TITLE: Multicenter Phase 2 Study of Nintedanib for Patients with Advanced Carcinoid Tumors

Roswell Park Cancer Institute Study Number:	**I259114 NCT02399215**
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Sponsor:	**Roswell Park Cancer Institute**
Funding:	**NCCN**
Industry/Other Supporter:	**Boehringer Ingelheim**

Study Contacts

(Study personnel outside of RPCI CRS who will be housing essential study documents)

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SYNOPSIS

Title / Phase	**Multicenter Phase 2 Study of Nintedanib for Patients with Advanced Carcinoid Tumors**
Roswell Park Cancer Institute Study Number	I 259114
Roswell Park Cancer Institute Investigator	Renuka V. Iyer, MD
Sponsor	Roswell Park Cancer Institute
Funding Organization	NCCN
Industry Support	Boehringer Ingelheim
Study Drug	Nintedanib (BIBF1120: provided by Boehringer Ingelheim)
Objectives	**Primary:** • To assess progression free survival (PFS), defined as the time interval from initiation of therapy, to its cessation for documentation of progressive disease (PD) or death **Secondary:** • To assess the clinical response (complete response + partial response) in all patients with measurable disease (using standard RECISTv1.1 criteria). • To assess overall survival (OS) in all patients. • Assess changes in QOL throughout treatment using the EORTC QLQ – GI.NET21 questionnaire for carcinoid patients with gastrointestinal neuroendocrine tumors, in all patients who have filled out at least two QOL questionnaires and, will be reported by groups based on response (response, stable disease or progressive disease). • Steady-state PK of nintedanib, biomarkers, Treg and cytokine expression and growth factors will be analyzed for all patients and reported in groups based on response. • Gene mutations and copy number alterations analysis in the mTOR pathway (will be performed only on the first 10 patients), protein expression of activation of Akt (as well as other downstream targets). • Toxicity (graded using the NCI CTCAE version 4.0) will be closely monitored and all toxicities will be tabulated
Study Design	This is an open label, multi-center phase II study in all patients with advanced low and intermediate grade neuroendocrine cancers (carcinoids), excluding PNETS (pancreatic neuroendocrine tumors).
Target Accrual and Study Duration	Two participating institutions will enroll maximum of 30 evaluable patients over a 24 month period.
Study Procedures	**Physical Examination (including pre –existing conditions, vital signs, and body weight):** Baseline, Day 1 of every cycle beginning with Cycle 2, End of Treatment **Hematology:** Baseline, Cycle 1-Week 1-Day 1, Cycle 1-Week 3-Day 15, Day 1 of subsequent cycles, End of Treatment.

	Chemistry: Baseline, Cycle 1-Week 1-Day 1, Cycle 1-Week 3-Day 15, Day 1 of subsequent cycles, End of Treatment. **Serum serotonin, Chromogranin A:** Baseline, every 8 weeks (x24 weeks) prior to treatment beginning at Cycle 3-Week 1-Day 1 followed by every 12 weeks (on same day as imaging). **Urine Sample (24-hr urine 5-HIAA test):** Baseline **Urine protein/Creatine ratio:** . Baseline and, prior to treatment every 8 weeks for 24 weeks followed by evaluations at every 12 week or as clinically indicated **Plasma Biomarkers:** Baseline, 8 weeks (+/- 3 days) after start of treatment **EORTC QLQ – GI.NET21:** Baseline, prior to treatment every 8 weeks from start of treatment (x24 weeks) followed by evaluations every 12 weeks (on same day as imaging)., End of Treatment **Pregnancy test (serum):** Baseline **ECOG Performance Status:** Baseline, prior to treatment every 8 weeks from start of treatment (x24 weeks) followed by evaluations every 12 weeks (on same day as imaging)., End of Treatment **Immune biomarkers:** Baseline **CT scan of (chest, abdomen, & pelvis):** Baseline, restaging will be performed every 8 weeks from start of treatment (x24 weeks), followed by every 12 weeks. **Electrocardiogram:** Baseline **Tumor/Disease assessment:** Baseline, every 8 weeks from start of treatment for 24 weeks, followed by every 12 weeks **Concomitant Medications:** Baseline, Cycle 1-Week 1-Day 1, Cycle 1-Week 3-Day 15, Day 1 of subsequent cycles, End of Treatment, PFS Follow-Up. **Adverse Events:** Baseline, Cycle 1-Week 1-Day 1, Cycle 1-Week 3-Day 1, Day 1 of subsequent cycles, End of Treatment, PFS Follow-Up.
Statistical Analysis	**Sample Size Determination:** Two participating institutions will enroll maximum of 30 evaluable patients over a 24 month period.The sample size calculation is based on testing the hypotheses concerning the PFS rate at 16 weeks in patients treated under the proposed therapy: H_0: $p \leq p_0$ versus H_A: $p > p_0$. This single-stage design requires a total of n patients in order to achieve approximately 1-β power to detect differences of Δ percentage points (p_0 versus $p_0 + \Delta$). For this study $\alpha = 0.10$ and $1-\beta = 0.90$; with $p_0 = 0.40$ and $\Delta = 0.24$ for this population of carcinoid patients. **Efficacy Analysis:** The primary objective of this study is to assess the efficacy of the investigational agent nintedanib in carcinoid patients. Let p represent the PFS rate at 16 weeks. A true PFS rate at 16 weeks of less than $p_0 = 0.40$ is considered unacceptable in

	carcinoid, and evidence of such will deem the treatment not worthy of further study. The null and alternative hypotheses to be tested are H_0: $p \leq p_0$ versus H_A: $p > p_0$. A one-sided exact binomial test (at a nominal α=0.10) and corresponding decision rules will be used to evaluate these hypotheses: • If *15* patients or less have not progressed at 16 weeks, then it is concluded that the therapy is not promising. • If *16* patients or more have not progressed at 16 weeks, then it will be concluded that the therapy is promising. *Secondary Analysis:* The time-to-event outcomes (PFS and OS) will be reported using standard Kaplan-Meier methods. Ninety-five percent confidence intervals for the median PFS and OS will be calculated using Greenwood's formula. Exact 90% confidence interval estimates using the Clopper-Pearson method will be given for the response and toxicity rates. An exact 90% confidence interval will be given for the rate of improved QOL. Changes in pre- and post- treatment cytokine expression and growth factors will be analyzed using permutation paired t-tests. Dichotomous variables, such as response and QOL, will be analyzed using the logistic regression to investigate their association with quantified variables, such as biomarker expression and gene mutation. The association between survival and quantified variables will be investigated using the Cox-proportional hazard model. **Safety Analysis:** The frequency of toxicities will be tabulated by grade across all dose levels and cycles. All participants who receive any study treatment will be considered evaluable for toxicity.

ROSWELL PARK CANCER INSTITUTE

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM

Participant Name: (Network sites use participant initials): _____

Medical Record No.: (Network sites use participant ID): _____

Title: Multicenter Phase 2 Study of Nintedanib for Patients with Advanced Carcinoid Tumors.

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	○ Patient must be on a stable dose of octreotide LAR or lanreotide for 3 months prior to study enrollment.	
☐	☐	☐	○ Patients must have histologically or cytologically confirmed well differentiated or moderately differentiated (low grade or intermediate grade) neuroendocrine tumor that is locally advanced or metastatic and not of pancreatic origin	
☐	☐	☐	○ Measurable disease determined by CT or MRI.	
☐	☐	☐	○ Age ≥ 18 years of age.	
☐	☐	☐	○ Have an ECOG Performance Status of 0 – 2.	
☐	☐	☐	○ Life expectancy greater than 3 months.	
☐	☐	☐	○ Have the following clinical laboratory values: ○ Leukocytes ≥ 3,000/μL ○ Absolute neutrophil count ≥1,500/μL ○ Total bilirubin ≤ 2 mg/dL AST / ALT, ○ AST/ALT ⩽ 1.5 X ULN and bilirubin ⩽ ULN for patients without liver metastases. ○ AST/ALT ⩽ 2.5 X ULN and bilirubin ⩽ ULN for patients with liver metastases. ○ Patients with Gilbert syndrome and bilirubin < 2 X ULN and normal AST/ALT ○ Creatinine ≤1.5 mg/dl	
☐	☐	☐	○ Prior treatment will be permitted including surgery ≥ 4 weeks), cytotoxic chemotherapy (maximum of 2 prior regimens); radiation, interferon, targeted growth factors ≥ 4 weeks); and prior treatment with octreotide, will be allowed.	
☐	☐	☐	○ Ability to swallow and retain oral medication.	
☐	☐	☐	○ Participants of child-bearing potential must agree to use adequate	

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
			contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry. 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.	
☐	☐	☐	○ 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.	
☐	☐	☐	○ Archival tissue of carcinoid biopsy must be available.	

Investigator Signature: _____ Date: _____

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM

Participant Name: (Network sites use participant initials): _____

Medical Record No.: (Network sites use participant ID): _____

Title: Multicenter Phase 2 Study of Nintedanib for Patients with Advanced Carcinoid Tumors.

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Uncontrolled hypertension, unstable angina, New York Heart Association Grade II or greater congestive heart failure, unstable symptomatic arrhythmia requiring medication, or clinically significant peripheral vascular disease (Grade II or greater). Refer to Appendix C.	
☐	☐	☐	2. Presence of brain metastases.	
☐	☐	☐	3. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to day 0, or anticipated need for major surgical procedure during the course of the study, or fine needle aspirations or core biopsies within 7 days prior to day 0.	
☐	☐	☐	4. Significant proteinuria at baseline (≥ 500 mg/ 24 h)	
☐	☐	☐	5. Serious non-healing wound, ulcer or bone fracture	
☐	☐	☐	6. Evidence of bleeding diathesis or coagulopathy.	
☐	☐	☐	7. Recent (≤ 6 months) arterial thromboembolic events, including transient ischemic attack, cerebrovascular accident, unstable angina, or myocardial infarction.	
☐	☐	☐	8. Poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma, adenocarcinoid, goblet cell carcinoma, or small cell carcinoma.	
☐	☐	☐	9. Hepatic artery embolization or ablation of hepatic metastasis within 3 months of enrollment, prior PRRT within 4 months or any other cancer therapy within 4 weeks . (As long as all toxicities are resolved).	
☐	☐	☐	10. Intolerance or hypersensitivity to octreotide.	
☐	☐	☐	11. Severe or uncontrolled medical conditions.	
☐	☐	☐	12. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.	
☐	☐	☐	13. Pregnant or nursing female participants.	

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	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.	

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 Carcinoid (Neuroendocrine) Tumors

Neuroendocrine tumors, also known as carcinoids, are uncommon tumors arising from various primary sites. Although thought to be rare, the incidence of neuroendocrine tumors is rising and the estimated prevalence in the United States is 103,312 cases, which is more than gastric and pancreatic cancer combined[1]. Nearly 50% of patients with neuroendocrine tumors have metastatic disease at presentation, and 65% will die within 5 years of diagnosis.

Carcinoids are generally slow growing tumors, but in the advanced setting can be very disabling and impact quality of life (QOL) due to diarrhea, bowel obstructions, pain, weight loss, depression and fatigue. Many of the abdominal symptoms are caused by the dense adhesions. Mid gut carcinoids often secrete serotonin that acts synergistically with platelet derived growth factor (PDGF) and stimulates DNA synthesis in fibroblasts acting through 5–HT_{1B} receptors coupled to a G_i-protein[2]. This may, in part explain the dense fibrotic reaction seen in small bowel carcinoids and subsequent obstructive symptoms. Carcinoids are highly vascular and VEGF, PDGF and FGF are all also thought to drive disease with the additional serotonin mediated fibroblast proliferation driving symptom progression.

Nintedanib is a promising new orally bioavailable targeted agent that targeted VEGFR1-3, FGFR 1/3 and PDGFR. Several agents targeting VEGF and PDGF have shown promising activity in pancreatic neuroendocrine tumors. However response rates for patients with non-pancreatic carcinoid tumors have been low. We hypothesize, that since fibroblast proliferation is a major driver of disease and clinical progression in non-pancreatic carcinoids that is shown in animal models to be driven by serotonin (5-HT) through FGFR2 [3] that targeting angiogenesis and FGFR merits study in this tumor. There are no prospectively validated predictors of response to FGFR inhibitor, but studies in in a study done by[4] in lung NET (neuroendocrine tumor) patient samples, FGFR1 amplification was seen in 52% of small cell neuroendocrine cancer and 19% of bronchial carcinoids. These expression data are much higher than those reported in breast, lung or bladder cancers, and make it much more likely to see activity with FGF inhibition.

Targeting angiogenesis with sunitinib has been shown to improve outcomes in patients with PNETs [5]. Similar benefit was seen in patients with PNETs with everolimus, an oral agent that targets the mTOR pathway known to drive NET progression [6]. Unfortunately median treatment duration was ~ 8 months and progression free survival was ~ 11 months in both trials and upon progression, unfortunately patients have no further options that palliate symptoms that can be disabling for PNETs due to hormonal overproduction and pain from bony metastases that seem to occur with reasonable frequency in these patients.

Furthermore, this is an area of unmet need as there are no approved anti-tumor agents for patients with carcinoids that are not of pancreatic origin. Octreotide is shown to improve symptoms and frequently used in these patients. Recently in a phase 3 trial, therapy with everolimus and octreotide was shown to prolong PFS compared to placebo [7]. Results from RADIANT-4 may confirm PFS with everolimus in this population of ~11 months but, given the long overall survival of these patients and morbidity from symptoms, clearly there remains a need for newer tolerable agents to continue to offer symptom and tumor control. These data form the background and rationale for our hypothesis that the combination of nintedanib with

octreotide LAR may offer disease control and clinical benefit in patients with carcinoid tumors and PNETs.

Lastly, a landmark study in carcinoid (small intestinal NETs) was recently published. They sequenced 48 small bowel tumors using massively parallel, next-generation DNA sequencing. Not surprisingly a paucity of mutations were identified: however, 197 protein-altering somatic SNVs affected a preponderance of cancer genes, including FGFR2, MEN1, HOOK3, EZH2, MLF1, CARD11, VHL, NONO, and SMAD1 were noted[8]. Integrative analysis of SNVs and somatic copy number variations identified recurrently altered mechanisms of carcinogenesis: chromatin remodeling, DNA damage, apoptosis, RAS signaling, and axon guidance. Candidate therapeutically relevant alterations were found in 35 patients, including *SRC*, SMAD family genes, *AURKA*, *EGFR*, *HSP90*, and *PDGFR*. Mutually exclusive amplification of *AKT1* or *AKT2* was the most common event in the 16 patients with alterations of PI3K/Akt/mTOR signaling. All of these genes are included in our IMPACT next generation sequencing platform. [8]We will therefore sequence 10 tumors to see if response and/or resistance to nintedanib is influence by these deregulated pathways.

Given the mutation alterations identified in the AKT1 or AKT2 genes, we also hypothesize that Akt activation may predict response and/or resistance to treatment. Pre-archived and post-treatment biopsies will be assessed for activity and will be determined by blotting for the phosphorylation of Akt downstream targets including p-Foxo, p-GSK3, p-PRAS40. IHC analysis of total AKT, p-Akt Ser473, PTEN, total 4E-BP1, p-4E-BP1Thr70, p-eIF-4G Ser1108 (peIF-4G), total S6, p-S6 Ser235/236 and Ser240/244, and proliferation marker Ki-67 will also be performed in formalin-fixed paraffin-embedded sections from the tumor samples

1.2 Nintedanib

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.

1.3 Preclinical Development and Pharmacokinetics of Nintedanib

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

Nintedanib inhibits the signalling cascade mediating angiogenesis by binding to the adenosine triphosphate (ATP) binding pocket of the receptor kinase domain, thus interfering with cross-activation via auto-phosphorylation of the receptor homodimers.

The specific and simultaneous abrogation of these pathways results in effective growth inhibition of both endothelial and, via PDGF- and FGF-receptors of perivascular cells which may be more

effective than inhibition of endothelial cell growth via the VEGF pathway alone. Furthermore, signaling by FGF-receptors has been identified as a possible escape mechanism for tumour angiogenesis when the VEGF pathway is disrupted.

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

In addition preclinical models show that nintedanib (BIBF1120) may have a direct anti-tumour effect on those malignant cells which overexpress PDGFR and/or FGFR (e.g. H1703 NSCLC cells). *In vitro*, the target receptors are all inhibited by nintedanib in low nanomolar concentrations (**Table 1**).

Table 1 Potency [IC50, nm] of nintedanib in *in vitro* Kinase Assays

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

In 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% [(9)].

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 [5]. The metabolic characteristics are predominantly independent of cytochrome P450-catalysed metabolic pathways [(10)].

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 [(10)].

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 can be found in the Investigator's Brochure.

1.4 Clinical Studies with 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.

1.4.1 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, diarrhea, 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[(11)].

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, diarrhea, vomiting, abdominal pain and fatigue of mostly low to moderate severity. Dose limiting toxicities (DLT) were mainly confined to reversible hepatic enzyme elevations (AST, ALT, γ-GT) which increased dose-dependently. Most cases occurring at doses of 250 mg and above, and a very low incidence at doses below

200 mg and were reversible after discontinuation of nintedanib treatment. All adverse events observed after single administration of single doses of nintedanib to healthy volunteers were only of CTCAE grade 1 severity and fully reversible [10].

1.4.2 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%), diarrhea (47.9%), vomiting (42.5%), anorexia (28.8%), abdominal pain (13.7%) and reversible alanine transaminase (13.7%) and aspartate aminotransferase elevations (9.6%) In conclusion it was generally well tolerated and displayed single agent activity in advanced or recurrent NSCLC patients. Median overall survival (OS) was 21.9 weeks. Eastern Cooperative Oncology Group (ECOG) 0–1 patients (n = 56) had a median PFS of 11.6 weeks and a median OS of 37.7 weeks. Tumour stabilization was achieved in 46% of patients (ECOG 0–1 patients: 59%), with one confirmed partial response (250 mg bid.)[12].

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, diarrhea, 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)[13].

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 [(14)].

1.4.3 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[(15)].

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[(16)].

1.4.4 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[(17)].

1.4.5 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[(18)].

1.4.6 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 in combination with mFOLFOX 6. In comparison to bevacizumab, nintedanib showed a similar magnitude of efficacy, a similar safety/tolerability profile, a similar exposure and dose intensity of mFOLFOX6 [19]. 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[20].

A Phase III study is going to start in late 2014 to evaluate the efficacy of nintedanib in patients with metastatic colorectal cancer (mCRC) after failure of previous treatment with standard chemotherapy and biological agents (ClinicalTrials.gov Identifier: NCT02149108).

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

1.5 Correlative Studies

1.5.1 Tissue biomarkers

1.5.1.1 Fibroblast Growth Factors (FGFs)

The family of fibroblast growth factors (FGFs) regulates a variety of developmental processes and the 18 mammalial FGFs are grouped into 6 subgroups based on sequence homology and phylogeny[21]. The FGF ligands carry out their diverse functions by binding and activating FGFR family tyrosine kinase receptors. Investigators from our group at Roswell Park recently found that response to another FGFR inhibitor, dovitinib correlated with FRS2 phosphorylation, FGFR2 mRNA levels and FGFR2 IIIb expression but not phosphorylation of VEGFR2 and PDGFRβ in pancreatic xenografts[22]. Using FGFR2 mRNA levels tumor sensitivity to FGFR inhibition among the tumor xenografts was able to be identified. The intracellular kinase domain of FGFRs is structurally similar to VEGFR2 and PDGFR. The extracellular domains II and III of FGFRs constitute the binding site for FGF ligands [23]. Alternative splicing in domain III in FGFR1–3, not FGFR4, creates isoforms (IIIb and IIIc) with varying binding affinity to various FGF ligands. Response to FGFR inhibition with dovitinib correlated with FGFR IIIb isoform but not FGFR2IIIc in our studies. This may be because isoform IIIc is associated with epithelial to mesenchymal transformation[24]. This forms the rationale for our hypothesis that high FGFR IIIb to IIIc ratio in tumors along with proliferative index (Ki-67) and microvessel density that are known predictors of biology in this tumor will predict benefit from nintedanib.

We hypothesize that a high FGFR IIIb/IIIc ratio (quantified using an image analyzer) and low Ki-67, microvessel density at baseline measured by IHC using validated methods in formalin-fixed paraffin embedded biopsy tissue will correlate with improved response to nintedanib[25, 26].

1.5.1.2 mTOR Pathway Mutations

We hypothesize that mutations along the mTOR pathway may predict response and/or resistance to nintedanib therapy. To test this hypothesis, we propose to determine mutations and copy number alterations in 341 cancer associated genes using a novel technology called IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets conducted in the Berger Laboratory at Memorial Sloan Kettering Cancer Center (MSKCC).

In addition, given the mutation alterations identified in the AKT1 or AKT2 genes, we also hypothesize that Akt activation may predict response and/or resistance to treatment. Pre-archived and post-treatment biopsies will be assessed for activity and will be determined by blotting for the phosphorylation of Akt downstream targets including p-Foxo, p-GSK3, p-PRAS40. IHC analysis of total AKT, p-Akt Ser473, PTEN, total 4E-BP1, p-4E-BP1Thr70, p-eIF-4G Ser1108 (peIF-4G), total S6, p-S6 Ser235/236 and Ser240/244, and proliferation marker Ki-67 will also be performed in formalin-fixed paraffin-embedded sections from the tumor samples.

We will send all samples to MSKCC for testing. In patients with a partial response by RECIST i.e., "outliers" (pre-archived and post-treatment biopsies) will be assessed for activity and will be determined by blotting for the phosphorylation of Akt downstream targets. This will also be done in those with long PFS (>/= 6 months). There they will extract DNA from core tissue and cytology specimens (and patient-matched normal tissue) using Qiagen nucleic acid extraction kits. They will prepare barcoded sequence libraries (New England Biolabs, Kapa Biosystems) and perform exon capture on barcoded pools by hybridization (Nimblegen SeqCap) using custom oligonucleotides to capture all exons and select introns of 341 cancer genes. DNA will subsequently be sequenced on an Illumina HiSeq 2000 to 500-1000X coverage in order to maximize sensitivity for detecting mutations.

DNA samples will be prepped and captured for sequencing, libraries will be sequenced, and FASTQ sequence files will be prepared all through MSKCC Diagnostic Molecular Pathology. Sequence data will be analyzed through MSKCC Diagnostic Molecular Pathology.

1.5.2 Plasma Markers/Modeling

Elevated plasma cytokine levels (e.g., Serum VEGF) often correlate with poor prognosis and changes in these markers have not been predictive of clinical outcomes to any anti-angiogenic agent. [27]. Our group evaluated sunitinib PK and modeled change in soluble VEGFR2 and this PK/PD model was able to successfully predict clinical benefit (PFS) to potent anti-VEGF therapy.

Using the previously developed PK/PD model (see **Section 13.1**), it will be determined if using decrease in circulating cytokines such as soluble vascular endothelial growth factor receptor (sVEGFR), fibroblast growth factor (FGF) and FGFR by ELISA before treatment and at week 8 (± 3 days) with steady state PK done in the same sample drawn at week 8 will correlate with drug level following start of therapy, with changes in cytokines post therapy compared to pre therapy in the model to see if it correlates with clinical benefit and has the potential to be a biomarker. We hypothesize that drug exposure combined with FGF and FGFR levels measured by ELISA and sVEGFr2- a pharmacodynamic marker validated prospectively may yield a noninvasive biomarker of response to this agent [28].

1.5.3 Immune Biomarkers

Carcinoid tumors are well known to have a variable biology and reasons for this are poorly understood. We have comprehensively studied and shown that immune dysfunction is a hallmark of cancer in peripheral blood samples taken from patients with liver cancer [29]. In two ongoing NCCN funded trials we are prospectively validating our preliminary data that antiangiogenic therapy results in immune changes that may have a functional impact on patient's anti-tumor immunity. We have successfully conducted these studies in banked frozen PBMCs and propose

to explore the biomarker potential of baseline Treg numbers defined as ($CD3^+CD4^+Foxp3^+CD127^-$ cells) on outcomes with nintedanib therapy and may provide insight into the patients biology. Banked specimens will allow future comprehensive assessment and given that immunotherapy is now a real option for treatment of some cancers, and will be the next frontier and major focus of oncology research, it may allow selection of patients who may benefit from other therapies in development.

1.5.4 Quality of Life

The EORTC QLQ – GI.NET21 questionnaire is intended for use among patients with G.I. related neuroendocrine tumors, who vary in disease stage and treatments. The module comprises 21 questions assessing disease symptoms, side effects of treatment, body image, disease related worries, social functioning, communication and sexuality.

The module has been found to be a valid and responsive tool for assessing quality of life in gut, pancreas and liver neuroendocrine tumors [(30)].

1.6 Risks and/or Benefits

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

- the gastro-intestinal tract (nausea, vomiting, diarrhea, abdominal pain-including upper and lower abdominal pain)
- increases in liver enzymes (AST, ALT, γ-GT)
- fatigue or asthenia
- decreased appetite, dehydration due to gastrointestinal side effects

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

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

Impairment of immune and of kidney function, thromboembolic events and GI perforations are considered possible side effects of treatment with nintedanib (BIBF1120) as they have been reported for some other drugs in the class of angiogenesis inhibitors. Thus far these side effects have been observed in the trials conducted with nintedanib (BIBF1120), but not to a relevant degree. Hypertension is also supposed to be a possible side effect of VEGFR inhibitors and a slightly increased frequency of hypertension has been observed in the trials with nintedanib (BIBF1120) to a mild to moderate degree and only few cases of CTCAE grade 3 or 4 hypertension have been observed. With respect to bleeding as one of the potentially serious side effects of antiangiogenesis agents in the LUME –Lung 1 trial involving 1314 patients more bleeding events were reported for nintedanib-treated squamous cell carcinoma (SCC) patients (all grades: 17.1% vs. 10.9%; grade ≥3: 2.9% vs. 1.3%) than for those with adenocarcinoma (all grades: 10.9% vs. 11.1%; grade ≥3: 1.5% vs. 1.3%). Fatal bleeding events, serious skin reactions, thrombosis, and perforations occurred at a low frequency and were balanced between both arms regardless of histology.

Based upon a non-clinical safety study in vitro, nintedanib (BIBF1120) may have a potential risk of phototoxicity (skin and eyes) in vivo. Few cases of photosensitivity reactions (less than 1 %) and of CTCAE grade 1 intensity only, have been reported from the clinical studies to date. If

adequate precautions are taken (avoidance of prolonged ultraviolet (UV) exposure, use of broad spectrum sunscreen and sunglasses), treatment with nintedanib (BIBF1120) is considered safe.

2 RATIONALE

Patients with progressing metastatic carcinoid tumors have no approved options and are a population with a clear unmet need. Targeting angiogenesis and the mammalian target of rapamycin (mTor) pathways has been shown to improve outcomes in patients with pancreatic NETs but have not proven to be beneficial in carcinoids. Studies, suggest, however that a subset of carcinoid patients may be sensitive to these therapies. Therapy is palliative and intended to improve quality of life (QOL).

Furthermore, this is an area of unmet need as there are no approved anti-tumor agents for patients with carcinoids that are not of pancreatic origin. Octreotide is shown to improve symptoms and frequently used in these patients. Recently in a phase 3 trial, therapy with everolimus and octreotide was shown to prolong PFS compared to placebo [(7)]. Results from RADIANT-4 may confirm PFS with everolimus in this population of ~11 months but given the long overall survival of these patients and morbidity from symptoms, clearly there remains a need for newer tolerable agents to continue to offer symptom and tumor control. Carcinoids are highly vascular and VEGF, PDGF and FGF are all also thought to drive disease with the additional serotonin mediated fibroblast proliferation driving symptom progression. Nintedanib is a promising new orally bioavailable targeted agent that targeted VEGFR1-3, FGFR 1/3 and PDGFR. Several agents targeting VEGF and PDGF have shown promising activity in pancreatic neuroendocrine tumors. However response rates for patients with non-pancreatic carcinoid tumors have been low. We hypothesize, that since fibroblast proliferation is a major driver of disease and clinical progression in non-pancreatic carcinoids that is shown in animal models to be driven by serotonin (5-HT) through FGFR2 that targeting angiogenesis and FGFR merits study in this tumor. There are no prospectively validated predictors of response to FGFR inhibitor, and in lung NET patient samples, FGFR1 amplification was seen in 52% of small cell neuroendocrine cancer and 19% of bronchial carcinoids. These expression data are much higher than those reported in breast, lung or bladder cancers and make it much more likely to see activity with FGF inhibition. As progression free survival is a valid endpoint in this disease given the long overall survival, we hypothesize that:

1. Targeting angiogenesis and the fibroblast growth factor pathway with nintedanib will result in clinical benefit measured as progression free survival (PFS) and radiographic response or stable disease in patients with carcinoid tumors progressing within the 12 months prior to study entry.
2. This therapy will be safe and tolerable in combination with octreotide. This will also lead to improved QOL measured using the EORTC QLQ – GI.NET21 questionnaire.

These data form the background and rationale for our hypothesis that the combination of nintedanib with octreotide LAR may offer disease control and clinical benefit in patients with carcinoid tumors and PNETs.

3 OBJECTIVES

3.1 Primary Objective

- To assess progression free survival (PFS), defined as the time interval from initiation of therapy, to its cessation for documentation of progressive disease (PD) or death.

3.2 Secondary Objectives

- To assess the clinical response (complete response + partial response) in all patients with measurable disease (using standard RECISTv1.1 criteria).
- To assess overall survival (OS) in all patients.
- Assess changes in QOL throughout treatment using the EORTC QLQ – GI.NET21 questionnaire for carcinoid patients with gastrointestinal neuroendocrine tumors, in all patients who have filled out at least two QOL questionnaires and, will be reported by groups based on response (response, stable disease or progressive disease).
- Steady-state PK of Nintedanib, biomarkers, Treg and cytokine expression and growth factors will be analyzed for all patients and reported in groups based on response.
- Gene mutations and copy number alterations analysis in the mTOR pathway (will be performed only on the first 10 patients), protein expression of activation of Akt (as well as other downstream targets).
- Toxicity (graded using the NCI CTCAE version 4.0) will be closely monitored and all toxicities will be tabulated.

4 METHODOLOGY

4.1 Study Design

This is an open label, multi-center phase II study in all patients with advanced low and intermediate grade neuroendocrine cancers (carcinoids), excluding PNETS.

Therapy will consist of Nintedanib (BIBF1120) 200 mg PO BID + Octreotide (or lanreotide) q 4 weeks.

CT **(chest, abdomen, & pelvis)** scan restaging q 8 weeks x 24 weeks and then q12 weeks.

In a subset of patients (10 total), post treatment biopsy samples for tissue studies to understand mechanisms of resistance will be done at progression if they are willing to have a second biopsy.

Quality of life questionnaires using the EORTC QLQ – GI.NET21 questionnaire (**Appendix K)** will be completed at baseline and at the same time points as imaging studies while on study. Treat until progression/ unacceptable toxicity.

Formalin-fixed paraffin embedded tumor biopsy samples from patients enrolled at the participating institutions will be sent to RPCI Core Pathology Laboratory for IHC studies. This is to be done in all patients accrued at all sites who may have additional studies for the gene expression studies described in the protocol.

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

Two participating institutions will enroll maximum of 30 evaluable patients over a 24 month period.

5 PARTICIPANT SELECTION

5.1 Inclusion Criteria

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

1. Patient must be on a stable dose of octreotide (Sandostatin®) LAR or lanreotide for 3 months prior to study enrollment.
2. Patient must have histologically or cytologically confirmed well differentiated or moderately differentiated (low grade or intermediate grade) neuroendocrine tumor that is locally advanced or metastatic and not of pancreatic origin.
3. Measurable disease determined by CT or MRI.
4. Age ≥ 18 years of age.
5. Have an ECOG Performance Status of 0 - 2. Refer to **Appendix B**.
6. Life expectancy greater than 3 months.
7. Have the following clinical laboratory values:
    - Leukocytes ≥3,000/μL
    - Absolute neutrophil count ≥ 1,500/μL
    - Total bilirubin ≤ 2 mg/dL
    - AST /ALT
        - AST/ALT ⩽ 1.5 X ULN and bilirubin ⩽ ULN for patients without liver metastases.
        - AST/ALT ⩽ 2.5 X ULN and bilirubin ⩽ ULN for patients with liver metastases.
        - Patients with Gilbert syndrome and bilirubin < 2 X ULN and normal AST/ALT
        - creatinine ≤1.5 mg/dl
8. Prior treatment will be permitted including surgery (≥ 4 weeks), cytotoxic chemotherapy (maximum of 2 prior regimens); radiation, interferon, targeted growth factors (≥ 4 weeks); and prior treatment with octreotide, will be allowed.
9. Ability to swallow and retain oral medication.
10. Participants of child-bearing potential (both male and female) must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry. 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.

11. 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.
12. Archival tissue of carcinoid biopsy must be available.

5.2 Exclusion Criteria

Participants will be excluded from this study for the following:

1. Uncontrolled hypertension, unstable angina, New York Heart Association Grade II or greater congestive heart failure, unstable symptomatic arrhythmia requiring medication, or clinically significant peripheral vascular disease (Grade II or greater). Refer to **Appendix C**.
2. Presence of brain metastases.
3. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to day 0, or anticipated need for major surgical procedure during the course of the study, or fine needle aspirations or core biopsies within 7 days prior to day 0.
4. Significant proteinuria at baseline ($\geq$ 500 mg/ 24 h).
5. Serious non-healing wound, ulcer or bone fracture.
6. Evidence of bleeding diathesis or coagulopathy.
7. Recent ($\leq$ 6 months) arterial thromboembolic events, including transient ischemic attack, cerebrovascular accident, unstable angina, or myocardial infarction.
8. Poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma, adenocarcinoid, goblet cell carcinoma, or small cell carcinoma.
9. Hepatic artery embolization or ablation of hepatic metastasis within 3 months of enrollment, prior PRRT within 4 months or any other cancer therapy within 4 weeks (as long as all toxicities are resolved).
10. Intolerance or hypersensitivity to octreotide.
11. Severe or uncontrolled medical conditions.
12. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
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.

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 1.6**. Appropriate dose modifications are described in **Section 6.2**.

All patients have to be on octreotide LAR or lanreotide, and dose has to be stable for 3 months prior to study enrolment. Nintedanib 200 mg PO BID will be given as an outpatient in 28 day cycles. The pills are to be swallowed, un-chewed, with a glass of water of about 250 mL with a dose interval of approximately 12 hours at the same times every day, at least 30 minutes after a meal. If a patient misses a dose he/she will be instructed to skip that dose and take their next dose at their scheduled time.

Reported adverse events (AEs) and potential risks are described in **Section 1.6**. Appropriate dose modifications are described in **Section 6.2**. No other investigational or commercial drugs or therapies other than those described below may be administered with the intent to treat the patient. Patients will continue nintedanib until disease progression, unacceptable toxicity, investigator's decision to remove patient from the study, patient refusal to continue, or alternative treatment.

Throughout the study, all patients will still continue on their scheduled dose of either Octreotide or Lanreotide: dosing information about Octreotide or Lanreotide should be tracked in the drug administration eCRF.

6.2 Dose Modifications

As initial measure for the management of side effects (**Table 2**) treatment with Nintedanib should be temporarily interrupted until the specific adverse reaction has resolved to levels that allow continuation of therapy. Nintedanib treatment may be resumed at a reduced dose. Dose adjustments in 100 mg steps per day (i.e. a 50 mg reduction per dosing) based on individual safety and tolerability are recommended as described in **Table 3**. In case of further persistence of the adverse reaction(s), i.e. if a patient does not tolerate 100 mg twice daily, treatment with Nintedanib should be discontinued and the patient will be taken off study.

*Nintedanib, maybe held per physician discretion for 2-4 weeks. Any extension beyond this duration will be on a case by case basis per primary investigator discretion.

Table 2 Criteria to Interrupt Nintedanib Treatment due to an Adverse Event

If one criterion is met, nintedanib is to be interrupted
• Nausea of CTCAE grade ≥ 3 despite optimal supportive care
• Vomiting of CTCAE grade ≥ 2 despite optimal supportive care
• Diarrhea 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 bleeding

Table 3 Management of Adverse Events

Grade of Event	Management / Next Dose
≤ Grade 1	No change in dose.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold[1] until < Grade 2. Resume at 1 dose level lower, if indicated.[2]
Grade 4	Off protocol therapy.

1 Participants requiring a delay of > 2 weeks should go off protocol therapy (see section 6.2 for further reference).

2 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.

*Please refer to table 4 for management of diarrhea.

6.2.1 Management of Diarrhea

For the disease population in this study, frequency of bowel movements may already be an issue with some patients prior to initiation of nintedanib treatment. Therefore, for this population, number/frequency of bowel movements will be documented at baseline prior to initiation of nintedanib and subsequent CTCAE grading of diarrhea will be evaluated relative to the patient's baseline evaluation.

Guidelines for the management of diarrhea are found in **Table 4**.

Table 4 Guideline for the Management of Diarrhea

CTCAE Grade	Action for Nintedanib and Anti-Diarrheal Treatment	Action for Nintedanib After Recovery of Diarrhea
Grade 1*	Continue nintedanib. No Antidiarrheal treatment.	No dose reduction of nintedanib.
Grade 2	Continue nintedanib. Antidiarrheal treatment according to the local standard (e.g., Loperamide p.r.n.).	No dose reduction of nintedanib.
Grade 2 > 7 days despite optimal medical management or Grade ≥ 3 or any diarrhea independent of CTCAE grade leading to hospitalization of the patient.		
1st Episode	Temporarily STOP nintedanib until recovery (≤ Grade 1). AND Antidiarrheal treatment according to the local standard (e.g., Loperamide p.r.n.).	Reduce nintedanib 1 dose level after recovery of diarrhea.
2nd Episode	Temporarily STOP nintedanib until recovery. AND Antidiarrheal treatment according to the local standard (e.g., Loperamide p.r.n.).	Reduce nintedanib 1 dose level after recovery of diarrhea.
3rd Episode	PERMANENTLY discontinue nintedanib treatment AND Antidiarrheal treatment according to the local standard (e.g., Loperamide p.r.n.).	PERMANENTLY discontinue nintedanib treatment.

*For this patient population, bowel movements equal to 3 or 4 per day may be present and considered baseline. Once treatment starts, CTCAE grading will be based on the number of bowel movements/day above baseline.

6.3 Management of Proteinuria

- **For proteinuria of ≥2+:** Confirm total urine protein with a 24-hour urine collection or urine protein to creatinine (UPC) ratio.
- **For urine protein 2-3.4 g/24hours or UPC ratio 2-3.4:** Delay Nintedanib until urine protein improves to UPC < 2. If Nintedanib is delayed more than 4 weeks due to proteinuria, then discontinue treatment.
- **For urine protein ≥ 3.5 g/24 hours or UPC ratio ≥3.5:** Discontinue treatment.

6.3.1 Dose Reduction

The following dose levels (**Table 5**) will be used in case dose reductions are required for management of undue toxicity. Nintedanib dosing will start at 200 mg PO BID for all patients.

Table 5 Nintedanib Dose Level Reduction

Dose Level	Nintedanib Dose
1	200 mg (two, 100 mg capsules) twice a day (starting dose)
- 1	150 mg twice a day
- 2	100 mg twice a day

6.4 General Concomitant Medication and Supportive Care

6.4.1 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 diarrhea. 6.3 % of the patients had diarrhea of grade ≥3 in combination treatment compared to 3.6 % treated with docetaxel alone. Diarrhea should be treated at first signs with adequate hydration and antidiarrheal medicinal products, e.g. loperamide, and may require interruption, dose reduction or discontinuation of therapy with nintedanib (see **Section 6.2.1**).

- *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 E** for procedures for follow-up for potential drug-induced liver injury).

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

6.4.2 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 in extremities after discussion with the Principle Investigator, provided that the radiotherapy does not affect target lesions, and the reason for the radiotherapy does not reflect progressive disease.

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.

See **Appendix J** for additional examples of *in vivo* inhibitors and inducers of the P-gp transporter.

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 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.

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.

6.5 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, or participant withdraws from study.

6.6 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.
- 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.
- Sponsor decision.
- NCCN decision
- Boehringer Ingelheim Decision

6.7 Compliance

Patients will be supplied with a medication diary to track self-administration of nintedanib (**Appendix F**). Additionally, nintedanib pill counts will be performed at the conclusion of each cycle.

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 two dose strengths corresponding to 100 mg (peach or orange oblong capsules) and 150 mg (brown or orange oblong capsules). The capsule fill is composed of medium chain triglycerides, hard fat and lecithin in addition to the drug substance.

7.2 Drug Shipment

Nintedanib will be provided and shipped by Boehringer Ingelheim Pharmaceuticals Inc. to each participating site. Study specific order forms will be provided.

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.

7.3 Storage and Stability

Nintedanib should be stored below 30°C. Specific information on the expiration date of each batch will be made available either on the drug labels or on the packing slips for each shipment. 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 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.

Excess drug (BIBF1120) will be destroyed according to standard practices after properly accounting for dispensing: study drug will not be re-used for other participants.

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

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.

8.1 Baseline Evaluations (≤ 28 Days Prior to Registration)

The following will be performed within 4 weeks prior to first dose of study drug:

- Medical history and pre-existing conditions (including all prior anti-tumoral therapy related to neuroendocrine cancer)
- Physical examination
- Vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight, and height)
- Hematology: complete blood count (CBC) with automated differentials.

- 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).
- Serum serotonin and chromogranin A
- Urine Sample for 24-hr 5-HIAA test
- Urine protein/ creatinine ratio (**Appendix G**)
- Plasma marker blood draw
- EORTC QLQ – GI.NET21 Questionnaire (**Appendix K)**
- Pregnancy test (serum) in females of childbearing potential. **Note:** This must be done within 7 days prior to the first dose of study drug (i.e., Cycle 1-Week 1-Day 1)
- ECOG Performance Status (**Appendix B**)
- Immune biomarker blood draw
- Electrocardiogram
- Tumor/Disease Assessment (CT scan of chest, abdomen, & pelvis)
- Archival Tissue Sample
- Concomitant Medications: List any medications ongoing or stopped within 1 week prior to first dose of study drug (to include Octreotide or Lanreotide dosing).

8.2 Evaluations Performed at Cycle 1-Week 1-Day 1

- Vital signs
- Hematology
- Chemistry
- ECOG Performance Status
- Nintedanib and study medication diary provided to study participant
- Concomitant Medications: List any ongoing medications with dose changes, as applicable (to include Octreotide or Lanreotide dosing).
- Adverse Events

8.3 Evaluations Performed at Cycle 1-Week 3-Day 15

- Vital signs
- Hematology
- Chemistry
- Concomitant Medications: List any ongoing medications with dose changes, as applicable (to include Octreotide or Lanreotide dosing).
- Adverse Events

8.4 Evaluations Performed at Cycle 2-Week 1-Day 1 (± 3 days)

The following evaluations will be performed prior to daily study drug treatment:

- Physical examination, including vital signs
- Hematology
- Chemistry
- Nintedanib and study medication diary provided to study participant.
- Concomitant Medications: List any ongoing medications with dose changes, as applicable (to include Octreotide or Lanreotide dosing).
- Adverse Events

8.5 Evaluations Performed Every 8 Weeks (x24) from the Start of Study Treatment (±3 days)

The following evaluations will be performed ***every 8 weeks from the start of study treatment (x24 weeks,*** (prior to daily study drug treatment), followed by evaluations to be performed every 12 weeks until disease progression or toxicity or patient/ physician preference.

- Physical examination (starting at cycle 2), including vital signs
- Hematology
- Chemistry
- Serum serotonin and chromogranin A
- Urine protein/ creatinine ratio Baseline and, prior to treatment every 8 weeks for 24 weeks followed by evaluations at every 12 week or as clinically indicated
- EORTC QLQ – GI.NET21 Questionnaire **(Appendix K)**
- ECOG Performance Status
- Tumor/ Disease Assessment (CT scan **of (chest, abdomen, & pelvis)**)
- Concomitant Medications: List any ongoing medications with dose changes, as applicable (to include Octreotide or Lanreotide dosing).
- Adverse Events

8.5.1 Plasma Biomarker/Steady-State PK Blood Sample Collection

- Plasma Biomarkers at Baseline and at Week 8 prior to nintedanib dosing

8.6 Evaluations Performed at End of Treatment (± 3 days)

The following evaluations will be performed at the end of treatment or at time of treatment discontinuation:

- Physical examination, including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, and body weight.)
- Hematology: complete blood count (CBC) with automated differentials.
- 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)
- Urine protein/ creatinine ratio:
- EORTC QLQ – GI.NET21 Questionnaire (**Appendix K)**
- ECOG Performance Status
- Concomitant medication: List any ongoing medications with dose changes, as applicable (to include Octreotide or Lanreotide dosing).
- Adverse events

8.7 Post-Treatment Follow-Up Evaluations (± 3 days)

Follow-up safety evaluations will occur 30 days (± 3 days) after last dose of study drug or until resolution of any drug-related toxicity (telephone contact is acceptable).

- Concomitant medications: List any ongoing medications with dose changes, as applicable (to include Octreotide or Lanreotide dosing).
- Adverse events

8.8 Long Term Follow-Up Evaluations

8.8.1 Patients off treatment due to reasons other than disease progression will be monitored every 3 months (± 7 days) after 30-day follow-up for 3 years (telephone contact is acceptable).

- Concomitant medications: List any ongoing medications with dose changes, as applicable (to include Octreotide or Lanreotide dosing).
- Adverse events

8.8.2 Patients off treatment due to disease progression will be monitored every 6 month (± 7 days) after 30-day follow-up for overall survival.

8.8.3 Participants who are unavailable for follow-up evaluations should be classified as lost to follow-up for 1 of the following reasons:

- Lost to follow-up: For a participant to be considered lost to follow-up, the investigator must make two separate attempts to re-establish contact with the participant. The attempts to re-establish participant contact must be documented (e.g., certified letter).

- Death: Date and cause of death will be recorded for those participants who die within 30 days after last dose of study drug (telephone verification is acceptable).

8.9 Schedule of Procedures and Observations

The schedule of procedures and observations for this study is summarized in **Table 6** below.

Table 6 Schedule of Procedures and Observations

Evaluation	Baseline: ≤ 28 Days Prior to Registration[1]	Cycle 1 Week 1 Day 1[2]	Cycle 1 Week 3 Day 15	Cycle 2 Week 1 Day 1 (± 3 days)[3]	8 Weeks From Start of Study Treatment (± 3 days)	End of Treatment (± 3 days)	Post Treatment Follow up Evaluation (± 3 days)[4]	Progression Free Survival Follow-Up (± 7 days)[5]
Medical History	X							
Pre-Existing Conditions	X							
Physical Examination	X			X	X	X		
Vitals	X	X	X	X	X	X		
Hematology[6]	X	X	X	X	X	X		
Chemistry[7]	X	X	X	X	X	X		
Urine Sample (24-hr 5-HIAA test	X							
Serum serotonin and chromogranin A[8]	X				X[8]			
Urine sample for Urine protein/ creatinine ratio[9]	X				X[9]	X		
Plasma Biomarkers[10]	X				X			
EORTC QLQ – GI.NET21 [11]	X				X[11]	X		
Pregnancy Test (Serum)[12]	X							
ECOG Performance Status[13]	X	X			X[13]	X		
Immune Biomarkers[14]	X							
Electrocardiogram	X							
Tumor/Disease Assessment[15]	X				X[15]			
Archival Tissue Sample	X							
Nintedanib[16]		X		X				

Concomitant Medications	X[17]	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X

1 Performed ≤28 days prior to registration start, except serum pregnancy (within 7 days prior to day 1).
2 Evaluations to be performed prior to treatment.
3 Evaluations performed prior to treatment on Day 1 (± 3 days) of subsequent cycles (1 cycle = 28 days).
4 Follow-up safety evaluations will occur 30 days (± 3 days) after last dose of study drug, (telephone contact is acceptable).
5 Participants will be monitored every 3 months (± 7 days) for 3 years (telephone contact is acceptable). Refer to Section 8.8.1.
6 Hematology: complete blood count (CBC) with automated differentials.
7 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).
8 Serum serotonin and chromogranin A: to be assessed at baseline and, prior to treatment every 8 weeks for 24 weeks, followed by evaluations at every 12 week (i.e., at all imaging time points).
9 Baseline and, prior to treatment every 8 weeks for 24 weeks followed by evaluations at every 12 week or as clinically indicated.
10 **Plasma** biomarkers: 1, 10 mL purple-top EDTA collection tube for correlative studies at Baseline and at 8 weeks (± 3days) after the start of treatment (**Section 8.10).**
11 Baseline and, prior to treatment every 8 weeks for 24 weeks, followed by evaluations at every 12 weeks (**Appendix K).**
12 Within 7 days prior to Day 1.
13 Baseline and, prior to treatment every 8 weeks for 24 weeks, followed by evaluations at every 12 week.
14 40 ml blood (4, 10 mL green-top heparinized collection tubes) will be collected at baseline and processed according to **Section8.11**.
15 CT scan of (chest, abdomen, & pelvis) restaging will be performed every 8 weeks for 24 weeks, followed by every 12 weeks.
16 Study drug (nintedanib) to be dispensed at the beginning of each new cycle.
17 Medications ongoing or stopped within 1 week prior to first dose of study drug (to include Octreotide or Lanreotide dosing).

8.10 Plasma Biomarker/Steady-State PK Blood Sample Collection and Processing

Whole blood samples for correlative cytokine levels will be collected via venipuncture using 1, 10 mL purple top EDTA collection tube

Sample collection will be obtained at Baseline and at Week 8 prior to nintedanib dosing.

Samples for the correlative analyses will be collected in the Phlebotomy Laboratory and sent to the Hematological Procurement Facility for processing.

The steady-state pharmacokinetic analysis for Nintedanib will be done on the plasma samples obtained at week 8 (Bioanalytics, Metabolomics & Pharmacokinetic Core Facility, see below).

Plasma will be separated from whole blood within 60 minutes following the extraction.

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 plasma 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. Frozen samples will then be analyzed in RPCI's Bioanalytics, Metabolomics & Pharmacokinetic Core Facility.

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
Attn: Regarding Study # – I 259114
Elm & Carlton Streets
Buffalo, New York 14263
PKPDcore@RoswellPark.org

Note: All laboratories housing research samples need to maintain current **Temperature Logs** and study-specific **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 batched and then-shipped via Fed Express Overnight on dry ice with delivery on Mon-Fri. NO SATURDAY OR SUNDAY DELIVERY. **Notification via email should also be made to PKPDcore@RoswellPark.org to include tracking number, time of shipment, site name** . All samples should be shipped to the address above with a copy of the Shipping Log.

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 Immune Biomarkers Blood Sample

Whole blood samples for immune biomarker analysis will be collected via venipuncture at Baseline (Four, 10 ml green-top heparinized collection tubes).

PBMC's will be separated from whole blood within 30 minutes following the extraction (refer to **Appendix H:** Isolation of Mononuclear Cells, for isolation details), and immediately frozen at -80ºC for cryopreservation procedure. PMBC's 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. Samples collected at RPCI will be processed and stored at RPCI's Hematological Procurement Facility. Frozen samples will then be analyzed in RPCI's Flow Cytometry Core Laboratory by Dr. Hans Minderman (see below for contact information).

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 participants study number, clinical study number, protocol time point, dose, and protocol day. Frozen samples will be batched and then shipped via Fed Express Overnight on dry ice with delivery on Mon-Fri. NO SATURDAY OR SUNDAY DELIVERY. **Notification via email should also be made to HansMinderman@RoswellPark.org with tracking number, site name and time of shipment**. All samples should be shipped to the address below with a copy of the Shipping Log:

Roswell Park Cancer Institute
Flow Cytometry Research Services Core Laboratory
Cancer Cell Center (CCC), Room C-311A
Attn: Dr. Hans Minderman – I 259114
Elm & Carlton Streets
Buffalo, NY 14263-001
Tel: 716-845-1162 (office)
Tel: 716-845-3470 (lab)
Fax: 716-845-8806
Hans.Minderman@RoswellPark.org

Note: All laboratories housing research samples need to maintain current **Temperature Logs** and study-specific **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.

8.12 Pathology

8.12.1 Formalin-Fixed Paraffin-Embedded (FFPE) Biopsy Samples

The following sections of tissue from carcinoid biopsy that exists in the Paraffin Archive in the Department of Pathology (or outside institution) will be collected:

1. Eight unstained sections cut at 4 microns on plus glass slides.
2. One H&E stained section

The study coordinator or designee will be responsible for entering the order into the EMR using the standard format for all clinical trial pathology requirements.

For Network Sites, de-identified tissue samples and de-identified pathology reports, using study-specific subject ID number and tissue accession number, are to be sent to RPCI Correlative Science Pathology Office (Attn: Protocol Lab Team). The shipping label should read as follows:

Roswell Park Cancer Institute
Elm & Carlton Streets
Correlative Science Pathology Office
Gratwick Basic Science Building, S-636
Attn: Protocol Lab Team, I 259114 Samples
Buffalo, NY 14263
(716) 845-8917
Email: CRSLabPathTeam@RoswellPark.org

Samples will be analyzed in RPCI's Core Pathology Laboratory by Dr. Omilan's group.

8.12.2 Tissue Samples for IMPACT Assay

The IMPACT assay (Integrated Mutation Profiling of Actionable Cancer Targets) will be performed on a maximum of 10 patients who have adequate pre-treatment tumor tissue and post-treatment biopsies. Ideally patients with good responses (aka the "outliers") will be chosen for biopsy upon disease progression. We will use MSK-IMPACT to perform NGS in pre-treatment

and drug-resistant tumor with germ-line DNA (whole blood) as a reference. Refer to **Appendix D for additional details on sample requirements**.

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.

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 6 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 6 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 8 weeks for 24 weeks, followed by assessments at every 12 weeks (timed to coincide with the end of a cycle) with a confirmatory assessment (required for non-randomized trials) no less than 6 weeks after a PR or CR is deemed. To determine time point response, refer to **Table 7** and **Table 8** below.

Table 7 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 8 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 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 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.

9.6 Retrospective Review of Disease status

Due to indolent biology of neuroendocrine tumors, disease status prior to enrollment onto this clinical trial can help further inform primary endpoint of the study. Treating physician and/or PI at respective site are to review images on patients enrolled on study to determine disease status prior to enrollment on trial. All imaging modalities utilized prior to enrollment onto study are acceptable and RECIST evaluations are not required. Clinician/PI are to review images and clinical evaluations prior to being enrolled on this trial and determine disease status. Progressive disease can be captured as “radiographic progression”, “clinical progression”, or “clinical and radiographic progression”. If in the year prior to enrollment the patient had radiographic stable disease, please note “stable disease” and comment further on reason for change in treatment. Furthermore, imaging modalities utilized for above retrospective review are to be captured. Date for scan and/or clinical evaluation where progression is noted are to be entered in EDC.

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 E** [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 10.2**), 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 9 Guidelines for Routine Adverse Event Reporting for 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 cycle 1 day 1, 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

Network Sites follow **Appendix A: Instructions for Network Sites**

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 investigator will report all SAEs and non-serious AEs which are relevant to a reported SAEs and AESIs by fax using BI IIS SAE form, or MedWatch 3500A, 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

(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 Reportable New Information (RNI) 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 Reportable New Information Form. The site Investigator or designated research personnel will report all unanticipated problems, to the **IRB in accordance with their local institutional guidelines**.

11 DATA AND SAFETY MONITORING

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

12.1 Endpoints

12.1.1 Primary

The primary endpoint is PFS, defined as the time interval from initiation of therapy, to its cessation for documentation of progressive disease (PD) or death. Disease progression will be determined by radiographic assessment every 8 weeks for first 24 weeks and then q 12 weeks thereafter.

12.1.2 Secondary

Clinical response (complete response + partial response) measured using standard RECISTv1.1 criteria will be reported in all patients with measurable disease. Median overall survival will be reported in all patients. Change in QOL throughout treatment using the EORTC QLQ – GI.NET21 questionnaire will be analyzed in all patients who have filled out at least two QOL questionnaires and reported in three groups based on response (response, stable disease or progressive disease). The circulating marker levels (Steady state PK, FGF and FGFR and sVEGFR2) and with dynamic contrast enhanced CT parameters will be reported and predictive value assessed using the PK/PD model previously developed by our group to explore association with PFS, clinical response, QOL and overall survival. The ratio of FGFR IIIb/IIIc and Ki-67, MVD scores will be obtained to investigate association with PFS, clinical response, QOL and survival. Gene mutations and copy number alterations in the several pathways particularly mTOR pathway will be evaluated as exploratory endpoints, and will be analyzed for all patients and correlated with clinical outcomes. Biomarkers, Treg and cytokine expression and growth factors will be analyzed for all patients and reported in groups based on response.

12.2 Sample Size Determination

Two participating institutions will enroll maximum of 30 evaluable patients over a 24 month period.

The sample size calculation is based on testing the hypotheses concerning the PFS rate at 16 weeks in patients treated under the proposed therapy: H_0: $p \leq p_0$ versus H_A: $p > p_0$. This single-stage design requires a total of n patients in order to achieve approximately 1-β power to detect

differences of Δ percentage points (p_0 versus p_0 +Δ). For this study α = 0.10 and 1-β =0.90; with p_0=0.40 and Δ=0.24 for this population of carcinoid patients.

12.3 Demographics and Baseline Characteristics

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

12.4 Efficacy Analysis

The primary objective of this study is to assess the efficacy of the investigational agent nintedanib in carcinoid patients. Let *p* represent the PFS rate at 16 weeks. A true PFS rate at 16 weeks of less than p_0 =0.40 is considered unacceptable in carcinoid, and evidence of such will deem the treatment not worthy of further study.

The null and alternative hypotheses to be tested are H_0: $p \leq p_0$ versus H_A: $p > p_0$. A one-sided exact binomial test (at a nominal α=0.10) and corresponding decision rules will be used to evaluate these hypotheses:

- If *15* patients or less have not progressed at 16 weeks, then it is concluded that the therapy is not promising.
- If *16*patients or more have not progressed at 16 weeks, then it will be concluded that the therapy is promising.

Additionally, a confidence interval for the 16-week PFS rate will be obtained using Jeffrey's prior method.

Secondary Analysis: The time-to-event outcomes (PFS and OS) will be reported using standard Kaplan-Meier methods. Ninety-five percent confidence intervals for the median PFS and OS will be calculated using Greenwood's formula. Exact 90% confidence interval estimates using the Clopper-Pearson method will be given for the response and toxicity rates. An exact 90% confidence interval will be given for the rate of improved QOL. Changes in pre- and post-treatment cytokine expression and growth factors will be analyzed using permutation paired t-tests. Dichotomous variables, such as response and QOL, will be analyzed using the logistic regression to investigate their association with quantified variables, such as biomarker expression and gene mutation. The association between survival and quantified variables will be investigated using the Cox-proportional hazard model.

12.4.1 Adverse Event

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

Toxicity (graded using the NCI CTC version 4.0) will be closely monitored and all toxicities will be tabulated. The PI, Data Safety Monitoring Board and IRB will monitor toxicities and close the study if the therapy appears too toxic.

12.5 Replacement

Patients that do not have a response assessment completed by 16-weeks are considered unevaluable for the primary end-point and will be replaced.

12.6 Interim Analysis and Criteria for Early Termination of the Study

There are no planned interim analyses (unless for safety reasons) or early termination criteria.

13 CORRELATIVE DATA ANALYSIS

Preliminary Data

Thalidomide is believed to be an inhibitor of FGF2 induced angiogenesis and Dr. Shah and others [31, 32] have shown in phase 2 trials that thalidomide has activity in neuroendocrine cancers. The cytokine assays are commercially available and the PK/PD model proposed to be used (see below) has already been developed and validated. The rationally selected IHC assays have been previously standardized by our group.

Recently our colleagues at Johns Hopkins and MSKCC determined the exomic sequences of 10 nonfamilial pNETs and then screened the most commonly mutated genes in 58 additional pNETs. The most frequently mutated genes specify proteins implicated in chromatin remodeling: 44% of the tumors had somatic inactivating mutations in MEN1, which encodes menin, a component of a histone methyltransferase complex, and 43% had mutations in genes encoding either of the two subunits of a transcription/chromatin remodeling complex consisting of DAXX (death-domain–associated protein) and ATRX (α thalassemia/mental retardation syndrome X-linked). They also found mutations in genes in the mTOR (mammalian target of rapamycin) pathway in 14% of the tumors, a finding that could potentially be used to stratify patients for treatment with mTOR inhibitors. These findings were provocative. However, clinical descriptions of these patients are unavailable. In addition, none of these tumors were resequenced at another point in time to better understand the evolution of these tumors. Indeed, most of the tumors were in patients that had early stage disease that was resected.

In addition, researchers at the Mayo clinic recently performed whole genome sequencing in small bowel carcinoids.

Our group has established assays for assessment of several immune subsets [29] showing T reg frequency and number in HCC patients being prospectively studied in another NCCN funded trial.

13.1 Plasma Biomarker 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, FGF23, along with cytokine modulation. Subsequently, diagnostic plots will be created to ascertain whether a trend exists among sVEGFR-2 levels, FGF23, immunological response, 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).

13.2 IMPACT Assay

These assays will be done in the first 10 patients who have adequate pre-treatment tumor tissue and, will have post treatment biopsies. Ideally patients with good response (aka the “outliers) will be chosen for biopsy upon disease progression.

Akt activity will be determined by blotting for the phosphorylation of Akt downstream targets including p-Foxo, p-GSK3, p-PRAS40. IHC analysis of total AKT, p-Akt Ser473, PTEN, total 4E-BP1, p-4E-BP1Thr70, p-eIF-4G Ser1108 (peIF-4G), total S6, p-S6 Ser235/236 and Ser240/244, and proliferation marker Ki-67 will also be performed in formalin-fixed paraffin-embedded sections from the tumor samples (Refer to **Appendix D)**.

14 ETHICAL AND REGULATORY STANDARDS

14.1 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. The clinical trial should be conducted in accordance with the ethical principles embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, consistent with good clinical practice and the applicable regulatory requirements and according to the guidelines in this protocol, including attached appendices.

14.2 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 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 applicable GCP guidelines, 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.

15 STUDY RESPONSIBILITIES

15.1 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 (as well as the BI SEA 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 Principal 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.

15.2 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.

16 ADMINISTRATIVE RULES

16.1 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.

16.2 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.

16.3 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.

17 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; 8: 00 AM to 4: 30 PM EST
716-845-3870 or 716-845-1205
After hours, weekends, and holidays request the RPCI Investigator
716-845-2300
Fax: 716-845-8743

E-mail: CRSNetworkcoordinators@roswellpark.org

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 2 Protocol Registration Instructions

The **Subject Screening and Enrollment Log** must be faxed 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 **Subject Registration Form** and fax 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.
- ALL study deviations 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 3500 A will be required only if it is necessary to report to the FDA.
- See **Section 10.4** of protocol for information on notifying the drug sponsor, Boehringer Ingelheim Pharmaceuticals.
- SAE reports are to be submitted to the NCCN: email ORPReports@NCCN.org or fax SAE's to 215-358-7699.
- SAE reports are to be submitted to BI as well.

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

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.

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 New York Heart Association Classification

New York Heart Association (NYHA) Congestive Heart Failure (CHF) Functional Classification System[a]	
Class	**Functional Description**
NYHA Class I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity (e.g., shortness of breath when walking, climbing stairs, etc.).
NYHA Class II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
NYHA Class III	Marked limitations in activity due to symptoms, even during less-than-ordinary activity [e.g., walking short distance (20-100 m)]. Comfortable only at rest.
NYHA Class IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

[a] The Criteria Committee of the New York Heart Association. (1994). *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels.* (9th ed.). Boston: Little, Brown & Co. pp. 253–256.

Appendix D IMPACT Assay (MSKCC)

MSK-IMPACT is a NGS platform that was recently developed at MSKCC and uses massively parallel sequencing and solution-phase exon capture to perform NGS.[33-35] The platform screens 341 oncogenes and tumor suppressor genes commonly altered across tumor types, and provides a comprehensive analysis of multiple genes in the PI3K/Akt/mTOR pathway, including PIK3CA, AKT1/2/3, PTEN, TSC1/2, and mTOR, as well as SMAD family genes, AURKA, EGFR, HSP90, and PDGFR that were identified in the small bowel sequencing project. The platform successfully identifies sequence variants, small insertions and deletions, copy number alterations, loss of heterozygosity, and select rearrangements. We will use MSK-IMPACT to perform NGS in pre-treatment and drug-resistant tumor with germ-line DNA (whole blood) as a reference.

After MSK-IMPACT sequencing has been performed in both pre-treatment and drug-resistant tumor, Dr Raj and Dr. Reidy will work with the genetics experts in the MSKCC Center for Molecular Oncology to clinically translate our findings, reviewing and interpreting the results for biologic and clinical significance. In particular, they will look at changes in the mTOR pathway (AKT) to investigate if any observed mutations may confer resistance to nintedanib. All IMPACT Assay Samples can be sent to the following address below along with site name and tracking number and copies of specimen and shipping log:

Diane Reidy-Lagunes
MSKCC
300 East 66th street room 1039
NY, NY 10065

Formalin-Fixed Paraffin-Embedded (FFPE) Biopsy Samples

- Any target tumor tissue can be collected per discretion of the PI, providing physician, and/or surgical/ radiology team members.
- At minimum, adequate tissue should be collected for 20 unstained and one (1)H&E stained slide that are 4-5μm thick and on positively charged slides. Tissue should be formalin fixed paraffin embedded (FPPE).
- Ideally, biopsy should be performed prior to introduction of new chemo/radiation; however, this is not required.

Blood Sample Collection and Processing

Germline DNA is required for comparison with tumor tissue. Patients will be asked to provide whole blood samples via venipuncture using one (1) 10 mL lavender top EDTA collection tubes. Samples will be labeled as "Post Treatment IMPACT Assay Blood Samples" along with date of collection, protocol number, and study participant identification number. Sample will be kept in ambient temperature and shipped overnight to MSK.

Ideally, the blood sample should be obtained on the same day and prior to the IMPACT biopsy. However, this blood sample can be collected any time after the patient is taken off nintedanib.

Results of the IMPACT assay will not be made available to the patient.

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

- Hematology:
- Thrombocytes*, eosinophils*

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

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

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

Appendix F 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 apart. Take with water within 30 minutes after the end of a meal. If a dose is missed write "0" in the # taken box. If your dose changes, record the new dose.

Start Date: _____ Nintedanib per dose #100mg: _____ #150mg: _____

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
Dose:														
100mg #														
150mg #														

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
Dose:														
100mg #														
150mg #														

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
Dose:														
100mg #														
150mg #														

Cycle Day	Day 22		Day 23		Day 24		Day 25		Day 26		Day 27		Day 28	
Date														
Nintedanib	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Dose:														
100mg #														
150mg #														

Please remember to bring this calendar and your capsule bottle (including any unused capsules) with you to your next study appointment.

Coordinator use only

Date of return: _____

Patient signature: _____ ____Date: _____

Investigator signature: _____ ____Date: _____

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Appendix G 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.

Appendix H Isolation of Mononuclear Cells

Protocol for Isolation of Mononuclear cells by Density Gradient Separation

Principle

This procedure describes a method for isolation of mononuclear cells from circulating blood. Histopaque®-1077 is a solution of polysucrose and sodium diatrizoate, adjusted to a density of $1.077^{+}0.001$ g/mL. This medium facilitates rapid recovery of viable mononuclear cells from small volumes of blood.

Anticoagulated blood is layered onto Histopaque®-1077. During centrifugation, erythrocytes and granulocytes are aggregated by polysucrose and rapidly sediment; whereas, lymphocytes and other mononuclear cells remain at the plasma-Histopaque®-1077 interface. Erythrocyte contamination is negligible. Most extraneous platelets are removed by low speed centrifugation during the washing steps.

Reagents and Supplies

Histopaque®-1077"Ficoll" (Sigma Aldrich cat#10771)

RPMI 1640

Hanks balanced salt Solution (HBSS)

Phosphate Buffered Solution (PBS)

Fetal calf serum (FCS)

15 or 50mL polypropylene tubes

Procedure

1 Dilute blood in a 1:1 dilution with either HBSS or PBS. Calculate the amount of Ficoll to be used; it will be half of the volume of diluted blood (e.g., for 8ml diluted blood you will need 4ml of Ficoll).

2 Place the Ficoll in the bottom of the polypropylene tube.

3 Carefully layer sample over the tube of Ficoll. Do not pipette the sample too quickly as mixing will occur.

4 Centrifuge the sample for 30 minutes at 400g, 25˚C and most importantly without the brake.

5 After the centrifuge has stopped, the cells need to be removed from the Ficoll immediately and washed because the Ficoll solution is toxic to cells. The mononuclear layer should be visible as a cloudy white disk at the interface of the plasma-Ficoll layers, roughly in the middle of the tube. Carefully remove and discard the top layer of plasma and media until there is only a small amount left above the cell layer.

6 Next, remove the mononuclear layer (the cloudy disk) taking care not to disturb the red cell layer below, and place in a sterile tube.

7 Dilute the mononuclear cells 3-6 times their volume in RPMI media containing 10% FCS and centrifuge for 5 min at 400g, 25˚C with the brake on.

8 Aspirate supernatant, resuspend the pellet in residual volume and add up to 5mls of RPMI 1640w 10% FCS.

9 Perform a cell count. Cells are now ready to be assayed.

Appendix I Protocol for Cryopreserving PBMCs

Materials and Reagents

RPMI 1640 media

Fetal Calf Serum

Dimethyl Sulfoxide (DMSO), Hybri- Max (Sigma Aldrich #D2650)

100% Isopropanol

Nalgene Cryo 1 freezing container (aka Mr. Frosty) (Catalogue #5100-0001)

Phosphate Buffered Saline Solution (PBS)

Method

1 Following Ficoll Histopaque (Sigma Aldrich #10771) density gradient separation, resuspend PBMC's in cold RPMI1640 and perform a cell count.

2 Adjust cell density to no more than $2x10^7$ cells/ml

3 Make up 2x cryopreservation solution fresh as needed, to contain 100% FCS, 20% DMSO. Add DMSO slowly to FCS on ice (it generates heat).

4 Add an equal amount of ice-cold 2x cryopreservation solution drop-wise to the ice-cold cell suspension while vortexing, making sure to slowly increase the DMSO concentration from 0 to 10%

5 Aliquot 1ml of cell mixture into labelled 1.5ml cryo vials.

6 Add room temperature 100% Isopropanol to the fill line of a Mr. Frosty Cryo container (source) and place vials in the insert.

7 Place the Mr. Frosty in a -80 degree freezer, for at least 4h then transfer the frozen vials to liquid N2 for long term storage.

Appendix J *In vivo* P-gp Transporter Inhibitors and Inducers

Examples of *in vivo* P-gp transporter inhibitors and inducers [a]

P-gp Inhibitors	P-gp Inducers
Amiodarone	Avasimibe
Azithromycin	Carbamazepine
Captopril	Phenytoin
Carvedilol	Rifampin
Clarithromycin	St John's wort
Conivaptan	Tipranavir/Ritonavir
Cyclosporine	
Diltiazem	
Dronedarone	
Erythromycin	
Felodipine	
Itraconazole	
Ketoconazole	
Lopinavir And Ritonavir,	
Quercetin,	
Quinidine	
Ranolazine	
Verapamil	

[a]adapted from Table 12:
http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Appendix K EORTC QLQ – GI.NET21

ENGLISH

EORTC QLQ – GI.NET21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31. Did you have hot flushes?		1	2	3	4
32. Have you noticed or been told by others that you looked flushed/red?		1	2	3	4
33. Did you have night sweats?		1	2	3	4
34. Did you have abdominal discomfort?		1	2	3	4
35. Did you have a bloated feeling in your abdomen?		1	2	3	4
36. Have you had a problem with passing wind/gas/flatulence?		1	2	3	4
37. Have you had acid indigestion or heartburn?		1	2	3	4
38. Have you had difficulties with eating?		1	2	3	4
39. Have you had side-effects from your treatment? *(If you are not on treatment please circle N/A)*	N/A	1	2	3	4
40. Have you had a problem from repeated injections? *(If not having injections please circle N/A)*	N/A	1	2	3	4
41 Were you worried about the tumour recurring in other areas of the body?		1	2	3	4
42. Were you concerned about disruption of home life?		1	2	3	4
43. Have you worried about your health in the future?		1	2	3	4
44. How distressing has your illness or treatment been to those close to you?		1	2	3	4
45. Has weight loss been a problem for you?		1	2	3	4
46. Has weight gain been a problem for you?		1	2	3	4
47. Did you worry about the results of your tests? *(If you have not had tests please circle N/A)*	N/A	1	2	3	4
48. Have you had aches or pains in your muscles or bones?		1	2	3	4
49. Did you have any limitations in your ability to travel?		1	2	3	4
During the past four weeks:					
50. Have you had problems receiving adequate information about your disease and treatment?		1	2	3	4
51. Has the disease or treatment affected your sex life (for the worse)? *(If not applicable please circle N/A)*	N/A	1	2	3	4

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