Phase Ib study of BVD-523 plus nab-paclitaxel and gemcitabine in patients with metastatic pancreatic cancer

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nab-Paclitaxel (Abraxane)

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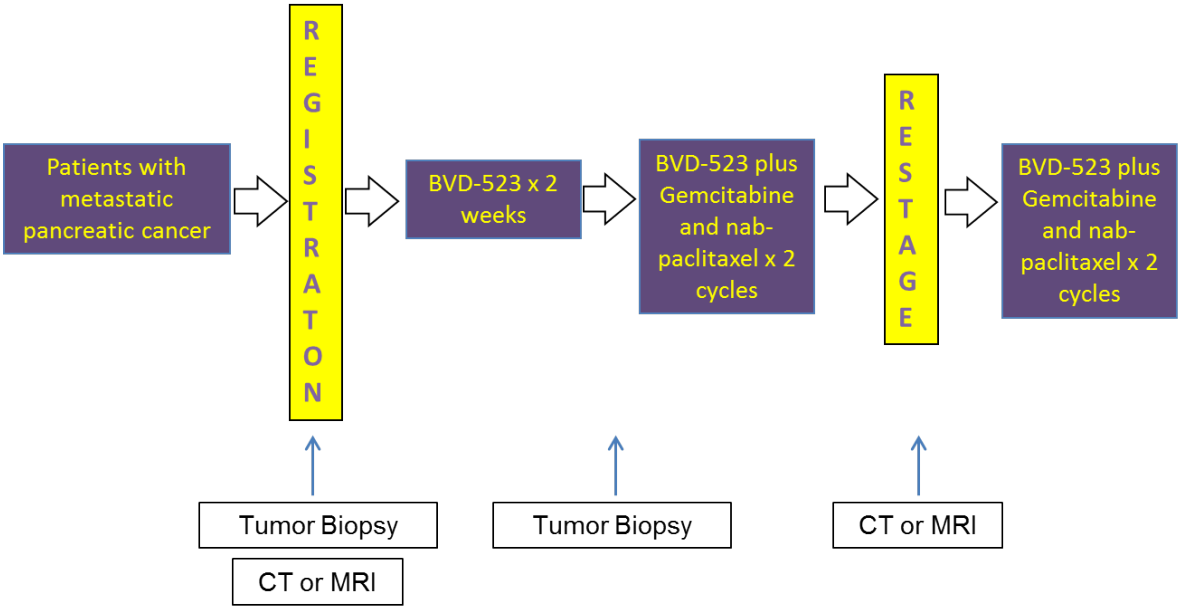
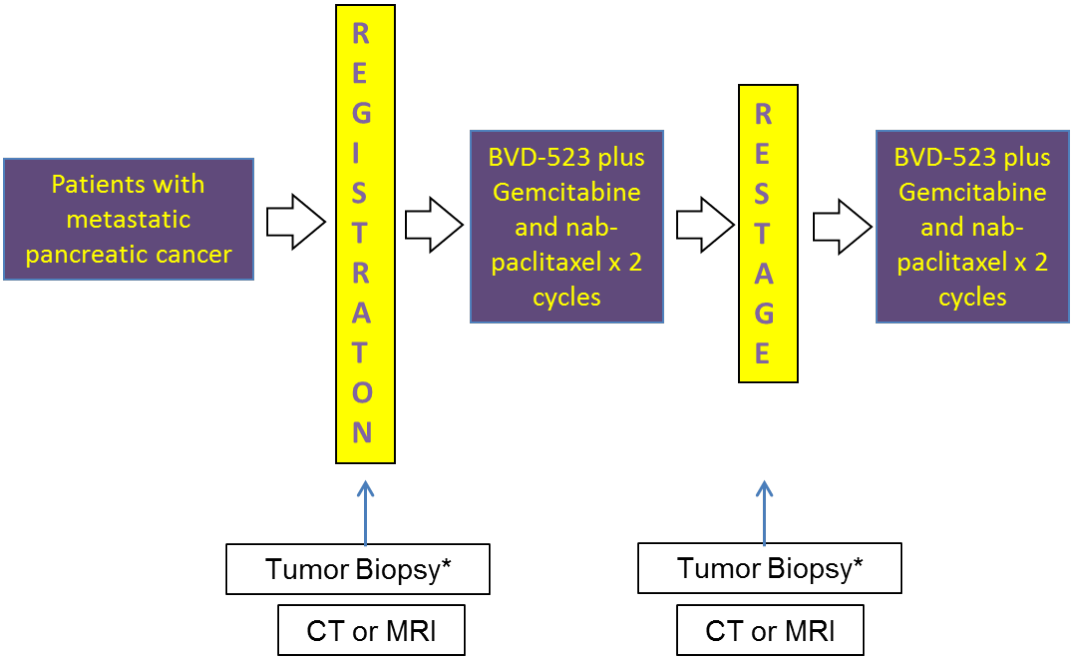
SCHEMA

Dose De-escalation Cohort



Expansion Cohort



Glossary of Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
B-HCG	Beta human chorionic gonadotropin
CBC	Complete blood count
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLT	Dose limiting toxicity
DNA	deoxyribonucleic acid
DSM	Data and Safety Monitoring
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
HIV	Human Immunodeficiency Virus
HRPO	Human Research Protection Office (IRB)
IND	Investigational New Drug
IRB	Institutional Review Board
ILLN	Institutional lower limit of normal
IULN	Institutional upper limit of normal
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan
OHRP	Office of Human Research Protections
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PI	Principal investigator
PR	Partial response
QASMC	Quality Assurance and Safety Monitoring Committee
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SD	Stable disease
UPN	Unique patient number

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1.0 BACKGROUND AND RATIONALE

1.1 Pancreatic Cancer

Pancreatic cancer remains the fourth leading cause of cancer-related mortality in 2013 in the United States (1) . Surgery is the only curative treatment; however, owing to the paucity of early detection methods, about 80% of pancreatic cancer patients are found to have unresectable or metastatic disease at the time of diagnosis, and their 5-year survival rate is less than 6% (1) . Novel therapy for pancreatic cancer is desperately needed.

1.2 Front-Line Treatment in Metastatic Pancreatic Cancer

Gemcitabine has been the cornerstone treatment for patients with pancreatic cancer since 1997, after it showed a modest survival advantage and better control of disease-related symptoms when compared with fluorouracil (5-FU) in a large randomized phase III clinical trial (2). The median overall survival (OS) was 5.65 months for gemcitabine-treated patients and 4.41 months for 5FU-treated patients (P=0.0025) (2). During the last decade, gemcitabine was combined with various drugs including platinum compounds, taxanes, topoisomerase inhibitors, and targeted therapies; however, the only combination that has resulted in a meaningful clinical survival advantage was nab-paclitaxel plus gemcitabine (3). Comparing with gemcitabine as a single agent, patients received the nab-paclitaxel plus gemcitabine had resulted superior survival benefit (8.5 months vs. 6.7months; hazard ratio (HR): 0.72; P<0.001). The progression-free survival (PFS) was also superior in the combination arm (5.5 months vs. 3.7 months; HR 0.69; P<0.001) (3). The combination of nab-paclitaxel plus gemcitabine has become a viable front-line therapy in patient with metastatic pancreatic cancer.

FOLFIRINOX (5-FU, leucovorin, oxaliplatin and irinotecan) is another treatment option has shown survival benefit compared with gemcitabine alone. Based on the ACCORD study, FOLFIRINOX resulted in superior median OS (11.6 months vs. 6.8 months; HR: 0.57; P<0.0001), and superior PFS (6.4 months vs. 3.3 months; HR 0.47; P<0.001) (4); however, the regimen was associated with moderate hematological and non-hematological toxicities. Thus, FOLFIRINOX is reserved for patients with good performance status (PS), and the adoption of this regimen as the front-line therapy is rather limited.

Although there are two options in the front-line setting for patients with metastatic pancreatic cancer, nab-paclitaxel plus gemcitabine has been used wildly because of better tolerability; therefore, the combination has been favored as the backbone regimen for adding novel therapy to enhance efficacy.

1.3 RAS/RAF/MEK/ERK Pathways as a Valid Target for Pancreatic Cancer

It is well known that the K-RAS mutation remains the predominant feature of pancreatic cancer molecular pathogenesis. Functional K-ras is a member of the GTP binding protein family, the members of which convert extracellular signals into intracellular signals by

cycling between the active (Ras-GTP) and inactive (Ras-GDP) states. Mutated K-ras results in constant activation of the Ras pathway by locking Ras into the active GTP-binding state and further triggering downstream multiple signaling pathways including cell proliferation, apoptosis, differentiation and survival (5,6). The K-RAS mutation is implicated in tumor initiation (7) and maintenance (8) , and the presence of the K-RAS mutation was detected in 30% of pre-malignant pancreatic lesions (9) and 90% of pancreatic cancer specimens (10). The crucial function of K-ras activation in cancer has led to the various strategies developed to down-regulate K-ras; however, the initial enthusiasm for this approach has been dampened by inherent complexities in the pathway. For example, attempts to block the post-translational modification of K-ras have not resulted in any clinical benefit (11).

Difficulty in targeting K-ras has led to an examination of its downstream pathways. Research has focused on evaluating inhibitors that block two main K-ras downstream signaling pathways: the phosphatidylinositol 3-kinase (PI3K) pathway and the RAF/MEK/ERK pathway. Various inhibitors targeting crucial mediators of both pathways have been developed in the preclinical and clinical setting. Among them, RAF and MEK inhibitors did not demonstrate any significant activity in pancreatic cancer patients (12,13). A recent study has suggested that there were several mechanisms of MEK resistance including mutation in the binding site of MEK or concurrent upstream amplification of KRAS mutation (ref). ERK inhibition may overcome MEK resistance regardless of the resistance mechanism (14). In parallel, a similar study reported rapid ERK activation may contribute the resistance of RAF inhibitor (15). ERK is not only a key effector of the crucial pathway in pancreatic cancer, but it is also involved in resistance to RAF and MEK inhibitor (16); Therefore, developing ERK inhibitors for pancreatic cancer is a logical and promising therapeutic strategy. In pancreatic cancer cell lines, inhibition of the MEK/ERK pathway leads to cell cycle arrest and apoptosis (17,18). Anti-tumor activity resulting from ERK inhibition has been seen in human orthotoptic primary pancreatic cancer xenografts, strengthening the argument for further development and investigation of ERK inhibitors in pancreatic cancer. At present, three small molecules targeting ERK have entered in early phase clinical trials.

1.4 BVD-523 (Ulixertinib)

BVD-523 (BioMed Valley Discoveries, Kansas City) is a small molecule that targets ERK1 and ERK2 in the sub-nanomolar range. It is a reversible, ATP-competitive kinase inhibitor that selectively inhibits ERK1 and ERK2 without any significant effect on the 75 other human kinases (Investigator Brochure, BioMed Valley Discoveries, 2012). BVD-523 has shown potent anti-tumor effects against pancreatic cancer cell lines and pancreatic tumor xenografts. BVD-523 is the leading ERK inhibitor to enter the oncology clinical study. The multi-site phase I trial of BVD-523 in patients with solid tumors is ongoing (NCT#01781429).

1.4.1 Preclinical Data

In the following sections a short summary of preclinical data is provided. Detailed information is presented in the BVD-523 Investigator's Brochure.

1.4.1.1 Potential Risk

Preliminary evidence from in vitro and in vivo toxicological assessments of BVD-523 suggests the molecule has a safety profile supportive of its development as an anti-cancer therapeutic. Additionally, human clinical trials have been conducted using other drugs known to affect the MAPK pathway and findings from these studies may provide information regarding possible safety risks that are mechanistically attributable to MAPK pathway inhibition.

Thus, BVD-523's risk profile may potentially include the following:

Dermatological Lesions
Dermatological lesions have been seen in rodent GLP toxicology studies of BVD-523. Several of the following findings displayed exposure-dependent increases in incidence and/or severity: non-specific dermal inflammation, pustular dermatitis, epidermal ulceration and acanthosis. These toxicities appeared to be associated with predominantly reversible pharmacodynamics, as the majority of findings were mild and/or of low incidence in animals that underwent dose cessation.

In clinical studies, other drugs that inhibit components of the MAPK pathway exhibit cutaneous toxicity. Multiple investigational inhibitors of MEK1/2 kinases exhibit exposure-dependent, dose-limiting and reversible skin toxicities in a proportion of patients. Specific toxicities include: non-specific rash and pruritus, acneiform dermatitis, epidermal fissure and paronychia. Additionally, clinical experience with both investigational agents and approved drugs that primarily target BRAF kinase have displayed exposure-dependent and reversible skin toxicities in a proportion of treated patients; relevant lesions here include keratoacanthoma-type squamous cell carcinomas, non-cancerous hyperkeratosis and actinic keratosis.

Phototoxicity
BVD-523 exhibits an absorbance peak in the range of UV-A/UV-B light, specifically at ~320 nm. Clinical studies of other drugs that modulate MAPK pathway components have exhibited skin phototoxicity.

Beyond dermatological monitoring (above), potential risks of direct phototoxicities induced by

BVD-523 will be further minimized by advising that patients minimize sun exposure, use broad-spectrum sunscreens, and wear sunglasses. Patients will be informed that relevant sun exposure may occur even through glass, such as while driving.

Ophthalmological Effects

Preclinical toxicology studies of BVD-523 have not revealed any exposure-dependent ophthalmological toxicities; however, clinical studies of MEK1/2 kinase inhibitors highlight ocular toxicities that may reflect mechanistically attributable risks observable in a proportion of patients. Of particular concern are the following dose-limiting toxicities comprising exposure-dependent, serious adverse events during clinical studies: retinal vein occlusion, retinal detachment and related vision abnormalities. While it is not definitively understood whether ocular toxicities reflect primary pharmacology associated with global inhibition of the MAPK pathway, specific management and exclusion criteria are defined in this clinical protocol, as the toxicities could potentially severely and irreversibly impact patient well-being.

Gastrointestinal Toxicity

Preclinical toxicity studies of BVD-523 have provided evidence of exposure-related, reversible gastrointestinal toxicities. The severity and reversibility of these toxicities, though, are viewed so as to not merit a specific monitoring or treatment plan, despite the possibility that GI toxicity may be observed during the proposed clinical study.

QTc Prolongation

The balance of preclinical evidence suggests BVD-523 has low, but observable, potential to cause QT prolongation. Given potentially unique species sensitivity, as well as possibly unknown consequences following chronic dosing, patients dosed with BVD-523 will be monitored for potential QTc prolongation and related cardiotoxicities.

Tissue Mineralization

Tissue mineralization has been observed in rodent toxicology studies of BVD-523. The incidence and severity of mineralization was dose-dependent and effects were observed in 1 or more tissues at toxic doses. In animals in which mineralization occurred after treatment with BVD-523, significantly increased serum phosphorus and modestly decreased serum calcium were seen; these effects were not observed in animals in which there was no mineralization.

Tissue mineralization has been reported in rodents with other compounds that target the MAPK pathway and published studies suggest that the MAPK pathway is a negative regulator of matrix mineralization both in vitro and in vivo.

Routine clinical laboratory tests, including blood chemistry analyses for calcium and inorganic phosphate, will be performed and any indication of abnormalities may result in further investigations. A clinical monitoring strategy similar to this was previously employed for related drugs that target the MAPK pathway.

Hematological Effects

Hematological effects observed in a rat repeat dose study included lowered reticulocyte counts, mean corpuscular volume, platelet counts (in females only) and increased neutrophil, monocyte, basophil and large unstained cell counts. In dogs the clinical pathology findings were consistent with inflammation (increased white blood cell count, neutrophils, fibrinogen and globulin) and decreased albumin and hemorrhage (decreased red cell mass).

In order to monitor for potential hematologic toxicity in humans, routine clinical laboratory hematology tests, should be performed and any indication of abnormalities may result in further investigations.

1.4.1.2 Pharmacology Studies

BVD-523 is highly efficacious in vivo when administered as a single agent in ectopic xenograft models of colon, pancreatic and melanoma cancers, 3 tumor types in which ERK is known to be highly activated. Notably, partial regression was achieved in a colon cancer model (Colo205) when the compound was administered at 50 mg/kg (b.i.d.). Biomarker analyses confirmed that improved efficacy obtained at higher doses of BVD-523 correlated with increasing ERK inhibition.

1.4.1.3 Toxicity and Safety Studies

When BVD-523 was characterized using in vitro screens against 66 receptors and ion channels no toxicologically significant interactions were identified. Additionally, BVD-523 was negative in bacterial mutation and in vivo micronucleus screening assays, so BVD-523 is not considered to have a significant genetic toxicology risk.

While BVD-523 modestly inhibits the hERG current (IC50 3.4 μM), no significant effects were seen in action potentials recorded from dog Purkinje fibers exposed to up to 10 μg/mL, and no significant cardiovascular findings were observed upon acute oral dosing of the compound at dose levels up to 50 mg/kg in dogs (Cmax = 17.3 μM). Thus BVD-523 is considered to have a low potential to cause QT prolongation in patients, but, as stated, the study will monitor for signs of cardiovascular effects of BVD-523 in humans.

No significant cytochrome P450 (CYP) inhibition has been observed with

the compound. In vitro studies suggest that the compound is metabolized primarily via oxidation by multiple CYPs, including 3A4, 2D6, and 1A2. Furthermore, no significant CYP induction was observed after up to 14 days drug treatment in rats, nor during in vitro studies with human hepatocytes. These data suggest a limited potential for drug-drug interactions.

BVD-523 HCl salt is orally available in multiple species (absolute bioavailability %F = 23% in dog to 100 % in monkey) when formulated as a simple suspension in 1% carboxymethylcellulose (CMC) and has a half-life of 2−4 hours across all species.

BVD-523 was administered to male and female Sprague-Dawley rats in several toxicology studies: a GLP study for up to 28 days at dose levels up to 50 mg/kg/day twice daily; for up to 14 days at dose levels up to 100 mg/kg twice daily; and for up to 5 days at dose levels up to 150 mg/kg/dose once daily. The incidence and severity of mineralization seen in these studies was dose-dependent and effects were observed in 1 or more tissues at toxic doses. In animals in which mineralization occurred after treatment with BVD-523, significantly increased serum phosphorus and modestly decreased serum calcium were seen; these effects were not observed in animals in which there was no mineralization. Therefore, the risk of tissue mineralization can be assessed by serum phosphorus and calcium monitoring. A clinical monitoring strategy similar to this was previously employed for related drugs that target the MAPK pathway because those compounds likewise elicited mineralization in rodents.

When BVD-523 was administered to male and female Sprague-Dawley rats for up to 28 days at a dose level of 25 or 50 mg/kg twice daily, it was poorly tolerated. Although most clinical signs and clinical pathology findings reversed following 4 weeks of recovery, skin lesions and histopathology findings persisted in many tissues at both dose levels after the recovery phase. Based on these findings, 25 and 50 mg/kg twice daily dose levels were considered severely toxic. Administration of 12.5 mg/kg twice daily for 28 days was generally well-tolerated by rats of both sexes; however, this dose level was associated with test article-related findings that included: swelling in the neck; decreased forelimb strength; multiple clinical pathology findings; enlarged lymph nodes, spleen, and mammary gland. Based on these findings, the severely toxic dose in 10% of the animals (STD10) for BVD-523 when administered for up to 28 days in Sprague-Dawley rats is 12.5 mg/kg given twice daily (25 mg/kg/day). On Day 28 of the dosing phase, this dose level corresponded with a Cmax of 28700 and 15323 ng/mL and AUC 0-12 of 264868 and 124341 hr.ng/mL for males and females, respectively.

BVD-523 was administered to male and female beagle dogs for up to 28 days at dose levels of 15, 5, or 2 mg/kg twice daily. Initial analysis of the

toxicity profile observed shows that BVD-523 was well tolerated in dogs. The rat was designated the most sensitive species and rat data were used to calculate the starting dose in man.

BVD-523 has a measured UV absorbance at 320 nm, which means that it can absorb both UV-A and UV-B. BVD-523 may therefore act as a photosensitizing agent in man.

Based on the data accumulated to date, BVD-523 possesses a toxicology profile which presents no impediment to its development as an anti-cancer agent.

For further information, please refer to the BVD-523 Investigator's Brochure.

1.4.2 Clinical Evaluation

The first-in-class phase I trial of BVD-523 in patients with advanced solid tumors is ongoing. The primary objective of the study is to define the safety and tolerability of BVD-523 by determining the dose-limiting toxicity (DLT), the maximum tolerated dose (MTD), and the RP2D. The study has successfully determined that the MTD of BVD-523 is 600 mg twice daily. The DLT at MTD was a grade 3 rash. Pharmacokinetic study showed linear and dose proportional up to 600 mg twice daily. Additionally, phosphorylation of ERK substrate RSK was inhibited in peripheral blood samples starting at 75 mg twice daily. Metabolic response was observed in 5 out 16 evaluable patients assessed by FDG-PET. Three of 25 patients had partial response according to the RECIST 1.1, and 7 had stable disease for at least 3 months. So far, the clinical data suggested that BVD-523 achieved pharmacologically relevant exposure, and resulted in early signal of clinical efficacy.

1.5 Study Rationale

In light of the central role of ERK in pancreatic cancer, we propose a phase I study to evaluate the ERK inhibitor BVD-523 at the RP2D in combination with nab-paclitaxel plus gemcitabine in patients with newly diagnosed metastatic pancreatic cancer. The primary endpoint will be MTD or RP2D and safety. The secondary endpoints include safety, response rate, biochemical response, PFS and OS. The exploratory endpoints include the assessing the impact of BVD-523 on the MEK/ERK pathway and other major pathway pertain to pancreatic cancer.

1.6 Correlative Studies Background

1.6.1 Pharmacodynamics markers evaluation

Since ERK is a valuable therapeutic target in pancreatic cancer, it is crucial to evaluate whether BVD-523 has reached its respective target in tumor. In pancreatic cancer, the drug delivery is extremely crucial given the tumor cells are nested in the dense stroma. It is known that the effectors of signaling pathways are primarily activated through phosphorylation; therefore, the ability to evaluate the phosphorylation status of effectors involved in signaling pathways are essential in understanding whether the targeted therapy has reached its target, and furthermore, how the complex signaling network responds to a specific pathway inhibitor, such as BVD-523. In the proposed study, we plan to compare the major effectors of KRAS pathways including the phosphorylation of ERK substrate RSK (pRSK) on the biopsies done prior and post two weeks administration of single agent BVD-523.

1.6.2 Determinations of genetic predictors associated with treatment response

The biopsy obtained at baseline and at the end of the second cycle (expansion cohort) of therapy will be collected for molecular correlative study. Gene expression levels will be determined by either RNASeq or transcriptome analysis, the changes between the paired biopsies will be correlated with treatment response. Exome sequencing will be performed to determine whether a particular set of genetic alterations would predict treatment response and resistance. The phosphorylation protein by proteomic approach will be compared to investigate whether certain signaling pathway activation could contribute treatment response or resistance. Other molecular analysis may be entertained based on the funding availability

2.0 OBJECTIVES

2.1 Primary Objective

To determine the MTD or RP2D of BVD-523 in combination with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic cancer.

2.2 Secondary Objectives

1. To evaluate the safety and toxicity profile of BVD-523 in combination with nab-paclitaxel and gemcitabine.
2. To determine biochemical response of BVD-523 in combination with nab-paclitaxel and gemcitabine.

3. To determine response rate of BVD-523 in combination with nab-paclitaxel and gemcitabine.
4. To determine time to tumor progression of BVD-523 in combination with nab-paclitaxel and gemcitabine.
5. To determine PFS of BVD-523 in combination with nab-paclitaxel and gemcitabine.
6. To determine OS of BVD-523 in combination with nab-paclitaxel and gemcitabine.

2.3 Exploratory Objectives

1. To assess pharmacodynamics biomarkers of BVD-523 in tumors.
2. To explore the biomarkers and genetic alterations associated with treatment response.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Histologically or cytologically confirmed newly diagnosed treatment-naïve metastatic adenocarcinoma of the pancreas with metastatic disease diagnosed no more than 6 weeks prior to enrollment. Patients with advanced pancreatic cancer progressed on 5-FU (or capecitabine) based regimen will be allowed in the expansion cohort.

2. Measurable disease defined as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan or MRI, as ≥ 20 mm by chest x-ray, or ≥ 10 mm with calipers by clinical exam.

3. At least 18 years of age.

4. Life expectancy > 3 months.

5. ECOG performance status ≤ 1 (see Appendix A)

6. Normal bone marrow and organ function as defined below:
   a. Absolute neutrophil count ≥ 1,500/mcL
   b. Platelets ≥ 100,000/mcL
   c. Hemoglobin ≥ 9.0 g/dL
   d. Total bilirubin ≤ IULN
   e. AST(SGOT)/ALT(SGPT) ≤ 2.5 x IULN, unless there are liver metastases in which case AST and ALT ≤ 5.0 x IULN
   f. Creatinine ≤ 1.5 x IULN OR GFR of ≥ 50 mL/min
   g. Cardiac function ≥ ILLN, e.g., LVEF of > 50% as assessed by MUGA or ECHO, QTc < 470 ms

7. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry, for the duration of study participation, and for three months following study discontinuation.

Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

8. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. Current use or anticipated need for alternative, holistic, naturopathic, or botanical formulations used for the purpose of cancer treatment.

2. A history of other malignancy with the exception of those treated with curative intent with no evidence of disease for 2 years.

3. Currently receiving any other investigational agents.

4. Known brain metastases or CNS involvement.

5. Significant ascites that require therapeutic paracentesis.

6. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to BVD-523, gemcitabine, nab-paclitaxel, or other agents used in the study.

7. Neuropathy ≥ grade 2.

8. History or current evidence/risk of retinal vein occlusion (RVO) or central serous retinopathy (CSR).

9. History of interstitial lung disease or pneumonitis.

10. Concurrent therapy with drugs known to be strong inhibitors of CYP1A2, CYP2D6, and CYP3A4, or strong inducers of CYP3A4 (see Appendix B).

11. Gastrointestinal condition which could impair absorption of BVD-523 or inability to ingest BVD-523.

12. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

13. Pregnant and/or breastfeeding. Women of childbearing potential must have a negative pregnancy test within 7 days of study entry.

14. Known HIV-positivity.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center OnCore database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center Oncore Database

All patients must be registered through the Siteman Cancer Center database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

This is a phase Ib study of BVD-523 in combination with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic adenocarcinoma. The trial comprises two parts, a dose de-escalation part and a cohort expansion part at the RP2D. We propose to do a dose de-escalation design because of minimal overlapping toxicities between BVD-523 and nab-paclitaxel and gemcitabine. The dose de-escalation portion will have a run-in with BVD-523 given as a single agent for two weeks prior to initiating the triple drug combination. A modified Fibonacci design will be used for the phase Ib study, starting with a cohort of 6 patients at the target dose

combination level. If 0 or 1 out of 6 patients experiences DLT at this level, it will be used for the expansion cohort portion. If 2 DLTs are observed, the dosing of BVD-523 will de-escalate with a new cohort of 6 patients. The maximal number of patients needed for this part is 18 and the minimal number of patients is 6. After the determination of MTD, the remaining patients (total N=25) will be enrolled to the expansion cohort.

5.1 Agent Administration

Treatment will be given in a 28-day cycle. BVD-523 is an oral drug which will be given at the protocol-dictated dose on a twice daily basis (at approximately 12-hour intervals). Phase Ib patients will take BVD-523 at 450 mg twice daily on its own for two weeks before initiating Cycle 1 treatment with gemcitabine and nab-paclitaxel. BVD-523 should be taken in a fasted state (one hour before food or two hours after food). All capsules should be taken within 10 minutes with 8 ounces of water. If a patient misses a dose, s/he should not make up that dose but simply resume dosing with the next scheduled dose. Patients will be instructed to bring all unused capsules and their medication diary (Appendix C) to each study visit for an assessment of compliance.

Nab-paclitaxel will be given at a dose of 125 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle over the course of 30-40 minutes Gemcitabine will be given at a dose of 1000 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle over the course of 30 minutes.

The study has enrolled two patients at level 1 dose in group B arm. Although there was no DLT encountered in those two patients, none of them could complete two cycles for evaluation of treatment assessment. One patient experienced pneumonitis related to gemcitabine and subsequently enrolled in the hospice care. The second patient withdrew from the study due to a constellation of low-grade adverse events such as fatigue, fever and rash et al. The patient also had a 3-hour drive, which also contributed to his decision of withdrawing from the study. After discussing with other investigators in the team, the PI felt that it is reasonable to start with level -1 dose of BVD-523 at 450 mg twice daily. The study will also include patients who progressed on 5-FU based therapy for the expansion cohort.

5.2 Dose Schema

Dose De-Escalation Schedule			
	BVD-523	**Gemcitabine**	**Nab-paclitaxel**
Level -2	300 mg BID	1000 mg/m^2 Days 1, 8, and 15	125 mg/m^2 Days 1, 8, and 15
Level -1	450 mg BID		
Level 1 (Starting Dose)	600 mg BID		

Dose Escalation Schedule (Expansion Cohort)			
	BVD-523 BID	**Gemcitabine Day 1, 8 and 15**	**Nab-paclitaxel Day 1, 8 and 15**

Level -1	300 mg	800 mg/m2	100 mg/m2
Level 1(starting dose)	450 mg	800 mg/m2	100 mg/m2
Level 2	450 mg	1000 mg/m2	125 mg/m2

Dose escalation for the expansion cohort will not occur until all patients in the cohort have completed the first cycle and the Principal Investigator has been able to review all toxicities.

5.3 Definition of MTD, DLT, Dose Escalation Criteria, and Toxicity, Response, and DLT Evaluations

5.3.1 Definition of Maximum Tolerated Dose (MTD)

The maximum tolerated dose (MTD) is defined as the Dose Level 1 if 0 or 1 DLTs are seen in patients at that dose level or Dose Level -1 if 2+ DLTs are seen in Dose Level 1 but only 0 or 1 DLTs are seen in patients at Dose Level -1. If 2+ DLTs are seen in patients at Dose Level -1, the study will be suspended so that further dose reductions may be planned prior to enrolling to the expansion cohort.

5.3.2 Dose Limiting Toxicities (DLTs)

Nab-paclitaxel plus gemcitabine is the standard front-line therapy in patients with metastatic pancreatic cancer, and the combination has been frequently used as a backbone for novel therapy combination. The toxicity profile of nab-paclitaxel plus gemcitabine is well known. This study is to determine the dose levels for the triple drug combination, so only DLTs occurring during the first cycle of the triple regimen administration will be considered. Events that occur prior to the start of gemcitabine and nab-paclitaxel will not be considered DLTs.

DLT is defined as BVD-523-related toxicity that occurs during the first cycle that results in:

- ≥ grade 4 hematologic toxicity.
- ≥ grade 3 hematologic toxicity with complications, e.g., thrombocytopenia with bleeding
- ≥ grade 3 non-hematologic toxicity, except untreated nausea, vomiting, constipation, pain, and rash (these become DLTs if the AE persists despite adequate treatment), or a doubling of AST/ALT in patients with grade 2 ALT/AST at baseline
- ≥ grade 3 nausea, vomiting and diarrhea greater than 72 hours despite adequate treatment
- A treatment interruption exceeding 14 days in Cycle 1, or inability to being Cycle 2 for > 14 days due to BVD-523-related toxicity
- Any toxicity that attributed to BVD-523 that resulted in delay of nab-paclitaxel and gemcitabine by more than 4 weeks

5.3.3 Dose Escalation Criteria

Dose escalations (expansion cohort) will proceed as follows:

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 6	Enter 6 patients at the next dose level.
>2	Dose escalation will be stopped. Prior dose level is defined as MTD or RP2D.
<1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

5.3.4 Toxicity, Response, and DLT Evaluations

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated from first receiving study treatment until a 30-day follow up after the conclusion of treatment or death.

All patients are evaluable for disease response unless they discontinue treatment due to treatment related adverse events(s) prior to completion of Cycle 2 and have not had any disease assessment.

A patient is evaluable for DLT assessment only during Cycle 1 of treatment (not including the lead-in prior to the start of gemcitabine and nab-paclitaxel). Patients experiencing excessive toxicity during the lead-in will be replaced and will not be considered evaluable for DLT assessment. If the patient is not able to be treated on Day 1 of Cycle 2, then s/he is still considered in Cycle 1 active treatment and can experience a DLT. Once the patient has been treated in Cycle 2, s/he will no longer be evaluated for DLTs in all subsequent cycles.

5.4 Dose Expansion Cohort

The dose expansion cohort will have a dose escalation schema with level 1 and level 2 dose levels planned (see 5.2). After determination of the MTD, additional patients (so that the total enrolled is 25) will be enrolled at the MTD. These patients will not have the 2-week BVD-523-only lead-in. In light of a lead-in study, to ensure the adequate assessment of toxicity and safety, the study has a stopping rule in the expansion cohort.

5.5 General Concomitant Medication and Supportive Care Guidelines

Supportive care will be administered as per routine practice. This typically will include loperamide as needed for diarrhea, and antiemetic medication for symptoms of nausea or emesis. Intravenous fluid support will be provided at the discretion of the treating physician

for patients who experience significant nausea, emesis, or diarrhea. For grade 3 or greater skin toxicity, dermatology consult is recommended. Oral antibiotics (such as minocycline or doxycycline should be considered at any sign of rash. Topical cleomycin should also be considered at the first sign of rash.

5.6 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative pregnancy test within 7 days prior to the first dose of study treatment.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and for 3 months following the last dose of study treatment.

If a patient is suspected to be pregnant, study treatment should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 3 months after the last dose of study treatment, the investigator must be notified in order to facilitate outcome follow-up.

5.7 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

5.8 Duration of Follow-up

Patients will be followed every month for 2 years or until death, whichever occurs first. Patients removed from study for unacceptable adverse events that are considered treatment-related will be followed until resolution or stabilization of the adverse event.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

6.1 Dose Modifications for BVD-523

Patients experiencing DLT or unacceptable toxicity will have their treatment interrupted until the toxicity returns to ≤ grade 1 or pre-treatment baseline, whichever is more severe. Resumption of BVD-523 treatment will be at the next lower dose level tested (450 mg BID if 600 mg BID was the starting dose, 300 mg BID if 450 mg BID was the starting dose).

Rash is quite common in patients receiving BVD-523. With the first onset of rash, it is important to consult dermatology for better management.

6.2 Dose Modifications for Gemcitabine and Nab-Paclitaxel

Dose Level	Gemcitabine	Nab-Paclitaxel
Full dose	1000 mg/m^2	125 mg/m^2
1st dose reduction	800 mg/m^2	100 mg/m^2
2nd dose reduction	600 mg/m^2	75 mg/m^2
If additional dose reduction required	Discontinue or further possible dose reduction at the discretion of the PI.	

Dose Modifications for Neutropenia and/or Thrombocytopenia

Cycle Day	ANC (cells/mm3)		Platelet count (cells/mm3)	Dosing Adjustment
Day 1	< 1500	OR	< 100,000	Delay doses until recovery
Day 8	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold doses[1]
Day 15 if Day 8 doses were reduced or given without modification	500 to < 1000	OR	50,000 to < 75,000	Reduce 1 dose level from Day 8
	< 500	OR	< 50,000	Withhold doses[1]
Day 15 if Day 8 doses were withheld	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1

	500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1
	< 500	OR	< 50,000	Withhold doses[1]

1 Doses held during a cycle (i.e. D8 or D15) will not be made up.

Dose Modifications for Other Treatment Related Adverse Drug Reactions

Adverse Drug Reaction	**Gemcitabine**	**Nab-Paclitaxel**
Febrile neutropenia (Grade 3 or 4)	Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level	
Peripheral neuropathy (Grade 2)	No dose reduction	Dose reduction allowed PI discretion
Peripheral neuropathy (Grade 3 or 4)	No dose reduction	Withhold until improves to ≤ grade 1; resume at next lower dose level
Cutaneous toxicity (Grade 2 or 3)	Reduce to next lower dose level; discontinue treatment if toxicity persists	
Gastrointestinal toxicity (Grade 3 mucositis or diarrhea)	Withhold until improves to ≤ grade 1; resume at next lower dose level	
Unexplained dyspnea or other evidence of severe pulmonary toxicity	Discontinue	No dose reduction
Severe hepatic toxicity	Discontinue	Do not administer to patients with total bilirubin > 1.5 x IULN or AST > 10 x IULN
Hemolytic-Uremic Syndrome	Discontinue	No dose reduction
Capillary Leak Syndrome	Discontinue	No dose reduction
Posterior Reversible Encephalopathy Syndrome	Discontinue	No dose reduction
Other grade 3 or 4 non-hematological toxicity (except nausea or vomiting)	Withhold or reduce by one dose level either one or both drugs	

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 7.2.

The FDA requires that all serious and unexpected adverse events be reported as outlined in Section 7.4. In addition, any fatal or life-threatening adverse experiences where there is a reasonable possibility of relationship to study intervention must be reported.

Biomed Valley Discoveries, Inc. requires that all reportable adverse events be reported as outlined in Section 7.5.

7.1 Definitions

7.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

7.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

All unexpected SAEs must be reported to the FDA.

7.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

Events that are both serious AND unexpected must be reported to the FDA.

7.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Life-threatening adverse experiences must be reported to the FDA.

7.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

7.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

7.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event.

7.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

7.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within 10 days of receipt of IRB acknowledgment via email to a QASMC auditor.

7.4 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the investigator to report any unanticipated problem to the FDA as follows:

- Report any unexpected fatal or life-threatening adverse experiences (Section 7.1.4) associated with use of the drug by telephone or fax no later than **7 calendar days** after initial receipt of the information.
- Report any serious, unexpected adverse experiences (Section 7.1.2), associated with use of BVD-523 as well as results from animal studies that suggest significant clinical risk within **15 calendar days** after initial receipt of this information.

All MedWatch forms will be sent by the investigator or investigator's team to the FDA at the following address or by fax:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
5901-B Ammendale Rd.
Beltsville, MD 20705-1266
FAX: 1-800-FDA-0178

7.5 Reporting to Biomed Valley Discoveries, Inc.

In the event of a reportable adverse event, please send the FDA MedWatch and BioMed Valley SAE form (See Appendix D) to the Clinipace Worldwide Safety Associate at safety@clinipace.com.

7.6 Timeframe for Reporting Required Events

Reportable adverse events will be tracked for 30 days following the last day of study treatment.

8.0 PHARMACEUTICAL INFORMATION

8.1 BVD-523 (Ulixertinib)

8.1.1 BVD-523 Description

IUPAC Name: *(S)*-4-(5-chlor-2-(isopropylamino)pyridin-4-yl)-*N*-(1-(3-chlorophenyl)-2-hydroxyethyl)-1*H*-pyrrole-2-carboxamide hydrochloride
Molecular Formula: $C_{21}H_{22}Cl_2N_4O^2 \cdot HCl$
Molecular Weight: 469.79 Daltons

8.1.2 Clinical Pharmacology

In preliminary studies, measurements of phorbol ester-dependent RSK phosphorylation of whole blood samples collected from patients dosed orally with BVD-523 have demonstrated dose-dependent bioactivity of BVD-523. These ERK inhibitory effects are manifest following a single dose of BVD-523 and after

repeated dosing, showing biological activity as predicted by the mechanism of action of BVD-523.

8.1.3 Pharmacokinetics and Drug Metabolism

In vitro studies using recombinant human enzymes showed that BVD-523 was metabolized by CYP1A2, CYP2D6, and CYP3A4, producing 7 potential metabolites. Pharmacokinetics samples are being taken from all patients in Part 1 of the study to measure plasma levels of BVD-523 and selected metabolites. To date no formal full analysis of the data has been made.

8.1.4 Supplier(s)

BVD-523 will be supplied by Biomed Valley Discoveries, Inc.

8.1.5 Dosage Form and Preparation

BVD-523 drug substance is manufactured according to cGMP as a mono-hydrochloride salt and is supplied in hard gelatin. The capsules are manufactured according to cGMP at 150 mg (yellow) of BVD-523 per capsule. The capsules are packaged in amber HDPE bottles.

8.1.6 Storage and Stability

Bottles of BVD-523 will be stored at controlled room temperature (15ºC-25ºC) environment under temperature monitoring in a location with access limited to authorized study personnel.

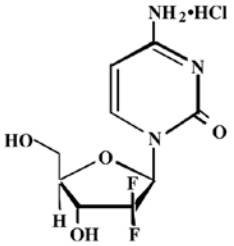
8.1.7 Administration

BVD-523 is an oral drug which will given at the protocol-dictated dose on a twice daily basis (at approximately 12-hour intervals). Phase Ib patients will take BVD-523 on its own for two weeks before initiating Cycle 1 treatment with gemcitabine and nab-paclitaxel. BVD-523 should be taken in a fasted state (one hour before food or two hours after food). All capsules should be taken within 10 minutes with 8 ounces of water. If a patient misses a dose, s/he should not make up that dose but simply resume dosing with the next scheduled dose.

8.2 Gemcitabine (Gemzar)

8.2.1 Gemcitabine Description

Gemcitabine is a nucleoside metabolic inhibitor that exhibits antitumor activity. Gemcitabine HCl is 2'-deoxy-2',2'-difluorocytidine monohydrochloride (β-isomer). The structural formula is as follows:



The empirical formula for gemcitabine HCl is $C_9H_{11}F_2N_3O_4 \cdot HCl$. It has a molecular weight of 299.66.

8.2.2 Clinical Pharmacology

Gemcitabine kills cells undergoing DNA synthesis and blocks the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized by nucleoside kinases to diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. Gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme responsible for catalyzing the reactions that generate deoxynucleoside triphosphates for DNA synthesis, resulting in reductions in deoxynucleotide concentrations, including dCTP. Gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP by the action of the diphosphate enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands, which eventually results in the initiation of apoptotic cell death.

8.2.3 Pharmacokinetics and Drug Metabolism

Gemcitabine disposition was studied in 5 patients who received a single 1000 mg/m^2/30 minute infusion of radiolabeled drug. Within one (1) week, 92% to 98% of the dose was recovered, almost entirely in the urine. Gemcitabine (<10%) and the inactive uracil metabolite, 2'-deoxy-2',2'-difluorouridine (dFdU), accounted for 99% of the excreted dose. The metabolite dFdU is also found in plasma.

The active metabolite, gemcitabine triphosphate, can be extracted from peripheral blood mononuclear cells. The half-life of the terminal phase for gemcitabine triphosphate from mononuclear cells ranges from 1.7 to 19.4 hours.

8.2.4 Supplier(s)

Gemcitabine will be given as per routine care from commercial supply.

8.2.5 Dosage Form and Preparation

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

a 10-mL size sterile single use vial or 1 g white to off-white lyophilized powder in a 50-mL size sterile single use vial.

8.2.6 Storage and Stability

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

8.2.7 Administration

Gemcitabine should be given as an intravenous infusion over the course of 30 minutes.

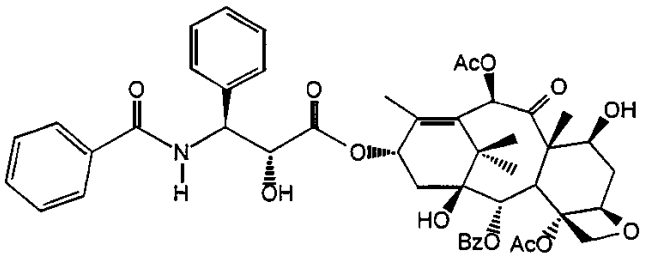
8.2.8 Special Handling Instructions

No special handling instructions.

8.3 Nab-Paclitaxel (Abraxane)

8.3.1 Nab-Paclitaxel Description

Nab-paclitaxel is an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers. The active agent is paclitaxel, a microtubule inhibitor. The chemical name for paclitaxel is 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine. Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the empirical formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.91. It is highly lipophilic, insoluble in water, and melts at approximately 216-217°C.

8.3.2 Clinical Pharmacology

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

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

8.3.3 Pharmacokinetics and Drug Metabolism

Following intravenous administration of nab-paclitaxel, paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline representing distribution to the peripheral compartment and the slower second phase representing drug elimination. The terminal half-life was approximately 27 hours.

In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6αhydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3'-*p*-hydroxypaclitaxel and 6α, 3'-*p*-dihydroxypaclitaxel, by CYP3A4. *In vitro*, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found *in vivo* following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel *in vitro*. The pharmacokinetics of paclitaxel may also be altered *in vivo* as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4.

8.3.4 Supplier(s)

Nab-paclitaxel will be given as per routine care from commercial supply.

8.3.5 Dosage Form and Preparation

It is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20mL of 0.9% sodium chloride injection, USP prior to intravenous infusion. Each single use vial contains 100 mg of paclitaxel (bound to human albumin) and approximately 900 mg of human albumin (containing sodium caprylate and sodium acetyltryptophanate). Each milliliter of reconstituted suspension contains 5 mg paclitaxel.

8.3.6 Storage and Stability

Store the vials in original cartons at 20°C to 25°C. Retain the original package to protect from bright light.

8.3.7 Administration

Nab-paclitaxel should be given as an intravenous infusion over the course of 30 to 40 minutes.

8.3.8 Special Handling Instructions

No special handling instructions.

9.0 CORRELATIVE STUDIES

9.1 Fresh Biopsies

9.1.1 Collection of Specimen(s)

Biopsies will be obtained prior to the start of treatment, at the end of the two week BVD-523 lead-in (dose de-escalation patients only), and at the end of the second cycle of therapy (expansion cohort patients only). Three cores will be collected at each time point. A baseline biopsy is mandatory for all patients. Tissue will only be collected at the end of C2 if deemed safe for the patient and feasible to obtain (per PI discretion). Four cores are desired for this study.

9.1.2 Handling of Specimen(s)

All biopsy samples will be placed on wet ice and transferred to the Dr. Kian-Huat Lim's lab. Tumor specimens will be divided into two potions. The first one will be formalin fixed and paraffin embedded (FFPE), while the second part will be snap frozen for further analysis. Two cores biopsy will be obtained and immediately placed in special cell culture medium to maintain cell viability. The tumor tissues will then be processed and immediately inoculated into the subcutaneous tissue of immunocompromised mice. Cell lines may be established from either the primary core or xenograft. If successful, the resulting tumors will be used for evaluation for treatment response and resistance.

9.1.3 Pharmacodynamics

A panel of biomarkers (pERK, pMEK, pRSK, p4EBP1, pS6 et al) will be evaluated by immunohistochemistry analysis to determine the effect of ERK pathway inhibition by BVD-523 on the paired biopsies collected in the dose de-escalation cohort. Other biomarkers may be evaluated as appropriate.

9.1.4 Predictive Biomarkers

Snap frozen paired core biopsies collected from patients in the expansion cohort will be thawed in the presence of RNA Later™. RNA will be made and transcriptome analysis will be done either by RNASeq or Affymetrix expression array analysis. Change of specific gene expression levels will be correlated with patient's treatment response.

Whole exome sequencing will be performed on those specimens to assess mutation status and burden.

10.0 STUDY CALENDAR

Screening/baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans and x-rays must be done no more than 4 weeks prior to the start of the protocol therapy. Cycles are 28 days. There is a window of +/- 3 days around the lead-in period. There is a window of +/- 1 day around each assessment.

	Baseline	**Lead-in[6]**	**All Cycles**			**End of every even-numbered cycle**	**EOT**	**F/U[7]**
			D1	**D8**	**D15**			
Informed consent	X							
H&P, ECOG PS	X		X				X	
CBC	X		X	X	X			
CMP	X		X		X			
β-hCG[1]	X							
CA19-9	X		X					
ECG	X			X[8]				
MUGA or ECHO[2]	X							
Radiographic imaging	X					X	X	
BVD-523		BID daily during each cycle						
Gemcitabine			X	X	X			
nab-Paclitaxel			X	X	X			
Research biopsy	X[3]		X[4]			X[5]		
AE assessment	Continuously while on treatment and for 30 days after the last day of treatment.							

1. Women of childbearing potential only
2. Echocardiogram preferred; prior approval from PI or designee required for MUGA
3. Baseline biopsy is mandatory. Biopsy to be collected after patient is deemed eligible but before the start of treatment. If a patient needs a standard of care (SOC) biopsy for pathology purposes, the three cores of research specimen can be collected during the SOC biopsy/procedure prior to confirmation of eligibility.
4. For patients in the de-escalation group only. Must be done at the conclusion of the lead-in period before the first doses of gemcitabine and nab-paclitaxel. Patient must not have missed any of the three BVD-523 doses preceding their biopsy.
5. End of Cycle 2 only. Expansion cohort patients only. Tissue will be collected if deemed safe and feasible per PI discretion.
6. Patients in the de-escalation group will take BVD-523 as directed for 2 weeks before beginning gemcitabine and nab-paclitaxel. There is a window of +/- 3 days to allow for BVD-523 dosing holds. Further extensions of lead-in period at PI discretion.
7. Monthly for 2 years following the end of treatment
8. Cycle 1 only
9. Optional

11.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Registration Form Eligibility Form On-Study Form	Prior to starting treatment
Treatment Form	Every cycle
Toxicity Form	Continuous
Treatment Summary Form	Completion of treatment
Follow Up Form	Monthly for 2 years after end of treatment
Tumor Measurement Form	Baseline, end of every even numbered cycles, and end of treatment
Biopsy Form	Prior to starting treatment End of lead-in (for de-escalation patients only) End of Cycle 2 (expansion cohort)
MedWatch Form	See Section 7.0 for reporting requirements

12.0 MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice

thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.3 Methods 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 and never more than 4 weeks before the beginning of the treatment.

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 unless the lesion(s) being

followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). 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: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

12.4 Response Criteria

12.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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

12.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

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

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

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.4.3 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR

Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

12.4.4 Duration of Response

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

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

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

12.4.5 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12.4.6 Response Review

It is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

During the phase I dose de-escalation, the Principal Investigator will review all patient data at least monthly (or before each dose-escalation if occurring sooner than monthly), and provide a semi-annual report to the Quality Assurance and Safety Monitoring Committee (QASMC). During the dose expansion, the Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities separated by cohorts with the number of dose-limiting toxicities indicated
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

14.0 STATISTICAL CONSIDERATIONS

This is a Phase Ib study using BVD-523 plus nab-paclitaxel and gemcitabine in patients with metastatic pancreatic cancer. It includes two phases- dose de-escalation part and expansion part at the RP2D.

14.1 Study Endpoints

The primary endpoint is the MTD or RP2D of BVD-523 in combination with nab-paclitaxel and gemcitabine using dose de-escalation cohort. The secondary endpoints include the safety and toxicity profile, biochemical response (BR), response rate (RR), time to tumor progression, progression free survival (PFS) and overall survival (OS) of BVD-523 in combination with nab-paclitaxel and gemcitabine. The exploratory endpoints are pharmacodynamics biomarkers of BVD-523, as well as, the association between biomarkers and genetic alterations with treatment response.

14.2 Sample Size Estimates

For the dose de-escalation phase, a modified Fibonacci design with three dose levels of BVD-523 (600 mg, 450 mg, and 300 mg), will be used, so 6 to 18 patients will be needed. For the expansion cohort, a total of 25 patients will be treated at RP2D, providing a reasonable precision for the estimate of the preliminary efficacy data, according to the extensive simulation study regarding the ideal sample size for pilot study.

14.3 Accrual

The rate of accrual for the study is expected to be about 2-3 patient per month. It is estimated the study is expected to complete within two years.

14.4 Toxicity Monitoring

A modified Fibonacci design will be used for the dose de-escalation phase, starting with a cohort of 6 patients at the target dose combination level. If 0 or 1 out of 6 patients experiences DLT at this level, it will be used for the expansion cohort portion. If 2 DLTs are observed, the dosing of BVD-523 will de-escalate with a new cohort of 6 patients. The maximal number of patients needed for this part is 18 and the minimal number of patients is 6. After the determination of MTD, the remaining patients (total N=25) will be enrolled to the expansion cohort. In light of a lead-in study, to ensure the adequate assessment of toxicity and safety, the study has a stopping rule in the expansion cohort. If two or more of the first 6 patients in the expansion cohort experience a DLT, then the study PI will consult with other study team members for the possibility of exploring the next lower dose level.

14.5 Statistical Analysis

A complete listing of adverse events will also be tabulated, including severity, relationship to treatment, onset, duration, and outcome. Laboratory data measured on a continuous scale

will be characterized by summary statistics (mean and standard deviation). For those patients treated at dose-level of MTD or above, the biochemical response (BR) is defined as more than 50% of decrease from baseline CA 19-9 and response rate (RR) is assessed according to the RECIST 1.1. BR and RR between BVD-523 combination will be summarized using contingency table and compared by the Fisher's Exact test. Time to tumor progression is defined as the days from registration to time of progressive disease. OS is defined as the days from the date of treatment start and death from any cause. Patients alive or lost to follow-up are censored. PFS is defined as the days from the date of treatment and death or progression, which occurs first. Patients alive without progression or lost to follow-up are censored. The differences in time to tumor progression, PFS and OS for BVD-523 combination will be performed using Kaplan-Meier curves and compared by log-rank tests. In the correlative studies, biopsies will be obtained prior to the start of treatment, 2 weeks after the administration of single agent BVD-523 (for dose de-escalation patients only), and at the end of the second cycle of therapy (expansion cohort only). Three cores will be collected at each time point. A panel of biomarkers (pERK, pMEK, pRSK, p4EBP1, pS6 et al) will be evaluated to determine the effect of ERK pathway inhibition by BVD-523 on the paired biopsies collected in the dose de-escalation cohort. Other biomarkers may be evaluated as appropriate. The change in exploratory endpoints between pre- and post-treatment biopsies will be summarized by descriptive statistics, such as means and standard deviation (SD) or frequencies, as appropriate. Their association with the clinical response will also be explored by a permutation analysis. Taking the relationship between pERK and the clinical response as an example, we will first compute the observed test statistics, such as the sample mean difference between responders versus non-responders. Next, we will simulate the null distribution of test statistics by randomly shuffling the response status. This will be repeated 10,000 times to obtain the distribution of the observed mean differences if there was truly no difference. The permutation p-value will equal the proportion of simulations that exceeds the observed test statistics from the null distribution.

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APPENDIX A: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: NON-PERMITTED CONCOMITANT MEDICATIONS

CYP3A4 Inhibitors
Indinavir
Nelfinavir
Ritonavir
Atazanavir
Clarithromycin
Itraconazole
Ketoconazole
Voriconazole
Nefazodone
Saquinavir
Telithromycin

CYP2D6 Inhibitors
Bupropion
Cinacalcet
Fluoxetine
Paroxetine
Quinidine

CYP1A2 Inhibitors
Fluvoxamine
Ciprofloxacin

CYP3A4 Inducers
Carbamazepine
Phenobarbital
Phenytoin
Rifabutin
Rifampin
Rifapentine

APPENDIX C: PATIENT'S MEDICATION DIARY

Today's Date: _____ Agent: ulixertinib Cycle: _____

Patient Name: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month. Take _____mg (___capsules) of ulixertinib twice daily, one hour before or two hours after a meal at approximately the same times each day. Take it with a glass of water and drink the glass of water in as little time as possible. Swallow the capsules whole and do not chew the capsules.
2. Record the date, the number of capsules taken, and when you took them.
3. If you forget to take your ulixertinib, then do not take that dose. Restart it with the next dose.
4. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
5. Please return the forms to your physician or your study coordinator when you go to your next appointment. Please bring your unused study medications and/or empty bottles with you to each clinic visit so that a pill count can be done.

Day	Date	What time was dose taken?		# of capsules taken		Comments
		AM dose	PM dose	AM dose	PM dose	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
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APPENDIX D: BIOMED VALLEY SAE FORM

BIOMED VALLEY
DISCOVERIES

SERIOUS ADVERSE EVENT REPORT FORM

Initial: ☐
Follow-up: ☐ #__

1. GENERAL INFORMATION		
Study Name:	Country:	Site ID:

2. SUBJECT INFORMATION			
Subject Initials (if applicable):	Subject number:	Year of Birth:	RACE: ☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Hispanic or Latino ☐ Caucasian ☐ Native Hawaiian or Other Pacific Islander ☐ Other:
Sex: Male ☐ Female ☐	Weight: ☐kgs *or* ☐lbs	Height: ☐cms *or* ☐inches	

3. SAE INFORMATION

Serious Adverse Event (a single event per form):

DATE OF ONSET __ __ / __ __ __ / __ __ __ __ (DD MMM YYYY) DATE OF RESOLUTION: __ __ / __ __ __ / __ __ __ __ (DD MMM YYYY)

TIME OF ONSET: __ __ : __ __ (HH:MM) TIME OF RESOLUTION: (If less than 24 hrs duration) __ __ : __ __ (HH:MM)

RELATIONSHIP:
☐ Related ☐ Possibly Related ☐ Unrelated

RELATIONSHIP TO UNDERLYING DISEASE:
☐ Related ☐ Possibly Related ☐ Unrelated ☐ Unknown

SERIOUSNESS: (check all that apply)
- ☐ Death
- ☐ Life threatening
- ☐ Disability
- ☐ Hospitalized
- ☐ Prolonged existing hospitalization
- ☐ Congenital anomaly or birth defect
- ☐ Other medically significant

INTENSITY: (check one only)
- ☐ Mild (Grade1)
- ☐ Moderate (Grade 2)
- ☐ Severe (Grade 3)
- ☐ Life-threatening (Grade 4)
- ☐ Death (Grade 5)

OUTCOME: (check one only)
- ☐ Death
- ☐ Ongoing
- ☐ Resolved
- ☐ Resolved with Sequelae
- ☐ Unknown/Lost to Follow-up

ANY TREATMENT REQUIRED?
☐ None ☐ Concomitant Medications ☐ Non-Drug therapies
☐ Concomitant Medications and Non-Drug Therapies

WAS THE EVENT(s) CONSIDERED A DLT?
☐ YES ☐ NO

A. Death Details		B. Hospitalization Details	
DATE OF DEATH	_ _/_ _ _/_ _ _ _ DD MMM YYYY	ADMISSION DATE	_ _/_ _ _/_ _ _ _ DD MMM YYYY
Autopsy Performed? ☐ Yes ☐ No Autopsy results available? ☐ Yes ☐ No *If Yes, please attach copy of autopsy report*		DISCHARGE DATE	_ _/_ _ _/_ _ _ _ DD MMM YYYY
Primary cause of death (specify):			

4. STUDY MEDICATION

Study Medication Name:		Indication:	
Blinded: ☐ Yes ☐ No		Dose:	Units:
Date and time of start	_ _/_ _ _/_ _ _ _ DD MMM YYYY _ _:_ _ HH:MM	Dosing Schedule: ☐ AM ☐ PM	
		Route:	
Last dose before the SAE:	_ _/_ _ _/_ _ _ _ DD MMM YYYY _ _:_ _ HH:MM	Lot No.	

5. ACTION TAKEN WITH STUDY MEDICATION

☐ None ☐ Discontinued ☐ Interrupted ☐ Other: _	DATE OF DISCONTINUATION _ _/_ _ _/_ _ _ _ DD MMM YYYY
WAS STUDY MEDICATION RE-ADMINISTERED? ☐ YES ☐ NO	DATE OF RE-ADMINISTRATION _ _/_ _ _/_ _ _ _ DD MMM YYYY
DID EVENT REAPPEAR AFTER STUDY MEDICATION RE-ADMINISTRATION?? ☐ YES ☐ NO	

6. EVENT DESCRIPTION

Briefly describe the sequence of the Serious Adverse Event (DIAGNOSIS PREFERRED) and/or signs and symptoms, onset date(s), dates of treatment therapies with subject's response and outcome. *Attach hospital discharge summary, if available.*

7. RELEVANT PROCEDURES OR LABS TO CONFIRM SAE

Briefly describe the relevant procedures and/or tests/laboratory data that confirm the SAE:

8. RELEVANT CONCURRENT MEDICATIONS
Briefly provide all relevant concurrent medications that the subject was receiving at the time of SAE:

9. RELEVANT MEDICAL HISTORY
Briefly describe any medical history that may be relevant for the SAE:

10. REPORTER INFORMATION	
Form completed by:	Contact phone:
Job title:	Reporter's signature:
Principal Investigator:	Contact phone:
Date of this report	Investigator's signature:

APPENDIX E: BIOMED VALLEY PREGNANCY REPORT FORM

BIOMED VALLEY DISCOVERIES

PREGNANCY REPORT FORM
Protocol #:

Page 1 of 3

SUBJECT ID #:	
SUBJECT INITIALS:	☐ N/A
Please check type of report: ☐ **Initial** ☐ **Follow-up**	**Date of this Report:** _____/_____/_____ DD MMM YYYY
Principal Investigator Name: (print)_____	

SUBJECT PARTICIPANT INFORMATION

Subject Date of Birth	Subject Gender	Subject Weight	Subject Height
_____/_____/_____ DD MMM YYYY	☐ Female ☐ Male (significant other pregnant)	____.___ ☐ kg ☐ lb	____.___ ☐ cm ☐ in

Race: ☐ White ☐ Black ☐ Asian ☐ American Indian/Alaskan Native ☐ Native Hawaiian or Other Pacific Islander ☐ Other: _____

PREGNANCY DETAILS

Pregnancy Confirmation Method	☐ **Serum βhCG** ☐ **Urine βhCG**	Confirmation results attached: ☐
Date Pregnancy Confirmed	_____/_____/_____ DD MMM YYYY	**Clinical Condition of Fetus**: ☐ Normal ☐ Unknown ☐ Abnormal (please explain): _____
First Day of Last Menstrual Period	_____/_____/_____ DD MMM YYYY	
Expected Delivery Date	_____/_____/_____ DD MMM YYYY	
Obstetric History	**Pregnancy History**: Gravida (total # pregnancies): ____ Para (birth of viable children): ____ Please describe outcomes other than viable birth (s): ☐ Induced abortion #____ ☐ Spontaneous abortion #____ Premature(<37wks)#:___ ☐ Malformation (please explain):_____ ☐ Congenital Anomalies (please explain):_____	
Contraception Used (Check all that apply)	☐ OC Pills: Type_____ ☐ IUD Type _____ ☐ Patch Type_____ ☐ Condom ☐ Diaphragm ☐ Other_____ ☐ None ☐ Unknown Appropriate use of method (s)? ☐ Yes ☐ No (specify): _____	
Risk Factors	☐ Alcohol Consumption[amount]_____ (circle) Maternal/Paternal ☐ Drug Abuse [amount]_____ (circle) Maternal/Paternal ☐ Smoking [amount]_____ppd (circle) Maternal/Paternal ☐ Diabetes (circle) Maternal/Paternal ☐ Radiation Exposure (ie: x-rays, etc.) _____(circle) Maternal/Paternal ☐ Other: _____ (circle) Maternal/Paternal ☐ Unknown ☐ None	

FAX REPORT TO XXX-XXX-XXXX

SUBJECT ID #:	☐☐☐☐☐☐☐☐☐☐
SUBJECT INITIALS:	☐☐☐ ☐ N/A

INVESTIGATONAL PRODUCT

Study Drug Start Date	____/____/____ DD MMM YYYY	**Last Dose Study Drug Prior to pregnancy awareness**	____/____/____ DD MMM YYYY
Relation of Pregnancy to Study Drug ☐ **Related** ☐ **Not Related**		**If study Participant is Male:** Study Drug Stop Date: ____/____/____ DD MM YYYY or ☐ **Ongoing**	

PREGNANCY OUTCOME

Date of Delivery	____/____/____ DD MMM YYYY
Outcome	☐ Full Term (37+ wks) ☐ Premature Birth **Gestational Age**: _____wks ☐ Neonatal death (20+ wks) ☐ Spontaneous Abortion **Gestational Age**: _____wks ☐ Elective Termination **Gestational Age**: _____wks Was Termination for a medical reason? ☐ Yes ☐ No If yes, please specify: _____
Method of Delivery	☐ Normal Vaginal ☐ Caesarean Section ☐ Forceps ☐ Vacuum ☐ Other: _____
Presentation	☐ Cephalic ☐ Breech ☐ Other (please explain): _____
	**For Multiple Births greater than 2 infants, please fill in an additional form
Multiple Birth	☐ No ☐ Yes
Baby 1	☐ Male ☐ Female **Length:**_____ ☐ cm ☐ in **Weight**: _____ ☐ kg ☐ lb **Apgar Score** At 1 minute _____ At 5 minutes _____ At 10 minutes _____ Unknown ☐
Details of Delivery (Baby 1)	☐ Healthy Baby ☐ Congenital Anomaly/Birth Defect ☐ Neonatal problem (ie: birth trauma, infection, etc): ☐ Stillbirth/Neonatal Death
Baby 2 ☐ **N/A**	☐ Male ☐ Female **Length:**_____ ☐ cm ☐ in **Weight**: _____ ☐ kg ☐ lb **Apgar Score** At 1 minute _____ At 5 minutes _____ At 10 minutes _____ Unknown ☐
Details of Delivery (Baby 2)	☐ Healthy Baby ☐ Congenital Anomaly/Birth Defect ☐ Neonatal problem (ie: birth trauma, infection, etc): ☐ Stillbirth/Neonatal Death

FAX REPORT TO XXX-XXX-XXXX

BIOMED VALLEY DISCOVERIES

PREGNANCY REPORT FORM
Protocol #:

SUBJECT ID #:	
SUBJECT INITIALS:	☐ N/A

STUDY PARTICIPANT CONCOMITANT MEDICATIONS ☐ **N/A (if submitting Concomitant Medication CRF)**
Medications administered within 30 days prior to pregnancy. ☐ **None reported**

Medication / Therapy *(Generic name)*	Indication	Dose/Unit	Route	Frequency	Start Date (dd-mmm-yyyy)	Continuing	Stop Date (dd-mmm-yyyy)

STUDY PARTICIPANT RELEVANT MEDICAL/SURGICAL HISTORY
☐ **N/A (if submitting Medical History CRF)** ☐ **None reported**

NARRATIVE/COMMENTS
Provide a brief description of the course of events, including any treatments or relevant procedures (eg ultrasound, amniocentesis etc).

INVESTIGATOR SIGNATURE
All of the information entered on this Pregnancy Report is accurate to the best of my knowledge

Reviewing Investigator Name (print):		
Investigator Signature:		**Date:**
Name of Person Preparing Report:		**Title:**
Phone Number:		**Fax Number:**

FAX REPORT TO XXX-XXX-XXXX