STUDY SYNOPSIS

Title: Phase 1/2 Safety and Feasibility of Gemcitabine and Nab-Paclitaxel in combination with LDE-225 (Sonidegib) as Neoadjuvant Therapy in Patients with Borderline Resectable Pancreatic Adenocarcinoma.

Novartis Study No: LDE225XUS03T

Johns Hopkins IRB No: NA_00047491

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Study Phase: Phase Ib/2

Patient Population: Patients with borderline resectable pancreatic adenocarcinoma

Concept and Rationale

Pancreatic ductal adenocarcinoma (PDA) is one of the most dismal malignancies in the gastrointestinal tract and remains the fourth leading cause of cancer related mortality [1] . A subgroup of patients present with "borderline resectable" (BR) disease in which the tumor is technically resectable but has increased risk of positive margins, particularly if no pre-operative or "neoadjuvant" therapy is administered [2]. There is a critical need to develop effective preoperative regimens to downstage the primary tumor to allow resection with negative margins in this group of patients. There is no established standard of care given the lack of prospective controlled studies.

Commonly used regimens are extrapolation of therapies used in the metastatic setting and have focused on delivering cytotoxic agents to eliminate tumor cells. However, these cells compose only 10% of tumor bulk, with the remaining been composed by the tumor microenvironment or stroma. There is increasing interest on developing therapies that may target and eradicate the stromal compartment as a new therapeutic strategy for successful treatment in pancreatic cancer. Agents of interest for are hedgehog (Hh) inhibitors which will be evaluated in this study.

The hedgehog (Hh) inhibitors are small molecules which block the Hh signaling pathway, also active in the stromal compartment through a paracrine mechanism [3-5]. The tumor cells secrete Hh ligand and activate the pathway in the stromal cells. The Hh ligand in the extracellular space binds to Patched (PTCH1), a 12 pass transmembrane receptor reliving the inhibitory effect of PTCH1 on Smoothened (SMO). Signal transduction by SMO then leads to the activation and nuclear localization of GLI1 transcription factors and induction of Hh target genes resulting in tumor cell proliferation, invasion/migration, and metastatic tumor spread [6]. In preclinical models, depletion of stromal compartment and revascularization of poorly perfused pancreatic tumors was achieved with a Hh inhibitor, IPI-926, on genetically engineered mouse models resulting in increased concentration of cytotoxic agent gemcitabine into the tumor and increased survival in the mouse models [7]. Sonidegib is a potent, selective and orally bioavailable SMO antagonist. Treatment with sonidegib has shown *in vivo* efficacy in models of pancreatic cancer and is currently ongoing phase 1 study with minimal side effects[8].

Thus, agents that target the stroma may be an effective therapeutic strategy to eradicate the

stroma, increase drug delivery and improve clinical outcomes. The following pilot phase 1/2 study will evaluate if adding a Hh inhibitor in a neoadjuvant approach is safe and improves resection rate in patients with BR pancreatic cancer.

Correlative studies aimed to elucidate how stromal depletion and drug delivery changes may affect the resection rate will be explored. The findings of this study will be the platform for larger phase II/III studies exploring these agents in patients with BR pancreatic adenocarcinoma.

Objectives:

Primary Objective (s)

Primary objective for phase I component of the trial:

- To evaluate the safety and feasibility of gemcitabine and nab-Paclitaxel combined with the Hh inhibitor sonidegib as neoadjuvant therapy in patients with borderline resectable PDA.

Primary objective for phase II component of the trial:

- To evaluate resection rate of two preoperative chemotherapy regimens in patients with borderline resectable PDA.

Secondary Objectives (s)

- To evaluate overall survival
- To evaluate tumor response
- To evaluate pathologic findings after neoadjuvant therapy.
- To increase the precision of the estimates of toxicities related to treatment.

Correlative Studies

- To evaluate changes in stromal desmoplasia with the use of Hh inhibitors.
- To evaluate changes of Hh signaling pathway on the biopsies and primary tumor using sonidegib.
- To evaluate drug delivery of cytotoxic agents with or without the Hh inhibitor sonidegib.

Primary Endpoint

Primary endpoint for phase I component of the trial:

- Safety Endpoints: Incidence, nature and severity of grade 3 and 4 toxicities that occur after Cycle 1, day 1. Grading according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE; version 4.0).

Primary endpoint for phase II component of the trial:

- Resection rate as defined by the percent of patients that undergo resection after completion of neoadjuvant therapy.

Secondary Endpoints

- Overall survival from day 1, cycle 1
- Complete response, partial response, stable disease and progressive disease per RECIST criteria and PERCIST criteria

- Post surgical pathologic findings including margin status, tumor differentiation and lymph node status after neoadjuvant therapy.
- Toxicity rate, overall and stratified by grade and type.

Correlative Endpoints:

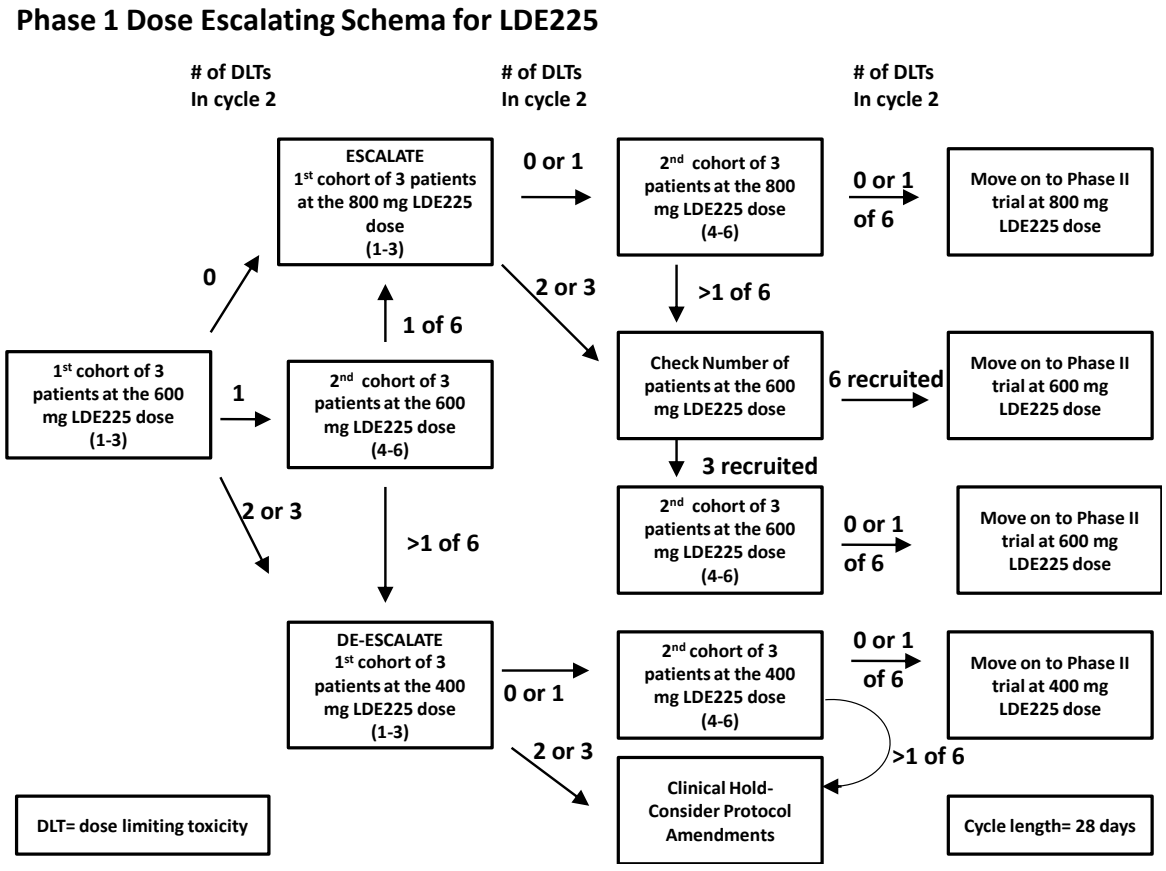
- Semiquantitative density of stroma. Results will be correlated with the primary endpoint resection rate.
- Semi-quantitative measurement of Gli-1, SHH and PATCH on the biopsies and resected tumor.
- Intratumoral gemcitabine triphosphate concentrations. Concentrations will be quantitated by UPLC with tandem mass spectrometry as previously done in preclinical models by our group[9].

Study Design: Safety and feasibility Open label, Phase 1/2 trial.

Phase 1 stage will be a single arm to find the maximal tolerated dose (MTD) of the combination of the three agents, which will be used in the phase II portion of the study, using 3 + 3 escalating design. The dose levels of gemcitabine (1000mg/m^2) and nab-Paclitaxel (125 mg/m$^{2)}$ will be fixed. To minimize toxicities, the starting dose of sonidegib will be 600 mg daily, which is one dose level below the MTD at the single agent phase 1 study ongoing at Novartis. If 0/3 or 1/6 toxicities are observed for this combination, then the level of sonidegib will be escalated to 800 mg. If ≥1/3 or ≥2/6 toxicities are observed then the dose level will be deescalated to 400 mg. The MTD is defined as the highest dose at which 0 or 1 out of 6 toxicities are observed. If no toxicities are found with the combination of the two drugs, the recommended phase 2 dose will be equivalent to the final dose established on the ongoing Novartis phase 1 study which is 800 mg. Toxicities will be evaluated after twomonth of therapy. The estimated number of patients for the phase 1 study is 6-12. The patients will have a pre-treatment and mid treatment biopsy which will be used for the correlative studies. Escalation will proceed as follows:

Table 1: Phase 1 Dose Escalation Schedule

Dose Level	***LDE 225 (mg)***	***Gemcitabine (mg/m^2)***	***Nab-Paclitaxel (mg/m^2)***
Level -1	**400**	1000	125
Level 1	**600**	1000	125
Level 2	**800**	1000	125



<u>Phase II stage</u> (**figure 1**) will be an open label randomized study with two arms. The phase 2 dose of sonidegib will be selected based on the findings of the above phase 1 study. The patients will have a pre-treatment and mid treatment biopsy which will be used for the correlative studies.

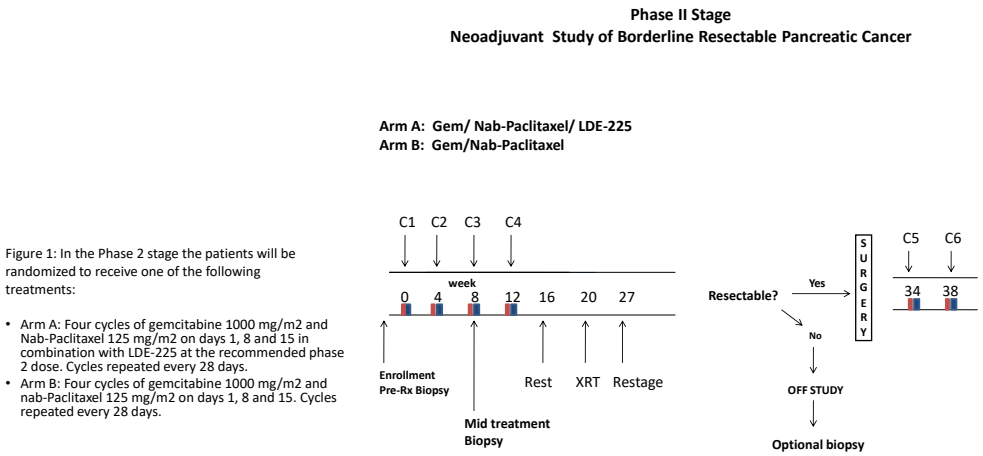


Figure 1: In the Phase 2 stage the patients will be randomized to receive one of the following treatments:

- Arm A: Four cycles of gemcitabine 1000 mg/m2 and Nab-Paclitaxel 125 mg/m2 on days 1, 8 and 15 in combination with LDE-225 at the recommended phase 2 dose. Cycles repeated every 28 days.
- Arm B: Four cycles of gemcitabine 1000 mg/m2 and nab-Paclitaxel 125 mg/m2 on days 1, 8 and 15. Cycles repeated every 28 days.

The primary endpoint for the phase II stage is the resection rate for each treatment arm, which is defined as the number of patients who complete neoadjuvant therapy and undergo resection. Secondary endpoints include overall survival from treatment initiation, response rates based upon RECIST and PERCIST criteria, post surgical pathologic characteristics (including margin status, tumor differentiation, lymph node status), as well as toxicity rates.

Number of Patients:

Estimated number of patients for phase 1 stage: 6-12 patients. Phase 2 stage: 40 patients (20 patients per arm)

Duration of Intervention and Evaluation

Patients will receive a total of eight months of therapy from the onset of neoadjuvant therapy. They will continue on treatment unless they experience progressive disease, unacceptable toxicity, withdraw consent or the physician feels it is not 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 progression/recurrence and overall survival. If an individual is lost to follow-up, then they will be censored at the time of the last contact.

Statistical Methods

Summary statistics for continuous outcomes (mean, SD, median, range) and categorical outcomes (count, percentage) will be calculated. The number and grade of toxicities will be tabulated. Percent of patients that achieved resection will be described with exact Binomial 95% confidence intervals. Kaplan-Meier techniques will be used to summarize time-to-event outcomes (overall survival and disease free survival) graphically and to estimate the median and one and two-year survival outcomes with 95% confidence intervals. Cox proportional hazards functions will be used to estimate the effect of risk factors (e.g. tumor grade, nodal status) on overall survival.

Patient Acceptability/Ethics and Concepts Issues: None

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse Event
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)
BR	Borderline Resectable
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CA19-9	Carbohydrate Antigen 19-9
CBC	Complete Blood Count
CI	Confidence Interval
CK	Creatinine Kinase
CR	Complete Response
CRO	Clinical Research Organization
CSC	Cancer Stem Cells
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
CRF	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
PDA	Pancreatic Ductal Adenocarcinoma
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
SCLC	Small Cell Lung Cancer
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

This study combines the chemotherapy agents gemcitabine and nab-paclitaxel with an orally bioavailable hedgehog inhibitor, sonidegib, for the treatment of patients with borderline resectable pancreatic adenocarcinoma.

Primary objective for phase I component of the trial:

- To evaluate the safety and feasibility of gemcitabine and nab-paclitaxel combined with the Hh inhibitor sonidegib as neoadjuvant therapy in patients with borderline resectable PDA.

Primary objective for phase II component of the trial:

- To evaluate resection rate of two preoperative chemotherapy regimens in patients with borderline resectable pancreatic adenocarcinoma.

1.2 Secondary Objectives

- To evaluate overall survival
- To evaluate tumor response
- To evaluate pathologic findings after neoadjuvant therapy.
- To increase the precision of the estimates of toxicities related to treatment.

1.3 Correlative Objectives

- To evaluate changes in stromal desmoplasia with the use of Hh inhibitors.
- To evaluate changes of Hh signaling pathway on the biopsies and primary tumor using sonidegib.
- To evaluate drug delivery of cytotoxic agents with or without the Hh inhibitor sonidegib.

2. BACKGROUND

2.1 Overview of Disease to be studied

Pancreatic ductal adenocarcinoma (PDA) is one of the most dismal malignancies in the gastrointestinal tract and remains the fourth leading cause of cancer related mortality[10]. In patients with clearly resectable disease, surgery is often the initial treatment provided with curative intent. A subgroup of patients present with "borderline resectable" (BR) disease in which the tumor is technically resectable but has increased risk of positive margins, particularly if no pre-operative or "neoadjuvant" therapy is administered [2]. Recent surgical consensus had developed a uniform definition of borderline resectable PDA including: (1) tumor associated deformity of the superior mesenteric vein (SMV) or portal vein (PV), (2) abutment of the SMV or PV $\leq 180^0$, (3) short-segment occlusion of the SMV or PV amenable to resection and venous reconstruction, (4) short-segment involvement of the hepatic artery or its branches amenable to resection and reconstruction or (5) abutment of the superior mesenteric artery (SMA) $\leq 180^0$ [11].

Unfortunately, not all patients with BR disease are taken to surgery, which is an outcome that would translate in increased survival. The largest report published to date retrospectively studied 160 BR patients. Using neoadjuvant chemotherapy or chemoradiation, resection was successfully achieved in 41% of the patients. Median survival was 40 months for the 66 borderline patients who completed all therapy and 13 months for the 94 patients who did not undergo pancreatectomy (P=0.001)[12]. In the absence of clinical trials to establish standard of care, pre-operative therapy using gemcitabine-based regimens is recommended [11]. Available regimens have focused on delivering cytotoxic agents to eliminate tumor cells. However, these cells compose only 10-30% of tumor bulk, with the remaining been composed by the surrounding tumor microenvironment or stroma. Abundant stromal desmoplasia is associated with decreased survival and poor outcomes [13,14]. Thus, agents that may target the stroma are of interest in this disease.

The hedgehog (Hh) signaling pathway is active in the stromal compartment through a paracrine mechanism [3-5]. The tumor cells secrete Hh ligand which activates the pathway in the stromal cells. The Hh ligand in the extracellular space binds to Patched (PTCH), a 12 pass transmembrane receptor relieving the inhibitory effect of PTCH on Smoothened (SMO). Signal transduction by SMO leads to the activation and nuclear localization of GLI1 transcription factors and induction of Hh target genes resulting in tumor cell proliferation, invasion/migration, and metastatic tumor spread [6]. In preclinical studies Hh inhibitors had demonstrated direct anti-tumor effects when used in combination with the cytotoxic agent gemcitabine. Hh inhibitors resulted in depletion of the stromal compartment, revascularization of poorly perfused tumors, and increased concentration of gemcitabine into the tumor, resulting in increased gemcitabine sensitivity and tumor lysis in a transgenic PDA mouse model. This ultimately resulted in increased survival of the mice in this mouse model [7]. In this study we will use the Hh inhibitor, sonidegib, which is a potent, selective and orally bioavailable SMO antagonist. Treatment with sonidegib has led to tumor regression *in vivo* in several genetically defined medulloblastoma models and has increased *in vivo* efficacy in models of PDA (Investigator's brochure). Sonidegib is currently undergoing testing in a phase 1 clinical trial in which minimal side effects has been observed[8].

2.2 Rationale for this study/ Study Purpose

Here we propose a phase 1/2 safety and feasibility study to evaluate whether or not combining these agents in a neoadjuvant setting is safe and improves the resection rate in patients with BR PDA. The pre-operative agents will include the cytotoxic agent gemcitabine and nab-Paclitaxel with the Hh inhibitor sonidegib. Correlative aims to elucidate how Hh inhibitors disrupt stromal-tumor signaling, provide clinical benefit, and affect drug delivery changes will be explored. We hypothesize that adding Hh inhibitors to cytotoxic agents is safe and will result in increased resection rates. Due to the lack of prospective controlled studies to estimate the true resection rate in patients with BR pancreatic cancer, stromal desmoplasia scores and intratumoral drug concentrations we will conduct a pilot safety and feasibility study.

2.3 Rationale for adding Nab-Paclitaxel

A new phase III trial was recently completed and final results were presented at the national meeting ASCO Gastrointestinal Malignancies in January 2013. The final results of the large randomized phase III trial in patients with metastatic pancreatic cancer included 861 patients randomized to *nab*-paclitaxel/gemcitabine (n=431) or gemcitabine (n=430). The results demonstrated that all clinical outcomes (survival, one year survival, objective response rates) favored the group of patients treated with gemcitabine and nab-Paclitaxel. Median OS was 8.5 months for *nab*-paclitaxel/gemcitabine versus 6.7 months for gemcitabine (HR=0.72, 95% CI:0.617–0.835, *P*=0.000015). The 1-year survival rate was 35% versus 22% and 2-year survival was 9% versus 4% for *nab*-paclitaxel/gemcitabine versus gemcitabine, respectively. Median PFS was 5.5 for *nab*-paclitaxel/gemcitabine versus 3.7 months for gemcitabine (HR=0.69, 95%CI:0.581–0.821, *P*=0.000024). ORR was 23% for *nab*-paclitaxel/gemcitabine versus 7% for gemcitabine, $P=1.1x10^{-10}$. For the present study pre-operative regimens to enhance response are needed to successfully undergo surgery. Nab-Paclitaxel will now be presented to the FDA as a standard regimen for pancreas cancer. The NCCN guidelines endorse utilizing regimens used in the metastatic setting in patients with localized disease. This includes nab-Paclitaxel. For this reason, findings of the phase III study and the need for substantial responses prior to surgery Nab-Paclitaxel is added to the study.

2.4 Rationale for adding radiation therapy prior to surgery

Specifically in patients with borderline resectable disease there are no standard regimens as no randomized controlled trial specific to borderline resectable PDAC has yet been completed. Radiation therapy has been given inconsistently either before or after surgery on single institution studies. At the time of the study design we included the radiation therapy after the surgery. We have now moved the radiation therapy prior to surgery for several reasons: 1) we had patients with local but no systemic progression while on treatment that needed radiation therapy prior to attempting definitive surgery. 2) It is more tolerable for the patients to receive the radiation therapy prior to surgery 3) The MD Anderson group published study that demonstrated benefit of chemoradiation therapy at the oncologically critical superior mesenteric artery (SMA) margin among patients with this disease stage. Patients who received chemoradiation, had longer SMA margin distances than those who did not. Patients who received chemoradiation and had a SMA margin of > 1 mm had the lowest recurrence rates. Administration of neoadjuvant chemoradiation and lower estimated blood loss were independently associated with longer progression-free survival on multivariate analysis (Katz, Wang et al. Journal of Gastrointestinal Surgery).

2.3 Study Drug LDE

2.3.1 Overview of the hedgehog (Hh) pathway and its role in tumorigenesis

Smoothened (Smo) is a G protein–coupled receptor (GPCR)–like molecule that positively regulates the Hedgehog (Hh) signal transduction pathway. Normally, the activity of Smo is repressed by the trans-membrane receptor Patched (PTCH). Upon Hh ligand (Sonic Hh, Indian

Hh or Desert Hh) binding to PTCH, its inhibitory effect on Smo is attenuated and the pathway becomes activated, leading to the release of Gli transcription factors from a complex of cytosolic inhibitory proteins. Active Gli transcription factors are translocated into the nucleus to induce Hh target genes, which control cell proliferation, survival and differentiation. The Hh signaling pathway plays a critical role in the embryonic development and homeostasis of many human organs and tissues. Genetic alterations in the Hh pathway are linked to the development of several human tumors (basal cell carcinoma (BCC), medulloblastoma (MB) and rhabdomyosarcoma). Aberrant Hh signaling without evidence of genetic defects has also been linked with other tumors, such as pancreatic cancer, small cell lung cancer, gastro-intestinal tumors and ovarian cancer. The pivotal role of Hh pathway in BCC was demonstrated in mice genetically engineered to express mutations of PTCH1 and SMO typically seen in human sporadic BCCs (Daya-Grosjean 2005).

2.3.1.1 Inhibition of Hh pathway by small molecules

The inhibition of the Hh signaling pathway as a therapeutic approach has increasingly become an area of extensive research. A number of small-molecule inhibitors of the Hh pathway, via smoothened inhibition, have progressed into clinical trials in a wide variety of cancers. GDC0449 (Roche) is being evaluated in clinical trials in basal cell carcinoma, medulloblastoma (recurrent and refractory in adults and young patients), ovarian cancer, advanced pancreatic cancer, advanced sarcoma, locally advanced prostrate cancer, advanced breast cancer, advanced esophageal junction and SCLC. XL-139 (BMS) is currently undergoing testing in combination with chemotherapy in SCLC, gastric/esophageal, multiple myeloma and chronic myeloid leukemia (CML). Recently, clinical trials have been initiated with PF-04449913 (Pfizer) and IPI 926 (Infinity) in combination in CML and in metastatic pancreatic cancer, respectively.

The anti-tumor activity of Smo inhibitors has recently been demonstrated in patients with locally advanced or metastatic BCC and recurrent medulloblastoma (von Hoff et al 2009, Scales and Sauvage 2009, Siu L EORTC-NCI-AACR 2009, Ahnert JR ASCO 2010, Ahnert JR ESMO 2010, Rudin et al ESMO 2010) and in superficial BCC in patients with Gorlin syndrome (De Rie et al 2010).

2.3.2 Overview of Sonidegib

Sonidegib is a potent selective and orally bioavailable SMO antagonist from a novel structural class N-[6-(cis-2,6-dimethylmorpholin-4-yl)pyridine-3-yl]-2-methyl-4'-(trifluoromethoxy)-1,1'-[biphenyl]-3-carboxamide diphosphate, currently being tested in clinical trials in patients with cancer.

2.3.2.1 Pharmacodynamics

Sonidegib potently inhibits both human and mouse Smo at low nanomolar concentrations (11 and 12 nM, respectively) in competitive binding *in vitro* assays. In a single dose pharmacokinetic–pharmacodynamic (PK-PD) study, 20 mg/kg sonidegib resulted in >90% inhibition Gli1 mRNA expression in tumor samples that was sustained for over 24 hrs. Daily multiple doses of sonidegib (20 mg/kg QD) caused >90% tumor regression in genetically defined *in vivo* MB xenograft models characterized by heterozygous deletion of PTCH.

2.3.2.2 Nonclinical pharmacokinetics and metabolism

Sonidegib was well absorbed with good oral bioavailability, ranging from 68 to 100% in the mouse, rat, dog, and monkey after oral (p.o.) administration either in the form of a solution or a phosphate salt suspension. The compound showed low to moderate plasma clearance relative to blood flow in mouse, rat, dog and monkey. Sonidegib exhibits high protein binding (approximately 98% in mouse, rat, dog and human plasma), independent of concentration. The compound was extensively distributed into tissues and its volume of distribution (Vss) at steady-state was greater than total body water (1.9-6.9L/kg). In rats, ~85% of sonidegib related radioactivity was eliminated into the feces, and renal excretion was minor, accounting for <3.0% of the administered dose.

Clearance of sonidegib is primarily hepatic by CYP3A4. Sonidegib was extensively metabolized, with the major metabolic pathway being via mono- or dioxygenation, demethylation, and oxidation leading to carboxylic acid formation, dealkylation, and dehydrogenation monohydroxylation. The elimination of metabolites was mainly through the bile.

Studies with human liver microsomes demonstrated that sonidegib is a competitive inhibitor of CYP2B6 (IC_{50} ~0.5 μM; K_i 0.045 μM), and CYP2C9 (IC_{50}~5 μM; K_i 1.7 μM), but showed very little or no inhibition of CYP1A2, 2A6, 2C8, 2C19, 2D6, 2E1 or 3A4/5 at concentrations of up to 100 μM. No apparent time-dependent inhibition of the major CYP450 enzymes was observed. Sonidegib is neither a substrate nor an inhibitor of P-glycoprotein (Pgp) or multi-resistance protein 2 (MRP2); but it has demonstrated inhibitory effects on breast cancer resistance protein (BCRP), with an estimated IC_{50} value of 1.5 μM. The potential of sonidegib and its metabolites to undergo covalent binding to cellular macromolecules was found to be low.

The results of toxicokinetics (TK) studies with sonidegib indicated that systemic exposure after oral administration, as measured by C_{max} and AUC, was not linear and in general was less than dose-proportional in both rats and dogs. There was drug accumulation after once daily repeat oral doses, which was more pronounced and dose-dependent in dogs. There was an apparent gender difference in exposure in rats following multiple dosing, with female rats exhibiting higher exposure than male rats. Please refer to the [Investigator's Brochure] for more details on the non-clinical toxicity, toxicokinetics and safety of sonidegib.

2.3.2.3 Toxicity and safety Studies with Sonidegib

The majority of adverse effects observed in toxicity studies in growing rats and dogs can be attributed to the pharmacologic action of sonidegib, and the effects in both species were similar. The most striking effects of sonidegib, which are consistent with literature reports on other Hh pathway inhibitors, were on bone and consisted of thinning or closure of growth plates in the sternum and femur and decreasing proliferating chondrocytes in the chostochondral junction of ribs. In addition, decreases in bone alkaline phosphatase were observed in dogs [Investigator Brochure]. The observations were more pronounced in rats, which is a species where the growth plate does not close. Similar observations have been reported for other Smo inhibitors in animal studies (e.g. GliLuc transgenic mice, IHH transgenic mice) including thinning and early closure of the growth plate, shortened bones, inhibition of tooth growth and abnormal bone structures, particularly the femur and tibia (Maeda 2007, Kimura 2008). This is likely due to the role of the

Hh pathway in bone development, particularly in the early stages of bone formation and growth (Kimura 2008).

These effects are not likely to occur in the adult cancer patient population intended for the clinical studies due to the maturity of their skeletal system. However, it anticipated that Smo inhibition may likely affect the development of bones and teeth in growing children. Hence, monitoring for these effects will be required during therapy with Smo inhibitors in children. Preclinical cardiovascular safety pharmacology data do not indicate a clinical risk for QTc prolongation. There is also no indication of effects on the central nervous and respiratory systems from the preclinical data. Please refer to the [Investigator's Brochure] for more details on the non-clinical toxicity and safety of sonidegib.

2.3.3 Clinical Experience with Sonidegib

2.3.3.1 Clinical safety and efficacy

Sonidegib is currently undergoing phase I evaluation in a first-in-human clinical trial, to assess the safety, tolerability, PK, PD and potential efficacy of continuous once daily oral administration in patients with malignant solid tumors [Study CLDE225X2101]. Data provided here are obtained from an active clinical trial database; therefore, they are preliminary and subject to change upon final QC review when the study is completed.

As of October 29, 2010, data were available on 76 patients with cancer who have been treated with sonidegib at dose levels of 100, 200, 400, 800, 1000, 1500, and 3000 mg once daily (QD) and 400 and 750 mg twice daily (BID). Once daily administration of sonidegib, up to 800 mg, has been found to be well tolerated. DLTs that are characterized by CTC grade 3 or 4 increases in plasma creatine phosphokinase (CK) (rhabdomyolysis) associated with muscle pain, muscular weakness and increased plasma myoglobin have been observed at once daily doses ≥1500 mg and twice daily doses ≥400 mg. Of the 13 patients who experienced CTC grade 3 or 4 CK elevation, ten were observed within the initial 6 weeks of treatment with sonidegib and three were observed after 6 weeks. None of the patients experienced impairment of renal function as a result of this toxicity. Of the 13 patients who experienced these DLTs, eleven cases resolved over a period of up to 4 weeks following discontinuation of sonidegib therapy, with the remaining two cases taking up to 8 weeks to resolve. sonidegib 1000 mg QD is currently being evaluated, and as of January 04, 2011, 1 out of 4 evaluable patients at this dose had developed CTC grade 4 CK elevation associated with muscle cramps. This DLT occurred on Cycle 2 Day 8 and the study treatment has since been withheld for this patient.

Table Incidence of dose limiting toxicities in Study CLDE225X2101

		Elevated plasma CK		
Dose of Sonidegib	Number of patients treated	Number of patients with CTCAE grade 3	Number of patients with CTCAE grade 4	Total (CTCAE grade 3 or 4)
100 mg QD	6	0	0	0
200 mg QD	6	0	0	0

400 mg QD	5	0	0	0
800 mg QD	19	0	0	0
400 mg BID	8	1	1	2
1000 mg QD	6	0	1	1
750 mg BID	8	0	5	5
1500 mg QD	9	0	3	3
3000 mg QD	9	0	3	3
Total	76	1	13	14

Commonly (>10%) reported CTCAE grade 1 or 2 that are suspected to be treatment-related include: nausea, vomiting, dysgeusia, decreased appetite, myalgia, muscle spasms and fatigue, (see Table 1-2). No treatment-related clinically significant changes in the other safety laboratory data (hematology, and urinalysis), vital signs or ECGs have been observed for any of the patients treated in the study. Refer to the Investigators Brochure for further details.

Table Adverse events suspected to be related with sonidegib, occurring in ≥5% of patients

AE (preferred term)	**All N= 76**	
	All grades N (%)	Grade 3/4 N (%)
Nausea	21 (27.6)	0
Dysgeusia	19 (25.0)	0
Muscle spasms	18 (23.7)	0
Blood creatine phosphokinase increased	17 (22.4)	12* (15.8)
Decreased appetite	11 (14.5)	0
Fatigue	11 (14.5)	0
Vomiting	9 (11.8)	0
Myalgia	8 (10.5)	0
Alopecia	7 (9.2)	0
Weight decreased	6 (7.9)	0
Diarrhea	5 (6.6)	0
Headache	5 (6.6)	0
Lethargy	5 (6.6)	0
Aspartate amino transferase increased	4 (5.3)	2 (2.6)
Asthenia	4 (5.3)	2 (2.6)
Myositis	4 (5.3)	2 (2.6)
Pain in extremity	4 (5.3)	0

* An additional patient who experienced grade 4 CK elevation was not captured in this table because the investigator had indicated the event was not treatment-related in the clinical database. However, the patient had high systemic sonidegib exposure, which was consistent with other patients who experienced DLTs. Also, the DLT of CK elevation at 1000 mg QD occurred after the database cut-off date on Oct 29, 2010.

Clinical Efficacy

Preliminary antitumor activity and evidence of disease stabilization has been observed with sonidegib treatment. Of the 5 patients with recurrent medulloblastoma (MB) treated, one patient achieved a partial response (PR) according to RECIST after 2 months of treatment (200 mg QD) and the response was maintained for 4 months. A second MB patient with bone metastases also achieved a partial metabolic response (PMR) on FDG-PET after 2 months of therapy (1500 mg QD). This metabolic response was associated with improvement in bone pain and was maintained for ~10 months. In addition, among the 10 patients with locally advanced and metastatic BCC, tumor responses and disease stabilization have been observed as follows:

- One patient with metastatic BCC has remained on therapy (200 mg QD) for > 18 months with stable disease (SD);
- A patient with multiple-recurrent infiltrating BCC on 400 mg BID achieved complete clinical and histological response (CR) after 4 months of therapy and is still tolerating treatment after 10 months;
- A Gorlin patient with locally advanced multifocal BCC, who was treated with 400 mg BID, achieved a partial response (PR) despite coming off treatment after approximately 6 weeks due to grade 4 CK elevation.
- A Gorlin syndrome patient with locally advanced multifocal BCC experienced a PR after only 7 weeks of therapy (800 mg QD);
- A patient with locally advanced auricular BCC has remained on study treatment (800 mg QD) for >5 months with SD; and
- Two metastatic BCC patients (800 mg and 1000 mg QD) experienced PRs after 2 months on therapy.

In summary, 1 CR, 4 PRs and 2 prolonged SDs have been observed. Based on the limited number of pre- and post-treatment tumor biopsies (from 4 BCC patients), sonidegib caused at least 95% reduction in Gli1 mRNA expression compared with baseline values (day 28 compared with day 1), except for the Gorlin syndrome patient at 800 mg QD, where the target inhibition in tumor appeared to be modest (40%) on day 28. Of note, the CR and complete histological clearance observed at 400 mg BID was associated with a 99% reduction in Gli1 mRNA expression in tumor.

2.3.3.2 Clinical Pharmacokinetics and pharmacodynamics

The available preliminary PK data demonstrate that the median peak plasma concentrations of sonidegib occurs at 4 hours (range: 2-24 hours) after dosing. Plasma exposure to sonidegib (Cmax and AUC) after single dose administration increases dose-proportionally from 100-800 mg and appears to plateau at higher dose levels (1500 mg to 3000 mg). On cycle 1 Day 15 C_{max} and AUC increase linearly with doses up to 400 mg/day, and in a less than dose-proportional manner with higher doses (800 to 3000mg/day). sonidegib exposure at 400 mg BID demonstrates ~30% higher mean AUC on day 15 compared with exposure at 800 mg QD, and AUC at 750mg BID is approximately 18% greater than the AUC achieved at 1500 mg QD. The median accumulation index is 3-fold (range: 0.5-12), and 6-fold (range: 2.22-22.1.) for C_{max} and AUC, respectively, on cycle 1 Day 15 compared with the single PK run-in dose. Due to the long

apparent terminal half-life of sonidegib, an accurate terminal half-life cannot be calculated using a non-compartmental approach. The estimated effective half-life, calculated on the basis of the accumulation index across dose groups, is greater than 4 days (range: 1-14 days). Successive measurements of plasma trough concentrations (C_{min}) over time suggest that steady-state appears to be achieved after 28 days of daily dosing. Trough levels on day 15 (pre-dose) correlate well with AUC and Cmax on day 15 during daily administration of sonidegib. The inter-patient coefficient of variation in sonidegib AUC is 40 to 58% across the dose range of 100 mg to 3000 mg/day. Exploratory analyses suggest that the odds of observing a CK DLT increase with AUC on day 15. In addition, the probability of a CK DLT is expected to be low (< 0.16) for exposure levels (AUC day 15) below 41 μM*hr (equivalent to an average steady state concentration of approximately 1.7 μM).

Analyses of skin punch biopsies taken at baseline and at the end of the first treatment cycle (day 28) have shown evidence of potent target modulation, as measured by Gli1 mRNA, in a dose- and exposure-dependent manner. The available data shows that sonidegib caused up to 95% mean reduction in Gli1 expression in skin compared with baseline values. The maximum observed inhibition of the target in skin (as measured by Gli1 expression) was observed at 1500 mg QD. Based on the limited data on PD effect in tumor biopsies (n=4 paired samples), where up to 99% reduction in Gli1 expression was observed, skin is a good surrogate tissue for assessing target inhibition. On the whole, the changes in Gli1 expression in skin appeared to be highly variable, particularly within the 800 mg QD cohort, where a relatively large number of paired samples were obtained compared with the other doses. Sonidegib, at 800 mg QD, demonstrated a mean reduction in Gli1 mRNA in skin of approximately 74% (n=13, range: 8.3% - 95.8%) compared with baseline values after 28 days of therapy. At 200 mg QD, approximately 68% (n=4, range: 25.9% - 89.3%) reduction in Gli1 expression in skin was observed, with 87% reduction in the MB patient who achieved objective partial response.

2.4 Other Drugs: 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).

2.5 Other Drugs: 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 equitotoxic 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/m^2. 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 malignances 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.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed adenocarcinoma of the pancreas. Patients who have not undergone biopsy but have highly suspected adenocarcinoma of the pancreas with borderline resectable features on imaging study may also be eligible for study and undergo the pretreatment biopsy as per protocol. The biopsy must confirm adenocarcinoma of the pancreas to continue on study. Biopsy is required within 14 days of starting therapy.

3.2.2 Patients must have borderline resectable pancreatic adenocarcinoma defined by one of the following criteria:

(1) Tumor associated deformity of the superior mesenteric vein (SMV) or portal vein (PV)
(2) Abutment of the SMV or PV $\leq 180^0$
(3) Short-segment occlusion of the SMV or PV amenable to resection and venous reconstruction
(4) Short-segment involvement of the hepatic artery or its branches amenable to resection and reconstruction or
(5) Abutment of the superior mesenteric artery (SMA) $\leq 180^0$

3.1.3 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 $\geq$20 mm with conventional techniques or as $\geq$10 mm with spiral CT scan. See Section 11 for the evaluation of measurable disease.

3.1.4 Patient must have received no previous radiotherapy, surgical resection, chemotherapy or investigational drug therapy for pancreatic adenocarcinoma.

3.1.5 Age $\geq$18 years. Because no dosing or adverse event data are currently available on the use of sonidegib in combination with gemcitabine in patients <18 years of age, children are excluded from this study but will be eligible for future pediatric phase 2 combination trials.

3.1.6 Life expectancy of greater than 1 month.

3.1.7 ECOG performance status $\leq$1 (Karnofsky $\geq$70%; see Appendix A).

3.1.8 Patients must have adequate organ and marrow function as defined below:

- leukocytes $\geq$3,000/mcL
- absolute neutrophil count $\geq$1,500/mcL

- platelets	≥100,000/mcL
- total bilirubin	< 1.5 ULN
- plasma creatinine phosphokinase (CK)	< 1.5 x ULN
- AST(SGOT)/ALT(SGPT)	<2.5 X institutional upper limit of normal
- creatinine	within normal institutional limits
OR	
- creatinine clearance	Creatinine clearance ≥50 mL/min/1.73 m^2 for patients with serum creatinine < 2 mg/mL

3.1.9 Patients should be asymptomatic for jaundice and ascites prior to Day 1. Pain symptoms should be stable.

3.1.10 The effects of sonidegib on the developing human fetus are unknown. For this reason and because other 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) for the duration of study participation, and for at least 20 months after the final dose of study 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 sonidegib (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. A positive urine test must be confirmed by a serum pregnancy test. Prior to dispensing sonidegib, the investigator must confirm and document the patient's use of two contraceptive methods, dates of negative pregnancy test, and confirm the patient understands of the possible teratogenic potential of sonidegib.

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.

3.1.11 For sexually active males, use of barrier form of contraception, even if they have had a vasectomy, during the study and for 6 months after stopping sonidegib is required. Males should not donate sperm during treatment, and for up to six months after last dose.

3.1.12 All patients should agree not to donate blood products for 12 months after stopping sonidegib

3.1.13 Ability to understand and the willingness to sign a written informed consent document.

3.1.13 Patient is willing to have two biopsies while on treatment for correlative studies.

3.2 Exclusion Criteria

3.2.1 Patients who have had previous radiotherapy, surgical resection, chemotherapy or investigational drug therapy for pancreatic adenocarcinoma.

3.2.2 Patients may not be receiving any other investigational agents.

3.2.3 Patient has known metastatic disease.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to sonidegib 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 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.

3.2.7 Pregnant women 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 sonidegib, breastfeeding should be discontinued if the mother is treated with sonidegib.

3.2.8 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.

3.2.9 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

3.2.10 Patients who are receiving treatment with medications known to be moderate and strong inhibitors or inducers of CYP3A4/5 or drugs metabolized by CYP2B6 or CYP2C9 that have narrow therapeutic index, and that cannot be discontinued before starting treatment with sonidegib. Medications that are strong CYP3A4/5 inhibitors should be discontinued at least 7 days and strong CYP3A/5 inducers for at least 2 weeks prior to starting treatment with sonidegib.

3.2.11 a) Patients who have neuromuscular disorders (e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis and spinal muscular atrophy) or are on concomitant treatment with drugs that are recognized to cause rhabdomyolysis, such as HMG CoA inhibitors (statins), clofibrate and gemfibrozil, and that cannot be discontinued at least 2 weeks prior to starting sonidegib treatment. If it is essential that the patient stays on a statin to control hyperlididemia, only pravastatin may be used with extra caution.
b) Patients who are planning on embarking on a new strenuous exercise regimen after initiation of study treatment. NB: Muscular activities, such as strenuous exercise, that can result in significant increases in plasma CK levels should be avoided whilst on sonidegib treatment.

3.2.12 Impaired cardiac function or clinically significant heart disease, including any one of the following:

- Angina pectoris within 3 months
- Acute myocardial infarction within 3 months
- QTcF > 450 msec for males and > 470 msec for females on the screening ECG
- A past medical history of clinically significant ECG abnormalities or a family history of prolonged QT-interval syndrome
- Other clinically significant heart disease (e.g. congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)

3.2.12 Patients unwilling or unable to comply with the protocol.

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. TREATMENT PLAN

4.1 Time to Event Schedule

4.1.1 Screening and Pre-study Assessments

Pretreatment biopsy for correlative studies, must be obtained within 14 days before cycle 1, day 1

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

• Signed informed consent

Clinical evaluations;
• Medical Oncology and Surgical Oncology evaluation

• 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, AST, and ALT), Creatinine Kinase (CK).

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 sonidegib (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. A positive urine test must be confirmed by a serum pregnancy test. Prior to dispensing sonidegib, 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 sonidegib.

• 12-lead ECG

• Tumor assessment (per RECIST 1.1; see section 10). 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). Imaging will be done at baseline, end of cycle 2, cycle 4, before radiation therapy, 4 weeks after radiation therapy and at the end of cycle 6.

• PET Scan must be obtained within 14 days before cycle 1, day 1 and after cycle 4.

4.1.2 Assessments during the study period

The study period begins on Day 1 of Cycle 1. 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. Imaging will be done at baseline, end of cycle 2, cycle 4, before radiation therapy, 4 weeks after radiation therapy and at the end of cycle 6.

• *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). 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.

• Sonidegib and gemcitabine should be administered as specified in 5.2 and study calendar in section 10.

4.1.3 Beginning of each cycle

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

• Drug will be dispensed to the patient on this day. Sonidegib 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

• 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 each cycle)

• 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) , Creatinine Kinase (CK).

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 C).

• Record concurrent medications.

• Record cancer-related medical or surgical procedures.

• Record adverse events.

4.1.4 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) will be done at baseline, end of cycle 2, cycle 4, before radiation therapy, 4 weeks after radiation therapy and at the end of cycle 6. An unscheduled CT scan for suspected progression may be performed at any time;

• PET scan will be done at baseline and at the end of cycle 4.

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 and CK. Labs can be obtained within three days prior to treatment.

• Adverse event evaluation.

Mid Treatment Biopsy

Will be obtained at the end of cycle 2. Labs (PT/PTT) can be obtained within a window of 7 days prior to the procedure.

Sample for Circulating Cancer Stem Cells

Will be obtained at the enrollment and at the end of cycle 4. A window of ± 3 days will be allowed.

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). 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. A positive urine test must be confirmed by a serum pregnancy test.

• Record concurrent medications.

• Record cancer-related medical or surgical procedures.

• Record adverse events.

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 will be followed for 30 days after the patient's last dose of study drug.

• 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;

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 with the patient's treating physician.

4.1.5 Radiation Therapy

All patients will receive neoadjuvant radiation therapy starting 4 weeks after last dose of chemotherapy. Standard either 3D conformal or intensity modulated radiation therapy (IMRT) planning techniques are allowed on this study. A window of +/- two weeks is allowed. Patients should undergo a restaging CT of the chest, abdomen, and pelvis with oral and intravenous contrast within 2 weeks of finishing chemotherapy. The patients may receive this treatment at Johns Hopkins or locally. 5-FU/Capecitabine -based chemotherapy and radiation therapy as adjuvant treatment following surgical resection of pancreatic adenocarcinoma are the accepted standard of care as described by a number of pancreas cancer groups including the RTOG, the American College of Surgeons Oncology Group (ACOSOG) and the National Comprehensive Cancer Network (NCCN) pancreatic adenocarcinoma practice guideline expert panel. We will be using capecitabine at a dose of 825 mg/m^2 orally twice daily on the days of radiation therapy.

- Patients should undergo a CT simulation (thin slices through the pancreas/bed) with IV (assuming adequate kidney function) and oral contrast. Preoperative CT scans and strategically- placed surgical clips are used to determine the tumor bed.

- The PTV should be defined per the ICRU-62 guidelines. The initial clinical treatment volume (CTV) includes high risk peri-pancreatic lymph nodes, anastomoses (optional), pancreatic tumor bed derived from pre-surgical imaging and strategically- placed surgical clips. CTV expansions are needed to include possible microscopic disease. Further expansion to the planning treatment volume (PTV) includes ITV for target/breathing motion and additional margin for patient set-up error (SM). Organs at risk (OARs) such as kidneys should also be contoured and evaluated in the dose volume histogram (DVH).

- Conformal, intensity modulated radiation therapy (IMRT) and breathhold/gating techniques can result in improved PTV coverage with decreased dose to organs at risk (OARs). If small CTV expansions are used for PTV, breathing motion and set-up error should be evaluated or controlled per the AAPM task group 76 guidelines (ABC/tracking/4D-CT scan/cone beam CT).

- 45-46 Gy (1.8-2.0 Gy fractions) is delivered to the initial PTV (tumor bed, surgical anastomosis, and regional lymph nodes). Additional radiation (~5-15 Gy) may be administered to the tumor bed/area of involved margins. It is preferred that high energy photon beams (>6 MV) are used.

- Atlases to assist with contouring and adjuvant radiation therapy planning are located at (http://www.rtog.org/atlases/pancreasAtlas/main.html).

Radiation Normal Tissue Volume Constraints

Structure	Adjuvant/Resected Constraints
Kidney (L & R)	If two functioning kidneys present, not more than 50% of the right and 65% of the left kidney should receive < 18 Gy. For IMRT planning mean dose to bilateral kidneys should be ≤18 Gy. If only one kidney is present not more than 15% should receive ≥ 18 Gy and no more than 30% should receive ≥ 14 Gy.
Stomach, duodenum, jejunum	Max dose ≤55Gy; <10% of each organ volume can receive between 50-53.99 Gy. < 15% of each organ volume can receive 45-49.99 Gy.
Liver	Mean liver dose ≤ 25 Gy.
Spinal cord	Max dose ≤ 45Gy

*Adapted from RTOG 0936 (3-D conformal, 1.8-50.5) and RTOG 1102 (IMRT, 2.2 to 55 Gy)
**Adapted from RTOG 0848 (3-D or IMRT)

4.1.6 Surgery

At the end of 4 cycles of chemotherapy and radiation therapy the patients will undergo CT and PET scans within 2 weeks. Each case will be discussed at the pancreatic cancer conference including the surgeons and the principal investigators to determine if the patient is candidate for resection. To avoid bias during the phase II portion of this study, the surgeons will not be informed at this point if the patients have been receiving the hedgehog inhibitor sonidegib. If the patient is deemed candidate for resection the surgery will occur four weeks after finishing radiation. A window of +/- two weeks is allowed. Standard surgery techniques will be decided by the surgeon. All patients must undergo the surgery at Johns Hopkins.

If a patient is not deemed candidate for surgical resection he/she will be off study. It will be recommended to the treating oncologist to proceed with alternative standard treatments. An optional biopsy can be obtained at this point.

4.1.7 End of Therapy (EOT) Evaluation

An EOT evaluation should be performed for all patients who end treatment. Patients who have the EOT evaluation after completing all planned therapy (chemotherapy, surgery, radiation) will continue on follow up for any evidence of progression/recurrence and survival as specified in section 4.6.

The following procedures will be completed at the EOT Visit:

• Physical examination

• Weight assessment

• Concomitant medication evaluation

• Concurrent procedures

• Vital signs

• ECOG performance status scale

• Clinical chemistry panel

• CBC, differential and platelet count

• 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.

4.2 Agent Administration

The investigator needs to instruct the patient to take the study drug as per protocol. All dosages prescribed and dispensed to the patient and any dose change or interruption must be recorded in the dosage administration record CRF, as appropriately.

Phase 1 Study:

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

Four cycles of Gemcitabine 1000 mg/m^2 and nab-Paclitaxel 125 mg/ m^2on days 1, 8, and 15 every 28 days cycle in combination with oral sonidegib 600 mg daily.

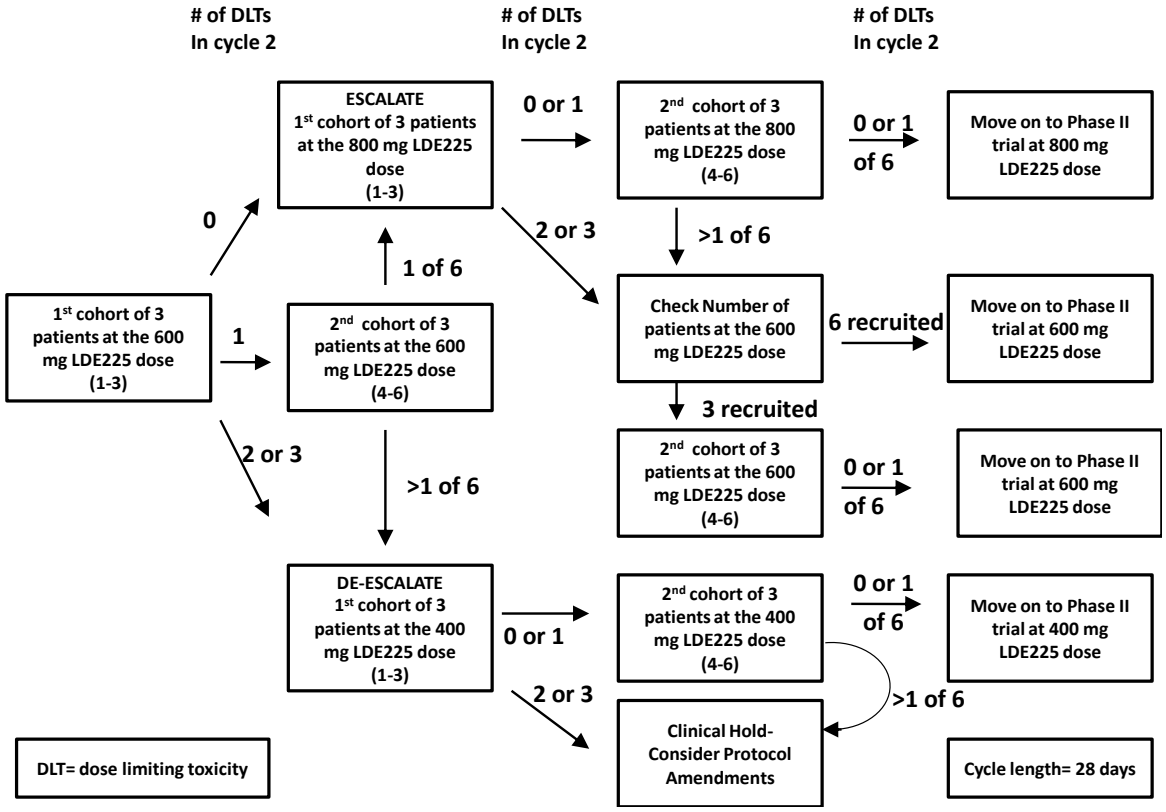
If the patient lives out of town and opts to receive gemcitabine and nab-Paclitaxel treatment locally it will be allowed with communications between the local treating oncologist and the study team members. All treatment and doses will occur as specified in this protocol. On the first day of each cycle all patients will need to have their evaluation and treatment with the Johns Hopkins investigators in order to participate in the study. Sonidegib (oral drug) will only be dispensed at Johns Hopkins Hospital. Day 8 and 15 intravenous Gemcitabine and nab-Paclitaxel treatments can be provided locally at the doses specified on this protocol. Patients will continue taking oral sonidegib as specified in the protocol.

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	
Sonidegib	Morning or PM.	600 mg	PO in the a.m.	Daily	

Dose escalation for subsequent cohort for sonidegib will occur as follows:

Dose Level	***LDE 225 (mg)***	***Gemcitabine (mg/m^2)***	***Nab-Paclitaxel (mg/m^2)***
Level -1	**400**	1000	125
Level 1	**600**	1000	125
Level 2	**800**	1000	125

Phase 1 Dose Escalating Schema for LDE225



Phase 2 Study:

In the Phase 2 stage the patients will be randomize (1:1) to receive one of the following treatments:

- Arm A: Four cycles of gemcitabine 1000 mg/m2 and nab-Paclitaxel 125 mg/m2 on days 1, 8 and 15 in combination with sonidegib at the recommended phase 2 dose. Cycles repeated every 28 days.

- Arm B: Four cycles of gemcitabine 1000 mg/m2 and nab-Paclitaxel 125 mg/m2 on days 1, 8 and 15. Cycles repeated every 28 days.

If the patient lives out of town and opts to receive gemcitabine and nab-Paclitaxel treatment locally it will be allowed with communications between the local treating oncologist and the study team members. All treatment and doses will occur as specified in this protocol. On the first day of each cycle all patients will need to have their evaluation and treatment with the Johns Hopkins investigators in order to participate in the study. Sonidegib (oral drug) will only be dispensed at Johns Hopkins Hospital. Day 8 and 15 intravenous Gemcitabine and nab-Paclitaxel treatments can be provided locally at the doses specified on this protocol. Patients will continue taking oral sonidegib as specified in the protocol.

An overview of the schedule of study assessments is provided in the Study Calendar in section 9.

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 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.

The 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.

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	
sonidegib	Morning or PM.	600 mg	PO in the a.m.	Daily	

4.2.1 Sonidegib

4.2.1.1 Administration

Sonidegib will be administered beginning on Cycle 1, Day 1 once daily by oral dosing, in combination with gemcitabine as described in section 4.1. Therapy should continue until one of the conditions specified in section 4.5 occurs.

Table Treatment and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or regimen
Sonidegib	Capsule for oral use	q.d.	Daily

Sonidegib will be administered orally, on a continuous once daily dosing schedule at a dose of 600 mg. Participating patients will receive flat doses on mg/day basis and not according to their body weight or body surface area. Sonidegib is supplied as 200-mg hard gelatin capsules in bottles. Patients will receive 3 capsules of sonidegib. Medication labels will be in the local language and comply with the legal requirements of each country.

Patients will be dosed on flat scale of 600 mg daily dosing of sonidegib. Hard gelatin capsules at 200 mg are available.

Sonidegib should be taken as follows:

- Patients should be instructed to take their once-a day dose at approximately the same time each day
- Each daily dose of sonidegib should be taken with a glass of water and consumed over as short a time as possible (e.g. 1 capsule every 2 minutes)
- Patients should be instructed to swallow capsules whole and to not chew or open them
- Each daily dose of sonidegib should be taken **2 hours after** a light breakfast (e.g., consisting of juice, toast and jam). If breakfast was completed at 08:00 a.m., then study drug

administration should occur at 10:00 a.m. Food intake should be avoided for at least 1 hour after study drug administration

- Patients must avoid grapefruit, pomegranate, star fruit and Seville (sour) oranges during the entire study. The juices and products containing these fruits may also be avoided.
- If vomiting occurs during the course of the treatment, then no re-dosing of the patient is allowed before the next scheduled dose
- If the patient forgets to take his/her daily morning dose, then he/she should take sonidegib within 6 hours after the missed dose. If more than 6 hours have passed, then that day's dose should be omitted and the patient should continue treatment with the next scheduled dose
- Patients should inform the investigational site staff of any missed or delayed dose

4.2.2 Gemcitabine

Gemcitabine Premedication

Please see gemcitabine prescribing information for recommended premedication strategies.

4.2.3 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.

4.2.4 Other Modality (ies) or Procedures

4.3 Definition of Dose-Limiting Toxicity

DLTs include any non-hematologic Grade 3/4 toxicity considered possibly related to

sonidegib occurring during the first two cycles (56 days). Grade 3 nausea, or vomiting will be considered a DLT only if unresponsive to therapy. Grade 4 neutropenia, leucopenia, and decreased hemoglobin will be considered DLTs.

Toxicities will be evaluated after two months of therapy. The MTD is defined as the highest dose for which ≤ 1/6 dose limiting toxicities (DLTs) are observed.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

4.4 General Concomitant Medication Supportive Care Guidelines with LDE

4.4.1 Permitted concomitant therapy requiring caution and/or action

Sonidegib is an inhibitor of breast cancer resistance protein (BCRP) in vitro. Therefore substrates, especially those with a narrow therapeutic range, should be used with caution. BCRP substrates include zidovudine, pantoprazole, cimetidine, sulfasalazine, nitrofuratoin, mitoxantrone, methotrexate, topotecan, imatinib, and irinotecan. However, the use of mitoxantrone, methotrexate, topotecan, imatinib, irinotecan or statins is generally prohibited during this study.

In vitro drug metabolism studies reveal that the metabolism of sonidegib is mediated by CYP3A4 and also a potent inhibitor of CYP2C9 and CYP2B6. Clinical studies have not yet been performed to confirm the potential effect of sonidegib on substrates drugs metabolized by CYP2C9 in patients. Also, it is not known the potential effect of low and moderate CYP3A4 inhibitors and inducers on sonidegib clearance. Therefore, investigators, at their discretion, may administer concomitant medications known to be metabolized by CYP2C9 and CYP2B6, except drugs which have narrow therapeutic index/sensitive substrates for these two isoforms and statins. Caution is advised when sonidegib is co-administered with drugs that are moderate inhibitors or inducers of CYP3A4. Patients receiving such medications must be monitored closely for any potentiation of toxicity or decrease of clinical benefit due to any individual concomitant medications, and may require dose titration or adjustment.

4.4.2 Prohibited concomitant therapy

Other investigational therapies

Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued from the treatment portion of the study.

Strong CYP3A inhibitors and inducers

No clinical studies have been performed to confirm if sonidegib is a sensitive CYP3A4 substrate, hence concomitant use of strong CYP3A4 inhibitors and inducers is not permitted.

Patients receiving concomitant medications known to strongly inhibit and/or induce CYP3A4/5 that are deemed medically necessary should be excluded from the study. A partial list of drugs that are inducers, and inhibitors of CYP3A4/5 is included in the table below. The above list of medications has been generated by Novartis Oncology Clinical Pharmacology (OncCP) (DDI database document: last update August 2010) that is compiled by using information listed under "draft guidance for industry, drug interaction studies, CDER 2006", Indiana University School of Medicine drug interaction tables at http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable, and "drug interaction from University of Washington. Patients should be instructed not to take grapefruit, St John Wort or Seville (sour) orange juice while receiving sonidegib treatment throughout the study due to potential CYP3A4/5 inhibition. The other drugs without an asterisk should be carefully used as concomitant therapy.

Medications that are CYP3A4/5 inducers or inhibitors

Medications	
Inhibitors	**HIV antivirals:** indinavir, nelfinavir, ritonavir*, saquinavir

Medications	
	Antibiotics: azithromycin, ciprofloxacin, chloramphenicol, clarithromycin, erythromycin*, fluconazole&, itraconazole*, ketoconazole*, voriconazole*, telithromycine, posaconazole, norfloxacin
	Calcium channel blockers: diltiazem&, verapamil&
	Antidepressants: , fluvoxamine, nefazodone*
	Miscellaneous: amiodarone, cimetidine, delavirdine, diethyl-dithiocarbamate (chlorzoxazone), interleukin-10*, mifepristone, mibefradil , grape fruit juice&, isoniazid&, apepritant&
Inducers	**HIV antivirals:** efavirenz, nevirapine
	Anticonvulsants: barbiturates**, carbamazepine**, Oxcarbazepine**, phenytoin**, phenobarbital**
	Systemic glucocorticoids: dexamethasone&, glucocorticoids, hydrocortisone, prednisolone, prednisone
	Antibiotics: rifabutin**, rifampicin**,rifapentine**
	Antidiabetics: pioglitazone, troglitazone
	Miscellaneous: modafinil, hormone replacement therapy, oral contraceptives, St John's wort**

***- Known strong inhibitors of CYP3A4 are estimated to cause a≥ 5 fold increase in the AUC values or a ≥80% decrease in clearance of a CYP3A4 substrate;**

& -a moderate inhibitor is estimated to cause a ≥2-but < 5 fold increase in the AUC values or a 50-80% decrease in the clearance of a sensitive substrate when the inhibitor is given at the highest approved dose.

**** -Known strong inducers of CYP3A4/5 (AUC decrease by 50-80%)**

Medications that are CYP2B6 and CYP2C9 substrates (narrow therapeutic index)

Sonidegib is a potent inhibitor of drugs metabolized by the cytochromes CYP2B6 and CYP2C9 *in vitro*. Because of the potential risk for drug-drug interactions, using concomitant medications known to be metabolized by these enzymes that have low therapeutic index (see table below) is not permitted in the study. The other drugs without an asterisk should be carefully used as concomitant therapy.

Drugs metabolized by CYP2B6 and CYP2C9

CYPs	Drugs metabolized by CYPs
CYP2B6	Bupropion , cyclophosphamide, efavirenz, ifosfamide, methadone
CYP2C9	**NSAIDs:** diclofenac, ibuprofen, lornoxicam, meloxicam, naproxen, piroxicam, suprofen
	Oral hypoglycemic agents: tolbutamide, glipizide
	Angiotensin II blockers: losartan, irbesartan
	Sulfonylureas: glyburide/glibenclamide, glipizide, glimepiride, tolbutamide
	Miscellaneous: amitriptyline, celecoxib, fluoxetine, pravastatin&, glyburide, nateglinide, phenytoin, rosiglitazone, tamoxifen, torsemide, warfarin*, quinidine*

* -narrow therapeutic index: drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g. Torsade de Pointes) are not allowed

&- statins – If it is essential that the patient takes a statin to control hyperlididemia [see Section 5.1.7.5], then only **pravastatin** may be used with extra caution. Pravastatin has the lowest potential of cause rhabdomyolysis compared with other statins (3 cases/ 6 millions of prescription from 1994 to 2002) (Evans et al. 2002) and the lowest risk for drug-drug interactions with sonidegib, as it is primarily transformed in the liver cytosol by sulfonation, not by CYP2C9 or CYP3A4. (Evans et al. 2002)

Warfarin and coumadin derivatives

Therapeutic doses of warfarin sodium (Coumadin®) or any other coumadin-derivative anticoagulants are not permitted since sonidegib is a competitive inhibitor of CYP2C9 based on the *in vitro* data. An alternative, therapeutic anticoagulation may be accomplished using low-molecular weight heparin.

Drugs that may increase risk of rhabdomyolysis when used concomitantly with sonidegib

Selected drugs that may increase risk of myopathy and rhabdomyolysis when used concomitantly with sonidegib should be avoided. Such drugs should be discontinued for at least 2 weeks prior to initiation of sonidegib and it must be ensured the plasma CK is within the normal range at baseline. The list compiled below is based on reported association of the individual drugs with muscle toxicity and in addition to the potential risk of clinically relevant PK drug-drug interaction with sonidegib through inhibitory effects on CYP3A4 (enzyme metabolized sonidegib) or the inhibitory effect on CYP2C9 by sonidegib of drugs that may induced rhabdomyolysis.

- Azoles antifungals: Itraconazole, ketoconazole, fluconazole, voriconazole
- Macrolides: azithromycin, clarithromycin, erythromycin, telitromycin
- Fibrates: gemfibrozil
- 3-hydroxy-3 methyl-glutaryl (HMG) Coa reductase inhibitors (Statins): Atovastatin, Fluvastatin, Fluvastatin XL, Lovastatin, Pravastatin*, Rosuvastatin- and Simvastatin
- Antiretrovirals: Indonavir and ritonavir
- Others: phenobarbital, barbiturates, phenytoin and isoniazid

* If it is essential that the patient stays on a statin to control hyperlididemia [see Section 5.1.7.5], only pravastatin may be used with extra caution; CK should be monitored weekly during the first 8 weeks on concomitant treatment with sonidegib and then bi-weekly thereafter for 8 weeks and then every four weeks .

4.4.3 Contraception allowed/excluded

The use of oral contraceptives and implantable hormonal contraception is not allowed during the study, as detailed in the exclusion criteria.

- **Women of child-bearing potential**, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and through **20 months** after the final dose of study treatment. Highly effective contraception is defined as either:
  1. Total abstinence: When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
  2. Sterilization: Patient has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

3. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female study patients, the vasectomised male partner should be the sole partner for that patient]
4. Use a combination of the following (both a+b):
   a. Placement of a non-hormonal intrauterine device (IUD) or non-hormonal intrauterine system (IUS)
   b. Barrier method of contraception: Condom or Occlusive cap (diaphragm or cervical vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

Note: Hormonal contraception methods (e.g. oral, injected, implanted) are not allowed as it cannot be ruled out that the study drug decreases the effectiveness of hormonal contraception

Note: Woman are considered post-menopausal and not child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL and estradiol < 20 pg/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential

- **Male patient** must use highly effective (double barrier) methods of contraception (e.g., spermicidal gel plus condom) for the entire duration of the study, and continuing using contraception and refrain from fathering a child for 6 months following the study drug. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner in order to prevent delivery of the study treatment via seminal fluid

Sexually active males who are unwilling to use a condom during intercourse while taking drug and for 6 months after stopping investigational medications and agree not to father a child in this period are excluded from participating in this trial

4.4.4 Other Considerations

Concomitant and Excluded Therapies

For information regarding other drugs that may interact with gemcitabine and affect their metabolism, pharmacokinetics, or excretion, please see the gemcitabine package insert.

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 other than specified in the treatment protocol.

Medications required to treat adverse events and manage cancer symptoms, concurrent stable disease (e.g., controlled hypertension) and supportive care agents such as erythropoietin, granulocyte growth factors, or blood transfusion, and pain medications are allowed (use of growth factors, erythropoietin, blood transfusion or granulocyte colony-stimulating factor (G-CSF) is not permitted, until the patients have developed dose-limiting anemia or neutropenia). The patient needs to notify the investigational site about any new medications he/she takes after the start of the study medication. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be listed on the CRF.

4.5 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 6 cycles (4 pre-operative and 2 post operative cycles) or until one of the following criteria applies:

- Disease progression to unresectable or metastatic disease,
- Patient is not eligible for resection after four cycles of treatment,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Intolerable (Grade 3 or 4) toxicity most probably attributable to sonidegib or other agents
- 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

4.6 Duration of Follow Up

Patients will be followed for 18 months after removal from study or until death, whichever occurs first. Unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Follow up will occur every 3 months by phone call (patient or treating physician). Patients will be followed for disease progression/recurrence and overall survival which will be documented in eCRF.

4.7 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 4.5 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

5. DOSING DELAYS/DOSE MODIFICATIONS

5.1 Sonidegib

Investigators should follow the guidelines described below for the modification of sonidegib treatment. Any plan to deviate from these guidelines in view of the patient safety must be previously discussed with Novartis unless there is an urgent need for action.

All dose modifications should be based on the worst preceding toxicity. If study treatment is being held due to toxicity, scheduled visits and all assessments should continue to occur except the dosing of the study drug.

A maximum of two dose reduction steps will be allowed (see Table below), after which the patient will be discontinued from study treatment if there is a need for further dose reduction. For patients who undergo dose interruptions (delays), if the same toxicity returns after re-initiation of treatment, regardless of duration, the second re-initiation must resume at a lower dose. If the patient requires a dose interruption of > 21 days from the previous dose, then the patient must be discontinued from study treatment. Patients who discontinue the treatment due to an adverse event or an abnormal laboratory value must be followed until resolution or stabilization of the event.

All dose changes or interruptions must be recorded in the dosage administration record CRF, as appropriately.

Dose reduction steps for sonidegib

Dose reduction*			
	Starting dose level – 0	Dose level – 1	Dose level -2
Sonidegib dose (mg QD)	600	400	200
*Dose reduction should be based on the worst toxicity demonstrated.			

Recommended Dose Modifications and Dose Delays for suspected treatment-related toxicities

Recommended dose modifications for sonidegib**	
Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Hematologic	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm^3)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm^3)	Maintain dose level
Grade 3 or 4 (ANC < 1000 - 500/mm^3 or < 500/mm^3)	Omit dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then decrease dose by 1 step
Thrombocytopenia (PLT)	
Grade 1 (PLT < LLN - 75,000/mm^3)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm^3)	Maintain dose level
Grade 3 or 4 (PLT < 50,000 - 25,000/mm^3 or < 25,000/mm^3)	Omit dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then decrease dose by 1 step
Febrile Neutropenia	
Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Omit dose until resolved, then decrease dose by 1 step

Recommended dose modifications for sonidegib**	
Worst toxicity CTCAE grade* (value)	During a cycle of therapy
<u>Muscle Toxicity</u>	
Elevated creatine phosphokinase (CK)	
Asymptomatic CK elevation	
Grade 2 [CK elevation >2.5 x ULN - 5 x ULN]	• *Continue treatment on the same dose and monitor CK levels weekly until resolution to baseline level. Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated.*
Symptomatic (new-onset or worsening of pre-existing muscle symptoms such as myalgia, myopathy, and/or spasms) CK elevation	
Grade 1 [CK elevation >ULN - 2.5 x ULN)]	Continue treatment at the same dose and monitor CK levels weekly until resolution to baseline level and then monthly thereafter. Monitor muscle symptoms for changes until resolution to baseline. Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated.

Recommended dose modifications for sonidegib**	
Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Grade 2 [CK elevation >2.5 x ULN - 5 x ULN	Interrupt treatment and monitor CK levels weekly until resolution to baseline level. Monitor muscle symptoms for changes until resolution to baseline. Upon resolution, resume treatment at the reduced dose level and measure CK monthly thereafter. Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated.
Asymptomatic or Symptomatic CK elevation	
Grade 3 or 4 **without** renal impairment [Grade 3 (CK elevation >5 x ULN - 10 x ULN)] [or Grade 4 (CK elevation >10 x ULN)]	• Interrupt treatment and monitor CK levels weekly until resolution to baseline level. Monitor muscle symptoms for changes until resolution to baseline. • Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated. If renal function is **not impaired** (normal serum creatinine) and CK resolves to baseline level, consider resuming treatment at a reduced dose. CK levels should be measured weekly for 2 months after re-administration of sonidegib and monthly thereafter.
Grade 3 or 4 **with** renal impairment	• Interrupt treatment and monitor CK levels weekly until resolution to baseline level. Monitor muscle symptoms for changes until resolution to baseline. • If renal function **is impaired** (≥50% above the baseline level), interrupt treatment. Ensure patient is adequately hydrated and evaluate other secondary causes. Continue monitoring of CK and creatinine levels weekly. If CK levels return to baseline level and creatinine levels return to baseline, consider resuming treatment at the reduced dose otherwise discontinue treatment permanently.
Muscle-related (muscle pain or cramps)	• If new-onset ≤ CTCAE grade 1 or 2 myalgia/muscle cramps without CK elevation or worsening of pre-existing myalgia/muscle cramps without CK elevation, continue treatment with sonidegib and consider symptomatic treatment. If associated with elevated CK, then it should be, managed as for symptomatic CK elevation (described above). • If ≥ CTCAE grades 3, interrupt sonidegib dosing for up to 21 days and resume therapy at a reduced dose if resolution or improvement to CTCAE grade 1 occurs. Collect blood sample for PK and CK measurement at the time of dose interruption. If CK is elevated, manage as for symptomatic CK elevation. If muscle symptoms persist and CK is elevated, consider performing electromyography and muscle biopsy and monitor blood and/or urine myoglobin.

Recommended dose modifications for sonidegib**	
Worst toxicity CTCAE grade* (value)	During a cycle of therapy
<u>Renal</u>	
Serum creatinine	
Serum creatinine <2 x ULN	Maintain dose level
Serum creatinine 2-3 x ULN	Omit dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then decrease dose by 1 step
Grade 3 Serum creatinine > 3.0 - 6.0 x ULN	Omit dose until resolved to ≤ grade 1, then decrease dose by 1 step
Grade 4 Serum creatinine > 6.0 x ULN	Omit dose and discontinue patient from study
<u>Hepatic</u>	
Bilirubin	
Total bilirubin <2 x ULN	Maintain dose level
Total bilirubin 2-3 x ULN	Omit dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then decrease by 1 step
Grade 3 Total bilirubin > 3.0 - 10.0 x ULN	Omit dose until resolved to ≤ grade 1, then decrease dose by 1 step
Grade 4 Total bilirubin > 10.0 x ULN	Omit dose and discontinue patient from study
AST or ALT	
Grade 1 (> ULN - 2.5 x ULN)	Maintain dose level
Grade 2 (> 2.5 - 5.0 x ULN)	Maintain dose level
Grade 3 (> 5.0 - 20.0 x ULN)	Omit dose until resolved to ≤ grade 1 or baseline then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then decrease dose by 1 step
Grade 4 (> 20.0 x ULN)	Omit dose until resolved to ≤ grade 1 or baseline, then decrease dose by 1 step

Recommended dose modifications for sonidegib**	
Worst toxicity CTCAE grade* (value)	During a cycle of therapy
Cardiac	
Cardiac - prolonged QTc interval ≥ grade 3 (QTcF > 500 msec or >60 ms from baseline on at least 2 separate ECGs)	**First Occurrence:** • Omit dose • Perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant medication usage must be reviewed. • Perform a repeat ECG within one hour of the first QTcF of > 500 ms • If QTcF remains > 500 ms, repeat ECG as clinically indicated but at least once a day until the QTcF returns to < 480 ms. • Once QTcF prolongation has resolved, study treatment may be restarted at a reduced dose level **Second Occurrence:** • discontinue patient from further study treatment
Cardiac general	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose and discontinue patient from study
Grade 4	Omit dose and discontinue patient from study
Other adverse events**	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then decrease dose by 1 step
Grade 4	Omit dose and discontinue patient from study
All dose modifications should be based on the worst preceding toxicity.	
If the dose-limiting toxicity recurs in a patient following 2 dose reductions, then further therapy with sonidegib will not be continued.	
If a patient requires a dose interruption of > 21 days from the intended day of the next scheduled dose because of an sonidegib-related toxicity, then the patient must be discontinued from the study.	
*Common Toxicity Criteria for Adverse Events (CTCAE Version 4.0).	
** If the investigator deems that a recommended dose reduction or the recommendation to maintain the same dose level is not in the best interest of the patient, this decision may be discussed with Novartis on a case-by-case basis.	

5.2 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[a]	Gemcitabine (mg/m^2)[a]	nab- Paclitaxel (mg/m^2)
Study Dose	1000	1000
-1	800	800
- 2	600	600
[a]Dose reductions may or may not be concomitant. Please refer to Tables 4-6 for specific recommendations regarding dose reductions		

If patients experience study drug-related toxicities that require a delay in scheduled gemcitabine dosing for ≥ 21 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 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
≥ 1.5 x 109/L	AND	≥ 100 x 109/L	Treat on time
< 1.5 x 109/L	OR	<100 x 109/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 dose this cycle
Grade 0, 1 or 2	Same as day 1 previous cycle
Grade 3 toxicity	Decrease gemcitabine to 800 mg/m2
Grade 4 toxicity	Off protocol treatment
Dose held in 2 previous consecutive cycles	Decrease gemcitabine to 800 mg/m2

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 BloodCount	**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*

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 teatment 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

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]

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.

Peripheral Neuropathy

Nab-Paclitaxel treatment should be withheld in patients who experience ≥ 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 ≤ Grade 1, *regardless of suspected cause*. Patients experiencing peripheral neuropathy that requires a delay in scheduled nab-Paclitaxel dosing for ≥ 28 days will be discontinued from further participation in this study. Additionally patients receiving a reduced dose of nab-Paclitaxel who experience ≥ Grade 3 peripheral neuropathy at that dose level requiring a dose delay ≥ 28 days without resolving to ≤ Grade 1 will be discontinued from further participation in this study.

As observed in other clinical trials, ≥ Grade 3 neuropathy related to nab-Paclitaxel is usually seen in later phases of the treatment (cycle 6 and beyond). If ≥ 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 ≤ Grade 1, then reinstituted at the next lower dose level of both drugs. Patients who develop Grade 4 mucositis or diarrhea should have treatment discontinued.

6. SAFETY MONITORING AND REPORTING

6.1 Adverse Events

Definitions and reporting

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy) even if the event is not considered to be related to study drug (or therapy). Study drug (or therapy) includes the drug (or therapy) under evaluation, and any reference or placebo drug (or therapy) given during any phase of the trial.

- if it is unclear what study treatment includes, list all drug(s), other therapies, changes to existing therapy, diagnostic procedure, etc. that are specified by the protocol

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, and are recorded.

Information about all serious adverse events will be collected and recorded on the FDA MedWatch 3500a form. To ensure patient safety each serious adverse event must also be reported to Novartis within 24 hours of learning of its occurrence. A serious adverse event is an undesirable sign, symptom or medical condition which:

1. is fatal or life-threatening
2. required or prolonged hospitalization
3. results in persistent or significant disability/incapacity
4. constitutes a congenital anomaly or a birth defect
5. is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events not considered to be serious adverse events are hospitalizations for the:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

Any serious adverse event occurring after the patient has provided informed consent, has started taking the study medication, and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the

standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication). The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated.

For instructions about returning Serious Adverse Event Report Forms to Novartis refer to the protocol Section entitled Instructions for Rapid Notification of Serious Adverse Events.

6.2 Instructions for rapid notification of serious adverse events

6.2.1 Reporting responsibility

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Clinical Safety and Epidemiology Department (CS&E)

6.2.2 Reporting procedures

The investigator must complete the FDA MedWatch 3500a form and Novartis SAE coversheet in English, assess the relationship to study treatment and send the initial completed MedWatch form and Novartis SAE coversheet by fax 1.888.299.4565 within 24 hours to the local Novartis Clinical Safety & Epidemiology (CS&E) Department. The investigator must then ensure that the form and coversheet are accurately and fully completed with follow-up information and fax those to Novartis CS&E Department within 2 to 3 calendar days for deaths or life-threatening events and 5 calendar days for other serious adverse events. The original and the duplicate copies of the FDA MedWatch form, Novartis SAE coversheet, and the fax confirmation sheet must be kept with the case report forms at the study site.

Follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or discontinued study participation. The MedWatch form, Novartis SAE coversheet, and fax confirmation sheet must be retained. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects.

6.3 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.

6.4 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 (sonidegib and Gemcitabine) and can be expected.

6.4.1 Adverse Event List(s) for Sonidegib

Table Adverse events suspected to be related with sonidegib, occurring in ≥5% of patients

AE (preferred term)	**All N= 76**	
	All grades N (%)	Grade 3/4 N (%)
Nausea	21 (27.6)	0
Dysgeusia	19 (25.0)	0
Muscle spasms	18 (23.7)	0
Blood creatine phosphokinase increased	17 (22.4)	12* (15.8)
Decreased appetite	11 (14.5)	0
Fatigue	11 (14.5)	0
Vomiting	9 (11.8)	0
Myalgia	8 (10.5)	0
Alopecia	7 (9.2)	0
Weight decreased	6 (7.9)	0
Diarrhea	5 (6.6)	0
Headache	5 (6.6)	0
Lethargy	5 (6.6)	0
Aspartate amino transferase increased	4 (5.3)	2 (2.6)
Asthenia	4 (5.3)	2 (2.6)
Myositis	4 (5.3)	2 (2.6)
Pain in extremity	4 (5.3)	0
* An additional patient who experienced grade 4 CK elevation was not captured in this table because the investigator had indicated the event was not treatment-related in the clinical database. However, the patient had high systemic sonidegib exposure, which was consistent with other patients who experienced DLTs. Also, the DLT of CK elevation at 1000 mg QD occurred after the database cut-off date on Oct 29, 2010.		

6.4.2 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).

6.4.3 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.

6.5 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.

"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.

<u>Investigator Reporting of AEs and SAEs</u>

The Investigator or designee must completely and promptly record each adverse event using the CRF, 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 Case Report Forms.

6.5.1 Pregnancies

Any pregnancy that occurs during study participation should be reported. To ensure patient safety each pregnancy must also be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

6.5.2 Reporting Serious Adverse Events (SAEs)

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

1. Novartis
2. IRB
3. FDA

Timelines for reporting SAE's

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. Novartis - within 24 hrs of learning of a potential AE.
   Fax: to IMS at-1-888-299-4565 (toll-free) or-1-973-781-6794. If a fax machine is not available, AEs must be reported directly to IMS by calling 1-888-NOW-NOVA (1-888-669-6682

3. FDA- . As per section 6.6

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

6.6 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** sonidegib. 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 Novartis 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 sonidegib. 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, Novartis 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:

Novartis Drug Safety- within 24 hrs of learning of a potential AE.

Fax: to IMS at-1-888-299-4565 (toll-free) or-1-973-781-6794. If a fax machine is not available, AEs must be reported directly to IMS by calling 1-888-NOW-NOVA (1-888-669-6682

For questions related to safety reporting, contact:

Novartis Drug Safety: 1-888-NOW-NOVA (1-888-669-6682

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 Novartis. Copies of such reports should be faxed to:

Novartis Drug Safety
Fax: to IMS at-1-888-299-4565 (toll-free) or-1-973-781-6794. .

6.7 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.

6.7.1 Internal review

The PI 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 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.

6.7.2 External review

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.

7. 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.

7.1 Sonidegib

Route of Administration: Oral

Mode of Action: Sonidegib is a potent antagonist of Hedgehog and Smoothened dependent signaling.

Packaging and labeling: Medication will be labeled for Clinical Trial use and will include storage conditions for the drug and the medication number but no information about the patient.

Packaging and labeling

Study drugs	Packaging	Labeling (and dosing frequency)
LDE-225 (sonidegib)	Capsules in bottles (200 mg)	Labeled as ”sonidegib”

How Supplied: Sonidegib is supplied by Novartis as a 200-mg hard gelatin capsules for oral use, packaged in bottles, and will be administered on a flat scale of mg/day.

Administration: Sonidegib should be taken as follows

- Patients should be instructed to take their once-a day dose at approximately the same time each day
- Each daily dose of sonidegib should be taken with a glass of water and consumed over as short a time as possible (e.g. 1 capsule every 2 minutes)
- Patients should be instructed to swallow capsules whole and to not chew or open them
- Each daily dose of sonidegib should be taken **2 hours after** a light breakfast (e.g., consisting of juice, toast and jam). If breakfast was completed at 08:00 a.m., then study drug administration should occur at 10:00 a.m. Food intake should be avoided for at least 1 hour after study drug administration
- Patients must avoid grapefruit, pomegranate, star fruit and Seville (sour) oranges during the entire study. The juices and products containing these fruits may also be avoided.
- If vomiting occurs during the course of the treatment, then no re-dosing of the patient is allowed before the next scheduled dose
- If the patient forgets to take his/her daily morning dose, then he/she should take sonidegib within 6 hours after the missed dose. If more than 6 hours have passed, then that day's dose should be omitted and the patient should continue treatment with the next scheduled dose
- Patients should inform the investigational site staff of any missed or delayed dose

Supply, receipt and storage:

- Study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, sonidegib should be stored according to the instructions specified on the drug labels. Study medication will be dispensed by an authorized person at the investigator's site.
- Patients will be provided with adequate supply of sonidegib for self-administration at home until at least their next scheduled study visit.

Drug Accountability:

- Clinical drug supply must be accounted for and patients will be asked to return all unused study drug and packaging on a regular basis, at the end of the study or at the time of study drug discontinuation.
- At the conclusion of the study, and, as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to Novartis.

Disposal and destruction:

- The drug supply will be destroyed at a Novartis facility, Drug Supply group or third party, as appropriate. Study drug destruction at the investigational site will only be permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.

7.2 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 Study Drug:

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

7.3 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- 30ºC [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:
Dosing volume (mL) = Total dose (mg) / 5 (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: Will be obtained by commercial means

8. CORRELATIVE/SPECIAL STUDIES

8.1 Laboratory Correlative Studies

We will evaluate three sources of patient material (tumor biopsies, resected tumor and blood) in order to evaluate the effects of sonidegib. We will also evaluate the effects combination therapy on stromal compartment, intratumoral drug levels. Tumor tissue (biopsies or resected tumor) and blood samples will be obtained pre- and mid-treatment in patients.

Biopsies: Pre-treatment biopsies will be done within 14 days before starting cycle 1. The second mid-treatment biopsy will occur after two cycles of chemotherapy with gemcitabine and the hedgehog inhibitor sonidegib. Resected tumors in patient who undergo resection will also be used for correlative studies. For patients with unresectable disease at the time of surgical exploration a core/wedge biopsy will be obtained intra-op for the correlative studies as a substitute to the resected specimen.

8.1.1 Specimen collection techniques

8.1.1.1. Core biopsy of tumor tissue

8.1.1.1.1 Patient preparation instructions for 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 small amounts of clear liquid only

8.1.1.1.2. Biopsy Procedure

Biopsies will be done by routine EUS. Biopsies will be done using a commercially available 22-gauge standard fine needle aspiration needle or ProCore needle will be used, and 2-4 samples will be obtained from the lesion.

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 from primary tumor under EUS guided biopsy.

8.1.1.1.3. Fine needle aspiration biopsy (FNAB) for core biopsy

We will obtain a tumor core biopsy via ultrasound-guided FNA biopsy of the primary tumor. An FNAB will be performed using a standard technique using 22-gauge standard FNA needle or ProCore needle, per standard technique, including on-site microscopic evaluation by a cytopathologist, or a specially trained cytotechnologist. A maximum of ten "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 gastroenterologist to the appropriate area of the lesion.

8.1.1.2. Blood

Blood samples for correlative biology and immunology evaluation will be collected up to 14 days prior to initiation of therapy and following cycle 1 of treatment. We will collect approximately 220mL of blood (20mL of serum for banking in order to perform biomarker studies, and 200mL of PBMCs for circulating cancer cells.)

8.1.2. Handling of specimens

8.1.2.1. Core biopsy

Samples of core biopsy will be equally divided into containers marked as "formalin" (containing 10% neutral buffered formalin), or "RNA" (containing RNAlater, Ambion, 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). Real time quantitative PCR (qRT-PCR) analysis will be performed for transcript levels of *Gli1, Ptch* in the samples, using *SDHA* as a housekeeping gene control. Further details on these assays are indicated in section 8.1.4.

8.1.2.2. Blood
PBMCs will be separated from whole blood using the Ficoll Hypaque density gradient centrifugation method, and used for flow cytometry for circulating cancer cells . The residual serum will be stored at -80^{0}C.

8.1.3. Evaluation of Specimens

All samples collected for laboratory correlative studies will be taken to Anirban Maitra's lab:

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

8.1.4 Specific laboratory assays

8.1.4.1 Technique for Stroma evaluation

Semiquantitative density of stroma by H&E using a scale of 1+, 2+ and 3+. Results will be correlated with the primary endpoint resection rate.

8.1.4.2. Technique for Drug levels evaluation

Using a genetic engineered mouse model, Tuveson and colleagues demonstrated decreased drug delivery of gemcitabine as one of the mechanisms for chemoresistance in PDA[7]. Subsequently, by co-administration of an Hh inhibitor as a stromal depleting agent, there was an increase in the intratumoral drug concentrations of the concomitant administered cytotoxic agent gemcitabine. We anticipate that co-administration of stromal modulating agents will result in increased drug levels of gemcitabine.

We will analyze the intratumoral gemcitabine triphosphate concentrations in the mid

treatment biopsy and the primary tumor of resected PDA. Gemcitabine triphosphate levels will be measured in the Johns Hopkins Analytical Pharmacology Laboratory by Michelle A. Rudek, Pharm.D., Ph.D. Concentrations will be quantitated by UPLC with tandem mass spectrometry. For gemcitabine triphosphate, tissue homogenates are prepared at a standardized concentration of 200 mg/mL in phosphate buffered saline which are then extracted by acetonitrile precipitation, dry down, and reconstitution. Gemcitabine triphosphate is quantitated over the range of 0.5-10 µg/mL (3-60 µg/g) which has been successfully utilized in preclinical models (Rudek, unpublished data). Results will be correlated with the primary endpoint of the phase 2 study, resection rate. The correlations are exploratory for hypothesis generation.

8.1.4.3. 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 sonidegib. All of the qRT-PCR primers are routinely used in the Maitra laboratory. 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.

8.1.4.4. **Flow cytometric analysis for cancer stem cells (CSCs) in resected tumors**

In prior work we found that treatment with hedgehog pathway inhibitors leads to a reduction in the frequency of pancreatic CSCs ($ALDH^+$ and $CD44^+CD24^+$ cells) [15,16]. Additionally, aldehyde dehydrogenase (ALDH; a marker for pancreatic CSCs) expression in primary tumors correlates with worse survival in patients undergoing resection for early stage pancreatic adenocarcinoma [17]. The rationale for these studies, therefore, is to quantitatively compare the frequency of CSCs in resected tumors from patients receiving therapy with or without the Hh inhibitor sonidegib. We will also correlate the frequency of CSCs in resected tumors with clinical outcomes (resection rate and overall survival). Tumors tissue (100-500 mm^3) will be dissociated into a single cell suspension as previously described using mechanical and enzymatic dissociation and Ficol gradient centrifugation [17]. Cells will then be stained using antibodies against CD31, CD45, and glycophorin (to eliminate endothelial and hematopoietic cells) as well as the ALDEFLUOR reagent (to mark ALDH+ cells) and antibodies against CD44 and CD24, which are markers of pancreatic CSCs. The percentage of $ALDH^+$ and $CD44^+CD24^+$ cells in each tumor tissue will be analyzed and quantified using a FACSAria flow cytometer.

8.1.4.5. **Xenograft formation from resected tumors**

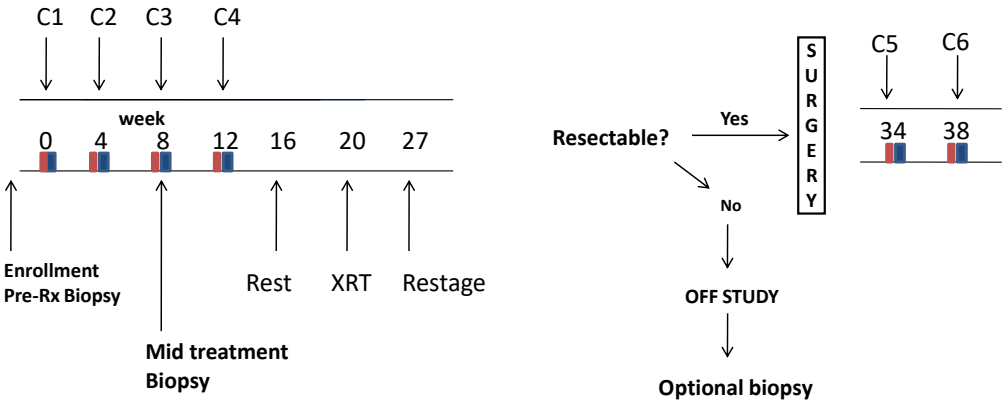
We have extensive experience with generating human pancreatic cancer xenografts in immunocompromised mice [18]. The ability of human tumors to form xenografts in mice is dependent on a number of factors, including the presence of CSCs that have long-term self-renewal potential and the capacity to differentiate. In these studies we will study the

effect of sonidegib on the ability of resected tumors to form xenografts. If the sonidegib abrogates CSC function, then we expect those tumors to have a reduced capacity to form xenografts in immunocompromised mice. We will correlate the ability of resected tumors to form xenografts with the frequency of CSCs in them (as described above) as well as with clinical outcomes (Progression free survival, time to relapse and overall survival). Tumor tissue will be cut into 2x2x2 mm pieces and implanted subcutaneously into the right and left flanks of five athymic (nu+/nu+) mice. Tumor formation and size will be measured weekly for 24 weeks. To confirm that actual tumor tissue was implanted a separate 2x2x2 mm tumor piece will be fixed in formalin, sectioned, and stained for histologic analysis.

9. STUDY CALENDAR

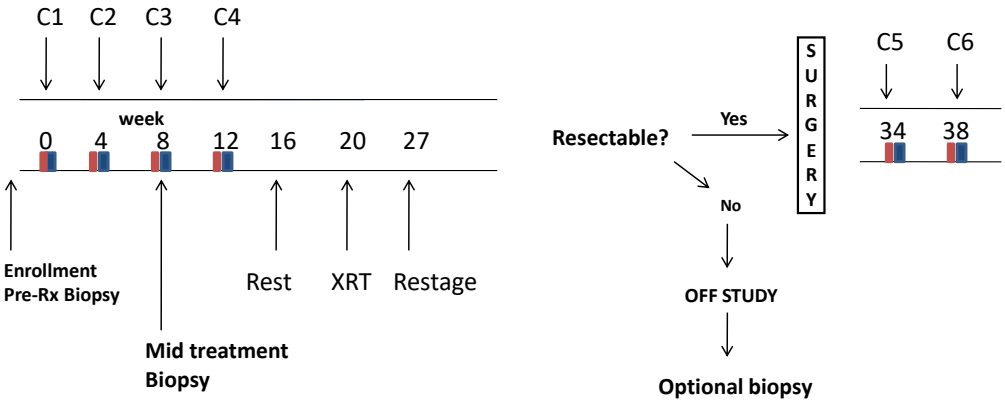
Phase I Stage
Neoadjuvant Study of Borderline Resectable Pancreatic Cancer

Arm A: Gem/ Nab-Paclitaxel/ LDE-225



Phase II Stage
Neoadjuvant Study of Borderline Resectable Pancreatic Cancer

Arm A: Gem/ Nab-Paclitaxel/ LDE-225
Arm B: Gem/Nab-Paclitaxel



CALENDAR FOR CHEMOTHERAPY

		Cycle 1-4 Cycle 5-6				
	Pre-Study	Day 1	Day 8	Day 15	Cycle 3 Day 1	EOT
Sonidegib[a] (daily, days 1-28)		X ---------- X				
Gemcitabine and Nab-Paclitaxel		X	X	X		
Informed consent	X					
Demographics	X					
Medical and Surgical evaluation	X	At baseline and at the end of radiation				
Concurrent meds	X	X ---------- X				X
Concurrent procedures	X	X ---------- X				X
Adverse event evaluation		X ---------- X				X
Physical exam	X	X				X
Vital signs	X	X	X	X		X
Height[g] and Weight	X	X				X
BSA calculation	X	X				
ECOG Performance	X	X				X
CBC w/diff, platelets, CK[f]	X	X	X	X[f]		X
Comprehensive Metabolic panel[f]	X	X				X
PT, PTT, INR[f]	X				X	
Surgery[b]	X	Four weeks after radiation				
EKG (as indicated)	X					
Radiologic evaluation CT scan or MRI[h]	X	Imaging will be done at baseline, end of cycle 2, cycle 4, before radiation therapy, 4 weeks after radiation therapy and at the end of cycle 6.				
PET Scan[h]	X	PET scan at baseline and at the end of cycle 4				
Pregnancy Test	X[c]	X[d]				
Pre-Treatment Biopsy	X					
Mid- treatment biopsy					X[e]	
Serum CA 19-9[f]		X				
Sample for Cancer Stem Cells	X	At baseline and at the end of cycle 4				

[a] Only for patients in a treatment arm that includes sonidegib
[b] After Surgery patients will have 4 weeks of recovery time before starting further treatment
[c] Pregnancy test (women of childbearing potential) at screening and 24 hours prior to first dose of sonidegib
[d] In women of childbearing potential. See next page for timings
[e] Mid treatment biopsy at cycle three day 1
[f] All blood tests will be done within +/- 3 days.
g Height is required at baseline only.
h All scans with a window of two weeks.

Baseline evaluations are to be conducted within 14 days 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.

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 sonidegib (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. A positive urine test must be confirmed by a serum pregnancy test. Prior to dispensing sonidegib, 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 sonidegib.

10. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every 8 weeks.

10.1 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.

10.1.1 Definitions

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

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.

10.1.2 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. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

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.

10.1.3 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. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in

ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).
The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

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.

10.1.4 Response Criteria

10.1.4.1 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.

10.1.4.2 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).

10.1.4.3 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 No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

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

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

10.1.5 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.

10.1.6 Response Review

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

10.1.7 PET Response Review

Response on PET will be assessed by expert radiologists based on PERCIST criteria [The Journal of Nuclear Medicine 2009 May;50 Suppl 1:122S-50S].

11. STATISTICAL CONSIDERATIONS

11.1 Study Design/Endpoints

Study Design: Open label, Phase 1/2 pilot trial.

Endpoints:

Primary endpoint for phase I component of the trial:

- Safety Endpoints: Incidence, nature and severity of grade 3 and 4 toxicities that occur after Cycle 1, day 1. Grading according to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE; version 4.0).

Primary endpoint for phase II component of the trial:

- Resection rate as defined by the percent of patients that undergo resection after completion of neoadjuvant therapy.

Secondary Endpoints:

- Overall survival from day 1, cycle 1
- Complete response, partial response, stable disease and progressive disease per RECIST criteria and PERCIST criteria
- Post surgical pathologic findings including margin status, tumor differentiation and lymph node status after neoadjuvant therapy.
- Toxicity rate, overall and stratified by grade and type.

Correlative Endpoints:

- Semiquantitative density of stroma. Results will be correlated with the primary endpoint resection rate.
- Semi-quantitative measurement of Gli-1, SHH and PATCH on the biopsies and resected tumor.
- Intratumoral gemcitabine triphosphate concentrations. Concentrations will be quantitated by UPLC with tandem mass spectrometry as previously done in preclinical models by our group [9].

11.2 Sample Size/Accrual Rate

For the Phase 1 stage it is estimated that 6-12 patients will be enrolled. Phase II stage will recruit 40 patients (20 patients per arm). The estimated recruitment is 3-4 patients per month.

11.3 Analysis

Phase I study. A standard 3+3 design will be used to determine the MTD. For a given dose level, if 0/3 toxicity are observed then the dose combination will be escalated. If 1/3 toxicities are observed, then an additional 3 patients will be enrolled at the current dose level. Escalation will continue if 1/6 toxicities are observed. If > 1/3 or > 1/6 toxicities are observed then escalation will be halted. The MTD is defined as the highest dose level for which 0 or 1 out of 6 toxicities are observed. With 2 dose levels, we expect to enroll between 6-9 patients with an expected accrual rate of 3 patients per month. The phase I portion of the study will be completed during the first year of the study. We will tabulate the number, type and grade of toxicities for each treatment cycle. The six patients enrolled and treated with gemcitabine and sonidegib will not be included in the analysis.

Phase II study. The phase 2 study will be used to prospectively establish resection rates and initial efficacy outcome estimates for each of the treatment combinations to be used for designing larger phase 2 or 3 studies. We will enroll a total of 40 patients (20 patients per arm). Expected enrollment is 3 patients per month. Enrollment will occur during the first two years of the study.

Summary statistics for continuous outcomes (mean, SD, median, range) and categorical outcomes (count, percentage) will be calculated. The number and grade of toxicities will be tabulated. Percent of patients that achieved resection will be described with exact Binomial 95% confidence intervals. Kaplan-Meier techniques will be used to summarize time-to-event outcomes (overall survival and disease free survival) graphically and to estimate the median and one and two-year survival outcomes with 95% confidence intervals. Cox proportional hazards functions will be used to estimate the effect of risk factors (e.g. tumor grade, nodal status) on overall survival.

Power calculations. With 20 patients in an arm, we have 81% power to detect an increase in the percentage of resectable patients from the null rate of 41% to 65% based upon a one-sample test of proportion with a one-sided type-1 error rate of 10%. This sample sizes allows us to estimate the proportion of resectable patients within ± 23%.

Correlative Studies: IHC analyses will be conducted using a semi-quantitative method. Either hematoxylin and eosin staining for stroma, or specific IHC staining with the protein targeted antibody and will be scored from 1+ to 3+, resulting in three groups: low (1+), intermediate (2+), and high (3+). We will correlate clinical outcomes (resection rate, tumor response and OS) with stroma density, SHH, Gli1 and Patch expression. Logistic regression will be used to assess the association between stromal scoring and resection. Cox proportional hazards functions will be used to estimate the effect of risk factors (e.g. stromal grade) on overall survival. Comparisons of scoring between treatment arms and time periods will be evaluated using χ^2 tests (or Fisher's exact test if appropriate) and with percent agreement and

Kappa statistics, respectively. Comparisons of expression across treatment groups and between time periods will be evaluated using t-tests (or Wilcoxon rank-sum tests) and paired t-tests (or Wilcoxon signed-rank tests), respectively. Pharmacokinetic (PK) data will be summarized using descriptive statistics. Logistic regression will be used to assess the association between drug concentrations and the clinical endpoint resection rate.

11.4 Futility Assessment and Toxicity Monitoring Guidelines

A single interim futility analysis will be included to eliminate any arms that do not show activity. The resection rate would have to be $\geq$ 40% to be considered clinically significant. For each arm, if 0 out of the first 10 patients are eligible for resection then the arm will be dropped. The upper boundary for the two sided 95% confidence interval for 0/10 is 26%, which is below the level of resection rate that would be considered clinically significant.

Toxicity will be monitored throughout the course of the trial since only 6 patients will have received the combination therapy during phase 1. Bayesian stopping guidelines have been developed. The prior distribution was chosen to be a Beta(1.5, 5.5) to reflect the toxicity criteria from the phase 1 portion of the study. As each patient completes 1 month of follow-up (the window initial for toxicity evaluation) or experiences an adverse event, the posterior probability that the toxicity exceeds 33% will be computed. An initial 6 patients will be enrolled prior to initiation of monitoring. Thereafter, if the probability that the toxicity level exceeds the target threshold (33%) is above 70%, then the study will be re-evaluated. The table below lists the number of toxicities that would trigger a re-evaluation at each stage of enrollment. Accrual will not be halted during the monitoring process unless excessive toxicity is encountered.

Stopping guidelines for toxicity monitoring.

Sample Size	Number of toxicities
3	3
4-6	4
7-9	5
10-12	6
13-14	7
15-17	8
18-20	9

Based upon 5000 simulated trials, applying these stopping guidelines would result in halting the trial early 29% of the time if the true level of toxicity were 33%. The table below gives the probability of stopping early under a number of different scenarios.

Probability of early stopping based upon the guidelines described above.

Underlying toxicity rate	Probability of re-evaluation
25%	11.1%
30%	22.2%
33%	29.3%
35%	35.8%
40%	51.5%
50%	81.4%

12 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

12.1 Ethics and good clinical practice

This study must be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
3. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
4. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

12.2 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. The name and occupation of the chairman and the members of the IRB/IEC/REB must be supplied to Novartis. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

12.3 Informed consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval.

12.4 Discontinuation of the study

Novartis reserves the right to discontinue support for any study under the conditions specified in the clinical trial agreement.

12.5 Amendments to the protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by Novartis and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC/REB. A copy of the written approval of the IRB/IEC/REB, must be sent to Novartis.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB of each center must be kept informed of such administrative changes.

12.6 Publication of results

Any formal presentation or publication of data from this trial may be published after review and comment by Novartis and prior to any outside submission. Novartis must receive copies of any intended communication in advance of publication (at least twenty-one working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Novartis' responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigation/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Novartis and, in accord with the trial contract and shall not permit disclosure of Novartis confidential or proprietary information.

12.7 Disclosure and confidentiality

The investigator agrees to keep all information provided by Novartis in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Novartis (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by Novartis to the investigator may not be disclosed to others without direct written authorization from Novartis, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

12.8 Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html.

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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, during their participation in the study and for 20 months following discontinuation of sonidegib.

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)

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

- Tubal ligation
- Partner's vasectomy
- 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:

- Hormonal contraception including birth control pills, patches, rings, or injections
- IUD progesterone T
- *Progesterone-only "minipill"*
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

APPENDIX C

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 BORDERLINE RESECTABLE adenocarcinoma of the pancreas. Patients who have not undergone biopsy but have highly suspected adenocarcinoma of the pancreas with borderline resectable features on imaging study may also be eligible for study and undergo the pretreatment biopsy as per protocol. The biopsy must confirm adenocarcinoma of the pancreas to continue on study. Borderline resectable disease is defined by one of the following criteria:

(1) Tumor associated deformity of the superior mesenteric vein (SMV) or portal vein (PV)
(2) Abutment of the SMV or PV $\leq 180^0$
(3) Short-segment occlusion of the SMV or PV amenable to resection and venous reconstruction
(4) Short-segment involvement of the hepatic artery or its branches amenable to resection and reconstruction or
(5) Abutment of the superior mesenteric artery (SMA) $\leq 180^0$

_____ ____ 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, surgical resection, chemotherapy or investigational drug therapy for pancreatic adenocarcinoma.

_____ _____ 4. Age ≥18 years.

_____ _____ 5. Life expectancy of greater than 1 month.

_____ _____ 6. ECOG performance status ≤1 (Karnofsky ≥70%; see Appendix A).
ECOG PS: _____

_____ _____ 7. Patients has adequate organ and marrow function as defined below:

- leukocytes ≥3,000/mcL
- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- total bilirubin < 1.5 ULN
- AST(SGOT)/ALT(SGPT) <2.5 X institutional upper limit of normal
- plasma creatinine phosphokinase (CK) < 1.5 x ULN
- 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

_____ _____ 10 For sexually active females: Patient has agreed to practice effective contraceptive measures throughout the study and for 20 months after last dose of study drug.

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 6 months after stopping sonidegib. Males should not donate sperm during treatment, and for up to six months after last dose.

_____ ____ 12. Patient agrees NOT to donate blood products for 12 months after stopping sonidegib

_____ ____ 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 is willing to have two biopsies while on treatment

____ ____ 16. Patient has NO history of allergic reactions attributed to compounds of similar chemical or biologic composition to sonidegib 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®).

<u>Instructions</u>: This eligibility checklist must be completed in its entirety.

Yes	No		ELIGIBILITY CRITERIA: (All answers must be YES)
____	____	18.	Patients is NOT taking medications known to be moderate and strong inhibitors or inducers of CYP3A4/5 or drugs metabolized by CYP2B6 or CYP2C9 that have narrow therapeutic index, and that cannot be discontinued before starting treatment with sonidegib. Medications that are strong CYP3A4/5 inhibitors should be discontinued at least 7 days and strong CYP3A/5 inducers for at least 2 weeks prior to starting treatment with sonidegib.
____	____	19.	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.
____	____	20.	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)
____	____	21.	Patient does NOT have 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
____	____	22.	Patient does NOT have history neuromuscular disorders (e.g. inflammatory Myopathies, muscular dystrophy, amyotrophic lateral sclerosis and spinal muscular atrophy) or is on concomitant treatment with drugs that are recognized to cause rhabdomyolysis, such as HMG CoA inhibitors (statins), clofibrate and gemfibrozil, and that cannot be discontinued at least 2 weeks prior to starting sonidegib treatment. If it is essential that the patient stays on a statin to control hyperlididemia, only pravastatin may be used with caution. b) Patient is NOT planning on embarking on a new strenuous exercise regimen after initiation of study treatment. NB: Muscular activities, such as strenuous exercise, that can result in significant increases in plasma CK levels should be avoided whie on sonidegib treatment.

____ ____ 23. Impaired cardiac function or clinically significant heart disease, including any one of the following:

- Angina pectoris within 3 months
- Acute myocardial infarction within 3 months
- QTcF > 450 msec for males and > 470 msec for females on the screening ECG
- A past medical history of clinically significant ECG abnormalities or a family history of prolonged QT-interval syndrome
- Other clinically significant heart disease (e.g. congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)

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 D
Registration Form
Please supply the following information for <u>all patients</u> who sign informed consent.*

Please Print Legibly

Study Number: ☐

Patient's History Number ☐ **(optional)**

Patient's Name: _____ _____ _____
First Name Middle Initial Last Name

Patient's Date of Birth: _____ _____ _____
Month Day Year

Race: (√ all that apply)
- ☐ American Indian or Alaskan Native
- ☐ Asian
- ☐ Black or African American
- ☐ Native Hawaiian or Other Pacific Islander
- ☐ White
- ☐ Other
- ☐ Unknown

Ethnicity: (√ one)
- ☐ Hispanic or Latino
- ☐ **<u>Not</u>** Hispanic or Latino
- ☐ Unknown

Gender: (√ one)
- ☐ Male
- ☐ Female

Patient's **USA** Zip Code: ___ ___ ___ ___ ___ Estimated start date: ___/____/____

Foreign Country (if does not reside in US): _____

Type of Cancer: _____ (e.g. colon, lung, ALL, etc.)

_____ _____
Signature of PE/Designee Completing Form **Date**

* Note: If a subject has more than one consent form for the same study, only complete this form **ONE** time.

APPENDIX E:

PROTOCOL SIGNATURE PAGE

Protocol Number: J1130, NA_00047491

Protocol Title: Phase 1/2 Safety and Feasibility of Gemcitabine and Nab-Paclitaxel in combination with LDE-225 (Sonidegib) as Neoadjuvant Therapy in Patients with Borderline Resectable PancreaticAdenocarcinoma.

Protocol Amendment 3.4, date August 13, 2014

IND Number: 112289

Sponsor: Investigator Initiated

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: Ana De Jesus-Acosta MD

Title: Assistant Professor

Address: The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins
1650 Orleans Street, CRBI, Room4M08,
Baltimore, MD 21231-1000

PI Signature: _____

Date: _____

APPENDIX F: AMENDMENT SUMMARIES

Amendment # 1, Feb 21, 2012

1. On page 27, modified the sentence for "Mid Treatment Biopsy" section as "A window of 3 days after the treatment will be allowed."

2. On page 66, Calendar for Chemotherapy section-
   a) Moved Mid-treatment Biopsy from Day 28 to Cycle 3 Day 1;
   b) Added PT/PTT/INR on Cycle 3 Day 1.
   c) Added "All blood tests will be done within +/- 3 days" to the notation section.

3. In the head section, changed the version and the date of the protocol Amend 1.
4. On the first page, deleted John Cameron, MD and Marcia Irene Canto, MD from the study.
5. Added Appendix E: Protocol Signature Page
6. Added Appendix F: Amendment Summaries

Amendment # 2, August 29, 2012

1. Header section with new amendment date was added
2. Page 2: Removed H. Cai from study. Added T. Brown as data manager / coordinator.
3. Section 3.1.8, Inclusion Criteria, page 22: Removed "unless liver metastases are clearly present, then <5X ULN is allowed".
4. Section 4.1.7, page 31: End of Therapy evaluation was added
5. Section 4.6, page 41: Specified schedule for follow up for progression/recurrence and overall survival.
6. Section 8.1, page 62: Added language "For patients found with unresectable disease at the time of surgical exploration a core/wedge biopsy will be obtained intra-op for the correlative studies as a substitute to the resected specimen."
7. Section 9, page 68: Study calendar section modified to reflect EOT evaluation and follow up schedule. Footnotes updated. Window of two weeks is added for all scans.
8. Consent form updated to JHM IRB template 13 and modified to reflect end of treatment visit.

Amendment # 3, April 25, 2013

1. Title: added Nab-Paclitaxel
2. Responsible research nurse information updated: Sheila Linden
3. Header section with new amendment date was added
4. Primary objective: added nab-Paclitaxel. Section 1.1
5. Section 2.3 Rationale for adding nab-Paclitaxel included
6. Section 2.4 Rationale moving radiation to pre-surgery included

7. Section 2.5: Other drugs nab-Paclitaxel added
8. Section 4.1.5 (Surgery) moved to after radiation
9. Radiation section now 4.1.5 and timing from chemotherapy within 4 weeks included
10. Section 4.2 added nab-Paclitaxel to agent administration, regimen description and dose escalation cohorts. Dose of nab-Paclitaxel is fixed as per phase II and III studies.
11. Nab-Paclitaxel added to phase 2 study
12. Section 4.2.3 Premedication description for nab-Paclitaxel
13. Section 5.2 modified to include dose modifications for nab-Paclitaxel on day 1 of each cycle and during treatment cycles. Also includes management for non-hematological toxicities.
14. Section 6.4.3 added adverse even list for nab-Paclitaxel
15. Section 6.3 was added with drug information for nab-Paclitaxel
16. Section 7.3 added: Pharmacy information for nab-Paclitaxel
17. Study calendar diagrams to reflect changes and addition of nab-Paclitaxel were modified.
18. Section 11.3 specifies that the six patients enrolled at this point will not be included in final analysis.

Amendment # 3.1, MAY 31, 2013

Protocol:

1. Section 3.1.10: “12” months changed to “6” months
2. Section 3.1.11: “3” months changed to “6” months
3. Appendix B: “12” months changed to “6” months
4. Eligibility form, near end of protocol, Item # 11: “12” months changed to “6” months

Consent:

5. Section 5: “12” months changed to “6” months (two times)
6. Section 5: “3” months changed to “6” months
7. Section 12: added
    a. “and governmental agencies in foreign countries)”
    b. “, the drug supplier (Novartis) and its authorized agents,”
    c. “During the study, you may not have access to some of your medical information obtained or created as part of this study. You will be allowed to access this information once the study is finished.”
    d. “If the results of this study are published or presented in a meeting, you will not be named and nobody will be able to tell that you were in the study from the publication or presentation.”

Amendment # 3.2, NOV 27, 2013

Protocol:

1. Section 3.1.4: Added "for pancreatic adenocarcinoma"
2. Section 3.2.1: Added/reworded: "Patients who have had previous radiotherapy, surgical resection, chemotherapy or investigational drug therapy for pancreatic adenocarcinoma."
3. Appendix C: Added "for pancreatic adenocarcinoma" to item # 3.

Amendment #3.3, JUNE 26, 2014

Protocol:

1. Header: Updated version number and date to Version # 3.3, JUNE 26, 2014.
2. All applicable sections: Changed LDE-225 to sonidegib.
3. Section 3.2.12, page 26: added "Impaired cardiac function or clinically significant heart disease" as exclusion.
4. Section 4.4.3, pages 43-44:
    a. "Hormonal" removed from section title.
    b. Added clarification of contraceptive methods.
5. Section 5.1, page 47-49: updated recommended dose modifications for sonidegib .
6. APPENDIX B, page 96:
    a. Page 96: Changed number of months women of child bearing potential must use contraception from 6 months post-last dose of study drug to 20 months post-last dose of study drug.
    b. Page 96: Removed hormonal contraceptive as acceptable method for this study.
7. Appendix C:
    a. Females must use birth control for 20 months after taking last dose.
    b. Added "Impaired cardiac function or clinically significant heart disease" as exclusion.

Consent:

1. Removed line for subject initials at bottom of each page, since not IRB required.
2. Section 3, Cycles 5-6: clarified language about addition of nab-paclitaxel.
3. Section 4, LDE225 risks:
    a. Added: instructions for females and males (females must use birth control for 20 months post last dose, and males must use condom during intercourse).
    b. Changed: 700 to 1000.
    c. Added: "including patients".
    d. Moved: risks of upper abdominal pain, back pain, and cough from less common to common side effects section.
4. Section 5, Pregnancy risks:
    a. Added "while receiving sonidegib, and for 20 months after taking the last dose".

b. Changed: 6 months to 20 months.

5. Section 15, added "Novartis will not provide financial assistance or compensation for injury, medical expenses, lost wages or any other damages or losses as a result of participation in this research study."

Amendment # 3.4, AUGUST 13, 2014

Protocol:

1. Header: updated version to 3.4, August 13, 2014.
2. Title page: added Amy Ryan, CRNP as co-investigator.
3. Table of contents: updated page numbers for tracked and clean versions.
4. Section 3.1.11, Eligibility: changed three to six. "Males should not donate sperm during treatment, and for up to six months after last dose."
5. Appendix C # 11, Eligibility: added "Males should not donate sperm during treatment, and for up to six months after last dose."

Consent:

1. Section 3, page 7: deleted "(initial and date)" since initials are sufficient, and the subject dates the final page of the consent form.
2. Section 5, page 15: added "Women of childbearing potential are required to have a negative serum pregnancy test within 10-14 days and within 24 hours prior to the first dose of sonidegib (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. A positive urine test must be confirmed by a serum pregnancy test."
3. Section 5, page 16: added "Males should not donate sperm during treatment, and for up to six months after last dose."