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Cover Page

Official Title: A Phase 1b and Pharmacodynamic Study of Nintedanib Monotherapy Followed by Combination Therapy of Nintedanib and Gemcitabine Plus nab-Paclitaxel for Advanced Pancreatic Cancer

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A Phase 1b and Pharmacodynamic Study of Nintedanib Monotherapy Followed by Combination Therapy of Nintedanib and Gemcitabine Plus nab-Paclitaxel for Advanced Pancreatic Cancer

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Signature Page

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

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

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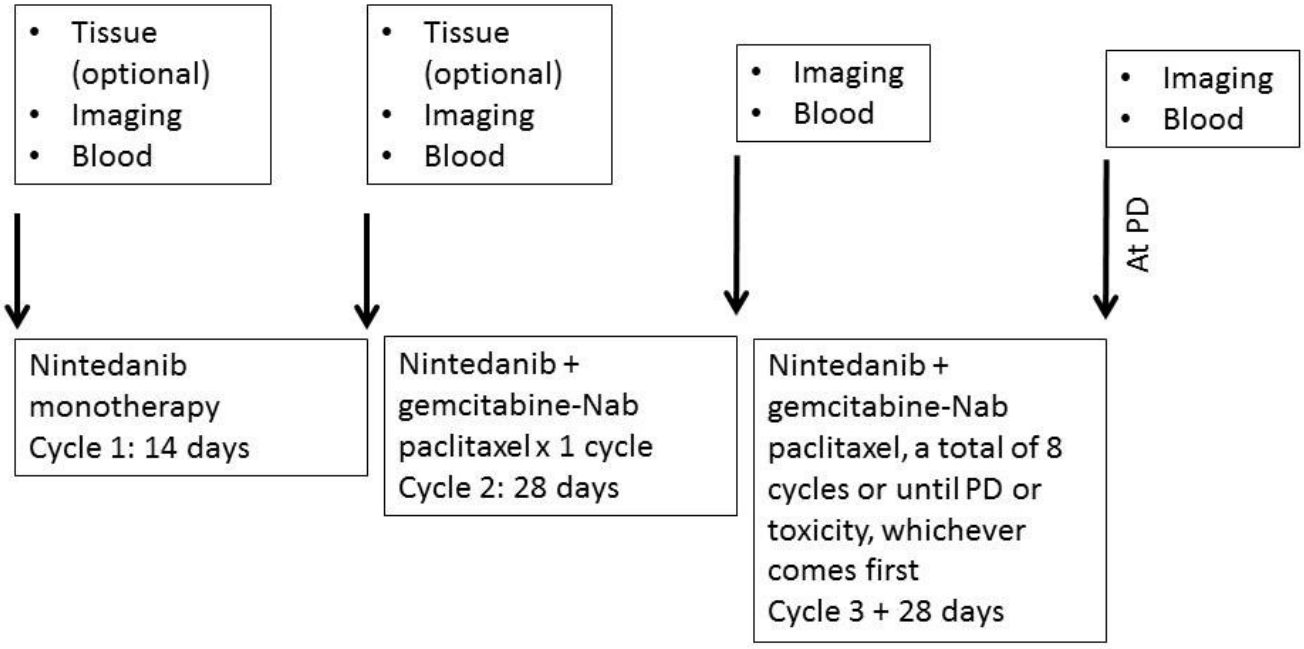
STUDY SCHEMA



PROTOCOL SYNOPSIS

Title:	Phase 1b and Pharmacodynamic Study of Nintedanib Monotherapy Followed by Combination Therapy of Nintedanib and Gemcitabine Plus Nab-paclitaxel for Advanced Pancreatic Cancer
Short Title:	Phase 1b Study of Nintedanib and Chemotherapy for Advanced Pancreatic Cancer
Protocol Number:	SCCC-06216
Phase:	Phase 1b
Methodology:	Single arm, open label study
Study Duration:	24 months (enrollment)
Study Center(s):	Multicenter: 1) UT Southwestern Medical Center at Dallas 2) UT Health Sciences San Antonio
Objectives	Primary Objectives: 1. Determine safety and tolerability of nintedanib administered with gemcitabine plus Nab-paclitaxel in advanced pancreatic cancer. Secondary Objectives: 1. Determine pharmacodynamic effects (blood and imaging) of nintedanib on angiogenesis and tumor microenvironment in advanced pancreatic cancer. 2. Determine preliminary efficacy (response rate, progression-free survival, overall survival) of nintedanib in combination with gemcitabine plus Nab-paclitaxel in advanced pancreatic cancer.
Number of Patients	20 (evaluable for safety analysis)
Diagnosis and Main Inclusion Criteria	1. Locally advanced and metastatic pancreatic adenocarcinoma; 2. Good ECOG performance status of 0-1; 3. Preserved hematologic, hepatic, and renal function.
Study Product(s), Dose, Route, Regimen	1. Nintedanib dose escalation: 150, 200 mg PO BID 2. Nab-paclitaxel: 125 mg/m^2 day 1,8,15 every 28 days 3. Gemcitabine: 1000 mg /m^2 day 1,8,15 every 28 days
Duration of administration	One cycle of Nintedanib monotherapy followed by a total of eight cycles of both Nintedanib and the chemotherapeutic agents, or until disease progression, whichever comes first.

Reference therapy	Historical (MPACT study, Von Hoff et al, ASCO 2013) http://meetinglibrary.asco.org/content/116827-132
Statistical Methodology	All patients receiving at least one dose of nintedanib will be considered evaluable for safety analysis. However only patients experiencing a dose limiting toxicity (DLT) or those who receive all scheduled full dosing regimen of nintedanib/gemcitabine/nab-paclitaxel will be considered evaluable for DLT assessment. In addition to the evaluation and categorization of adverse events, listing of laboratory test results collected at baseline and during the study will be generated. Descriptive statistics summarizing the changes in those laboratory tests over time will be collected. Patients who have received at least 2 cycles of therapy and had at least one disease assessment following the initiation of therapy will be considered evaluable for response. The antitumor activity (RECIST) will be exploratory.

List of Abbreviations

AEs – adverse events

ALT – alanine amino transferase

AST – aspartate amino transferase

ATP - adenosine triphosphate

BIBF1120 – Nintedanib

BID – twice daily

BUN – blood urea nitrogen

CBC – complete blood count

CI – confidence interval

Cmax – maximum plasma concentrations

CR - complete response

CRF – case report form

CRO – Clinical Research Office

CT – computed tomography

CTCAE - Common Terminology Criteria for Adverse Events

DLT – dose-limiting toxicity

DSMC - Data and Safety Monitoring Committee

ECOG - Eastern Oncology Cooperative Group

EGFR – epidermal growth factor receptor

Flt-3 – Fms-related tyrosine kinase 3

FGF/FGFR – fibroblast growth factor/fibroblast growth factor receptor

FOLFIRINOX – folinic acid, fluorouracil, irinotecan, oxaliplatin

FOLFOX – folinic acid, fluorouracil, oxaliplatin

LDH – lactate dehydrogenase

IPF – idiopathic pulmonary fibrosis

IRB – institutional review board

Nab-paclitaxel – albumin-bound paclitaxel

TKI – tyrosine-kinase inhibitor

PDGF/PDGFR – platelet-derived growth factor/

platelet-derived growth factor receptor

VEGF/VEGFR – vascular endothelial growth factor/ vascular endothelial growth factor receptor

γ-GT – gamma-glutamyl transpeptidase

PD - pharmacodynamics

NSCLC – Non-Small Cell Lung Cancer

MCRC – metastatic colorectal cancer

RET – ret proto-oncogene

Lck – lymphocyte-specific protein tyrosine kinase

OS – overall survival

PFS – progression free survival

NCCN – national comprehensive cancer network

DCE-MRI – dynamic contrast-enhanced MRI

PI - principal investigator

PR - partial response

RECIST - Response Evaluation Criteria in Solid Tumors

SCCC -Simmons Comprehensive Cancer Center

TDP - time to disease progression

MRI – magnetic resonance imaging

SD – stable disease

PD – progressive disease

1.0 BACKGROUND

1.1. Disease Background

Metastatic pancreatic adenocarcinoma is a universally fatal disease accounting for most of the approximately 40,000 deaths from pancreatic cancer in the United States annually[1]. Whereas the mainstay of therapy for metastatic cancer has been systemic chemotherapy, currently available treatment strategies for pancreatic cancer have been unable to make a significant impact on long term outcomes. Gemcitabine has long been used for management of stage IV pancreatic cancer due to a reduction of cancer-related symptoms and improvement in performance status.[2]

Anti-epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) erlotinib gained approval for first-line treatment, when given in combination with gemcitabine, based on a modest improvement in overall survival[2]. Recently, the first non-gemcitabine combination therapy FOLFIRINOX (5-fluorouracil/ leucovorin given in combination with oxaliplatin and irinotecan) demonstrated activity in the PRODIGE trial [3], but broad applicability of this regimen has been hampered by its high toxicity rate. In addition, studies are underway to evaluate FOLFIRINOX with Algenpantucel-L in locally advanced pancreatic cancer. Encouraging Phase I/II study of 67 patients treated with a combination of nab-paclitaxel (a nanoparticle albumin-bound (nab) formulation of paclitaxel) and gemcitabine [4] lead to a larger Phase III 'MPACT' study which was initially reported at the 2013 Gastrointestinal Cancers Symposium. Combination therapy with Gemcitabine and nab-paclitaxel demonstrated a statistically significant improvement in overall survival over gemcitabine alone (8.5 vs 6.7 months) and an increase overall response rate (23% vs. 7%). Given the lack of significant activity of currently used treatments, and the toxicity of FOLFIRINOX, the success of combination of gemcitabine and nab-paclitaxel may prove to be a major turning point for pancreatic cancer patients who are in great need of more effective systemic therapy.

Angiogenesis is crucial for the growth of malignant tumors and metastases. Angiogenesis inhibitors offer a novel approach for cancer therapy. Most drugs target VEGF as an important proangiogenic factor that can drive tumor angiogenesis, although platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) also play an important role. PDGF receptor tyrosine kinases, expressed on the surface of pericytes and smooth muscle cells, contribute to the stability of blood vessel walls; PDGF signaling is important for pericyte survival and maintaining pericyte-endothelial cell contacts [5]. FGF receptor (FGFR) tyrosine kinases are expressed on the surfaces of endothelial cells and smooth muscle cells. FGFR signaling pathways promote cell proliferation and survival, playing a role in the development and stabilization of blood vessels [6]. PDGF and FGF may also be upregulated in tumors trying to escape from sustained VEGF inhibition [7,8]. In recent years, there has been increasing interest in targeting angiogenesis either in monotherapy or in combined therapeutic strategy.

1.2 STUDY AGENT(S) BACKGROUND AND ASSOCIATED KNOWN TOXICITIES

1.2.1 Nintedanib

Preclinical studies of Nintedanib

Nintedanib is a potent, orally available triple kinase inhibitor targeting VEGFRs, PDGFRs, and FGFRs. Nintedanib inhibits the signaling cascade mediating angiogenesis by binding to the adenosine triphosphate (ATP) binding pocket of the receptor kinase domain, thus interfering with cross-activation via auto-phosphorylation of the receptor homodimers. The specific and simultaneous abrogation of these pathways results in effective growth inhibition of both endothelial and, via PDGF- and FGF-receptors of perivascular cells, which may be more effective than inhibition of endothelial cell growth via the VEGF pathway alone. Furthermore, signaling by FGF-receptors has been identified as a possible escape mechanism for tumor angiogenesis when the VEGF pathway is disrupted.

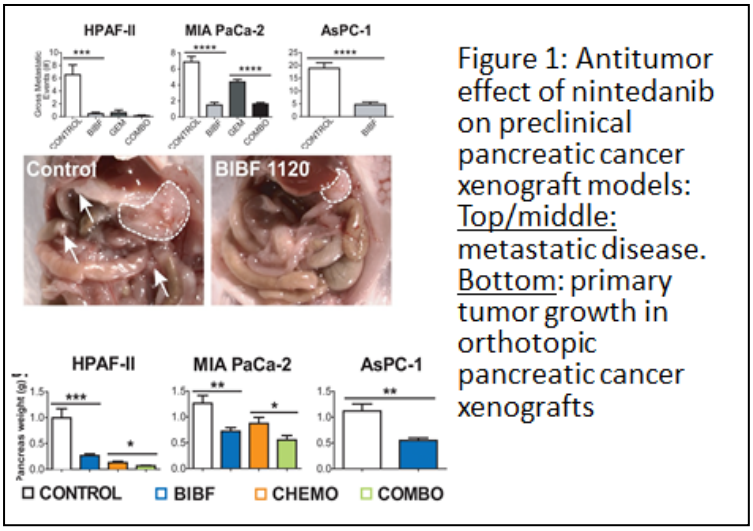


Figure 1: Antitumor effect of nintedanib on preclinical pancreatic cancer xenograft models: Top/middle: metastatic disease. Bottom: primary tumor growth in orthotopic pancreatic cancer xenografts

In vitro, the target receptors are all inhibited by nintedanib in low nanomolar concentrations. In in vivo nude mouse models, nintedanib showed good anti-tumor efficacy at doses of 50 – 100 mg/kg, leading to a substantial delay of tumor growth or even complete tumor-stasis in xenografts of a broad range of differing human tumor types. Histological examination of treated tumors showed a marked reduction of tumor vessel density by approximately 80% (Figure 1)[12].Besides inhibition of neo-angiogenesis, it may alter tumor maintenance by inducing apoptosis of tumor blood vessel endothelial cells. Inhibition of receptor kinases may also interfere with autocrine and paracrine stimulation of tumor angiogenesis via activation loops involving VEGF, PDGF, and bFGF utilized by vascular and perivascular cells such as pericytes and vascular smooth muscle cells (Figure 2).

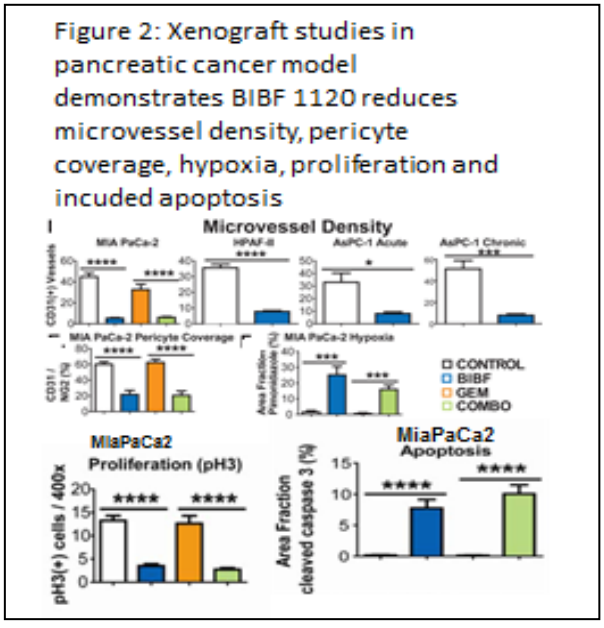


Figure 2: Xenograft studies in pancreatic cancer model demonstrates BIBF 1120 reduces microvessel density, pericyte coverage, hypoxia, proliferation and incuded apoptosis

The metabolism of nintedanib (was predominantly characterized by the ester cleavage of the methyl ester moiety yielding BIBF 1202, which was further metabolized by conjugation to glucuronic

acid yielding the 1-O-acylglucuronide. Data collected in this study show that nintedanib has a favorable PK and excretion profile with almost no elimination via the urine, only 0.7% of total [14C] radioactivity was eliminated via the urine[5]. The metabolic characteristics are predominantly independent of cytochrome P450-catalysed metabolic pathways[13]
In addition preclinical models show that nintedanib may have a direct anti-tumor effect on those malignant cells which overexpress PDGFR and/or FGFR (e.g. H1703 NSCLC cells).

	IC_{50} (nmol/L)
VEGFR (1 / 2 / 3)	34 / 21 / 13
PDGFR (α / β)	59 / 65
FGFR (1 / 2 / 3)	69 / 37 / 108
Flt-3	26
RET	35
Src, Lck, Lyn	156 / 16 / 195

A soft gelatin capsule formulation of nintedanib is used in man. After oral administration, nintedanib is absorbed quickly. Maximum plasma concentrations (Cmax) generally occur 2 to 4 hours after administration. So far, no evidence for a deviation from dose proportionality of the PK of nintedanib has been observed. Steady state is reached latest after one week of dosing. The terminal half-life of nintedanib is in the range of 7 to 19 h. Nintedanib is mainly eliminated via faeces[13].

Nintedanib is non-mutagenic, even at high doses. Two exploratory studies in rats revealed a teratogenic effect of nintedanib with a steep dose/effect relationship and an early onset of embryo fetal deaths at low dosages. This effect was observed at dose levels resulting in plasma drug concentrations comparable to or below those in humans. Because the concentration of nintedanib in semen is unknown, males receiving nintedanib and having sexual intercourse with females of childbearing potential should use latex condoms. Women of childbearing potential should be advised to use adequate contraception during and at least 3 months after the last dose of nintedanib.

Clinical development of Nintedanib

Nintedanib is being evaluated in several cancers. Additionally, nintedanib was approved for use in the U.S. in 2014 for the non-cancer indication idiopathic pulmonary fibrosis (IPF). As of 15th April 2014, 3470 cancer patients, over 1000 patients with IPF, and 143 healthy volunteers had been treated with nintedanib or nintedanib matching placebo, in monotherapy or in combination with chemotherapy.

Phase I

Phase I dose selection monotherapy studies revealed that nintedanib is generally well tolerated with mild to moderate adverse effects such as gastrointestinal symptoms (nausea, diarrhea, vomiting, abdominal pain), decreased appetite, anorexia, asthenia and reversible elevations of liver enzymes. Initial signs of clinical activity including an encouraging rate of patients with stabilization of their tumor of 54% and 68% respectively, have been observed in patients with various solid tumors[9].

Based on the Phase I dose escalation trials with nintedanib monotherapy, the maximum tolerated dose was defined to be 250 mg for twice daily dosing in Caucasians and 200 mg twice daily in Japanese patients with a manageable safety profile in advanced cancer patients. Based on the overall safety profile, the RP2D for nintedanib as monotherapy is 200 mg twice daily (BID).

The maximum tolerated dose for combination therapy of nintedanib in combination with pemetrexed, docetaxel, paclitaxel/carboplatin and FOLFOX is 200mg twice daily. Combination of nintedanib with other anti-cancer drugs revealed a similar adverse event profile as compared to nintedanib monotherapy except for the chemotherapy related toxicities. There was no change of the pharmacokinetic parameters of nintedanib or of the cytotoxic compounds due to the combined treatment. Dose limiting toxicity consisted mostly of liver transaminase elevations as in the monotherapy phase I trials with the exception of the combination of nintedanib with pemetrexed, where fatigue was the most relevant dose limiting toxicity.

Available pharmacokinetic data indicate that the systemic exposure needed for biological activity can be achieved starting with doses of 100 mg nintedanib once daily.
The predominant adverse events were nausea, diarrhea, vomiting, abdominal pain and fatigue of mostly low to moderate severity. Dose limiting toxicities (DLT) were mainly confined to reversible hepatic enzyme elevations (AST, ALT, γ-GT) which increased dose-dependently. Most cases occurring at doses of 250 mg and above, and a very low incidence at doses below 200 mg and were reversible after discontinuation of nintedanib treatment. All adverse events observed after single administration of single doses of nintedanib to healthy volunteers were only of CTCAE grade 1 severity and fully reversible[13].

NSCLC

In a phase II trial in NSCLC patients the safety profile of nintedanib observed in phase I trials could be confirmed. Most commonly reported drug-related AEs were nausea (57.5%), diarrhea (47.9%), vomiting (42.5%), anorexia (28.8%), abdominal pain (13.7%) and reversible alanine transaminase (13.7%) and aspartate aminotransferase elevations (9.6%) In conclusion it was generally well tolerated and displayed single agent activity in advanced or recurrent NSCLC patients. Median overall survival (OS) was 21.9 weeks. Eastern Cooperative Oncology Group (ECOG) 0–1 patients (n = 56) had a median PFS of 11.6 weeks and a median OS of 37.7 weeks. Tumor stabilization was achieved in 46% of patients (ECOG 0–1 patients: 59%), with one confirmed partial response (250 mg BID.)[10]. .

LUME-Lung 1 was an international, randomized, double-blind, phase III trial assessing the efficacy and safety of docetaxel plus nintedanib as second line therapy for non-small-cell lung cancer (NSCLC). In total, 1314 patients with Stage IIIB/IV or recurrent NSCLC (all

histologies) who had progressed after 1st line chemotherapy were randomized in 1:1 fashion to either receive Nintedanib 200mg BID + Docetaxel (n=655) or Placebo BID + Docetaxel (n=659).

LUME-Lung 1 met its primary endpoint by showing a statistically significant improvement of PFS for all patients regardless of histology (median PFS 3.4 versus 2.7 months; HR 0.79, p=0.0019) for Nintedanib in combination with docetaxel. A significant improvement in OS was demonstrated in patients with adenocarcinoma; median OS 12.6 months [95% CI 10.6–15.1] vs 10.3 [95% CI 8.6–12.2] months; HR 0.83 [95% CI 0.70–0.99], p=0.0359);

The Kaplan-Meier survival curves separate at 6 months, continuing throughout the 36-month study observation period. One year overall survival was 52·7% (95% CI 46·8–57·9) in the docetaxel plus nintedanib group compared with 44·7% (38·9–49·8) in the docetaxel plus placebo group; 2 year overall survival was 25·7% (95% CI 20·5–30·2) in the docetaxel plus nintedanib group compared with 19·1% (14·4–23·2) in the docetaxel plus placebo group.

In the predefined population of patients with adenocarcinoma who had progressed within 9 months after start of first-line therapy, overall survival was significantly longer in the docetaxel plus nintedanib group than in the docetaxel plus placebo group (median overall survival 10·9 months [95% CI 8·5–12·6] vs 7·9 months [6·7–9·1]; HR 0·75 [95% CI 0·60–0·92], p=0·0073).

In the total population of patients (all histologies), there was no difference in overall survival between the two groups: median overall survival was 10·1 months (95% CI 8·8–11·2) in the docetaxel plus nintedanib group compared with 9·1 (8·4–10·4) months in the docetaxel plus placebo group (HR 0·94 [95% CI 0·83–1·05], p=0·2720).

Nintedanib plus docetaxel had a manageable safety profile with no unexpected safety findings. The predominant adverse events were nausea, diarrhea, vomiting, abdominal pain and fatigue of mostly low to moderate intensity after monotherapy with nintedanib. Adverse events that were more common (≥5% difference) in the docetaxel plus nintedanib group than the docetaxel plus placebo group were: diarrhea (all grades, 276 of 652 [42·3%] vs 143 of 655 patients [21·8%]; grade ≥3, 43 [6·6%] vs 17 [2·6%]), increases in alanine aminotransferase (all grades, 186 [28·5%] vs 55 [8·4%]; grade ≥3, 51 [7·8%] vs six [0·9%]), nausea (all grades, 158 [24·2%] vs 118 [18·0%]; grade ≥3, five [0·8%] vs six [0·9%]), increases in aspartate aminotransferase (all grades, 147 [22·5%] vs 43 [6·6%]; grade ≥3, 22 [3·4%] vs three [0·5%]), decreased appetite (all grades, 145 [22·2%] vs 102 [15·6%]; grade ≥3, nine [1·4%] vs eight [1·2%]), and vomiting (all grades, 110 [16·9%] vs 61 [9·3%]; grade ≥3, five [0·8%] vs three [0·5%];).Most of these adverse events were manageable with supportive treatment or dose reduction[10].

LUME-Lung 2 was a similar randomized, double-blind, phase III study of nintedanib plus pemetrexed versus placebo plus pemetrexed in patients with advanced non-squamous non-small cell lung cancer after failure of first line chemotherapy.

Based on a preplanned futility analysis of investigator-assessed PFS, enrollment was halted after 713/1300 planned patients had been enrolled. The analysis (based on conditional power for PFS by investigator assessment) suggested that the study was futile and that the primary endpoint of centrally assessed PFS would likely not be met. The futility analysis

was based on conditional power; there was no formal testing of null hypothesis as planned for primary analysis no safety issues were identified.

Even though the study was stopped prematurely, the primary endpoint of this Phase III trial was met; treatment with nintedanib plus pemetrexed resulted in a significant prolongation of centrally reviewed PFS compared with placebo plus pemetrexed (median PFS 4.4 vs. 3.6 months with a HR 0.83; p=0.0435). The disease control rate was also increased significantly in nintedanib-treated patients. There was no improvement in OS in nintedanib-treated patients. Nintedanib 200 mg BID in combination with pemetrexed had an acceptable and manageable safety profile, with no new or unexpected safety findings. The most frequent AEs were reversible increases in liver enzymes and gastrointestinal events.

Ovarian Cancer

A randomized phase II maintenance trial in ovarian cancer in which the efficacy and safety of nine months of continuous twice daily doses of nintedanib following chemotherapy was investigated, has identified the potential activity of nintedanib with a 36-week PFS of 15.6 % compared to 2.9 % in the control group. The safety profile was consistent with findings previously reported for nintedanib administered as monotherapy as mentioned above[11].

Nintedanib was evaluated in a Phase III randomized, placebo-controlled, double-blind, multicentre ovarian study with 1366 patients. Patients received nintedanib plus paclitaxel and carboplatin or placebo plus paclitaxel and carboplatin for six cycles. This was followed by monotherapy nintedanib or placebo for up to 120 weeks. The trial met its primary endpoint by demonstrating a statistically significant improvement in progression-free survival (HR 0.84; 95%CI 0.72 - 0.98; p=0.0239, median PFS 17.3 months for nintedanib and 16.6 months for placebo). The trial remains blinded for OS as the data were immature at the time of the primary analysis. Main adverse events were GI side effects and increased hematological toxicity (DuBois [8]).

Colorectal Cancer

A Phase I/II, open-label, randomized study of nintedanib plus mFOLFOX6 compared to bevacizumab plus mFOLFOX6 in 126 patients with metastatic colorectal cancer was performed, demonstrating an acceptable safety profile of nintedanib in combination with mFOLFOX 6. In comparison to bevacizumab, nintedanib showed a similar magnitude of efficacy, a similar safety/tolerability profile, a similar exposure and dose intensity of mFOLFOX6 (van Cutsem [9]).

An ongoing Phase III study evaluating the efficacy of nintedanib in patients with metastatic colorectal cancer (mCRC) after failure of previous treatment with standard chemotherapy and biological agents can be found on ClinicalTrials.gov (Identifier: NCT02149108).

Renal Cell Cancer

Nintedanib has been studied in a randomized phase II study in metastatic clear cell RCC with sunitinib as the control arm. Similar efficacy was seen in both arms of this study. AEs observed more frequent in the nintedanib arm included diarrhea, nausea, fatigue and infection, whereas AEs more frequent in the sunitinib arm consisted of bleeding, anemia, hypertension, hand-foot syndrome and stomatitis (Eisen [10]).

Hepatocellular Cancer
The efficacy and safety of nintedanib versus sorafenib in Asian Patients with Advanced Hepatocellular Carcinoma was investigated in a randomized phase II trial. Nintedanib showed similar efficacy to sorafenib, with a favorable and manageable AE profile. More patients in the sorafenib arm had severe AEs and drug-related AEs compared with patients in the nintedanib arm, and more patients in the sorafenib arm required dose reduction compared with the nintedanib arm. Nintedanib AEs were manageable; in the nintedanib arm there were fewer hypertension, palmar-plantar erythrodysesthesia syndrome, and transaminase elevation events (Yen [11]).

For more details please refer to the investigator drug brochure for nintedanib (Version 14).

1.2.2 Gemcitabine + nab-Paclitaxel (ABRAXANE)

Preclinical studies have demonstrated that nab-paclitaxel may play a role in sensitizing the tumor to chemotherapeutic agents and specifically increases the antitumor efficacy when combined with gemcitabine. While the mechanism of action for the synergy is unclear, preclinical studies have generated hypothetical models. One hypothesis is a remodeling and weakening of the stromal barrier, allowing the chemotherapeutic agents to have better access to the tumor cells. Weakening the tumor-stroma barrier is particularly important in cancer that is characterized by dense stroma, such as pancreatic cancer. In mice with primary patient derived pancreatic tumor xenografts, nab-paclitaxel plus gemcitabine versus gemcitabine alone resulted in increased tumor regression and depleted the desmoplastic stroma as observed by the less dense, disorganized, wisps of collagen type1 fibers after 4 weeks of treatment[4]. In this study, the intratumoral concentration of gemcitabine was increased by 2.8-fold after 5 days of treatment when nab-paclitaxel was added to gemcitabine. It was hypothesized that nab-paclitaxel may play a role in reducing the dense stroma and may have contributed to the increased intratumoral gemcitabine uptake. Additional preclinical studies in a genetically engineered mouse model of pancreatic adenocarcinoma, coadministration of nab-paclitaxel and gemcitabine also demonstrated tumor regression and increased intratumoral gemcitabine levels after 8 days of treatment. Apoptosis of tumor epithelial cells were observed; however, there were no changes in stromal components or collagen density in this short term treatment model (Frese, 2012). The increased intratumoral gemcitabine levels were attributed to a marked decrease in the primary gemcitabine metabolizing enzyme, cytidine deaminase, by nab-paclitaxel. Finally, a recent clinical study in patients with resectable pancreatic cancer treated with neoadjuvant nab-paclitaxel plus gemcitabine showed reduction in fibrotic collagenous stroma, further supporting a stroma active mechanism for nab-paclitaxel (Alvarez-Gallego, 2013).

In a clinical Phase 1/2 dose ranging study (CA040, NCT003980860), nab-paclitaxel plus gemcitabine antitumor activity and tolerability were established in patients who had no prior treatment for metastatic pancreatic cancer[4]. The maximum tolerated dose and recommended dose for further studies was determined to be 125 mg/m^2 nab-paclitaxel in combination with 1000 mg/m^2 gemcitabine.

In the subsequent randomized international Phase 3 study (MPACT, CA046, NCT00394251) that enrolled 861 patients with metastatic pancreatic cancer, nab-paclitaxel in combination with gemcitabine exhibited a clinically meaningful, statistically significant improvement in OS and progression-free survival (PFS). The median OS (primary endpoint) in the intent-to-treat population was 8.5 months (95% CI = 7.89-9.53) with nab-paclitaxel/gemcitabine compared with 6.7 months (95 % CI = 6.01-7.23) with gemcitabine, p < 0.0001, HR = 0.72 (95% CI = 0.617-0.835). Long-term survival was improved in the nab-paclitaxel/gemcitabine arm versus gemcitabine alone, with a 59% increase at 1 year (35% versus 22%) and doubling at 2 years (9% versus 4%). The secondary (PFS, overall response rate [ORR]) and all other efficacy endpoints showed consistent, statistically significant improvements with nab-paclitaxel/gemcitabine, supporting the results from the primary analysis of OS. Specifically, PFS (by independent review) was 5.5 months (95% CI = 4.47-5.95) versus 3.7 months (95% CI = 3.61-4.04) in the nab-paclitaxel/gemcitabine arm versus gemcitabine alone arms, respectively p < 0.0001; HR =0 .69; 95% CI = 0.581-0.821). The improvement in PFS corresponded to a 31% reduction in the risk of progression or death with nab-paclitaxel/gemcitabine. Furthermore, in this study of metastatic unresectable adenocarcinoma of the pancreas, patients in the combination arm were on therapy longer than those receiving single agent gemcitabine, indicating disease improvement and tolerable treatment[24]. The suitability of the dosing regimen was confirmed by the observation that the majority of patients did not require a dose reduction, and that 71% of nab-paclitaxel doses were delivered at the starting dose of 125 mg/m2. The safety profile for both regimens was consistent with previous reports. Serious life threatening toxicities were not increased; AEs were acceptable and manageable. The most notable differences in toxicity between the two treatment arms was peripheral neuropathy, which was cumulative and rapidly reversible with dose delay and reduction, and neutropenia, which was manageable with dose delays and dose reductions. The incremental risks of sepsis and pneumonitis were managed by protocol amendments to increase awareness, and for early diagnosis and treatment to reduce the risk of fatal outcomes.

To date, the only other trial that resulted in clinically meaningful improvement in OS in pancreatic adenocarcinoma was the Phase 2/3 FOLFIRINOX versus gemcitabine study, which was conducted in one country (Conroy, 2011). While numerous promising Phase 2 studies have been conducted in advanced pancreatic cancer, most subsequent large Phase 3 studies have failed to show significant improved survival (Colucci, 2010; Cunningham, 2009; Kindler, 2010; Oettle, 2005; Philip, 2010; Poplin, 2009; Rocha Lima, 2004).

As a result of the clinically meaningful benefit observed in the MPACT trial, the 2013 NCCN guidelines were updated to include nab-paclitaxel plus gemcitabine under treatment option category 1 for patients with metastatic pancreatic adenocarcinoma (NCCN, 2013).

1.3. Study Rationale

Our preclinical data suggest nintedanib inhibits primary tumor growth in *in vivo* xenograft models of pancreatic cancer, as well as inhibiting metastasis in pancreatic cancer models [14]. (See figure 1 and figure 2). This effect appears primarily due to nintedanib anti-angiogenic properties.

We would like to perform a clinical study evaluating the safety and tolerability of nintedanib when combined with standard chemotherapy (Gemcitabine + nab-Paclitaxel) for metastatic pancreatic cancer.

We will utilize advanced imaging correlates including dynamic contrast enhanced Magnetic Resonance Imaging (DCE-MRI) which correlates with tumor grade and microvessel density[15].

1.4. Benefit – Risk Assessment

Although considerable progress has occurred in understanding the biological characteristics of cancer as well as the development of more effective treatment regimens, most patients with locally advanced or metastatic tumors succumb to their disease. Thus, there is a substantial need for novel therapeutic strategies to improve the outcome for patients with advanced or metastatic pancreatic cancer.

Antiangiogenic treatment with the orally available triple angiokinase inhibitor nintedanib with inhibition of VEGFR, PDGFR and FGFR offers the chance to control both locally recurrent and distant metastatic disease on an outpatient basis. Treatment with nintedanib may have the potential to provide significant benefit to patients with locally advanced and/or metastatic pancreatic cancer by slowing tumor progression and metastasis, since its cellular target is expressed on the tumor vasculature in most malignancies. Induction of endothelial cell apoptosis may result in subsequent degradation of tumor vessels and subsequent tumor necrosis. Additionally tumor growth may be affected by direct anti-tumor effects, e.g. tumor cells that express VEGFR, PDGFR, or FGFR.

The risks of antiangiogenic therapy with nintedanib as single agent or in combination with standard doses of chemotherapy in adult patients are primarily related to: the gastro-intestinal tract (nausea, vomiting, diarrhea, abdominal pain), increases in liver enzymes (AST, ALT, γ-GT), fatigue, anorexia, low white blood cell count, peripheral neuropathy and rashes.

Liver enzymes must be followed closely during treatment with nintedanib. Therapy with the trial drugs must be interrupted in the event of relevant hepatic toxicity and further treatment is to be withheld until recovery of the abnormal laboratory parameters.

Impairment of immune and of kidney function, thromboembolic events and GI perforations are considered possible side effects of treatment with nintedanib as they have been reported for some other drugs in the class of angiogenesis inhibitors. Thus far these side effects have been observed in the trials conducted with nintedanib, but not to a relevant degree. Hypertension is also supposed to be a possible side effect of VEGFR inhibitors and a slightly increased frequency of hypertension has been observed in the trials with nintedanib to a mild to moderate degree and only few cases of CTCAE grade 3 or 4 hypertension have been observed.

Based upon a non-clinical safety study in vitro, nintedanib may have a potential risk of phototoxicity (skin and eyes) in vivo. Few cases of photosensitivity reactions (less than 1 %) and of CTCAE Grade 1 intensity only have been reported from the clinical studies to date. If adequate precautions are taken (avoidance of prolonged ultraviolet (UV) exposure, use of broad spectrum sunscreen and sunglasses), treatment with nintedanib is considered safe.

In addition for combination trials:
The major clinical side effects observed after therapy with gemcitabine + nab-Paclitaxel are distinct from nintedanib induced adverse events, yet some overlap may occur e.g. regarding mild gastrointestinal toxicity or hepatotoxicity (please refer to the labels included in the investigator site file for listed adverse events of gemcitabine + nab-Paclitaxel). In view of the low potential for drug-drug interactions of nintedanib, it is not likely that enhanced toxicity due to pharmacokinetic interaction between the drug and the cytotoxic chemotherapy will occur.

2.0 STUDY OBJECTIVES

2.1 Primary Objective:

2.1.1 Determine safety and tolerability of nintedanib administered with gemcitabine plus nab paclitaxel in advanced pancreatic cancer.

2.2 Secondary Objectives:

2.2.1 Determine pharmacodynamic effects (blood and imaging) of nintedanib on angiogenesis and tumor microenvironment in advanced pancreatic cancer;

2.2.2 Determine preliminary efficacy (response rate, progression-free survival, overall survival) of nintedanib in combination with gemcitabine plus nab paclitaxel in advanced pancreatic cancer.

3.0 PATIENT SELECTION

Eligibility waivers are not permitted. In the case that the principal investigator would like consideration of an exception, a request must be submitted to the DSMC Chair or designee for approval prior to registration of any patient.

3.1 Inclusion Criteria

3.1.1 Signed and dated written informed consent prior to admission to the study;
3.1.2 Histologically or cytologically confirmed metastatic or locally advanced adenocarcinoma of the pancreas;
3.1.3 At least one measurable disease lesion according to Response Evaluation Criteria In Solid Tumors (RECIST, version 1.1);
3.1.4 Age ≥ 18 years;
3.1.5 No more than one prior line of non-gemcitabine/nab-paclitaxel containing systemic therapy for metastatic/locally advanced pancreatic cancer;
3.1.6 Eastern Cooperative Oncology Group (ECOG) Performance Score of 0-1;
3.1.7 Women of childbearing potential must have a negative urine pregnancy test (or serum) within 14 days prior to registration; (Note: Patients will be considered to be of childbearing

potential unless surgically sterilized by hysterectomy or bilateral tubal ligation/salpingectomy, or post-menopausal for at least two years.)

3.1.8 Adequate biological parameters at baseline (obtained within 14 days prior to registration).

Absolute Neutrophil Count (ANC)	≥1,500 cells/mm3
Platelets	≥100,000 cells/mm3
Hemoglobin	≥9 g/dl
AST (SGOT) / ALT (SGPT)	AST and ALT ≤ 1.5 x ULN (2.5 x ULN in case of liver metastases)
Total Bilirubin	≤ ULN
INR	≤ 2
PT / PTT	≤ 50% increase from institutional ULN
Serum Creatinine	≤ 1.5 x ULN

If elevated liver function tests develop at the time of initial presentation or develop during workup and are the result of mechanical obstruction of the biliary drainage by tumor compression or invasion, a biliary drain may be placed. If drainage allows the liver function tests to come within inclusion criteria, the patient may be enrolled.

3.2 Exclusion Criteria

3.2.1 More than one systemic therapy regimen of any type for metastatic or locally advanced disease. Adjuvant gemcitabine that ended more than 6 months prior to diagnosis of recurrent disease is not considered as a regimen;

3.2.2 Prior treatment with nintedanib or any other VEGFR inhibitor;

3.2.3 Known hypersensitivity to nintedanib, gemcitabine and nab-Paclitaxel, peanut or soy or any other trial drug, their excipients;

3.2.4 Chemotherapy, hormonal therapy, radiotherapy (except for brain and extremities),immunotherapy or therapy with monoclonal antibodies or small tyrosine kinase inhibitors within the past 4 weeks prior to treatment with the trial drug;

3.2.5 Target lesions that have previously received radiation must have shown radiographic progression following radiation or must have other non-radiated lesions present

3.2.6 Persistence of clinically relevant therapy related toxicity from previous chemo and/or radiotherapy;

3.2.7 Active brain metastases (e.g. stable for <4 weeks, no adequate previous treatment with radiotherapy, symptomatic, requiring treatment with anti-convulsants; dexamethasone therapy will be allowed if administered as stable dose for at least one month before registration);

3.2.8 Leptomeningeal disease;

3.2.9 Radiographic evidence of cavitary or necrotic tumors;

3.2.10 Treatment with other investigational drugs or treatment in another clinical trial within the past 4 weeks before start of therapy or concomitantly with the trial;

3.2.11 Therapeutic anticoagulation with drugs requiring INR monitoring (except low-dose heparin and/or heparin flush as needed for maintenance of an in-dwelling intravenous device) or anti-platelet therapy (except for low-dose therapy with acetylsalicylic acid < 325mg per day);

3.2.12 Major injuries and/or surgery within the past 4 weeks prior to start of study treatment with incomplete wound healing and/or planned surgery during the on-treatment study period;

3.2.13 History of clinically significant hemorrhagic or thromboembolic event in the past 6 months;

3.2.14 Known inherited predisposition to bleeding or thrombosis;

3.2.15 Significant cardiovascular diseases (i.e. uncontrolled hypertension, unstable angina, history of infarction within the past 12 months prior to start of study treatment, congestive heart failure > NYHA II, serious cardiac arrhythmia, pericardial effusion);

3.2.16 Proteinuria CTCAE grade 2 or greater;

3.2.17 Creatinine > 1.5 x ULN or GFR < 45 mL/min;

3.2.18 Hepatic function: total bilirubin outside of normal limits; ALT or AST > 1.5 ULN in pts without liver metastasis. For Pts with liver metastasis: total bilirubin outside of normal limits, ALT or AST > 2.5 ULN;

3.2.19 Coagulation parameters: International Normalized Ratio (INR) > 2, prothrombin time (PT) and partial thromboplastin time (PTT) > 50% of deviation of institutional ULN;

3.2.20 Absolute neutrophil count (ANC) < 1500/mL, platelets < 100,000/mL, Hemoglobin < 9.0 g/dl;

3.2.21 Any known active cancer other than pancreatic primary;

3.2.22 Active serious infections in particular if requiring systemic antibiotic or antimicrobial therapy;

3.2.23 Known or chronic hepatitis C and/or B infection;

3.2.24 Gastrointestinal disorders or abnormalities that would interfere with absorption of the study drug;

3.2.25 Serious illness or concomitant non-oncological disease such as neurologic, psychiatric, infectious disease or active ulcers (gastro-intestinal tract, skin) or laboratory abnormality that may increase the risk associated with study participation or study drug administration and in the judgment of the investigator would make the patient inappropriate for entry into the study;

3.2.26 Pregnancy or breast feeding female;

3.2.27 Psychological, familial, sociological or geographical factors potentially hampering compliance with the study protocol and follow-up schedule;

3.2.28 Active alcohol or drug abuse;

3.2.29 Significant weight loss (> 20% of BW) within past 6 months prior to inclusion into the trial or actual body weight of less than 50 kg;

3.2.30 Patients who are sexually active and unwilling to use a medically acceptable method of contraception (e.g. such as implants, injectable, combined oral contraceptives, some intrauterine devices, sexual abstinence or vasectomized partner for participating females, condoms for participating males) during the trial and for at least three months after end of active therapy.

4.0 TREATMENT PLAN

4.1 Agent Administration

For each patient, treatment will have two phases:

- Nintedanib monotherapy for a two week period (Days 1-14) followed by
- Combination phase of nintedanib plus chemotherapy (Cycle 2+).

Using standard phase 1 3+3 dose escalation rules, two dose levels of nintedanib will be explored: 150 mg BID and 200 mg BID.

After completion of 150 mg BID cohort, the dose of nintedanib will be increased to 200 mg BID for the next cohort. No intrapatient dose escalation is planned. No dose escalation of gemcitabine and nab-paclitaxel will be performed.

4.1.1 Monotherapy Phase, Cycle 1 (Nintedanib only)

The capsules of the defined dose should be swallowed whole with a glass of water of about 250 mL. The time between each dose of nintedanib should be of around 12 hours at the same times every day, usually in the morning and the evening after food intake.

In case of a missed dose patients should proceed with the intake of medication according to the predefined schedule and take the next scheduled dose when it is due.

See **section 6** for dosing schedule/delays/dose modifications.

Vomited dose will not be replaced.

4.1.2 Combination Therapy Phase, Cycle 2+

The combination phase will include Gemcitabine + Nab-Paclitaxel, and Nintedanib. Patient treatment will consist of

- Gemcitabine (1000 mg/m^2)
- Nab-Paclitaxel (125 mg/m^2)

Treatment will be administered intravenously on days 1, 8, 15 every 28 days.

Nintedanib dose in the combination phase will be the same dose given in the monotherapy phase.

Future cycles will only include combination therapy.

Gemcitabine dosing schedule/delays/dose modifications: See Section 6

Nab-Paclitaxel dosing schedule/delays/dose modifications: See Section 6

4.1.3 General Concomitant Medication and Supportive Care Guidelines

Follow local standards.

See Table 1 for a treatment overview and supportive medications:

	Table 1: Treatment Overview					
	Agent	**Supportive pre-Medications**	**Dose**	**Route**	**Frequency**	**Cycle Length**
Monotherapy Phase	Nintedanib		150 or 200 mg, BID	Orally	Twice daily, Days 1-14	2 weeks (Days 1-14)
Combination Therapy Phase	Nab-paclitaxel	Antiemetics per institutional standard of care	125 mg/m^2	IV over 30 minutes	Days 1, 8, 15	4 weeks (28 days)
	Gemcitabine		1000 mg/m^2	IV over 30 minutes after infusion of Nab-paclitaxel	Days 1, 8, 15	

	Nintedanib		150 or 200 mg	Orally	Twice daily, Days 1-28. NOTE: For safety reasons, Nintedanib should not be given the same days as chemotherapy, Days 1, 8, and 15	

5.0 FOLLOW UP

5.1 Duration of Follow Up

Patient will be followed once at 4 weeks after 'End of Treatment Visit' (completion of therapy or early withdrawal from study). If there are unresolved AEs, this visit will be repeated every 4 weeks until all study related AEs have resolved to grade 1 or less.

The patient will be considered 'off study' if at 4 weeks post 'End of Treatment Visit' all AE's have resolved or patient has expired, whichever comes first. At this point, the patient will only be followed for survival at the discretion of the investigator.

5.2 Criterion for Removal from Study

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

a) Patient voluntarily withdraws from treatment (follow-up permitted);
b) Patient withdraws consent (termination of treatment and follow-up);
c) Patient is unable to comply with protocol requirements;
d) Patient demonstrates disease progression (unless continued treatment with study drug is deemed appropriate at the discretion of the investigator);
e) Patient experiences toxicity that makes continuation in the protocol unsafe;
f) Treating physician determines that continuation on the study would not be in the patient's best interest;
g) Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);
h) If a research patient cannot be located to document survival after a period of 2 months, the patient may be considered "lost to follow-up." All attempts to contact the patient during the two months must be documented.

5.3 Patient Replacement

Three patients within a dose level must be observed for the DLT period (comprising of 4 weeks of the combination phase) before accrual to the next higher dose level may begin.

If a patient is withdrawn from the study prior to completing 28 days of combination therapy without experiencing a DLT, an additional patient may be added to that dose level.

If a patient misses 2 doses of gemcitabine or nab-paclitaxel during DLT period for reasons other than adverse events, an additional patient may be added to that dose level.

Once the maximum tolerated dose has been established using phase 1 3+3 dose escalation rules, the remaining patients will be treated as part of the 'expansion cohort' .No patient replacement will occur in the expansion cohort. The final assessments on patient replacement or determination of DLT will be made at the discretion of the PI and cohort review committee.

6.0 DOSING SELECTION / DELAYS / DOSE MODIFICATIONS

Including management of side effects.

Criteria for initiation, subsequent treatments, interruption of administration, and re-challenge, as well as recommendations for dose adaptations will be assessed for each drug.

Treating investigators will determine attribution of AEs as being related to nintedanib, gemcitabine or nab-paclitaxel and the following guideline will be used in AE management and dose modifications.

Recommendations for modification of therapy and appropriate supportive treatments are outlined in this section.

6.1 CRITERIA FOR **INITIATION** OF NINTEDANIB TREATMENT (MONOTHERAPY):

Table 2: Criteria for initiation of Nintedanib treatment, provided inclusion & exclusion criteria are met:

All of the following criteria have to be met
□ Nausea CTCAE grade ≤ 1 □ Vomiting CTCAE grade 0 □ Diarrhea CTCAE grade ≤ 1 □ AST and ALT ≤ 1.5 x ULN (2.5 x ULN in case of liver metastases) □ Total bilirubin ≤ upper normal limit □ ANC ≥ 1500 /µL (* or WBC > 3000/µL) □ Platelet count ≥ 100,000/µL □ Hemoglobin ≥ 9 g/dl □ No uncontrolled infection

6.2 CRITERIA FOR **INTERRUPTION** OF TREATMENT WITH NINTEDANIDNIB (MONOTHERAPY OR COMBINATION PHASE):

Treatment with nintedanib has to be interrupted in case any of the criteria listed in Table 3 is not fulfilled.

Table 3: Criteria when to interrupt treatment with nintedanib due to an adverse event

If one criterion is met, nintedanib has to be interrupted
□ Nausea of CTCAE grade ≥ 3 despite supportive care □ Vomiting of CTCAE grade ≥ 2 despite supportive care □ Diarrhea of CTCAE grade ≥ 2 for more than 3 consecutive days despite supportive care □ AST and/or ALT elevations of > 2.5 x ULN in conjunction with bilirubin of > 1.5 x ULN □ AST and/or ALT elevations of > 5x ULN □ Other non-hematological adverse event of CTCAE grade ≥ 3 considered drug-related □ *Neutropenia and fever > 38.5° □ *Neutropenia CTCAE grade 4 for more than 7 days without fever □ * Platelets <50,000mm³ with bleeding

6.3 CRITERIA TO **RESTART** NINTEDANIB TREATMENT IF PREVIOUSLY INTERRUPTED (MONOTHERAPY OR COMBINATION PHASE)

A patient is eligible to restart Nintedanib if **ALL** criteria listed in Table 4 are met.

If a patient has to interrupt intake of Nintedanib due to an adverse event for more than 14 days, the decision to restart treatment with nintedanib needs to be discussed and agreed upon between the investigator and the study PI.

Table 4: Criteria to assess eligibility to restart Nintedanib treatment

All criteria have to be met in order to restart Nintedanib, meaning AEs have to return to Grade 1 or baseline except as detailed below
□ Nausea CTCAE grade ≤ 2 □ Vomiting CTCAE grade ≤ 1 □ Diarrhea CTCAE grade < 2 □ AST and ALT < 2.5 x ULN; bilirubin < 1.5 x ULN □ No other non-hematological adverse event grade CTCAE ≥ 3 which is considered drug-related □ *Neutropenia CTCAE grade ≤ 1, without fever or equal to the patient's pre-therapy value at study enrolment □ *Platelets CTCAE grade ≤ 1 or equal to the patient's pre-therapy value at study enrolment

6.4 **DOSE MODIFICATION** OF NINTEDANIB

As initial measure for the management of side effects (see section 6.6 Management of Adverse Events) treatment with nintedanib should be temporarily interrupted until the specific adverse reaction has resolved to levels that allow continuation of therapy.

Nintedanib treatment may be resumed at a reduced dose. Dose adjustments in 100 mg steps per day (i.e. a 50 mg reduction per dosing) based on individual safety and tolerability are recommended as described in Table 1.

In case of further persistence of the adverse reaction(s), i.e. if a patient does not tolerate 100 mg twice daily, treatment with nintedanib should be discontinued.

The following dose modification will be used in case dose adjustments are required for management of toxicity (see table 5 and 6).

Table 5: Nintedanib dose level- starting dose 150 mg twice daily

Dose-level:	0	-1	-2	-3
Dose:	150 mg BID	100 mg BID	STOP	STOP

Table 6: Nintedanib dose levels –starting dose of 200mg twice daily

Dose-level:	0	-1	-2	-3
Dose:	200 mg BID	150 mg BID	100 mg BID	STOP

Of note!
If the dose of nintedanib had to be reduced due to toxicity, dose will stay on the lower dose level for the entire time of administration.

6.5 DOSE ADJUSTMENTS FOR GEMCITABINE + NAB-PACLITAXEL

The most common adverse events noted with the MPACT study that resulted in a dose reduction, delay or withholding of chemotherapy was neutropenia and thrombocytopenia[25].

Standard recommended dose modifications for gemcitabine and nab-paclitaxel per the MPACT trial as highlighted in Tables 7, 8 and 9:

Table 7: Nab-Paclitaxel + Gemcitabine Dose Adjustments

Dose level	Nab-Paclitaxel (mg/m^2)	Gemcitabine (mg/m^2)
0 / Full dose	**125**	**1000**
-1	**100**	**800**
-2	**75**	**600**
Additional	**Discontinue**	**Discontinue**

Table 8: Dose Modifications for Hematologic Toxicities of Gemcitabine + nab-Paclitaxel (modified per MPACT study)				
Cycle Day	**ANC ($cells/mm^3$)**		**Platelet count ($cells/mm^3$)**	**Modification**
Day 1				
	<1500	OR	<100,000	Delay treatment until recovery
Day 8				
	500 to <1000	OR	50,000-75,000	Reduce 1 dose level and treat
	<500	OR	<50,000	Withhold dose by one week
Day 15 – If Day 8 doses were reduced or given without modification				
	500 to <1000	OR	50,000-75,000	Reduce 1 dose level from Day 8
	<500	OR	<50,000	Withhold doses
Day 15 – If Day 8 doses were withheld				
	≥ 1000	OR	≥75,000	Reduce 1 dose level from Day 1
	500 - <1000	OR	50,000-<75,000	Reduce 2 dose levels from Day 1
	<500	OR	<50,000	Withhold doses

Table 9 – **Chemotherapy Dose Modifications for Non-Hematologic Toxicities**	
Adverse Reaction	**Modification**
Febrile neutropenia: Grade 3 or 4	. Withhold treatment until fever resolves and ANC ≥ 1500 cells/mm^3 . Resume at next lower dose level
Peripheral neuropathy: Grade 3 or 4	. Withhold Nab-paclitaxel until improvement to Grade ≤ 1 . Resume Nab-paclitaxel at next lower dose level
Cutaneous toxicity: Grade 2 or 3	. Reduce 1 dose level of gemcitabine and nab-paclitaxel . Discontinue treatment if toxicity persists
Gastrointestinal toxicity: Grade 3 mucositis or diarrhea	. Withhold doses until improvement to Grade ≤ 1 . Resume at next lower dose level for all drugs
Other toxicity: Grade 3 or 4	. Withhold doses until improvement to Grade ≤ 1 . Resume at next lower dose level for all drugs

Decision guidelines for chemotherapy (Gemcitabine and nab-Paclitaxel)

Day 1 of each Cycle:

If patient does not meet above day 1 criteria, treatment will be delayed in one week intervals until recovery. Day 1 can be delayed for a maximum of 4 weeks.

If Day 1 of any cycle is delayed by more than 14 days (with no Day 8 or Day 15 reductions), future Day 1 doses will be decreased by 1 level for future cycles.

If Day 1 of any cycle is delayed and the prior cycle Day 8 or Day 15 doses required dose reduction, then the dose for that Cycle Day 1 will be reduced by 1 dose level.

If the dose for Day 8 or Day 15 of the previous cycle was reduced and the day 1 of current cycle has not been delayed, then prescribe the same dose on Day 1 of the current cycle as was administered on day 1 of the previous cycle.

6.6 MANAGEMENT OF ADVERSE EVENTS

- Diarrhea
- Nausea and vomiting
- Liver enzyme elevations
- Other non-hematological or hematological adverse reaction

un Table 10: Recommended dose adjustments for Nintedanib

CTCAE* Adverse reaction	Dose adjustment
Diarrhea ≥ grade 2 for more than 7 consecutive days despite anti-diarrheal treatment** OR diarrhea ≥ grade 3 despite anti-diarrheal treatment**	For dose level starting at 200 mg twice daily: 1st episode Reduce dose from 200 mg twice daily to 150 mg twice daily 2nd episode Reduce dose from 150 mg twice daily to 100 mg twice daily 3rd episode Stop treatment For dose level starting at 150 mg twice daily: 1st episode Reduce dose from 150 mg twice daily to 100 mg twice daily 2nd episode Stop treatment
Vomiting ** ≥ grade 2 AND/OR Nausea ≥ grade 3 despite anti-emetic treatment**	
AST and/or ALT elevations of > 2.5 x ULN in conjunction with bilirubin of > 1.5 x ULN OR AST and/or ALT elevations of > 5x ULN	
Other non-hematological or hematological adverse reaction of ≥ grade 3	
Elevation of AST and/or ALT values to > 3 x ULN in conjunction with an increase of total bilirubin to ≥ 2 x ULN and ALKP < 2 x ULN	Unless there is an alternative cause established, nintedanib should be permanently discontinued

*CTCAE: Common Terminology Criteria for Adverse Events
** see also section 6.8. Additional precautions

6.7 **PERMANENT DISCONTINUATION** TREATMENT WITH NINTEDANIB

Patients should PERMANENTLY discontinue treatment with nintedanib in the event of:

- Intolerable Adverse Events (CTCAE grade 3 or 4) that cannot be managed by best supportive care and dose reduction.

6.8 **ADDITIONAL PRECAUTIONS** FOR NINTEDANIB

- *Diarrhea*

Diarrhea was the most frequently reported gastro-intestinal event and appeared in close temporal relationship with the administration of docetaxel in the clinical trial LUME-Lung 1. The majority of patients had mild to moderate diarrhea. 6.3 % of the patients had diarrhea of grade

≥3 in combination treatment compared to 3.6 % treated with docetaxel alone. Diarrhea should be treated at first signs with adequate hydration and anti-diarrheal medicinal products, e.g. loperamide, and may require interruption, dose reduction or discontinuation of therapy with nintedanib.

- *Nausea and vomiting*

  Nausea and vomiting, mostly of mild to moderate severity, were frequently reported gastrointestinal adverse events in the clinical trial LUME-Lung 1. Interruption, dose reduction or discontinuation of therapy with nintedanib may be required despite appropriate supportive care. Supportive care for nausea and vomiting may include medicinal products with anti-emetic properties, e.g. glucocorticoids, anti-histamines or 5-HT3 receptor antagonists and adequate hydration.

  In the event of dehydration, administration of electrolytes and fluids is required. Plasma levels of electrolytes should be monitored, if relevant gastrointestinal adverse events occur.

- *Neutropenia and Sepsis*

  A higher frequency of neutropenia of CTCAE grade ≥ 3 was observed in patients treated with nintedanib in combination with docetaxel as compared to treatment with docetaxel alone in the clinical trial LUME-Lung 1. Subsequent complications such as sepsis or febrile neutropenia have been observed.

  Blood counts should be monitored during therapy, if nintedanib is combined with a myelosuppressive agent.

- *Hepatic Function*

  The safety and efficacy of nintedanib has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Therefore treatment with nintedanib is not recommended in such patients.

  Administration of nintedanib was associated with an elevation of liver enzymes (ALT, AST, ALKP (alkaline phosphatase), and bilirubin, with a potentially higher risk for female patients. These increases were reversible in the majority of cases and not associated with clinically manifest liver disorders. Hepatic transaminases, ALKP and bilirubin levels are recommended to be closely monitored after start of therapy with nintedanib (periodically, i.e. in the combination phase with chemotherapy at the beginning of each treatment cycle).

  If relevant liver enzyme elevations are measured, interruption, dose reduction or discontinuation of the therapy with nintedanib may be required.

  Alternative causes of the liver enzyme elevations should be investigated and respective action should be taken as necessary. In case of specific changes in liver values (AST/ALT > 3 x ULN; total bilirubin ≥ 2 x ULN and ALKP >2 x ULN) treatment with nintedanib should be interrupted.

Unless there is an alternative cause established, nintedanib should be permanently discontinued.

- *Special populations*
  Nintedanib exposure increased linearly with patient age, was inversely correlated to weight, and was generally higher in patients of Asian race. This may result in a higher risk of developing liver enzyme elevations. Close monitoring is recommended in patients with several of these risk factors.

  In study 1199.13 (LUME-Lung 1), there was a higher frequency of SAEs in patients treated with nintedanib plus docetaxel with a body weight of less than 50 kg compared to patients with a weight ≥ 50 kg; however the number of patients with a body weight of less than 50 kg was small. Therefore close monitoring is recommended in patients weighing < 50 kg.

Rescue medication and additional treatments

Rescue medication to reverse the actions of nintedanib is not available. Potential side effects of nintedanib have to be treated symptomatically.

6.9 CONCURRENT CANCER TREATMENTS RESTRICTIONS

- Additional chemo-, immuno-, hormone- or radiotherapies are not allowed during the active treatment period of this trial.

- Palliative radiotherapy may be permitted for symptomatic control of pain from bone metastases in extremities after discussion with the Principle Investigator, provided that the radiotherapy does not affect target lesions, and the reason for the radiotherapy does not reflect progressive disease.

Combined inducers of CYP3A4 and P-gp should be avoided. Drugs that are combined inhibitors of CYP3A4 and P-glycoprotein (i.e. both a moderate or strong inhibitor of CYP3A4 and an inhibitor of P-glycoprotein) should be used with caution. Drugs that are inducers of CYP3A4 and P-glycoprotein recognized as both a moderate-to-strong inducer of CYP3A4 and an inducer of P-glycoprotein should be avoided (may decrease nintedanib exposure.)

7.0 STUDY EVENTS

7.1 Screening Assessments

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within **21 days prior to registration** unless otherwise stated. The screening procedures include:

- Informed Consent
- Medical history

- Demographics
- Inclusion/Exclusion criteria
- Concomitant Medications assessment
- Physical Exam (PE)
- Height and weight
- ECOG Performance Status (PS)
- Vital Signs (blood pressure, pulse, temperature, respirations)
- Hematology including Hemoglobin, Platelets, WBC, ANC
- Comprehensive Metabolic Panel including Albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, total bilirubin, and total protein
- Other labs: LDH and uric acid
- Serum pregnancy test (WOCBP)
- Coagulation including PT/INR, PTT
- Urinalysis
- RECIST Tumor assessment
- CT or MRI of chest, abdomen, and pelvis
- DCE-MRI for correlative studies
- ECG
- Blood draw for correlative studies
- Biopsy tissue for correlative studies(If archival tissue is available a fresh biopsy will not be needed)
- PROMIS QOL Assessment

Performed **within 14 days** prior to registration:

- Hematology including Hemoglobin, Platelets, WBC, ANC
- Comprehensive Metabolic Panel including Albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, total bilirubin, and total protein
- Other labs: LDH and uric acid
- Urinalysis
- Serum pregnancy test (WOCBP)
- Coagulation including PT/INR, PTT
- Height and weight
- Completion of Inclusion/ Exclusion checklist

7.2 On-Study Treatment Assessments

7.2.1 Monotherapy (Cycle 1, Days 1-14)

Cycle 1, Day 1

- Vital Signs
- PE and History
- Weight
- ECOG PS
- AE Assessment
- ConMeds Assessment
- Review criteria for initiation of nintedanib (section 6.1)

- Hematology,
- Comprehensive Metabolic Panel
- LDH
- Uric Acid
- PT/INR
- CA19-9
- Provide Patient Diary
- Start oral Nintedanib Monotherapy
- PROMIS QOL Assessment (if needed)
- Blood draw for correlative studies (if not done during screening)

Cycle 1, Day 8 (+/- 3)

- Vital Signs
- Symptom-directed PE (as clinically indicated)
- Hematology, Comprehensive Metabolic Panel, LDH, Uric Acid
- Confirm Nintedanib Monotherapy
- AE Assessment
- ConMeds Assessment

Cycle 1, Day 10-14

- AE Assessment
- Conmed Assessment
- Symptom-directed PE (as clinically indicated)
- DCE-MRI for correlative studies (all efforts will be made to perform MRI before starting 'Combination Therapy and Chemotherapy' phase)
- Blood draw for correlative studies
- End Nintedanib Monotherapy (Day 14)

7.2.2 Combination Therapy

Cycle 2, Day 1 (Study Day 15)

- Vital Signs
- PE and History
- Weight
- ECOG PS
- PROMIS QOL Assessment
- AE Assessment
- ConMeds Assessment
- Hematology, Comprehensive Metabolic Panel, LDH, Uric Acid, PT/INR CA 19-9
- Collect and review Patient Diary from previous cycle for AE's and drug compliance
- Provide new Patient Diary for nintedanib
- Begin Nintedanib Combination Therapy – NOTE: Nintedanib will NOT be administered on chemotherapy days 1, 8, and 15 of the 28 day cycle
- Gemcitabine/nab-Paclitaxel Administration
- Blood draw for correlative studies

Cycle 2 Day 8 (+/- 3)

- Vital Signs
- Symptom-directed PE (as clinically indicated)
- AE Assessment

- ConMeds Assessment
- DLT Evaluation
- Hematology, Comprehensive Metabolic Panel, LDH, Uric Acid
- Nintedanib Combination Therapy - NOTE: Nintedanib will NOT be administered on chemotherapy days 1, 8, and 15 of the 28 day cycle
- Gemcitabine/nab-Paclitaxel Administration

Cycle 2 Day 15 (+/- 3)

- Vital Signs
- Symptom-directed PE (as clinically indicated)
- AE Assessment
- ConMeds Assessment
- DLT Evaluation
- Hematology, Comprehensive Metabolic Panel, LDH, Uric Acid
- Nintedanib Combination Therapy - NOTE: Nintedanib will NOT be administered on chemotherapy days 1, 8, and 15 of the 28 day cycle;
- Gemcitabine/nab-Paclitaxel Administration

Cycle 2, Day 22-28

- Chemo Holiday from Gemcitabine + nab-Paclitaxel
- Nintedanib Combination Therapy
- DLT Evaluation
- AE Assessment

Cycles 3+, Day 1 (+/- 3)

- Vital Signs
- PE and History
- Weight
- ECOG PS
- PROMS QOL Assessment
- AE Assessment
- ConMeds Assessment
- Hematology, Comprehensive Metabolic Panel, LDH, Uric Acid, -PT/INR
- CA19-9 (after cycle 3 performed on odd cycles only)
- Urinalysis
- Safety Assessment Form after cycle 2 (Appendix D) – only required on cycle 3 day 1
- Collect and review Patient Diary from previous cycle for AE's and drug compliance
- Provide new Patient Diary for Nintedanib Combination Therapy – NOTE: Nintedanib will NOT be administered on chemotherapy days 1, 8, and 15 of the 28 day cycle
- Gemcitabine/nab-Paclitaxel Administration
- Blood draw for correlative studies

Cycles 3+, Day 8 (+/- 3)

- Vital Signs
- Symptom-directed PE (as clinically indicated)
- Hematology, Comprehensive Metabolic Panel, LDH, Uric Acid
- Nintedanib Combination Therapy - NOTE: Nintedanib will NOT be administered on chemotherapy days 1, 8, and 15 of the 28 day cycle;
- Gemcitabine/nab-Paclitaxel Administration

- AE Assessment
- ConMeds Assessment

Cycles 3+, Day 15 (+/- 3)

- Vital Signs
- Symptom-directed PE (as clinically indicated)
- Hematology, Comprehensive Metabolic Panel, LDH, Uric Acid
- Nintedanib Combination Therapy - NOTE: Nintedanib will NOT be administered on chemotherapy days 1, 8, and 15 of the 28 day cycle;
- Gemcitabine/nab-Paclitaxel Administration
- AE Assessment
- ConMeds Assessment

Cycles 3+, Days 22-28

- Chemo Holiday from Gemcitabine + nab-Paclitaxel
- Nintedanib Combination Therapy
- CT or MRI Chest/Abdomen/Pelvis (odd cycles only)
- RECIST Tumor Assessment (odd cycles only)
- AE Assessment

7.2.3 End of Treatment Visit or Early-Withdrawal Visit (+/- 7)

Cycle 9, Day 22-28 = 'End of Treatment Visit' or 'Early-Withdrawal' Visit

- Vital signs
- PE and History
- ECOG PS
- Weight
- PROMIS QOL Assessment
- AE Assessment
- Conmed Assessment
- Hematology
- Comprehensive Metabolic Panel
- LDH
- uric acid
- PT/INR
- Serum Pregnancy (WOCBP only),
- CA 19-9
- Urinalysis
- Blood work for correlative studies
- CT or MRI Chest/Abdomen/Pelvis
- RECIST Tumor Assessment
- End nintedanib Combination Therapy
- Collect and review Patient Diary for AE and patient compliance

7.2.4 Follow-Up Visit

Follow-up Visit (+/- 7)

After completion of the 'End of Treatment' or 'Early-Withdrawal' visit, a Follow-Up Visit will be performed within 4 weeks. If there are unresolved AEs this visit will be repeated every 4

weeks until all AEs have resolved to ≤ grade 1 or baseline. The following procedures will be performed at this visit:

- Vital Signs
- PE and History
- ECOG PS
- Weight
- AE Assessment
- Conmed Assessment
- Hematology, Comprehensive Metabolic Panel, LDH, Uric Acid, -PT/INR Urinalysis, CA19-9

7.2.5 Survival Follow-Up

Survival follow-up will be performed at the discretion of the study team and the investigator. Non-intrusive procedures will be performed such as reviewing the patient's medical chart for survival status or placing a call to the patient or patient's family to confirm survival status. The patient will be considered lost to follow-up after three attempts have been made to confirm survival status.

7.2.6 Safety Laboratory Investigations

Blood samples have to be collected at the specified time points as detailed in study table. Safety laboratory examinations will include hematology, Comprehensive Metabolic Panel, coagulation parameters.

The following parameters will be reviewed:

Hematology	Comprehensive Metabolic Panel	Other Labs	Coagulation	Tumor Markers
• Hemoglobin • WBC • ANC • Platelets	• Glucose • Sodium • Calcium • Potassium • Chloride • Bicarbonate (CO_2) • Creatinine • Albumin • Aspartate Amino transferase (AST) • Alanine Amino Transferase (ALT) • Alkaline Phosphatase (ALK) • Bilirubin* • BUN • Total protein	• LDH • Uric Acid	• PT/INR • aPTT	• CA19-9

* in case of elevated bilirubin, please provide direct and indirect bilirubin levels

7.3 Study Calendar:

Study Procedures	Screening (-21 Days)	Screening (-14 Days)	Monotherapy Nintedanib			Combined Therapy Nintedanib with Gem + nab-Paclitaxel								End of Tx Visit or ET ±7	Follow - Up ±7	Survival
Cycles			Cycle 1			Cycle 2				Subsequent Cycles 3, 4, 5 …9						
Study Days			1	8 ±3	10-14	1	8 ±3	15 ±3	22-28	1 ±3	8 ± 3	15 ±3	22-28			
Informed Consent	X															
Demographics	X															
Review of I/E Criteria	X	X														
Completion of Inclusion/ Exclusion checklist (Appendix D)		X														
Review criteria for Nintedanib initiation			X[c]													
Vital Signs	X		X	X		X	X	X		X	X	X		X	X	
PE and History	X		X			X				X				X	X	
Weight and Height [a]	X	X	X			X				X				X	X	
Symptom-Driven PE (as clinically indicated)				X	X		X	X			X	X				

ECOG Performance Status	X		X			X				X				X	X	
DLT Evaluation							X	X	X							
Safety Assesment – End of Cycle 2 (Appendix E)										X[e]						
AE Assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	
Conmed Assessment	X		X	X	X	X	X	X		X	X	X		X	X	
Blood for correlative studies (Research)	X		X[d]		X	X				X				X		
Biopsy for correlative studies (Research)	X[*&]															
DCE-MRI (Research)	X				X[%]											
CT or MRI Chest/Abdomen/Pelvis	X												X[$]	X		
Disease Assessment per RECIST 1.1	X												X[$]	X		
CA 19-9	X		X			X				X[f]				X	X	
CBC with differential	X	X	X	X		X	X	X		X	X	X		X	X	

Comprehensive Metabolic Panel	X	X	X	X		X	X	X		X	X	X		X	X	
LDH, Uric Acid	X	X	X	X		X	X	X		X	X	X		X	X	
PTT	X	X														
PT/INR	X	X	X			X				X				X	X	
Serum Pregnancy (WOCBP) Only	X	X												X		
Urinalysis	X	X												X	X	
Proteinuria assessment [g]	X		X							X[f,g]						
ECG	X															
Nintedanib (Study Drug)[@]																
Gemcitabine+nab-Paclitaxel						X	X	X		X	X	X				
Review of Patient's Chart OR Phone call																X
PROMIS QOL Assessment	X[#]				X	X				X				X		
Review of Patient Study Drug Diary			X[b]	X		X[b]				X[b]				X		

$ Scan at end of cycle 3 then every 2 cycles

* Archival biopsy tissue

& At baseline, if archival tissue is available, a fresh biopsy will not be needed.

% All efforts will be made to perform MRI before starting 'Combination Therapy and Chemotherapy' phase. Fail to perform DCE-MRI would not affect continuous treatments.

PROMIS QOL can also be completed prior to initial treatments on cycle 1 day 1.

$ CT or MRI chest/abdomen/pelvis need to be done at the end of cycle 3 and every two cycles thereafter.

@ tPatient should not take Nintedanib (study drug) on days 1, 8 and 15 (days of IV chemo) of the combination chemotherapy cycle.

a. height only at screening/baseline

b. collect previous cycles completed drug diary provide a new patient drug diary and (except cycle 1 day 1)

c. refer to section 6.1

d. if not completed during screening

e. complete the form after 28 days of treatment

f. perform at cycle 3 then at odd cycles

g. must be ≤ grade 2

8.0 MEASUREMENT OF EFFECT

8.1 Antitumor Effect- Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

8.1.1 Definitions

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

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of combination 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 2 will also be considered evaluable.)

8.1.2 Disease Parameters

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

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

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 3 lesions per organ and 6 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) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 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 or absence of each should be noted throughout follow-up.

8.1.3 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 21 days 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 when both methods have been used to assess the antitumor effect of a treatment.

For timing of imaging, refer to section 7.3. Other procedures/imaging will be done per discretion of the MD.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. As is described in RECIST v1.1, when 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). More details concerning the use of both CT and MRI for assessment of objective tumor response evaluation are provided in RECIST v1.1.

8.1.4 Response Criteria

8.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions. Any pathologic lymph nodes must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameters (LD) of target lesions, taking as reference the baseline sum diameters LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters LD 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 progression).

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

8.1.4.2 Evaluation of Non-Target Lesions

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

Incomplete Response/Stable Disease (SD): 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

8.1.4.3 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.

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response for this Category Also Requires:**
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	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	

* 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.

Note: If patients respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

8.1.5 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 recurrent disease is objectively documented.

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

8.1.6 Progression-Free Survival

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

8.1.7 Safety / Tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.0 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html) and modified criteria for hematologic adverse events.

9.0 Adverse Events

9.1 Experimental Therapy

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

9.2 Adverse Event Monitoring

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

All subjects experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;

- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study therapy for the changes observed; or
- death.

9.2.1 Definition

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

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

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

Severity

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

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

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious

adverse events, independent of relatedness to the study itself. As examples, a car accident requiring overnight hospitalization would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

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

The term "unanticipated problem" is found, but not defined in the regulations for the Protection of Human Subjects at 45 CFR 46, and the FDA regulations at 21 CFR 56. Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ***each*** of the following criteria:

- Unexpected (in terms of nature, severity or frequency) ***AND***
- Definitely or probably related to participation in the research ***AND***
- Serious or a possible unexpected problem in that the research places subjects or others at greater risk of harm than was previously known or recognized. Note: Any serious adverse event would always suggest a greater risk of harm.

Follow-up

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

9.2.3 Reporting

The UTSW IRB requires reporting of all UPIRSOs according to the guidance below. For participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events. All SAEs occurring during the protocol-specified monitoring period should be submitted to the UTSW study team within 2 business days of the center learning of the event.

9.2.3.1 UPIRSOs occurring on the study require expedited reporting, and are submitted to the UTSW IRB through the UTSW eIRB by the UTSW study team and to the SCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the UTSW study team and will be forwarded to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE documentation that is available are also submitted to the DSMC Chair who determines if further action is required. *(See Appendix IV of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB is not required).*

All serious adverse events which occur on research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. Hardcopies or electronic versions of the FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator.

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons

Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all serious adverse events upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Telephone reports to: **Investigator: Dr. Salwan Al Mutar** **214-648-4008**
Written reports to: **Investigator: Dr. Salwan Al Mutar** **c/o Phase 1 Manager** **5323 Harry Hines Blvd., NB2.402** **214-648-1578 (fax)** UTSW SCCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-5949 or deliver to BLB.306 UTSW Institutional Review Board (IRB) Submit via eIRB with a copy of the final sponsor report as attached supporting documentation

SAE reporting to Boehringer Ingelheim (BI) Pharmaceutical, Inc.

The investigator/Lead coordinator shall report all SAEs and non-serious AEs, which are relevant to a reported SAE, by fax using BI IIS SAE form to BI Unique Entry Point as detailed below in accordance with the following timelines:

- Within five (5) calendar days upon receipt of initial and follow-up SAEs containing at least one fatal or immediately life-threatening event;
- Within ten (10) calendar days upon receipt of any other initial and follow-up SAEs.

Boehringer Inglehiem Pharmaceuticals, Inc
900 Ridgebury Road
Ridgefield, CT 06877
Fax: 1-203-837-4329

The investigator does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred after the patient has completed the clinical trial (including any protocol specified follow-up period), it should be reported to BI if investigator considers it as relevant to the BI study drug.

1. SAEs

Serious adverse events (SAEs) for studies where the SCCC DSMC is the DSMC of record

require reporting to the DSMC coordinator within 2 working days of PI awareness, or as described in the protocol.

2. Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs)

Local Serious Adverse Event UPIRSOs require reporting to the UTSW IRB within 48 hours of PI awareness of the event (life threatening or fatal events experienced by subjects enrolled by the investigator(s) under UTSW IRB jurisdiction).

Local UPIRSOs (non-serious events experienced by subjects enrolled by the investigator(s) under UTSW IRB jurisdiction) require reporting to the UTSW IRB within 5 business days of PI awareness of the event.

External UPIRSOs including those that occur as non-local events require reporting to the UTSW IRB within 10 working days of PI awareness of the event.

For further guidance for Investigators regarding safety reporting requirements for INDs and BA/BE studies, refer to FDA Draft Guidance document: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

9.3 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

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

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

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

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

- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

9.4 Adverse Events and Laboratory Values of Special Interest

The following events are considered as Protocol-specified adverse events of special interests (AESI):

Any gastrointestinal- and non-gastrointestinal perforation, leakage, fistula formation, abscess

In such case the following additional information need to be collected, documented in the respective comment field of the CRF page and the respective narratives of the SAE.
That has to be forwarded to Boehringer Ingelheim:

- Location of perforation, leakage, fistula, abscess
- Location/extent of abdominal tumor manifestations,
- Imaging & reports (CT, ultrasound, endoscopy, pathology, etc.)
- Prior surgery (location, wound healing complications)
- Concomitant diseases with GI involvement (e.g., M Crohn, vasculitis, tuberculosis, diverticulitis)
- Thromboembolic events (or predisposition)

Drug-induced liver injury is under constant surveillance by sponsors and regulators and is considered a protocol-specified adverse event of special interest (AESI). Timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to distinguish an effect of the investigational drug from other causes are important for patient safety and for the medical and scientific interpretation of the finding. The following are considered as protocol-specified AESI:

- An **elevation of ALT and / or AST > 5x ULN** without bilirubin elevation measured in the same blood draw sample
- An **elevation of AST and/or ALT >2.5 fold ULN combined with an elevation of bilirubin to >1.5 fold ULN** measured in the same blood draw sample

Patients showing above laboratory abnormalities need to be followed up until the protocol specific retreatment criteria have been met.

Protocol-specified AESI are to be reported in an expedited manner similar to Serious Adverse Events, even if they do not meet any of the seriousness criteria.

9.5 DOSE LIMITING TOXICITY (DLT) FOR PHASE I TRIALS OF NINTEDANIB

Dose limiting toxicity (DLT):

DLT will be defined by the occurrence of any of the following toxicities possibly or probably related to drug during cycle 2 (combination phase) only as defined by CTCAE version 4.03 (Adverse events occurring during the monotherapy period (cycle 1) will not be considered DLT)

a) Any drug related grade 3 or grade 4 non-hematological toxicity, except alopecia, or asymptomatic elevation of hepatic transaminases thought to be secondary to gemcitabine or as defined below.

Grade ≥ 3 diarrhea, vomiting, or nausea that persists for > 3 days despite optimal supportive care.

b) Hematological toxicity

- CTCAE Grade 4 neutropenia that is uncomplicated (not associated with fever ≥38.5°C) only if continuing for > 7 Days
- CTCAE Grade 4 febrile neutropenia of any duration if associated with fever ≥ 38.5ºC
- Platelet decrease to CTCAE Grade 4, or decrease to CTCAE grade 3 associated with bleeding or requiring transfusions.

c) Nintedanib related liver toxicity except GGT*** as specified below:

AST/ALT > 5x ULN* independent of bilirubin
AST/ALT > 2.5 x ULN **together with** total bilirubin > 1.5 ULN

*** isolated GGT elevation with no corresponding ALT/AST increase will not be considered as DLT

d) Missing two consecutive weekly doses of gemcitabine and nab-paclitaxel because of unresolved toxicity.

e) Any other toxicity possibly or probably related to treatment in the view of the investigator that represents a clinically significant hazard to the patient.

f) Inability to resume nintedanib dosing within 14 days of stopping due to treatment related toxicity

- In case adverse events with CTCAE Grade 3/4 were not judged as DLT from a clinical point of view, Boehringer Ingelheim may obtain a confirmation from the investigator regarding the appropriateness of the judgment.

- Adaptations should be considered according to the combination to be investigated and the respective adverse event profiles of the combinations partners

Maximum tolerated dose (MTD):

MTD will be determined by:

- If a dose limiting toxicity (DLT) is observed in 1 out of 3 patients at a given dose level, up to 3 additional patients will be enrolled and treated at that dose level.
- If 2 out of 3-6 patients at that dose level have DLTs, the dose will be decreased to the previous dose level, and up to 3 additional patients will be enrolled at that dose level for a total of 6 patients.
- When up to 3 additional patients are added to a given dose level, if 0-1 of 6 patients has a DLT then the dose will be recommended as MTD.

9.6 Safety Assessment Form

The Safety Assessment: End of Cycle 2 form (Appendix D) must be completed and provided to the phase 1 manager either via fax to the attention the Phase 1 Operations Manager or Designee at 214-648-1578. This form will be reviewed by the Principal Investigator then

submitted to the DSMC for review and approval for dose escalation. Allow at least **48 hours** for the cycle 2 safety assessment review process and once approval to proceed to the next dose level has been received, an email notification from the Phase 1 Operations Manager or Designee will be sent.

9.7 Stopping Rules

In the absence of progressive disease or unacceptable toxicity, therapy will continue for 9 cycles. At this stage continuing study drug and chemotherapy will be based on treating physician/PI discretion.

10.0 PHARMACEUTICAL INFORMATION

10.1 Nintedanib (Study Drug)

Pharmaceutical form	Soft gelatin capsule
Pharmaceutical code	Nintedanib
Source:	Boehringer-Ingelheim Pharma GmbH & Co. KG
Unit Strength	100 mg and 150 mg capsules
Daily Dose:	300 mg or 400 mg (150 mg or 200 twice daily), dose reduction according to Section 5
Duration of Use:	Continuous daily dosing until progression of disease or until criteria for interruption of treatment (section 6) are met, no intake of nintedanib on days of chemotherapy administration. The maximum planned time on treatment will be 34 weeks.
Route of Administration	Oral.
Posology	Twice daily (to be swallowed unchewed with a glass of water of about 250 mL with a dose interval of around 12 hours at the same times every day, ususally in the morning and the evening after food intake).

< Very common (equal or more than 10%) risks and adverse drug reactions may include:

- diarrhea
- nausea
- vomiting
- increased liver function tests (blood tests that show the liver is not working the way it should)
- tiredness
- decreased appetite
- low white blood cell count (which can make it easier to catch an infection)

- Pain e.g., abdominal pain, muscle cramps, chest pain, back pain, tumor pain…
- skin problems such as: itching, rash, hair loss, dry skin, hand foot syndrome, nail disorder
- electrolyte imbalance
- abnormal skin sensations
- bleeding e.g. epistaxis, coughing up small amounts of blood, rectal bleeding
- mouth ulceration

Common (equal or above 1% but below 10%) risks and adverse drug reactions may include:

- taste changes
- constipation
- fever
- anemia (low level of hemoglobin in your blood)
- high blood pressure
- decrease in weight
- headache
- infections including those in the urine, chest and sinuses
- dry mouth,
- flatulence (gas)
- dizziness
- dehydration
- insomnia
- blood clots in vein (venous thromboembolism) or in arteries (arterial thromboembolism including myocardial infarct)
- Low blood platelet count which increases the risk of bruising and bleeding

Uncommon (less than 1%):

- cough
- chills
- vertigo
- low blood pressure
- eye disorders, such as eye dryness, eye redness, conjunctivitis, vison blurred
- drug hypersensitivity
- skin swelling
- abnormal heart beats, fast or slow heart beats
- low blood sugar
- changes in kidney function
- perforation (holes in the bowels)
- bleeding into the brain
- underfunction of the thyroid
- pancreatitis (swelling and inflammation of the pancreas)

10.2 Gemcitabine and nab-paclitaxel are commercially available

10.2.1 Agent: Gemcitabine:

Brand Name (U.S.):	Gemzar® (Gemcitabine)
Source:	Eli Lilly and Company; Gemcitabine Package Insert

Duration of Use:	Pancreatic Cancer: Recommended Dose and Schedule The recommended dose of Gemzar® (Gemcitabine) is 1000 mg/m^2 over 30 minutes intravenously. The recommended treatment schedule is as follows: **Weeks 1-8: weekly dosing for the first 7 weeks followed by one week rest. **After week 8: weekly dosing on Days 1, 8, and 15 of 28-day cycles.
Route of Administration:	Intravenous
Preparation for Intravenous Infusion Administration:	Reconstitute the vials with 0.9% Sodium Chloride Injection without preservatives. Add 5 mL to the 200-mg vial or 25 mL to the 1-g vial. These dilutions each yield a Gemzar® concentration of 38 mg/mL. Complete withdrawal of the vial contents will provide 200 mg or 1 g of Gemzar®. Prior to administration the appropriate amount of drug must be diluted with 0.9% Sodium Chloride Injection. Final concentrations may be as low as 0.1 mg/mL Reconstituted Gemzar® is a clear, colorless to light straw-colored solution. Inspect visually prior to administration and discard for particulate matter or discoloration. Gemzar® solutions are stable for 24 hours at controlled room temperature of 20° to 25°C (68°to 77°F). Do not refrigerate as crystallization can occur.

Adverse Reactions Significant

Frequency of adverse reactions reported for single-agent use of gemcitabine only.

>10%:

Cardiovascular: Peripheral edema (20%), edema (13%)

Central nervous system: Fever (38% to 41%), somnolence (11%)

Dermatologic: Rash (28% to 30%), alopecia (15% to 16%), pruritus (13%)

Gastrointestinal: Nausea/vomiting (69% to 71%; grade 3: 10% to 13%; grade 4: 1% to 2%), diarrhea (19% to 30%), stomatitis (10% to 11%)

Hematologic: Anemia (68% to 73%; grade 4: 1% to 2%), leukopenia (62% to 64%; grade 4: ≤1%), neutropenia (61% to 63%; grade 4: 6% to 7%), thrombocytopenia (24% to 36%; grade 4: ≤1%), hemorrhage (4% to 17%; grades 3: ≤2%; grade 4: <1%); myelosuppression is the dose-limiting toxicity

Hepatic: AST increased (67% to 78%; grade 3: 6% to 12%; grade 4: 2% to 5%), alkaline phosphatase increased (55% to 77%; grade 3: 7% to 16%; grade 4: 2% to 4%), ALT increased (68% to 72%; grade 3: 8% to 10%; grade 4: 1% to 2%), bilirubin increased (13% to 26%; grade 3: 2% to 6%; grade 4: ≤2%)

Renal: Proteinuria (32% to 45%; grades 3/4: <1%), hematuria (23% to 35%; grades 3/4: <1%), BUN increased (15% to 16%)

Respiratory: Dyspnea (10% to 23%)

Miscellaneous: Flu-like syndrome (19%), infection (10% to 16%; grade 3: 1% to 2%; grade 4: <1%)

1% to 10%:

Local: Injection site reactions (4%)

Neuromuscular & skeletal: Paresthesia (10%)

Renal: Creatinine increased (6% to 8%)

Respiratory: Bronchospasm (<2%)

<1% (Limited to important or life-threatening; reported with single-agent use or with combination therapy): Acute/adult respiratory distress syndrome, anaphylactoid reaction, arrhythmias, bullous skin eruptions, cellulitis, cerebrovascular accident, CHF, desquamation, fulminant hepatic failure, gangrene, GGT increased, hemolytic uremic syndrome (HUS), hepatic sinusoidal obstruction syndrome (SOS; veno-occlusive liver disease), hepatotoxicity (rare), hyper-/hypotension, interstitial pneumonitis, liver failure, MI, neuropathy, peripheral vasculitis, petechiae, pulmonary edema, pulmonary fibrosis, radiation recall, renal failure, respiratory failure, reversible posterior leukoencephalopathy syndrome (RPLS), sepsis, supraventricular arrhythmia, thrombotic thrombocytopenic purpura

Contraindications

Hypersensitivity to gemcitabine or any component of the formulation

Warnings/Precautions:

Concerns related to adverse effects:

• Bone marrow suppression: May cause bone marrow suppression (leukopenia, thrombocytopenia, and anemia); myelosuppression is generally the dose-limiting toxicity. Monitor blood counts; dosage adjustments are frequently required.

• Fever: May cause fever in the absence of clinical infection.

• Hemolytic uremic syndrome: Hemolytic uremic syndrome (and/or renal failure) has been reported; monitor for evidence of microangiopathic hemolysis (elevation of bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or renal failure).

• Hepatotoxicity: Serious hepatotoxicity (including liver failure and death) has been reported (when alone or used in combination with other hepatotoxic medications); use with caution in patients with hepatic impairment (history of cirrhosis, hepatitis, or alcoholism) or in patients with hepatic metastases; may lead to exacerbation of hepatic impairment. Dose adjustments may be considered with elevated bilirubin.

• Pulmonary toxicity: Pulmonary toxicity has been observed; discontinue if severe and institute supportive measures.

Ethanol: Avoid ethanol (due to GI irritation).

Pregnancy Risk Factor D

10.2.2 Drug: Nab-paclitaxel (Abraxane)

Paclitaxel (nanoparticle albumin bound): Drug information

Brand Name:	Abraxane® (Nab-paclitaxel) is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, UPS prior to intravenous infusion.
Source:	Abraxane® is a registered trademark of Abraxis BioScience, LLC, manufactured for Celgene Corporation – Package Insert.
Dosing:	The recommended dose of Abraxane® is 125 mg/m^2 administered as an intravenous infusion over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle. Administer gemcitabine immediately after Abraxane on days 1, 8, and 15 of each 28-day cycle.
Route of Administration:	Intravenous

Preparation for Intravenous Infusion Administration:

1. Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.

2. Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the INSIDE WALL OF THE VIAL.

3. DO NOT INJECT the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized cake as this will result in foaming.

4. 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.

5. 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.

6. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

Each mL of the reconstituted formulation will contain 5 mg/mL paclitaxel. Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient: Dosing volume (mL) = Total dose (mg)/5 (mg/mL).

The reconstituted suspension should be milky and homogenous without visible particulates. If particulates or settling are visible, the vial should be gently inverted again to ensure complete resuspension prior to use. Discard the reconstituted suspension if precipitates are observed. Discard any unused portion.

Inject the appropriate amount of reconstituted ABRAXANE into an empty, sterile intravenous bag [plasticized polyvinyl chloride (PVC) containers, PVC or non-PVC type intravenous bag]. The use of specialized DEHP-free solution containers or administration sets is not necessary to prepare or administer ABRAXANE infusions. The use of an in-line filter is not recommended.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Stability

Unopened vials of ABRAXANE are stable until the date indicated on the package when stored between 20ºC to 25ºC (68ºF to 77ºF) in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Stability of Reconstituted Suspension in the Vial

Reconstituted ABRAXANE in the vial should be used immediately, but may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) for a maximum of 8 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion. Stability of Reconstituted Suspension in the Infusion Bag The suspension for infusion when prepared as recommended in an infusion bag should be used immediately but may be stored at ambient temperature (approximately 25ºC) and lighting conditions for up to 4 hours. Discard any unused portion.

ALERT: U.S. Boxed Warning

The FDA-approved labeling includes a boxed warning. See Warnings/Precautions section for a concise summary of this information. For verbatim wording of the boxed warning, consult the product labeling or www.fda.gov.

Brand Names: U.S. Abraxane®

Adverse Reactions Significant

Adverse reactions and incidences reported are associated with monotherapy unless otherwise stated.

>10%:

Cardiovascular: ECG abnormal (60%; 35% in patients with a normal baseline)

Central nervous system: Fatigue (25% combination therapy for NSCLC)

Dermatologic: Alopecia (56% [combination therapy for NSCLC] to 90%)

Gastrointestinal: Nausea (27% to 30%; grades 3/4: 3%), diarrhea (15% to 27%; grades 3/4: <1%), vomiting (12% to 18%; grades 3/4: 4%), appetite decreased (17% combination therapy for NSCLC), constipation (16% combination therapy for NSCLC)

Hematologic: Neutropenia (80%; grades 3/4: 34%; combination therapy for NSCLC: 85%; grades 3/4: 47%), anemia (33%; grades 3/4: 1%; combination therapy for NSCLC: 98%; grades 3/4: 28%), thrombocytopenia (2%; grades 3/4: <1%; combination therapy for NSCLC: 68%; grades 3/4: 18%), myelosuppression (dose-related)

Hepatic: AST increased (39%), alkaline phosphatase increased (36%), GGT increased (grades 3/4: 14%)

Neuromuscular & skeletal: Sensory neuropathy (71%; grades 3/4: 10%; dose dependent; cumulative), weakness (47%; severe 8%; combination therapy for NSCLC: 16%), myalgia/arthralgia (44%; combination therapy for NSCLC: 10% to 13%)

Ocular: Vision disturbance (13%; severe [keratitis, blurred vision]: 1%)

Renal: Creatinine increased (11%; severe 1%)

Respiratory: Dyspnea (12%)

Miscellaneous: Infection (24%; primarily included oral candidiasis, respiratory tract infection, and pneumonia)

1% to 10%:

Cardiovascular: Edema /fluid retention (10%), peripheral edema (10% combination therapy for NSCLC), hypotension (5%), cardiovascular events (grades 3/4: 3%; included chest pain, cardiac arrest, supraventricular tachycardia, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension)

Dermatologic: Rash (10% combination therapy NSCLC)

Gastrointestinal: Mucositis (7%; grades 3/4: <1%)

Hematologic: Bleeding (2%), neutropenic fever (2%)

Hepatic: Bilirubin increased (7%)

Neuromuscular & skeletal: Peripheral neuropathy (grade 3: 10%; combination therapy for NSCLC: 3%)

Respiratory: Cough (7%), epistaxis (7% combination therapy for NSCLC)

Miscellaneous: Hypersensitivity reaction (4%, includes anaphylactic reactions, chest pain, dyspnea, flushing, hypotension; severe: <1%)

<1% (Limited to important or life-threatening): Arrhythmia, autonomic neuropathy, bradycardia, cardiac ischemia, cerebrovascular attack, congestive heart failure, cranial nerve palsies, cystoid macular edema (transient), dehydration, embolism, hand-foot syndrome (in patients previously exposed to capecitabine), injection site reaction (mild), interstitial pneumonia, intestinal obstruction, intestinal perforation, ischemic colitis, left ventricular dysfunction, maculopapular rash, MI, motor neuropathy, optic nerve damage (rare), pancreatitis, pancytopenia, paralytic ileus, photosensitivity reaction, pneumonitis, pneumothorax, pulmonary embolism, radiation pneumonitis with concurrent radiation therapy, radiation recall, Stevens-Johnson syndrome, stroke, thrombosis, toxic epidermal necrolysis, transient ischemic attack, ventricular dysfunction, vocal cord paresis

Adverse reactions reported with paclitaxel, which may occur with paclitaxel (protein bound): Cellulitis, conjunctivitis, extravasation recall, hepatic encephalopathy, hepatic necrosis, induration, lacrimation increased, lung fibrosis, neutropenic enterocolitis (typhlitis), optic nerve damage (persistent), phlebitis, pulmonary embolism, skin exfoliation, skin fibrosis, skin necrosis

Pregnancy Risk Factor D

11.0 CORRELATIVE STUDIES

11.1 DCE-MRI

We will utilize advanced imaging correlates including dynamic contrast enhanced Magnetic Resonance Imaging (DCE-MRI) which correlates with tumor grade and microvessel density [15]. The DCE-MRI has been shown to positively correlate with the tumor MVD in multiple human cancer specimens [16-18].

Another study demonstrated a significant correlation between histopathologic parameters including fibrosis content and MVD counts in focal lesions and nontumoral tissue and DCE MRI quantitative parameters derived from two pharmacokinetic models in pancreatic solid lesions and in nontumoral pancreatic tissue. The f and v_i were positively correlated with MVD counts [19]. DCE-MRI has also shown to predict early response to therapy in a pancreatic cancer preclinical models [20,21]. Ktrans changes in the tumor on day 3 of therapy correlated with 21 day decrease in microvessel densitity[20].

Additionally, a clinical experience of DCE MRI demonstrated changes in Ktrans after treatment of pancreatic cancer with antiangiogenic therapy [22,23]. Therefore, DCE-MRI is a feasible and relevant tool for detecting response to therapy in pancreatic cancer.

Research MRI will be obtained before the monotherapy phase and prior to starting combination therapy.

11.2 Pharmacodynamic Samples

Approximately 16 mL of blood sample will be obtained from patients at each time point and analyzed for correlative studies. The timing of collections is indicated in the study calendar.

Assay methodology for correlative studies and the tested biomarkers will be determined by the investigators of the trial. Details of the blood processing procedures can be found in Appendix C.

11.3 Biopsies

FNA or core biopsy of most accessible lesion as determined by physician will be performed by Gastroenterology or Interventional radiology as indicated on diagnosis. If archival tissue is available a fresh biopsy will not be needed prior to starting treatment in the monotherapy phase.

11.4 Specimen Banking

Patient samples collected for this study will be retained in storage areas designated by the study PI. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

PI and Co-I of this study will be responsible for reviewing and approving requests for clinical specimen from potential research collaborators outside of UT Southwestern Medical Center. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimen will be the property of UT Southwestern Medical Center for publication and any licensing agreement will be strictly adhered to.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the patient that there is the potential for financial gain by UT Southwestern Medical Center, the investigator or a collaborating researcher or entity.

The following information obtained from the patient's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

12.0 STATISTICAL CONSIDERATIONS

12.1 MTD Determination:

The maximum tolerated dose (MTD) will be determined using a standard 3+3 phase I design. Three patients will be enrolled at the first dose level. If none of the first three patients experiences DLT, then the following three patients are enrolled at the next dose level (escalated). If one of three patients experiences DLT at a given dose level, three more patients are enrolled at the same dose level. If two or more patients experience DLT at a given dose level, no further escalation is allowed and MTD is determined to be the previous dose level. Six patients are to be enrolled at the highest attainable dose level even if no DLT

has been recorded. After MTD has been determined, no patient can be dose escalated beyond that dose level.
Accrual will then continue at the MTD to complete a total of 20 patients on this study.
If 2 or more patients experience a DLT at the first dose level, a lower (- I dose level) will be explored after discussion with the cohort review committee.

12.2 Data Analysis Plans

All patients receiving at least one dose of nintedanib will be considered evaluable for safety analysis, however only patients who received full dosing regimen of nintedanib in combination with gemcitabine+nab-paclitaxel will be considered evaluable for dose limiting toxicity (DLT). In addition to the evaluation and categorization of adverse events, listing of laboratory test results collected at baseline and during the study will be generated. Descriptive statistics summarizing the changes in those laboratory tests over time will be collected.

Patients who have received at least 2 cycles of combination therapy and had at least one disease assessment following the initiation of therapy will be considered evaluable for response. The antitumor activity (RECIST) will be exploratory.

The dose-limiting toxicity (DLT) and the maximum tolerable dosage (MTD) will be determined based on this Phase I design. The assessment of safety will be mainly based on the frequency of adverse effects. The incidence of AEs together with the 95% confidence interval will be reported. The overall complete response rate and corresponding 95% confidence interval will be presented. The rate from this trial will be compared with the rate for historical controls using Fisher's exact test. Progression-free survival (PFS) and overall survival (OS) will be described using Kaplan-Meier curves with appropriate summary statistics. The PFS and OS from this trial will be compared with those for historical controls using a two-sided log-rank test.

12.3 Imaging Correlates

The correlation between each DCE MRI parameter (Ktrans, Kep etc) and each RECIST response (PR, SD, PD, CR etc) will be quantified based on generalized linear regression model. We will conclude that there is a significant association if p-value<0.05.

Measurements at Day 10-14 will be used to assess change in microvessel density/vasculature with monotherapy NINTEDANIB alone.

The exploration of DCE MRI parameters at each designated point will enable detection of the most relevant marker which can, in turn, be used to design and power a larger follow up, clinical study.

Sample size: 20.

Preliminary data from Akisik et al[22] evaluating DCE-MRI changes with antiangiogenic therapy in pancreatic cancer demonstrated a significant reduction in median K trans from 1.36 mL/mL/ min (pretreatment) to 0.27 mL/mL/min (posttreatment) (p=0.02). Based on t-test for paired samples and preliminary data from previous study[23], 20 patients will distinguish a one

standard error (0.023) difference in means of pre and post treatment Ktrans with 94% power at a one-sided 5% significance level.

13.0 STUDY MANAGEMENT

13.1 Conflict of Interest

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

13.2 Institutional Review Board (IRB) Approval and Consent

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

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

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

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

13.3 Required Documentation (For Multi-Site Studies)

Before the study can be initiated at any site, the following documentation must be provided to the Simmons Cancer Center – Clinical Research Office:

- A copy of the official IRB approval letter for the protocol and informed consent;
- IRB membership list or Federal wide Assurance letter;
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study;
- PI signature on the protocol signature page;
- A copy of the IRB approved consent form;
- CAP and CLIA Laboratory certification numbers and institution lab normal values;
- Executed clinical research agreement (CTA)

13.4 Patient Recruitment

Eligible study patients will be recruited, screened, enrolled, and treated at the following institutions:

1) University of Texas Southwestern Medical Center (UTSW):

a. Harold C. Simmons Comprehensive Cancer Center;
b. University Hospital – William Clements, Jr;
c. University Hospital – Zale Lipshy;

Study patients will be recruited from the practices of the researchers. Potentially eligible patients will be approached by their health care providers who can refer them to the study coordinator for screening.

13.5 Registration Procedures

13.5.1 Study Patient Identification Number

All patients will be assigned a study number that is not linked to their personal identifiers to prevent loss of confidentiality. The number will be the Site Number, 01, 02, etc. followed by a sequential number starting with number 001. For example, the first patient enrolled from site # 01 will be assigned study patient number 01-001; the next will be 01-002, and so forth. For this protocol, current sites are: 01 – UTSW, 02 – PHHS, 03 – UTHSCSA. Any additional sites added to this protocol will be numbered sequentially…04, 05, etc. This number will be assigned by the UTSW - Clinical Research Manager (CRM) or delegate upon confirmation of patient eligibility during the patient registration process.

13.5.2 Patient Registration

Following completion of baseline assessments and confirmation of patient eligibility, patients will be assigned a patient identification number by the UTSW - CRM or delegate and registered into Velos, the UTSW Clinical Trial Management System (CTMS). Patient registration will be confirmed (within 24 hours) once the following documents have been received by the UTSW-CRM or delegate.

- Signed copy of the Informed Consent signature page;
- Inclusion/Exclusion Checklist completed and signed by both the coordinator and treating physician;
- Completed patient eligibility verification registration form
- Source documentation (which includes, but not limited to, pathology, labs, progress notes, etc) that confirms all eligibility items on the inclusion-exclusion checklist has been met

All patients must be registered with the UTSW - CRM before enrollment to study. To register a patient, fax the above supporting documents to: Phase 1 Operations Manager or Designee at 214-648-1578 or call 214-648-7007, Monday through Friday, 8:30a.m.to 4:30p.m. CST.

13.6 Data Management and Monitoring/Auditing

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for this and all SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements.

Other institutions participating in this trial as sub-sites will be expected to enter data into REDCap and upload de-identified source materials when instructed by the Simmons Comprehensive Cancer Center study team to facilitate remote source to case report form verification.

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT, which includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

Toxicity and dose escalation reviews will be performed at the Phase 1 DOT meetings. These reviews will be documented by the meeting minutes.

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

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

13.7 Adherence to the Protocol

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

13.7.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial patients without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

13.7.2 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, please follow the guidelines below:

If {non-Research Office} managed study, please maintain the following language in your protocol:

Protocol Deviations: Personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Study personnel should report violations within two (2) weeks of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

13.8 Amendments to the Protocol

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

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

13.9 Record Retention

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

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

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

13.10 Obligations of Investigators

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

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

14.0 REFERENCES

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15.0 APPENDICES

Appendix A – ECOG Performance Status Scale

Eastern Cooperative Oncology Group (ECOG) Performance Status

These criteria will be used to assess how the disease of a patient is progressing, to assess how the disease affects the daily living abilities of the patient, and to determine appropriate treatment and prognosis.

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix B – PROMIS QOL Assessment

PROMIS Global – QOL (v 1.0-1.1 SF)

Patient ID: _____ Date of Assessment: _____

Please respond to each item by marking one answer per question:

In general, would you say your health is:...	◯ 5 Excellent ◯ 4 Very good ◯ 3 Good ◯ 2 Fair ◯ 1 Poor
In general, would you say your quality of life is:...	◯ 5 Excellent ◯ 4 Very good ◯ 3 Good ◯ 2 Fair ◯ 1 Poor
In general, how would you rate your physical health?...	◯ 5 Excellent ◯ 4 Very good ◯ 3 Good ◯ 2 Fair ◯ 1 Poor
In general, how would you rate your mental health, including your mood and your ability to think?...	◯ 5 Excellent ◯ 4 Very good ◯ 3 Good ◯ 2 Fair ◯ 1 Poor
In general, how would you rate your satisfaction with your social activities and relationships?...	◯ 5 Excellent ◯ 4 Very good ◯ 3 Good ◯ 2 Fair ◯ 1 Poor
In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.)...	◯ 5 Excellent ◯ 4 Very good ◯ 3 Good ◯ 2 Fair ◯ 1 Poor
To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?...	◯ 5 Completely ◯ 4 Mostly ◯ 3 Moderately ◯ 2 A little ◯ 1 Not at all

PROMIS Global – QOL (v 1.0-1.1 SF)

Patient ID: _____ Date of Assessment: _____

In the past 7 days..

How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?...	◯ 1 Never ◯ 2 Rarely ◯ 3 Sometimes ◯ 4 Often ◯ 5 Always
How would you rate your fatigue on average?...	◯ 1 None ◯ 2 Mild ◯ 3 Moderate ◯ 4 Severe ◯ 5 Very severe
How would you rate you pain on average?...	◯ 0 No pain ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8 ◯ 9 ◯ 10 Worst imaginable pain

Form Completed by: _____ Date: _____

Form Reviewed by: _____ Date: _____

Appendix C - Pharmacodynamic Studies

Isolation of Peripheral Blood Mononuclear Cells (PBMC)

Blood samples will be obtained using BD Vacutainer CPT™ Cell Preparation Tubes. A total of 16 mL (8 mL x 2 tubes) of blood will be collected at each time point as indicated in the study calendar. After collection, store CPT upright at room temperature until centrifugation. Sample should be centrifuged within 2 hours of collection. Remix the blood sample immediately prior to centrifugation by gently inverting several times.

1. Centrifuge CPT at room temperature for 30 minutes at 1700 g (RCF). After centrifugation, mononuclear cells will be in the layer above the gel and below the plasma layer.

2. Remove approximately half of the plasma, without disturbing the cell layer.

3. Transfer the cell layer to a 15-ml polypropylene conical tube: It is difficult to pipet out just the cell layer, so transfer the entire remainder of the contents above the gel into the 15-ml conical tube. Add cold PBS to bring volume to 14 ml. Mix by inverting several times.

4. Centrifuge at 300 g for 15 min. at 4°.

5. Aspirate as much supernatant as possible without disturbing the cell pellet. Resuspend cell pellet in 10 ml of cold PBS.

6. Centrifuge at 300 g for 10 min. at 4°.

7. Aspirate off supernatant. RESUSPEND CELL PELLET in 1 ml of cold PBS and count cell number. *

*When cells are counted, remove 10 µl of cells for counting. Add 90µl trypan blue. To determine the cell number using a hemocytometer, count the number of cells in 4 large squares. To determine the count of cells/ml, the number counted in 4 large squares is divided by 4 and then multiplied by 10^4. This number must then be multiplied by 10 to account for the dilution in trypan blue.

cells/ml = # cells counted in 4 large squares /4 x 10^4 x 10 (dilution factor)

8. PBMCs can be placed at -80°C for use in western blotting at a later date.

9. Samples should be delivered to the Biomarker Research Core at the Harold C. Simmons Cancer Center at UT Southwestern or other designated vendors on dry ice or room temperature as appropriate. Contact information for the Simmons Biomarker Research Core:

Simmons Cancer Center Biomarker Research Core
Harold C. Simmons Comprehensive Cancer Center
University of Texas Southwestern Medical Center
5323 Harry Hines Blvd., ND2. 210K
Dallas, Texas 75390-8807
Phone: (214) 645-6371
Fax: (214) 645-6347

Appendix D – Safety Assessment Form

A Phase 1b and Pharmacodynamic Study of Nintedanib Monotherapy Followed by Combination Therapy of Nintedanib and Gemcitabine Plus nab-Paclitaxel for Advanced Pancreatic Cancer

Safety Assessment: During Cycle 2 (combination phase)

Study Center	Patient Study ID	Patient Initials	Cohort

Submit this form upon completion of Cycle 2 (dosing day 1 of cycle 3) or in the event of early discontinuation during the first two cycles. One form per patient; please maintain a copy of this document with the patient's case report forms.

Assigned Dose: (mg, bid)	◻ 150 mg	◻ 200 mg

Nintedanib administered during Cycle 2:	**Study Status for this Patient:**
Date of first dose (mm/dd/yy): _____ Date of last dose(mm/dd/yy): _____	◻ Continuing on study ◻ Continuing at a reduced dose: _____ mg ◻ Off study due to disease status ◻ Off study due to toxicity

Did the patient experience a DLT? ◻ No ◻ Yes

- *DLT will be defined by the occurrence of any of the following toxicities possibly or probably related to drug during cycle 2 (combination phase). AE occurring during the monotherapy phase (cycle 1) will not be considered DLT.*

If yes, describe below and check the DLT criterion that was met

◻ Any drug related grade 3 or grade 4 non-hematological toxicity, except alopecia, or asymptomatic elevation of hepatic transaminases thought to be secondary to gemcitabine or as defined below.

◻ Grade ≥ 3 diarrhea, vomiting, or nausea that persists for > 3 days despite optimal supportive care.

◻ Hematological toxicity
- CTCAE Grade 4 neutropenia that is uncomplicated (not associated with fever ≥38.5°C) only if continuing for > 7 Days
- CTCAE Grade 4 febrile neutropenia of any duration if associated with fever ≥ 38.5ºC
- Platelet decrease to CTCAE Grade 4, or decrease to CTCAE grade 3 associated with bleeding or requiring transfusions.

◻ Nintedanib related liver toxicity except GGT*** as specified below:

AST/ALT > 5x ULN* independent of bilirubin
AST/ALT > 2.5 x ULN **together with** total bilirubin > 1.5 ULN

*** isolated GGT elevation with no corresponding ALT/AST increase will not be considered as DLT

◻ Missing two consecutive weekly doses of gemcitabine and nab-paclitaxel because of unresolved toxicity

◻ Inability to resume Nintedanib dosing within 14 days of stopping due to treatment related toxicity

◻ Any other toxicity possibly or probably related to treatment in the view of the investigator that represents a clinically significant hazard to the patient (please attach a detailed report).

Describe details of toxicity:

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Revised: 8/27/18

Consider both clinical and laboratory events when answering the following questions.
Did the patient experience an SAE during Cycle 2? ☐ No ☐ Yes If yes, describe below*
Did the patient experience any other significant toxicity during cycle 2? ☐ No ☐ Yes If yes, describe below*
Please comment on relationship to Nintedanib
Person providing assessment (print):
Signature: / Date:
I have reviewed this completed safety assessment and certify that the information is correct and accurate to the best of my knowledge.
Investigator (print):
Signature: / Date:
Give completed form to Phase 1 study manager
To be completed by study manager & PI
This is cohort _____/ Patient _____ of _____ ☐ No safety concerns noted; accrual to continue ☐ No safety concerns noted; dose escalation authorized/ Next dose level to be evaluated: _____ mg/m^2 ☐ Safety concerns noted; additional patients to be added to this cohort ☐ Safety concerns noted; dose escalation to cease ☐ Other comments: _____
Study Manager (print):
Signature: / Date:
Principal Investigator (print):
Signature: / Date:
Evaluations of all subjects in a cohort must be completed before the next cohort can begin enrolling.

Created: 1/12/16
Revised: 8/27/18

Appendix E: Procedures for the follow-up of a potential DILI case (Hy`s Law case) in IIS with Nintedanib

Introduction

Drug-induced liver injury
Drug-induced liver injury (DILI) has been the most frequent single cause of safety-related drug marketing withdrawals for the past 50 years (e.g., iproniazid), continuing to the present (e.g., ticrynafen, benoxaprofen, bromfenac, troglitazone, nefazodone). Accordingly, detection of drug-induced liver injury of an investigational compound has become an important aspect of patient´s safety guarding in drug development.

The US-FDA has published a Guidance for Industry entitled, “Drug-Induced Liver Injury: Premarketing Clinical Evaluation” which outlines the detection, evaluation, follow-up and reporting of drug-induced liver injury in clinical trials. Drugs that have the potential for inducing severe liver injury may be identified by marked peak aminotransferase elevations (10x-, 15xULN), or the combination of hepatocellular injury (aminotransferase elevation ≥3xULN) and altered liver function (hyperbilirubinemia ≥2xULN) which is defined as potential “Hy´s law case” if not explained by other causes including evidence of biliary obstruction (i.e., significant elevation of alkaline phosphatase, ALP, >2X ULN) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis, concomitant use of other known hepatotoxic drugs). This constellation predicts a poor outcome and although very rare, these potential cases have to be well characterized as soon as being identified as other confounding conditions may be the cause.

In further consideration of this FDA Guidance, any potential “Hy’s Law case” has to be reported in an expedited manner to the FDA (i.e., even before all other possible causes of liver injury have been excluded) and be followed-up appropriately. The follow-up includes a detailed clinical evaluation and identification of possible alternative etiologies for the “Hy´s Law case” constellation such as concomitant diseases (e.g. Hepatitis B) and/or other concomitant therapies that might potentially be hepatotoxic.

Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients´ safety.

The concept below has been worked out by Boehringer Ingelheim (BI) in order to guard patient´s safety and to respond to regulatory requirements. It is the basis for all clinical studies and should be applied as appropriate.

Definition

The following changes in the laboratory values are considered to be a protocol-specific significant adverse event for all patients with normal values for ALT/AST at baseline:

- an elevation of ALT and / or AST > 5x ULN without bilirubin elevation measured in the same blood draw sample
- an elevation of AST and/or ALT >2.5 fold ULN combined with an elevation of bilirubin to >1.5 fold ULN measured in the same blood draw sample.

These definitions are in line with the current dose reduction recommendations as outlined in all study protocols for BIBF 1120.

Patients showing these laboratory abnormalities need to be followed up until the protocol specific retreatment criteria have been met.

For patients with elevated ALT/AST values at baseline special considerations apply, if they are eligible for inclusion into the trial, e.g. if liver metastasis are present and do not qualify as exclusion criterion. For those special cases, the BI contact person should be involved.

Procedures

1. Protocol-specified significant events are to be reported in an expedited manner similar as Serious Adverse Events, even if they do not meet any of the seriousness criteria and documented in the eCRF.

2. Replication of the following laboratory tests for confirmation within 48 hours:

    - AST, ALT
    - Bilirubin measurement (total and direct bilirubin)
    - Alkaline Phosphatase
    - Haptoglobin
    - Complete blood count and cell morphology
    - Reticulocyte count
    - CK
    - LDH

    The results of these repeated laboratory tests must be documented on the eCRF /CRF forms and reported immediately via the SAE form to BI.

3. An evaluation of the patient within 48 hours with respect to but not limited to:

    - Abdominal ultrasound or clinically appropriate other imaging and investigations adequate to rule out biliary tract, pancreatic, intra- or extrahepatic pathology, e.g. bile duct stones, neoplasm, hepatic tumor involvement, biliary tract, pancreatic or intrahepatic pathology, vascular hepatic conditions such as portal vein thrombosis or right heart failure. These data need to be collected, documented in the respective field of the eCRF / CRF / additional documentation form, and the respective SAE form has to be updated and forwarded to BI
    - detailed history of current symptoms and concurrent diagnoses and medical history
    - detailed history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations and eg steroids as concomitant, supportive treatment), alcohol use, recreational drug use, and special diets detailed history of exposure to environmental chemical agents

4. In case that both imaging and laboratory value did not unequivocally confirm cholestasis as the reason of ALT / AST increase, in particular if AP < 2x ULN,
then please complete the following laboratory tests:

- Clinical chemistry
  alkaline phosphatase, cholinesterase (either plasma or red blood cell), albumin, PT or INR, CK, CK-MB, coeruloplasmin*, α-1 antitrypsin*, transferrin, ferritin, amylase*, lipase*, fasting glucose*, cholesterol, triglycerides
- Serology
  Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG)*, Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive)*, Anti-Smooth Muscle antibody (titer)*, Anti-nuclear antibody (titer)*, Anti-LKM (liver-kidney microsomes) antibody*, Anti-mitochondrial antibody*, Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM)
- Hormones, tumor marker
  TSH*
- Hematology
  Thrombocytes*, eosinophils*

  *If clinically indicated and in case additional investigations are needed (e.g immunocompromised patients.)

5. Initiate close observation of all patients with elevated liver enzyme and bilirubin elevations by repeat testing of ALT, AST, bilirubin (with fractionation into total and direct) and AP at least weekly until the laboratory values return to normal or to the values as defined in the protocol.

6. In case that transaminases and/or bilirubin increase despite cessation of the experimental therapy, more frequent intervals will be warranted.
   Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and Good Clinical Practices

APPENDIX F: Monotherapy Patient Diary

MONOTHERAPY DOSING DIARY – DAYS 1-14

Subject ID:	
Cycle Number:	
Current Cycle Day 1 Visit Date:	
Study Drug: Nintedanib	Assigned Dose: _____ Number of Capsule(s): _____ Take same dose twice (2 times) a day.

- Please be sure to ask the research study staff if you have any questions during this process.
- Store your study drug in a safe place out of the reach of children.
- **Take your study drug at or around the same time every day about 12 hours apart.**
- Please record the date, time and the actual number of capsules you take or the reason why any capsules were not taken - if you forget or you miss a dose, make sure you report it and make note of it on this dosing diary.
- Please bring your study drug bottle(s) (including empty bottles) and this dosing diary with you to each clinic visit.
- Please keep your study drug tablets in their bottle until you are ready to take them.
- If you experience any ill feelings or side effects after taking your study drug please write down how you are feeling and discuss with your physician and study staff at your next visit.
- If you have any questions about your study drug please contact the study staff.

Treatment will have two phases:

Nintedanib monotherapy (you will only take the study drug) for a two week period (days 1-14) followed by a combination phase of nintedanib plus chemotherapy (cycle 2+)

NINTEDANIB PATIENT DOSING DIARY

Patient Initials: _____ Patient number: _____

Nintedanib Daily Dose: _____ Cycle number: _____

	Dose	Date Nintedanib Taken			Nintedanib Taken?		Time Taken		Number of Capsules	Comments
X	Example:	12	MAR	2016	Yes [X]	No [ ]	15	30	Example: 2	Example: no drug taken
		DD	MMM	YYYY			HR	MIN		
Day 1	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 2	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 3	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 4	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 5	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 6	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 7	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		

NINTEDANIB PATIENT DOSING DIARY

Patient Initials: _____ Patient number: _____

Nintedanib Daily Dose: _____ Cycle number: _____

	Dose	Date Nintedanib Taken			Nintedanib Taken?		Time Taken		Number of Capsules	Comments
x	Example:	12	MAR	2016	Yes [X]	No [ ]	15	30	Example: 2	Example: no drug taken
		DD	MMM	YYYY			HR	MIN		
Day 8	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 9	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 10	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 11	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 12	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 13	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 14	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		

APPENDIX G: Combination Therapy Patient Diary

COMBINATION DOSING DIARY – DAYS 1-28

Subject ID:	
Cycle Number:	
Current Cycle Day 1 Visit Date:	
Study Drug: Nintedanib	Assigned Dose: _____ Number of Capsule(s): _____ Take same dose twice (2 times) a day.

- Please be sure to ask the research study staff if you have any questions during this process.
- Store your study drug in a safe place out of the reach of children.
- **Take your study drug at or around the same time twice daily about 12 hours apart.**
- Please record the date, time and the actual number of capsules you take or the reason why any capsules were not taken - if you forget or you miss a dose, make sure you report it and make note of it on this dosing diary.
- On clinic visit days please do not take your study drug at home.
- Please bring your study drug bottle(s) (including empty bottles) and this dosing diary with you to each clinic visit.
- Please keep your study drug capsules in their bottle until you are ready to take them.
- If you experience any ill feelings or side effects after taking your study drug please write down how you are feeling and discuss with your physician and study staff at your next visit.
- If you have any questions about your study drug please contact the study staff.

Treatment will have two phases:

Nintedanib monotherapy (you will only take the study drug) for a two week period (days 1-14) followed by a combination phase of nintedanib plus chemotherapy (cycle 2+)

NINTEDANIB PATIENT DOSING DIARY

Patient Initials: _____ Patient number: _____

Nintedanib Daily Dose: _____ Cycle number: _____

	Dose	Date Nintedanib Taken			Nintedanib Taken?		Time Taken		Number of Capsules	Comments
x	Example:	12	MAR	2016	Yes [X]	No [ ]	15	30	Example: 2	Example: no drug taken
		DD	MMM	YYYY			HR			
Day 1	DO NOT TAKE Nintedanib capsules									
Day 2	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 3	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 4	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 5	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 6	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 7	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		

NINTEDANIB PATIENT DOSING DIARY

Patient Initials: _____ Patient number: _____

Nintedanib Daily Dose: _____ Cycle number: _____

	Dose	Date Nintedanib Taken			Nintedanib Taken?		Time Taken		Number of Capsules	Comments
x	Example:	12	MAR	2016	Yes [X]	No [ ]	15	30	Example: 2	Example: no drug taken
		DD	MMM	YYYY			HR	MIN		
Day 8	DO NOT TAKE Nintedanib capsules									
Day 9	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 10	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 11	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 12	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 13	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 14	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		

NINTEDANIB PATIENT DOSING DIARY

Patient Initials: _____ Patient number: _____

Nintedanib Daily Dose: _____ Cycle number: _____

	Dose	Date Nintedanib Taken			Nintedanib Taken?		Time Taken		Number of Capsules	Comments
x	Example:	12	MAR	2016	Yes [X]	No [ ]	15	30	Example: 2	Example: no drug taken
		DD	MMM	YYYY			HR	MIN		
Day 15	DO NOT TAKE Nintedanib capsules									
Day 16	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 17	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 18	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 19	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 20	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
Day 21	1st Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes [ ]	No [ ]				
		DD	MMM	YYYY			HR	MIN		

NINTEDANIB PATIENT DOSING DIARY

Patient Initials: _____ Patient number: _____

Nintedanib Daily Dose: _____ Cycle number: _____

	Dose	Date Nintedanib Taken			Nintedanib Taken?		Time Taken		Number of Capsules	Comments
x	Example:	12	MAR	2016	Yes ☒	No ☐	15	30	Example: 2	Example: no drug taken
		DD	MMM	YYYY			HR	MIN		
Day 22	1st Dose				Yes ☐	No ☐				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes ☐	No ☐				
		DD	MMM	YYYY			HR	MIN		
Day 23	1st Dose				Yes ☐	No ☐				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes ☐	No ☐				
		DD	MMM	YYYY			HR	MIN		
Day 24	1st Dose				Yes ☐	No ☐				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes ☐	No ☐				
		DD	MMM	YYYY			HR	MIN		
Day 25	1st Dose				Yes ☐	No ☐				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes ☐	No ☐				
		DD	MMM	YYYY			HR	MIN		
Day 26	1st Dose				Yes ☐	No ☐				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes ☐	No ☐				
		DD	MMM	YYYY			HR	MIN		
Day 27	1st Dose				Yes ☐	No ☐				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes ☐	No ☐				
		DD	MMM	YYYY			HR	MIN		
Day 28	1st Dose				Yes ☐	No ☐				
		DD	MMM	YYYY			HR	MIN		
	2nd Dose				Yes ☐	No ☐				
		DD	MMM	YYYY			HR	MIN		