TITLE: A Phase I/ II Study of Nintedanib and Capecitabine in Refractory Metastatic Colorectal Cancer

Roswell Park Cancer Institute

Study Number: **I 265514**

Initial Date: **07 November 2014**

Amendment #1: **03.23.15**

Amendment #2: **04.17.15**

Amendment #3: **01.29.16**

Amendment #4: **02.16.16**

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Sponsor: **Roswell Park Cancer Institute**

Funding: **NCCN**

Industry/Other Supporter: **Boehringer Ingelheim**

Confidentiality Statement

List of Abbreviations

5-HT3	5-Hydroxy-Tryptamin receptor 3
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
bFGR	basic Fibroblast Growth Factor
BIBF 1120	Nintedanib
BIBF 1202	metabolite of nintedanib
BID	twice daily
C_{max}	maximum measured concentration of the analyte in plasma
CAF	Circulating Angiogenic Factor/Cytokine
CEA	Carcinoembryonic Antigen
CRF/eCRF	Case Report Form / electronic Case Report Form
CSF-1R	Colony Stimulating Factor 1 Receptor
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
ECG	Electro Cardio Gram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic Acid
ELISA	Enzyme-Linked Immunosorbent Assay
FGF	Fibroblast Growth Factor

FGFR	Fibroblast Growth Factor Receptor
Flt-1	synonym for vascular endothelial growth factor receptor 1
Flt-3	synonym for vascular endothelial growth factor receptor 3
Flt-4	synonym for vascular endothelial growth factor receptor 4
GGT	Gamma Glutamyl Transpeptidase
GI	Gastrointestinal
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
HDPE	High Density Polyethylene
IL	Interleukin
INR	International Normalized Ratio
KIT	Gene that encodes for a protein that is a type 3 transmembrane receptor for MGF (mast cell growth factor, also known as stem cell factor)
Lck	Lymphocyte-specific protein-tyrosine kinase, member of the Src family of kinases
LDH	Lactate Dehydrogenase
Lyn	Yamaguchi sarcoma viral (v-yes-1) oncogene homolog, cellular protein tyrosine kinase member of the Src family of kinases
mFOLFOX-6	An abbreviation for a combination chemotherapy regimen that is used to treat colorectal cancer
mg	milligram
min	minute
ml/mL	Milliliter
mm	millimeter
MRI	Magnetic Resonance Imaging
NSCLC	Non-Small Cell Lung Cancer

OS	Overall Survival
PD	Progressive Disease
PDGF	Platelet Derived Growth Factor
PDGFR	Platelet Derived Growth Factor Receptor
PFS	Progression Free Survival
P1GF	Placenta derived growth factor: an angiogenic factor involved in tumor neovascularization
PK	Pharmacokinetic(s)
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RECIST	Response Evaluation Criteria in Solid Tumors
RET	Gene that encodes for a tyrosine kinase transmembrane receptor
RP2D	Recommended Phase II Dose
RTKI	Receptor Tyrosine Kinase Inhibitor
SAE	Serious Adverse Event
SD	Stable Disease
SRC	Src tyrosine kinase
TKI	Tyrosine Kinase Inhibitor
TSH	Thyroid Stimulating Hormone
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

SYNOPSIS

Title / Phase	A Phase I/ II Study of Nintedanib and Capecitabine in Refractory Metastatic Colorectal Cancer
Roswell Park Cancer Institute Study Number	I 265514
Roswell Park Cancer Institute Investigator	Patrick M. Boland, MD
Sponsor	Roswell Park Cancer Institute
Funding Organization	NCCN
Industry Support	Boehringer Ingelheim
Study Drug(s)	Nintedanib Provided by Boehringer Ingelheim) Capecitabine
Objectives	**Primary:** • Phase I: To estimate the maximum tolerated dose (MTD) and examine the dose-limiting toxicities of nintedanib when administered with capecitabine within the study population and, establish the Recommended Phase II Dose (RP2D).. • Phase II: To assess progression free survival at 18 weeks. This will be assessed via the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines after every 3 cycles (9 weeks) of therapy. **Secondary (**phase II**):** • To assess median progression free survival (at 18 weeks). This will be assessed via the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines [after every 3 cycles (9 weeks) of therapy]. • To assess median overall survival from the date of enrollment to the time of death will be documented. • To assess the objective response rate as measured by RECIST v 1.1. • To assess the toxicity of dose regimen using the CTEP NCI Common Terminology Criteria for Adverse Events (CTCAE Version 4.0). **Tertiary:** • Measurement of circulating angiogenic cytokines (CAFs): VEGF, sVEGFR 1/2, PlGF, GMCSF, Leptin, IL-1a, IL-8, IL-6, FGFb, Osteopontin, and Pentraxin-3. • Measurement of drug levels and PK/PD modeling
Study Design	Multicenter phase I/II study of nintedanib and capecitabine in refractory metastatic colorectal cancer

Target Accrual and Study Duration	Between 9 and 18 patients will be treated in the phase I portion of this study. Phase I patients (n=6) treated at the recommended phase II dose will be included in the phase II portion of the study. Up to an additional 30 patients will be recruited to the phase II study, for a phase II sample size of 36. The study is expected to accrue 9 patients to the phase I portion for a total sample size of 39 patients (9 + 36 - 6). If 18 patients were necessary for enrollment to the Phase I study, a maximum of 48 patients might be required (18+36-6). Accrual is expected to take up to 2 years, with patients remaining on study for 18 weeks.
Study Procedures	**Physical Examination (including vital signs, and body weight):** Baseline, Day 1 of all Cycles, Cycle 1-Day 8and Cycle 2-Day 8 (physical exam for phase I only), End of Treatment **Medical History:** Baseline **Hematology:** Baseline, Day 1 of all Cycles, End of Treatment **Chemistry:** Baseline, Day 1 of all Cycles, Cycle 1-Day 8and Cycle 2-Day 8 (Day 8 chemistry for phase I only), End of Treatment **PT/INR, PTT:** Baseline **Urine Sample for UPCR:** Baseline **CEA:** Cycle 1-Day 1, Cycle 4-Day 1, every 3 cycles from Cycle 4 onward. **PK/PD Sampling:** Cycle 1-Day 1, Day 2 and Day 15 **Biomarker (CAF) Sampling;** Cycle 1-Day 1 and Day 15, Cycle 3 -Day 1 **Pregnancy Test (serum):** Baseline **ECOG Performance Status:** Baseline, Day 1 of all cycles **CT Scan (chest, abdomen, pelvis):** Baseline, every 9 weeks after cycle 1-day 1 (± 7 days) **Concomitant Medications:** Baseline, Day 1 of all Cycles, Cycle 1-Day 8and Cycle 2-Day 8 (for phase 1 only), End of Treatment **Adverse Events:** Day 1 of all Cycles, Cycle 1-Day 8and Cycle 2-Day 8 (for phase 1 only), End of Treatment.

Statistical Analysis	**Sample Size Determination:** Sample size determination for the phase I portion will depend upon the dose-toxicity profile, but is expected to be between 9-18 patients. For the phase II portion, with an alpha of 0.1, assessment of 36 patients allows for a power of 0.8 to detect a minimum difference of 17% in the PFS at 18 weeks, assuming a rate of 25% under standard of care. **Randomization:** No randomization is required. **Efficacy Analysis:** Primary interest is in the PFS at 18 weeks after enrollment. The PFS at 18 weeks will be described by binomial proportion estimates and 90% confidence intervals. All patients in the phase II study and those treated at the RP2D in the phase I study will be included for analysis. **Safety Analysis:** Adverse events will be tabulated. AE rates will be described using binomial proportions and 90% confidence intervals. **Correlative Data Analysis:** Mechanistic PK/PD modeling will be employed**,** examining the relationship between nintedanib pharmacokinetics, modulation of CAFs and PFS.

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INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM

Participant Name: _____

Medical Record No.: _____

Title: A Phase I/ II Study of Nintedanib and Capecitabine in Refractory Metastatic Colorectal Cancer

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Age ≥ 18 years of age.	
☐	☐	☐	2. Have an ECOG Performance Status of 0 – 1. Refer to **Appendix B**.	
☐	☐	☐	3. Have the following clinical laboratory values: • Hemoglobin ≥ 9 g/ dL • Absolute neutrophil count ≥ 1500/ mm^3 • Platelet count ≥ 100,000/ mm^3 • Creatinine ≤ 1.5 x ULN AND CrCl > 50 mL/min by Cockcroft and Gault equation o Males = (140 – age [yrs])(Body weight [kg])/(72)(serum creatinine [mg/dL]) o Females = 0.85 * (140 – age [yrs])(Body weight [kg])/(72)(serum creatinine [mg/dL]) • Bilirubin ≤ ULN • AST / ALT ≤ 1.5 ULN if without liver metastases • AST/ ALT ≤ 2.5 x ULN if with liver metastases • Coagulation parameters: International normalized ratio (INR) ≤ 2, prothrombin time (PT) and partial thromboplastin time (PTT) < 1.5 X institutional ULN, unless the abnormality is related to anticoagulant.	
☐	☐	☐	4. Have measurable disease per RECIST 1.1 criteria.	
☐	☐	☐	5. Histologically or cytologically proven adenocarcinoma of the colon or rectum.	
☐	☐	☐	6. Prior progression following a fluoropyrimidine-based therapy and progression following or intolerance to irinotecan and oxaliplatin, as well as anti-EGFR therapy (e.g., panitumumab or cetuximab) for RAS wild-type patients.	

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	7. Ability to swallow and retain oral medication.	
☐	☐	☐	8. Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry and for three months following completion of therapy. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.	
☐	☐	☐	9. Participant or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	

Investigator Signature: _____ Date: _____

ROSWELL PARK CANCER INSTITUTE

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM

Participant Name: _____

Medical Record No.: _____

Title: A Phase I/ II Study of Nintedanib and Capecitabine in Refractory Metastatic Colorectal Cancer

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Prior treatment with nintedanib.	
☐	☐	☐	2. Prior treatment with regorafenib.	
☐	☐	☐	3. Major injuries or surgery within the 4 weeks prior to initiation of therapy with incomplete wound healing or planned surgery during the on-study treatment period.	
☐	☐	☐	4. Uncontrolled hypertension: systolic blood pressure ≥ 160, diastolic blood pressure ≥ 90.	
☐	☐	☐	5. Urine Protein/creatinine ratio ≥ 1.0 Refer to **Appendix E**.	
☐	☐	☐	6. History of clinically significant hemorrhagic or thrombotic event within the past 6 months, not including uncomplicated catheter-associated venous thrombosis. Patients on anti-coagulation are not permitted to be on any oral formulations of anticoagulation (warfarin, rivaroxaban, dabigatran, etc.) due to concern for drug-drug interaction.	
☐	☐	☐	7. Unstable angina, symptomatic congestive heart failure or cardiac arrhythmia requiring anti-arrhythmic therapy (Beta-blockers, calcium channel blockers and digoxin are allowed).	
☐	☐	☐	8. History of cerebrovascular or myocardial ischemia within 6 months of initiation	
☐	☐	☐	9. Known inherited predisposition to bleeding or thrombosis	
☐	☐	☐	10. Known active or chronic hepatitis B or C, or HIV	
☐	☐	☐	11. Untreated brain metastases.	
☐	☐	☐	12. History of second primary malignancy diagnosed within 3 years prior to enrollment, excluding: a. *In-situ* cervical carcinoma b. Superficial bladder cancer c. Non-melanoma skin cancer d. Stage I breast cancer	

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
			e. Low grade (Gleason ≤ 6) localized prostate cancer f. Any additional malignancy which has been in clinical remission for at least 1 year.	
☐	☐	☐	13. Pregnant or nursing female participants.	
☐	☐	☐	14. Unwilling or unable to follow protocol requirements.	
☐	☐	☐	15. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.	
☐	☐	☐	16. Received an investigational agent within 4 weeks prior to enrollment	
☐	☐	☐	17. **Phase I:** History of intolerance to capecitabine at doses ≤ 1000 mg/m^2 BID, as defined by documented ≥ grade 3 hand-foot syndrome, documented severe diarrhea requiring hospitalization, or other documented severe AEs attributable to capecitabine	
☐	☐	☐	18. **Phase II:** History of intolerance to capecitabine at doses below 1000 mg/m^2 BID, as defined by documented ≥ grade 3 hand-foot syndrome; documented severe diarrhea requiring hospitalization; or other documented severe AEs attributable to capecitabine.	

Participant meets all entry criteria: ☐ **Yes** ☐ **No**
If "NO", do not enroll participant in study.

Investigator Signature: _____ Date: _____

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IN-TEXT TABLES

APPENDICES

1 BACKGROUND

1.1 Colorectal Cancer

It is estimated that almost 140,000 new colorectal cancers will be diagnosed in 2014. Despite advances in early detection, surgical technique, and adjuvant treatment, colorectal cancer remains the 2rd most common cause of cancer-related death in the United States with >50,000 attributable mortalities annually(1). In the metastatic setting, improvements in systemic therapy have improved the median survival of patients from less than six months to nearly 30 months. Bevacizumab, a monoclonal antibody targeting VEGF-A, has become routinely integrated into treatment regimens in combination with chemotherapy, demonstrating a survival benefit when utilized in the first or second line setting (2, 3). More recently, the data from the TML18147 trial demonstrated a modest survival benefit of 1.4 months when bevacizumab was continued through lines of therapy, specifically when administered with second-line chemotherapy after utilization in the first-line setting (4). Interestingly, nearly identical survival advantages (approximately 1.4 months) emerged with utilization of the VEGF-TRAP (aflibercept) with second-line chemotherapy, as well as with the multi-targeted small molecule tyrosine kinase inhibitor (TKI), regorafenib, as a single agent in the refractory setting(5, 6). The precise mechanism by which regorafenib confers benefit remains unclear, though there is speculation that inhibition of pro-angiogenic signaling is the major driver. To some, these data have suggested that angiogenic blockade should be continued throughout therapy.

1.2 Angiogenesis

Angiogenesis is involved in tumour growth and development of metastases. Vascular Endothelial Growth Factor (VEGF) and its high affinity receptor VEGFR-2 are crucial for the formation of new tumour vessels. In addition, there is preclinical evidence that fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) and their associated receptor tyrosine kinases substantially contribute to tumour angiogenesis. The VEGF - VEGFR-2 axis, besides promoting angiogenesis, may also be involved in stimulating growth of tumour cells themselves via an autocrine growth factor loop. This is suggested by in vitro data and immunohistochemical studies, e.g. for non-small cell lung cancer, ovarian carcinoma, gastric carcinoma, and malignant mesothelioma. Therefore, suppression of neoangiogenesis via inhibition of VEGFR-2 is a promising strategy for the treatment of human solid cancers. A substantial number of clinical trials with various inhibitors of VEGF or VEGFRs in various types of malignant tumors demonstrated this approach can convey clinical benefit, in particular in combination therapy with standard chemotherapeutic drugs.

1.3 Treatment for Metastatic Colorectal Cancer

Bevacizumab and other VEGF targeting agents have been explored in the refractory colorectal cancer setting to a lesser extent than traditional cytotoxic drugs, predominantly in small phase I and phase II studies. By traditional response criteria, very limited activity has been noted, though a sub-set of patients appear to achieve prolonged stable disease; this may reflect selection bias for patients with more indolent disease or perhaps, a group of colorectal cancer patients with tumors persistently dependent upon pro-angiogenic signaling. The NCI TRC-0301 study

evaluated 5-FU and bevacizumab in patients who were refractory to irinotecan and oxaliplatin-based therapies. Independent review demonstrated a response rate of only 1%, with a median PFS of 3.5 months and OS of 9 months [7]. A slightly smaller study utilizing bevacizumab and infusional 5-FU in 48 patients with refractory disease showed nearly identical results: a response rate of 6.5%, median PFS of 3.5 months and median OS of 7.7 months [8]. A third study which evaluated the duo of capecitabine and sunitinib, a small molecule TKI of VEGF, KIT, RET, CSF-1R, and FLT3, replicated these results - 47% of patients achieved stable disease, with a median PFS of 137 days (~4.6 months) and a median OS of 291 days (9.7 months), though increased toxicity, namely fatigue and hand-foot syndrome, was demonstrated[9].

Trials of monotherapy with anti-angiogenic agents have seemingly conferred slightly shorter progression free survival advantages. In the refractory setting, aflibercept and sunitinib have separately demonstrated a median PFS of 2-2.4 and 2.2-2.5 months with a median OS of 8.5-10.4 and 7.1 – 10.2 months, respectively [10].These numbers are very similar to that achieved by use of regorafenib, comparing favorably refractory trials where best-supportive care has supported a progression-free survival of less than 2 months and an overall survival of just 4.5-5 months[6, 11]. The lack of improvement by metrics such as objective response has resulted in a general reluctance to pursue randomized trials to more definitively evaluate the benefit of continued anti-angiogenic therapies in the refractory setting. While regorafenib has recently been approved in the chemotherapy refractory setting, the perception of marked toxicity and provision of modest clinical benefit has significantly dampened the initial enthusiasm. Additional regimens which provide clinical benefit with improved tolerability are desperately needed.

1.4 Nintedanib (BIBF1120)

Nintedanib (BIBF 1120) is a small molecule TKI of VEGFR 1/2/3 (IC_{50} 34/21/13 nM), FGFR 1/2/3 (IC_{50} 69/37/109 nM), and PDGFR A/B (IC_{50} 59/65 nM), with additional activity against Flt-3, RET, Src, Lck, and Lyn. In preclinical colorectal cancer models, anti-tumor efficacy has been demonstrated, with a marked reduction in tumor vessel density. Maximum plasma concentrations occur 2-4 hours following administration with a terminal half-life of 7-19 hours. Based upon phase I data, the recommended phase II dose is 200 mg orally twice daily, as a single agent as well as in combination with chemotherapy. When administered as monotherapy, the most common side effects are nausea, diarrhea, vomiting, abdominal pain and fatigue. Liver enzyme increases were the most common DLT in early phase trials and a common AE in later stage studies, though predominantly seen at higher doses (> 200 mg bid) and largely reversible with cessation of therapy.

1.5 Preclinical Development and Pharmacokinetics of Nintedanib

Nintedanib (BIBF 1120) is an oral small molecule triple receptor tyrosine kinase inhibitor that potently blocks VEGFR 1-3 (vascular endothelial growth factor-receptor), FGFR 1 and 3 (fibroblast growth factor/receptor), as well as PDGFR α/β (platelet derived growth factor receptor) in low nanomolar concentrations (**Table 1**). These receptors are expressed on perivascular cells, such as pericytes and smooth muscle cells, that are also involved in tumour angiogenesis and therefore their inhibition may contribute to the overall efficacy of nintedanib. In addition, Nintedanib also inhibits the kinase activity of Flt-3, one of the most frequently

mutated genes in acute myeloid leukemia (AML) and Ret. More than 20 other kinases were also analyzed and showed no inhibition by the compound (e.g. insulin receptor, HER2, and several cyclin dependent kinases) with the exception of the three members of the Src family of tyrosine kinases: Src, Lck, and Lyn (**Table 1**). Src is one of the most intensively studied oncogenes and is functionally involved in the control of a variety of cellular processes such as proliferation, differentiation, motility, and adhesion. c-Src has been shown to be involved in the development and progression of human tumors [(12)]. Lck is functionally required for T-cell activation through the T-cell antigen receptor (TCR) [(13)] and possibly T-cell survival [(14)]. Lyn is involved in B-cell antigen receptor (BCR) signalling both positively and negatively, i.e. in the initiation of the BCR signal and in B cell proliferation.

Table 1 Potency [IC50, nM] of Nintedanib in *in vitro* Kinase Assays

Kinase	IC_{50} (nmol/L)
huVEGFR-1	34
huVEGFR-2	21
muVEGFR-2	13
PDGFRα	59
PDGFRβ)	65
FGFR 1	69
FGFR2	37
FGFR3	108
Flt-3	26
RET	35
Src	156
Lck	16
Lyn	195

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 (basic fibroblast growth factor) 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).

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 tumors showed a marked reduction of tumour vessel density by approximately 80% [15].

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. The metabolic characteristics are predominantly independent of cytochrome P450-catalysed metabolic pathways [16].

A soft gelatin capsule formulation of nintedanib is used in man. After oral administration, nintedanib is absorbed quickly. Maximum plasma concentrations (Cmax) generally occur 2 to 4 hours after administration. So far, no evidence for a deviation from dose proportionality of the PK of nintedanib has been observed. Steady state is reached latest after one week of dosing. The terminal half-life of nintedanib is in the range of 7 to 19 hr. Nintedanib is mainly eliminated via faeces [16].

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.

A detailed discussion of the preclinical pharmacology, pharmacokinetics, and toxicology of nintedanib (BIBF1102) can be found in the Investigator's Brochure.

1.6 Clinical Development of Nintedanib

Nintedanib is being evaluated in several cancers. Additionally, nintedanib has been FDA approved 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.

1.6.1 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 stabilization of their tumour of 54% and 68%, respectively; have been observed in patients with various solid tumors [17].

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 200 mg 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, GGT) 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 [16].

1.6.2 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 stabilization was achieved in 46% of patients (ECOG 0–1 patients: 59%), with one confirmed partial response (250 mg bid.)[18].

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 200 mg 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) [19].

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

Based on a preplanned futility analysis of investigator-assessed PFS, 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 [20].

1.6.3 Ovarian Cancer

A randomized phase II maintenance trial in ovarian cancer in which the efficacy and safety of nine months of continuous twice daily doses of nintedanib (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 [21].

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 [22].

1.6.4 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 [23].

1.6.5 Hepatocellular Cancer

The efficacy and safety of nintedanib versus sorafenib in Asian Patients with Advanced Hepatocellular Carcinoma was investigated in a randomized phase II trial. Nintedanib showed similar efficacy to sorafenib, with a favorable and manageable AE profile. More patients in the sorafenib arm had severe AEs and drug-related AEs compared with patients in the nintedanib arm, and more patients in the sorafenib arm required dose reduction compared with the nintedanib arm. Nintedanib AEs were manageable; in the nintedanib arm there were fewer hypertension, palmar-plantar erythrodysesthesia syndrome, and transaminase elevation events [24].

1.6.6 Colorectal Cancer

A Phase I/II, open-label, randomized 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, 200 mg po bid, in combination with mFOLFOX6. In comparison to bevacizumab, nintedanib showed a similar magnitude of efficacy, a similar safety/tolerability profile, a similar exposure and dose intensity of mFOLFOX6 [25]. This is in contrast to multiple prior trials of small molecule inhibitors of VEGFR-2 with demonstrated increased toxicity and, as a result, decreased efficacy [26].

A Phase III study is going to start in late 2014 to evaluate the efficacy of nintedanib as compared to placebo in patients with metastatic colorectal cancer (mCRC) after failure of previous treatment with standard chemotherapy and biological agents (ClinicalTrials.gov Identifier: NCT02149108). Data from this phase III study of single agent nintedanib in the refractory setting will be instructive as to the single agent activity of nintedanib in refractory colorectal cancer.

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

1.7 Correlative Studies

Rationale/justification: A significant challenge in the development and clinical use of VEGF pathway inhibitors is the lack of reliable biomarkers that can predict for biological activity, patient response and benefit, and toxicity[27]. However, results from several prospective and retrospective trials analyzing patient blood following the treatment of VEGF RTKIs suggest that consistent changes in the levels of circulating proteins following treatment may be tailored to a particular drug, and have the potential as a surrogate biomarker in guiding both dosing and patient outcome[28-30]. This study will evaluate several circulating angiogenic factors (CAFs) in patient plasma using ELISA methods. CAFs will include VEGF, sVEGFR 1/2, PlGF, GMCSF, Leptin, IL-1a, IL-8, IL-6, FGFb, Osteopontin, Pentraxin-3, which have been chosen because of previous studies demonstrating i) plasma changes which may correlate to patient response, ii) the potential involvement in resistance or compensatory pathways following VEGF pathway inhibition, and iii) the potential for disruption based on FGF pathway inhibition (including with Nintedanib) [31-34].

1.8 Risks and/or Benefits

1.8.1 Nintedanib (BIBF1120)

The risks of therapy with nintedanib (BIBF1120) in adult patients are primarily related to:

- the gastro-intestinal tract (nausea, vomiting, diarrhoea, abdominal pain)
- increases in liver enzymes (AST, ALT, GGT)
- 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.

1.8.2 Capecitabine

Common side effects associated with the use of capecitabine include:

- diarrhea, stomatitis, hand foot syndrome, fatigue, lymphopenia, neutropenia, anemia, thrombocytopenia, alopecia, erythema, and rash
- hepatic insufficiency with hyperbilirubinemia has been observed
- dizziness, headaches, fatigue, anorexia, conjunctivitis, and epistaxis have also been observed
- Cardiovascular side effects have included myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy.

The major clinical side effects observed after therapy with capecitabine are distinct from nintedanib (BIBF1120) induced adverse events, yet some overlap may occur e.g. gastrointestinal toxicity or hepatotoxicity (please refer to the labels included in the investigator site file for listed adverse events of capecitabine). In view of the low potential for drug-drug interactions of nintedanib (BIBF1120), it is not likely that enhanced toxicity due to pharmacokinetic interaction between the drug and the cytotoxic chemotherapy will occur. However, due to the partially overlapping toxicity profile, the occurrence of nausea, vomiting and diarrhoea may be increased.

2 RATIONALE

Fluoropyrimidines, such as 5-FU and capecitabine, remain among the most active chemotherapeutics in colorectal cancer and are administered across lines of therapy, as is the case with anti-angiogenics, such as bevacizumab. In colorectal cancer, as in other malignancies, anti-angiogenic therapy is most commonly administered with chemotherapy due to additive benefit. As described previously, there is data to suggest activity, as measured by maintenance of stable disease, when 5-fu or capecitabine is combined with anti-angiogenic therapy, even after progression on prior fluoropyrimidine containing regimens. Further, on the whole, the PFS and OS results from trials in the refractory setting which combine the two therapeutic classes appear

superior to the results from administration of anti-angiogenic therapy alone. Though caution must be exercised in such cross-trial comparisons, as differences in the populations studied have great potential for bias, one might hypothesize that combining capecitabine with nintedanib has potential to offer greater benefit than nintedanib alone, in multiple settings.

Capecitabine is most frequently administered in a three week cycle, as a single agent or in combination with other chemotherapeutics. It is dosed twice daily for two weeks, followed by a 1 week rest. In the treatment of colorectal cancer, capecitabine has demonstrated equivalent activity to 5-FU in both the adjuvant and metastatic settings [35, 36]. When capecitabine and infusional 5-FU are combined with additional agents, capecitabine demonstrates a comparatively greater incidence of hand-foot syndrome as well as slightly higher incidence of diarrhea, but lesser rates of stomatitis and cytopenia [37]. In a US population, the approved dose of 1250 mg/m^2 BID is regarded as causing excess toxicity and 1000 mg/m^2 is most commonly employed. In this study, we plan to combine nintedanib with capecitabine at the standard 1000 mg/m^2 dose. Nintedanib will be administered at a dose 25% below the recommended Phase II dose due to concern for overlapping toxicity, namely diarrhea. This would represent a novel combinatorial oral chemotherapeutic regimen.

The primary objective will be to assess anti-tumor activity of nintedanib and capecitabine when given in combination. Secondary objectives will include assessment of the toxicity of the agents in combination, identification of biomarkers predictive of benefit, along with a development of a novel PK/PD biomarker driven approach to elucidate the optimal dosing regimen of nintedanib and capecitabine.

The combination of nintedanib and capecitabine would be relevant for treatment in the refractory setting and potentially in future investigations as maintenance therapy after initial bevacizumab-based chemotherapy. All patients in this study are expected to have received prior anti-angiogenic therapy with progression or intolerance. To date, there is no data on the efficacy of nintedanib in patients who have progressed on prior anti-angiogenic therapies. A placebo controlled study of nintedanib in the refractory setting is being conducted, as described (ClinicalTrials.gov Identifier: NCT02149108). If the placebo controlled study demonstrates a clinical benefit, this current combination may be able to build upon those findings, if this combination demonstrates tolerability. Should the placebo controlled study fail to demonstrate benefit, this regimen may yet create an avenue for further investigation via potentiation of nintedanib monotherapy, as previously suggested.

3 OBJECTIVES

3.1 Phase 1

3.1.1 Primary Objective

- To estimate the maximum tolerated dose (MTD) and examine the dose-limiting toxicities of nintedanib when administered with capecitabine within the study population and, establish the Recommended Phase II Dose (RP2D).

3.2 Phase II

3.2.1 Primary Objective

- To assess progression free survival at 18 weeks. This will be assessed via the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines after every 3 cycles (9 weeks) of therapy.

3.2.2 Secondary Objectives

- To assess median progression free survival. This will be assessed via the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines after every 3 cycles (9 weeks) of therapy].
- To assess median overall survival from the date of enrollment to the time of death will be documented.
- To assess the objective response rate as measured by RECIST v 1.1.
- To assess the toxicity of dose regimen using the CTEP NCI Common Terminology Criteria for Adverse Events (CTCAE Version 4.0).

3.3 Tertiary Objectives of phase 1 and 2

- Measurement of circulating angiogenic cytokines (CAFs): VEGF, sVEGFR 1/2, PlGF, GMCSF, Leptin, IL-1a, IL-8, IL-6, FGFb, Osteopontin and Pentraxin-3.
- Measurement of drug levels and PK/PD modeling

4 METHODOLOGY

4.1 Study Design

This is an open-label, non-randomized, multicenter, Phase I/II study of nintedanib and capecitabine in patients with metastatic colorectal cancer refractory to irinotecan and oxaliplatin based therapy. The study will include a Phase I dose-finding portion, followed by a non-randomized Phase II component. Nintedanib and capecitabine are both oral formulations, to be taken twice daily as prescribed in the present study. Nintedanib will be administered at a fixed dose as dictated in the protocol. The total daily dose of capecitabine will be calculated based upon actual body weight and split into two comparable portions, and doses of both drugs are to be self-administered approximately 12 hours apart (+/- 2 hours), within 30 minutes of a meal. For the purposes of this study, a cycle will be defined as 3 weeks (i.e., 21 days). Nintedanib is to be self-administered twice daily for 21 days (i.e., 1 complete cycle), while capecitabine will be dosed cyclically, in a 2 weeks on / 1 week off fashion. Disease assessment will occur after every three cycles of therapy (9 weeks). For the Phase I study, patients will be evaluated for toxicity on days 1 and 8 of the first two cycles. Otherwise, all patients will be evaluated on day one of each cycle of therapy. Treatment will continue until disease progression, in the absence of undue toxicity.

4.1.1 Phase I

A small initial Phase I lead-in will be conducted, utilizing a 3+3 design to determine the recommended phase II dose (RP2D). The Phase 1 portion provides limited toxicity information about the combination therapy in refractory metastatic colorectal cancer patients. The maximum tolerated (or administered) dose level from the Phase 1 will be utilized as the recommended Phase 2 dose. Two dose levels are planned, with dose level 2 expected to be the RP2D. Full details including the initial dosing strategies and dose escalation schema are present in **Section 6.**

4.1.2 Phase II

The RP2D from the Phase I study has been determined to be dose level 2. There is no formal interim analysis planned or early stopping rules. However, toxicity and safety outcomes will be regularly reviewed.

4.1.3 Correlative Studies

For both the Phase I and Phase II study, correlative blood will be drawn at baseline, cycle 1 day 15, and cycle 3 day 1 for analysis of a panel of cytokines and growth factors (see below), to be correlated to PK data, for a select biomarker panel and outcomes. This will be performed only on the 1st 32 patients enrolled in the study only. Following administration of both nintedanib (BIBF1120) and capecitabine, PK samples for nintedanib will be collected on Day 1, Cycle 1 at pre-dose, and at 0.5-1 hr, 2-4 hr, 5-6 hr, and 6-8 hr post dose and Day 2 (trough level). In addition, PK samples will be collected on Day 15 at predose, 2-4 hr post-dose, and 5-6 hr post-dose (**Section 8.10**). Circulating angiogenic cytokines (CAFs) will additionally be analyzed via blood collection on Day 1, Cycle 1 at pre-dose and 2-4 hr post-dose, on Day 15 2-4 hr post-dose and on Day 1, Cycle 3, 2-4 hr post-dose. Details of collection and timing are summarized in **Section 8.11**.

All participants will sign an informed consent prior to study related tests. All participants will meet the inclusion and exclusion criteria summarized in **Section 5.1** and **Section 5.2**. Participants will be treated on an outpatient basis.

4.2 Target Accrual and Study Duration

It is expected that a total of 9 patients will be enrolled at two dose levels in the Phase I portion, with potential for a maximum of 18 patients. The number of participants required is a function of the unknown dose-toxicity relationship. Patients treated at the RP2D (n=6) will be included in the Phase II study analysis. Up to an additional 30 patients will be enrolled in the Phase II portion of the study, for a Phase II sample size of 36. Summarily, the study is expected to accrue 39 patients (9 + 36 - 6). However, if toxicity is greater than expected, a maximum of 48 patients might be required (18 + 36 - 6). Enrollment is expected to be split between the two sites involved: Roswell Park Cancer Institute and City of Hope. Thus, in the case of 39 patients being enrolled, it is anticipated that approximately 20 patients would be enrolled at RPCI and 19 at City of Hope. Accrual is expected to take up to 2 years. Median PFS has historically stood at approximately 2 months and this study aims to provide a PFS rate at 18 weeks (~4 months) of 40%. It is anticipated that patients will be on study for approximately 18 weeks.

5 PARTICIPANT SELECTION

5.1 Inclusion Criteria

To be included in this study, participants must meet the following criteria:

1. Age ≥ 18 years of age.
2. Have an ECOG Performance Status of 0 – 1. Refer to **Appendix B**.
3. Have the following clinical laboratory values:
   - Hemoglobin ≥ 9 g/ dL
   - Absolute neutrophil count ≥ 1500/ mm^3
   - Platelet count ≥ 100,000/ mm^3
   - Creatinine ≤ 1.5 ULN AND CrCl > 50 mL/min by Cockcroft-Gault equation:
     - Males = (140 – age [yrs])(Body weight [kg])/(72)(serum creatinine [mg/dL])
     - Females = 0.85 * (140 – age [yrs])(Body weight [kg])/(72)(serum creatinine [mg/dL])
   - Bilirubin ≤ ULN
   - AST / ALT ≤ 1.5 ULN if without liver metastases
   - AST/ ALT ≤ 2.5 x ULN if with liver metastases
   - Coagulation parameters: International normalized ratio (INR) ≤ 2, prothrombin time (PT) and partial thromboplastin time (PTT) < 1.5 X institutional ULN
4. Have measurable disease per RECIST 1.1 criteria.
5. Histologically or cytologically proven adenocarcinoma of the colon or rectum.
6. Prior progression following a fluoropyrimidine-based therapy and progression following or intolerance to irinotecan and oxaliplatin, as well as anti-EGFR therapy (e.g., panitumumab or cetuximab) for RAS wild-type patients.
7. Ability to swallow and retain oral medication.
8. Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry and for three months following completion of therapy. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
9. Participant or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

5.2 Exclusion Criteria

Participants will be excluded from this study for the following:

1. Prior treatment with nintedanib.
2. Prior treatment with regorafenib.
3. Major injuries or surgery within the 4 weeks prior to initiation of therapy with incomplete wound healing or planned surgery during the on-study treatment period.
4. Uncontrolled hypertension: systolic blood pressure ≥ 160, diastolic blood pressure ≥ 90.
5. Urine Protein/creatinine ratio ≥ 1.0. Refer to **Appendix E**.
6. History of clinically significant hemorrhagic or thrombotic event within the past 6 months, not including uncomplicated catheter-associated venous thrombosis. Patients on anti-coagulation are not permitted to be on any oral formulations (warfarin, rivaroxaban, dabigatran, etc.) due to concern for drug-drug interaction.
7. Unstable angina, symptomatic congestive heart failure or cardiac arrhythmia requiring anti-arrhythmic therapy (Beta-blockers, calcium channel blockers and digoxin are allowed).
8. History of cerebrovascular or myocardial ischemia within 6 months of initiation.
9. Known inherited predisposition to bleeding or thrombosis.
10. Known active or chronic hepatitis B or C or HIV.
11. Untreated brain metastases.
12. History of second primary malignancy diagnosed within 3 years prior to enrollment, excluding:
    a. *In-situ* cervical carcinoma
    b. Superficial bladder cancer
    c. Non-melanoma skin cancer
    d. Stage I breast cancer
    e. Low grade (Gleason ≤ 6) localized prostate cancer
    f. Any additional malignancy which has been in clinical remission for at least 1 year.
13. Pregnant or nursing female participants.
14. Unwilling or unable to follow protocol requirements.
15. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.
16. Received an investigational agent within 4 weeks prior to enrollment.
17. **Phase I:** History of intolerance to capecitabine at doses ≤ 1000 mg/m^2 BID, as defined by documented ≥ grade 3 hand-foot syndrome; documented severe diarrhea requiring hospitalization; or other documented severe AEs attributable to capecitabine.

18. **Phase II:** History of intolerance to capecitabine at doses below 1000 mg/m^2 BID, as defined by documented ≥ grade 3 hand-foot syndrome; documented severe diarrhea requiring hospitalization; or other documented severe AEs attributable to capecitabine.

5.3 Inclusion of Women and Minorities

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

6 TREATMENT PLAN

6.1 Dosing and Administration

Treatment will be administered on an outpatient basis. Reported adverse events (AEs) and potential risks are described in **Section 1.8**. Appropriate dose modifications are described in **Section 6.5**.

In this study, a cycle will be defined as 21 days. Dosing for capecitabine will be established based upon actual body weight, with capecitabine being prescribed in oral (PO) tablet forms of 500 mg or 150 mg. The administration will be twice daily for two weeks (the first 2 weeks of each 21 day cycle), followed by a 1 week rest. Capecitabine is to be taken with water, within 30 minutes following a meal. The total daily dose will be calculated with dosing split so that comparable doses are administered, approximately 12 hours apart. The PM dose will be 12 hours (+/- 2 hours) after the AM dose. Doses will be rounded to the nearest 150 or 500 mg tablet increment, but may be rounded down at investigators discretion.

Nintedanib is available in 100 mg and 150 mg capsules, which will be administered twice daily for 21 days (i.e., 1 complete 3-week cycle). Both capecitabine and nintedanib may be taken together, with water, within 30 minutes following a meal. Doses should be separated by approximately 12 hours, with the PM dose being 12 hours (+/- 2 hours) after the AM dose.

Patients will be supplied with medication diaries to assess compliance. If a dose is missed, vomited or otherwise not ingested, it will not be replaced; rather, the patient will wait until the next scheduled dose to resume therapy. In the event that dosing is interrupted mid-cycle, the duration of the cycle will not be extended. Doses missed during the interruption will be captured as omitted rather than delayed.

6.2 Cohort Management

Phase I

The planned dose levels for Phase I are depicted in **Table 2**.

Table 2 Available Dose Levels

Dose level	Capecitabine [a]	Nintedanib [b]
-1	1500 mg/m2 PO daily (in two divided doses)	150 mg PO bid
1	2000 mg/m2 PO daily	150 mg PO bid

	(in two divided doses)	
2	2000 mg/m2 PO daily (in two divided doses)	200 mg PO bid

[a] Capecitabine will be taken only on the first 14 days (followed by 7 days off) of the 21 day cycle.

[b] Nintedanib will be taken for the complete 21 day cycle.

Dose escalation will proceed in a 3+3 fashion. Standard 3+3 rules will be followed until the maximum tolerated (or administered) dose is found. Initially, 3 patients are enrolled at dose level 1. If no dose limiting toxicities (DLTs) are observed, then 3 new patients are escalated to dose level 2. If ≥ 2 DLTs are observed, then 3 new patients are de-escalated to dose level -1. If 1 DLT is observed, then an additional 3 patients are enrolled at dose level 1. In those 6 patients at dose level 1, if ≤ 1 DLTs are observed we proceed to dose level 2; otherwise we proceed to dose level -1. The same basic principles are followed until the Phase II recommended dose is identified. Planned dose escalation will proceed according to **Table 3.**

Table 3 Dose Escalation Scheme

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

The recommended Phase 2 dose will be considered tolerable if DLT(s) are observed in at most 1 of 6 patients completing at least 1 treatment cycle at that dose level. Available toxicity information about these drugs suggests that Dose Level 2 will be the recommended Phase 2 dose, and that 9 patients will be required for the Phase 1. Dose escalation will not proceed beyond dose level 2.

Phase II

- Nintedanib – treatment will be initiated at the RP2D orally twice daily, administered in a continuous fashion.
- Capecitabine – treatment will be initiated at the RP2D orally twice daily, taken for 14 days, followed by a 7 day break.

As in the Phase I study, therapy will be administered in 3 week cycles. Treatment will continue until progression, undue toxicity or at the physician/patient discretion. The primary endpoint is the PFS rate, defined as the proportion of patients who survive without disease progression (per RECIST criteria) for at least 18 weeks after the start of treatment. The 6 patients in Phase 1 patients treated at the recommended Phase 2 dose will be included in Stage 1 of the Phase 2 study. As of 1/29/16, dose level 2 has been determined to be the RP2D.

6.3 Criteria for Retreatment

The following criteria must be met prior to initiation of a cycle of therapy:

- ANC > 1000 / mm^3
- Platelet count > 100,000 / mm^3
- AST and/or ALT CTCAE grade ≤ 5X ULN and bilirubin ≤ ULN
- Any additional non-hematologic toxicity of grade ≥ 3 which is potentially attributable to either drug must have resolved to grade ≤ 1 (or baseline)

If a patient achieves a response or stable disease which is maintained ≥ 6 months and discontinues therapy for a reason other than progressive disease, he/she may be considered for retreatment within 3 months of cessation of therapy. This must be approved by the study PI prior to re-initiation of treatment.

6.4 Definition of Dose-Limiting Toxicity

Dose limiting toxicity will be defined as any event which meets the criteria below and occurs within the 1st cycle of therapy (21 days).

The following drug-related adverse events will qualify as DLT if considered drug-related:

- Non-hematologic toxicity ≥ Grade 3 (CTCAE v4) ***except:*** transient electrolyte abnormality, alopecia, sub-optimally treated nausea, vomiting or diarrhea, and isolated elevation of gamma glutamyl transpeptidase. In particular,
    - Gastrointestinal toxicity (e.g. nausea, vomiting, diarrhoea, abdominal pain) or hypertension ≥ CTCAE Grade 3 despite optimal supportive care/ intervention.
    - Nintedanib (BIBF1120) related liver toxicity except GGT*** as specified below:
        - AST/ALT > 5x ULN* independent of bilirubin
        - AST/ALT > 2.5 x ULN** **together with** total bilirubin > 1.5 ULN**

      * corresponding to CTCAE Grade 3 toxicity

** corresponding to CTCAE Grade 2 toxicity
*** An isolated GGT elevation with no corresponding ALT/AST increase will not be considered as DLT.

- Hematological toxicity
  - CTCAE Grade 4 neutropenia that is uncomplicated (not associated with fever ≥ 38.5°C) only if continuing for > 7 days
  - CTCAE Grade 4 febrile neutropenia of any duration if associated with fever ≥ 38.5ºC
  - Platelet decrease to CTCAE Grade 4, or decrease to CTCAE Grade 3 associated with bleeding or requiring transfusions
- Inability to resume nintedanib (BIBF1120) dosing within 14 days of stopping due to treatment related toxicity
- In case adverse events with CTCAE Grade 3/4 were not judged as DLT from a clinical point of view, the Principle Investigator will obtain a confirmation from the individual investigator regarding the appropriateness of the judgment

Dose escalation will proceed within each cohort according to the scheme in **Table 3.**

Participants who do not have a DLT and who do not complete a full cycle of treatment (at least 75% of the prescribed dose of both nintedanib and capecitabine) will be replaced in the study.

Management and dose modifications associated with the above AEs are outlined in **Section 6.5** and **Section 6.5.2**.

6.5 Dose Modifications

6.5.1 Treatment Delay

Treatment with both nintedanib (BIBF1120) and capecitabine must be interrupted in case any of the criteria listed in **Table 4** is fulfilled.

Table 4 Criteria to Interrupt Nintedanib and capecitabine due to an Adverse Event

If one criterion is met, nintedanib (BIBF1120) + capecitabine is to be interrupted
• Nausea of CTCAE grade ≥ 3 despite optimal supportive care • Vomiting of CTCAE grade ≥ 2 despite optimal supportive care • Diarrhoea of CTCAE grade ≥ 2 for more than 7 consecutive days despite optimal supportive care • AST and/or ALT > 3 X ULN conjunction with bilirubin of > 1.5 X ULN • AST and/or ALT of CTCAE grade >5 X ULN • Other non-hematological adverse event of CTCAE grade ≥ 3 considered drug-related* • Neutropenia and fever > 38.5°C • Neutropenia CTCAE grade 4 for more than 7 days without fever • Platelets <50,000 /mm³ with clinically relevant bleeding

***Excluding palmar-plantar erythrodysesthesia or other AE which is attributed to capecitabine alone (see Table 6).**

Criteria for reinitiating therapy

Criteria for reinitiating therapy: After therapy is stopped for toxicity, a patient is eligible to restart nintedanib (BIBF1120) and capecitabine if all the criteria listed in **Table 5** are met.

Capecitabine should only be restarted if the patient still falls within days 1 - 14 of the cycle. It should not be reinitiated during the scheduled 7 days off. If criteria to reinitiate therapy fall within the scheduled 7 day off period, nintedanib may be reinitiated as a single agent to complete that cycle.

If a patient has to interrupt intake of nintedanib (BIBF1120) + capecitabine due to an adverse event for more than 14 days, the decision to restart therapy needs to be discussed and agreed upon between the investigator and the sponsor.

Table 5 Criteria to Restart Nintedanib and Capecitabine after Interruption

All criteria have to be met in order to restart nintedanib (BIBF1120) + capecitabine
• Nausea CTCAE grade ≤ 2 • Vomiting CTCAE grade ≤ 1 • Diarrhea CTCAE grade < 2 • AST and ALT CTCAE grade < 5 X ULN and bilirubin ≤ 1X ULN • No other non-hematological adverse event grade CTCAE ≥ 3 which is considered drug-related • Absolute neutrophil count of ≥ 1000 / mm3, without fever • Platelets > 75,000 / mm3

6.5.1.1 Capecitabine

Criteria for interruption of capecitabine alone (**Table 6**):

Table 6 Criteria for Interruption of Capecitabine Alone

Special Criteria for Interrupting Capecitabine Only [Grading as per CTCAE (v4.0)]
• Palmar-plantar erythrodysesthesia (PPE) (Hand-foot syndrome) ≥ CTCAE grade 2. • Additional grade 3 toxicity which is felt to be attributable to capecitabine alone

Criteria for reinitiating capecitabine: The AE of concern in Table 6 must have resolved to grade 1 or less prior to reinitiating capecitabine. As per missed doses, capecitabine should not be reinitiated on the 1 week of scheduled rest.

6.5.2 Dose Reduction

As initial measure for the management of side effects, treatment with nintedanib and capecitabine should be temporarily interrupted until the specific adverse reaction has resolved to levels that allow continuation of therapy. Nintedanib and capecitabine treatment may be resumed at a reduced dose. Dose adjustments of nintedanib based on individual safety and tolerability are recommended as described in **Table 7 and Table 8.**

The following dose levels will be used in case dose adjustments are required for management of undue toxicity.

Table 7 Nintedanib Dose Level Reduction Scheme[1]

Dose Level	Nintedanib
1	200 mg (2 x 100 mg) po bid(starting dose)
- 1	150 mg po bid
- 2	100 mg po, qAM and 150 mg po, qPM
- 3[2]	100 mg po bid[2]

1 This table is based upon a phase 1 dose and/or recommended Phase 2 dose of 200 mg bid. The dose level would not proceed beyond dose level -2 in that circumstance. Should the recommended phase 2 dose be less than 200 mg bid, dose levels would be adjusted accordingly.

2 Patients requiring greater than two dose reductions will be taken off protocol therapy. Dose level -3 would only be utilized in the case that nintedanib was initiated at a dose of less than 200 mg bid.

Table 8 Capecitabine Dose Level Reduction Scheme[1]

Dose Level	Capecitabine
1	2000 mg/m^2/day (starting dose), divided bid
- 1	1500 mg/m^2/day, divided bid
- 2	1250 mg/m^2/day, divided bid
- 3[2]	1000 mg/m^2/day, divided bid[2]

1 This table is based upon a phase 1 dose and/or recommended Phase 2 dose of 2000 mg/m^2/day. The dose level would not proceed beyond dose level -2 in that circumstance. Should the recommended phase 2 dose be less than 2000 mg/m^2/day, dose levels would be adjusted accordingly.

2 Patients requiring greater than two dose reductions will be taken off protocol therapy. Dose level -3 would only be utilized in the case that capecitabine was initiated at a dose of less than 2000 mg/m2/day.

Note: If the dose of nintedanib (BIBF1120) or capecitabine has to be reduced due to toxicity, it will stay on the lower dose level for the entire time of administration.

6.5.3 Management of specific AEs

- Diarrhea
- Nausea and vomiting
- Liver Enzyme Elevations

Table 9 Recommended Dose Adjustments for Nintedanib (BIBF1120) and Capecitabine

CTCAE (v4.0) Adverse Reactions	Dose Adjustment
Diarrhea ≥ grade 2 for more than 7 consecutive days despite optimal antidiarrheal treatment **OR** Diarrhea ≥ grade 3 despite optimal antidiarrheal treatment	**1st episode** • Reduce 1 dose level **2nd episode** • Reduce 1 further dose level
Vomiting ≥ grade 2 **AND/OR** Nausea ≥ grade 3 despite optimal anti-emetic treatment	

AST and/or ALT elevations > 3 X ULN in conjunction with bilirubin of > 1.5 X ULN **OR** AST and/or ALT elevations of > 5 X ULN	**3rd episode** • Stop treatment

Management of all other AEs:

Table 10 Management of Additional Adverse Events for Either Drug

Grade of Event	During a Course of Therapy	Dose Adjustment for Next Cycle
≤ Grade 1	No change in dose.	Resume at same dose level
Grade 2[1] 1st occurrence	Hold until ≤ Grade 1	Resume at same dose level.
Grade 2[1] 2nd occurrence	Hold until ≤ Grade 1	Resume at 1 dose level lower
Grade 2[1] 3rd occurrence	Hold until ≤ Grade 1	Resume at 1 dose level lower
Grade 2[1] 4th occurrence	Hold until ≤ Grade 1	Permanently discontinue
Grade 3	Hold until < Grade 2[2]	Resume at 1 dose level lower, if indicated[3]
Grade 4	Discontinue permanently or, if physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1.	Permanently discontinue OR Reduce capecitabine by 50% AND Reduce nintedanib 1 dose level

1 Excludes sub-optimally treated grade 2 diarrhea/ nausea and hypertension. At the investigator's discretion, dose reduction of capecitabine may be pursued after the first occurrence of grade 2 Palmoplantar erythrodysesthesia.

2 Participants requiring a delay of > 2 weeks should go off protocol therapy.

3 Participants requiring > 2 dose reductions should go off protocol therapy.

Recommended management for nausea and vomiting: antiemetics.

Recommended management for diarrhea: Loperamide antidiarrheal therapy. Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg / 24 hours) Adjunct antidiarrheal therapy is permitted and should be recorded when used.

Of note, in many cases, it will be difficult to firmly establish one of the agents as being causative of the adverse event (i.e. fatigue, nausea or diarrhea). As suggested above, in these instances, temporary cessation and/or dose reductions of both nintedanib and capecitabine are to be carried out. In the circumstance that an adverse event, which is not otherwise described herein, is felt to be clearly attributed to one of the two agents, but not the other, the putative inciting agent should be held, with dose modification of that agent only, as appropriate.

Patients should PERMANENTLY discontinue treatment in the event of:

- Intolerable Adverse Events (CTCAE grade 3 or 4) that cannot be managed by dose reduction.
- Withdrawal of informed consent.
- AEs requiring a delay in therapy of > 2 weeks (except as above, in the case that a patient is felt to be deriving clinical benefit and, this is first discussed and agreed upon between the individual investigator and the principal investigator.).

6.6 General Concomitant Medication and Supportive Care

6.6.1 Additional precautions and supportive care.

- *Diarrhea*

Diarrhea was the most frequently reported gastro-intestinal event and appeared in close temporal relationship with the administration of docetaxel in the clinical trial LUME-Lung 1. The majority of patients had mild to moderate diarrhoea. 6.3 % of the patients had diarrhoea of grade ≥3 in combination treatment compared to 3.6 % treated with docetaxel alone. Diarrhea should be treated at first signs with adequate hydration and antidiarrheal medicinal products, e.g. loperamide, and may require interruption, dose reduction or discontinuation of therapy with nintedanib.

- *Nausea and vomiting*

Nausea and vomiting, mostly of mild to moderate severity, were frequently reported gastrointestinal adverse events in the clinical trial LUME-Lung 1. Interruption, dose reduction or discontinuation of therapy with nintedanib (BIBF1120) may be required despite appropriate supportive care. Supportive care for nausea and vomiting may include medicinal products with anti-emetic properties, e.g. glucocorticoids, anti-histamines or 5-HT3 receptor antagonists and adequate hydration.

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

- *Neutropenia and Sepsis*

A higher frequency of neutropenia of CTCAE grade > 3 was observed in patients treated with nintedanib (BIBF1120) in combination with docetaxel as compared to treatment with docetaxel alone in the clinical trial LUME-Lung 1. Subsequent complications such as sepsis or febrile neutropenia have been observed.

- *Hepatic Function*

The safety and efficacy of nintedanib has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Therefore treatment with nintedanib (BIBF1120) is not recommended in such patients. Administration of nintedanib was associated with an elevation of liver enzymes (ALT, AST, ALKP (alkaline phosphatase), and bilirubin, with a potentially higher risk for female patients.

These increases were reversible in the majority of cases and not associated with clinically manifest liver disorders. Hepatic transaminases, ALKP and bilirubin levels are recommended to be closely monitored after start of therapy with nintedanib (BIBF1120) (periodically, i.e. in the combination phase with docetaxel at the beginning of each treatment cycle). If relevant liver enzyme elevations are measured, interruption, dose reduction or discontinuation of the therapy with nintedanib may be required (see **Appendix C** for procedures for follow-up for potential drug-induced liver injury).

6.6.2 Concomitant medications

Additional chemo-, immuno-, hormone- or radiotherapies are not allowed during the active treatment period of this trial. Palliative radiotherapy may be permitted for symptomatic control of pain from bone metastases after discussion with the Principle Investigator, provided that the radiotherapy does not affect target lesions, and the reason for the radiotherapy does not reflect progressive disease.

Metabolism of nintedanib by CYP450 enzymes plays only a minor role (5%). Additionally, nintedanib did not show relevant induction or inhibition of the major drug metabolizing cytochrome P450 enzymes and specifically no irreversible CYP3A4 inhibition. However, if co-administered with nintedanib, strong P-gp inhibitors may increase exposure to nintedanib (e.g. ketoconazole or erythromycin). Thus, such medications are to be avoided unless deemed to be absolutely necessary. In such cases, patients should be monitored closely for tolerability of nintedanib. Management of side effects may require interruption, dose reduction or discontinuation of therapy with nintedanib.

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

Because there is a potential for interaction of drug with other concomitantly administered drugs, the electronic case report form (eCRF) must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Investigator should be alerted by the study clinical research coordinator if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes, P-gp inducers or inhibitors.

Aluminum hydroxide and magnesium hydroxide containing products should be avoided while taking capecitabine. Investigation has documented increase plasma levels of capecitabine and one metabolite with the use of Maalox. Post marketing reports indicate that some patients taking both capecitabine and phenytoin experienced toxicity with elevated phenytoin levels. The level of phenytoin should be carefully monitored in patients taking capecitabine and phenytoin doses may need to be reduced.

During cycle 1 of the phase I study, the use of myeloid growth factors (including Neupogen and Neulasta) is not permitted. After cycle 1 and during the phase II study, growth factor support may be utilized at the discretion of the investigator.

Participants may be pretreated for nausea and vomiting with appropriate anti-emetics.

Rescue medication to reverse the actions of nintedanib (BIBF1120) is not available. Potential side effects of nintedanib (BIBF1120) have to be treated symptomatically.

6.7 Duration of Treatment

Participants may remain on study and continue to receive treatment in the absence of disease progression, unacceptable toxicity or withdrawal from study, intercurrent illness that prevents further administration of treatment, participant demonstrates an inability/refusal to comply with oral medication regime, and participant withdraws from study.

6.8 Treatment Discontinuation

Upon treatment discontinuation all end of treatment evaluations and tests will be conducted. All participants who discontinue due to an AE must be followed until the event resolves or stabilizes. Appropriate medical care should be provided until signs and symptoms have abated, stabilized, or until abnormal laboratory findings have returned to acceptable or pre-study limits. The final status of the AE will be reported in the participant's medical records and the appropriate eCRF.

Reasons for treatment discontinuation should be classified as follows:

- Death
- Progressive disease
- Toxicity; related or unrelated toxicity
- Investigator judgment
    - The Investigator may discontinue a participant if, in his/her judgment, it is in the best interest of the participant to do so.
- Noncompliance
- Participant voluntary withdrawal
    - A participant may withdraw from the study at any time, for any reason. If a participant discontinues treatment, an attempt should be made to obtain information regarding the reason for withdrawal.
- Boehringer Ingelheim decision
- NCCN decision

6.9 Compliance

Patients will be supplied with a medication diary to track self-administration of capecitabine and nintedanib (**Appendix D**). After the first cycle, nintedanib pill counts will be performed at the initiation of each subsequent cycle for reconciliation as well as to assess compliance.

7 INVESTIGATIONAL PRODUCT

7.1 Active Substance and Source

Nintedanib is provided as soft gelatin capsules containing a suspension of milled active as the ethane sulphonate salt. It is available for clinical investigations in five dose strengths corresponding to 50 mg (brown, oval capsules), 100 mg (peach or orange, oblong capsules), 125 mg (orange, oblong capsules), 150 mg (brown or orange, oblong capsules) and 200 mg (brown, oblong capsules). The capsule fill is composed of medium chain triglycerides, hard fat and lecithin in addition to the drug substance.

In oncological studies, the 100 mg and 150 mg capsules will be used either with the trial formulation (all capsules orange) or with the intended market formulation (100 mg: peach, 150 mg: brown).

Capecitabine is supplied as biconvex, oblong, film-coated tables. Capecitabine is available in two strengths: 150 mg (light peach) or 500 mg (peach).

7.2 Drug Shipment

Nintedanib will be provided by Boehringer Ingelheim Pharmaceuticals, Inc. and shipped to the participating site. Boehringer Ingelheim will provide study specific drug order forms.

The date of receipt and the amount of drug received will be documented. Drug shipment records will be retained by the investigational pharmacist or designee.

Commercially available capecitabine will be used during this study. Patients will be given a prescription (or institutional support, case managers, as appropriate) to fill at the pharmacy of their choice prior to the start of each treatment cycle.

7.3 Storage and Stability

7.3.1 Nintedanib

The current shelf life for all dosage strengths and formulations of nintedanib is 60 months. The expiration date will be supplied in the shipping receipt or on the bottles. The capsules are packaged in child resistant high density polyethylene (HDPE) bottles and have to be stored below 30°C. The capsules should be protected from exposure to high humidity which is ensured by storage in the original package. Please refer to investigator's brochure for complete details.

The Investigator or designate will be responsible for ensuring that the investigational, nintedanib, product is securely maintained in a locked, limited-access facility, as specified by Boehringer Ingelheim and in accordance with the applicable regulatory requirements.

Drug storage temperature will be maintained and recorded, as applicable.

7.4 Handling and Disposal

The Investigator or designee will be responsible for dispensing and accounting for all investigational drug provided by Boehringer Ingelheim exercising accepted medical and

pharmaceutical practices. Study drugs must be handled as cytotoxic agents and appropriate precautions taken per the institution's environmentally safe handling procedures. All investigational drugs will be dispensed in accordance with the Investigator's prescription or written order.

All products dispensed will be recorded on a product accountability record. Records of product lot numbers and dates received will be entered on a product accountability form. It is the Principal Investigator's responsibility to ensure that an accurate record of investigational drug issued and returned is maintained.

Under no circumstances will the Investigator supply investigational drug to a third party or allow the investigational drug to be used in a manner other than as directed by this protocol.

8 STUDY PROCEDURES

8.1 Participant Registration

Eligibility of each participant will be established prior to enrollment.

Informed consent ***MUST*** be completed prior to receiving any study related procedures.

Unless otherwise defined in the written protocol text, all procedures/assessments will be conducted in accordance with RPCI Clinical Research Services Standard Operating Procedures.

8.2 Baseline Evaluations

The following will be performed within 2 weeks prior to first dose of study drug (unless otherwise noted):

- Medical history (including all prior anti-tumoral therapy related to colorectal cancer)
- Physical examination
- Vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight, and height)
- Hematology (i.e., complete blood count (CBC) with automated differentials)
- Chemistry (i.e., complete metabolic panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).
- Pregnancy test serum in females of childbearing potential
- Urine spot protein and urine spot creatinine levels (UPCR)
- Coagulation studies - INR/PT, PTT
- ECOG Performance Status (**Appendix B**)
- Concomitant Medications: List any medications that were ongoing, or stopped, within 1 week prior to first dose of study drug.
- Baseline imaging – CT chest/abdomen/pelvis (within 4 weeks)

8.3 Evaluations Performed On Therapy (Day 1 of each cycle, +/- 3 days)

- Physical examination
- Vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight)
- Hematology (i.e., complete blood count (CBC) with automated differentials)
- Chemistry (i.e., complete metabolic panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).
- Blood draw for PK and biomarker (first 32 patients only, on cycle 1 and 3). See sections **8.10**and **8.11** for collection time points.
- ECOG Performance Status (**Appendix B**)
- Concomitant Medications: List any ongoing medications with dose changes, as applicable.
- Adverse events
- CT scan of the chest/abdomen/pelvis with IV contrast (or if unable to receive IV contrast, a non-contrast CT of the chest + MRI of the abdomen/pelvis) every 9 weeks after Cycle- 1 Day 1 (±7 days)
- CEA:
    - Cycle 1 – Day 1
    - Cycle 4 – Day 1
    - Every 3 cycles (on Day 1) from Cycle 4 onward.
- Study Drug Reconciliation – Beginning with Cycle 2 – Day 1 (reconciliation for Cycle 1) and on Day 1 of all subsequent cycles prior to the initiation of a new cycle.

8.4 Evaluations Performed On Therapy (Day 2 cycle 1)

- Blood draw for PK (first 32 patients only)

8.5 Evaluations Performed On Therapy (Day 8 of cycles 1 and 2, phase I only, +/- 3 days)

- Physical examination
- Vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight)
- Chemistry (i.e., complete metabolic panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).
- Hematology (i.e., complete blood count (CBC) with automated differentials).
- Adverse events
- Concomitant Medications: List any ongoing medications with dose changes, as applicable.

8.6 Evaluations Performed On Therapy (Day 15 of cycle 1)

- Blood draw(s) for PK and biomarker (CAFs on first 32 patients only)

- Concomitant Medications: List any ongoing medications with dose changes, as applicable.
- Adverse events

8.7 Evaluations Performed at End of Treatment (30 +/- 7 days post last dose of study drug)

The following evaluations will be performed following treatment discontinuation. In the case of persistent drug-related toxicity, patients will be followed every 28 days until resolution or satisfactory stabilization is achieved. Telephone contact is acceptable.

- Physical examination, including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight)
- Hematology (i.e., complete blood count (CBC) with automated differentials)
- Chemistry (i.e., complete metabolic panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).
- Concomitant medication: List any ongoing medications with dose changes, as applicable
- Adverse events
- Drug reconciliation

8.8 Medical Record Review

Every 6 months for overall survival.

8.9 Schedule of Procedures and Observations

The schedule of procedures and observations for this study is summarized in **Table 11** (Phase I) and **Table 12** (Phase II) below.

Note: Except for cycle 1- day 1 and day 2 procedures*, all other procedures may be performed ± 3 days from the proposed date.* Disease assessment (CT imaging) may be performed up to 7 days prior to day 1 of the corresponding cycle.

Table 11 Phase I: Schedule of Procedures and Observations

Evaluation	Baseline[1]	Cycle 1				Cycle 2		Cycle 3	Cycle 4	Further Cycles	End of Treatment[2]	Follow-Up[3]
Day		1	2	8	15	1	8	1	1	1		
Medical History	X											
Pre-Existing Conditions	X											
Physical Examination , including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight, and height)[4]	X	X		X		X	X	X	X	X	X	
Hematology[5]	X	X		X		X	X	X	X	X	X	
Chemistry[6]	X	X		X		X	X	X	X	X	X	
INR/PT, PTT	X											
CEA		X							X	X[11]		
Urine Sample for Urine Protein Creatinine Ratio (UPCR)	X											
Pharmacokinetic Sampling[7]		X	X		X							
Biomarker Sampling[7]		X			X			X				
Pregnancy Test (Serum)[8]	X											
ECOG Performance Status	X	X				X		X	X	X		
CT Chest/Abdomen/Pelvis[9]	X								X	X[9]		
Study Drug Reconciliation[12]						X		X	X	X	X	
Concomitant Medications	X[10]	X		X	X	X	X	X	X	X	X	
Survival Assessment												X
Adverse Events		X		X	X	X	X	X	X	X	X	

1 Performed within 2 weeks prior to first dose of study drug.

2 Follow-up safety evaluations will occur 30 days (± 7 days) after last dose of study drug. In the case of persistent drug-related toxicity, patients will be followed every 28 days until resolution or satisfactory stabilization is achieved. Telephone contact is acceptable.

Evaluation	Baseline[1]	Cycle 1				Cycle 2		Cycle 3	Cycle 4	Further Cycles	End of Treatment[2]	Follow-Up[3]
Day		1	2	8	15	1	8	1	1	1		

3 Medical record review every 6 months to assess overall survival.

4 Height collected at baseline only.

5 Hematology (complete blood count (CBC) with automated differentials)

6 Chemistry (complete metabolic panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).

7 Pharmacokinetic samples and biomarker samples will be collected according to **Section 8.10** and **Section 8.11**, respectively.

8 For women of child-bearing potential only.

9 Baseline imaging within 4 weeks prior to treatment start. Additional scans will be taken every 9 weeks after cycle 1 –day 1 (± 7days). CT chest + MRI abdomen/pelvis is acceptable for disease assessment, if patients are unable to undergo a contrast enhanced CT.

10 Medications ongoing, or stopped, within 1 week prior to first dose of study drug.

11 CEA is to be performed every 3 cycles from cycle 4 onward (i.e. cycle 4, 7, 10…)

12 Study drug reconciliation from previous cycle, prior to starting new cycle.

Table 12 Phase II: Schedule of Procedures and Observations

Evaluation	Baseline[1]	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Further Cycles	End of Treatment[2]	Follow-Up[3]
Day		1	2	15	1	1	1	1		
Medical History	X									
Pre-Existing Conditions	X									
Physical Examination , including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight, and height)[4]	X	X			X	X	X	X	X	
Hematology[5]	X	X			X	X	X	X	X	
Chemistry[6]	X	X			X	X	X	X	X	
INR/PT, PTT	X									
CEA		X					X	X[11]		
Urine Sample for Urine Protein Creatinine Ratio (UPCR)	X									
Pharmacokinetic Sampling[7]		X	X	X						
Biomarker Sampling[7]		X		X		X				
Pregnancy Test (Serum)[8]	X									
ECOG Performance Status	X	X			X	X	X	X		
CT chest/abdomen/pelvis[9]	X						X	X[9]		
Study Drug Reconciliation[12]					X	X	X	X	X	
Concomitant Medications	X[10]	X		X	X	X	X	X	X	
Survival Assessment										X
Adverse Events		X		X	X	X	X	X	X	

Evaluation	Baseline[1]	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Further Cycles	End of Treatment[2]	Follow-Up[3]
Day		1	2	15	1	1	1	1		

1 Performed within 2 weeks prior to treatment start.

2 Follow-up safety evaluations will occur 30 days (± 7 days) after last dose of study drug. In the case of persistent drug-related toxicity, patients will be followed every 28 days until resolution or satisfactory stabilization is achieved. Telephone contact is acceptable.

3 Medical record review every 6 months to assess overall survival.

4 Height collected at baseline only.

5 Hematology (complete blood count (CBC) with automated differentials)

6 Chemistry (complete metabolic panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).

7 Pharmacokinetic samples and biomarker samples will be collected according to **Section 8.10**and **Section 8.11**, respectively.

8 For women of child-bearing potential only.

9 Baseline imaging within 4 weeks prior to treatment start. Additional scans will be taken every 9 weeks after cycle 1 –day 1 (± 7days). CT chest + MRI abdomen/pelvis is acceptable for disease assessment, if patients are unable to undergo a contrast enhanced CT.

10 Medications ongoing, or stopped, within 1 week prior to first dose of study drug.

11 CEA is to be performed every 3 cycles from cycle 4 onward (i.e. cycle 4, 7, 10…)

12 Study drug reconciliation from previous cycle, prior to starting new cycle.

8.10 Pharmacokinetic Blood Sample Collection and Processing

Whole blood samples for pharmacokinetic (PK) analysis of nintedanib levels will be collected via venipuncture. This will only be performed on the first 32 patients enrolled in the study.

Samples for pharmacokinetic analysis (PK) of nintedanib levels will be collected using 1, 10 mL purple EDTA collection tube.

Pharmacokinetic sample (PK) collection will be obtained on:

- Cycle 1/Day 1 – Pre-dosing: PK
- Cycle 1/Day 1 – 0.5-1 hr post-dosing: PK
- Cycle 1/Day 1 – 2-4 hr post-dosing: PK
- Cycle 1/Day 1 – 5-6 hr post-dosing: PK
- Cycle 1/Day 1 – 7-8 hr post-dosing: PK
- Cycle 1/Day 2 – Pre-dosing: PK
- Cycle 1/Day 15 – Pre-dosing: PK
- Cycle 1/Day 15 – 2-4 hr post-dosing: PK
- Cycle 1/Day 15 – 5-6 hr post-dosing: PK

Note: All dosing dates and times must be recorded on the study medication diary **and** in the eCRF for all doses taken from the first dose to the day of the last PK sample.

NOTE: *Any samples that have been hemolyzed should be re-drawn if possible.*

Nintedanib is degraded by plasma esterases; therefore, whole blood samples should be immediately maintained in an ice bath until centrifuged. Centrifugation for separation of plasm should be done **within 60 min** after sampling:

- Centrifuge whole blood samples as soon as possible at 4°C using a refrigerated centrifuge at approximately 3000 rpm for about 10 min.
- Transfer at least 500 µL of the supernatant plasma into polypropylene vials (e.g., Nunc cryo-tubes, 1.8 mL).

NOTE: *Strictly avoid contamination with erythrocytes: If this occurs, the specimen must be centrifuged again.*

Plasma will be aliquoted into 2 cryovials per time-point. The screw cap polypropylene cryogenic tube will be labeled with the participant's MR number,(for RPCI participants) participant's initials, participant's study number, clinical study number, protocol time point, dose, and protocol day. The samples will immediately be frozen at - 70ºC or below until analyzed.

Samples collected at RPCI will be processed and stored at RPCI's Hematological Procurement Facility. Frozen samples will then be analyzed in RPCI's Bioanalytics, Metabolomics & Pharmacokinetic Core Facility:

Roswell Park Cancer Institute
Bioanalytics, Metabolomics & Pharmacokinetic Core Facility
Center for Genetics and Pharmacology, Room L1-140
Regarding Study #: I 265514
Elm & Carlton Streets
Buffalo, New York 14263

PKPDcore@RoswellPark.org

Note: All laboratories housing research samples need to maintain current, study-specific **Temperature Logs** and **Sample Tracking and Shipping Logs**. The Principal Investigator/Laboratory Manager **must** ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens (ICH 8.3.25). This is required for both observational and interventional clinical studies collecting clinical samples.

NETWORK SITES: Follow directions above for sample collection and processing. The cryogenic tubes will be labeled with the Subject ID # (unique to Network patients), initials, the participant's study number, clinical study number, protocol time point, dose, and protocol day. Frozen samples will be shipped via Fed Express Overnight on dry ice with delivery on Mon-Fri. NO SATURDAY DELIVERY. ***All samples should be shipped batched at the end of the study to the address below with shipping log***:

Roswell Park Cancer Institute
Bioanalytics, Metabolomics & Pharmacokinetic Core Facility
Center for Genetics and Pharmacology, Room L1-140
Regarding Study #: I 265514
Elm & Carlton Streets
Buffalo, New York 14263

PKPDcore@RoswellPark.org

For additional information regarding the handling of pharmacokinetic samples please contact RPCI's Bioanalytics, Metabolomics & Pharmacokinetic Core Facility laboratory at 716-845-3303 (Tel) or 716-845-1579 (Fax).

8.11 Biomarker Blood Sample Collection and Processing

Whole blood samples for biomarker analysis (CAF: Circulating Angiogenic Factors) will be collected via venipuncture. This will only be performed on the first 32 patients enrolled in the study.

Samples for ***biomarker analysis*** (CAF) will be collected using 1, 10 mL green-top heparinized collection tube and 1, 10 mL purple EDTA collection tube.

Biomarker sample (CAF) collection will be obtained on:

- Cycle 1/Day 1 – Pre-dosing: CAF

- Cycle 1/Day 1 – 2-4 hr post-dosing: CAF
- Cycle 1/Day 15 – 2-4 hr post-dosing: CAF
- Cycle 3/Day 1 – 2-4 hr post-dosing: CAF

Plasma will be separated from whole blood within 30 minutes following the extraction (collection tubes are to be centrifuged at 1000g for 10 min at room temperature). Plasma will be aliquoted into 3 cryovials (approximately 1 mL/cryovial) per time-point. The screw cap polypropylene cryogenic tube will be labeled with the participant's MR number,(for RPCI participants) participant's initials, participant's study number, clinical study number, protocol time point, dose, and protocol day. The samples will immediately be frozen at -70ºC or below until analyzed. Samples collected at RPCI will be processed and stored at RPCI's Hematological Procurement Facility. Frozen CAF samples will then be analyzed in RPCI's Genitourinary Malignancies Laboratory by Dr. John Ebos:

Roswell Park Cancer Center
Genitourinary Malignancies Laboratory
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Attn: John Ebos – I 265514
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Buffalo, NY 14263
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Note: All laboratories housing research samples need to maintain current, study-specific **Temperature Logs** and **Sample Tracking and Shipping Logs**. The Principal Investigator/Laboratory Manager **must** ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens (ICH 8.3.25). This is required for both observational and interventional clinical studies collecting clinical samples.

NETWORK SITES: Follow directions above for sample collection and processing. The cryogenic tubes will be labeled with the Subject ID # (unique to Network patients), initials, the participant's study number, clinical study number, protocol time point, dose, and protocol day. The samples will immediately be frozen at -70ºC or below (samples are to be stored until requested for batch mailing). Samples are to be **batch shipped frozen at the end of study with shipping log, on dry ice**.

Frozen samples will be shipped via Fed Express Overnight on dry ice with delivery on Mon-Fri. NO SATURDAY DELIVERY. Do not ship on a Friday or the day before a holiday.

Address shipments and any questions regarding specimen processing to:

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Genitourinary Malignancies Laboratory
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9 EFFICACY EVALUATIONS

9.1 Objective Tumor Response

All protocol-defined imaging studies must be performed at the investigative site or sponsor-approved facility using protocol-defined parameters. 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. RECIST 1.1 will be used to assess objective tumor response. Evaluation will be carried out for both the phase I and II study portions.

9.2 Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, will be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size. Lesions with the longest diameter (short axis for lymph nodes) and are ≥ 10 mm (CT and MRI), ≥ 15 mm lymph nodes, > 20 mm CXR and are for accurate repetitive measurements (either by imaging techniques or clinically) will be chosen. A sum of the longest diameter (short axis for lymph nodes) of all target lesions will be calculated and reported as the baseline sum diameters. This will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

- **Complete Response (CR):** Disappearance of all target lesions. Any lymph nodes must have a reduction in short axis to < 10 mm. Changes in tumor measurements must be confirmed by repeat studies performed no less than 9 weeks after the criteria for response are first met.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Changes in tumor measurements must be confirmed by repeat studies performed no less than 9 weeks after the criteria for response are first met.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as references 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. The appearance of one or more new lesions is also considered progression.

- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest sum diameter while on study. Participants having a documented response with no confirmation of the response will be listed with stable disease.

9.3 Non-Target Lesions

All other small lesions (longest diameter < 10 mm or lymph nodes ≥ 10 mm to < 15 mm short axis) and non-measurable lesions (i.e., leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, blastic bone lesions, or abdominal masses / abdominal organomegaly identified by physical exam that is not measurable by imaging) should be identified as non-target lesions and indicated as present in the source documents at baseline. The general location will also be documented on the images drawing a regularly-shaped Region of Interest. Measurements of the non-target lesions will not be performed, but the presence or absence of each should be noted throughout follow-up and evaluation.

- **Complete Response:** Disappearance of all non-target lesions and normalization of tumor marker level, if applicable. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- **Non-Complete Response/Non-Progressive Disease:** Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the upper limits of normal.
- **Progressive Disease:** Appearance of 1 or more new lesions or the unequivocal progression of existing non-target lesions. Although a clear progression of non-target lesions is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed at a later time.

9.4 Evaluation of Response

Time point response assessments will be performed every 9 weeks (timed to coincide with the end of a cycle) with a confirmatory assessment (required for non-randomized trials) within 9 weeks after a PR or CR is deemed. To determine time point response, refer to **Table 13** and below.

Table 13 Time Point Response Criteria (+/- non-target disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 14 Time Point Response Criteria (non-target disease only)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[1]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

The best overall response is the best response recorded from the start of study treatment until patients are removed from the study for any reason (the end of treatment taking into account any requirement for confirmation). In general, the participant's best response assignment will depend on the achievement of both measurement and confirmation criteria and will be determined by combining the participant's status of target lesions, non-target lesions, and new lesions.

- **Residual Disease:** Provide the appropriate information that pertains to this study.
- **Symptomatic Deterioration:** Participants with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not related to study treatment or other medical conditions should be reported as progressive disease due to "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment due to symptomatic deterioration. Symptomatic deterioration that may lead to discontinuation of treatment include, but is not limited to, symptoms such as:
  - Weight loss > 10% of body weight.
  - Worsening of disease-related symptoms (e.g., worsening dyspnea, increasing pain/increasing requirement for narcotic analgesics).
  - Decline in performance status of > 1 level on ECOG scale.

9.5 Confirmation Measurement

Response will be confirmed within 9 weeks.

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

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

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

10 SAFETY EVALUATION

10.1 Adverse Events

10.1.1 Definition

An adverse event or adverse experience (AE) is defined as any untoward medical occurrence (including an exacerbation of a pre-existing condition) associated with the use of a drug in humans, whether or not considered drug related (i.e., the event does not necessarily have to have a causal relationship with the treatment). Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite'). In addition, each study site will also be responsible for reporting causality of AEs to Boehringer Ingelheim as per **Section 10.2.1**).

An AE is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan in other study-related documents.

10.1.1.1 Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

10.1.1.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.

However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

10.1.1.3 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose

modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7 mEq/L should be recorded as "hyperkalemia"

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

10.1.1.4 Preexisting Medical Conditions (Baseline Conditions)

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

10.1.1.5 Vital Signs, ECG and Physical Examination Results

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

10.2 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, or abscess.**

  In such cases the following additional information will need to be collected, documented in the respective comment field of the CRF page and the respective narratives of the SAE, and 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.**

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 the above laboratory abnormalities need to be followed up until the protocol specific retreatment criteria have been met and according to **Appendix C** [Boehringer Ingelheim: *Procedures for the follow-up of drug-induced liver injury (DILI)*].

Protocol-specified AESI are to be reported to Boehringer Ingelheim an expedited manner similar to Serious Adverse Events (**Section 10.4**), even if they do not meet any of the seriousness criteria.

10.2.1 Grading and Relationship to Drug

The descriptions and grading scales found in the CTEP Version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 4 of the CTCAE is identified and located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs not covered by specific terminology listed should be reported with common medical terminology, and documented according to the grading scales provided in the CTCAE Version 4.

The relationship of event to study drug will be documented by the Investigator as follows:

- **Unrelated:** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.
- **Unlikely:** The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible:** The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs.
- **Probable:** The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be

reasonably explained by other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs.

- **Definite:** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

Boehringer Ingelheim Reporting Requirements

- The severity of the AE should be judged based on the following:
- The severity of adverse events should be classified and recorded in the eCRF according to the Common Terminology Criteria for Adverse Events (CTCAE) CTEP Version 4 of the NCI CTCAE located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm 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 ("Yes" is equivalent to: Possible, Probable or, Definite).

No: There is no reasonable causal relationship between the investigational product administered and the AE ("No" is equivalent to Unrelated or Unlikely).

10.2.2 Reporting Adverse Events

Table 15 Guidelines for Routine Adverse Event Reporting for Phase 1 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated	X	X	X	X
Unlikely	X	X	X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

Table 16 Guidelines for Routine Adverse Event Reporting Phase 2 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated			X	X
Unlikely			X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

Routine AEs occurring from the date the participant signs the study consent until 30 days after the last intervention or until the event has resolved, the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported. New information will be reported after it is received.

10.3 Serious Adverse Events

10.3.1 Definition

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or sponsor results in **ANY** of the following:

- Death.
- A life-threatening adverse event (experience). Any AE that places a participant or participants, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does **NOT** include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Patients may be hospitalized 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 hospitalizations planned at the beginning of the trial do not need to be reported as an SAE.

10.3.2 Reporting Serious Adverse Events

All new SAEs occurring from the date the participant signs the study consent until 30 days after the last intervention or a new treatment is started, whichever comes first, will be reported. The RPCI SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information.

SAEs occurring after the 30 day follow-up period that the investigator determines to be possibly, probably or definitely related to the study intervention should be reported.

SAEs identified as an Unanticipated Problem by the Investigator must be reported. Please refer to Section 10.6 for details on reporting Unanticipated Problems.

10.4 Investigator Reporting: Notifying Boehringer Ingelheim (BI) and NCCN

The principle investigator at each respective site will report all SAEs and non-serious AEs which are relevant to a reported SAEs and AESIs by fax using a MEDWATCH 3500A form with the completed BI FAX Cover Sheet to BI Unique Entry Point and NCCN, as detailed below in accordance with the following timelines:

- **Within 5 calendar days** upon receipt of initial and follow-up SAEs containing at least one fatal or immediately life-threatening event.
- **Within 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

Fax: (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.

10.5 Follow-Up for Serious Adverse Events

All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

10.6 Unanticipated Problems

10.6.1 Definition

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
    a) The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.
    b) The characteristics of the participant 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).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is also deemed **Serious** per **Section 10.3**.

10.6.2 Reporting Unanticipated Problems

Unanticipated problem reporting will begin at the time of participant consent. The Unanticipated Problem Form will be submitted to the CRS Compliance Office within 1 business day of becoming aware of the Unanticipated Problem.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to CRS Compliance with an updated Unanticipated Problem Form. The site Investigator or designated research personnel will report all unanticipated problems, whether related or unrelated to the investigational agent(s) to the **IRB in accordance with their local institutional guidelines**.

10.7 FDA Reporting

When RPCI is the IND holder the following describes the FDA reporting requirements by timeline for AEs and new safety findings that meet the criteria outlined below:

Within 7 Calendar Days

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Fatal or life-threatening.

Within 15 Calendar Days

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Serious but not fatal or life-threatening;

Or, meets **ANY** of the following criteria:

- A previous adverse event that is not initially deemed reportable but is later found to fit the criteria for reporting (report within 15 days from when event was deemed reportable).
- Any findings from other studies, including epidemiological studies, pooled analysis of multiple studies, or other clinical studies conducted with the study drug that suggest a significant risk in humans exposed to the drug.
- Any findings from animal or in vitro testing that suggest a significant risk for human participants including reports of mutagenicity, teratogenicity, or carcinogenicity or reports of significant organ toxicity at or near the expected human exposure.
- Any clinically important increase in the rate of occurrence of a serious, related or possibly related adverse event over that listed in the protocol or investigator brochure.

Sponsors are also required to identify in IND safety reports, all previous reports concerning similar adverse events and to analyze the significance of the current event in the light of the previous reports.

Reporting Process

The principal investigator or designee will complete and submit a FDA Form 3500A MedWatch for any event that meets the above criteria. Forms will be submitted to the CRS Compliance Office via email to CRSCompliance@RoswellPark.org. Network Sites refer to **Appendix A**.

11 DATA AND SAFETY MONITORING

Phase 1 studies will be reviewed at the scheduled RPCI Phase 1 meetings and the minutes are forwarded to the IRB for review. Phase I meets on a regular basis per the RPCI Data Safety Monitoring Plan.

The RPCI Data and Safety Monitoring Board will assess the progress of the study, the safety data, and critical efficacy endpoints. The DSMB will review the study annually and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design (c) or termination of the study. Per request, all annual DSMB study outcomes will be made available to NCCN and BI.

12 STATISTICAL METHODOLOGY

This is a Phase I/II study. The Phase 1 is included to compensate for the current lack of toxicity information about nintedanib and capecitabine combination treatment. A standard 3+3 dose escalation design is considered, where a maximum of 18 patients are enrolled.

Phase II is a single arm – single stage study, where a total of n=36 (including 6 treated at the RP2D in Phase I) patients with refractory metastatic colorectal cancer will be enrolled and treated with a combination of nintedanib and capecitabine, as previously outlined. There is no formal interim analysis planned or early stopping rules. However, toxicity and safety outcomes will be regularly reviewed.

Endpoints

- **Phase I**
  - Primary: Establishment of the recommended phase II dose.
- **Phase II**
  - Primary**:** The primary endpoint is the progression free survival (PFS) at 18 weeks. This will be assessed via the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines after every 3 cycles (9 weeks) of therapy.
  - Secondary**:** Median progression free survival will be established. Median overall survival from the date of enrollment to the time of death will be documented. Aggregate rates of adverse events as measured by CTCAE v 4.0 will be recorded to objectively measure toxicities of the two agents.

The primary objectives of this study are:

- Phase I: To estimate the maximum tolerated dose (MTD) and examine the dose-limiting toxicities of nintedanib when administered with capecitabine within the study population and, establish the Recommended Phase II Dose (RP2D).
- Phase II: To assess progression free survival at 18 weeks. This will be assessed via the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines after every 3 cycles (9 weeks) of therapy.

12.1 Sample Size Determination

A maximum of 48 participants, 18 in Phase I and up to 30 additional patients for Phase II will be enrolled in this study. The number of participants required is a function of the unknown dose-limiting toxicity relationship and 18-week PFS rate. Accrual is expected to take 2 years.

Sample Size Justification:

In Phase I, using the standard 3+3 design, there will be a minimum of 9 and maximum of 18 patients enrolled.

In Phase II, the sample size calculations are based on the primary analysis of the 18-week PFS rate. Historically, the 18-week PFS rate is 5% and 25% for refractory metastatic colorectal cancer patients treated with placebo and regorafenib, respectively. The combination of nintedanib and capecitabine is expected to provide an 18-week PFS of at least 40% in patients with refractory metastatic colorectal cancer. The sample size calculation is based on testing hypotheses concerning the proportion of the treated population alive and progression free 18 weeks after enrollment. Let p represent the proportion of patients surviving with no evidence

of disease progression by RECIST at 18 weeks after start of treatment. A true PFS rate of less than p0 = 0.25 is considered unacceptable and evidence of such will deem the treatment not worthy of further study, as regorafenib has historically achieved this success rate. The null and alternative hypotheses to be tested are H_0: $p = p_0$ versus H1: $p > p_0$.

This single-stage design requires a total of 36 evaluable patients to achieve approximately $1 - \beta$ power to detect a difference of at least Δ percentage points (p_0 versus $p_0 + \Delta$). For calculations in this study, $p_0 = 0.25$, $\alpha = 0.10$, $1 - \beta = 0.80$ and $\Delta = 0.17$. With these design parameters, the sample size was calculated using PASS v11 [38].

12.2 Demographics and Baseline Characteristics

Descriptive statistics (as appropriate: n, percent, mean, median, min and max) will be used to summarize demographic and baseline characteristics.

12.3 Efficacy Analysis

Objective tumor response will be tabulated overall (and by dose level if appropriate). Only participants who have completed at least 2 cycles will be evaluable for response.

Primary Analysis:

The Phase I portion of the study begins by enrolling 3 patients at Dose Level 1 (see **Table 2**). Standard 3+3 rules will be followed until the maximum tolerated (or administered) dose is found. The recommended Phase 2 dose will be considered tolerable if DLT(s) are observed in at most 1 of 6 patients completing at least 2 treatment cycles at that dose level. Available toxicity information about these drugs suggests that Dose Level 2 will be the recommended Phase 2 dose, and that 9 patients will be required for the Phase 1. The 6 Phase 1 patients treated at the recommended Phase 2 dose will be included in Stage 1 of the Phase 2 study.

The Phase 2 study's primary endpoint is the PFS rate, defined as the proportion of patients who survive without disease progression (per RECIST criteria) for least 18-weeks after the start of treatment. Patients who progress or die (due to disease or any cause) prior to 18-weeks will be counted as failures.

The following hypothesis about the true 18-week PFS rate (p) will be evaluated using a one-sided exact binomial test:

$$H_0: p = 0.25 \text{ versus } H_1: p > 0.25.$$

If $T = 12$ or fewer PFS responses are observed among the total $n_1 + n_2 = 36$ evaluable patients, the therapy will be deemed ineffective; otherwise, it will be concluded that the therapy is promising. The analysis will be conducted in SAS v9.4 (Cary, NC) at a nominal significance level of α=0.10.

Secondary Analysis: In Phase II the secondary outcomes include: overall (OS) and progression free (PFS) survival, and toxicities. A survival event is defined as a patient who experiences death from cancer or any cause, while a patient is considered censored if they are alive at the end of the

study or at last visit before being lost to follow-up. The survival time is defined as the time from treatment until the survival event or censoring. The PFS will be as defined in the primary analysis. The OS and PFS are considered bivariate time-to-event data, and will be summarized using standard Kaplan-Meier methods. Estimates of median OS and PFS will be obtained with corresponding 90% confidence intervals. If the true median OS or PFS with the new treatment is 10.2 or 3.0 months, a 60% improvement over historical controls (6.4 and 1.9 month median OS and PFS, respectively); then Phase II estimates of the median will have interval widths of approximately 9.9 or 3.2 months for OS and PFS, receptively. The observed toxicities and adverse events will be reported as frequencies and relative frequencies, with toxicity rates estimated by 90% Wilson confidence intervals. If the true overall toxicity or adverse event rate is 0.10 to 0.50; then Phase II estimates of these rates will have interval widths of approximately 0.17 to 0.26.

12.4 Safety Analysis

DLTs are the primary endpoint of this study and are used in the estimation of the MTD and the accompanying of the dose escalation decisions. However, no formal analyses of DLTs are planned. Participants who do not have a DLT and who do not complete a full cycle of treatment will be considered non-evaluable for DLT.

12.4.1 Adverse Event

The frequency of toxicities will be tabulated by grade across all dose levels and cycles. The frequency of toxicities will also be tabulated for the dose estimated to be the MTD. All participants who receive any study treatment will be considered evaluable for toxicity.

12.5 Interim Analysis and Criteria for Early Termination of the Study

The first portion of this study is a Phase 1 study and as such will be monitored and discussed by RPCI's Phase 1 Committee, which meets on a regular basis per the RPCI Data Safety Monitoring Plan. Drug safety will be monitored and evaluated continuously throughout the study including 30 day safety follow-up period by obtaining, reviewing and analyzing data on AEs, changes in laboratory values, vital signs, electrocardiograms (ECGs), and physical examination findings. Potential early termination decisions are an inherent part of the Phase 1 study monitoring.

There is no formal interim analysis planned or early termination criteria for the Phase II study. However, toxicity and safety outcomes will be regularly reviewed.

12.6 Pharmacokinetic or Pharmacokinetic/Pharmacodynamic Analysis

PK/PD Modeling:

A mechanistic PK/PD model will be developed to characterize the time course of nintedanib concentrations in relation to target decreases in sVEGFR-2 and FGF23. Subsequently, diagnostic plots will be created to ascertain whether a trend exists among sVEGFR-2 levels, FGF23, and progression free survival (PFS). If trends exist, these endpoints will also be included in the PK/PD model. A variety of compartmental population PK models will be evaluated using a nonlinear mixed effects modeling approach. The PK models explored will be described by the

estimation of mean structural parameters (e.g., plasma volumes of distribution and clearances), the magnitude of inter-individual variability (IIV) in these parameters, and residual variability (RV). The model for IIV will be assumed that the variance is proportional with respect to the typical value of the PK parameter. This analysis will include evaluation of the influence of a limited number of patient covariates, such as demographics along with other cofactors, on the variability in select PK/PD parameters. Based on our sparse sampling approach, prior information on PK parameters and variances can be used with a Bayesian estimation method. For comparisons of hierarchical models, the change in the minimum value of the objective function (MVOF), a statistic that is proportional to minus twice the log likelihood of the data, will be examined. A change in the MVOF of greater than 7.88 between two hierarchical models represents a statistical difference at a p-level of 0.005 for the addition of one parameter (df = 1). The goodness-of-fit analyses will be additionally assessed by: (1) scatterplots of measured concentrations and weighted residuals versus population predicted concentrations, and weighted residuals versus time since first and last dose; (2) scatterplots of measured concentrations, individual weighted residuals, and absolute individual weighted residuals versus individual predicted concentrations; (3) the precisions of the parameter estimates as measured by the percent standard error of the mean (%SEM = standard error/parameter estimate * 100%); (4) changes in the estimates of IIV and RV; and (5) histograms, boxplots, and plots of quantiles of individual and population weighted residuals versus quantiles of the normal distribution (QQ plots).

13 ETHICAL AND REGULATORY STANDARDS

13.1 Ethical Principles

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC) at each investigational site. Each participant (or legal guardian) shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the participant is made aware of the investigational nature of the treatment and that informed consent is given.

The Investigator is responsible for the retention of the participant log and participant records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining participant authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the participant is treated, in accordance with the Declaration of Helsinki, Good Clinical Practice, and according to the guidelines in this protocol, including attached appendices.

13.2 Informed Consent

The Investigator (or IRB specified designee) is responsible for obtaining written consent from each participant or the participant's legally authorized representative in accordance with ICH-GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the participant according to ICH-GCP, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The participant should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

The Investigator shall provide a copy of the signed consent form to the participant and the signed original shall be maintained in the Investigator File. A copy of the signed consent form must be filed in the participant file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

14 STUDY RESPONSIBILITIES

14.1 Data Collection

Data entry into the database is to be completed in a timely fashion (within 30 days) after the participant’s clinic visit. If an AE is considered serious it is captured on both the Adverse Event page and the Serious Adverse Event Source Form, which is handled in an expedited fashion.

Data management activities will be performed using eClinical. eClinical is a suite of software tools that enables the collection, cleaning and viewing of clinical trial data. CRS data management will design the study-specific database and facilitate its development by the eClinical Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database will be put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs (via the EXPeRT Module). eClinical is compliant with all relevant technical aspects of relevant GCP guidelines.

- The system can generate accurate copies of stored data and audit trail information in human readable form.
- System access is limited to authorized individuals through the controlled assignment of unique ID and password combinations.
- The system is designed to periodically force users to change their passwords and verifies that user ID and password combinations remain unique.
- The system automatically generates a permanent time-stamped audit trail of all user interactions.

When data entry is complete, data management will review the data and will query any missing, incomplete, or invalid data points for resolution by the Clinical Research Coordinator and

Investigator. Once all queries have been resolved, the data can be released to the statistician for analysis.

14.2 Maintenance of Study Documents

Essential documents will be retained per RPCI's policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with RPCI.

15 ADMINISTRATIVE RULES

15.1 Revisions to the Protocol

RPCI may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation.

15.2 Termination of the Study

It is agreed that, for reasonable cause, either the RPCI Investigators or NCCN or Boehringer Ingelheim, may terminate this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement. In addition, RPCI may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of participants enrolled in the study.

15.3 Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

16 APPENDICES

Appendix A Instructions for Network Sites

1. CONTACT INFORMATION

All questions related to the protocol or study implementation should be directed to:

Roswell Park Cancer Institute
CRS Network Office
ASB K 104
Buffalo, New York 14263
Telephone:
Monday - Friday; 7: 00 AM to 4: 00 PM EST
716-845-8084
After hours, weekends, and holidays request the RPCI Investigator
716-845-2300
Fax: 716-845-8743

2. INFORMED CONSENT

- Informed consent must be obtained by the site Investigator/designee from any participants wishing to participate, prior to any research procedures or treatment.
- An informed consent template is provided by RPCI and can be amended to reflect institutional requirements.
- All consent changes must be reviewed by RPCI Network Office prior to submission to the site IRB.
- The informed consent must be IRB approved.
- Always check that the most up to date version of the IRB approved consent is being used.
- Within 5 business days, notify the RPCI Network Office of all participant withdrawals or consent to limited study participation and appropriately document the discontinuation and the reason(s) why.

3. PARTICIPANT REGISTRATION

The participant completes the Gender, Race, and Ethnicity Form and this is placed in the study binder.

RPCI does not grant exceptions to eligibility criteria.

Phase 1 Protocol Registration Instructions

Contact the RPCI Network Monitor to verify that a slot is available in the open cohort when a participant has been identified. **Do not have the participant sign consent prior to verifying an open slot.**

- After the participant signs consent, the Subject Screening and Enrollment Log must be faxed or emailed to the RPCI Network Monitor within 1 business day. The RPCI Network Monitor

will confirm receipt of the Subject Screening and Enrollment Log and email the participant ID number.

- When the participant has met eligibility, a signed eligibility checklist and other requested documentation will be faxed or emailed to the RPCI Network Monitor.
- Within 1 business day of receipt of the eligibility check list, the RPCI Network Monitor will fax or email the cohort assignment and dose level.
- An email must be sent by the site to confirm receipt of the cohort assignment and to provide the planned treatment start date.

Phase 2 Protocol Registration Instructions

The Subject Screening and Enrollment Log must be faxed or emailed to the RPCI Network Office within 1 business day of the date the participant is consented. Once the Investigator has determined that eligibility has been met, complete the eligibility check list and fax or email it to the RPCI Network Monitor at 716-845-8743.

4. STUDY DEVIATIONS

- If a deviation has occurred to eliminate hazard, this must be reported to the RPCI Network, site IRB and any other regulatory authority involved in the study.
- ANY study deviation will be recorded on the **Study Deviation Log**.
- Participants inadvertently enrolled with significant deviation(s) from the study-specified criteria will be removed from the study, at the discretion of the Principle Investigator.

5. STUDY DOCUMENTATION

- Study documents must be filled out completely and correctly. Ditto marks are not allowed.
- If an entry has been documented in error put a single line through the entry and initial and date the change. The RPCI Network Monitor must be able to read what has been deleted.
- Do **NOT** use white-out, magic marker, scratch-outs.
- Do **NOT** erase entries.
- Use only black ink for documentation on the accountability form and any other study forms.
- It is the responsibility of RPCI to inform the Investigator/ institution as to when these documents no longer need to be retained. If, for any reason, the Investigator desires to no longer maintain the study records, they may be transferred to another institution, another investigator, or to RPCI upon written agreement between the Investigator and RPCI.

6. DRUG ACCOUNTABILITY

Drug accountability must be strictly maintained.

- Responsibility rests solely with the Investigator but can be delegated as appropriate (e.g., to pharmacy personnel).
- A drug accountability record form (DARF) will record quantities of study drug received, dispensed to participants and wasted, lot number, date dispensed, participant ID number and initials, quantity returned, balance remaining, manufacturer, expiration date, and the initials of the person dispensing the medication.
- Study drug supply will only be used in accordance with the IRB approved study.
- Drug accountability forms are protocol and agent specific, they are study source documents and will be used to verify compliance with the study.
- An inventory count must be performed with each transaction. Any discrepancies shall be documented and explained.
- Drug accountability forms must be stored with study related documents.
- Each medication provided for this study and each dosage form and strength must have its own DARF.
- Dispensing the wrong study supply is considered a **medication error**.
- **NEVER** replace investigational agents with commercial product.
- Do **NOT** "transfer", "borrow" or "replace" supplies between studies.

7. SERIOUS ADVERSE EVENT REPORTING

The site Investigator or designated research personnel will report all SAEs, whether related or unrelated to the investigational agent(s) to the **IRB in accordance with their local institutional guidelines**. The site will notify the RPCI Network Monitor within 1 business day of being made aware of the SAE. A preliminary written report must follow within 1 business day of the first notification using the following forms:

- RPCI SAE Source form
- MedWatch 3500A

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

AND

NCCN at

ORPReports@nccn.org
or

Fax: (215) 358-7699

A complete follow-up report must be sent to the RPCI Network Monitor when new information becomes available.

- If this is a Phase 1 study the site Investigator or designated research personnel will complete and send the **Serious Adverse Event / Possible Dose Limiting Toxicity Memo** to notify the appropriate RPCI personnel of an SAE or potential DLT via email: Phase1DLTnetwork@Roswellpark.org.

8. UNANTICIPATED PROBLEM REPORTING

An unanticipated problem (UP) is any incident, experience, or outcome that meets all of the criteria in **Section 10.6**.

For all adverse events occurring that are unanticipated and related or possibly related to the research drug, biologic or intervention, the participating physician or delegated research staff from each site will notify their local **IRB in accordance with their local institutional guidelines**. The site must also notify the RPCI Network Monitor within 1 business day of being made aware of the Unanticipated Problem by completing the **RPCI Unanticipated Problem Report Form** and faxing or emailing it to the RPCI Network Monitor.

9. DATA AND SAFETY MONITORING

Weekly or bi-weekly teleconferences will be scheduled to review participant adverse events and study status. The site Investigator and study coordinator are expected to attend.

Appendix B ECOG Performance Status Scores

Description	Status
Fully active, able to carry on all pre-disease performance without restriction.	0
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.	1
Ambulatory and capable of all self-care but unable to carry out any work activities.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead	5

Appendix C Drug-Induced Liver Injury Follow-Up Procedures

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" (http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf) which outlines the detection, evaluation, follow-up and reporting of drug-induced liver injury in clinical trials. Drugs that have the potential for inducing severe liver injury may be identified by marked peak aminotransferase elevations (10x-, 15xULN), or the combination of hepatocellular injury (aminotransferase elevation ≥3xULN) and altered liver function (hyperbilirubinemia ≥2xULN) which is defined as potential "Hy´s law case" if not explained by other causes including evidence of biliary obstruction (i.e., significant elevation of alkaline phosphatase, ALP, >2X ULN) or some other explanation of the injury (e.g., viral hepatitis, alcohol hepatitis, concomitant use of other known hepatotoxic drugs). This constellation predicts a poor outcome and although very rare, these potential cases have to be well characterized as soon as being identified as other confounding conditions may be the cause.

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

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

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

Definition

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

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

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

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

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

Procedures

1. Protocol-specified significant events are to be reported in an expedited manner similar as Serious Adverse Events, even if they do not meet any of the seriousness criteria and documented in the eCRF.
2. Replication of the following laboratory tests for confirmation within 48 hours:

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

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

The investigator will report all SAEs and non-serious AEs which are relevant to reported SAEs and AESIs by fax using BI IIS SAE form or MedWatch 3500A form, and completed BI SAE Fax Cover sheet to BI Unique Entry Point as detailed below:

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
Ridgefield, CT 06877

Fax: 1-203-837-4329

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 e.g., steroids as concomitant supportive treatment), alcohol use, recreational drug use, and special diets detailed history of exposure to environmental chemical agents.
- In case that both imaging and laboratory value did not unequivocally confirm cholestasis as the reason of ALT / AST increase, in particular if AP < 2x ULN, then please complete the following laboratory tests:
- Clinical chemistry:
- Alkaline phosphatase, cholinesterase (either plasma or red blood cell), albumin, PT or INR, CK, CK-MB, coeruloplasmin*, α-1 antitrypsin*, transferrin, ferritin, amylase*, lipase*, fasting glucose*, cholesterol, triglycerides
- Serology:
- Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HBsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG)*, Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive)*, Anti-Smooth Muscle antibody (titer)*, Anti-nuclear antibody (titer)*, Anti-LKM (liver-kidney microsomes) antibody*, Anti-mitochondrial antibody*, Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM)
- Hormones, tumor marker:

- TSH*
- Hematology:
- Thrombocytes*, eosinophils*

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

4. 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.
5. 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 Study Medication Diary for Nintedanib

Protocol No.: _____ **Patient Name**: _____

Cycle _____ **ID#** _____ **Medical Record No**.: _____

Please complete this calendar on a daily basis. Take the AM and PM doses approximately 12 hours (+/- 2 hours) apart. Take with water within 30 minutes after the end of a meal. Both Nintedanib and Capecitabine may be taken at the same time. If a dose is missed write "0" in the # taken box. If your dose changes, record the new dose on the day it changed on the study calendar.

Start Date: _____ Nintedanib per dose #100mg: _____ #150mg: _____ (Total daily dose = _____mg)
Capecitabine per dose #150mg: _____ #500mg: _____ (Total daily dose = _____mg)

Cycle Day	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7	
Date														
Nintedanib	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Time Dose Taken														
100mg #														
150mg #														
Capecitabine	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Time Dose Taken:														
150mg #														
500mg #														

Cycle Day	Day 8		Day 9		Day 10		Day 11		Day 12		Day 13		Day 14	
Date														
Nintedanib	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Time Dose Taken:														
100mg #														
150mg #														
Capecitabine	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Time Dose Taken:														
150mg #														
500mg #														

Cycle Day	Day 15		Day 16		Day 17		Day 18		Day 19		Day 20		Day 21	
Date														
Nintedanib	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Time Dose Taken:														
100mg #														
150mg #														
Capecitabine	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Time Dose Taken:	X	X	X	X	X	X	X	X	X	X	X	X	X	X
150mg #	X	X	X	X	X	X	X	X	X	X	X	X	X	X
500mg #	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Bring this calendar and your pill bottles (including any unused pills) with you to all scheduled study appointments.

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Clinical Research Services

Study Medication Diary for Nintedanib: Coordinator Use Only

Protocol No.: _____ **Patient Name**: _____

Cycle _____ **ID#** _____ **Medical Record No**.: _____

Coordinator use only
Nintedanib #1 _____
Date of return: _____
# of pills
(dispensed: _____ -- returned: _____)
_____ x 100 = % adherence: _____
# of pills scheduled _____

Coordinator use only
Capecitabine #2 _____
Date of return: _____
# of pills
(dispensed: _____ -- returned: _____)
_____ x 100 = % adherence: _____
# of pills scheduled _____

Patient signature: _____ Date: _____

Investigator signature: _____ Date: _____

Appendix E Procedure for Obtaining a Urine Protein/ Creatinine Ratio

1. Obtain at least 4 ml of a random urine sample (does not have to be a 24-hour urine)
2. Determine protein concentration (mg/dL)
3. Determine creatinine concentration (mg/dL)
4. Divide #2 by #3 above: urine protein / creatinine ratio = protein concentration (mg /dL) / Creatinine concentration (mg/*dL)*

The UPC directly correlates with the amount of protein excreted in the urine per 24 hr (i.e., a UPC of 1 should be equivalent to 1 g protein in a 24 hr urine collection)

Protein and creatinine concentrations should be available on standard reports of urinalyses, not dipsticks. If protein and creatinine concentrations are not routinely reported at an Institution, their measurements and reports may need to be requested.

17 REFERENCES

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