and data collection and evaluation processes are of high quality and meet Sponsor, GCP/ICH and regulatory guidelines. The Monitoring Plan shall define aspects of the monitoring process.

13 ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This trial will be conducted in accordance with the International Conference on Harmonization (ICH) guideline on Good Clinical Practice (GCP) (E6), Title 21 of the Code of Federal Regulations (CFR) parts 50, 54, 56 and 312, applicable government regulations, institutional research policies and procedures, and any other applicable local regulatory requirements.

13.1 IRB/EC Approval

The trial protocol, ICF, IB, available safety information, patient documents (e.g., trial diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., PI

payments) and compensation available to the patients and documentation evidencing the PI's qualifications should be submitted to the IRB/EC for ethical review and approval if required by local regulations, prior to the trial start.

The PI, BERG and/or designee will follow all necessary regulations to ensure appropriate, initial, and ongoing IRB/EC trial review. The PI, BERG or designee (as appropriate) must submit and, where necessary, obtain approval from the IRB/EC for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by BERG or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB/EC.

Safety updates for BPM31510 will be prepared by the Sponsor or its representative as required for submission to the relevant IRB/EC.

13.2 Regulatory Approval

As required by local regulations, BERG will ensure all legal aspects are covered and approval of the appropriate regulatory bodies is obtained prior to trial initiation. If required, BERG will also ensure that the implementation of substantial amendment to the protocol and other relevant trial documents happen only after approval by the relevant regulatory authorities.

Safety updates for BPM31510 will be prepared by BERG or its representative as required for submission to the relevant regulatory authority.

13.3 Insurance and Indemnity

Details of insurance and/or indemnity will be contained within the written agreement between the PI or site and BERG.

13.4 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

The informed consent form will be submitted for approval to the IRB/EC that is responsible for review and approval of the trial. Each consent form must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the trial, each prospective candidate will be given a full explanation of the trial. Once the essential information has been provided to the prospective candidate and the Investigator is sure that the individual candidate understands the implications of participating in this trial, the candidate will be asked to give consent to participate in the trial by signing an informed consent form. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the informed consent form, to include the patient's signature, will be provided by the Investigator to the patient.

If an amendment to the protocol substantially alters the trial design or the potential risks to the patients, the patient's written re-consent to continue participation in the trial should be obtained.

13.5 Confidentiality

13.5.1 Patient Confidentiality

Confidentiality of the patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPPA), General Data Protection Regulations 2018 (GDPR) and country specific national data protection laws, as applicable. HIPAA regulations require that, in order to participate in the trial, a patient must sign an authorization from the trial that he or she has been informed of the following:

- What protected health information (PHI) will be collected from patients in this trial;
- Who will have access to that information and why;
- Who will use or disclose that information;
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal, state or regional privacy laws;
- The information collected about the research trial will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the trial;
- Whether the authorization contains an expiration date; and
- The rights of a research patient to revoke his or her authorization.

In the event that a patient revokes authorization to collect or use his or her PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled trial period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the Investigator and Study Site permit authorized representatives of BERG, the regulatory and competent authorities, and the IRB/EC direct access to review the patient's original medical records at the site for verification of trial-related procedures and data.

Measures to protect confidentiality include:

- Only a unique trial number and initials will identify patients on the CRF or other documents submitted to BERG.
- This information, together with the patient's date of birth, will be used in the database for patient identification.
- Patient's name and address will not be entered in the CRF or database.
- No material bearing a patient's name will be kept on file by BERG.
- Patients will be informed of their rights within the ICF.

13.5.2 Investigator and Staff Information

Personal data of the Investigators and sub-Investigators may be included in the BERG database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the Investigator or sub-Investigator, BERG shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

13.6 Financial Information

BERG is sponsoring this trial. BERG will provide funding and the trial drug BPM31510 for all trial participants for the duration of the trial. The physicians participating in this trial will receive compensation from BERG, LLC.

14 RECORD RETENTION AND DOCUMENTATION OF THE STUDY

14.1 Amendments to Protocol

Amendments to the protocol shall be planned, documented and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by BERG. The written amendment must be reviewed and approved by BERG, and submitted to the IRB at the Investigator's facility for the Board's approval.

Items requiring a protocol amendment with IRB/EC and/or FDA/CA approval include, but are not limited to, the following:

- Change to trial design
- Change in risk to patient
- Increase of the dose or patient exposure to drug
- Patient number increase
- Addition or removal of tests and/or procedures
- Addition/removal of a new Investigator

The amendment will be submitted formally to the FDA or other Regulatory /Competent authorities by BERG after IRB/EC approval and specifically when an increase to dosing or patient exposure and/or patient number has been proposed, or when the addition or removal of an Investigator is necessitated.

It should be further noted that, if an amendment to the protocol substantially alters the trial design or the potential risks to the patients, the informed consent form must be updated accordingly, and their consent to continue participation in the trial should be obtained.

14.2 [redacted]

Documents at a minimum required to begin a trial include, but are not limited to, the following:

- A signature-authorized protocol and contract;
- A copy of the official IRB/EC approval of the trial and the IRB/EC members list (or statement of assurance);
- Current Curricula Vita and Current Medical License/Certifications for the principal Investigator who will be involved in the trial;
- Indication of appropriate accreditation for any laboratories to be used in the trial and a copy of the normal ranges for tests to be performed by that laboratory;
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed;
- A copy of the IRB/EC-approved consent form containing permission for audit by representatives of BERG, the IRB/EC, and regulatory authorities;
- Financial disclosure forms for all Investigators listed on Form FDA 1572 or Investigator Agreement;
- Site qualification reports, where applicable;
- Verification of Principal Investigator acceptability from local and/or national debarment list(s).

14.3 Trial Documentation and Storage

The PI must maintain a list of appropriately qualified persons to whom he/she has delegated trial duties and should ensure that all persons assisting in the conduct of the trial are informed of their obligations. All persons authorized to make entries and/or corrections on the CRFs are to be included on this document. All entries in the patient's CRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the patient's CRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG tracings, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The PI and research staff are responsible for maintaining a comprehensive and centralized filing system (Site Trial File/SSF or ISF) of all trial-related (essential) documentation, suitable for inspection at any time by representatives from BERG and/or applicable regulatory authorities. The ISF/SSF must consist of those documents that individually or collectively permit evaluation of the conduct of the trial and the quality of the data produced. The ISF/SSF should contain at a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, copies of completed CRFs, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the trial drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain PI name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the CRF must be maintained and be readily available.

BERG shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation. The IRB/EC shall maintain adequate documentation/ records of IRB/EC activities as per 21CFR Part 56.115 or local/regional requirements for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories and any other trial-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use is discontinued and FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from BERG or its representative, the Investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., eCRFs and medical records), all original, signed informed consent forms, and copies of all eCRFs, SAE Report Forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). BERG or its representative will notify the investigator(s)/Study Site(s) when the trial-related records are no longer required.

If the Investigator relocates, retires, or for any reason withdraws from the trial, both BERG and its representative should be prospectively notified. The trial records must be transferred to an acceptable designee, such as another Investigator, another Study Site, or BERG. The Investigator must obtain the Sponsor’s written permission before disposing of any records, even if retention

requirements have been met. All trial files will be maintained by BERG or its representative throughout the trial, and will be transferred to BERG at the conclusion of the trial.

14.4 Quality

14.4.1 Source Documents

Source data/records, are those data elements that represent the first recording of study data. Examples of Source documents are 1) patient information used in a clinical trial whether collected on paper or electronically at the time of the subject's visit, 2) certified copies of original records, 3) observations, and 4) laboratory data from clinical laboratories. Clinical Investigators maintain control over source data from inception and until the end of the regulatory retention period. The Investigator must permit access to these data during sponsor monitoring visits, audits, IRB reviews and regulatory inspections. Per GDPR requirements in the European Union, certain individuals from BERG or their designee, and regulatory organizations may look at patient medical and research records to check the accuracy of the research study. BERG will only receive information without any identifying information. The people who analyze the information will not be able to identify patients and will not be able to find out patient name, medical record /insurance numbers or contact information.

14.4.2 Electronic Data Capture System

Personnel at the study site will enter all required clinical trial data into the study Electronic Data Capture (EDC) system, a validated 21 CFR Part 11 compliant Internet-based EDC system. Site personnel will be expected to enter data in English and manage all changes to the clinical trial data, through the EDC system's change management functionality that is subject to a full audit trail.

Site Investigators and staff will be provided training on the use of the EDC system prior to enrollment of the first subject. [redacted] maintains a list of authorized users and grants role-based access to the EDC system only after ensuring that site personnel have received system training. BERG restricts access to the EDC database only to authorized personnel.

At the end of the study, the monitor will contact the clinical Investigator or authorized sub-Investigator and provide him/her the "*Principal Investigator's Sign off Form"* for eCRFs submitted for each subject enrolled. At the end of the trial, and after all approval forms have been signed off by the clinical Investigator and confirmed by the monitor, [redacted] will provide each site with an electronic file containing all eCRF records for all subjects.

14.4.3 Data Monitoring Plan (DMP)

The DMP identifies the monitoring schedule and the rationale for the frequency and type of monitoring visits. The DMP also provides details with regard to the use of risk-based monitoring and source document verification. If the monitor is not allowed access to any e-source records during source document verification, certified printouts provided by sites can be used. In addition to on-site monitoring, monitors and/or Data Managers will perform central (i.e., remote) monitoring, electronically reviewing data in near real-time.

Data monitoring procedures will be carried out by Cancer Research And Biostatistics [redacted]

for all participating sites, and will be performed on a regular basis to comply with Good Clinical Practice guidelines.

Review of the case report forms, cross-reference with source documentation (including radiology review), review of study related regulatory documents and logs (e.g., enrollment, study site staff, drug accountability), and review of drug accountability will be monitored on an ongoing basis during monitoring sessions. The monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements.

At the conclusion of the monitoring visit, the site monitor will meet with the site staff to discuss and request specific corrections to the case report forms, and/or request clarification, and/or additional source documentation. The site Clinical Research Coordinator responsible for the study will be provided with a copy of the written monitoring notes for resolution of the findings.

The site monitor will complete a written monitoring report and forward it to the site Principal Investigator and to BERG. The report will include a summary of what the site monitor reviewed and the site monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to ensure compliance. The site Principal Investigator will be expected to submit any Corrective Action Plans, in writing, to [redacted] BERG and the site monitor. The Corrective Action Plan will be reviewed/ approved by the BERG (Operations and Quality Assurance), the study Project Manager, Regulatory Manager, and Monitor. A copy of the monitoring forms, final monitoring reports, and Corrective Action Plan will be kept in the site study file located in the TMF for follow-up at the next monitoring session.

14.4.4 Centralized Monitoring

Study monitors and/or Data Managers carry out centralized (i.e., remote) monitoring of entered data daily or at an agreed-upon frequency, as defined in the Monitoring Plan (MP).

14.4.5 Patient Enrollment Instructions

Patients must be registered for screening at a minimum of 1 and maximum of 14 calendar days prior to initiation of protocol therapy. This study uses an EDC [redacted]

14.4.6 Data Submission Instructions

This study uses a web based electronic data capture system for data submission through the data management services of [redacted] All study case report forms may be accessed online through the study website at w[redacted] (for Clinicians/ Current Members page). This website is used to register patients and submit data using eCRFs. In addition, study resource information (SAE submission forms, protocol documents and other study guidelines) and can be found on the website. For questions or assistance using this site, please contact: [redacted]. The original reports, traces and films must be uploaded in the EDC system where indicated and copies of scans / images provided to BERG upon request. Original reports, traces and films must

be retained by the Investigators as part of the patient's study file.

14.5 Quality Assurance and Quality Control

In addition to the Clinical Monitoring component of this protocol, BERG shall establish an Auditing Plan document separate from the protocol to establish the criteria by which independent auditing shall be conducted during the conduct of the trial to assess compliance with GCP and applicable regulatory requirements. The Audit Plan may be developed in coordination with BERG's QA, or independently, if so desired by BERG. Data or documentation audited shall be assessed for compliance to the protocol, accuracy in relation to source documents and compliance to applicable regulations.

Each trial site shall be required to have Standard Operating Procedures (SOPs) to define and ensure quality assurance/control processes for trial conduct, data generation and collection, recording of data/documentation and reporting according to the protocol, GCP and any applicable local, national or international regulations.

14.6 Disclosure and Publication Policy

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential. BERG reserves the right to release literature publications based on the results of the trial. Results from the trial will be published/presented as per BERG's publication strategy.

The financial disclosure information will be provided to BERG prior to trial participation from all PIs and sub-Investigators who are involved in the trial and named on the FDA 1572 form.

BERG will register the trial on www.clinicaltrials.gov. In addition, BERG will publish the results of the trial.

Inclusion of the Investigator in the authorship of any multicenter publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the trial. The Investigator acknowledges that the trial is part of a multicenter trial and agrees that any publication by the Investigator of the results of the trial conducted at the research site shall not be made before the first multicenter publication. In the event there is no multicenter publication within fifteen (15) months after the trial has been completed or terminated at all trial sites, and all data has been received, the Investigator shall have the right to publish its results from the trial, subject to the notice requirements described herein and subject to acknowledgement of BERG as appropriate. Investigator shall provide BERG thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the trial for the purpose only of determining if any confidential or patentable information is disclosed thereby. If BERG requests in writing, the Investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit BERG to seek patent protection and to remove any BERG Confidential Information from all publications.

Confidentiality Disclosure Agreements (CDAs) shall be executed between BERG and Study Sites. The document shall address areas of confidentiality, like patents that may result as part of

the trial, but it is intended to address confidentiality of the protocol, the drug, and findings/results.

Clinical Trial Agreement (CTA) shall be executed between BERG and Study Site. The document shall address any offers, especially monetary offers, by BERG to the Study Site for services/results with acceptance by all involved.

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16 APPENDICES

Appendix A: ECOG Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death no imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead

Appendix B: New York Heart Association (NYHA) Classifications

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

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

Appendix C: Guidelines Regarding Women of Childbearing Potential

Women of Child-Bearing Potential are Defined as Follows:

- Any female who has experienced menarche and until becoming post-menopausal unless permanently sterile and does not meet the criteria for "Women Not of Childbearing Potential".

Women Not of Childbearing Potential are Defined as Follows:

- Women who are permanently sterilized (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
- Women who are >45 years of age, not using hormone replacement therapy, and who have experienced total cessation of menses for at least 1 year OR who have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40pg/mL (140 pmol/L) without an alternative medical cause
- Women who are >45 years of age, using hormone replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone replacement therapy.

Acceptable Contraception Methods:

Male patients with female partners of child-bearing potential and women patients of childbearing potential are required to use two forms of acceptable contraception, including one barrier method, during their participation in the trial and for 6 months (men and women) following discontinuation of BPM31510.

Sexual abstinence, is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The choice by the study patient (and their partner) of sexual abstinence as their contraceptive method should be evaluated by the investigator in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Ongoing assessment of patient compliance throughout the trial should be made to ensure that patients understand the need for contraception.

Male patients must also refrain from donating sperm for 6 months following discontinuation of BPM31510.

The following are acceptable forms of barrier contraception:

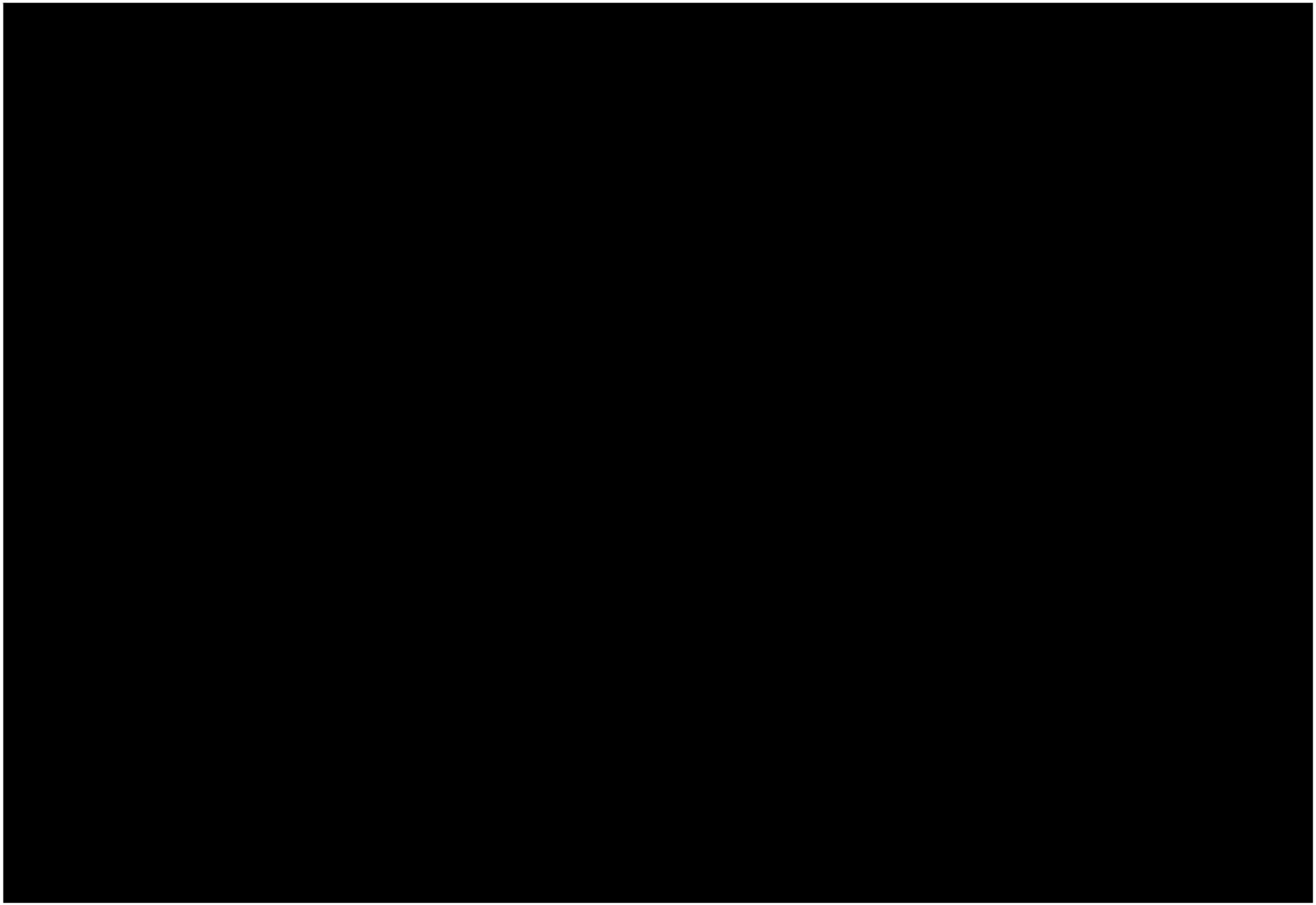
- Latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/film/cream/suppository.

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

- True abstinence. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
- Placement of an intrauterine device (IUD) or intrauterine system (IUS), with the exception of IUD progesterone T.

The following are **unacceptable** forms of contraception for women of childbearing potential:

- IUD progesterone T
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield



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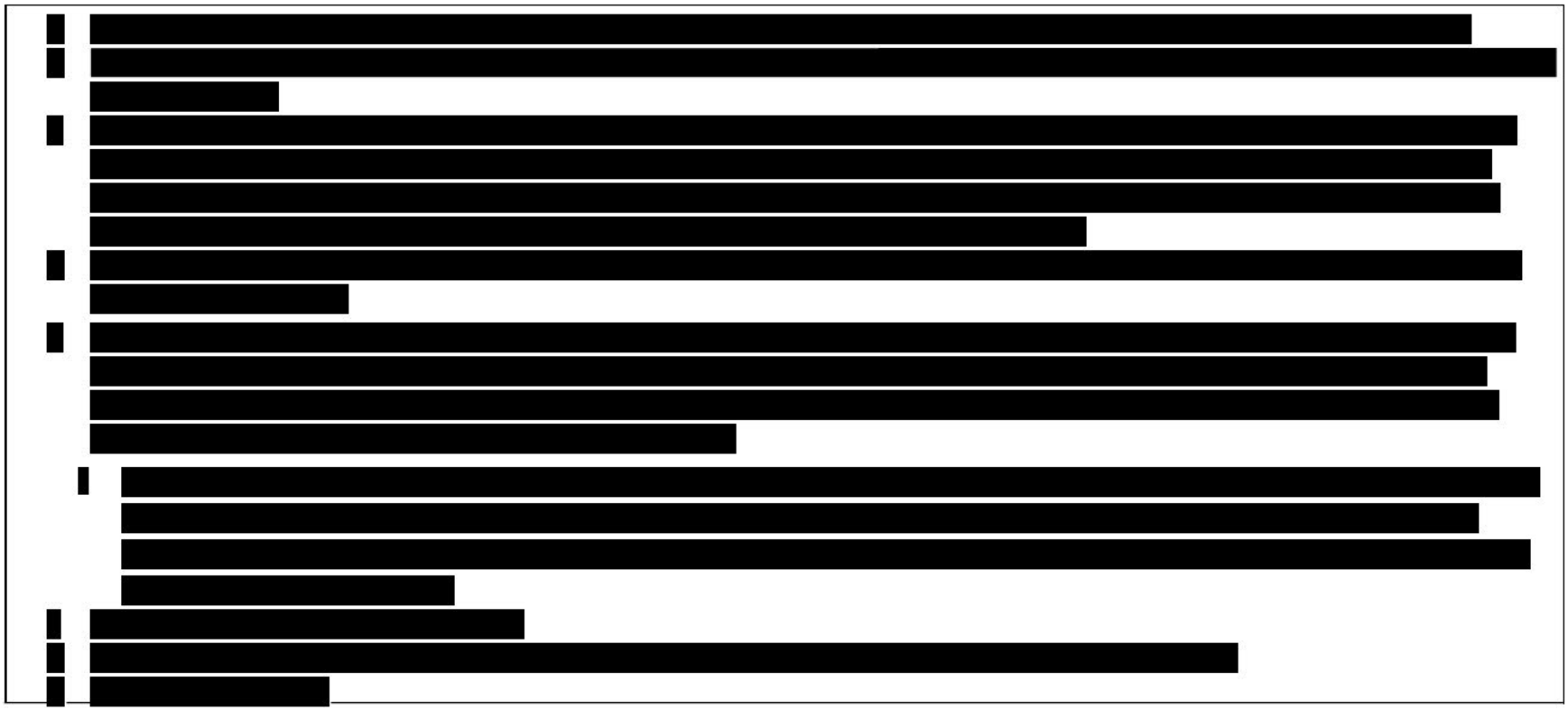

Appendix E: RECIST Response Criteria for Solid Tumors

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions.
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest (nadir) sum LD since the treatment started.
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest (nadir) sum since the treatment started, or the appearance of one or more new lesions. Requires not only 20% increase, but absolute increase of a minimum of 5 mm over sum.

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor markers. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD:	Persistence of one or more non-target lesions and/or persistence 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. When the patient also has measurable disease, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

Eisenhauer et al Eur J Cancer 45 (2009); 228-247

Appendix [redacted]

Appendix G: Hy's Law Criteria for Concomitant Elevations of Transaminases and Bilirubin

According to the FDA Guidance "Drug-Induced Liver Injury: Premarketing Clinical Evaluation", Hy's law can be followed when assessing for drug-induced liver injury. Hy's law is based on the work of Hy Zimmerman, a major scholar of drug-induced liver injury.

Hy's Law cases have the following 3 components:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo.
2. Among trial subjects showing such aminotransferase (AT) elevations, often with aminotransferases much greater than 3× ULN, one or more also show elevation of serum total bilirubin (TBL) to >2 ×ULN, without initial findings of cholestasis (elevated serum ALP).
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

Finding one Hy's Law case in the clinical trial database is worrisome; finding 2 is considered highly predictive that the drug has the potential to cause severe drug-induced liver injury when given to a larger population.

[redacted]

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