

**SCHEMA
(STUDY SYNOPSIS)**

**A Phase II Study of Gemcitabine and nab-Paclitaxel in Combination with
Vismodegib (GDC-0449; Hedgehog Pathway Inhibitor) in Patients with
Previously Untreated Metastatic Adenocarcinoma of the Pancreas**

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Key Principal Investigator: Daniel Laheru, M.D.

(Johns Hopkins)

The Sidney Kimmel Comprehensive Cancer Center
at Johns Hopkins
Bunting Blaustein Cancer Research Building
1650 Orleans Street, 4M09
Baltimore MD 21231-1000
(410) 955-8974
laherda@jhmi.edu

**Co-Principal Investigator:
(Johns Hopkins)**

Ana De Jesus-Acosta MD
The Sidney Kimmel Comprehensive Cancer Center
at Johns Hopkins
Bunting Blaustein Cancer Research Building
1650 Orleans Street, 4M08
Baltimore MD 21231-1000
adejesu1@jhmi.edu

Principal Investigators:

Ramesh K. Ramanathan, MD
Peter O'Dwyer MD

**Co-Investigators:
(Johns Hopkins)**

Anirban Maitra, MD
Ross Donehower, MD
Luis Diaz, MD
Dung Thi Le, MD
David Cosgrove, MBBCh
Nilofer S Azad, MD
Lei Zheng, MD PhD
Marcia Irene Canto, MD
Eun Shin, MD
Zeshaan Rasheed, MD
Pamela Johnson, MD
Emily Petito, CRNP
Keith McIntyre, CRNP
Atif Zaheer, MD
Ilene Browner, MD

Study Coordinating Center: Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Study Center (s): Translational Genomics Research Institute, Scottsdale AZ
University of Pennsylvania, PA

Statistician:

Elizabeth Sugar
 615 North Wolfe St, W5010
 Baltimore, MD 21205
 410-502-3913
 Fax: 410-502-4621
 esugar@jhsp.edu

Study Coordinator:

Yvette Cetasaan, CCRP
 550 North Broadway, Suite 415
 Baltimore, MD 21205
 410-955-4035
 Fax: 443-287-6566
 freemyv@jhmi.edu

Responsible Research Nurse:

Rosalind Walker
 550 North Broadway, Suite 415
 Baltimore, MD 21205
 410-955-9628
 Fax: 443-287-6566
 Rwalker3@jhmi.edu

Responsible Data Manager:

Yvette Cetasaan, CCRP
 550 North Broadway, Suite 415
 Baltimore, MD 21205
 410-955-4035
 Fax: 443-287-6566
 freemyv@jhmi.edu

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Study Phase: Phase II

Patient Population: Patients with untreated metastatic pancreatic adenocarcinoma

Concept and Rationale

Pancreatic cancer is one of the most dismal malignancies in the gastrointestinal tract and remains the fourth leading cause of cancer related mortality. The majority of patients with pancreatic adenocarcinoma have evidence of metastatic disease at presentation with a median survival of 6 months. New therapies are urgently needed.

The Hedgehog (Hh) signaling pathway is persistently activated in several malignancies including pancreatic cancer leading to activation and nuclear localization of GLI1 transcription factors, with subsequent induction of Hh target genes, many of which are involved in proliferation, survival and angiogenesis. The Hh signaling pathway also plays a role in maintaining subpopulations of cancer stem cells (CSC) in pancreatic cancer. Based on previous preclinical studies, pancreatic CSC comprise 0.2-0.8% of all pancreatic cancer cells, are highly tumorigenic and possessed the ability of self-renew and produce a differentiated progeny. These CSC can elicit tumor progression and metastases and confer potential resistance to available therapeutic approaches including chemotherapy and radiation.

In preclinical studies pharmacologic blockade of the Hh signaling pathway using Hh inhibitors decreased tumor proliferation, increased survival in animal models and decreased CSC markers in primary and metastatic tumors. Inhibition of the Hh signaling pathway in pancreatic cancer may provide a therapeutic strategy by treating the primary tumor, systemic metastases and targeting CSC by Hh pathway inhibition. Other postulated mechanisms for clinical benefit using Hh inhibitors in pancreatic cancer include modulation of surrounding stroma and increased drug delivery of cytotoxic agents into tumor tissue.

In a phase I study in patients with advance solid tumors GDC-0449 was well tolerated with no dose limiting-toxicities. We hypothesize that the combination of GDC-0449 with chemotherapy (gemcitabine and nab-paclitaxel) will provide clinical benefit as measured by progression free survival in patients with metastatic previously untreated pancreatic adenocarcinoma.

Primary Objective (s)

- To evaluate whether the addition of a vismodegib (GDC-0449; Hedgehog Pathway Inhibitor) to cytotoxic chemotherapy (Gemcitabine and nab-paclitaxel) in patients with metastatic adenocarcinoma of the pancreas increases progression free survival (PFS).

Secondary Objectives (s)

- To evaluate overall survival
- To evaluate for tumor response (complete response, partial response), stable disease and progressive disease
- To evaluate the safety of the combination gemcitabine + nab-paclitaxel with GDC-0449 in patients with metastatic adenocarcinoma of the pancreas

- To evaluate the presence of pancreatic CSC in tissue and peripheral blood and its changes with therapy using above combination
- To evaluate changes of Hh signaling pathway using GDC-0449
- To evaluate if serum and/ or tumor biomarkers predict clinical benefit with GDC-0449

Primary Endpoints(s)

- PFS as defined by the time from first therapy received to the earlier documented disease progression or death from any cause. PFS will be determined by the investigator. Imaging studies to assess response will be evaluated by expert radiologists using RECIST 1.1 criteria.

Secondary Endpoint(s)

Efficacy endpoints

- Overall survival from the time of cycle 1, day 1 until death from any cause
- Objective tumor response (partial response, complete response) or stable disease based on CT scans (or MRI scans if patient is allergic to contrast agent or has some other contraindication to a CT scan). These will be evaluated according to RECIST 1.1 criteria.

Safety endpoints

- Number of grade 3 and 4 toxicities according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE; Version 4.0) that occur after Cycle 1, day 1
- Incidence, nature and severity of all adverse events that occur on or after Cycle 1, Day 1

Correlative studies endpoints

- Quantitative pancreatic CSC identification using functional assays and phenotypic assays. Functional assays include immunohistochemistry or RT-PCR for ALDH bright cells. Phenotypic assays include immunohistochemistry, quantitative RT-PCR or flow cytometry for pancreatic cancer stem cell markers (CD24+/CD44+/ESA+ and CD133+) in tissue biopsy and peripheral blood.
- Semi-quantitative measurement of Hh ligand expressions in pre-post treatment biopsies and Hh signaling pathway downregulation as measured by Gli 1 and Patch
- Biomarker changes as measured by serum CA19-9 and plasma and tumor SPARC

Study Design:

This is an open-label, single arm, multi-center, Phase II trial to evaluate progression free survival in patients with metastatic adenocarcinoma of the pancreas treated with a Hh inhibitor and chemotherapy. This trial will also assess for objective tumor response and evaluate changes in pancreatic CSC markers and Hh signaling pathway inhibition using the Vismodegib (GDC-0449; hedgehog pathway inhibitor) in combination with chemotherapy (gemcitabine and nab-paclitaxel). Following the determination of eligibility patients will receive the following treatment:

1. One cycle of Gemcitabine 1000 mg/m² and nab-Paclitaxel 125 mg/m² on days 1, 8, and 15 (28 days cycle) then
2. Gemcitabine 1000 mg/m² and nab-Paclitaxel 125 mg/m² on days 1, 8, and 15 every 28 days cycle in combination with oral GDC-0449 150 mg daily

Number of Patients: 72 patients

Duration of Intervention and Evaluation

Patients may continue on treatment regimen until they experience progressive disease or unacceptable toxicity, require palliative radiotherapy, withdraw consent or the physician feels it is no longer in their best interest to continue on treatment. If a patient is removed from treatment he/she will be followed to gather information of overall survival. If an individual is lost to follow-up, then they will be censored at the time of the last contact.

Statistical Methods

The patient demographics will be described using summary statistics (mean, S.D., median, range, count, percentage). Kaplan-Meier techniques will be used to summarize time to event outcomes (progression free survival and overall survival) graphically and to estimate the median and one-year survival outcomes with 80% confidence intervals. The percent change from the pre to the post-treatment biopsies will be calculated for the correlative outcomes. The outcomes will be summarized using means, standard deviations, medians and ranges.

The study is power to determine whether the addition of GDC-0449 provides benefit over chemotherapy alone (gemcitabine and nab-paclitaxel). The primary outcome is progression free survival. In previous trial using chemotherapy with gemcitabine and nab-paclitaxel, the median progression free survival was 5.5 months. We have powered our study with the assumption of 24 months accrual. Based upon these assumptions, a sample size of 72 patients will have an 80% power to detect an increase in the median progression free survival to 7.15 months from the null rate of 5.5 months using a one sided type 1 error of 0.10. Up to an additional 10% will be accrued in order to control for loss to follow-up. The expected accrual rate is between 4-5 patients per month.

Funding, Regulatory, and Feasibility Issues: Genentech will provide GDC-0449. Abraxis will provide nab-paclitaxel. Gemcitabine will be obtained by commercial means.

Patient Acceptability/Ethics and Concepts Issues: None

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
ALDH	Aldehyde dehydrogenase
ALT (SGPT)	Alanine Aminotransferase (SGPT)
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST (SGOT)	Aspartate Aminotransferase (SGOT)
β-hCG	Beta subunit of human chorionic gonadotropin (hCG)
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CA19-9	Carbohydrate Antigen 19-9
CBC	Complete Blood Count
CI	Confidence Interval
CrEL	Cremophor-EL
CRAB	Cancer Research and Biostatistics
CR	Complete Response
CRO	Clinical Research Organization
CSC	Cancer Stem Cells
CT	Computed Tomography
CTC	Circulating Tumor Cells
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOS	End of Study
FDA	Food and Drug Administration
G-CSF	Granulocyte Colony-Stimulating Factor
Hh	Hedgehog
Hgb	Hemoglobin
IB	Investigator Brochure
ICF	Informed Consent Form
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous(ly)
MRI	Magnetic Resonance Imaging

MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NIH	National Institutes of Health
NCI CTCAE	National Cancer Institute Common Terminology Criteria of Adverse Effects
PD	Progressive Disease
PE	Paraffin Embedded
PFS	Progression-free Survival
PK	Pharmacokinetics
PR	Partial Response
PT	Prothrombin Time
PTCH	Patched
PTT	Partial Thromboplastin Time
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
S.D.	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SKCCC	Sidney Kimmel Comprehensive Cancer Center
SMO	Smoothened
SPARC	Secreted Protein Acidic and Rich in Cysteine (a glycoprotein)
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell

1. OBJECTIVES

1.1. Primary Objectives

- To evaluate whether the addition of a **Vismodegib (GDC-0449; Hedgehog Pathway Inhibitor)** to cytotoxic chemotherapy (Gemcitabine and nab-paclitaxel) in patients with metastatic adenocarcinoma of the pancreas increases progression free survival (PFS).

1.2. Secondary Objectives

- To evaluate overall survival
- To evaluate for tumor response (complete response, partial response), stable disease and progressive disease
- To evaluate the safety of the combination gemcitabine + nab-paclitaxel with GDC-0449 in patients with metastatic adenocarcinoma of the pancreas
- To evaluate the presence of pancreatic cancer stem cells in tissue and peripheral blood and its changes with therapy with above combination
- To evaluate changes of hedgehog signaling pathway with therapy with GDC-0449
- To evaluate if serum and/ or tumor biomarkers predict clinical benefit with GDC-0449

2. BACKGROUND

2.1 Study Disease

Pancreatic cancer continues to be one of the most dismal malignancies in the gastrointestinal tract and remains the fourth leading cause of cancer related mortality. In the United States an estimated total of 42,470 pancreatic cancers are expected in the year 2009 with 35, 240 estimated deaths among these patients[1]. The majority of patients with pancreatic adenocarcinoma have evidence of metastatic disease at presentation with a median survival of 6 months [2]. More recent strategies have focused on improving the efficacy of Gemcitabine by either improving the method of delivery or by combining Gemcitabine with other non-cross resistant agents. However, the clinical benefits, response rates, and the duration of responses have been modest.

The most recent advance for the management of this disease was achieved with the combination of gemcitabine and nab-paclitaxel. The phase I/ II study with this combination was presented at the American Society of Clinical Oncology (ASCO) 2009 annual meeting and demonstrated promising results with improvement of response rate and overall survival [3]. Given these findings a phase III trial with that particular combination is under way. Novel therapeutic approaches and a better understanding of disease's biology for tumor driven disease progression are needed.

Hedgehog Signaling pathway in pancreatic cancer

The Hedgehog (Hh) signaling pathway regulates epithelial and mesenchymal interactions in a variety of tissues during mammalian embryogenesis[4]. The Hh ligand in the extracellular space binds to Patched (PTCH), a 12 pass transmembrane receptor on the surface of cells. Hh binding relieves the inhibitory effect of PTCH on Smoothed (SMO), a 7 pass transmembrane domain protein and a member of the G-protein coupled receptor superfamily. Signal transduction by SMO then leads to the activation and nuclear localization of GLI1 transcription factors and induction of Hh target genes, many of which are involved in proliferation, survival and angiogenesis in different malignancies.

Investigations suggest that the Hh signaling pathway is persistently activated in several malignancies including pancreatic adenocarcinoma [5], [6]. Berman and colleagues demonstrated that upper gastrointestinal malignancies derived from the esophagus, biliary tract, stomach, and pancreas display increased Hh pathway activity. Cell growth was mediated by endogenous expression of Hh ligands through demonstration of the growth inhibitory activity of Hh-neutralizing antibody and the growth stimulatory activity of exogenously added Hh ligand [6]. Hh pathway activation is mediated either through aberrant ligand overexpression by pancreatic cancer cells [5], aberrant activation of Hh signaling pathway in the surrounding stromal compartment through a paracrine model [7-9] or alternative proposed mechanism through silencing of the pathway inhibitor human Hh interacting protein by promoter hypermethylation [10]. The Hh signaling promotes epithelial-mesenchymal transition and increases motility and invasiveness of pancreatic cancer cells. Several genes have been identified as potential hedgehog downstream targets in the setting of pancreatic cancer including BIRC3, TGM2, PLAU, and BMP2 and these genes have been previously found to be mechanistically involved in tumor cell proliferation, invasion/migration, and metastatic tumor spread [11].

Relation with pancreatic cancer stem cells

More recent interest has emerged with the identification of cancer stem cells (CSC) and it is believed that these cells can elicit tumor progression and metastases. In pancreatic cancer two different subset of CSC have been identified. First Li et al identified CD24+/CD44+/ESA+ cells [12]. These cells composed 0.2-0.8% of all pancreatic cancer cells, were highly tumorigenic and possessed the ability of self-renew and produce a differentiated progeny. More recently, Hermann and colleagues identified a subset of CD133+ cells and found that this marker also discriminates for cells in pancreatic cancer and pancreatic cell lines with enhanced proliferative capacity [13].

The clinical significance of pancreatic CSC is related to resistance to available therapeutic approaches. In other malignancies including chronic myeloid leukemia, brain tumors, and colon cancer, stem cells have been found to be resistant to conventional chemotherapy and radiation. In pancreatic cancer some evidence suggests resistance of pancreatic CSC to chemotherapy and radiation in cell lines. Hermann and colleagues found that CD133+ populations in the L3.6 pancreatic cancer cell line were enriched after exposure to gemcitabine. Treatment with ionizing radiation and the chemotherapeutic agent gemcitabine resulted in enrichment of the CD44+CD24+ESA+ population in human pancreatic cancer xenografts. These findings indicate that novel therapies that target CSC may be crucial for successful anti-cancer therapy. One approach to

do so is by identifying signaling pathways that may sustain such stem cells and developing targeted therapies against it.

The hedgehog signaling pathway plays a role in maintaining subpopulations of cancer cells with increased tumorigenic potential [12, 14]. Several points suggest an element of hedgehog dependence in a subset of pancreatic cancer cells with tumor-initiating properties. First Sonic Hedgehog ligand (SHH) might be specifically overexpressed in a subpopulation of CD24+/CD44+/ESA+ pancreatic cancer cells with increased tumorigenic potential and other stem cell-like properties [12]. Second, overexpression of Gli1, the major activating hedgehog transcription factor, is observed at the mRNA level in a subset of SSC-low /aldehyde dehydrogenase (ALDH)-“bright” cells with increased clonogenic potential [12].

Pharmacologic blockade of Hh in pancreatic cancer

Several small molecules with capacity of Hh pathway inhibition have been studied in the preclinical setting.

Studies with Cyclopamine: Cyclopamine is a steroidal alkaloid that inhibits Hh signaling through direct interaction with SMOH. *In vitro* Hh blockade with cyclopamine in pancreatic cancer cell lines led to tumor growth inhibition [11]. *In vivo*, cyclopamine retarded the growth of s.c. pancreatic cancer xenografts [5, 6], prolonged the median survival of transgenic mouse models, [11], and prevented metastatic tumor spread using murine orthotopic xenograft models of human pancreatic cancer [14]. Cyclopamine caused downregulation of the Hh target genes Gli1 and Ptch in genetically engineered mouse models of pancreatic cancer [11].

Studies with IPI-269609: Feldman and colleagues tested IPI-269609, another inhibitor of the Hh pathway, using *in vitro* and *in vivo* model systems. Single agent IPI inhibited systemic metastases in orthotopic xenografts established from human pancreatic cell lines. Hh blockade had minimal effect on primary tumor volume, but the phenotype observed within the treated primary tumor showed a reduction in the population of aldehyde dehydrogenase-bright cells (which has been previously identified as clonogenic tumor-initiating population in pancreatic cancer). Selective ex-vivo depletion of aldehyde dehydrogenase-bright cells with IPI-269609 was accompanied by significant reduction in tumor engraftment rates in athymic mice. Their data suggested that pharmacologic blockade of aberrant Hh signaling might be an effective strategy for inhibition of systemic metastases in pancreatic cancer by targeting subsets of cancer cells with tumor-initiating, or CSC properties[15].

Studies with GDC-0449: GDC-0449 is a small-molecule antagonist of the Hh signaling pathway that binds to and inhibits SMO, blocking Hh signal transduction. *In vitro* and *in vivo* preclinical studies have demonstrated inhibition of Hh signaling following GDC-0449 administration. GDC-0449 has demonstrated anti-tumor activity against a variety of primary human tumor xenografts and tumor cell line xenograft models (Investigator Brochure). These include CRC, in which activity was seen both as a single agent and in combination with cytotoxic agents, as well as in primary xenograft models of pancreatic carcinoma. In murine models, the anti-tumor effect of GDC-0449 correlates with blockade of the Hh pathway measured by reduction in the expression of stromal *Gli1* mRNA, which is itself a transcriptional target of Hh signaling. Specifically, sustained reduction of *Gli1*

expression is associated with inhibition of tumor growth. Nonclinical efficacy studies suggest that sustained inhibition of Hh signaling is necessary to achieve an anti-tumor effect. For this reason, regimens of continuous dosing over 28 days are being examined. In a phase I studies, in patients with advance solid tumors, GDC-0449 was well tolerated with no dose limiting-toxicities. The recommended Phase II dose is 150 mg by oral administration on a continuous daily schedule[16] [17]. Phase II studies using GDC-0449 150 mg orally once daily on a continuous schedule are ongoing in first-line metastatic CRC, recurrent ovarian cancer, and advanced BCC.

Pharmacologic blockade of Cancer Stem Cells: Jimeno et al used a direct pancreatic cancer xenograft model as a platform for CSC therapeutic development. Tumors from a gemcitabine-sensitive xenograft were treated with gemcitabine induction first, and randomized, after tumor regression to continuing treatment with gemcitabine, a Hh inhibitor alone (cyclopamine) or in combination with gemcitabine. They tested markers described in association with CSC such as CD24, CD44, ALDH, nestin and the hedgehog pathway. After induction with gemcitabine, treated tumor showed enrichment in CSC markers such as ALDH and CD24. Subsequently, combined treatment with gemcitabine and Hh inhibitor (cyclopamine) induced further tumor regression, decreased CSC markers and Hh signaling. Hh inhibitors as part of a dual compartment therapeutic approach were able to further reduce tumor growth and decreased both static and dynamic markers of CSC[18].

Other proposed mechanisms for Hh inhibitors in pancreatic cancer

In addition to the CSC theory, other mechanisms for potential clinical benefit using Hh inhibitors in the setting of pancreatic cancer have been described. The Hh signaling pathway is active in a paracrine model in which the tumor cells secrete Hh ligand to induce tumor-promoting Hh target genes in adjacent stroma [7-9]. Olive and colleagues found that IPI-926, a small molecule inhibitor of SMO, can be a strategy to enhance drug delivery and overcome the well-known chemoresistance of pancreatic cancer if combined with gemcitabine in genetically engineered models of pancreatic cancer. IPI-926 targets the Hh pathway in the stroma of malignant tumors reducing the fibrotic reaction that occurs with pancreatic cancer. IPI-926 was able to increase the intratumoral vascular density and increase intratumoral concentration of gemcitabine [19].

2.2 Rationale for this study

The emergence of new small molecules with capacity of blocking the Hh signaling pathway provides a novel therapeutic approach in pancreatic adenocarcinoma treating the primary tumor, stroma, systemic metastases and CSC by Hh pathway inhibition. These preclinical findings and the lack of significant effective therapies in patients with metastatic pancreatic cancer resulted in our interest to do this clinical trial. We propose an open label phase 2 clinical trial evaluating the progression free survival (PFS) in patients with previously untreated metastatic pancreatic adenocarcinoma. Given the promising survival advantage on recent clinical trial with the combination of gemcitabine and nab-paclitaxel both agents will be included in this study and will be considered our historical control[20]. The combination of gemcitabine with our without nab-Paclitaxel is currently been evaluated in a multi-institutional phase III clinical trial.

We hypothesize that the combination of cytotoxic agents (gemcitabine and nab-paclitaxel) with the

Hh inhibitor GDC-0449 may increase PFS in patients with previously untreated metastatic adenocarcinoma of the pancreas. We will include correlative studies to attempt to understand the stem cell biology and mechanism for any observed clinical benefits with the use of Hh inhibitor GDC-0449. We will evaluate the changes in Hh pathway downregulation and changes in pancreatic CSC markers with pre and post treatment biopsies. Finally this study will also evaluate the incidence of detectable Hh expression in pancreatic adenocarcinoma to assess whether Hh expression might be used as a predictive factor for GDC-0449 clinical benefit, which may be necessary for appropriate patient selection in future trials. Given the lack of prior experience with the combination of the three drugs, the safety of GDC-0449 when combined with chemotherapy gemcitabine and nab-paclitaxel will also be monitored continuously during the study by evaluating adverse event rate.

2.3 Correlative Studies

We will evaluate the changes in the pre- and post-treatment Hh signaling pathway down regulation and the presence of pancreatic CSC. The biopsies will be obtained by core biopsy or fine needle aspiration (FNA) both pre and post treatment. The findings will be correlated with clinical response to GDC-0449.

1. To identify presence of pancreatic cancer stem cells in biopsy samples
 - By functional assay with Aldehyde dehydrogenase (ALDH) bright cells by immunohistochemistry if core biopsy is obtained or RT-PCR for ALDH if fine needle aspiration is obtained.
 - By phenotypic assays CD24+/ CD44+/ESA+ and CD133+ by immunohistochemistry if core biopsy is obtained or by quantitative RT-PCR if FNA is obtained.
2. To evaluate for hedgehog signaling pathway downregulation
 - Evaluate for the Hh target genes Gli1 and Ptch at the mRNA level in primary tumor
3. Circulating pancreatic cancer stem cells in peripheral blood by flow cytometry

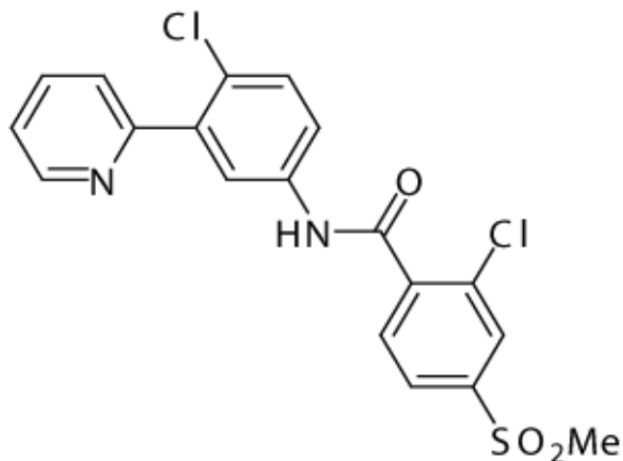
2.4 Study Drugs

2.4.1 GDC-0449

GDC-0449 is a small-molecule inhibitor of the Hh signal pathway with a molecular weight of 421.30 g/mol. The International Union of Pure and Applied Chemistry name for GDC-0449 is 2-chloro-*N*-(4-chloro-3-pyridin-2-yl-phenyl)-4-methanesulfonylbenzamide. Its structure is shown in Figure 1. GDC-0449 binds to and inhibits SMO that

results in blocking of the Hh signal. GDC-0449 has proven to be efficacious in nonclinical tumor models of both mutated and ligand-overexpressing tumors.

Figure 1: Clinical Structure of GDC-0449



GDC-0449 is a small-molecule antagonist of the Hh signal pathway. Specifically GDC-0449 has demonstrated anti-tumor activity against a variety of primary human tumor xenografts and tumor cell line xenograft models (Investigator Brochure). These include CRC, in which activity was seen both as a single agent and in combination with cytotoxic agents, as well as in primary xenograft models of pancreatic carcinoma (Investigator Brochure). In murine models, the anti-tumor effect of GDC-0449 correlates with blockade of the Hh pathway measured by reduction in the expression of stromal *Gli1* mRNA, which is itself a transcriptional target of Hh signaling. Specifically, sustained reduction of *Gli1* expression is associated with inhibition of tumor growth.

Preclinical studies with GDC-0449: A range of preclinical studies in the appropriate species have been completed with GDC-0449 including single and repeat-dose toxicity studies and toxicity studies. A thorough discussion of these is included in the Investigator's Brochure (IB). Preclinical studies had combined GDC-0449 with gemcitabine in a pancreatic model without any evidence of antagonism or unexpected toxicity.

Clinical Experience

GDC-0449 was studied in Phase I and is currently undergoing Phase II studies (Investigator Brochure, Edition 3).

Phase 1 study with GDC-0449

In the Phase I study (SHH3925g), GDC-0449 was given orally on a continuous daily schedule to patients with advanced solid malignancies that were refractory to standard therapy or for whom no standard therapy exists. Enrollment in this study occurred in two stages. Stage 1 was the dose-escalation portion of the study, with a “3+3” design and modified dose-doubling. The objectives for Stage 1 were to assess safety, tolerability, and pharmacokinetics/pharmacodynamics of GDC-0449 and to determine the MTD. In Stage 1, GDC-0449 is administered orally as a single dose on Day 1, followed by a 7-day PK observation period, and then continues on Day 8 as a once-daily regimen on a continuous 28-day schedule (Cycle 1 = 35 days). Patients who withdraw without DLT in the first cycle are replaced. Stage 2 had three cohorts to collect additional safety data, preliminary efficacy in advanced BCC, and safety/PK data with the new Phase II drug product (150 mg). Patients treated in Stage 2 received GDC-0449 orally once daily on a continuous, uninterrupted 28-day schedule.

The phase 1 study SHH3925g enrolled a total of 68 patients by December 2008 and has been completed to date. The recommended Phase II dose is 150 mg GDC-0449 given orally on a continuous daily schedule. Dose-limiting toxicities (DLTs) were not seen with GDC-0449; however, reversible Grade 3 fatigue and asymptomatic hyponatremia have been reported beyond the DLT window.

Study SHH4318g was conducted with a single refractory medulloblastoma pediatric patient and has also been completed. Study SHH4433g was a healthy volunteer pharmacokinetic (PK) study to further characterize and understand the unique plasma PK profile observed during the Phase I dose-escalation trial, in which GDC-0449 displayed an unusual pharmacokinetic profile with high sustained micromolar plasma concentrations and a long terminal half-life.

Potential Risks

GDC-0449 has been given to 68 patients in the Phase I study SHH3925g. The following side effects were observed in a small number of patients and may be related to GDC-0449: changes in or lack of taste sensation for food; loss of appetite; heartburn and stomach upset; nausea; vomiting; weight loss; decrease in sodium and magnesium levels in the blood; severe fatigue; loss of hair on the scalp, body, eyelashes, and face; joint pain; acne-like skin rash; skin peeling; numbness; and muscle spasms (cramps). There may be risks that have not yet been identified and that were not predicted by nonclinical testing.

In this Phase I clinical study, Grade 3 adverse events attributable to study drug have been reversible and minimal in number. No Grade 4 or 5 events related to study drug have been reported. The safety profile of GDC-0449 supports single-agent studies of this drug in the Phase II setting.

Notable findings in the nonclinical toxicity studies included tremors, alopecia, follicular cysts and pilomatricoma, effects on male and female reproductive parameters, and

alterations of epiphyses and incisors in rats, as well as decreased platelet count and red cell mass, increased serum cholesterol, alopecia, localized skin inflammation, and paw swelling in dogs. Because of the relatively slow clearance of GDC-0449 in humans, the exposures achieved at the highest doses that were tolerated in the repeat-dose toxicity studies were comparable to those that are typically observed in patients. However, with the exception of pharmacologically mediated alopecia, the toxicities evident in the nonclinical studies were not clearly correlated with drug-related adverse events in the Phase I clinical trial.

In general, the results of the nonclinical toxicity studies conducted with GDC-0449 demonstrate a favorable safety profile to support the proposed clinical trials. The finding of pilomatricoma (a benign, cutaneous neoplasm that is readily excisable in humans) at a low incidence at the high dose level in the chronic rat toxicity study is not considered to substantially impact the risk/benefit profile for clinical trials in patients with late-stage or advanced cancers.

As of 14 July 2009, there has been one IND safety report from this study. This Grade 3 atrial fibrillation AE was assessed as serious, unexpected, and related to study drug.

As of January 2011 the following list of IND safety reports have been submitted as related to GDC-0449: atrial fibrillation, convulsion, dyspnea, lung infiltration, pulmonary embolism, diarrhea, renal failure, dehydration, abdominal pain, paranoia, gastroenteritis, cholestasis, elevated hepatic enzymes, pneumonia, cholestasis, cardiac failure, syncope. One episode of sudden death assessed due to myocardial infarct was reported as non-related by investigator and assessed as related by Genentech.

The toxicities possibly related to GDC-0449 reported in previous phase 1 clinical trial included:

- *Constitutional*: Fatigue, weight loss
- *Cardiovascular*: atrial fibrillation
- *Gastrointestinal*: anorexia, dyspepsia (heartburn or stomach upset), nausea, vomiting
- *Metabolic*: hyponatremia, hypomagnesemia
- *Neurologic*: hypoesthesia (sensory neuropathy), dysgeusia (taste alteration), numbness
- *Musculoskeletal*: arthralgia, muscle spasms
- *Skin and subcutaneous tissue disorders*: skin exfoliation, alopecia (scalp, body, eyelashes and face), dermatitis acneiform

Reproductive and developmental Toxicity

Studies to assess the reproductive and developmental toxicity of GDC-0449 have not been conducted to date. However, based on the central role of the Hh signaling pathway in embryogenesis and published studies with other small-molecule Hh pathway inhibitors, GDC-0449 is expected to be teratogenic to humans, and pregnant women should avoid exposure to the compound. The teratogenic potential of Hh pathway inhibitors has been well established with observational and experimental studies in animals. A description of all these observational studies is included in the investigator brochure.

Women who are pregnant, plan to become pregnant, or are lactating (during the study or for up to 7 months after the last dose) are excluded from all clinical studies with GDC-0449. Pregnancy prevention measures will be undertaken in this study.

Proposed dose for GDC-0449

Based on the PK parameters and the lack of AEs observed, the proposed starting dose for oral administration of GDC-0449 to cancer patients is 150 mg/day (92.5 mg/m²/day)

Other ongoing phase II studies with GDC-0449

Study SHH4429g is an ongoing randomized, placebo-controlled, double-blind Phase II trial of GDC-0449 added to biochemotherapy standard of care regimens (FOLFOX or FOLFIRI chemotherapy with bevacizumab) for first-line metastatic colorectal cancer (CRC). The primary goal of this study is to determine if adding GDC-0449 to the standard of care therapy increases antitumor efficacy as measured by PFS when compared with the standard of care therapy alone.

2.4.2 nab-paclitaxel

Nab- paclitaxel is a Cremophor EL-free, albumin-bound paclitaxel particle with a mean size of approximately 130 nm. Each 50 mL vial contains 100 mg of paclitaxel, and approximately 900 mg of human albumin, as a white to yellow sterile lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection.

Nab- paclitaxel is a unique protein formulation of a non-crystalline, amorphous form of paclitaxel in an insoluble particle state. It has been developed to reduce the toxicities associated with Taxol (paclitaxel) Injection (in which paclitaxel - from the native crystalline form - is in solution with Cremophor EL/ethanol as the solvent) while maintaining or improving its chemotherapeutic effect. Nab- paclitaxel has been approved in the US, Canada, India, the EU, Korea and China (and is under review in a number of other countries) for the treatment of women with metastatic breast cancer (MBC). Nab-paclitaxel alone and in combination is being evaluated in a number of cancers including: metastatic melanoma, pancreatic cancer, cervical cancer and other solid tumors. Conditions which are responsive to paclitaxel such as non-hematological solid tumor malignancies are good clinical candidates for treatment with nab- paclitaxel.

Preclinical studies with nab- paclitaxel: A range of preclinical studies in the appropriate species have been completed with nab- paclitaxel including single and repeat-dose toxicity studies, carcinogenicity evaluations, reproductive toxicity assessments, and mutagenicity and toxicity studies. A thorough discussion of these is included in the Investigator's Brochure (IB).

Preclinical studies comparing nab-paclitaxel to Taxol demonstrated lower toxicities, with a MTD approximately 50% higher for nab-paclitaxel compared to Taxol. At equitoxic doses of paclitaxel, nab-paclitaxel was found to be markedly more efficacious in animal models than Taxol.

In an on-going study of nab- paclitaxel in combination with gemcitabine administered weekly (Abraxis Protocol CA040; updated results as of October 2008), a total of 41 patients with advanced metastatic pancreatic cancer were treated with doses ranging from 100 to 150 mg/m². Though results are preliminary and follow-up is on-going, 27 patients (66%) experienced at least 1 treatment-related AE and 11 (27%) patients experienced at least one treatment-emergent SAE. With the exception of the "Gastrointestinal: Dehydration", "not classified" and "pain: other" categories (2 (5%) events each), no treatment-emergent SAE categories had more than a single event.

Dose delays were mainly due to blood/bone marrow treatment-related AEs (mostly neutrophils). There were no nab- paclitaxel dose interruptions due to treatment-related AEs, and 2 instances of dose interruptions for gemcitabine (dermatology/skin: injection site reaction). Also, 2 patients had a total of 3 treatment-related AEs involving blood/bone marrow (neutrophils and platelets) resulting in dose reductions and 2 treatment-related AE resulted in dose discontinuation (gastrointestinal: diarrhea and infection: systemic). There were 3 treatment-emergent AEs resulting in death (lung infection, systemic infection, and gastrointestinal obstruction), but only systemic infection was considered treatment-related. Patients treated with nab- paclitaxel in combination with gemcitabine had levels of myelosuppression consistent with those expected following treatment with taxanes.

Potential Risks for nab- paclitaxel based on previous clinical studies

Nab- paclitaxel is not formulated in Cremophor and thus the risk of hypersensitivity reactions is much less than that of Taxol. The major risks of nab- paclitaxel have been assessed in clinical trials in patients with a variety of malignancies and reflect the known toxicities of paclitaxel. See the IB for a complete description of all toxicities reported in conjunction with nab- paclitaxel administration.

The most common toxicities reported in previous clinical trials included:

- *Myelosuppression, predominantly neutropenia.* Grade 4 neutropenia was reported and typically resolved in < 7 days and did not require colony stimulating factor support.
- *Peripheral neuropathy, predominantly sensory.* Grade 3 peripheral neuropathy

was reported and typically improved to Grade 1 or 2 within 21 days of interrupting the nab-paclitaxel dose. Following resolution of the peripheral neuropathy to acceptable levels, clinicians were able to restart nab-paclitaxel dosing at a lower dose levels.

- *Nausea and vomiting.* Nausea and vomiting were seen, typically at Grade 1 or 2 levels. This AE responded well to standard anti-emetic regimens.
- *Myalgias and arthralgias.* Myalgias and arthralgias were reported and typically were Grade 1 or 2; these were responsive to standard acetaminophen-containing medication.
- *Mucositis.* Mucositis was reported typically Grade 1 or 2. It was not dose limiting
- *Alopecia.* Alopecia was reported by most patients and was similar to that seen with Taxol.

2.4.3 Gemcitabine:

Gemcitabine is approved for the treatment of metastatic pancreatic cancer. For more information please refer to package insert. The most common toxicities reported with gemcitabine are:

- *Hematological-* In studies in pancreatic cancer, myelosuppression is the dose-limiting toxicity with Gemzar®, but <1% of patients discontinued therapy for anemia, leukopenia, or thrombocytopenia. Red blood cell transfusions were required by 19% of patients. The incidence of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, was reported in 16% of patients; less than 1% of patients required platelet transfusions. Patients should be monitored for myelosuppression during Gemzar therapy and dosage modified or suspended according to the degree of hematologic toxicity.
- *Gastrointestinal* - Nausea and vomiting were commonly reported (69%) but were usually of mild to moderate severity. Severe nausea and vomiting (WHO Grade 3/4) occurred in <15% of patients. Diarrhea was reported by 19% of patients, and stomatitis by 11% of patients.
- *Hepatic* - In clinical trials, Gemzar was associated with transient elevations of one or both serum transaminases in approximately 70% of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to Gemzar or with greater total cumulative dose. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving Gemzar.
- *Renal* - In clinical trials, mild proteinuria and hematuria were commonly reported. Hemolytic Uremic Syndrome (HUS) has been reported rarely (0.25%) with the use of Gemzar. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required.

- *Fever* - The overall incidence of fever was 41%. This is in contrast to the incidence of infection (16%) and indicates that Gemzar may cause fever in the absence of clinical infection. Fever was frequently associated with other flu-like symptoms and was usually mild and clinically manageable.
- *Rash* - Rash was reported in 30% of patients. The rash was typically a macular or finely granular maculopapular pruritic eruption of mild to moderate severity involving the trunk and extremities. Pruritus was reported for 13% of patients.
- *Pulmonary*- In clinical trials, dyspnea, unrelated to underlying disease, has been reported in association with Gemzar therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of Gemzar. The etiology of these effects is unknown. If such effects develop, Gemzar should be discontinued. Early use of supportive care measures may help ameliorate these conditions.
- *Edema*: Edema (13%), peripheral edema (20% %), and generalized edema (<1%) were reported. Less than 1% of patients discontinued due to edema.
- *Neurotoxicity* - There was a 10% incidence of mild paresthesias and a <1% rate of severe paresthesias
- *Flu-like Symptoms* - “Flu syndrome” was reported for 19% of patients. Individual symptoms of fever, asthenia, anorexia, headache, cough, chills, and myalgia were commonly reported. Fever and asthenia were also reported frequently as isolated symptoms. Insomnia, rhinitis, sweating, and malaise were reported infrequently. Less than 1% of patients discontinued due to flu-like symptoms.
- *Infection* - Infections were reported for 16% of patients. Sepsis was rarely reported.
- *Alopecia*- Hair loss, usually minimal, was reported by 15% of patients

Please see gemcitabine prescribing information for more details on the known precautions, warnings, and adverse reactions of gemcitabine (current version of Prescribing Information is provided in the Study Manual).

3. PATIENT SELECTION

3.1 Eligibility Criteria

- 3.1.1 Patients must have histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas. Patients with islet cells tumors are excluded. Biopsy is required within 14 days before starting treatment.

- 3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan. See Section 11 for the evaluation of measurable disease.
- 3.1.3 Patient must have received no previous radiotherapy, surgery or chemotherapy or investigational drug therapy for the treatment of metastatic disease. Radiotherapy, chemotherapy or investigational therapy in the adjuvant setting should be completed 3 weeks prior to enrollment. Prior therapy with 5FU, gemcitabine or other agents in the adjuvant setting is allowed. If a patient received gemcitabine in the adjuvant setting, tumor recurrence must have occurred at least six months after completing the last dose of gemcitabine
- 3.1.4 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of GDC-0449 in combination with nab-paclitaxel and gemcitabine in patients < 18 years of age, children are excluded from this study but will be eligible for future pediatric phase 2 combination trials.
- 3.1.5 Life expectancy of greater than 1 month.
- 3.1.6 ECOG performance status ≤ 1 (Karnofsky $\geq 70\%$; see Appendix A).
- 3.1.7 Patients must have adequate organ and marrow function as defined below:
- leukocytes $\geq 3,000/\text{mcL}$
 - absolute neutrophil count $\geq 1,500/\text{mcL}$
 - platelets $\geq 100,000/\text{mcL}$
 - total bilirubin < 1.5 ULN
 - AST(SGOT)/ALT(SGPT) < 2.5 X institutional upper limit of normal, unless liver metastases are clearly present, then < 5 X ULN is allowed
 - creatinine within normal institutional limits
- OR
- creatinine clearance Creatinine clearance ≥ 50 mL/min/ 1.73 m^2 for patients. Serum creatinine < 2 mg/mL
- 3.1.8 Patients should be asymptomatic for jaundice and ascites prior to Day 1. Pain symptoms should be stable.
- 3.1.9 The effects of GDC-0449 on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because Hh signal pathway inhibitors are known to be teratogenic, women of child-bearing potential and men must use two forms of contraception (i.e., barrier contraception and one other method of contraception) at least 4 weeks prior to study entry, for the duration of study participation, and for at least 7 months post-treatment. For appropriate methods of

contraception considered acceptable see Appendix B. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

Pregnancy Testing. Women of childbearing potential are required to have a negative serum pregnancy test (with a sensitivity of at least 25 mIU/mL) within 10-14 days and within 24 hours prior to the first dose of GDC-0449 (serum or urine). A pregnancy test (serum or urine) will be administered every 4 weeks if their menstrual cycles are regular or every 2 weeks if their cycles are irregular while on study within the 24-hour period prior to the administration of GDC-0449. A positive urine test must be confirmed by a serum pregnancy test. Prior to dispensing GDC-0449, the investigator must confirm and document the patient's use of two contraceptive methods, dates of negative pregnancy test, and confirm the patient's understanding of the teratogenic potential of GDC-0449.

Women of childbearing potential are defined as follows:

- Patients with regular menses
- Patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding
- Women who have had a tubal ligation

Women are considered not to be of childbearing potential for the following reasons:

- The patient has undergone hysterectomy and/or bilateral oophorectomy.
- The patient is post-menopausal defined by amenorrhea for at least 1 year in a woman > 45 years old.

- 3.1.10 For sexually active males, use of barrier form of contraception, even if they have had a vasectomy, during the study and for 2 months after stopping GDC-0449 is required. Males should not donate sperm during treatment or up to three months after last dose.
- 3.1.11 All patients should agree not to donate blood products for 7 months after stopping GDC-0449
- 3.1.12 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

- 3.2.1 Patients who have had chemotherapy or radiotherapy for metastatic disease
- 3.2.2 Patients may not be receiving any other investigational agents.
- 3.2.3 Patient has known brain metastases, unless previously treated and well controlled for at least three months (defined as clinically stable, no edema, no steroids and stable in 2 scans at least 4 weeks apart)

- 3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to GDC-0449 or other agents used in the study.
- 3.2.5 Patients taking medications with narrow therapeutic indices that are metabolized by cytochrome P450 (CYP450), including warfarin sodium (Coumadin®) are ineligible.
- 3.2.6 GDC-0449 inhibits CYP2C8, CYP2C9, and CYP2C19 drug metabolism enzymes *in vitro* at concentrations that may be clinically relevant. Therefore, caution should be exercised when dosing GDC-0449 concurrently with medications that are substrates of CYP2C8, CYP2C9, and CYP2C19 and have narrow therapeutic windows.

In addition, GDC-0449 is a substrate of CYP3A4; however, the *in vitro* metabolic conversion of GDC-0449 is low. Effects of CYP inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort, and troglitazone) on clinical concentrations of GDC-0449 are unknown. Likewise, the effects of strong inhibitors of CYP3A4 (e.g., clarithromycin, erythromycin, itroconazole, ketoconazole, nefazodone, and telithromycin) on GDC-0449 clinical concentrations are unknown, and caution should be exercised when dosing GDC-0449 concurrently with inhibitors of CYP3A4 (refer to Appendix C for a list of drugs that may potentially interact with CYP3A4).

- 3.2.7 Uncontrolled illness including, but not limited to, ongoing or active infection requiring IV antibiotics, symptomatic congestive heart failure not controlled with medication, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- 3.2.8 Pregnant and nursing women are excluded from this study because GDC-0449 is a Hh pathway inhibiting agent with the potential for teratogenic or abortifacient effects. Women planning to become pregnant during treatment and for 7 months after last dose of treatment are excluded from this study. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with GDC-0449, breastfeeding should be discontinued if the mother is treated with GDC-0449. These potential risks may also apply to other agents used in this study.
- 3.2.9 Patient has undergone a major surgery, other than diagnostic surgery (i.e. surgery done to obtain a biopsy for diagnosis without removal of an organ) within four weeks prior to Day 1 of treatment on this study.
- 3.2.10 History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or that might affect interpretation of the results of the study or render the patient at high risk from treatment complications

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. REGISTRATION PROCEDURES

4.1 General Guidelines

All sites should call the Study Coordinator Yvette Cetasaan, CCRP at 410-955-4035 (or Rosalind Walker at 410-955-9628) to verify agent availability. A signed informed consent document must be obtained prior to entry onto the study. This study uses a web based data entry system for data submission through Cancer Research and Biostatistics (CRAB). Patient enrollment materials may be accessed online through the study website at: www.crab.org/SU2C.

Eligibility criteria must be verified according to the eligibility checklist located in Appendix F and stored in the patient chart. The Principal investigator of each site is responsible to verify that all the eligibility criteria are met. Following completion of the eligibility checklist, subjects must be registered on the CRAB study website to be considered on study. Each patient will be automatically assigned a patient identification number following enrollment.

Signed and completed informed consent forms should be faxed to Yvette Cetasaan at 443-287-6566.

Following registration, patients should begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center.

4.2 Data Submission Procedures

Data will be completed and submitted electronically using the study web based system provided by CRAB. Electronic case report forms (eCRFs) can be accessed on-line through the study website at: www.crab.org/SU2C. This website is used to register patients and submit data using eCRFs. In addition, study resource information (SAE submission forms, protocol documents and other study guidelines) can be found on the website.

4.3 Coordinating Center Guidelines

Responsibility of the Protocol Chair

- The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center (SKCCC)

- The Coordinating Center will maintain documentation of AE reports. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- The Coordinating Center is responsible for overseeing and approving the distribution of the investigational study medication, GDC-0449, to each participating site.

Responsibilities of the CRO: Cancer Research And Biostatistics (CRAB):

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. CRAB is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- CRAB is responsible for providing an electronic data capture (EDC) system and maintaining the study web based system that is used for registration and data submission. CRAB is responsible for assuring IRB approval has been obtained at each participating site prior to the first patient registration from that site. During the registration process, CRAB will collect the date each patient signs the informed consent form and HIPAA authorization form.
- CRAB is responsible for the preparation of all submitted data for review by the Protocol Chair.
- CRAB is responsible for conducting on-site monitoring as described in Section 7.7 – Data and Safety Monitoring Plan.
- Due to budget constraints CRO QA will conduct on-site monitoring as described in Section 7.7 – Data and Safety Monitoring Plan however CRAB will continue to monitor the CRAB database.

5. TREATMENT PLAN

Following the determination of eligibility patients will receive the following treatment:

1. One cycle of Gemcitabine 1000 mg/m² and nab-Paclitaxel 125 mg/m² on days 1, 8, and 15 (28 days cycle) then
2. Gemcitabine 1000 mg/m² and nab-Paclitaxel 125 mg/m² on days 1, 8, and 15 every 28 days cycle in combination with oral GDC-0449 150 mg daily

Table 1. Drug Schedule

Week	1	2	3	4	5	6	7	8
Gemcitabine + nab- paclitaxel	Cycle 1				Cycle 2 onward			
	X	X	X		X	X	X	
GDC-0449					Daily Dose Administration			

5.1 Time and Events Schedule

An overview of the schedule of study assessments is provided in the Study Calendar in section 10.

Informed consent will be obtained prior to any study procedures being performed. Each participant will be given a copy of the signed informed consent form (ICF). The ICF must be approved by an Institutional Review Board (IRB)/Ethics Committee (EC).

A complete medical history and physical examination will be conducted on each patient for a review of systems and determination of any concurrent symptoms or conditions prior to the first dose of study drug. Routine study evaluations will be conducted to monitor for existing adverse events and the development of new adverse events.

Patients are to be encouraged to call the site to report any unexpected symptoms or problems they encounter between study visits. Medical symptoms or conditions present at or before study drug administration that manifest with the same intensity or frequency subsequent to study drug administration do not need to be recorded as adverse events in the CRF. However, any pre-existing condition that presents with increased intensity or increased frequency following study drug administration, or any exacerbation of an event that is present at the time of study drug administration, should be considered an adverse event. All adverse events occurring from initial dosing through study end, inclusive, should be followed as outlined in section 7. All adverse events must be completely and promptly recorded in the patient's source document (e.g., patient hospital records, patient clinic charts, and laboratory reports) and on the CRF. Note that individual signs/symptoms should not be recorded in the CRF as adverse events. If a unifying diagnosis is

known, it is the diagnosis that should be recorded as the adverse event.

Clinically significant laboratory abnormalities present at the pre-study (baseline) visit will be recorded as pretreatment signs and symptoms. After study treatment administration, laboratory abnormalities will not be recorded as adverse events unless considered clinically significant by the Investigator, and clinically significant laboratory abnormalities will not be recorded as serious adverse events unless the event meets the definition of serious.

Each Investigator is responsible for assessing the clinical significance of all abnormal laboratory values using the NCI CTCAE Scale version 4.0 (see <http://ctep.cancer.gov/reporting/ctc.html>), where applicable. It is also the responsibility of the Investigator to assess the clinical significance of all abnormal laboratory values as defined by the list of normal values provided by the local laboratory. All abnormal laboratory tests that are judged to be at least possibly drug related, or clinically relevant abnormal laboratory tests of uncertain causality, must be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator. In some cases, significant changes within the range of normal values will require similar judgment.

5.1.1 Screening and Pre-study Assessments

The following evaluations and procedures will be performed within 28 days prior to Day 1:

- Signed informed consent
- Clinical evaluations
- Medical and surgical history (including demographics and prior cancer therapy history)
- Complete physical examination
- Vital Signs: Height, weight, pulse, blood pressure, respiratory rate, and temperature
- ECOG performance status (see Appendix A)
- Concurrent medications: Record all concurrent medications administered within the 28 days preceding Day 1
- Laboratory assessments

Hematology: hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, white blood cell (WBC) count, and percent and absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells)

Serum chemistries (glucose, BUN, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, total protein, albumin, serum total bilirubin, alkaline phosphatase, LDH, phosphorus, Chloride, AST, AST, and ALT)

Complete Urinalysis

Coagulation: PT, PTT, INR

Pregnancy Testing. Women of childbearing potential are required to have a negative serum pregnancy test (with a sensitivity of at least 25 mIU/mL) within 10-14 days and within 24 hours prior to the first dose of GDC-0449 (serum or urine). A pregnancy test (serum or urine) will be administered every 4 weeks if their menstrual cycles are regular or every 2 weeks if their cycles are irregular while on study within the 24-hour period prior to the administration of GDC-0449. A positive urine test must be confirmed by a serum pregnancy test. Prior to dispensing GDC-0449, the investigator must confirm and document the patient's use of two contraceptive methods, dates of negative pregnancy test, and confirm the patient's understanding of the teratogenic potential of GDC-0449.

- 12-lead ECG
- Tumor assessment (per RECIST 1.1; see section 11). The method used for a patient must be the same throughout the study. CT scan of chest, abdomen and pelvis (or MRI if patient allergic to contrast agent).
- Consent to obtain tissue biopsy by ultrasound or ct guided biopsy
- Pretreatment biopsy for correlative studies, must be obtained within 14 days before cycle 1, day 1

5.1.2 Assessments during the study period

The study period begins on Day 1 of Cycle 1 and continues until documented disease progression. A window of ± 3 days will be allowed for all visits and radiographic assessments performed during the study period. All assessments and procedures should be performed prior to study treatment on the scheduled treatment day, unless otherwise specified.

- *Response assessments:* Response assessment CT scans should be performed at Baseline, Cycle 1 Day 1 (only if Baseline CT scan not done within 14 days prior to Cycle 1 Day 1), every 8 weeks (at any time during that week), and EOS (if required per the defined study imaging schedule). The same mode of imaging for target lesions must be used at Baseline and throughout the study. CT image preparation will follow the specifications provided in the RECIST 1.1 response guidelines. CT imaging should include contrast unless medically contraindicated and conventional CT should be performed with contiguous cuts of 10 mm or less in slice thickness. If spiral CT is used, it should be performed by use of a 5 mm contiguous reconstruction algorithm.
- *Drug related toxicities:* If the investigator suspects a drug-related toxicity, an extra-

unscheduled visit with additional laboratory tests may be performed.

- GDC-0449, nab paclitaxel and gemcitabine should be administered as specified in 5.2 and study calendar in section 10.

5.1.3 Beginning of each cycle

The following assessments will be performed on Day 1 of each treatment cycle:

- GDC-0449 drug accountability. The first dose of GDC-0449 will be taken on Day 1 of Cycle 2 while the patient is at the site. Drug will be dispensed to the patient on this day. GDC-0449 drug accountability and review of the Medication Diary will occur at the beginning of each subsequent visit. GDC-0449 will be dispensed every 4 weeks. Unused medication should not be re-dispensed.
- Clinical evaluations: Weight, pulse, blood pressure, respiratory rate, and temperature
- BSA calculations (Day 1 of cycle 1, and then subsequently if there is a weight change of more than 10%)
- Concurrent procedures
- Adverse event evaluation
- Peripheral neuropathy assessment
- Cycle 1, Day 1 CT scan (only if baseline CT not done within 14 days prior to Cycle 1, Day 1)
- Serum CA19-9 (Day 1 of Cycle 1, Cycle 2, Cycle 4 and every even cycle onward)
- Plasma SPARC (Day 1 of Cycle 1, Cycle 2, Cycle 4 and every even cycle onward)
- Local laboratory assessments
- Day 1 evaluations may be omitted if Baseline evaluations are performed within 72 hours of Cycle 1, Day 1.

Hematology: hemoglobin, hematocrit, platelet count, red blood cell (RBC) count, white blood cell (WBC) count, and percent and absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells)

Serum chemistries (glucose, BUN, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, total protein, albumin, serum total bilirubin, alkaline phosphatase, AST, and ALT)

Serum or urine pregnancy test (for women of childbearing potential). If a urine test is positive should be confirmed with serum pregnancy test. For all other women, documentation must be present in their medical histories confirming that the patient is not of childbearing potential (see Appendix B).

- Record concurrent medications.
- Record cancer-related medical or surgical procedures.
- Record adverse events.

5.1.4 Follow up assessments

Efficacy Response Assessments

The following efficacy response assessments will be performed:

- CT scan (or MRI if patient is allergic to contrast agent) every 8 weeks at any time during that week, starting from Cycle 1 Day 1. In order to confirm objective response, an unscheduled CT scan will be allowed 4 weeks (a minimum of 28 days) from the initial documented complete or partial response. For such patients, all subsequent CT scans should return to the original schedule performed every 8 weeks starting from the date of first dose of study therapy. An unscheduled CT scan for suspected progression may be performed at any time;

Per Cycle Evaluations

On Days 8 and 15 of each cycle, the following assessments will be performed:

- Concomitant medication evaluation
- Vital signs (prior to dosing)
- CBC, differential and platelet count
- Adverse event evaluation.

At the beginning of each cycle

Note: The following procedures should be performed during the entire study period.

- Brief physical examination
- Clinical evaluations (performed at beginning of each chemotherapy cycle or, if chemotherapy has been stopped, every 3-4 weeks): Weight, pulse, blood pressure,

respiratory rate, and temperature

- Local laboratory assessments (performed at beginning of each chemotherapy cycle or, if chemotherapy has been stopped, every 3-4 weeks)

Hematology: hemoglobin, hematocrit, platelet count, RBC count, WBC count, and percent and absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells)

Serum chemistries (glucose, BUN, creatinine, sodium, potassium, magnesium, bicarbonate, calcium, total protein, albumin, serum total bilirubin, alkaline phosphatase, AST, and ALT)

- ECOG performance status (see Appendix A)
- Serum or urine pregnancy test every 4 weeks (for women of childbearing potential)
- Record concurrent medications.
- Record cancer-related medical or surgical procedures.
- Record adverse events.

Every 8 weeks

Note: The following procedures should be performed during the entire study period. If chemotherapy has been stopped every 8 weeks

- Tumor assessment (per RECIST 1.1; see section 11). The method used for a patient must be the same throughout the study
- Record concurrent medications.
- Record cancer-related medical or surgical procedures.
- Record adverse events.

End-of-Study (EOS) Evaluations

An EOS evaluation should be performed for all patients who end treatment. The following procedures will be completed at the EOS Visit:

- Physical examination
- Weight assessment
- Concomitant medication evaluation

- Concurrent procedures
- Vital signs
- ECOG performance status scale
- Clinical chemistry panel
- CBC, differential and platelet count
- CT scan (or MRI if patient is allergic to contrast agent) only if required per the defined study imaging schedule;
- Adverse event evaluation.

The Investigator must follow all SAEs observed during the study until these events have resolved or stabilized, the patient is lost to follow-up, or the events are otherwise explained. The Investigator should report these SAEs in accordance with the procedures described in Section 7. Clinical laboratory tests may be repeated during the post-treatment period if clinically indicated.

Follow-up for Adverse Events

Any AE or SAE whose onset occurred between the first administration of study drug to 30 days after the last dose of study drug or EOS (whichever is later) will be collected. The Investigator should report SAEs in accordance with the procedure described in Section 7. Adverse event follow-up will be conducted as follows:

- Non-serious adverse events, other than neuropathy, will be followed for 30 days after the patient's last dose of study drug.
- Neuropathy will be followed until improvement to Grade 1 occurs, or at least 3 months have elapsed without improvement or worsening, or the patient initiates any other anticancer therapy during follow-up.
- All serious adverse events (regardless of relationship to study drug) will be followed until resolution. Clinical laboratory tests may be repeated during follow-up if clinically indicated. Follow-up evaluations include studies necessary to document the resolution or persistence of any unresolved AEs and could include:
 - Physical examination, weight;
 - Concomitant medication evaluation;
 - Concurrent procedures;
 - Vital signs;

- ECOG Performance Status scale;
- CBC, differential, platelet count, and clinical chemistries;
- Peripheral neuropathy assessment.

Follow-up for Disease Progression

Patients who are discontinued from treatment in the absence of disease progression (e.g., patients removed for unacceptable toxicity or patient/investigator discretion) should undergo repeat imaging and tumor response assessments until disease progression is documented. Imaging studies (CT scans) should be continually performed into follow-up every 8 weeks (at any time during that week), regardless of regimen. It is recommended that subsequent therapy not be instituted until disease progression is documented. Ideally this repeat imaging should be done at the treating institution.

Follow-up for Overall Survival

Post-study, overall survival status will be monitored on a monthly basis for 6 months and then every 3 months thereafter for 12 months. Patients will be followed for a total of 18 months. This evaluation may be by record review and/or telephone contact.

5.2 Agent Administration

Patients will be treated on an outpatient basis. Patients receiving nab-Paclitaxel +gemcitabine will receive 125 mg/m² nab-Paclitaxel as a 30-minute infusion followed by 1000 mg/m² gemcitabine as a 30-minute infusion for 3 weeks followed by a week of rest. Supportive care per the institution's normal standard of care can be provided at the Investigator's discretion.

REGIMEN DESCRIPTION					
Agent	Premedications; Precautions	Dose	Route	Schedule	Cycle Length
Gemcitabine	Dexamethasone 12 mg PO or IV 30-60 min prior to Gemcitabine	1000 mg/m ²	IV	Days 1, 8 and 15	4 weeks (28 days)
Nab- paclitaxel	Not required	125 mg/m ²	IV	Days 1, 8 and 15	
GDC-0449	Morning or PM.	150 mg tablet	PO in the a.m.	Daily starting on cycle 2	

5.2.1 GDC-0449

Administration

GDC-0449 150 mg will be administered beginning on Cycle 2, Day 1 once daily by oral dosing, in combination with gemcitabine and nab-paclitaxel as described in section 5.1. Therapy should continue until one of the conditions specified in section 5.4 occurs.

Drug should be taken at approximately the same time each day, with or without food. If a patient misses a dose (e.g., due to emesis), he or she should be instructed not to take or make up that dose and to resume dosing with the next scheduled dose. Missed doses will not be made up. Patients will be instructed to bring all unused capsules and their medication diary to each study visit for assessment of compliance.

The terminal half-life of GDC-0449 is currently unknown, but is expected to be longer than 1 week, and may be as high as 2 to 3 weeks. If plasma levels of GDC-0449 need to be lowered emergently, animal studies suggest that oral administration of activated charcoal may lower drug plasma levels more quickly than dose cessation alone.

5.2.2 nab-paclitaxel

nab-Paclitaxel Premedication

Patients do not require premedication prior to nab-Paclitaxel administration, as hypersensitivity reactions are not expected, though initial antiemetic prophylaxis is recommended due to administration of gemcitabine following nab-Paclitaxel treatment.

Hypersensitivity reactions are not expected with either nab-paclitaxel or gemcitabine. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema, or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Patients who develop a severe hypersensitivity reaction to nab-paclitaxel should not be re-challenged.

If a hypersensitivity reaction occurs, the infusion should be stopped and not restarted. If felt to be in the patient's best interests, at the investigator's discretion, treatment may continue on subsequent cycles using the premedication regimen the institution typically uses for Taxol.

Chemotherapy Dose

The cycle length is 4 weeks (28 days). Treatment with protocol therapy will continue until one or more of the criteria listed in Section 5.4 are met.

5.2.3 Gemcitabine

Gemcitabine Premedication

Please see gemcitabine prescribing information for recommended premedication strategies.

5.2.4 Other Modality (ies) or Procedures

Administration of other chemotherapy, immunotherapy, or anti-tumor hormonal therapy during the study is not allowed. All concomitant treatments, including blood and blood products, must be reported on the case report form (CRF). Erythropoietin may be administered at the discretion of the Investigator, consistent with institutional guidelines. Guidelines for administration of GCSF are described in Table 5 but will be to the discretion of the investigator and according to institutional guidelines.

Planned Surgical Procedures

If, during the course of therapy, a planned surgical procedure is anticipated, chemotherapy, GDC-0449 may be stopped 4 weeks prior to minimize surgical complications. Patients may restart chemotherapy as appropriate. GDC-0449 must be restarted within 8 weeks of stopping in order to continue treatment with GDC-0449.

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 GDC-0449

- GDC-0449 inhibits CYP2C8, CYP2C9, and CYP2C19 drug metabolism enzymes in vitro at clinically relevant concentrations. There is a potential for GDC-0449 to also inhibit CYP1A2 and 2D6. Caution should be exercised and dose reduction of the concomitant substrate drug should be considered when dosing GDC-0449 concurrently with medications with narrow therapeutic windows that are substrates of CYP2C8, CYP2C9, CYP2C19, CYP1A2 and 2D6 because their concentrations may become elevated and their effects increased or prolonged.
- GDC-0449 did not significantly inhibit CYP3A4 at clinically relevant concentrations in vitro; however, the clinical impact of GDC-0449 on substrates of CYP3A4 is unknown. GDC-0449 is a substrate of CYP3A4; however, the in vitro metabolic conversion of GDC-0449 is low. Effects of CYP inducers (i.e., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St John's wort, and troglitazone) on clinical concentrations of GDC-0449 are unknown, it is possible that these drugs could reduce concentrations of GDC-0449. Likewise, the effects of strong inhibitors of CYP3A4 (i.e., clarithromycin, erythromycin, itraconazole, ketoconazole, nefazodone, and telithromycin) on GDC-0449 clinical concentrations are unknown; it is possible that these drugs could increase the concentrations of GDC-0449. Use of these drugs with GDC-0449 should be documented in the eCRFs.

- The following table lists clinically significant substrates of CYP2C8, CYP2C9, CYP2C19, CYP1A2 and 2D6. This is not necessarily a complete list; other medications may also interact with GDC-0449.

2C8	2C9	2C19
<u>Miscellaneous</u>	<u>NSAIDs</u>	<u>Proton-pump inhibitors</u>
Repaglinide	Diclofenac	Omeprazole
Rosiglitazone	Ibuprofen	Lansoprazole
Paclitaxel	Piroxicam	Pantoprazole
Torsemide	Naproxen	Rabeprazole
Cerivastatin	Celecoxib	Esoprazole
Amiodaquine		
	<u>Oral hypoglycemic agents</u>	
	Glipizide	<u>Anti-epileptics</u>
	Tolbutamide	Diazepam
		Phenytoin
	<u>Angiotensin II blockers</u>	Phenobarbitone
	Irbesartan	
	Iosartan	
	NOT candesartan	
	NOT valsartan	<u>Miscellaneous</u>
		Amitriptyline
	<u>Miscellaneous</u>	Clomipramine
	Fluvastatin	Clopidogrel
	Phenytoin	Cyclophosphamide
	Sulfamethoxazole	
	Tamoxifen	
	Torsemide	
	Warfarin	

NSAIDs = Non-steroidal anti-inflammatory drugs

1A2	2D6	
<u>Amitriptyline</u>	Tamoxifen	Atomoxetine
<u>Clomipramine</u>		Bufuralol
<u>Clozapine</u>	BBlockers	Chlorpheniramine
<u>Cyclobenzaprine</u>	Carvedilol	Chlorpromazine
<u>Estradiol</u>	S-metoprolol	Codeine
<u>Fluvoxamine</u>	Propafenone	Debrisoquine
<u>Haloperidol</u>	Timilol	Dexfenfluramine
<u>Imipramine</u>		Dextromethorphan
<u>Mexiletine</u>	Antidepressants	Donepezil
<u>Naproxen</u>	Amitriptyline	Duloxetine
<u>Olanzapine</u>	Clomipramine	Encainide
<u>Ondansetron</u>	Desipramine	Flecainide
<u>Phenacetin</u>	Fluoxetine	Fluvoxamine
<u>Acetaminophen</u> →NAPQI	Imipramine	Lidocaine
<u>Propranolol</u>	Paroxetine	Metoclopramide

<u>Riluzole</u>		Methoxyamphetamine
<u>Ropivacaine</u>	Antipsychotics	Mexiletine
<u>Tacrine</u>	Haloperidol	Minaprine
<u>Theophylline</u>	Perphenazine	Nebivolol
<u>Tizanidine</u>	Risperidone	Nortriptyline
<u>Verapamil</u>	Thioridazine	Ondansetron
<u>Warfarin</u>	Zuclopenthixol	Oxycodone
<u>Zileuton</u>		Perhexiline
<u>Zolmitriptan</u>	Alprenolol	Phenacetin
	Amphetamine	
	Aripiprazole	

Because there is a potential for interaction of GDC-0449 with other concomitantly-administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes (refer to Appendix C for a list of drugs that may potentially interact with CYP3A4).

- Use of medications or food that may interfere with the metabolism of GDC-0449 is prohibited, including ketoconazole and fresh-squeezed grapefruit juice.
- If plasma levels need to be lowered emergently, animal studies have suggested that oral administration of activated charcoal may lower drug plasma levels more quickly than drug cessation alone.
- Women of childbearing potential (defined in Appendix B) are required to have a negative serum pregnancy test (with a sensitivity of at least 25 mIU/mL) within 10-14 days and within 24 hours prior to the first dose of GDC-0449 (serum or urine). A pregnancy test (serum or urine) will be administered every 4 weeks if their menstrual cycles are regular or every 2 weeks if their cycles are irregular while on study within the 24-hour period prior to the administration of GDC-0449. Prior to dispensing GDC-0449, the investigator must confirm and document the patient's use of two contraceptive methods, dates of negative pregnancy test, and confirm the patient's understanding of the teratogenic potential of GDC-0449.

Female patients are required to use two forms of acceptable contraception (refer to Appendix B), including one barrier method **during participation in the study and for the 7 months following the last dose**. Women of childbearing potential are also advised to have monthly pregnancy tests for 12 months after discontinuation of GDC-0449. All patients should receive contraceptive counseling either by the investigator, or by an obstetrician(OB)/gynecologist or

other physician who is qualified in this area of expertise. If a woman of childbearing potential believes that her contraceptive method has failed, emergency contraception should be considered.

If a patient is suspected to be pregnant, GDC-0449 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 with GDC-0449.

If a female patient becomes pregnant during therapy or within 7 months after the last dose of GDC-0449, or if the female partner of a male patient exposed to the drug becomes pregnant while the male patient is receiving GDC-0449 or within 7 months after the last dose of GDC-0449, the investigator must be notified in order to facilitate outcome follow-up.

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious. Any congenital anomaly/birth defect in a child conceived during the study or within 7 months after the last dose of GDC-0449 to a female patient or to a female partner of a male patient exposed to the agent during treatment or within 7 months after the last dose of GDC-0449 should be recorded and reported as an SAE.

- Female patients should not breastfeed a baby while on this study.
- Female patients must NEVER donate ova while being treated with GDC-0449.
- All sexually active male subjects (including those who have undergone vasectomy) should utilize a barrier form of contraception **during study treatment and for 7 months after the last dose** as it is not known whether GDC-0449 that may be present in seminal fluid would cause teratogenic effects in a fetus born to the female partner of a male subject. Males should also not donate sperm during treatment or up to 3 months after the last dose.
- All patients are prohibited from donating blood for 7 months after the last dose of GDC-0449.

5.3.2 Other Considerations

5.3.2.1 Concomitant and Excluded Therapies

For information regarding other drugs that may interact with either nab-paclitaxel or gemcitabine and affect their metabolism, pharmacokinetics, or excretion, please see the gemcitabine and nab-paclitaxel package inserts.

5.3.2.2 Supportive Care and administration of additional therapies

Over the course of this trial, additional medications may be required to manage aspects of the disease state of the patients; including side effects from trial treatments or disease progression. Supportive care not otherwise specified in this protocol may be administered per institutional standard of care. Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the Investigator. Irradiation is not allowed during the study.

Colony stimulating factors may be given according to institutional guidelines for the treatment of neutropenic fever or infections associated with neutropenia. References on use of granulocyte colony-stimulating factors can be used as recommended by the American Society of Clinical Oncology (ASCO) guidelines.

5.4 Duration of Therapy

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

- Disease progression
- Intolerable (Grade 3 or 4) toxicity most probably attributable to GDC-0449 or other agents
- Intercurrent illness that prevents further administration of treatment
- Require palliative radiotherapy
- Withdrawal from the study
- Initiation of other anticancer therapy.
- The physician feels it is not longer in their best interest to continue on treatment
- If the patient becomes pregnant
- Noncompliance (e.g., missed doses, visits)

5.5 Duration of Follow Up

Patients will be followed for 18 months after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.6 Criteria for removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS/DOSE OMISSIONS

6.1 GDC-0449

Dose modifications of GDC-0449 are not planned. Treatment with GDC-0449 may be interrupted for up to 4 weeks for evaluation of a toxicity finding or up to 8 weeks for a planned surgical procedure. If a treatment interruption occurs and it is determined that GDC-0449 will be restarted, the original dose will be maintained. There are no planned dose reductions of GDC-0449.

6.2 Gemcitabine and nab-Paclitaxel

Rules for Dose Omissions and Modified Schedules

Day 1 dose missed:

If the dose held or missed was to be given on Day 1 of the next cycle, that next cycle will not be considered to start until the day the first dose is actually administered to the patient (i.e., 1-2-3-Rest, X-1-2-3-Rest, etc.)

Day 8 dose is missed:

Cycle continues per protocol, with one dose not given (i.e., 1-2-3-Rest, 1-X-3-Rest, 1-2-3-Rest, etc.). Day 15 is administered as per cycle calendar if counts and chemistries permit.

Day 15 dose missed:

That week becomes the week of rest. Next dose (if counts and chemistries permit) becomes Day 1 of a new cycle, and the patient is considered to have had a x2q3 (21-day) cycle (i.e., 1-2-3-Rest, 1-2-X, 1-2-3-Rest, etc).

Doses will be reduced for hematologic and other non-hematologic toxicities. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI CTCAE Version 4.0. Two dose modifications are permitted according to the criteria below. If a toxicity requiring dose modification occurs following the second dose reduction, further treatment should be discontinued.

Dose Level	nab- Paclitaxel (mg/m ²)		Gemcitabine (mg/m ²) ^a
Study Dose	125		1000
-1	100		800
- 2 ^b	75		600

^aDose reductions may or may not be concomitant. Please refer to Tables 4-6 for specific recommendations regarding dose reductions

^bAdditional 25% dose modifications are permissible to establish the tolerable dose for an individual patient

If patients experience study drug-related toxicities that require a delay in scheduled nab-paclitaxel and gemcitabine dosing for ≥ 28 days will be discontinued from further participation in this study.

When a dose reduction is required for Day 1 of any cycle, no dose re-escalation will be permitted for the duration of study treatment.

DOSE MODIFICATIONS AT DAY 1

In the event dose modifications are required at the beginning of a cycle due to AEs or hematologic toxicities, doses of nab-paclitaxel and gemcitabine may be adjusted as detailed in Table 3 and Table 4 below:

Table 3. Dose Modifications for Hematologic Toxicities (Day 1 of Each Cycle)

Absolute Granulocytes		Platelets	Timing
$\geq 1.5 \times 10^9/L$	AND	$\geq 100 \times 10^9/L$	Treat on time
$< 1.5 \times 10^9/L$	OR	$< 100 \times 10^9/L$	Delay by one week intervals until recovery

Table 4. Dose Modifications for Non-Hematologic Toxicity (Day 1 of Each Cycle)

Non Hematologic Toxicity and/ or Dose Hold with Previous Cycle	
Toxicity/ dose held	Gemcitabine/ Gemcitabine + nab-paclitaxel dose this cycle
Grade 0, 1 or 2	Same as day 1 previous cycle
Grade 3 toxicity	Decrease gemcitabine and nab-Paclitaxel to next lower dose level ^a
Grade 4 toxicity	Off protocol treatment ^b
Dose held in 2 previous consecutive cycles	Decrease gemcitabine to next lower dose level and continue throughout the rest of treatment

a If the toxicity only affects neuropathy, then only nab-Paclitaxel should be reduced

b Pulmonary embolism (a Grade 4 toxicity in CTCAE tables) if mild or asymptomatic, will be exempt from this requirement.

DOSE ADJUSTMENTS WITHIN A TREATMENT CYCLE

In the event that patients must have treatment delayed within a treatment cycle due to toxicities, those doses held during a cycle will not be made up. Dose modifications due to hematologic toxicity (as represented by the blood counts and toxicities, below) within a treatment cycle should be adjusted as outlined in Table 5.

Table 5. Dose Modifications for Hematologic Toxicity within a Cycle

Day 8 Blood Count	Day 8 Nab-Paclitaxel	Day 8 Gemcitabine	Day 15 Blood Count	Day 15 Nab-Paclitaxel	Day 15 Gemcitabine
ANC > 1000 and Platelets ≥ 75,000	100%	100%	ANC > 1000 and Platelets ≥ 75,000	100%	100%
			ANC 500-1000 or Platelets 50,000-74,999	Full Dose(treat on time) +GCSF*	Full Dose(treat on time) +GCSF*
			ANC < 500 or Platelets < 50,000	Hold+GCSF*	Hold+GCSF*
ANC 500-1000 ^a or Platelets 50,000-74,999	Decrease dose by 1 level (treat on time)	Decrease dose by 1 level (treat on time)	ANC > 1000 and Platelets ≥ 75,000	Return to Full Dose(treat on time) + GCSF*	Return to Full Dose(treat on time) + GCSF*
			ANC 500-1000 or Platelets 50,000-74,999	Same Dose(as Day 8, treat on time) +GCSF*†††	Same Dose(as Day 8, treat on time) +GCSF*†††
			ANC < 500 or Platelets < 50,000	Hold+GCSF*	Hold+GCSF*
ANC < 500 ^a or Platelets < 50,000	Hold	Hold	ANC > 1000 and Platelets ≥ 75,000	Decrease Day 8 dose by 1 level (treat on time)+GCSF*	Decrease Day 8 dose by 1 level (treat on time)+GCSF*
			ANC 500-1000 or Platelets 50,000-74,999	Decrease Day 8 dose by 1 level (treat on time)+GCSF*	Decrease Day 8 dose by 1 level (treat on time)+GCSF*
			ANC < 500 or Platelets < 50,000	Hold+GCSF*	Hold+GCSF*

Febrile Neutropenia (Grade 3 or 4) ^b	Hold. Upon resuming dosing, decrease to next lower level and do not re-escalate throughout the rest of treatment	Hold. Upon resuming dosing, decrease to next lower level and do not re-escalate throughout the rest of treatment		Hold. Upon resuming dosing, decrease to next lower level and do not re-escalate throughout the rest of treatment	Hold. Upon resuming dosing, decrease to next lower level and do not re-escalate throughout the rest of treatment
Recurrent Febrile neutropenia (Grade 3 or 4) ^b	Decrease to next lower dose level and do not re-escalate throughout the rest of treatment	Decrease two dose levels (to 600 mg/m ²) and do not re-escalate throughout the rest of treatment		Decrease to next lower dose level and do not re-escalate throughout the rest of treatment	Decrease two dose levels (to 600 mg/m ²) and do not re-escalate throughout the rest of treatment

a If patient do not experience resolution of neutropenia within 21 days, despite uninterrupted G-CSF treatment, study treatment will be discontinued

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

* G-CSF to the investigator discretion. It is optional if descent only affects platelets

††† If episode of myelosuppression occurred starting day 15 of this cycle decrease day 8 dose by 1 level

Dose modifications may also be made for non-hematological toxicity within a cycle as specified in Table 6.

**Table 6. Dose Modifications for Non-Hematological Toxicity within a Cycle
CTC Grade**

CTC Grade	Percent of Day 1
0-2 (and Grade 3 nausea/ vomiting and alopecia)	100%
3 (except nausea/vomiting and alopecia)	50% or Hold ^a
4	Hold ^a
<p>a This decision as to which drug should be modified will depend upon the type of non-hematologic toxicity seen and which course is medically most sound in the judgment of the physician/investigator. Treatment may be reinstated on Day 1 of the next cycle.</p>	

Peripheral Neuropathy

Nab-Paclitaxel treatment should be withheld in patients who experience \geq Grade 3 peripheral neuropathy. Gemcitabine administration can continue during this period at the discretion of the investigator. Nab-Paclitaxel treatment may be resumed at the next lower dose level in subsequent cycles after the peripheral neuropathy improves to \leq Grade 1, *regardless of suspected cause*. Patients experiencing peripheral neuropathy that requires a delay in scheduled nab-Paclitaxel dosing for \geq 28 days will be discontinued from further participation in this study. Additionally patients receiving a reduced dose of nab-Paclitaxel who experience \geq Grade 3 peripheral neuropathy at that dose level requiring a dose delay \geq 28 days without resolving to \leq Grade 1 will be discontinued from further participation in this study.

Similarly, GDC-0449 should be held in the event that patients experience \geq Grade 3 peripheral neuropathy. GDC-0449 may be resumed at the same dose of 150 mg daily after the peripheral neuropathy improves to \leq Grade 1.

As observed in other clinical trials, \geq Grade 3 neuropathy related to nab-Paclitaxel is usually seen in later phases of the treatment (cycle 6 and beyond). If \geq Grade 3 neuropathy occurs in early treatment cycles, other factors predisposing the patient to neuropathy might be present (eg. diabetes, alcohol consumption, concomitant medications). To maintain dose intensity during the first 6 treatment cycles, careful consideration should be exercised when these predisposing factors are present.

Cutaneous Toxicity

Patients who develop Grade 2 or 3 cutaneous toxicity should have their dose reduced to the next lower dose level of both drugs. If the patient continues to experience these reactions, nab-paclitaxel despite dose reduction, treatment should be discontinued. Patients who develop Grade 4 cutaneous

toxicity should have treatment discontinued.

Gastrointestinal Toxicity

If Grade 3 mucositis or diarrhea occurs, study drug should be withheld until resolution to \leq Grade 1, then reinstated at the next lower dose level of both drugs. Patients who develop Grade 4 mucositis or diarrhea should have treatment discontinued.

7. ADVERSE EVENTS

These adverse event management guidelines are intended to ensure the safety of each patient while attempting to characterize the safety and tolerability of the test products. **In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for prompt notification of SAEs to the Coordinating Center (Johns Hopkins), Genentech, Cancer Research and Biostatistics (CRAB) and IRB.**

7.1 Adverse Events (AE) definition

An adverse event is any untoward medical occurrence in a patient receiving a marketed pharmaceutical product or in a patient who is participating on a clinical trial who is receiving an investigational or non-investigational pharmaceutical agent. **The AE does not necessarily have a causal relationship with the patient's treatment.** Therefore, an adverse event can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered to be related to the medicinal product. In cancer clinical trials, many AEs are in fact related to progression of the patient's underlying malignancy.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with pancreatic cancer that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).

If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

An adverse event includes:

- an exacerbation of a pre-existing illness;
- an increase in frequency or intensity of a pre-existing episodic event or condition;
- a condition detected or diagnosed after study drug administration even though it may

have been present prior to the start of the study

- continuously persistent disease or symptoms that were present at Baseline and worsen following the start of the study.

An adverse event does not include:

- medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, or transfusion); however, the condition that leads to the procedure **is** an adverse event.
 - pre-existing diseases, conditions, or laboratory abnormalities present or detected at the start of the study that do not worsen;
 - hospitalizations or procedures that are done for elective purposes not related to an untoward medical occurrence (e.g., hospitalizations for cosmetic or elective surgery or social/convenience admissions);
 - the disease being studied or signs/symptoms associated with the disease unless more severe than expected for the patient's condition;
- overdose of study drug without any clinical signs or symptoms.

7.2 Serious Adverse Events (SAE) Definition

A serious adverse event (SAE) is defined as any untoward medical occurrence at any dose that:

- is **fatal**;
- is **life-threatening** (defined as an immediate risk of death from the event as it occurred);
- results in **persistent or significant disability or incapacity**;
- requires **in-patient hospitalization or prolongs an existing hospitalization**. (Exception: Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an adverse event. NOTE: Complications that occur during hospitalization are adverse events and if a complication prolongs hospitalization, then the event is serious);
- **is a congenital anomaly/birth defect in the offspring of a patient who received medication**;
- conditions not included in the above definitions that may jeopardize the patient or may require intervention to prevent one of the outcomes listed above unless clearly related to the patient's underlying disease.

The Investigator should exercise medical and scientific judgment when deciding whether expedited reporting is appropriate in other situations not strictly meeting the criteria outlined above. Examples of important medical events which may also meet the definition of a SAE include: intensive treatment in an emergency room or at home for a reversible condition that did not result in hospitalization (e.g., allergic bronchospasm or convulsions), certain laboratory abnormalities (e.g., blood dyscrasias), or development of drug dependency or drug abuse. If there is any question, please consult the relevant Medical Monitor.

7.3 Grading and Assessing Causality

Adverse events occurring during the study will be graded according to the NCI CTCAE Scale version 4.0 (see <http://ctep.cancer.gov/reporting/ctc.html>), where applicable. Adverse events that are not included on the toxicity scale will be designated as Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = life-threatening, and Grade 5 = death.

The Investigator should evaluate all adverse events and should make an immediate effort to determine their etiology. Adverse events that are determined *not* to be possibly, probably, or definitely related to study drug may not require further evaluation but will need to be recorded on the CRAB eCRFs. Study medications may be interrupted for an adverse event at the discretion of the Investigator. Patients requiring toxicity management should be assessed and evaluated at least weekly as indicated by the severity of the event.

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

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the {study drug} (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the {study drug}, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the {study drug}; and/or the AE abates or resolves upon discontinuation of the {study drug} or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than the {study drug} (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to {study drug} administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert or current Investigator Brochure.

Unexpected adverse events are those not listed in the Package Insert (P.I.) or current Investigator Brochure (I.B.) or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

[Insert additional unexpected adverse events applicable to this disease state]

PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- “How have you felt since your last clinical visit?”
- “Have you had any new or changed health problems since you were last here?”

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 5.1.2), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions

should be reported as medical and surgical history. A preexisting medical condition should be reassessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

e. Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within [insert time period (e.g., 90 days)] after the last dose of study drug, a report should be completed and expeditiously submitted to the Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the {study drug} should be reported as an SAE.

f. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior {study drug} exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

g. Reconciliation

The Sponsor agrees to conduct reconciliation for the product. Genentech and the Sponsor will agree to the reconciliation periodicity and format, but agree at minimum to exchange monthly line listings of cases received by the other party. If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution.

h. AEs of Special Interest (AESIs)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the Product

The [study drug] Events of Special Interest are: [List of Events of Special Interest HERE]

7.4 Potential Risks for Study Drugs

The following adverse events has been reported in previous clinical trials with the drugs that are used in the current study (GDC-0449, nab-Paclitaxel and Gemcitabine) and can be expected during the study.

7.4.1 Adverse Event List(s) for GDC-0449

The toxicities possibly related to GDC-0449 reported in previous phase 1 clinical trial included:

- *Constitutional*: Fatigue, weight loss

- *Cardiovascular*: atrial fibrillation
- *Gastrointestinal*: anorexia, dyspepsia (heartburn or stomach upset), nausea, vomiting
- *Metabolic*: hyponatremia, hypomagnesemia
- *Neurologic*: hypoesthesia (sensory neuropathy), dysgeusia (taste alteration), hypogeusia (decrease taste), ageusia (loss of taste), numbness
- *Musculoskeletal*: arthralgia, muscle spasms
- *Skin and subcutaneous tissue disorders*: skin exfoliation, alopecia (scalp, body, eyelashes and face), dermatitis acneiform

GDC-0449 has been administered in a limited number of clinical studies. The following adverse events had been observed in **animal studies**. The adverse events of GDC-0449 with other combinations chemotherapy are not known. Several studies in humans combining GDC-0449 with other chemotherapy agents are currently underway.

Dogs:

Decreased platelets; prolonged QTc; increased salivation; increased cholesterol; proteinuria; weight loss; weight gain; foamy vomitus; orange mucoid feces; alopecia, increased male germ cell degeneration in seminiferous tubules and epididymides, decreased sperm motility and decreased number of corpora lutea.

Rats:

Hunched appearance; increased stomach weight; weight gain; weight loss; rough haircoat; dehydration; few feces; increased incidence of malocclusion; microscopic lesions on incisors; hyperalbuminemia; increased cholesterol; decreased alkaline phosphatase; decreased grip strength; decreased motor activity; reversible mild body tremors (male), twitching, ataxia.

Note: GDC-0449 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Teratogenic Effects of GDC-0449

Studies have demonstrated that inhibition of the Hh pathway in embryos results in brain, facial, and other midline defects, including holoprosencephaly or microencephaly, cyclopia, absent nose, cleft palate, tooth abnormalities, and bone development abnormalities. While the effects of GDC-0449 on the developing human fetus at the recommended therapeutic dose are unknown, women of childbearing potential and men must agree to use two methods of contraception (i.e., barrier contraception and another method of contraception) prior to study entry, for the duration of study participation, and for 7 months following treatment.

Women of childbearing potential are defined as follows:

- Patients with regular menses
- Patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding
- Women who have had a tubal ligation

Women are considered not to be of childbearing potential for the following reasons:

- The patient has undergone hysterectomy and/or bilateral oophorectomy.
- The patient is post-menopausal defined by amenorrhea for at least 1 year in a woman > 45 years old.

Women of childbearing potential are required to use two forms of acceptable contraception (refer to Appendix B), including one barrier method during participation in the study and for the 12 months following the last dose. Women of childbearing potential are also advised to have monthly pregnancy tests for 7 months after discontinuation of GDC-0449. All patients should receive contraceptive counseling either by the investigator or by an OB/gynecologist or other physician who is qualified in this area of expertise. If a woman of childbearing potential believes that her contraceptive method has failed, emergency contraception should be considered.

If a patient is suspected to be pregnant, GDC-0449 should be IMMEDIATELY discontinued and the study physician contacted. 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 with GDC-0449.

If a female patient becomes pregnant during therapy or within 7 months after the last dose of GDC-0449, or if the female partner of a male patient exposed to the drug becomes pregnant while the male patient is receiving GDC-0449 or within 7 months after the last dose of GDC-0449, the investigator must be notified in order to facilitate outcome follow-up.

Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious. Any congenital anomaly/birth defect in a child conceived during the study or within 7 months after the last dose of GDC-0449 to a female patient or to a female partner of a male patient exposed to the agent during treatment or within 7 months after the last dose of GDC-0449 should be recorded and reported as an SAE.

In addition, it is not known whether GDC-0449 that may be present in seminal fluid would cause teratogenic effects in a fetus born to the female partner of a male subject. Sexually active male subjects should utilize a barrier form of contraception, even those who have had a vasectomy, during study treatment and for 7 months after the last dose. Male patients should advise their partners to use an additional method of contraception during the study and for at least 7 months after discontinuation of GDC-0449. Male subjects should also not donate sperm during treatment or up to 7 months after the last dose.

Risk of Male Germ Cell Degeneration

Effects on testes and epididymides characterized by mild to moderate germ cell degeneration in seminiferous tubules, relative paucity of spermatozoa, and increased cellular debris in epididymides were observed in male dogs at all dose levels tested and were consistent with the pharmacologic activity of the drug. There were no changes in Leydig or Sertoli cells in any animal. Evidence of partial recovery was noted after a 4-week recovery period.

Germ cell degeneration in male patients is likely to occur at pharmacologically active doses. There is no specific mitigation strategy for this GDC-0449 toxicity; however, male patients should be made aware of it during the consent process. Although this effect is expected to be reversible with discontinuation of dosing, long-term effects on male fertility cannot be excluded at this time.

7.4.2 Adverse Event List(s) for nab-Paclitaxel

The most common toxicities reported in previous clinical trials included:

- *Myelosuppression, predominantly neutropenia.* Grade 4 neutropenia was reported and typically resolved in < 7 days and did not require colony stimulating factor support.
- *Peripheral neuropathy, predominantly sensory.* Grade 3 peripheral neuropathy was reported and typically improved to Grade 1 or 2 within 21 days of interrupting the nab-Paclitaxel dose. Following resolution of the peripheral neuropathy to acceptable levels, clinicians were able to restart nab-Paclitaxel dosing at a lower dose levels.
- *Nausea and vomiting.* Nausea and vomiting were seen, typically at Grade 1 or 2 levels. This AE responded well to standard anti-emetic regimens.
- *Myalgias and arthralgias.* Myalgias and arthralgias were reported and typically were Grade 1 or 2; these were responsive to standard acetaminophen-containing medication.
- *Mucositis.* Mucositis was reported typically Grade 1 or 2. It was not dose limiting
- *Alopecia.* Alopecia was reported by most patients and was similar to that seen with Taxol.

7.4.3 Adverse Event List(s) for Gemcitabine

The most common toxicities reported with gemcitabine are:

- *Hematologic* - In studies in pancreatic cancer, myelosuppression is the dose-limiting toxicity with Gemzar®, but <1% of patients discontinued therapy for anemia,

leukopenia, or thrombocytopenia. Red blood cell transfusions were required by 19% of patients. The incidence of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, was reported in 16% of patients; less than 1% of patients required platelet transfusions. Patients should be monitored for myelosuppression during Gemzar therapy and dosage modified or suspended according to the degree of hematologic toxicity

- *Gastrointestinal* - Nausea and vomiting were commonly reported (69%) but were usually of mild to moderate severity. Severe nausea and vomiting (WHO Grade 3/4) occurred in <15% of patients. Diarrhea was reported by 19% of patients, and stomatitis by 11% of patients.
- *Hepatic* - In clinical trials, Gemzar was associated with transient elevations of one or both serum transaminases in approximately 70% of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to Gemzar or with greater total cumulative dose. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving Gemzar.
- *Renal* - In clinical trials, mild proteinuria and hematuria were commonly reported. Hemolytic Uremic Syndrome (HUS) has been reported rarely (0.25%) with the use of Gemzar. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required.
- *Fever* - The overall incidence of fever was 41%. This is in contrast to the incidence of infection (16%) and indicates that Gemzar may cause fever in the absence of clinical infection. Fever was frequently associated with other flu-like symptoms and was usually mild and clinically manageable.
- *Rash* - Rash was reported in 30% of patients. The rash was typically a macular or finely granular maculopapular pruritic eruption of mild to moderate severity involving the trunk and extremities. Pruritus was reported for 13% of patients.
- *Pulmonary*- In clinical trials, dyspnea, unrelated to underlying disease, has been reported in association with Gemzar therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of Gemzar. The etiology of these effects is unknown. If such effects develop, Gemzar should be discontinued. Early use of supportive care measures may help ameliorate these conditions.
- *Neurotoxicity* - There was a 10% incidence of mild paresthesias and a <1% rate of severe paresthesias
- *Edema*: Edema (13%), peripheral edema (20% %), and generalized edema (<1%) were reported. Less than 1% of patients discontinued due to edema.
- *Flu-like Symptoms* - “Flu syndrome” was reported for 19% of patients. Individual

symptoms of fever, asthenia, anorexia, headache, cough, chills, and myalgia were commonly reported. Fever and asthenia were also reported frequently as isolated symptoms. Insomnia, rhinitis, sweating, and malaise were reported infrequently. Less than 1% of patients discontinued due to flu-like symptoms.

- *Infection* - Infections were reported for 16% of patients. Sepsis was rarely reported.
- *Alopecia*- Hair loss, usually minimal, was reported by 15% of patients

Please see gemcitabine prescribing information for more details on the known precautions, warnings, and adverse reactions of gemcitabine (current version of Prescribing Information is provided in the Study Manual).

7.5 Reporting Adverse Events

The Investigator is responsible for recording, reporting and following all adverse events, regardless *of causality*, observed during the study period, starting with initial study drug administration and ending at the time the patient goes off study or 30 days after patient's last dose of study drug, whichever is later. Events occurring within 30 days prior to study drug administration should be recorded as pre-treatment signs and symptoms.

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

“Lack of efficacy” (progressive disease) is not considered an adverse event. The signs and symptoms or clinical sequelae resulting from lack of efficacy should be reported if they fulfill the adverse event or SAE definitions.

Laboratory Results as Serious Adverse Events

According to the NCI CTCAE system of adverse event grading, laboratory values of Grade 3 or 4 are described as “severe” or “life-threatening.” For example, a neutrophils count <500/mm³ would meet laboratory criteria as Grade 4 (“life-threatening”). This description is not always synonymous with the assessment of the “serious” criteria of an AE as “life threatening”.

In order for adverse events to be considered serious by “life-threatening” criteria, it must be medically judged as possessing “an immediate risk of death from the event as it occurred,” not because of the theoretical potential for life-threatening consequences. In the case of a neutrophil count <500/mm³, the AE would be captured as an AE of Grade 4 neutropenia, but it would not automatically be considered a SAE unless the investigational physician determined this represented an immediately life-threatening event for the patient.

Specifically, uncomplicated Grade 4 neutropenia should not be reported as a SAE. Neutropenia associated with fever, infection, or hospitalization should be reported as a SAE.

Investigator Reporting of AEs and SAEs

The Investigator or designee must completely and promptly record each adverse event using the eCRF, regardless of relationship to study drug as determined by the Investigator. **The Investigator must assess AE/SAE causality for any patients treated at his/her site.** The Investigator should attempt, if possible, to establish a diagnosis based on the patient's signs and symptoms. When a diagnosis for the reported signs or symptoms is known, the Investigator should report the diagnosis, not the symptoms, as the adverse event.

Clinically significant laboratory abnormalities present at the Baseline visit will be recorded as pre-treatment signs and symptoms. After study treatment administration, laboratory abnormalities will not be recorded as adverse events unless considered clinically significant by the Investigator, and clinically significant laboratory abnormalities will not be recorded as serious AEs unless the event meets the definition of serious.

AEs and SAEs should be reported on the electronic Case Report Forms provided by CRAB.

Reporting Serious Adverse Events (SAEs)

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment [or “initiation of any study procedures”] and ends 30 days [or insert other time period] following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

ALL sites should report ALL Serious adverse events, regardless of causality, to ALL of the following:

- 1. Coordinating Site (Johns Hopkins Hospital)**
- 2. Genentech Safety Group**
- 3. Cancer Research and Biostatistics (CRAB)**
- 4. Institution IRB**

Timelines for reporting SAE's

- 1. Participating sites are responsible for reporting SAE's to the Coordinating Site (Johns Hopkins) within 24 hours of becoming aware of the event occurrence. All SAEs should be recorded on the Serious Adverse Event Reporting Form accessible on the website. This 2 page form must be completed and faxed to:**

Study Coordinating Site

Daniel Laheru MD (Principal Investigator)

Yvette Cetasaan, CCRP

Fax: 443-287-6566

2. Participating sites are responsible for reporting to their Institution IRB in accordance with their institution guidelines.
3. Participating sites are responsible for reporting to the Genentech Safety Group by facsimile within 24 hours of becoming aware of the event occurrence. All SAEs should be recorded on CRAB eCRF and faxed to:

Genentech Drug Safety

Fax: (650) 225-4682 or (650) 225-5288

4. Participating sites are responsible for reporting to Cancer Research and Biostatistics (CRAB) within 24 hours of becoming aware of the event occurrence. All SAEs should be recorded on CRAB eCRF.

The Johns Hopkins Investigators will report all SAEs on CRAB eCRF and faxed to all the following agencies:

1. IRB- within 3 days if the SAE is related to the study drug. If the SAE is not considered related to the study drug within 10 days.

Johns Hopkins Medicine IRB
Reed Hall B-130
1620 McElderry St.
Baltimore, MD 21205-1911
Phone: 410-955-3008

2. Genentech Drug Safety- within 24 hrs
Fax: (650) 225-4682 or (650) 225-5288
3. FDA- . As per section 7.6
4. CRAB- within 24 hrs

Follow up on SAE reports should also be send to all the above agencies within two weeks of receipt of information at the site.

Investigators must report all SAEs to Genentech within the timelines described below. The completed Medwatch/case report should be faxed immediately upon completion to Genentech Drug Safety at:

(650) 225 4682
OR
(650) 225 5288

- Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it

becomes available.

- Serious AE reports that are related to the [study drug] and AEs of Special Interest (regardless of causality) will be transmitted to Genentech within fifteen (15) calendar days of the Awareness Date.
- Serious AE reports that are unrelated to the [study drug] will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
- Additional Reporting Requirements to Genentech include the following:
- Any reports of pregnancy following the start of administration with the [study drug] will be transmitted to Genentech within thirty (30) calendar days of the Awareness Date.
- All Non-serious Adverse Events originating from the Study will be forwarded in a quarterly report to Genentech.

Note: Investigators should also report events to their IRB as required.

MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form

- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom and adverse event was reported. For questions regarding SAE reporting, you may contact the Genentech Drug Safety representative noted above or the MSL assigned to the study. Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A (Mandatory Reporting) form is available at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm>

7.6 Safety Reporting Requirements for IND Holders

For **Investigator Sponsored IND Studies**, there are some additional reporting requirements for the FDA in accordance with the guidance set forth in 21 CFR 212.32. Sponsor-investigators of studies conducted under an IND must comply with the following safety reporting requirements:

a. Expedited IND Safety Reports:

7 Calendar-Day Telephone or Fax Report:

The Sponsor-Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is **unexpected and assessed by the investigator to be possibly related to the use of GDC-0449**. An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech within 7 calendar days of first learning of the event. Each telephone call or fax transmission (see fax number below) should be directed to the FDA new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever is responsible for the review of the IND.

15 Calendar-Day Written Report:

The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered possibly related to the use of GDC-0449. An unexpected adverse event is one that is not already described in the Investigator Brochure.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech Drug Safety, and all participating investigators within 15 calendar days of first learning

of the event. In this study electronic CRF will be used.

FDA fax number for IND Safety Reports:

1 (800) FDA - 0178

All written IND Safety Reports submitted to the FDA by the Sponsor-Investigator must also be faxed to:

1. Genentech Drug Safety

Fax: (650) 225-4682 or (650) 225-5288

For questions related to safety reporting, contact:

Genentech Drug Safety

Tel: 1-888-835-2555

(Please use the safety reporting fax cover sheet attached to this document for your fax transmission)

b. IND Annual Reports

In accordance with the regulation 21 CFR § 312.32, the Sponsor-Investigator shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.32 for a list of the elements required for the annual report. All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. Copies of such reports should be mailed to:

Genentech, Inc.

ATTN: GDC-0449 IST Coordinator

1 DNA Way, Mailstop 445-A

South San Francisco, CA 94080-4990

Tel: (650) 225-7121 (Oncology Hotline)

STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Vismodegib (GDC0449) Protocols

Email: hedgehog-gsur@gene.com

Fax: 866-741-3639

7.7 Data and Safety Monitoring Plan

This is a Level II study under the SKCCC Data Safety Monitoring Plan (DSMP). Data Monitoring of this study will occur after the first three patients are enrolled and every six months thereafter.

The study will be monitored internally by the Principal Investigator and externally by CRO in

accordance with SKCCC guidelines.

7.7.1 Internal review in all participating centers

The PI in each participating center will have a regular internal monitoring.

The internal review should occur after the first three patients are enrolled and have completed two cycles of therapy. The process should occur every six months thereafter. The PI at each institution will review data to assure the validity of data, as well as, the safety of the subjects. The PI will also monitor the progress of the trial. The PI will review safety reports and clinical trial efficacy endpoints and to confirm that the safety outcomes favor continuation of the study.

The PI will be responsible for maintaining the clinical protocol, reporting adverse events, assuring that consent is obtained and documented, reporting of unexpected outcomes, and reporting the status of the trial in the annual report submitted to the IRB. Content of the report will include year-to-date and full trial data on: accrual and eligibility, protocol compliance, treatment administration, toxicity and adverse events, response, survival, regulatory compliance, compliance with prearranged statistical goals. The following will be reviewed:

- Original, signed consent forms to ensure that one is available for each subject.
- Case report forms and source documentation for validity and consistency in the completed entries, as well as, accuracy, legibility, signatures and dates.
- Treatment administration records to ensure concurrence between dispensing records and CRFs as to subject identity, and dosage of study drug administered.
- Compliance with the protocol will also be checked.
- Pharmacy drug accountability records for accuracy and completeness, and study drug storage to ensure proper maintenance and supply levels.

7.7.2 External review in all participating centers

Johns Hopkins SKCCC: The protocol will be monitored externally by the SKCCC CRO in accordance with SKCCC guidelines. Trial monitoring and reporting will be done through the Safety Monitoring Committee (SMC) at SKCCC.

Participating sites: The protocol will be monitored by an external CRO (TD2). A report of the reviews will be submitted to Johns Hopkins principal investigator and SKCCC CRO.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

8.1 GDC-0449

Route of Administration:	Oral
Mode of Action:	GDC-0449 provides anticancer responses by inhibiting the Hedgehog pathway. The Hedgehog signaling pathway controls cell differentiation, growth, and proliferation. It is most active during embryogenesis but may also play a role in the regulation of adult stem cells involved in the maintenance and regeneration of adult tissues.
How Supplied:	<p>GDC-0449 is supplied by Genentech/ JHH Investigational Drug Services (IDS). It is available as:</p> <ul style="list-style-type: none">• 25-mg orange, size 3 capsules containing microcrystalline cellulose, sodium lauryl sulfate, talc, sodium glycolate and magnesium stearate as excipients.• 150-mg grey and pink, size 1 capsules containing microcrystalline cellulose, lactose monohydrate, sodium lauryl sulfate, povidone, talc, sodium glycolate, and magnesium stearate. <p>Capsules are packaged in 75-mL round, white, high-density polyethylene (HDPE) bottles and closed with 38/400 two-piece HDPE child-resistant caps. Each bottle contains 32 capsules.</p>
Clinical Formulation:	<p>For the clinical studies, hard gelatin capsules containing 150 mg vismodegib are available. For the 150 mg strength, placebo capsules are also available.</p> <p>The 150-mg vismodegib drug product is a hard gelatin capsule formulation for oral administration. The capsule fill consists of vismodegib and the following excipients: microcrystalline cellulose PH101, lactose monohydrate, sodium lauryl sulfate, povidone K29/32, sodium starch glycolate, talc, magnesium stearate, and purified water. All of these excipients are compendial (USP/NF-EP) grade. The capsule shell consists of gelatin, red iron oxide, black iron oxide, and titanium dioxide. A compendial-grade black printing ink may be used.</p> <p>The placebo for the 150-mg drug product is a hard gelatin capsule formulation for oral administration. The capsule fill consists of the following excipients, without the active pharmaceutical ingredient (API): microcrystalline cellulose PH102, lactose monohydrate, sodium lauryl sulfate, sodium</p>

starch glycolate, talc, and magnesium stearate. All of these excipients are compendial (USP/NF-EP) grade. The capsule shell consists of gelatin, red iron oxide, black iron oxide, and titanium dioxide. A compendial-grade black printing ink may be used.

Storage: GDC-0449 capsules should be stored in the recommended storage conditions at 59°F and 86°F (15°C and 30°C) and should be protected from excessive exposure to light. Information on the shelf life of the capsules is provided on the label.

Drug Administration: Patients should take GDC-0449 at approximately the same time each day, with or without food. If a patient misses a dose (e.g., due to emesis), he or she should be instructed not to take or make up that dose and to resume dosing with the next scheduled dose. Missed doses should not be made up.

Patient Care Implications: The terminal half-life of GDC-0449 is currently unknown, but is expected to be longer than 1 week, and may be as high as 2 to 3 weeks. If plasma levels of GDC-0449 need to be lowered emergently, animal studies suggest that oral administration of activated charcoal may lower drug plasma levels more quickly than dose cessation alone.

Drug Interactions: Avoid any concurrent drug metabolized by cytochrome P450 that has a narrow therapeutic index.

Supply: GDC-0449 will be obtained from JHH IDS.

8.2 nab-Paclitaxel

Route of Administration: Intravenous

Packaging, Labeling, and Storage of Study Drug:

Nab-Paclitaxel will be supplied by Abraxis BioScience (Abraxis) /JHHIDS, in single-use vials. Each single-use 50 mL vial will contain paclitaxel (100 mg) and approximately 900 mg human albumin (HA) as a stabilizer. Each vial will be labeled according to country-specific regulatory requirements for labeling of investigational products. Unreconstituted nab-paclitaxel should be stored at controlled room temperature (25°C or 77°F; excursions permitted to 15- 30°C [See USP

controlled room temperature]). Reconstituted nab-paclitaxel should be used immediately. If not used immediately, the vial of reconstituted Nab-Paclitaxel must be placed in its carton and be placed in a refrigerator at 2° to 8°C (36° to 46°F) for a maximum of 8 hours. Both forms should be stored in an area free of environmental extremes and must be accessible only to study personnel. Temperature records for nab-paclitaxel must be made available to the Abraxis or other sponsor nominated monitoring teams for verification of proper study drug storage.

Administration

NOTE: It is not a requirement to use filter needles in the preparation of, or in-line filters during the administration of nab-paclitaxel. In any event, filters of pore-size less than 15 micrometers must not be used.

nab-paclitaxel will be reconstituted by appropriate study personnel and administered to the patient at the study site. The Investigator will calculate the body surface area (BSA) of the patient in order to determine the total amount of paclitaxel to be administered.

Reconstitution and use of nab-paclitaxel:

1. Calculate the patient's BSA according to standard institutional methods. BSA will be calculated at Baseline and recalculated only if body weight changes by more than 10%. Dosing BSA may be capped if the treating physician believes it is in the best interest of an obese patient.

2. Calculate the total dose (in mg) to be administered by:
Total Dose (mg) = BSA x (study dose mg/m²)

3. Calculate the total number of vials required by:
Total Number of Vials = Total Dose (mg) 100 (mg/vial)
Round up the number of vials to be reconstituted to the next higher whole number when a fractional number of vials is obtained by the above formula (e.g., if the total number of vials = 4.05 or 4.5, then 5 vials would be reconstituted).

4. Using sterile technique, prepare the vials for reconstitution.

5. Swab the rubber stoppers with alcohol.

6. Reconstitute each nab-paclitaxel vial by using a 50 or 60 cc sterile syringe to inject 20 mL of 0.9% Sodium Chloride Injection or equivalent

into each vial over a period of not less than 1 minute (Note: Change the syringes after reconstituting every 3 vials).

- **Slowly** inject the 20 mL of 0.9% Sodium Chloride Injection, over a minimum of 1 minute, using the sterile syringe directing the solution flow onto the **inside wall** of the vial.
- **DO NOT INJECT** the 0.9% Sodium Chloride Injection solution directly onto the lyophilized cake as this will result in foaming.
- Once the injection is complete, allow the vial to sit for a **minimum of 5 minutes** to ensure proper wetting of the lyophilized cake/powder.
- **Gently** swirl and/or invert the vial **slowly** for at least **2 minutes** until complete dissolution of any cake/powder occurs. **Avoid** generation of foam.
- If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.
- Each mL of reconstituted product will contain 5 mg of paclitaxel.

7. Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient:

$$\text{Dosing volume (mL)} = \text{Total dose (mg)} / 5 \text{ (mg/mL)}$$

8. The reconstituted sample should be milky and homogeneous without visible particulates. If unsuspended powder is visible, the vial should be **gently** inverted again to ensure complete resuspension, prior to use.

9. Use immediately following reconstitution. If not used immediately, replace the reconstituted vial in the carton and store reconstituted nab-Paclitaxel in a refrigerator for not more than 8 hours.

10. Using a new, sterile 50 or 60 cc syringe, withdraw the reconstituted nab-Paclitaxel solution. Do not remove the rubber stopper from the nab-Paclitaxel vials as this can compromise the sterility of the drug preparation.

11. Inject the calculated dosing volume of reconstituted nab-Paclitaxel suspension into an empty sterile, standard PVC IV bag, using an injection port. Inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag. Repeat steps 9 and 10 until the patient's entire required dose is injected into the IV bag.

12. Remove the injection port.

13. Once the exact volume of reconstituted nab-Paclitaxel has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures for cytotoxic drugs.

14. Administer the calculated dosing volume of reconstituted nab-Paclitaxel suspension by IV infusion over 30 minutes. The use of in-line filters is not necessary; if used, in-line filters with pore sizes of < 15 microns (15 µm) should not be used.

Supply: nab-Paclitaxel will be obtained from JHH IDS.

8.3 Gemcitabine

Route of Administration: Intravenous

Description:

For complete details on drug administration, storage, clinical pharmacology, and the human pharmacokinetics of gemcitabine, please see the gemcitabine package insert (current version of Prescribing Information is provided in the Study Manual).

Formulation:

Gemcitabine (difluorodeoxycytidine) is a pyrimidine antimetabolite, which is an analogue of deoxycytidine. It was initially synthesized as a potential antiviral drug but selected for anticancer development because of its activity in *in-vivo* and *in vitro* tumors. **Gemcitabine is approved for the treatment of patients with pancreatic cancer and will be obtained commercially.** Gemcitabine should be stored, reconstituted and administered according to the manufacturer's recommendation

Packaging, Labeling, and Storage of Gemcitabine:

Instructions for Storing Gemcitabine

Store at controlled room temperature (20° to 25°C) (68° to 77°F). The USP has defined controlled room temperature as “A temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25°C (68° to 77°F); that results in a mean kinetic temperature calculated to be not more than 25°C; and that allows for excursions between 15° and 30°C (59° and 86°F) that are experienced in pharmacies, hospitals, and warehouses.”

Administration:

Preparation and administration of gemcitabine should be per the gemcitabine package insert (current version of Prescribing Information is provided in the Study Manual).

Instructions for Use/Handling of Gemcitabine

The recommended diluent for reconstitution of gemcitabine is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for gemcitabine upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided. To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200-mg vial or 25 mL of 0.9% Sodium Chloride Injection to the 1-g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL which includes accounting for the displacement volume of the lyophilized powder (0.26 mL for the 200-mg vial or 1.3 mL for the 1-g vial). The total volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/mL. Reconstituted gemcitabine is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution or container permits. If particulate matter or discoloration is found, do not administer.

When prepared as directed, gemcitabine solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F) [See USP]. Discard unused portion. Solutions of reconstituted gemcitabine should not be refrigerated, as crystallization may occur. The compatibility of gemcitabine with other drugs has not been studied. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets. Unopened vials of gemcitabine are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C (68° to 77°F) [See USP].

Supply: Will be obtained by commercial means

8.3 Study Medication Accountability and Destruction (GDC-0449 and nab-Paclitaxel)

All study drug required for completion of this study will be provided by Johns Hopkins Hospital (JHH) Investigational Drug Services (IDS).

The recipient will acknowledge receipt of the drug by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug received at, dispensed from, returned to and disposed of by the study site should be recorded by using the Drug Inventory Log. Inspections of the study drug supply for inventory purposes and assurance of proper storage will be conducted as necessary. Any significant discrepancy will be recorded and reported to JHH IDS or their designee and a plan for resolution will be documented.

Study drugs will not be loaned or dispensed by the Investigator to another Investigator or site, unless specifically requested by JHH IDS in writing.

Temperature records for nab-Paclitaxel must be made available to the JHH IDS or other Sponsor nominated monitoring teams for verification of proper study drug storage.

Only completely unused study drug vials (nab-Paclitaxel) should be retained by the site until a representative from JHH IDS or other JHH IDS-designated personnel have completed an inventory. Partially used and completely used vials should be destroyed according to the site's guidelines, and their disposition should be recorded on the Investigational Drug Accountability Record Form.

Study drug will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to JHH IDS with the appropriate documentation. JHH IDS or someone else designated by the JHH IDS will personally inspect the study drug inventories before returning or destroying supplies of either medication. If the study site chooses to destroy study drug, the method of destruction must be documented and JHH IDS must evaluate and approve the study site's drug destruction standard operating procedure prior to the initiation of drug destruction by the study site.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Laboratory Correlative Studies

We will evaluate two sources of patient material (tumor core biopsies and blood) in order to evaluate the effects of GDC-0449 on the tumor-initiating CSC compartment in treated tumors. We will also evaluate the effects combination therapy with nab-paclitaxel on circulating biomarker levels, including CA 19-9 and SPARC. Tumor core biopsies and blood samples will be obtained pre- and post-treatment in patients.

Biopsies: Pre-treatment biopsies will be done at screening within 14 days before starting cycle 1. The second post-treatment biopsy will occur after two months of being on the study.

Patients who have response to therapy (partial response or complete response) but then subsequently develop disease progression while on treatment may be asked to provide an optional third biopsy. This will be utilized to evaluate the hedgehog signaling pathway markers (section 9.1.5.3) or tests to evaluate for mechanisms of acquired resistance.

9.1.1 Specimen collection techniques

9.1.1.1. Core biopsy of tumor tissue

9.1.1.1.1 Patient preparation instructions for core biopsy procedure

Detailed instructions may be provided to patients who are planning to have a tumor biopsy and their health care providers. A tumor biopsy eligibility checklist will be completed prior to the tumor biopsies by a member of the clinical study team.

Medication and Supplement Restrictions:

- Must be off Plavix, Coumadin, aspirin and aspirin-containing medications, herbal, fish oil based (omega 3), and vitamin E supplements for 7 days prior to procedure
- Must be off all non-steroidal anti-inflammatory drugs (NSAIDs) for 4 days prior to procedure (this includes but is not limited to ibuprofen, naproxen, celecoxib, indomethacin, etodolac)
- Must be off Heparin for 6 hours prior to procedure.

Labwork:

- PT/PTT, and the platelet level must be within normal ranges within 7 days of the procedure.

Day of Procedure Restrictions:

- If procedure is in the morning, NPO after 12 midnight,
- If procedure is in the afternoon, may have a liquid breakfast only

9.1.1.1.2. Biopsy Procedure

Biopsies will be done by routine U/S or CT-guided procedures depending on the imaging characteristics of the area to be biopsied. 18-22 G core biopsy needles will be used, and 2-4 samples will be obtained from the lesion. Prior to biopsy, potential biopsy "targets" will be evaluated by a radiologist, to assess whether the lesion can be safely biopsied.

Analgesia and Anesthesia

Local anesthesia will be achieved with lidocaine 2% injection. Post-procedure analgesia, which is rarely needed, will consist of acetaminophen (<3 gm total in any 24-hour period), NSAID's (for patients with platelet count > 50,000 mm³ without overt bleeding), or oxycodone as needed. Unexpectedly severe post-procedure pain will be immediately evaluated by the study subject's primary oncologist or research personnel.

Anatomical sites to be biopsied

Biopsies will be obtained only from sites that constitute minimal risk to the subject. The biopsy service will make the final decision independent of the principal investigator or co-investigators.

It is not possible to designate every conceivable site, but acceptable areas include:

- liver metastasis (not immediately adjacent to major vessels)
- peripheral accessible lymph nodes (cervical, axillary, inguinal, extremities)
- Primary pancreatic mass by Endoscopic ultrasound and core biopsy

Of these, the liver is the most commonly biopsied site in patients with advanced pancreatic cancer, in our experience. Sites that will not be biopsied for research purposes only include:

- lung
- brain
- mediastinum
- intra-pelvic viscera
- any site deemed by the patient's primary oncologist, study investigator, or radiologist to represent greater than minimal risk to the subject.

JHH/JHU and Published Experience

At Johns Hopkins, the following data is available regarding biopsy complication rates. This data was compiled by the biopsy service for fiscal year 2002:

- There were 0 complications of 89 lymph node biopsies
- There were 0 complications of 479 liver core biopsies.

Published literature on the complications of tumor biopsies is typically organ-specific. For study subjects with colorectal cancer, it is expected that the liver will be the most common site of tumor biopsies. For liver biopsies, published reviews quote a complication rate of 0.06 – 0.32%. The complication rate does not appear to be affected by peri-hepatic ascites. Extrapolation to an oncology study population is somewhat problematic given that the indication for such biopsies in the general population is often severe liver disease or dysfunction; such patients would not be candidates for oncology clinical trials.

9.1.1.1.3. Fine needle aspiration biopsy (FNAB) as an alternative procedure to core biopsy

In the unlikely event that no sites amenable to core biopsy are available, we will obtain tumor material via ultrasound-guided FNA of the primary tumor, a routine diagnostic procedure for establishing the diagnosis of pancreatic adenocarcinoma. An FNAB will be performed using a standard technique using 22 to 27 G needle, per standard radiologic practice, including on-site microscopic evaluation by a cytopathologist, or a specially trained cytotechnologist. A maximum of four FNA “passes” will be performed. The first pass will be used for on-site examination of the material, to determine presence and quality of lesional tissue. The subsequent passes will be performed either for tissue procurement for the end-point assays, or to guide the radiologist to the appropriate area of the lesion. The first FNA pass will be examined on air-dried, DiffQuick-stained slides, as well as ethanol-fixed for Papanicolaou staining. Second and third FNA pass will be used for mRNA collection in RNALater buffer (Ambion, Inc.). The fourth pass will be used for suspension in 10% neutral buffered formalin, then processed using the thrombin clot technique, and embedded in paraffin. The FNAB material collected in RNALater will be used for the real time quantitative PCR assays, as described subsequently (see section 9.1.5.), and the formalin fixed “cytospin” sample will be used for immunohistochemical assessment of the CSC compartment using a panel of biomarkers.

9.1.1.2. Blood

Blood samples for the biomarkers CA19-9 and SPARC will be collected at the beginning of the first two cycles and every eight weeks afterwards. CA19-9 is considered standard of care. Blood samples for circulating stem cells will be collected twice during the study. The first sample will be obtained at the beginning of treatment (cycle one day 1). The second sample will be obtained at the beginning of cycle 3. We will collect approximately 150mL of blood (20mL of serum for banking in order to perform biomarker studies, and 120mL of PBMCs for circulating CSCs.)

9.1.2. Handling of specimens

9.1.2.1. Core biopsy

Samples of core biopsy will be equally divided into containers marked as “formalin” (containing 10% neutral buffered formalin), or “RNA” (containing RNeasy Lysis Buffer, Qiagen, Inc.). Samples fixed in formalin will be processed as per routine protocols for archival samples, and 5µM recuts from the paraffin-embedded blocks will be obtained as follows: one reference hematoxylin and eosin slide, and five serial unstained slides on ChemMate (Ventana Medical Systems, Inc). One or more of the latter sections will be utilized for immunohistochemical analysis of the CSC compartment using a panel of biomarkers, including aldehyde dehydrogenase (ALDH), CD24, CD44, and CD133. Samples fixed in RNeasy Lysis Buffer will undergo total mRNA extraction using the RNeasy Mini Kit (Qiagen, Inc.), followed by reverse transcription to cDNA using the SuperScript II cDNA Synthesis kit (Invitrogen). Real time quantitative PCR (qRT-PCR) analysis will be performed for transcript levels of *Gli1*, *Ptch*, *Aldh*, *CD24* and *CD44* in the samples, using *SDHA* as a housekeeping gene control. Further details on these assays are indicated in section 9.1.5.

9.1.2.2. Blood

PBMCs will be separated from whole blood using the Ficoll Hypaque density gradient centrifugation method, and used for flow cytometry for circulating CSCs as described in section 9.1.5. The residual serum will be stored at -80°C, and used for measurement of circulating CA19-9 and SPARC levels.

9.1.3. Shipping of Specimens

All samples collected for laboratory correlative studies will be shipped to:

Anirban Maitra, MBBS
Associate Professor of Pathology and Oncology
The Sol Goldman Pancreatic Cancer Research Center
Johns Hopkins University School of Medicine
Room 345, CRB II
1550 Orleans Street,
Baltimore, MD 21212

Ph 410 955 3511 / Fax 410 614 0671

Email: amaitra1@jhmi.edu

9.1.4. Sites performing correlative studies

Johns Hopkins University
Translational Genomics (TGEN), Inc.
University of Pennsylvania

(Note: Only archival core biopsy specimens will be obtained from patients recruited in Spain due to logistics and restrictions on international shipping of fresh human tissues).

9.1.5. Specific laboratory assays

9.1.5.1. Immunohistochemical analysis of the CSC compartment

Multiple lines of evidence suggest that Hh antagonists impact the survival of tumorigenic CSC populations in solid tumors, including pancreatic cancer. Studies in orthotopic xenograft models of pancreatic cancer demonstrate that Hh inhibitors significantly reduce the proportion of CSCs. We hypothesize that the addition of GDC-0449 in the treatment cocktail (beginning at cycle 2) will similarly diminish the proportion of tumorigenic CSCs in pancreatic cancer lesions, and thereby, improve PFS by limiting subsequent metastatic events. To test this hypothesis, we will obtain pre-and post-treatment biopsies in patients enrolled in this trial, and interrogate the CSC compartment in matched biopsies using a diverse panel of immunohistochemical markers. The biomarkers included are ALDH, CD24, CD44, and CD133, which have all been shown to label distinct, and partially non-overlapping, subsets of CSCs in solid tumors. These CSC markers are routinely used, and published, in the Maitra laboratory. Unstained 5 μ M thick ChemMate slides will be stained with antibodies against these markers (all obtained from Cell Signaling Technologies, Ltd), and chromogenic detection performed using the Catalyzed Signal Amplification kit (Dako). Quantitative Image Analysis for CSC markers will be performed using the Frida Image Analysis Software (<http://bui2.win.ad.jhu.edu/frida/>). The percentage of cells staining for each CSC marker will be utilized for calculating the mean and standard deviation in pre- and post-biopsy cohorts, and any statistical significance in difference calculated using Chi-square analysis. Patients enrolled in the trial will be stratified as “progressors” *versus* “non-progressors” based on defined criteria, and differences in CSC amelioration between these two cohorts compared as a potential measure of treatment response to Hh antagonists. In a subset of ~10 patients, we will also determine if anti-metabolite therapy increases the proportion of CSCs at the culmination of cycle 1 of therapy, based on previous preclinical data in xenograft models. We anticipate these correlative studies will establish a framework for judging the *in vivo* efficacy of CSC-directed therapies in future trials with this class of antagonists.

9.1.5.2. Quantitative real time PCR analysis for CSC markers

The rationale for analyzing CSC-related transcripts (*ALDH*, *CD24* and *CD44*) remains identical to that of immunohistochemical analysis, but provides an additional layer of internal validation. Moreover, in the event that adequate material is not obtained from core biopsies, qRT-PCR will be the assay of choice in FNAB material. Expression analysis will be performed on cDNA

synthesized from total mRNA obtained from samples preserved in RNAlater buffer. All of the qRT-PCR primers are routinely used in the Maitra laboratory, and the assay will be performed on a ABI 7500 Fast real-Time PCR machine (Applied Biosystems), using *SDHA* as a housekeeping gene. Relative fold expression of various transcripts will be calculated using the $2^{-\Delta\Delta Ct}$ method (Schmittgen and Livak, 2001). All of the assays will be performed in triplicate.

9.1.5.3. Quantitative real time PCR analysis for Hh gene targets

In addition to evaluation of the CSC compartment, we will also evaluate expression of key Hh gene targets, *Gli1* and *Ptch*, which are known to be downregulated in the tumor tissues secondary to Hh inhibitor therapy. While recent studies have shown that bulk of these Hh targets are expressed in the stromal (rather than epithelial) compartment in pancreatic cancer, this will not be differentiated in the assays performed. The rationale for these assays is to establish a tissue-specific pharmacodynamic measure of drug availability to the tumor site, and to correlate with pharmacokinetic analysis of GDC-0449. All of the qRT-PCR primers are routinely used in the Maitra laboratory, and the assay will be performed on a ABI 7500 Fast real-Time PCR machine (Applied Biosystems), using *SDHA* as a housekeeping gene. Relative fold expression of various transcripts will be calculated using the $2^{-\Delta\Delta Ct}$ method (Schmittgen and Livak, 2001). All of the assays will be performed in triplicate.

9.1.5.4. Flow cytometry for circulating CSCs

The published data correlating circulating tumor cells (CTCs) with prognosis is uneven, with a wide range of correlation (or lack thereof) in various solid tumors. The underlying hypothesis for this correlative study is that only circulating CSCs (rather than the entire complement of CTCs) is responsible for metastatic seeding and colonization at secondary sites, and therefore likely to be a more reliable measure of PFS. Gradient centrifuged PBMCs will be analyzed for the fraction of circulating CSCs using the Aldefluor reagent (Stem Cell Technologies), which provides a quantitative measure of enzyme activity in viable cells. Cells with highest ALDH activity will be gated. Additionally, surface co-expression of CD24/CD44 will be analyzed in order to further enrich for the population of circulating CSCs. Normal peripheral blood cells (i.e., B and T cells) may also express the CD44 and CD24, but they do not appear to express ALDH, and we would not expect to detect CD24+CD44+ALDH+ cells in normal individuals. Furthermore, cells will also be stained with a monoclonal antibody against ESA that is not expressed by lymphocytes, but is expressed by pancreatic CSC. For further confirmation of epithelial origin, CD24+CD44+ALDH+ cells will be isolated by FACS, cytocentrifuged onto glass slides then stained for the expression of epithelial-specific cytokeratins CK9 and CK19 by standard immunohistochemical techniques. It is anticipated that in patients with advanced pancreatic cancer, there will be a reduction in the proportion of circulating CSCs upon treatment with GDC-0449, especially in patients that have a tangible improvement in subsequent PFS.

9.1.5.5. Circulating CA19-9 and SPARC

ELISA will be performed on plasma samples for circulating CA19-9 and SPARC levels. Standard assay formats for ELISA will be utilized, including kits for CA19-9 (Calbiochem, Inc.) and SPARC (Hematologic Technologies, Inc). CA19-9 is the standard-of-care tumor marker for

pancreatic cancer, and measurement of this analyte will be used as a surrogate tumor response measure to therapy. CA19-9 should be analyzed locally at each participating site using standard laboratory measures.

SPARC (secreted protein acidic and rich in cysteine, a.k.a. osteonectin) is abundantly expressed in the stroma of pancreatic cancers, and is an albumin-binding protein that is responsible for enrichment of nab-paclitaxel in the peritumoral milieu. Recent preclinical data have shown that nab-paclitaxel therapy ameliorates the tumor stroma, and enhances delivery of gemcitabine to the site of cancer. Thus, it is anticipated that reduction in circulating SPARC levels post-therapy with nab-paclitaxel will be a surrogate measure for stromal depletion at the tumor site. Reduction in pre-treatment circulating SPARC levels will be correlated with PFS. In this protocol we wish to obtain data on a potential correlation between plasma SPARC protein expression and response to albumin-bound drugs therapy. This method will become a potential means of following treatment response of nab-Paclitaxel drugs.

Patient plasma will be extracted at different time points during the course of the treatment and used as the analyte for SPARC ELISA (enzyme-linked immunosorbent assay). To obtain the analyte, collect 10cc of blood in a vacutainer containing sodium heparin. The use of a heparin-based anticoagulant containing platelet inhibitors is required to minimize the contribution of osteonectin in plasma due to platelet activation during phlebotomy. Plasma processed from the blood should be frozen at -20°C and shipped to the Alta Analytical for analysis.

ALTA Analytical Laboratory
Attention: Trang Le
Project Manager/Principal Investigator
Immunochemistry Services
Intertek Chemicals and Pharmaceuticals
3985 Sorrento Valley Blvd., Suite C
San Diego, CA-92121
Tel: 858-558-2599
Fax: 858-558-2600
Email: trang.le@intertek.com

10. STUDY CALENDAR

		Cycle 1				Cycle 2				Cycle 3 on						
	Pre-Study	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Every 8 weeks	End of Study ^c	
GDC-0449						X ----- X										
Gemcitabine		X	X	X		X	X	X		X	X	X				
Nab-Paclitaxel		X	X	X		X	X	X		X	X	X				
Informed consent	X															
Demographics	X															
Medical history	X															
Concurrent meds	X	X-----X													X	
Concurrent procedures	X	X-----X													X	
Adverse event evaluation		X-----X													X	
Peripheral Neuropathy Evaluation		X-----X													X	
Physical exam	X	X				X				X					X	
Vital signs	X	X	X	X		X	X	X		X	X	X		X	X	
Weight	X	X				X				X						
BSA calculation	X	X				X				X					X	
ECOG Performance	X	X				X				X					X	
CBC w/diff, platelets ^g	X	X	X	X		X	X	X		X	X	X			X	
Serum chemistry ^a , Mg, phosphate ^g	X	X				X				X					X	
Complete Urinalysis ^g	X															
PT, PTT ^g	X															
EKG (as indicated)	X															
Radiologic evaluation CT scan or MRI	X	Radiologic measurements should be performed every 8 weeks.													X ^c	
Pregnancy Test ^g	X ^b	Every 4weeks if regular menstrual cycles. Every 2 weeks if irregular menstrual cycles													X ^c	
Biopsy for correlative studies	X ^f									X						
Serum CA 19-9 ^g and SPARC		X				X								X		
Blood Circulating CSC ^g		X								X						
Phone f/u for Survival															X	
Taste Questionnaire						X				X						
	a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. b: Pregnancy test (women of childbearing potential), at screening, within 10-14 days and within 24 hrs prior to first dose of GDC-0449 c: End of-study evaluation, f: pretreatment biopsy within 14 days before first treatment day g: All blood tests and biopsies will be done within +/- 3 days															

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done 14 days prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

11. MEASUREMENT OF EFFECT

11.1 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 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.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment.

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

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm 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).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

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.

11.1.3 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.

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.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 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.

11.1.4.2 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).

11.1.4.3 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	PD	

		No		
Any	Any	Yes	PD	
<p>* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.</p> <p>** Only for non-randomized trials with response as primary endpoint.</p> <p>*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.</p> <p><u>Note:</u> 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 “<i>symptomatic deterioration.</i>” Every effort should be made to document the objective progression even after discontinuation of treatment.</p>				

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
<p>* ‘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</p>		

11.1.5 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.

11.1.6 Response Review

Response on imaging studies will be assessed by expert radiologists based on above RECIST 1.1 criteria.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

This is an open-label, single arm, multi-center, Phase II trial.

Primary Endpoints(s)

- PFS as defined by the time from first therapy received to the earlier documented disease progression or death from any cause. PFS will be determined by the investigator. Imaging studies to assess response will be evaluated by expert radiologists using RECIST 1.1 criteria.

Secondary Endpoint(s)

Efficacy endpoints

- Overall survival from the time of cycle 1, day 1 until death from any cause
- Objective tumor response (partial response, complete response) or stable disease based on CT scans (or MRI scans if patient is allergic to contrast agent or has some other contraindication to a CT scan). These will be evaluated according to RECIST 1.1 criteria.

Safety endpoints

- Number of grade 3 and 4 toxicities according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE; Version 4.0) that occur after Cycle 1, day 1
- Incidence, nature and severity of all adverse events that occur on or after Cycle 1, Day 1

Correlative studies endpoints

- Quantitative pancreatic cancer stem cell identification using functional assays and phenotypic assays. Functional assays include immunohistochemistry or RT-PCR for ALDH bright cells. Phenotypic assays include immunohistochemistry or flow cytometry for pancreatic cancer stem cell markers (CD24+/CD44+/ESA+ and CD133+) in tissue biopsy and peripheral blood.
- Semi-quantitative measurement of hedgehog ligand expressions in pre-post biopsies and hedgehog signaling pathway downregulation as measured by Gli 1 and Patch
- Biomarker changes as measured by serum CA19-9 and plasma SPARC levels

12.2 Statistical Considerations

This is a single-arm, Phase II trial of Gemcitabine, nab-Paclitaxel and GDC-0449 in patients with previously untreated metastatic adenocarcinoma of the pancreas. Progression-free survival (PFS) is the primary endpoint. Eighty patients will be accrued.

12.2.1 Primary Endpoint Analysis Plan

PFS will be timed from the first treatment received (cycle 1, day 1) until the earlier of disease progression or death due to any cause. The product-limit (Kaplan-Meier) that estimate the specific

survival functions will be calculated. Median survival will be calculated from the Kaplan-Meier estimate, along with a 80 % confidence interval. The proportion surviving to one year will be calculated, along with a 80 % exact binomial confidence interval.

The null hypothesis that the median survival is less than or equal to 7.9 months will be tested using a one-sided test at a 0.1 significance level.

12.2.2 Secondary Endpoint Analysis Plans

1 Overall survival will be summarized using the product-limit (Kaplan-Meier) estimator. Median OS and 1-year surviving proportion will be estimated as in the primary objective.

2 Objective tumor response will be summarized by the proportion of patients (with 95% exact binomial confidence intervals) that achieve a confirmed complete or partial response based on radiology assessment of response using RECIST 1.1 response guidelines. Confirmation will be at least 4 weeks after the initial response.

3 The number and attribution of Grade 3 and 4 adverse events will be tabulated. Safety will also be assessed through summaries of all adverse events, including serious adverse events and adverse events leading to discontinuation of chemotherapy or GDC-0449. All treatment-emergent adverse events will be graded by NCI CTCAE, Version 4.0.

4 Hematology parameters: In order to investigate the maximal degree of myelosuppression, the NCI CTCAE grade for WBC, ANC, platelet count and hemoglobin will be summarized by the most severe grade in each treatment cycle and by the most severe grade during the study. The incidence of patients with NCI CTCAE hematology values of Grade 3 or 4 that occurred after the first dose of study drug also will be presented. Data for patients with Grade 3 or 4 hematology values will be listed. The nadir of each of these parameters will be presented in each cycle and overall. For ANC and WBC, time to overall nadir and time to recovery will be analyzed using the Kaplan-Meier method.

5 Clinical chemistry: Liver and renal function will be summarized using the NCI CTCAE for alkaline phosphatase, serum glutamate oxaloacetate transaminase (SGOT), total bilirubin, and creatinine. The number and percentage of patients that have each NCI CTCAE grade will be summarized using the most severe grade for the first cycle of therapy and for anytime during the study. The incidence of patients with NCI CTCAE chemistry values of Grade 3 or 4 that occurred after the first dose of study drug also will be presented. Data for patients with Grade 3 or 4 chemistry values will be listed.

6 The percent of cancer stem cells measured in primary tissue and peripheral blood will be determined. The percent change from the pre to the post-treatment biopsies will be calculated for the clinical outcomes (PFS, OS, and response rate). These endpoints will be summarized using means, standard deviations, medians and ranges.

7 Hh- ligand expression in tissue by IHC or flow cytometry will be quantified as either continuous or semi-quantitative measurement. The effect of Hh expression and/or pathway signaling on primary and secondary endpoints may be examined using proportional hazards

regression (for PFS, OS and other time-to-event-endpoints) or logistic regression (for dichotomous endpoints, such as objective response).

8 SPARC and CA19-9: Logistic regression will be used to assess the relationship between SPARC

and CA19-9 and objective response. Product-limit (Cox) regression will be used to assess the relationship between these markers as predictors of response, PFS and OS.

12.2.3 Justification of Design

This Phase II trial is designed to make a preliminary assessment of the efficacy of treatment, as measured by PFS. In previous trials the use of chemotherapy with gemcitabine and nab-paclitaxel, the median PFS was 7.9 months. We have powered our study with the assumption of 24 months accrual with 12 months follow up. Based upon these assumptions, a sample size of 80 patients will have an 80% power to detect an increase in the median progression free survival to 10.4 months from the null rate of 8 months using a one sided type 1 error of 0.10. The one-sided test with 0.10 significance level is appropriate for an early Phase II proof-of-principle study designed to accumulate evidence motivating a later multi-center confirmatory Phase III study with stricter test criteria.

This trial is hypothesis-generating and is only able to detect a relatively large benefit (30% increases) of GDC-0449 added to chemotherapy use with gemcitabine and nab-paclitaxel. In particular, this trial will not have adequate power to detect minimum clinically meaningful differences between current treatment and historical control (gemcitabine and nab-paclitaxel). Thus, formal hypothesis testing is limited in that statistically negative outcomes do not necessarily rule out clinically significant treatment effects.

12.2.4 Safety Monitoring

This trial will combine three agents and we must allow for the possibility of an interaction between the treatments in terms of toxicity as well as efficacy. In phase 1 and 2 studies, the combination of gemcitabine and nab paclitaxel were associated with grade 3 or higher toxicities in at most 36% of patients (the most significant being neutropenia). No neutropenia or myelosuppression was reported with GDC-0449. Therefore, we set the upper boundary for an acceptable level of grade 3 or higher hematologic toxicity at 50%.

Toxicities will be recorded and evaluated for severity according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE; Version 4.0). The number of individuals with any toxicities of grade 3 or higher will be tabulated.

Toxicity and adverse events will be closely monitored by the study statistician and the principal investigators throughout the study. After the first 10 patients have been accrued and treated on to this study accrual will be temporarily halted until these patients have been assessed for toxicity for one cycle of treatment with GDC. If five or more of the first ten patients experience grade 3 hematologic toxicities that are possibly, probably or definitely related to study treatment, safety of this study will be re-evaluated by the principal investigators to determine whether they are unexpected and pose an excessive safety risk and whether the study needs to be permanently closed to accrual. In addition, accrual to the trial will be halted if unexpected, significant, or unacceptable risk to patients occurs at any time during this study. A thorough safety review by the principal investigators will then determine whether the trial needs to be terminated.

12.2.5 Futility Monitoring

An interim futility analysis will be performed once 66% of the patients (53) have completed 6 months of follow-up. At that time, we will construct 99.5% confidence intervals for progression free survival. If the upper bound of the CI does not contain the alternative PFS (7.05) months and the other efficacy outcomes do not show benefit then we will halt the trial for futility. This test is equivalent to "spending" 0.0025 of the type I error

12.3 Sample Size/Accrual Rate

We have powered our study with the assumption of 24 months accrual with 12 months follow up. Based upon these assumptions, a sample size of 72 patients will have an 80% power to detect an increase in the median progression free survival to 7.15 months from the null rate of 5.5 months (HR = 1.3) using a one sided type 1 error of 0.10. Up to an additional 10% will be accrued in order to control for loss to follow-up. The expected accrual rate is between 4-5 patients per month.

Rationale: We have decided to decrease the sample size based on the following points:

- New data presented at ASCO GI and now published at NEJM demonstrated the PFS of gem/abraxane based on phase 3 study is 5.5 mo (MPACT study, Von Hoff NEJM 2014). Given these findings reducing the sample size will not alter the power initially planned for the study. Our study would still have 80% power with N=72 if PFS of 5.5 months (as per MPACT study) were known at study design, and study planned to detect a 30% increase in median PFS from 5.5 months to 7.15 months at the 1-sided 10% significance level, upper bound used for futility should have been 7.15.
- Accrual has been significantly slow over the past two years as new standard treatments have become available (gem/abraxane and FOLFIRINOX) and less patients are participating in our first line clinical trials.
- New data (one study) has become available demonstrating that hedgehog inhibitors have not increased progression free survival in patients with pancreatic cancer (Kim et al. CCR Oct 2014)
- We have evaluated our data in every six months basis at the AACR SU2C meetings (planned to review the trial) and our mPFS remains 5.5 mo with upper limit CI not including 7.15

Rationale for changing the statistical analysis

When the study was originally designed, previous trials using gemcitabine and nab-paclitaxel reported a PFS of 7.9 months. A sample size of 80 participants recruited over a 2 year period and followed for a minimum of 1 year would provide 80% power to detect an increase in PFS from a median of 8 months to 10.4 months using a one sided type I error rate of 10%. An interim futility analysis was included to enable us to halt the trial if the efficacy after 50% of the patients completed 6 months of follow-up was much lower than expected, specifically if the upper bound of the 99.5% confidence interval did not include the alternative (10.4 months). The interim analysis was completed and the estimated median was 5.0 months with a 99.5% confidence interval of 4.4 to 7.2 months. Since the upper bound was much lower than the hypothesized alternative, recruitment of the trial was halted. Participants already enrolled in the trial continued follow-up.

On previous phase 2 PFS was 7.9 months. On January 25, 2013 the results of a large (N = 861) phase III trial of gemcitabine and nab-paclitaxel were reported. This is the data that would have been used if these results were available at the time of design of this clinical trial. The median PFS was 5.5 months, which a much lower value than was previously reported. In light of the new information, we re-ran our power calculations and interim analysis guidelines to see if the new reference value would have impacted our decision to halt the trial. Using the same accrual and

follow-up assumptions outlined above, we would have 80% power to detect an increase in median PFS from 5.5 months (the new reference) to 7.05 months (HR = 1.28) with a one-sided type I error rate of 10%. The interim stopping rule therefore changed to comparing the upper boundary of the 99.5% confidence interval to 7.05. In this case the observed upper boundary was 7.2 months; hence the stopping criteria would not be met. Given the updated phase III data and we believe that it is appropriate to re-open accrual.

12.4 Stratification Factors

None

12.5 Reporting and Exclusions

12.5.1 Evaluation of toxicity. All patients will be evaluable for toxicity from the time of their first treatment with GDC-0449, gemcitabine and nab-paclitaxel

12.5.2 Evaluation of response. All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the “unknown” status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

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 21. Ivanova, A., B.F. Qaqish, and M.J. Schell, *Continuous toxicity monitoring in phase II trials in oncology*. Biometrics, 2005. **61**(2): p. 540-5.
 22. Pocock S: *Group sequential methods in the design and analysis of clinical trials*. Biometrika: 191-199.

Appendices

APPENDIX A

Performance Status Criteria

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

APPENDIX B
Definition of Women of Childbearing Potential and
Acceptable and Unacceptable Forms of Contraception

Women of childbearing potential are defined as follows:

- Patients with regular menses
- Patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding
- Women who have had a tubal ligation

Women are considered not to be of childbearing potential for the following reasons:

- The patient has undergone hysterectomy and/or bilateral oophorectomy.
- The patient is post-menopausal defined by amenorrhea for at least 1 year in a woman >45 years old.

Women of childbearing potential are required to use two forms of acceptable contraception, including one barrier method with spermicide, during their participation in the study and for 12 months following discontinuation of GDC-0449.

The following are acceptable forms of barrier contraception:

- Latex condom (always used with spermicide)
- Diaphragm (always used with spermicide)
- Cervical cap (always used with spermicide)
- Male subject must use condoms at all times, even after a vasectomy, during sexual intercourse with female partner of reproductive potential during treatment with GDC-0449, and for 2 months after the last dose to avoid exposing a pregnant partner and unborn fetus to GDC-0449.

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

- Tubal ligation
- Partner's vasectomy
- Combination hormonal contraceptives including birth control pills, patches, rings, or injections, medroxyprogesterone acetate depot, *with the exception of the progesterone-only "minipill"*

- Intrauterine device (non–progesterone T)
- Vaginal sponge (containing spermicide)

In addition, 100% commitment to abstinence is considered an acceptable form of contraception. The following are **unacceptable** forms of contraception for women of childbearing potential:

- IUD progesterone T
- *Progesterone-only “minipill”*
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

APPENDIX C

LIST OF CYP3A4 INHIBITORS AND INDUCERS

CYP3A4 Inhibitors

Acetaminophen	Diclofenac	Lomustine	Primaquine
Acetazolamide	Dihydroergotamine	Losartan	Progesterone
Amiodarone	Diltiazem	Lovastatin	Propofol
Amlodipine	Disulfiram	Mefloquine	Propoxyphene
Amprenavir	Docetaxel	Mestranol	Quinidine
Anastrozole	Doxorubicin	Methadone	Quinine
Aprepitant	Doxycycline	Methimazole	Quinupristin
Atazanavir	Drospirenone	Methoxsalen	Rabeprazole
Atorvastatin	Efavirenz	Methylprednisolone	Ranolazine
Azelastine	Enoxacin	Metronidazole	Risperidone
Azithromycin	Entacapone	Miconazole	Ritonavir
Betamethasone	Ergotamine	Midazolam	Saquinavir
Bortezomib	Erythromycin	Mifepristone	Selegiline
Bromocriptine	Ethinyl estradiol	Mirtazapine	Sertraline
Caffeine	Etoposide	Mitoxantrone	Sildenafil
Cerivastatin	Felodipine	Modafinil	Sirolimus
Chloramphenicol	Fentanyl	Nefazodone	Sulconazole
Chlorzoxazone	Fluconazole	Nelfinavir	Tacrolimus
Cimetidine	Fluoxetine	Nevirapine	Tamoxifen
Ciprofloxacin	Fluvastatin	Nicardipine	Telithromycin
Cisapride	Fluvoxamine	Nifedipine	Teniposide
Clarithromycin	Fosamprenavir	Nisoldipine	Testosterone
Clemastine	Glyburide	Nizatidine	Tetracycline
Clofazimine	Grapefruit juice (2)	Norfloxacin	Ticlopidine
Clotrimazole	Haloperidol	Olanzapine	Tranlycypromine
Clozapine	Hydralazine	Omeprazole	Trazodone
Cocaine	Ifosfamide	Orphenadrine	Troleandomycin
Conivaptan	Imatinib	Oxybutynin	Valproic acid
Cyclophosphamide	Indinavir	Paroxetine	Venlafaxine
Cyclosporine	Irbesartan	Pentamidine	Verapamil
Danazol	Isoniazid	Pergolide	Vinblastine
Dasatinib (1)	Isradipine	Phencyclidine	Vincristine
Delavirdine	Itraconazole	Pilocarpine	Vinorelbine
Desipramine	Ketoconazole	Pimozide	Voriconazole
Dexmedetomidine	Lansoprazole	Pravastatin	Zafirlukast
Diazepam	Lidocaine	Prednisolone	Ziprasidone

CYP3A4 Inducers

Aminoglutethimide	Nevirapine	Phenytoin	Rifapentine
Carbamazepine	Oxcarbazepine	Primidone	St. John's wort (3)
Fosphenytoin	Pentobarbital	Rifabutin	
Nafcillin	Phenobarbital	Rifampin	

When GDC-0449 is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of GDC-0449 is the potential outcome. The co-administration of 'inducers' would potentially lower plasma GDC-0449 concentrations.

Note: Adapted from Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 15TH ed. Hudson, OH; LexiComp Inc. 2007: 1899-1912.

Only major substrates and effective inducers are listed.

Additional information for drug interactions with cytochrome P450 isoenzymes can be found at CYTOCHROME P450 DRUG INTERACTION TABLE (Version 5.0 released on January 12, 2009) <http://medicine.iupui.edu/clinpharm/ddis/>

7.3.5

- (1) Investigator's Brochure: Dasatinib (BMS 354825). Bristol-Myers Squibb. October 2006.
- (2) Malhotra *et al.* (2001). Clin Pharmacol Ther. 69:14-23.
- (3) Mathijssen *et al.* (2002). J Natl Cancer Inst. 94:1247-1249.
Frye *et al.* (2004). Clin Pharmacol Ther. 76:323-329.

Updated on May 1, 2007

**APPENDIX D
PATIENT'S MEDICATION DIARY**

Today's date _____

Agent: **GDC-0449**

Patient Name _____ (initials acceptable)

Patient Study ID _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment.
2. You will take **GDC-0449 150mg** (___capsule(s)) once daily. You should take the capsule(s) at approximately the same time each day with a full glass of water (200mls) with or without food.
3. Record the date, the number of capsules of each size of capsule that you took, and when you took them.
4. If you forget to take you daily dose or vomit a dose you will not need to make up missed dose.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Please bring this form and your bottles of **GDC-0449** capsules when you return for each appointment.

Day	Date	Time of dose	# of capsules taken	Comments
			150 mg	
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Patient's signature _____

Physician's Office will complete this section:

1. Date patient started protocol treatment _____
2. Date patient was removed from study _____
3. Patient's planned total daily dose _____
4. Total number of capsules taken this month _____
5. Physician/Nurse/Data Manager's Signature _____

APPENDIX E

An eligibility form must be completed for every subject and must be kept in the research chart.

Instructions:

This eligibility checklist must be completed in its entirety.

Yes	No	ELIGIBILITY CRITERIA: (All answers must be YES)	
_____	_____	1.	Patients has histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas. Patients with islet cells tumors are excluded.
_____	_____	2.	Patients has measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with spiral CT scan.
_____	_____	3.	Patient has NOT received previous radiotherapy, surgery or chemotherapy or investigational drug therapy for the treatment of <u>metastatic</u> disease. If the patient received radiotherapy, chemotherapy or investigational therapy in the <u>adjuvant</u> setting it should be completed 3 weeks prior to enrollment. If a patient received gemcitabine in the adjuvant setting, tumor recurrence must have occurred at least six months after completing the last dose of gemcitabine
_____	_____	4.	Age ≥ 18 years.
_____	_____	5.	Life expectancy of greater than 1 month.
_____	_____	6.	ECOG performance status ≤ 1 (Karnofsky $\geq 70\%$; see Appendix A). ECOG PS: _____
_____	_____	7.	Patients has adequate organ and marrow function as defined below: - leukocytes $\geq 3,000/\text{mcL}$ - absolute neutrophil count $\geq 1,500/\text{mcL}$ - platelets $\geq 100,000/\text{mcL}$ - total bilirubin < 1.5 ULN - AST(SGOT)/ALT(SGPT) < 2.5 X institutional upper limit of normal, unless liver metastases are clearly present, then < 5 X ULN is allowed - creatinine within normal institutional limits OR - creatinine clearance Creatinine clearance ≥ 50 mL/min/1.73 m ² for patients. Serum creatinine < 2 mg/mL

Instructions:

This eligibility checklist must be completed in its entirety.

Yes	No	ELIGIBILITY CRITERIA: (All answers must be YES)
_____	_____	8 Patient is asymptomatic from jaundice and ascites prior to Day 1 of therapy. Pain symptoms should be stable.
_____	_____	9 Patient is NOT pregnant or lactating. Not planning pregnancy during treatment and for 7 months after last dose of treatment
_____	_____	10 Patient has agreed to practice effective contraceptive measures throughout the study.

Women of childbearing potential are required to have a negative serum pregnancy test (with a sensitivity of at least 25 mIU/mL)

Women of childbearing potential are defined as follows:

- Patients with regular menses
- Patients with amenorrhea, irregular cycles, or using a contraceptive method that precludes withdrawal bleeding
- Women who have had a tubal ligation

Women are considered not to be of childbearing potential for the following reasons:

- The patient has undergone hysterectomy and/or bilateral oophorectomy.
- The patient is post-menopausal defined by amenorrhea for at least 1 year in a woman > 45 years old.

_____	_____	11. For sexually active males: Patient is willing to use of barrier form of contraception, even if they have had a vasectomy, during the study and for 2 months after stopping GDC-0449.
_____	_____	12. Patient agrees NOT to donate blood products for 7 months after stopping GDC-0449
_____	_____	13. Patient has given written informed consent to participate in this study.
_____	_____	14. Patient is NOT receiving concurrent anticancer therapy or any other investigational agents while on study.
_____	_____	15. Patient does NOT have uncontrolled brain metastases. Patients with brain metastases must have been previously treated and well controlled for at least three months (defined as clinically stable, no edema, no steroids and stable in 2 scans at least 4 weeks apart)

Instructions:

This eligibility checklist must be completed in its entirety.

- ____ 16. History has NO history of allergic reactions attributed to compounds of similar chemical or biologic composition to GDC-0449 or other agents used in the study.
- ____ 17. Patients is NOT taking medications with narrow therapeutic indices that are metabolized by cytochrome P450 (CYP450), including warfarin sodium (Coumadin®).
- ____ 18. Patient does NOT have an 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.
- ____ 19. Patient has NOT undergone a major surgery within the past 4 weeks, other than diagnostic surgery (i.e. surgery done to obtain a biopsy for diagnosis without removal of an organ)
- ____ 20. Patient does NOT has history of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory fining giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug or that might affect interpretation of the results of the study or render the patient at high risk from treatment complications
- ____ 21. Patient agrees to have two biopsies during the study

Confirmation of Eligibility

- Patient meets all Inclusion Criteria as defined by the protocol.

Signature of site Study Coordinator

Printed name of site Study Coordinator

Phone: _____

Fax to return registration: _____

Email contact: _____

APPENDIX G: PROTOCOL SIGNATURE PAGE

Protocol Number: J1013, NA_00036883

**A Phase II Study of Gemcitabine and nab-Paclitaxel in Combination with GDC-0449
(Hedgehog Inhibitor) in Patients with Previously Untreated Metastatic Adenocarcinoma of
the Pancreas**

Protocol Amendment 12, date December 4, 2014

IND Number: 108819

Sponsor: SU2C

Coordinating Center: Johns Hopkins University

I have read and understand the contents of the clinical protocol and agree to perform this study in accordance with the protocol and Good Clinical Practice (GCP) 21 CFR Parts and applicable regulations/guidelines.

I agree to conduct the clinical study in accordance with these principals and the procedures described in this protocol. I am aware of my responsibilities as an investigator.

PI Name: _____

Title: _____

Address: _____

PI Signature: _____

Date: _____

APPENDIX H: MEDICAL MONITOR SIGNATURE PAGE

Protocol Number: J1013, NA_00036883

Medical Monitor Signature Page

A Phase II Study of Gemcitabine and nab-Paclitaxel in Combination with GDC-0449 (Hedgehog Inhibitor) in Patients with Previously Untreated Metastatic Adenocarcinoma of the Pancreas

Protocol Amendment 12, date December 4, 2014

IND Number: 108819

Sponsor: SU2C

Coordinating Center: Johns Hopkins University

I have read and approved the protocol and appendices. My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical trial will be conducted in accordance with the protocol and all applicable laws and regulations, including, but not limited to, the ICH Guidelines for the Good Clinical Practice (GCP) and US 21 CFR Parts and the ethical principles that have their origins in the Declaration of Helsinki, as well as all applicable privacy laws.

Name: _____

Title: _____

Address: _____

Medical Monitor Signature: _____

Date: _____

APPENDIX I: AMENDMENTS SUMMARIES

Amendment 1, June 8, 2010

1. Section 3.1.10 was updated to explain that sexually active male patients need a barrier of contraception until 12 months after stopping GDC-0449.
2. In the dose modification section (section 6.2), the second paragraph in the portion entitled “Peripheral Neuropathy” was modified to clarify that nab-Paclitaxel will be held in patients with grade 3 neuropathy until resolution to \leq grade 1 neuropathy, *regardless of suspected cause*. In the same section the protocol now states that GDC-0449 should be held for grade 3 neuropathy until resolution to \leq grade 1 neuropathy.

Amendment 2, June 11, 2010

1. The protocol was modified in section 5.3.1 to reflect there is a potential for GDC-0449 to also inhibit CYP1A2 and 2D6 in addition to 2C8, 2C9, and 2C19. Caution should be exercised and dose reduction of the concomitant substrate drug be considered when dosing GDC-0449 concurrently with medications with narrow therapeutic windows that are substrates of CYP1A2 and 2D6. In the same section a table of drugs that may interfere with CYP1A2 and 2D6 was added.

Amendment 3, July 6, 2010

1. Section 3.1.1: Eligibility criteria made clear to reflect that biopsy is required within 14 days before starting treatment.
2. Protocol Cover Page
3. Table of contents was updated to reflect changes
4. Version date in the protocol was changed to protocol amendment 3, date July 6, 2010
5. Study calendar was modified. Circulating stem cells are collected also at the time of the second biopsy.

Amendment 4, August 16, 2010

1. Protocol cover page, the principal Investigator has been changed at Translational Genomics Research Institute, Scottsdale AZ site, they deleted Dan Van Hoff, MD as the principal investigator and added Ramesh K. Ramanathan, MD as the principal investigator.
2. Protocol cover page, deleted Ana De Jesus-Acosta, MD as the co-investigator. Added Ana De Jesus-Acosta as the Co-Principal Investigator. Added Pamela Johnson as the co-investigator.
3. Protocol cover page, added Van Andel Research Institute, MI as the new site; added —Timothy J. O'Rourke, M.D. as the principal investigator for the site.
4. It was added to eligibility checklist that biopsies are required in this study. Already —included in the inclusion criteria and consent forms.
5. Version date in the protocol was changed to protocol amendment 4, date August 16, 2010
6. Section 4 and 7.5 were modified to reflect the registration process using a centralized uniform database by CRAB. This includes electronic forms for adverse events and serious adverse events reporting.
7. Section 5.1 follow up for survival will be done by telephone contact
8. Changed fax number from 410-502-0834 to 443-287-6566 for the study
9. Added Urinalysis test at the screening.
10. In section 9: Amount of blood that will be obtained for circulating cancer stem cells was decreased to 150 ml.
11. Inserted Appendix G—Protocol signature page
12. Inserted Appendix H- Medical Monitor Signature page
13. Added drug destruction accountability instructions for nab-Paclitaxel and GDC-0449 in section 8 (pharmaceutical information)
14. Section 9.1.5 for collection of SPARC and CA19-9 was updated

15. Laboratory manual for processing of correlative studies samples was modified
16. Modified statistical section 12.1.4 for practical purposes of multicenter trial.
17. Updated Appendix I- Summary of changes
18. Table of contents was updated to reflect changes.
19. Study calendar modified Day 28 changed to day 22.
20. Baseline CT scans will be done within 14 days prior to starting treatment. Section 5.1.2, 5.1.3 and Study calendar were modified to reflect this.
21. Protocol page 60, added “JHH Investigational Drug Services (IDS)” to section How Supplied GDC-0449.
22. Protocol page 61, added “Supply: GDC-0449 will be obtained from JHH IDS.”
23. Protocol page 61, added “JHHIDS” in section “Packaging, Labeling, and Storage of Study Drug:”
24. Protocol page 63, deleted “Upon receipt of the study drug supplies, the Investigator or designee will conduct an inventory and sign both copies of the study drug receipt and forward one copy to the address indicated on the form. One copy of the receipt and the packing slip must be retained in the Investigator’s regulatory file records. A representative from Abraxis or his/her designee will inspect the study drug inventory, and will arrange for the return of any remaining unused study drug. No study drug may be returned without the representative from Abraxis or other Abraxis-designated personnel first inspecting the study drug inventory. Study drug may be destroyed according to the institutional policy of study sites. Supply: Will be obtained from Abraxis Bioscience using a commercial Badge” from section “Reconstitution and use of nab-paclitaxel #14”.
25. Protocol page 64, added “Supply: nab-Paclitaxel will be obtained from JHH IDS.”
26. Protocol page 64, added “Gemcitabine” in section “Packaging, Labeling, and Storage”
27. Protocol page 66, added section 8.3 Study Medication Accountability and destruction (GDC-0449 and nab-Paclitaxel)

Amendment 5, February 1, 2011

1. Protocol cover page, deleted principal investigator Manual Hidalgo, MD.
2. Protocol cover page, deleted site Centro Integral Oncology Clara Campal, Madrid Spain
3. On foot section, insert “ Protocol amendment 5, date February 1, 2011
4. Page 3, added “Oct 19, 2010” as the approval date for amendment 4
5. On page 46, Table 4 modified
6. On page 47-48, modified the “Table 5. Dose Modifications for Hematologic Toxicity within a Cycle”
7. On page 75, the shipping contacts for SPARC at section 9.1.5.5 was modified
8. Appendix D: updated Patient Medication Diary
9. On page 9, Table of contents was updated to reflect changes.
10. On page 29, we removed second bullet
11. On page 39, added “Guidelines for administration of GCSF are described in Table 5 but will be to the discretion of the investigator and according to institutional guidelines.” In section 5.2.4
12. On page 72, deleted “National cancer Research Center (CNIO), Madrid” from section 9.1.4
13. On page 87, added “and treated on” and “with GDC” in section 12.2.4

Amendment 6, August 3, 2011

1. On foot section, insert “ Protocol amendment 6, date August 3, 2011
2. Modified the name of the study drug on the title page and page 3
3. Deleted principal investigator: Timothy J. O’Rourke, MD from the title page
4. Deleted “Van Andel Research Institute, MI ” sub site from the title page
5. Added IRB approval date on page 3
6. Table of Contents has been updated
7. Table 5 modified

8. Section 2.4.1: The list of potential risks of GDC-0449 was updated. A list of the safety IND reports submitted to IND was added.
9. Page 20, section “changed “12” to “7” months in section ~~Reproductive and developmental Toxicity~~
10. Eligibility criteria 3.1.10 was modified. Sexually active males must use a barrier form of contraception during GDC-0449 treatment and for 7 months after last dose. Based on the new Investigator Brochure. Eligibility checklist was modified to reflect this change.
11. Eligibility criteria 3.1.11 was modified. The time period after which patients can donate blood or blood products following treatment with GDC-0449 was reduced from 12 months to 7 months. Based on new Investigator Brochure. Eligibility checklist was modified to reflect this change.
12. Page 42, changed 12 month to 7 month
13. Eligibility criteria 3.2.8 was modified. Women pregnant and nursing women are excluded. Women planning to become pregnant during treatment or 7 months after last dose of treatment are excluded. Based on new Investigator Brochure. Eligibility checklist was modified to reflect this change.
14. Section 7.4.1 adverse events of GDC-0449 were updated. Added ageusia and hypogeusia.
15. Section 5.3.1 CYP2C8 inhibitors updated
16. Section 9.1: An optional biopsy upon progression for patients with previous response to therapy was added.
17. Study Calendar modified to explain that taste questionnaire will be filled at the beginning of cycle 2 and cycle 3
18. Taste Questionnaire added as appendix J

Amendment 7, January 11, 2012

1. On foot section, insert “ Protocol amendment 7, date January11, 2012
2. Added the IRB approval date August 30, 2011 for the amendment 6 on the page 3.
3. Table of Contents has been updated
4. Section 9.1 (Correlative studies) has been modified. The second biopsy and blood sample collection for circulating stem cells will occur in all patients after receiving two cycles of treatment. Will be perform on Cycle 3, Day 1.
5. Study Calendar (Section 10) modified to explain that second research biopsy and second blood sample for circulating stem cells will be obtained after two cycles of treatment.
6. Consent form modified to reflect above changes.

Amendment 8, February 7, 2012

1. On foot section, insert “ Protocol amendment 8, date February 15, 2012
2. Added the IRB approval date February 7, 2012 for the amendment 8 on the page 3.
3. University of Pennsylvania will re-open enrollment. See attached letter.
4. Table at section 6.2 was modified. Additional 25% dose modifications are permissible to establish the tolerable dose for an individual patient.
5. Section 6 modified. Delays for toxicities can be permitted up to 4 weeks (28 days). If longer than 28 days patients will be discontinued from the study.

Amendment 9, February 22, 2013

1. Section 12.25 and 12.3 for statistics and futility analysis were modified in light of new data available from a large Phase III study conducted using Gemcitabine and Abraxane presented in ASCO GI 2013.
2. Study reopens to enrollment.

Amendment 10, April 16, 2013

1. Eligibility 3.1.10 was modified. Male patients need to use a form of contraception for a period of 2 months after stopping GDC-0449. Time was changed from 7 months to 2 months as per updated IB.
2. Eligibility checklist was modified to reflect above change.

Amendment 11, August 16, 2013

1. Updated safety language and precautions
2. Updated contraception language
3. Updated storage language

Amendment 12, December 4, 2014

1. Revised accrual number from 80 to 72
2. Revised on site monitoring from CRAB to CRO QA

APPENDIX J: GENENTECH FAX COVER SHEET

SAFETY REPORTING FAX COVER SHEET

GENENTECH SUPPORTED RESEARCH

AE / SAE FAX No: (650) 225-4682

Alternate Fax No: (650) 225-5288

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[] - [] - []
--	-----------------

SAE or Safety Reporting questions, contact Genentech Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

APPENDIX K: TASTE AND SMELL QUESTIONNAIRE

A Phase II Study of Gemcitabine and Nab-Paclitaxel in Combination With GDC-0449 (Hedgehog Inhibitor) in Patients With Previously Untreated Metastatic Adenocarcinoma of the Pancreas: Changes in Smell and/or Taste

TASTE INFORMATION

1. Since beginning this clinical trial, have you experienced a change in your sense of taste? Check all of the following statements that apply to you now:

My sense of taste has NOT CHANGED (If not, please skip to question #13)

My sense of taste is ALTERED, that is, things taste peculiar

I experience a taste when nothing is there (PHANTOM TASTE)

My sense of taste is HEIGHTENED (Hypersensitive)

My sense of taste is DIMINISHED (partial loss)

My sense of taste is ABSENT (complete loss)

2. When did you notice this change? / / (Month/Day/Year)

3. For each type of taste problem you experience, indicate by a check how your symptoms have changed in the past week:

	Unchanged	Improved	Worsened
TASTE LOSS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
HYPERSENSITIVITY	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
TASTE ALTERED	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
PHANTOM TASTE(S)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

4. For each of the following taste qualities, indicate with a check whether your perception of it is currently normal, diminished, absent, **altered or heightened:**

	<u>Normal</u>	<u>Diminished</u>	<u>Absent</u>	<u>Altered</u>	<u>Heightened</u>
SWEET	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
SALTY	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
SOUR(e.g., lemon, vinegar)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
BITTER(e.g., tonic water, medicine)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

IF YOU DO NOT EXPERIENCE ALTERED TASTE, PLEASE SKIP TO QUESTION #7

5. The kinds of things that taste **ALTERED** (different) to you are (check all that apply):

- FOODS/BEVERAGES (specify): _____
- TOBACCO PRODUCTS (specify): _____
- OTHER (specify): _____
- EVERYTHING TASTES **ALTERED**

6. Does everything you believe to be altered now taste the same to you?

- NO, THINGS STILL TASTE DIFFERENTLY, BUT THEY DO NOT HAVE THE SAME QUALITY THEY USED TO.
- YES, THEY ALL TASTE THE SAME.

IF YOU DO **NOT EXPERIENCE AN ORAL PHANTOM** (a taste when nothing is there), PLEASE SKIP TO QUESTION #13

7. Do you currently experience more than one type of oral phantom?

- NO
- YES

8. The oral phantom(s) is (check all that apply):

	<u>Not at All</u>	<u>Weakly</u>	<u>Moderately</u>	<u>Strongly</u>
SWEET	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
SALTY	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
SOUR	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
BITTER	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
ROTTEN	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
METALLIC	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
BURNING	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
TINGLING	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
OTHER	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Specify quality: _____

9. Does the oral phantom come from your (check all that apply):

- TONGUE (specify where): _____
- THROAT
- GUMS
- DENTURES OR CAPS
- ROOF OF MOUTH
- SALIVA
- WHOLE MOUTH
- OTHER (specify): _____

10. How often do you experience the oral phantom(s)?

- CONSTANTLY (ALWAYS PRESENT)
- DAILY
- AFTER EACH STUDY TREATMENT
- ONLY OCCASIONALLY
- OTHER (specify): _____

11. How long does your oral phantom usually last?

- THE PHANTOM IS ALWAYS THERE.
- 24 HOURS OR MORE
- SEVERAL HOURS
- MINUTES
- BRIEF or TEMPORARY

12. How strong is your oral phantom(s) usually?

- VERY WEAK
- WEAK
- MODERATE
- STRONG

SMELL INFORMATION

13. Since beginning this clinical trial, have you experienced a change in your sense of smell? Check all of the following statements that apply to you now:

- My sense of smell has NOT CHANGED (If not, please skip to question #23)
- My sense of smell is ALTERED, that is, things smell peculiar
- I experience a smell when nothing is there (PHANTOM SMELL)
- My sense of smell is HEIGHTENED (Hypersensitive)
- My sense of smell is DIMINISHED (partial loss)
- My sense of smell is ABSENT (complete loss)

14. When did you notice this change? / / (Month/Day/Year)

15. For each type of smell problem you experience, indicate by a check how your symptoms have changed in the past week:

	Unchanged	Improved	Worsened
SMELL LOSS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
HYPERSENSITIVITY	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
SMELL DISTORTIONS	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
PHANTOM SMELL(S)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

IF YOU DO NOT EXPERIENCE AN ALTERED SMELL, PLEASE SKIP TO QUESTION #18

16. The kinds of odors that smell ALTERED (peculiar) to you are (check all that apply):

- FOODS/BEVERAGES (specify): _____
- PERFUMES (specify): _____
- TOBACCO PRODUCTS (specify): _____
- OTHER (specify): _____
- EVERYTHING SMELLS ALTERED _____

17. Do all of the odors you believe to be altered now smell the same to you?
- NO, ODORS STILL SMELL DIFFERENT, BUT THEY DO NOT HAVE THE SAME QUALITY THEY USED TO.
 - YES, THEY ALL SMELL THE SAME.

IF YOU DO NOT EXPERIENCE A PHANTOM SMELL, PLEASE SKIP TO QUESTION #23

18. Do you currently experience more than one type of phantom smell sensation?
- NO
 - YES

19. The phantom odor(s) smell(s) like (check all that apply):

	<u>Not at All</u>	<u>Weakly</u>	<u>Moderately</u>	<u>Strongly</u>
INFECTED TISSUE	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
SMOKY/BURNT	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
FECAL	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
ROTTEN	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
MUSTY/MOLDY	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
SWEET	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
METALLIC	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
CHEMICAL	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
OTHER	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Specify quality: _____

20. How often do you experience the phantom odor(s)?
- CONSTANTLY (ALWAYS PRESENT)
 - DAILY
 - AFTER EACH STUDY TREATMENT
 - ONLY OCCASIONALLY

21. How long does your phantom usually last?

- THE PHANTOM ODOR IS ALWAYS THERE.
- 24 HOURS OR MORE
- SEVERAL HOURS
- MINUTES
- FLEETING

22. How strong is your phantom odor(s) usually?

- VERY WEAK
- WEAK
- MODERATE
- STRONG

NUTRITIONAL INFORMATION

23. Since beginning this clinical trial, your appetite has been:

- BETTER
- UNCHANGED
- WORSE

24. Since beginning this clinical trial, you have enjoyed food:

- MORE
- THE SAME
- LESS

25. Since beginning this clinical trial, have you changed the way you eat (e.g., types of foods, meal and snacking frequency)?

- NO
- YES (describe change): _____

26. Since beginning this clinical trial, have you altered the amount of salt, sugar or spices you add to your food?

- NO
- YES (describe change): _____

27. Since beginning this clinical trial, have you started to strongly dislike or avoid certain foods?

NO

YES (specify foods): _____

28. Since beginning this clinical trial, have you had a strong desire or craving for certain foods?

NO

YES (specify foods craved): _____

29. Do you feel nauseated or sick to your stomach often?

NO

YES

How severely?

MILDLY

EXTREMELY

When? _____