A Pilot Study of Nintedanib in Molecularly Selected Patients with Advanced Non-Small Cell Lung Cancer (NSCLC)

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Principal Investigator Signature Page

Principal Investigator (printed):

Name of Institution:

PI Signature *Date*

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

Glossary of Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
ATP	Adenosine triphosphate
BID	Bis in die (twice a day)
BW	Body weight
CBC	Complete blood count
CMP	Comprehensive metabolic panel
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DLTs	Dose Limiting Toxicities
DNA	deoxyribonucleic acid
DSM	Data and Safety Monitoring
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin-fixed paraffin-embedded
GGT	Gamma glutamyltransferase
HIV	Human Immunodeficiency Virus
HRPO	Human Research Protection Office (IRB)
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
IULN	Institutional upper limit of normal
mCRC	Metastastic colorectal cancer
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NIH	National Institutes of Health
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OHRP	Office of Human Research Protections
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography

PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetic
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QASMC	Quality Assurance and Safety Monitoring Committee
QD	Quaque die (each day)
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
RR	Response rate
SAE	Serious adverse event
SCC	Siteman Cancer Center
SD	Stable disease
SNV	Single nucleotide variant
SOC	Standard of care
TKI	Tyrosine kinase inhibitor
UPN	Unique patient number

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1.0 BACKGROUND AND RATIONALE

1.1 Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer related death in both men and women in the United States.[1] Over 200,000 patients are diagnosed with lung cancer every year in the United States. More than 80% of these patients have non-small cell lung cancer (NSCLC) and over half of them present with advanced stage disease at the time of diagnosis. Platinum based chemotherapy remains the mainstay of first line treatment for patients with advanced stage NSCLC. In a prospective randomized study that compared four commonly used platinum-based chemotherapy regimens for patients with stage IIIB or stage IV disease: cisplatin plus paclitaxel, cisplatin plus gemcitabine, cisplatin plus docetaxel, and carboplatin plus paclitaxel, no regimen was found to have a significantly better response rate or survival time.[2] The response rate for all 1,158 of the eligible patients was 19%, and the median survival time was 7.9 months (95% CI, 7.3-8.5 months). The results from this study indicate that the combination of platinum with third generation chemotherapeutic agents (paclitaxel, docetaxel, vinorelbine, gemcitabine) has limited benefit in the treatment of patients with metastatic NSCLC. Unfortunately treatment benefit from 1st line cytotoxic chemotherapy is usually short lived with a median time to progression of 3 to 5 months. Standard second line treatment options are few, limited to docetaxel, pemetrexed, and erlotinib for patients with good performance status. [3-5] Therefore it is essential to develop effective treatment options for patients with relapsed/refractory NSCLC. Many patients with relapsed/refractory NSCLC also have marginal performance status and it is important to develop therapies that are tolerable.

1.2 Angiogenesis

Angiogenesis, an essential step for tumor growth and progression is defined as the growth of new blood vessels from existing vasculature.[6] Due to its critical role in several tumors including NSCLC, its inhibition represents a rational therapeutic strategy. *VEGF* is key ligand and regulator of both physiological and pathological angiogenesis, including from tumors, with the signaling occurring mostly through *VEGFR2*.[7] The two main mechanisms of *VEGF* inhibition are the use of monoclonal antibodies against circulating *VEGF* and small molecules that inhibit its tyrosine kinase activity. Several *VEGFR* TKIs have been tested as single agents in patients with NSCLC, and it is not surprising that the response rates to these drugs in molecularly unselected patients have been disappointing.[8-10] Sunitinib is an oral tyrosine kinase inhibitor (TKI) of *VEGFR* and *PDGFR*. The phase II study of sunitinib in 47 previously treated NSCLC patients showed potential therapeutic benefit (median progression-free survival (PFS) 11.9 weeks), and one patient had a confirmed partial response.[8]

Bevacizumab, a humanized monoclonal antibody against circulating *VEGF* was the first antiangiogenic drug to be approved for NSCLC, with its use restricted to patient with non-squamous histology due to the increased risk of life-threatening bleeding in squamous cell carcinoma.[11] Two randomized clinical trials, Eastern Cooperative Oncology Group (ECOG) 4599 and Avastin in Lung (AVAiL), comparing chemotherapy alone or with bevacizumab,

showed improved response rate and progression-free survival (PFS) for the combination therapy.[12,13] However, only the ECOG 4599 study showed a survival benefit. *VEGFR* tyrosine kinase inhibitors (TKIs) compete with adenosine triphosphate (ATP) for the active site of the kinase domain. Due to the well-conserved ATP binding site of the kinases, most *VEGFR* TKIs inhibit multiple receptors including *PDGFR*.[14,15] Additionally, recently published research shows that expression of VEGF-A correlated with mutations in TP53, suggesting that TP53 mutational status may also play a role in response to antiangiogenic therapies. [16,17]

PDGF promotes tumor cell proliferation, invasion, migration and angiogenesis.[18] The *PDGF* pathway plays a significant role in angiogenesis through its effects on pericytes and vascular smooth muscle cells, which in turn secrete *VEGF*.[19] This signaling cooperation could be explored with a dual inhibitor. One of the major obstacles for further development of anti-angiogenesis inhibitors is the lack of reliable predictors for response. We believe that with the use of a potent single agent TKI against *VEGFR* and *PDGFR* in a molecularly selected patient population may lead to a significant benefit in some patients and further evaluation of responders with a comprehensive molecular profile both at diagnosis and at progression, may provide valuable information predictors for response and mechanisms of resistance.

1.3 Nintedanib (BIBF1120)

Nintedanib is a TKI of *VEGFR1-3, PDGFR-A, PDGFR-B,* and *FGFR1-3*.[20] In the phase I monotherapy study, nintedanib was well tolerated with dose limiting toxicities of elevated AST, ALT, and GGT. Other toxicities included nausea, diarrhea, vomiting, abdominal pain, and fatigue. The maximum tolerated dose (MTD) determined at 200 mg bid. When nintedanib (at 200mg bid) was used in combination with chemotherapy (FOLFOX, pemetrexed, docetaxel, and paclitaxel/carboplatin) it showed no added safety concerns. This led to two separate phase III studies in patients with NSCLC in the 2nd line setting comparing chemotherapy alone to chemotherapy in combination with nintedanib. Both studies met their primary endpoint of PFS with no unexpected toxicities. [21]

1.3.1 Preclinical Development and Pharmacokinetics

Nintedanib (BIBF1120) is a potent, orally available triple kinase inhibitor targeting VEGFRs, PDGFRs, and FGFRs.

Nintedanib inhibits the signalling 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, signalling by FGF-receptors

has been identified as a possible escape mechanism for tumour angiogenesis when the VEGF pathway is disrupted.

Besides inhibition of neo-angiogenesis, it may alter tumour maintenance by inducing apoptosis of tumour blood vessel endothelial cells. Inhibition of receptor kinases may also interfere with autocrine and paracrine stimulation of tumour angiogenesis via activation loops involving VEGF, PDGF, and bFGF utilized by vascular and perivascular cells such as pericytes and vascular smooth muscle cells.

In addition, preclinical models show that nintedanib (BIBF1120) may have a direct anti-tumour 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

In vitro, the target receptors are all inhibited by nintedanib in low nanomolar concentrations. In in vivo nude mouse models, nintedanib showed good anti-tumour efficacy at doses of 50 – 100 mg/kg, leading to a substantial delay of tumour growth or even complete tumour-stasis in xenografts of a broad range of differing human tumour types. Histological examination of treated tumours showed a marked reduction of tumour vessel density by approximately 80% .[20]

The metabolism of nintedanib (BIBF1120) 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 (BIBF1120) 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.[21] The metabolic characteristics are predominantly independent of cytochrome P450-catalysed metabolic pathways.[22]

A soft gelatine 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.[22]

Nintedanib (BIBF1120) is non-mutagenic, even at high doses.

Two exploratory studies in rats revealed a teratogenic effect of nintedanib (BIBF1120) with a steep dose/effect relationship and an early onset of embryofetal 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 (BIBF1120) in semen is unknown, males receiving nintedanib (BIBF1120) 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.

1.3.2 Clinical Development of Nintedanib

Nintedanib is being evaluated in several cancers. Additionally, nintedanib is in advanced phase III for the non-cancer indication idiopathic pulmonary fibrosis (IPF). As of 15 Feb 2013, 3556 cancer patients, over 1000 patients with IPF, and 140 healthy volunteers had been treated with nintedanib or nintedanib matching placebo, in monotherapy or in combination with chemotherapy.

Phase I
Phase I dose selection studies revealed that nintedanib (BIBF1120) is generally well tolerated with mild to moderate adverse effects such as gastrointestinal symptoms (nausea, diarrhoea, vomiting, abdominal pain) and reversible elevations of liver enzymes. Initial signs of clinical activity including an encouraging rate of patients with stabilisation of their tumour of 54% and 68%, respectively, have been observed in patients with various solid tumours.[23]

Based on the Phase I dose escalation trials with nintedanib (BIBF1120) 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 bid

The maximum tolerated dose for combination therapy of nintedanib (BIBF1120) in combination with pemetrexed, docetaxel, paclitaxel/carboplatin and FOLFOX is 200mg bid. Combination of nintedanib (BIBF1120) with other anti-cancer drugs revealed a similar adverse event profile as compared to nintedanib (BIBF1120) monotherapy except for the chemotherapy related toxicities. There was no change of the pharmacokinetic parameters of nintedanib (BIBF1120) 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 (BIBF1120) 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 (BIBF1120) once daily.

The predominant adverse events were nausea, diarrhoea, 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.[22]

NSCLC

In a phase II trial in NSCLC patients the safety profile of nintedanib (BIBF1120) observed in phase I trials could be confirmed. Most commonly reported drug-related AEs were nausea (57.5%), diarrhoea (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. Tumour stabilisation was achieved in 46% of patients (ECOG 0–1 patients: 59%), with one confirmed partial response (250 mg bid.).[24]

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 (HR 0.83, p=0.0359, median 10.3 to 12.6 months).

Patients with a poor prognosis defined as time since start of 1st line therapy <9 months also experienced significant OS improvement from the addition of nintedanib to docetaxel (HR 0.75, p=0.0073, median OS 7.9 to 10.9 months).

The predominant adverse events were nausea, diarrhoea, vomiting, abdominal

pain and fatigue of mostly low to moderate intensity after monotherapy with nintedanib (BIBF1120). Dose limiting toxicities were dose dependent hepatic enzyme elevations that were reversible after discontinuation of nintedanib (BIBF1120) treatment. These liver enzyme elevations were only in few cases accompanied by a simultaneous increase of bilirubin. In general common terminology criteria for adverse events (CTCAE version 3, grade three liver enzyme increases were reported in the dose groups of 250 mg twice daily or higher. They also were reversible and usually occurred within the first two months of treatment.

Hypertension or thromboembolic events were rare and did not suggest an increased frequency as a consequence of therapy with nintedanib (BIBF1120).[21]

LUME-Lung 2 was a similar randomised, 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, enrolment 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.[25]

Ovarian Cancer

A randomised phase II maintenance trial in ovarian cancer in which the efficacy and safety of nine months of continuous twice daily doses of nintedanib (BIBF1120) following chemotherapy was investigated, has identified the potential activity of nintedanib (BIBF1120) with a 36-week PFS of 16.3 % compared to 5.0 % in the control group. The safety profile was consistent with findings previously reported for nintedanib (BIBF1120) administered as monotherapy as mentioned above.[26]

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). Overall survival data are immature but currently show no trend in either direction. Main adverse events were GI side effects and increased hematological toxicity.[27]

Colorectal Cancer

A Phase I/II, open-label, randomised study of nintedanib plus mFOLFOX6 compared to bevacizumab plus mFOLFOX6 in 120 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.[28]

A Phase III study is going to start in late 2014 to evaluate the efficacy of nintedanib in patients with metastatic colorectal cancer (mCRC) after failure of previous treatment with standard chemotherapy and biological agents (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 diarrheal, nausea, fatigue and infection, whereas AEs more frequent in the sunitinib arm consisted of bleeding, anaemia, hypertension, hand-foot syndrome and stomatitis.[29]

Hepatocellular Cancer

The efficacy and safety of nintedanib versus sorafenib in Asian Patients with Advanced Hepatocellular Carcinoma was investigated in a randomised phase II trial. Nintedanib showed similar efficacy to sorafenib, with a favourable 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 erythrodysaesthesia syndrome, and transaminase elevation events.[30]

For more details please refer to the investigator drug brochure for nintedanib (BIBF1120).

1.4 Next Generation Sequencing

It is a standard of care at our institution to perform next-generation sequencing in the tumor specimens from patients with metastatic NSCLC and at the time of disease progression when feasible following targeted therapies. Next generation sequencing involves targeted exon sequencing of 'clinically significant' cancer genes using next-generation sequencing technology.

1.5 Rationale

There has been limited benefit with angiogenesis inhibitor drugs when used with molecularly selected patients in NSCLC. We propose that patients who are molecularly selected for treatment with nintedanib based on the presence of mutations (*VEGFR1-3, PDGFR-A, PDGFR-B, RET*[21,31], and *FGFR1-3*) will have clinically meaningful benefits in terms of RR and PFS. Furthermore we plan to perform exome sequencing of paired tumor (pre and post treatment) in order to better define molecular marker predictors for response and resistance.

1.6 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 non-small cell lung cancer.

Antiangiogenic treatment with the orally available triple angiokinase inhibitor nintedanib (BIBF1120) with inhibition of VEGFR, PDGFR, RET and FGFR offers the chance to control both locally recurrent and distant metastatic disease on an outpatient basis. Treatment with nintedanib (BIBF1120) may have the potential to provide significant benefit to patients with locally advanced and/or metastatic non-small cell lung 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-tumour effects, e.g. tumor cells that express VEGFR, PDGFR, RET, or FGFR.

The risks of therapy with nintedanib (BIBF1120) 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, asthenia and anorexia.

Liver enzymes must be followed closely during treatment with nintedanib (BIBF1120).

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 (BIBF1120) 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 (BIBF1120), 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 (BIBF1120) to a mild to moderate degree and only few cases of CTCAE grade 3 or 4 hypertension have been observed. With respect to bleeding as one of the potentially serious side effects of antiangiogenesis agents in the LUME –Lung 1 trial involving 1314 patients more bleeding events were reported for nintedanib-treated squamous cell carcinoma (SCC) patients (all grades: 17.1% vs. 10.9%; grade ≥3: 2.9% vs. 1.3%) than for those with adenocarcinoma (all grades: 10.9% vs. 11.1%; grade ≥3: 1.5% vs. 1.3%). Fatal bleeding events, serious skin reactions, thrombosis, and perforations occurred at a low frequency and were balanced between both arms regardless of histology.

Based upon a non-clinical safety study *in vitro*, nintedanib (BIBF1120) 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 (BIBF1120) is considered safe.

2.0 OBJECTIVES

2.1 Primary Objectives

To evaluate the response rates for patients with advanced NSCLC with mutations in the target genes for nintedanib.

2.2 Secondary Objectives

1. To evaluate progression free survival.
2. To correlate outcomes with specific mutations.
3. To further evaluate extreme responders with exome and transcriptome sequencing.
4. To evaluate the mechanisms of secondary resistance.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Histologically confirmed diagnosis of advanced (metastatic or unresectable) NSCLC with mutations, rearrangement and fusion involving RET oncogene, or abnormalities (non-synonymous SNV or amplification) in the nintedanib target genes *VEGFR1-3*,

TP53, *PDGFR-A*, *PDGFR-B*, or *FGFR1-3*.CLIA certified lab testing for nintedanib target genes using cell free DNA from peripheral blood and/or assays performed on tumor tissues are acceptable

2. Patients with EGFR mutations or ALK rearrangements must have disease progression on appropriate FDA-approved therapy for these genomic aberrations prior to enrollment.

3. Disease progression on platinum-doublet chemotherapy prior to enrollment.

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

5. Prior treatment of cancer (chemotherapy, radiation therapy, and surgery) is allowed if completed at least 3 weeks prior to start of treatment with nintedanib and if all treatment-related toxicities are resolved.

6. At least 18 years of age.

7. ECOG performance status 0-1 (see Appendix A).

8. Normal bone marrow and organ function as defined below:
   a. Leukocytes ≥ 3,000/mcL
   b. Absolute neutrophil count ≥ 1,500/mcL
   c. Platelets ≥ 100,000/mcL
   d. Hemoglobin ≥ 9.0 g/dL
   e. INR < 2.0
   f. PT and PTT < 50% of deviation from IULN
   g. Total bilirubin ≤ 1.5 x IULN
   h. AST(SGOT)/ALT(SGPT) ≤ 1.5 x IULN for patients without liver metastases and ≤ 2.5 x IULN for patients with liver metastases
   i. Urine protein < 2+
   j. Creatinine within normal institutional limits
      OR
      Creatinine clearance > 45 mL/min for patients with creatinine levels above institutional normal

9. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry, for the duration of study participation, and for 3 months after the end of treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

10. Able to understand and willing to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. Prior treatment with *VEGFR* tyrosine kinase inhibitors.

2. A history of other malignancy ≤ 5 years previous with the exception of basal cell or squamous cell carcinoma of the skin which were treated with local resection only or carcinoma *in situ* of the cervix.

3. Currently receiving any other investigational agents, or received an investigational agent within 3 weeks of the first dose of nintedanib.

4. Radiotherapy to the target lesion within the past 3 months prior to baseline imaging.

5. Symptomatic brain metastases. Patients with known brain metastases are eligible if the metastases are asymptomatic and previously treated.

6. Leptomeningeal disease.

7. Radiographic evidence of cavitary or necrotic tumors.

8. Centrally located tumors with radiographic evidence (CT or MRI) of local invasion of major blood vessels.

9. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to nintedanib or other agents used in the study.

10. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure > NYHA II, active coronary artery disease, unstable angina pectoris, serious cardiac arrhythmia, uncontrolled hypertension (defined as systolic pressures > 150 mmHg or diastolic pressure > 90 mmHg), pericardial effusion, uncontrolled seizure disorder, or psychiatric illness/social situations that would limit compliance with study requirements.

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

12. History of clinically significant hemorrhagic or thromboembolic event in the past 6 months.

13. Known inherited predisposition to bleeding or thrombosis.

14. History of cardiac infarction within the past 12 months prior to the start of study treatment.

15. Receiving therapeutic anticoagulation (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 < 325 mg QD).

16. Pregnant and/or breastfeeding. Patients of childbearing potential must have a negative pregnancy test within 14 days of study entry.

17. Significant weight loss (> 10% of BW) within past 6 months prior to inclusion into the trial.

18. Known active or chronic hepatitis B or C infection.

19. Active alcohol or drug abuse.

20. Gastrointestinal disorder or abnormality that would interfere with absorption of the study drug.

21. Known HIV-positivity on combination antiretroviral therapy because of the potential for pharmacokinetic interactions with nintedanib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.3 Inclusion of Women and Minorities

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

4.0 REGISTRATION PROCEDURES

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

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

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

Once the patient has been entered in the Siteman Cancer Center OnCore database, the WUSM coordinator will forward verification of enrollment and the UPN via email.

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the research coordinator listed in the *Siteman Cancer Center Clinical Trials Core Protocol Procedures for Secondary Sites* packet at least one business day prior to registering patient:

1. Your name and contact information (telephone number, fax number, and email address)
2. Your site PI's name, the registering MD's name, and your institution name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and a dash) for the patient's initials
5. Current approved protocol version date
6. Copy of signed consent form (patient name may be blacked out)
7. Planned date of enrollment
8. Completed eligibility checklist, signed and dated by a member of the study team
9. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

Registrations may be submitted Monday through Friday between 8am and 5pm CT. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the Washington University research coordinator. Registration will be confirmed by the research coordinator or his/her delegate by email within one business day. Verification of eligibility and registration should be kept in the patient chart.

All patients at all sites must be registered through the Siteman Cancer Center OnCore database at Washington University.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

5.1 Agent Administration

Nintedanib is an oral drug which will be administered on an outpatient basis at a dose of 200 mg twice daily during each 28-day cycle. Starting with cycle 64, cycles will last 12 weeks. Patients should take nintedanib approximately 12 hours apart at around the same time every day after food intake. Capsules should not be opened and should be swallowed unchewed with approximately 8oz of water. If a patient misses a dose, the patient should

be instructed not to take or make up that dose and to resume dosing with the next scheduled dose. Patients will be instructed to bring all unused capsules and their medication diary to each study visit for assessment of compliance.

5.2 General Concomitant Medication and Supportive Care Guidelines

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.

Supportive care for nausea and vomiting may include medicinal products with anti-emetic properties, e.g. glucocorticoids, antihistamines, 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 GI AEs occur. Interruption, dose reduction, or discontinuation of therapy may be required despite appropriate supportive care.

If co-administered with nintedanib, strong P-gp inhibitors, e.g. ketoconazole or erythromycin, may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of nintedanib.

Strong P-gp inducers, e.g. rifampicin, carbamazepine, phenytoin, and St. John's Wort, may decrease exposure to nintedanib. Co-administration with nintedanib should be carefully considered.

5.3 Women of Childbearing Potential

Women of childbearing potential are required to have a negative pregnancy test within 14 days prior to the first dose of nintedanib. Women 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.

Female and male patients (along with their female partners) are required to use a highly effective method of birth control during participation in the study and for 3 months following the last dose of nintedanib. A highly effective method of birth control is defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine devices (IUDs), sexual abstinence, or vasectomized partner.

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

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

5.4 Duration of Therapy

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

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

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

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

5.5 Duration of Follow-up

There is a 28-day follow-up visit following the last dose of study drug. Patients will be monitored as per routine care thereafter for progression and survival, and that data will be captured in the case report forms. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

6.1 Criteria for Interruption of Treatment with Nintedanib

Treatment with nintedanib has to be interrupted in case any of the criteria listed in the table below is fulfilled.

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 of CTCAE grade ≥ 2 in conjunction with bilirubin of CTCAE grade ≥ 1 • AST and/or ALT of CTCAE grade ≥ 3 • other non-hematological adverse event of CTCAE grade ≥ 3 considered drug-related

6.2 Criteria to Restart Nintedanib

A patient is eligible to restart nintedanib if all criteria listed in the table below 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 supporter.

All criteria have to be met in order to restart nintedanib
• nausea CTCAE grade ≤ 2 • vomiting CTCAE grade ≤ 1 • diarrhoea CTCAE grade < 2 • AST and ALT CTCAE grade ≤ 2 and bilirubin CTCAE grade ≤ 1 • no other non-hematological adverse event grade CTCAE ≥ 3 which is considered drug-related

6.3 Dose Adjustments of Nintedanib

As initial measure for the management of side effects, 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 the sections above. 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 levels will be used in case dose adjustments are required for management of undue toxicity.

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

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

6.4 Management of Adverse Events

CTCAE Adverse reaction	Dose adjustment
Diarrhea ≥ grade 2 for more than 7 consecutive days despite anti-diarrheal treatment ***OR*** diarrhoea ≥ grade 3 despite anti-diarrheal treatment	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
Vomiting ≥ grade 2 ***AND/OR*** Nausea ≥ grade 3 despite anti-emetic treatment	
AST and/or ALT elevations grade 2 in conjunction with bilirubin of ≥ grade 1 ***OR*** AST and/or ALT elevations of ≥ grade 3	
Other non-hematological or hematological adverse reaction of ≥ grade 3	

Please note, dose adjustments are only required in adverse events that are drug-related.

If nintedanib will be combined with compounds that are solely metabolized by the liver and / or induce liver enzyme elevations, both molecules should be reduced in case of liver enzyme elevations according to the defined dose reductions for nintedanib as mentioned above and for the other compound as mentioned in their prescribing information.

7.0 REGULATORY AND REPORTING REQUIREMENTS

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

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

Boehringer Ingelheim and NCCN require that all events as defined in Section 7.6 be reported as outlined.

7.1 Definitions

7.1.1 Adverse Events (AEs)

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

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

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

7.1.2 Serious Adverse Event (SAE)

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

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

7.1.3 Unexpected Adverse Experience

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

7.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does

not include a reaction that, had it occurred in a more severe form, might have caused death.

7.1.5 Unanticipated Problems

Definition:

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

7.1.6 Noncompliance

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

7.1.7 Serious Noncompliance

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

7.1.8 Protocol Exceptions

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

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

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

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

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

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

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

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

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

7.4 Reporting Requirements for Secondary Sites

The research team at each secondary site is required to promptly notify the Washington University PI and research coordinator of all reportable events (as described in Section 7.6) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report (using either an FDA MedWatch form if required or an institutional SAE reporting form if not). A formal written report must be sent to the Washington University PI and research coordinator within **10 working days** of the occurrence of the event or notification of the secondary site's PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines.

7.5 Reporting to Secondary Sites

The Washington University PI (or designee) will notify the research team at each secondary site of all reportable events that have occurred at other sites within **10 working days** of the

occurrence of the event or notification of the PI of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable.

7.6 Reporting to Boehringer Ingelheim and NCCN

7.6.1 Definitions

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Serious adverse event
A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Patients may be hospitalised for administrative or social reasons during the trial (e.g. days on which infusion takes place, long distance from home to site…). These and other hospitalisations planned at the beginning of the trial do not need to be reported as an SAE.

Severity of adverse event
The severity of the AE should be judged based on the following:
The severity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) <add version> in the (e)CRF.

Causal relationship of adverse event
Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship must be recorded for each adverse event.

Causality will be reported as either “Yes” or “No”.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.

No: There is no reasonable causal relationship between the investigational product administered and the AE.

Worsening of the underlying disease or other pre-existing conditions
Worsening of the underlying disease or of other pre-existing conditions will be recorded as an AE in the CRF.

Changes in vital signs, ECG, physical examination, and laboratory test results
Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an AE in the CRF , if they are judged clinically relevant by the investigator.

7.6.2 Adverse Events of Special Interests (AESI)

The following events are considered as protocol-specified events of special interests:

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 and according to Appendix C of this clinical trial protocol.

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.

7.6.3 SAE reporting to Boehringer Ingelheim (BI)

Upon inclusion into a trial, the patient's condition is assessed (e.g. documentation of history / concomitant diagnoses and diseases), and relevant changes from baseline are noted subsequently.

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through 30 days following cessation of treatment) will be collected, documented by the investigator.

The investigator shall report all SAEs and non-serious AEs which are relevant to a reported SAEs and AESIs by fax using BI IIS SAE form (Appendix D) 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 Ingelheim Pharmaceuticals, Inc
900 Ridgebury Road
Ridgefield, CT 06877
Fax: 1-203-837-4329

AND

NCCN at ORPReports@nccn.org or 215-358-7699

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship and expectedness with the investigational drug to all AEs as defined in the listed adverse event section of Boehringer Ingelheim's (BI's) Investigator Brochure for the Product.

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 considered relevant by the investigator.

7.7 Timeframe for Reporting Required Events

Adverse events will be tracked during study treatment and for 30 days following the last day of study treatment. For the purposes of this protocol, adverse events collected and documented on CRFs are grade 3, 4, or 5 adverse events.

8.0 PHARMACEUTICAL INFORMATION

8.1 Nintedanib (BIBF1120)

8.1.1 Nintedanib Description

Molecular formula: $C_{33}H_{39}N_5O_7S$
Molecular weight: 649.8

8.1.2 Clinical Pharmacology

Ten hours following the first intake of nintedanib, mean plasma levels of VEGF and bFGF showed a trend to increase in relation to the baseline level, which could be indicative of successful blockade of angiogenesis receptors.

8.1.3 Pharmacokinetics and Drug Metabolism

After oral administration, maximum plasma concentrations generally occurred between 2-4 hours after dose. Steady state was latest reached within one week of dosing. The pharmacokinetics of nintedanib can be considered time-independent.

Nintedanib is mainly metabolized by esterases.

The terminal half-life of nintedanib varied between 7 and 19 hours. The major route of elimination was via fecal/biliary excretion. The contribution of renal excretion to the total clearance was low. The overall recovery was considered complete within 4 days after single dosing.

8.1.4 Suppliers

Nintedanib will be provided by Boehringer Ingelheim.

8.1.5 Dosage Form and Preparation

Nintedanib is provided as soft gelatin capsules containing a suspension of milled active as the salt. It is available in two dose strengths corresponding to 100 mg and 150 mg.

8.1.6 Storage and Stability

Store below 30°C. Protect from exposure to high humidity.

8.1.7 Administration

Patients should take nintedanib approximately 12 hours apart at around the same time every day after food intake. Capsules should not be opened and should be swallowed unchewed with approximately 8oz of water.

9.0 CORRELATIVE STUDIES

9.1 Specific Hypothesis

The genomic landscape of cancer is complex and evolves through the process of clonal evolution innately and in response to treatment. Unbiased exome and transcriptome sequencing performed on tumor samples at time of diagnosis in responders and non-responders will help us identify unique variations that confer susceptibility to nintedanib. Moreover, genomic analysis at time of progression after treatment with nintedanib (after response (CR/PR/SD) lasting for 6 months or longer) will provide some unique insights into mechanisms underlying acquired resistance.

9.2 Tumor Biopsy Specimens for Research

9.2.1 Collection of Specimens

If archival tissue samples are available and/or a biopsy is obtained for clinical purposes at the time of disease progression, WUSM may request a tissue samplefor research sequencing, including whole exome and transcriptome sequencing. The specimens will be collected in accordance with standard of care practice and will be taken to the Washington University Tissue Procurement core for processing and storage per institutional practice.

10.0 STUDY CALENDAR

All visits have a window of +/- 3 days.

	Screening	Day 1 of Each Cycle	End of Every Cycle	End of Treatment
Informed consent	X			
H&P, ECOG PS	X	X		X
CBC[6]	X	X		X
CMP[7]	X	X		X
Coagulation panel[8]	X			
Urinalysis[9]	X			
Pregnancy test	X[1]			
CT scan – chest and abdomen with contrast	X		X	
Nintedanib		X[2]		
Fresh biopsy for research sequencing[3]				X[4]
Adverse events assessment	X	X ---------- X[5]		

1. Women of childbearing potential only; serum or urine
2. Taken twice a day every day of each 28-day cycle. Starting with cycle 64 cycles will last 12 weeks.
3. If a biopsy is obtained for clinical purposes at the time of disease progression, a sample may be collected for research purposes
4. To be monitored for 28 days after end of treatment
5. One follow-up visit at 28 days after end of treatment, then routine follow-up as per standard of care, with data collection regarding progression and survival to take place for the study
6. CBC with differential includes: WBCs, RBCs, Hemoglobin, Hematocrit, MCV, MCH, MCHC, RDW-CV, Platelets, MPV, Absolute Neutrophils, Lymphocytes, Monocytes, Eosinophils, and Basophils
7. CMP includes: Sodium, Potassium, Carbon Dioxide, BUN, Glucose, Creatinine, Calcium, Chloride, Albumin, AST, ALT, Alkaline Phosphatase, Bilirubin, Plasma Protein and Anion Gap
8. CoAg panel includes PT, PTT, and INR
9. Urinalysis includes: Color, Clarity, Specific Gravity, pH, Protein, Glucose, Ketones, Bilirubin, Blood, Urobilinogen, Nitrites and Leukocyte Esterase

11.0 DATA SUBMISSION SCHEDULE

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

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Tumor Biopsy Form	Prior to starting treatment
Treatment Form	End of every cycle
Toxicity Form	Continuous

Treatment Summary Form Tumor Biopsy Form	Completion of treatment
Tumor Measurement Form	Baseline, end of every even numbered cycles (after every cycle starting with cycle 64), and end of treatment
Follow-Up Form	As per routine care

Any queries generated by Washington University must be responded to within 28 days of receipt by the participating site. The Washington University research team will conduct a regular review of data status at all secondary sites, with appropriate corrective action to be requested as needed.

12.0 MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

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

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[32] Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.2 Disease Parameters

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

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

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

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

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

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

12.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice

thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

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

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

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

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

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published.[33-35] In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.[36]

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

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

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

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

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

12.4 Response Criteria

12.4.1 Evaluation of Target Lesions

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

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

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

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

12.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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

12.4.3 Evaluation of Best Overall Response

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

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

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

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

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

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

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

12.4.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded)

until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

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

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

12.4.5 Progression-Free Survival

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

12.4.6 Response Review

It is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion.

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, an independent Data and Safety Monitoring Committee (DSMC) will be specifically convened for this trial to review toxicity data at least every 6 months. A DSMC will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. Like investigators, DSMC members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMC will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMC must also be disclosed.

The DSM report will be prepared by the study statistician with assistance from the study team, will be reviewed by the DSMC, and will be submitted to the Quality Assurance and Safety Monitoring Committee (QASMC). This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study

- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities at all participating sites
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Further DSMC responsibilities are described in the DSMC charter.

Until such a time as the first secondary site activates this protocol, a semi-annual DSM report to be prepared by the study team will be submitted to the QASM Committee beginning 6 months after study activation at Washington University.

The study principal investigator and coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines (please refer to Section 7.0).

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMC at https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf

14.0 AUDITING

As coordinating center of this trial, Washington University (via the Quality Assurance and Safety Monitoring Committee (QASMC) will monitor each participating site to ensure that all protocol requirements are being met; that applicable federal regulations are being followed; and that best practices for patient safety and data collection are being followed per protocol. Participating sites will be asked to send copies of all audit materials, including source documentation. The audit notification will be sent to the Washington University Research Patient Coordinator, who will obtain the audit materials from the participating institution.

Notification of an upcoming audit will be sent to the research team one month ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review (up to 10 for each site) will be sent to the research team. However, if during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Items to be evaluated include:

- Subject screening and enrollment
- Reporting of adverse events
- Maintenance of HIPAA compliance
- Completeness of regulatory documentation
- Completeness of participant documentation
- Acquisition of informed consent
- IRB documentation
- Issues of protocol adherence

Additional details regarding the auditing policies and procedures can be found at https://siteman.wustl.edu/wp-content/uploads/2015/10/QASMC-Policies-and-Procedures-03.31.2015.pdf

15.0 STATISTICAL CONSIDERATIONS

15.1 Study Objectives and Endpoints

15.1.1 Primary Endpoint

Response rate (partial response plus complete response) after two cycles of therapy

15.1.2 Secondary Endpoints

- To evaluate progression free survival
- To correlate outcomes with specific mutations
- To further evaluate extreme responders with exome and transcriptome sequencing.
- To evaluate the mechanisms of secondary resistance

15.2 Study Design

This is an open label, single-arm pilot study to obtain preliminary information of the efficacy of single agent nintedanib. A total of 20 patients will be enrolled in this study. The sample size is determined primarily based on clinical feasibility rather than statistical power. However, the proposed sample size will provide us a reasonable precision to estimate the preliminary information. [37]If 4 responders are observed out of 20 patients, for example, we would have 80% confidence that the "true" rate would fall between 9% and 36%. If the

"true" response rate is 20% or higher, there would be 80% chance of observing at least 3 responders out of 20 patients. Conversely, there would be <10% chance to observe 3 or more responders if the true rate is less than 5%.

15.3 Data Analysis

As a pilot study for proof of principal, the data analysis will be descriptive in nature. Demographic and clinical characteristics of the sample, as well as response, toxicity by grade and loss to follow up will be summarized using descriptive statistics. Kaplan-Meier product limit estimator will be used to describe the distribution of progression free survival. The 95% confidence interval (CI) for RR and 6-month PFS will also be calculated.

15.4 Correlative Studies Analysis

The association between response and specific mutation status will be assessed by permutation analysis. Taking the relationship between *FGFR1* expression and RR as an example, for instance, we first compute the observed test statistics, e.g., the sample mean difference between responders versus non-responders. Then to simulate the null distribution of the test statistics, or the distribution of the observed mean differences if there were truly no difference, we repeat the following 10,000 times: we randomly shuffle the response status, and then calculate the sample difference between the newly designated groups. The permutation p-value equals the proportion of simulations from the null distribution that exceed the observed test statistics.

16.0 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Regulatory Coordinator (or designee) prior to IRB/IEC submission.

Site activation is defined as when the secondary site has received official written documentation from the coordinating center that the site has been approved to begin enrollment. At a minimum, each participating institution must have the following documents on file at Washington University prior to study activation:

- Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution's IRB. This documentation must show which version of the protocol was approved by the IRB.
- Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.
- Documentation of FWA, signed FDA Form 1572 (if applicable), and the CVs of all participating investigators.
- Protocol signature page signed and dated by the investigator at each participating site.

The coordinating center Principal Investigator (or designee) is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 4 weeks of obtaining Washington University IRB approval. Activated secondary sites are expected to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt unless otherwise noted. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

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APPENDIX A: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: PATIENT'S MEDICATION DIARY

Today's Date: _____ Agent: nintedanib Cycle: _____ Study ID#: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle. Take _____mg (___capsules) of nintedanib twice daily, approximately 12 hours apart, after a meal and with a glass of water. Swallow the capsules whole and do not chew them.
2. Record the date, the number of capsules taken, and when you took them.
3. If you forget to take a dose, then just take the next scheduled dose.
4. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
5. Please return the forms to your physician or your study coordinator when you go to your next appointment. Please bring your unused study medications and/or empty bottles with you to each clinic visit so that a pill count can be done.

Day	Date	AM Dose		PM Dose		Comments
		Time taken	# of capsules taken	Time taken	# of capsules taken	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
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APPENDIX C: Procedures for the follow-up of a potential DILI case (Hy's Law case) in IIS with nintedanib (BIBF 1120)

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.

Defintion

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 tumour 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 concomittant suppportive 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, tumormarker
     TSH*
   - Haematology
     Thrombocytes*, eosinophils*

     *If clinically indicated and in case that 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 D: SAE Reporting Form

Boehringer Ingelheim

INVESTIGATOR-INITIATED STUDY (IIS) SERIOUS ADVERSE EVENT REPORTING FORM

BI Trial No: 1199.219	Country: USA
Site No:	Patient No:

No. of pages, including this page:

To: Boehringer Ingelheim Pharmaceuticals [Address] Fax number : ***1-203-837-4329***	From: [site stamp]

Received at BI OPU or CRO **FOR BI USE ONLY** [Date or date stamp]	Received at BI Global Pharmacovigilance **FOR BI USE ONLY** [Date or date stamp]

Is this case being submitted as an expedited report to the Regulatory Authority? ☐ Yes ☐ No

BY SIGNING THIS FORM, YOU ARE CONFIRMING THAT THE INFORMATION CONTAINED HEREIN IS ACCURATE.

Record all dates in dd mmm yyyy format.

Type of report	Date	Investigator's signature	Remarks
☐ Initial	___ ___ ___		
☐ Follow-up	___ ___ ___		
☐ Follow-up	___ ___ ___		
☐ Follow-up	___ ___ ___		
☐ Follow-up	___ ___ ___		
☐ Follow-up	___ ___ ___		
☐ Follow-up	___ ___ ___		

PATIENT DEMOGRAPHICS

At the onset of the SAE

Date of birth: ___ ___ ___ Height _____ (cm) *If unknown, record 'UNK'* Weight _____ (kg)

Sex: ☐ Male ☐ Female Pregnant: ☐ No ☐ Yes, weeks ____

Race: ☐ Asian ☐ Black ☐ White ☐ Other

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IIS_SAE form_*1199.219_18Mar2015_locked*

Boehringer Ingelheim

INVESTIGATOR-INITIATED STUDY (IIS) SERIOUS ADVERSE EVENT REPORTING FORM

BI Trial No: 1199.219	Country: USA
Site No:	Patient No:

EVENT INFORMATION

Record all dates in dd mmm yyyy format. If ongoing, enter 'CONT.' Record all times in 24-hour (hh:mm) format. If time is unknown, record 'UNK.'

		Event No. [ ]	Event No. [ ]	Event No. [ ]
If possible, enter diagnosis.				
Onset date				
Onset time				
End date				
End time				
Event occurred during the following trial phase: (*select all that apply; more than one option possible if event continued*)				
Pre-treatment (no study medication administered)		☐	☐	☐
Run-in phase (study medication administered)		☐	☐	☐
Wash-out between treatments		☐	☐	☐
Randomisation/treatment during observation phase		☐	☐	☐
Post-treatment (after protocol-defined observation phase)		☐	☐	☐
Was the event listed?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Is this an adverse event of special interest?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Was the event serious?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
If yes, mark reason for seriousness.	Results in death	☐	☐	☐
	Immediately life-threatening	☐	☐	☐
	Persistent or significant disability/incapacity	☐	☐	☐
	Requires patient hospitalisation	☐	☐	☐
	Prolongs patient hospitalisation	☐	☐	☐
	Congenital anomaly/birth defect	☐	☐	☐
	Other comparable medical criteria (*specify in Description of Event section*)	☐	☐	☐
Was therapy for the event administered?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
If yes, specify therapy in Description of Event section.				
Was a dechallenge performed?		☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A
If yes, did the event diminish after the study medication was stopped or the dose was reduced?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Was a rechallenge performed?		☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A
If yes, did the event reappear after reintroduction?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Is there a reasonable causal relationship that the SAE is related to: (*provide description of rationale on page 3*)				
Study medication		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Study design		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
If no to either question, specify other possible cause.				
Outcome of event (*check only one*)				
Recovered		☐	☐	☐
Not yet recovered		☐	☐	☐
Sequelae		☐	☐	☐
Unknown		☐	☐	☐
Fatal (*do not record protocol-specific fatal outcome events that are not reportable*)		☐	☐	☐
If fatal, was this event the primary cause of death?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
If patient died, record date of death:				
Was an autopsy performed? ☐ No ☐ Yes				

☐ Check if more events on additional page

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IIS_SAE form_*1199.219_18Mar2015_locked*

Boehringer Ingelheim

INVESTIGATOR-INITIATED STUDY (IIS) SERIOUS ADVERSE EVENT REPORTING FORM

BI Trial No: 1199.219	Country: USA
Site No:	Patient No:

RATIONALE FOR CAUSALITY ASSESSMENT

State your rationale for the causal relationship between the event and the study medication. Include medical judgement considering all relevant factors, including pattern of reaction, temporal relationship, positive dechallenge or re-challenge, confounding factors such as co-medication, co-diseases and relevant history. Limit: 20 lines

DESCRIPTION OF THE EVENT(S)

Please use this page to give any additional information about the case, including symptoms, alternative explanations (e.g. underlying disease, laboratory values), any other treatment for event, including protocol-specified rescue medication, and other relevant information. Limit: 20 lines

☐ Check if there is additional information.

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Boehringer Ingelheim

INVESTIGATOR-INITIATED STUDY (IIS) SERIOUS ADVERSE EVENT REPORTING FORM

BI Trial No: 1199.219	Country: USA
Site No:	Patient No:

BASELINE CONDITIONS INCLUDING PAST MEDICAL HISTORY

Record all dates in dd mmm yyyy format.

☐ None ☐ Yes (*specify below*)	If concomitant, provide onset date	If started and ended in the past, check box only; do not enter date
1.		☐
2.		☐
3.		☐
4.		☐
5.		☐
6.		☐
7.		☐
8.		☐
9.		☐
10.		☐

STUDY MEDICATION

Indication: _____

Was treatment code broken due to any of the events? ☐ No ☐ Yes ☐ N/A *If yes, specify date:*

		Study Medication 1	Study Medication 2	Study Medication 3
Name of study medication				
Formulation (*e.g. tablet, capsule, injection*)				
Strength				
Total daily dose at onset of event (*dose, unit*)				
Route (*e.g. oral, IV, IM*)				
Onset date				
Onset time				
End date				
End time				
Was the administration of study medication correct?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
If no, check all applicable boxes:		☐ Misuse / Abuse ☐ Overdose ☐ Other: _____	☐ Misuse / Abuse ☐ Overdose ☐ Other: _____	☐ Misuse / Abuse ☐ Overdose ☐ Other: _____
Action taken with study medication at the time of the event (*check one*)	Dose not changed	☐	☐	☐
	Dose reduced	☐	☐	☐
	Study medication discontinued	☐	☐	☐
	Dose increased	☐	☐	☐
	Not applicable	☐	☐	☐

☐ Check if more baseline conditions or study medications on additional page

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INVESTIGATOR-INITIATED STUDY (IIS) SERIOUS ADVERSE EVENT REPORTING FORM

BI Trial No: 1199.219	Country: USA
Site No:	Patient No:

RELEVANT PAST AND CONCOMITANT THERAPY, INCLUDING PROTOCOL-SPECIFIED NON-INVESTIGATIONAL MEDICINAL PRODUCTS (NIMPS), E.G. BACKGROUND AND / OR RESCUE MEDICATIONS

*If drug, preferably use trade name. Do **not** include medications used **solely** to treat the adverse event(s).*
Record all dates in dd mmm yyyy format. If ongoing, enter 'CONT.'

☐ None ☐ Yes (*specify below*)	Indication	Past	Start/end dates	Total daily dose at onset of event (*dose/ unit*)	Route	Is there a reasonable causal relationship between the event and the past or concomitant therapy? **If Yes, record event number.**
1.		☐	Start: End:			☐ No ☐ Yes Event # __
2.		☐	Start: End:			☐ No ☐ Yes Event # __
3.		☐	Start: End:			☐ No ☐ Yes Event # __
4.		☐	Start: End:			☐ No ☐ Yes Event # __
5.		☐	Start: End:			☐ No ☐ Yes Event # __
6.		☐	Start: End:			☐ No ☐ Yes Event # __
7.		☐	Start: End:			☐ No ☐ Yes Event # __
8.		☐	Start: End:			☐ No ☐ Yes Event # __
9.		☐	Start: End:			☐ No ☐ Yes Event # __
10.		☐	Start: End:			☐ No ☐ Yes Event # __

☐ Check if more concomitant medications on additional page