PHASE II EVALUATION OF NINTEDANIB (BIBF 1120) IN THE TREATMENT OF BEVACIZUMAB-RESISTANT PERSISTENT OR RECURRENT EPITHELIAL OVARIAN, FALLOPIAN TUBE, OR PRIMARY PERITONEAL CARCINOMA (NCT01669798)

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SCHEMA

Nintedanib will be administered at a daily oral dose of 200 mg BID until disease progression or adverse effects prohibit further therapy. One cycle is defined as 28 days of treatment.

This is an open label multi-center study with Duke University Medical Center serving as the coordinating center.

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1.0 OBJECTIVES

1.1 Primary Objectives

1.1.1 To assess the activity of Nintedanib as measured by the proportion of patients who survive progression-free for at least 6 months after initiating study therapy in patients with bevacizumab-resistant, persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.

1.2 Secondary Objectives

1.2.1 To determine the proportion of patients who have objective tumor response (complete or partial) based on RECIST 1.1.

1.2.2 To determine the proportion of patients who have objective tumor response (complete or partial) based Gynecologic Cancer InterGroup (GCIG) CA-125 criteria.

1.2.3 To determine the frequency and severity of adverse events as assessed using NCI Common Toxicity Criteria version 4.

1.2.4 To characterize the duration of progression-free survival and overall survival.

1.2.5 To elicit patient preferences for outcomes of ovarian cancer treatment.

1.2.6 To characterize baseline quality of life and cancer-related symptoms.

1.3 Translational Research Objectives

1.3.1 To measure baseline levels of VEGF and correlate with treatment outcome.

1.3.2 To measure baseline and on treatment levels of additional growth factors (listed in section 2.5) that may be co- or counter- regulated with VEGF and correlate with response to treatment.

1.3.3 To measure baseline and on treatment levels of coagulation and endothelial cell activation markers that may predict for thrombotic or bleeding risks related to treatment.

2.0 BACKGROUND & RATIONALE

2.1 Ovarian Cancer

Ovarian cancer patients with platinum-resistant and refractory disease have the lowest response rates to relapse chemotherapy: various chemotherapeutic agents, such as paclitaxel, liposomal doxorubicin, topotecan, docetaxel, platinum, etoposide, ifosfamide, gemcitabine, and vinorelbine are available but result in response rates of 7-40% [1, 2]. Unfortunately, relapse therapy is not curative and treatment is only palliative. Recently two phase II trials demonstrated that anti-angiogenic therapy with bevacizumab alone or in combination with chemotherapy in women with recurrent disease had response rates ranging from 16-24% with an acceptable toxicity profile [3, 4]. However resistance can develop to VEGF inhibition. Therefore other novel anti-angiogenic agents, such as Nintedanib, should be evaluated in the treatment of ovarian cancer.

2.2 Background Information and Experience with Anti-Angiogenic agents in Ovarian Cancer

The most commonly used anti-angiogenic agent is bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor (VEGF). Several clinical trials have evaluated bevacizumab in recurrent ovarian cancer. In a GOG phase II study that evaluated bevacizumab in patients who had failed prior chemotherapy, Burger and colleagues reported a response rate of 21% and a median response duration of 10 months with 40.3% of patients remaining progression-free at 6 months [3]. Another phase II trial evaluated the efficacy of combination bevacizumab and low-dose cyclophosphamide and demonstrated a response rate of 16%, a median PFS was 4.4 months with 27.8% of patients remaining progression free at 6 months [4]. In these two trials the most common adverse events (AEs) were proteinuria, hypertension, and arterial thrombotic events [3-5]. In view of the promising results with bevacizumab in the treatment of ovarian cancer seen in the phase II setting, there are four phase III trials examining whether the addition of this anti-angiogenic therapy to carboplatin-based chemotherapy improves clinical outcome in the primary and recurrent settings. The results of these trials have recently been presented and demonstrated a PFS benefit for concurrent followed by maintenance therapy as part of the first-line treatment of ovarian cancer [6, 7]. We anticipate increased use of bevacizumab in patients with newly diagnosed advanced stage ovarian, peritoneal, and tubal cancers.

2.3 Resistance to VEGF Inhibition

Despite an initial response to bevacizumab, the development of resistance against bevacizumab induced VEGF-blockade may occur. The development of resistance is not via the classic mechanisms noted for conventional cytotoxic agents. Tumor vascular endothelial cells are part of the tumor microenvironment but not the malignant clone and therefore are not prone to mutation. Rather the tumor endothelial cells adapt to VEGFR inhibition by recruitment of vasculature using

multiple secondary signaling pathways, such as those mediated by PDGF, basic FGF, or other cytokines. However, since VEGF is the primary angiogenic pathway, there may be an advantage to continue VEGF-blockade, and this has been demonstrated clinically. In a phase II trial, 40 patients with metastatic colorectal cancer (mCRC) who had previously been treated with bevacizumab (PMH Phase II Consortium Trial) were treated with aflibercept (VEGF Trap). Of the 24 evaluable patients there was 1 partial response, 17 with stable disease, and 7 with stable disease at 16 weeks. Nine patients were not yet evaluable for response. The 4 month PFS rate and median PFS were 29% and 3.4 (1.9-NR), respectively, and were similar compared to those patients who were bevacizumab naïve [8]. Furthermore, in a prospective observational study, 1,445 of 1,953 previously untreated patients with mCRC who were enrolled in the BRiTE study and whose disease progressed were classified into three groups. The groups were separated based on whether they received any treatment or bevacizumab beyond first progression (BBP): (1) no post-progressive disease (PD) treatment (n=253); (2) post-PD treatment without bevacizumab (no BBP; n=531); and (3) BBP (n=642). The median OS rates were highest in the BBP group (31.8 months vs. 12.6 vs. 19.9), in the no post-PD treatment and no-BBP groups, respectively. In multivariate analyses, compared with no BBP, BBP was strongly and independently associated with improved survival (HR, 0.48; $P < .001$). These findings strongly suggest that continued VEGF inhibition, in this case with bevacizumab, beyond initial PD may have utility in the management of previously bevacizumab-treated patients [9]. Theoretically, an agent, such as Nintedanib, that can simultaneously inhibit the VEGF pathway as well as the alternate pro-angiogenic pathways, may prevent tumor resistance to VEGFR inhibition and enhance anti-tumoral effects.

2.4 Background Information and Experience with Nintedanib

Nintedanib is a potent small molecule multi receptor tyrosine kinase inhibitor (PDGFR α/β (platelet derived growth factor receptor), FGFR 1/3 (fibroblast growth factor receptor), VEGFR 1-3 (vascular endothelial growth factor receptor))[10]. On the molecular level, Nintedanib is thought to inhibit the signaling cascade mediating angiogenesis by binding to the adenosine triphosphate (ATP) binding pocket of the receptor kinase domain, thus interfering with cross-activation via autophosphorylation of the receptor homodimers. Besides inhibition of neo-angiogenesis, tumor regression may also be achieved by inducing apoptosis of tumor blood vessel endothelial cells. Inhibition of receptor kinases may also interfere with autocrine and paracrine stimulation of tumor angiogenesis via activation loops involving VEGF, PDGF, and bFGF utilized by perivascular cells such as pericytes and vascular smooth muscle cells. In vitro, the target receptors are all inhibited by Nintedanib in low nanomolar concentrations. In *in vivo* nude mouse models, Nintedanib showed good anti-tumor efficacy at doses of 50 – 100 mg/kg, leading to a substantial delay of tumor growth or even complete tumor stasis in xenografts of a broad range of differing human tumor types including SKOV3 ovarian cancer xenografts [11].

Safety of Nintedanib: A total of 2092 patients have been treated with Nintedanib or placebo for oncological indications, of which more than 1400 patients (numbers estimated for ongoing studies involving blinded controls) have received the verum compound. In total, 433 patients have received Nintedanib as monotherapy in phase I and phase II studies, 195 patients received Nintedanib (verum) in combination with cytotoxic chemotherapy mostly in phase I dose escalation trials, and of the 1338 patients who have been included in the ongoing phase III trials 1199.13, 1199.14 and 1199.15, it is estimated that 698 patients have received Nintedanib in combination with the cytotoxic chemotherapy that is standard for the respective indication [10]. Despite targeting three kinases involved in angiogenesis there was not an exacerbation of expected toxicities associated with anti-angiogenic therapies. The predominant AEs were nausea, diarrhea, vomiting, abdominal pain and fatigue of mostly low to moderate intensity. Dose limiting toxicities (DLT) were mainly confined to reversible hepatic enzyme elevations (AST, ALT, and γ-GT) which increased dose-dependently [10].

The results from phase I monotherapy trials indicated that the MTD was 250 mg bid Nintedanib in the studies including Caucasian patients, and 200 mg bid Nintedanib in Japan.

The predominating dose limiting AEs of Nintedanib were increases of liver enzymes that were rapidly reversible upon cessation of therapy. Hepatic transaminase elevations of grade > 2 were absent at doses below the MTD, occurred occasionally at the MTD dose, and increased in frequency at doses above the MTD.

The safety profile overall appeared largely similar between Caucasian and Japanese patients, with the sole exception that the propensity to experience liver enzyme increases may be higher in Japanese patients. The lower MTD for bid dosing in Japanese patients was primarily due to a higher incidence of reversible liver enzyme increases of grade > 2, which started to occur at the dose of 200 mg bid, whereas in trials including primarily Caucasian patients, liver enzyme increases of grade > 2 were only observed starting at a dose of 250 mg bid.

According to data from trials 1199.1-3, splitting the cumulative daily dose into two doses increased the tolerability of Nintedanib: at a total daily dose of 500 mg of Nintedanib (250 mg bid), 25% of the patients had dose limiting toxicities compared to more than 60% of the patients treated with once daily 450 mg of Nintedanib (1199.1-1199.3).

The phase I data indicate that continuous treatment with 250 mg bid of Nintedanib in Caucasians and 200 mg bid in Japanese patients have an acceptable and manageable safety profile in patients suffering from advanced cancer. Gastrointestinal AEs were the predominate AEs of Nintedanib and were mostly of low to moderate severity. AEs commonly considered as class effects of small molecule antiangiogenic receptor tyrosine kinase inhibitors such as hypertension, proteinuria or thromboembolic events occurred at low frequencies

in the phase I monotherapy trials which may not be distinct from the background incidence in advanced cancer patients.

Safety in pooled Phase I and II monotherapy trials with starting doses of 100 mg bid to 250 mg bid, also including all respective patients from phase I trials treated at these doses in addition to the data from the phase II trials. The overview includes data of 334 patients: 81 patients from phase I trials, and 253 patients from the phase II trials. Patients who have not received Nintedanib in these trials (e.g., placebo-treated patients from trial 1199.9) are not considered.

Gastrointestinal side effects and liver enzyme increases represented the leading AEs. Gastrointestinal AEs rarely were of CTCAE grade > 2, and the frequency did not obviously increase with increased doses of Nintedanib up to 250 mg bid.

Similar to the phase I studies, liver enzyme increases of grade > 2 were only observed in the high dose group of 250 mg bid, and across all trials the only exception were Japanese patients (phase I trial 1199.19), and Asian patients with hepatic impairment (1199.39, Asian patients with hepatocellular cancer). As in the phase I trials, increases of liver enzymes occurred within the first two months of treatment. Liver enzyme increases of grade > 2 were less frequent at a dose of 200 mg bid Nintedanib. Among the phase II trials using 250 mg bid Nintedanib as starting dose, the frequency of liver enzyme increases grade > 2 exceeded 33%.

This frequency was higher than observed in other phase II trials for the same dose. In view of this observation, the absence of grade > 2 liver enzyme increases at 200 mg bid in Caucasian patients and the MTD of 200 mg bid in Japanese patients, the dose currently recommended for Nintedanib monotherapy is 200 mg bid.

Experience with Nintedanib in ovarian cancer: With respect to the phase II trials in ovarian cancer, Nintedanib was evaluated as maintenance therapy in patients with relapsed ovarian cancer that had responded to a preceding line of chemotherapy (Study 1199.9) [10]. Eighty-four patients were randomized to either Nintedanib or placebo. The median treatment duration was 116 days with 5 patients randomized to Nintedanib completing 9 months of therapy compared to none of those in the placebo group. The dose was 250 mg twice daily. The 36-wk PFS rates were 15.6% (95% confidence interval (CI)): 3.8 - 27.3) for Nintedanib and 2.9% (95% CI: 0.0, 8.4) for placebo. Although the trial was not powered for a direct comparison, the PFS hazard ratio was 0.68 (95% CI: 0.42, 1.09). Median time to progression based on RECIST criteria was 4.8 months for Nintedanib, and 2.8 months for placebo. Grade 3 and 4 AEs were reported in 54 and 7% compared to 25 and 3% in the Nintedanib and placebo groups, respectively. Expected grade 3 gastrointestinal toxicities as well as elevated liver enzymes occurred more frequently in the Nintedanib group (GI: 16% vs. 10%; elevated LFTs: 43% vs. 6.3%). The findings suggested that maintenance Nintedanib could delay disease progression in patients with ovarian cancer who had previously responded to chemotherapy [12]. A randomized placebo-controlled phase III

trial, LUME OVAR1, evaluating paclitaxel and carboplatin with or without Nintedanib has been developed and was activated in November 2009. This trial is evaluating a 200 mg po twice daily dosing schedule.

In conclusion, based on the available preclinical and clinical data, Nintedanib displays a favorable safety profile and may have activity in a select patient population with ovarian cancer, such as those with bevacizumab-resistant disease. This proposed study will evaluate single-agent Nintedanib (200 mg po twice daily) in participants with bevacizumab-resistant recurrent or persistent ovarian, peritoneal, and tubal cancer. Patients will be treated to disease progression or toxicity.

2.5 Biomarker Discovery for Ovarian Cancer – Blood-based Angiome Profiling

The Phase I Biomarker Laboratory at Duke University Medical Center acts as a molecular profiling laboratory for blood-based biomarkers of targeted therapies particularly targeted anti-angiogenic agents. Drs. Andrew Nixon and Herbert Hurwitz serve as co-directors of the facility and direct the overall research of the laboratory. The laboratory has quality control procedures in place to address many of the issues involved in clinical trials research including sample quantity, sample integrity, and sample heterogeneity.

Additionally, the laboratory has been selected to act as a core facility for the oncology cooperative group, The Cancer and Leukemia Group B (CALGB). CALGB is a national clinical research group sponsored by the National Cancer Institute, with the Central Office headquartered at the University of Chicago and Statistical Center located at Duke University. The services offered align with their programmatic focus around the interrogation of blood and urine samples using multiplex or standard ELISA technologies. The multiplex design for this study addresses the specific drug target(s) for this drug as well as attempting to capture the relevant co- and counter-regulated proteins.

All samples will have appropriate chain-of-custody documentation to ensure compliance with FDA and IRB regulations. The lab currently has systems in place detailing the location, transfer, and use of any and all human research subject samples. Any discrepancies or omissions in flow sheets and/or sample labels are resolved upon receipt of the sample in the lab. All sample and data handling procedures will be fully compliant with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Sample handling protocols will provide step-by-step details for sample isolation, sample handling, and sample receipt/shipment. Samples will be housed in ultra-low temperature freezers (-80°C). The freezers are monitored daily and are equipped with an alarm system designed to alert laboratory personnel upon freezer malfunction. Additionally, secondary, independent alarm systems exist on all ultra-low freezers currently used to store all patient samples. Use of these redundant systems greatly reduces the chance of freezer failure, which could potentially result in the loss of irreplaceable samples from clinical trial patients.

Blood-based Biomarkers: In the past, the gold standard for detection of growth factors and cytokines in blood was the use of ELISAs; however, multiplex

technology offers an attractive alternative approach for cytokine and growth factor analysis. This novel technology allows for the measurement of multiple analytes simultaneously from a single sample. The advantages of multiplex technology compared to traditional ELISA assays are conservation of patient sample, increased sensitivity, and significant savings in cost, time and labor. Furthermore, all plate designs are validated in order to 1) limit cross-reactivity of the antibodies 2) optimize sensitivity and specificity and 3) maximize the linearity of the assay's dynamic range.

Several systems exist, the plate-based platforms being the Meso Scale Discovery (MSD) multiplex system and the SearchLight system, produced by Aushon Biosystems (formerly of Thermo Fisher Scientific). The assay design in both cases is similar to a sandwich ELISA, except multiple capture antibodies are pre-spotted into individual wells of a 96-well plate. Samples or standards are added which bind to the specific capture antibodies and are detected using various outputs. Over the past 2 years, we have worked to optimize the design of customized multiplex ELISA plates via extensive collaborations with the SearchLight. We have devoted considerable effort to this and have developed an appropriately designed panel for the simultaneous evaluation of up to 40 regulators of tumor and normal angiogenesis. The list of analytes that can be evaluated are shown in Table 1 below. Standard ELISA assays will also be included to evaluate soluble TGFbRIII and IGF-1 as additional blood markers.

Biomarker Selection: Since VEGF signaling is the fundamental pathway promoting angiogenesis, it will be informative to evaluate an array of VEGF and non-VEGF angiogenic factors. Since many angiogenic factors can be targeted with agents that are available or in development, information gained regarding mechanisms of resistance to anti-VEGF agents could direct novel combination therapies. Currently, it is not known which set of these factors will predict for baseline resistance to Nintedanib, which factors mediate acquired resistance to Nintedanib after initial response, and which factors may predict for greater or lesser risk of Nintedanib related toxicity. This lack of information represents a major gap in our understanding of the clinical mechanisms of efficacy, resistance, and toxicity for this agent. For bevacizumab, the fact that VEGF alone is not predictive of response likely reflects the complexity and redundancy of tumor angiogenesis, presumably mediated by multiple other angiogenic proteins. Given the limitations of preclinical modeling, it is critical that these mechanisms of clinical efficacy, resistance and toxicity be validated and prioritized in patients.

Extracellular matrix (ECM) proteins interact with endothelial cells (EC) and serve as a scaffolding structure to support angiogenic sprouting. Matrix Metalloproteinase (MMP)-mediated remodeling of the ECM coordinates directly with VEGF-dependent angiogenesis. Therefore, information of matrix-derived angiogenic factors will take the microenvironment into consideration. Additionally, there are complex interactions between the coagulation system and the angiogenic process. For example, Tissue Factor (TF) is a principal initiator of coagulation; altered TF expression on EC membrane has been implicated in wound healing and angiogenesis, leading to VEGF upregulation. VEGF and TF levels are both increased by hypoxia in tumors and several studies suggest a

survival benefit in patients with malignant disease who have been treated with anticoagulation drugs. The growing recognition of the link between coagulation and angiogenesis led us to test coagulation biomarkers in anti-angiogenic therapies.

All multiplex plate designs have been validated in order to limit cross-reactivity of the antibodies, optimized for sensitivity and specificity, and maximize the linearity of the assay's dynamic range. The coefficient of variation (CVs) of the multiplex arrays is approximately 15-20%, depending on the particular assay. Any study samples that fall outside the linear portion of the standard curve are retested. Samples that read below the limit of detection are retested, if possible. Samples that read above the linear portion of the standard curve are serially diluted and retested to obtain accurate measurements. Any analyte that does not meet the aforementioned criteria will result in the sample being re-evaluated. Analytes of interest that are not available in our multiplex plates will be evaluated using commercial ELISA kits or ELISAs developed in the Biomarker Laboratory.

Table 1. Plasma-based marker identification

Soluble Angiogenic Factors	Matrix-Derived Angiogenic Factors	Markers of Coagulation	Markers of Vascular Activation and Inflammation
bFGF	MMP2	Tissue Factor	Gro-α
HGF	MMP9	PAI-1 Active	IL-6
PlGF	TGFβ1	PAI-1 Total	IL-8
VEGF-A	TGFβ2	CRP	P-selectin
VEGF-C	Osteopontin	D-dimer	E-selectin
VEGF-D	TSP1	Von Willebrand Factor	SDF-1β
ANG-2	TSP2		ICAM-1
PDGF-AA			VCAM-1
PDGF-BB			MCP-1
IGFBP1			E-cadherin
IGFBP3			TNF-α
PEDF			IFN-γ
sVEGFR1			NT-proBNP
sVEGFR2			

2.6 Inclusion of Women and Minorities

The participating institutions will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire ovarian, fallopian tube, and primary peritoneal cancer population treated by participating institutions.

2.7 Background for quality of life and patient preferences addenda

As clinical endpoints, neither OS nor PFS considers the rate of adverse events, quality of life (QOL), or other patient-reported outcomes (PROs) while on treatment. This context is critically important to frame survival metrics to better understand the implication of therapy. In trials as well as in current practice, biologic therapies such as bevacizumab are now often continued as maintenance regimens following discontinuation of cytotoxic treatments, sometimes until disease progression. The practice of continuing treatment over a prolonged period brings into focus the question of what effect such treatment has on quality of life. At a minimum, it results in more trips for medical care and higher out of pocket expense on the part of both patients and caregivers.

Development of a composite endpoint

In phase III studies of ovarian cancer, quality of life is now often examined, usually as a secondary endpoint. However, other patient-reported outcomes such as diverse symptoms, adverse event rates, and patient preferences have almost never been formally incorporated into primary trial endpoints for this disease. Our working group plans to develop a composite endpoint for ovarian cancer treatment trials that will incorporate PFS, severe adverse event rates, QOL and other PROs into the development of a composite endpoint for ovarian cancer trials.

Patient preferences

If a composite endpoint is to be considered, it is critical to ensure that the endpoint will successfully address the outcomes that are most important to patients. To this end, there is a need to determine how patients prioritize the factors and conditions that are most important to their treatment. For example, surviving 5 years with severe peripheral neuropathy is not likely to be as desirable as surviving 5 years with no side effects. Patients are likely to have opinions about how important each factor is and how it should be weighted when compared to the other factors. The preferences of cancer patients concerning quality versus length of life have been reported(1, 2), but never specifically for women with ovarian cancer.

The proposed pilot study will query women with ovarian cancer about their preferences for the possible effects of treatments on (1) progression-free survival, (2) overall survival, (3) development of severe side effects, (4) overall quality of life, and (5) ovarian-cancer specific health symptoms. This study will allow us to determine the feasibility of assigning patient-determined weights to different individual endpoints for the future construction of a patient-centered composite endpoint. Because preferences are often sensitive to the method of elicitation, multiple methods of elicitation will be used to assess the robustness of preferences. Baseline quality of life and symptom index elicitation will allow examination of subjects' preferences in relation to their current symptoms and well being.

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligibility Criteria

a) Patients must have recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. Histologic documentation of the original primary tumor is required via the pathology report. The following histologic epithelial cell types are eligible:
   - serous, endometrioid, mucinous, or clear cell adenocarcinoma;
   - undifferentiated, mixed epithelial or transitional cell carcinoma;
   - Brenner's Tumor;
   - adenocarcinoma N.O.S.

b) Patients must be considered bevacizumab-resistant, i.e., have a treatment-free interval following a response to bevacizumab (CR, PR, or SD) of less than **6 months**, or have progressed during treatment with a bevacizumab-containing therapy.

c) Patients must have measurable disease or detectable (non-measurable) disease:
   - Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT, MRI, or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest x-ray. Lymph nodes must be > 15 mm in short axis when measured by CT or MRI. Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.
   - Detectable disease in a patient is defined as one who does not have measurable disease but has at least one of the following conditions in the setting of a CA125 >2x ULN:
     - Ascites and/or pleural effusion attributed to tumor
     - Solid and/or cystic abnormalities on radiographic imaging that do not meet RECIST 1.1 definitions for target lesions

d) For patients with measurable disease, patient must have at least one "target lesion" to be used to assess response on this protocol as defined by RECIST 1.1. Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

e) Patients who must have a ECOG Performance Status of 0 or 1.

f) Patients should be free of active infection requiring antibiotics (with the exception of uncomplicated UTI).

g) Recovery from effects of recent surgery, radiotherapy, or chemotherapy
   - Any hormonal therapy directed at the malignant tumor must be discontinued at least one week prior to registration. Continuation of hormone replacement therapy is permitted.
     Any other prior therapy directed at the malignant tumor, including immunologic agents, must be discontinued at least three weeks prior to registration. If the

prior therapy was with bevacizumab then at least 4 weeks after treatment discontinuation must have elapsed prior to treatment on this study.

h) Prior therapy
   - Patients must have had one prior platinum-based chemotherapeutic regimen for management of primary disease containing carboplatin, cisplatin, or another organoplatinum compound. This initial treatment may have included intraperitoneal therapy, high-dose therapy, consolidation, non-cytotoxic agents or extended therapy administered after surgical or non-surgical assessment.
   - Patients are allowed to receive, but are not required to receive, two additional **cytotoxic regimens** (a total of 3 cytotoxic regimens) for management of recurrent or persistent disease according to the following definition:
     - Patients who have received only one prior cytotoxic regimen (platinum-based regimen for management of primary disease), must have a platinum-free interval of less than 12 months, or have progressed during platinum-based therapy, or have persistent disease after a platinum-based therapy. Patients must NOT have received any non-cytotoxic therapy for management of recurrent or persistent disease other than bevacizumab-containing regimens. Patients are allowed to receive, but are not required to receive, biologic (non-cytotoxic) therapy as part of their primary treatment regimen.

i) Patients must have adequate:
   - Bone marrow function: Absolute neutrophil count (ANC) greater than or equal to 1,500/mcl, equivalent to NCI Common Toxicity Criteria version 4.0 (CTCAE v4.0) grade 1. Platelets greater than or equal to 100,000/mcl. Hemoglobin (Hb) greater than or equal to 9.0 g/dL.
   - Renal function: Creatinine less than or equal to 1.5 x institutional upper limit of normal (ULN), equivalent to the active version of the NCI AE grade 1.
   - Hepatic function: Bilirubin should be within normal limits (CTCAE v4.0, grade 1). ALT/AST, should be less than or equal to 1.5 x ULN (CTCAE v4.0 grade 1). For patients with liver metastases, ALT/AST should be less than or equal to 2.5 x ULN. Alkaline phosphatase should be less than or equal to 2.5 x ULN (CTCAE v4.0 grade 1).
     Neurologic function: Neuropathy (sensory and motor) less than or equal to CTCAE v4.0 grade 1.

j) Blood coagulation parameters: PT such that the international normalized ratio (INR) is < 1.5 x ULN and a PTT < 1.5 x ULN. Prophylactic heparin or low molecular weight heparin (enoxaparin or alternative anticoagulants (other than warfarin)) are acceptable.

k) Patients must have signed an approved informed consent and authorization permitting release of personal health information.

l) Patients of childbearing potential must have a negative serum pregnancy test prior to the study entry and be practicing an effective form of contraception up until three months after of receiving the last drug treatment.

m) Patients may have undergone a major or minor surgical procedure as long as the following apply:

- Major surgical procedure, open biopsy or significant traumatic injury greater than 28 days prior to the first date of study therapy.
- Core biopsy or IV Port placement greater than 7 days prior to the first date of study therapy.

n) Patient must be at least 18 years of age.

3.2 Ineligibility Criteria

a) Patients who have had previous treatment with Nintedanib.
b) Patients who are pregnant or breastfeeding.
c) Patients who have received radiation to more than 25% of marrow-bearing areas (See Appendix I).
d) Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer, are excluded if there is any evidence of other malignancy being present within the last three years. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.
e) Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis OTHER THAN for the treatment of ovarian, fallopian tube, or primary peritoneal cancer within the last three years are excluded. Prior radiation for localized cancer of the breast, head and neck, or skin is permitted, provided that it was completed more than three years prior to registration, and the patient remains free of recurrent or metastatic disease.
f) Patients who have received prior chemotherapy for any abdominal or pelvic tumor OTHER THAN for the treatment of ovarian, fallopian tube, or primary peritoneal cancer or localized breast cancer within the last three years are excluded. Patients may have received prior adjuvant chemotherapy for localized breast cancer, provided that it was completed more than three years prior to registration, and that the patient remains free of recurrent or metastatic disease.
g) Patients with a history of abdominal or tracheal-esophageal fistula, or gastrointestinal perforation are not eligible. Patients with a history of intra-abdominal abscess within 6 months of enrollment.
h) Patients with serious, uncontrolled, concomitant disorder(s) such as diabetes mellitus.
i) Patients with clinically significant cardiovascular disease including: uncontrolled hypertension defined as systolic > 150 mm Hg or diastolic > 90 mm Hg; unstable angina or who have had a myocardial infarction within the past six months prior to registration; NYHA grade II or greater congestive heart failure; serious cardiac arrhythmia requiring medication (this does not include asymptomatic atrial fibrillation with controlled ventricular rate); or CTCAE v4.0 grade 2 or greater peripheral vascular disease (peripheral ischemia), defined as having at least brief (< 24 hour) episodes of ischemia managed non-surgically and without permanent deficit.
j) Patients with serious non-healing wound, ulcer, or bone factor. Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection are eligible but require weekly wound examinations.

k) Patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorder, coagulopathy, or tumor involving major vessels.
l) Patients with history or evidence upon physical examination of CNS disease; seizures not controlled with standard medical therapy; any brain metastases; or history of CVA, TIA, or subarachnoid hemorrhage within 6 months of the first date of treatment on this study. Patients diagnosed with primary brain tumors within the last three years are also excluded.
m) Patients with central pulmonary metastases or recent hemoptysis (≥ 1/2 tsp. of red blood) within 28 days of registration.
    - Patients with clinically significant proteinuria (i.e. > Grade 1) or UPC ratio above 1.0.
    - Patients with suspicion of transmural tumor bowel involvement based on the investigator's discretion may not enroll on this study.
n) Patients with clinical symptoms or signs of gastrointestinal obstruction and who require parenteral hydration and/or nutrition.
o) Patients taking warfarin are not eligible. Patients on therapeutic doses of anticoagulants are excluded from study.

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4.0 STUDY MODALITIES

4.1 Drug Information: Nintedanib

Investigator Brochure: The most recent version of the Nintedanib Investigator Brochure will be provided to each site. Please contact the Medical IIS Office at BIPI at 877-757-7354 with questions regarding the Investigator Brochure.

4.1.1 Formulation:
Other Names: BIBF 1120, Nintedanib

Classification: Tyrosine kinase inhibition

Molecular Formula: $C_{33}H_{39}N_5O_7S$

4.1.2 Mode of Action*:* Small molecule triple receptor tyrosine *kinase inhibitor* (PDGFR αβ (platelet derived growth factor receptor), FGFR 1/3 (fibroblast growth factor receptor), VEGFR 1-3 (vascular endothelial growth factor receptor)).

4.1.3 How Supplied: Nintedanib is provided by Boehringer-Ingelheim Pharmaceuticals, Inc as soft gelatin capsules containing a suspension of milled active as the salt. It is available in two dose strengths corresponding to 100 mg (orange or peach, oblong capsules), 150 mg (orange or brown, oblong capsules).

The capsule fill is composed of medium chain triglycerides, hard fat and lecithin in addition to the drug substance.

Each bottle will be labeled in an open labeled fashion. Labels will contain, at a minimum, the following information: product name, tablet strength, batch number, directions for use, storage conditions, and appropriate caution statements.

4.1.4 Storage: The capsules are packaged in child resistant high density polyethylene (HDPE) bottles and have to be stored below 30°C.

4.1.5 Stability: The current shelf life is 36 months.

4.1.6 Route of Administration: Oral. Missed doses will not be made up. Every effort should be made to take the capsules at the same time every day. If vomiting occurs the participant should not retake the dose and should be instructed to take the next dose at the next scheduled time.

4.1.7 Rescue medication and additional treatments: Rescue medication to reverse the actions of Nintedanib is not available. Potential side effects of Nintedanib have to be treated symptomatically.

4.1.8 Incompatibilities:

4.1.8.1 Potential Drug Interactions: After oral administration of [^{14}C] Nintedanib to rats, radioactivity showed an early peak in blood (0.5 hours post dose) and in the liver (2 hours post dose). In most of the other tissues the concentration of radioactivity followed a time course with maximum at 8 hours post dose. The highest exposure was seen in the liver, followed by the blood, lung and kidney. Nintedanib did not cross the blood brain barrier. In human liver microsomes, the cleavage of [^{14}C] Nintedanib by esterase-catalyzed hydrolysis (formation of BIBF 1202) was the prevalent metabolic reaction (about 25 %). Metabolism of Nintedanib by CYP450 enzymes plays only a minor role (5%); CYP 3A4 was the predominant enzyme involved in the formation of hydroxylated Nintedanib and desmethylated Nintedanib. Nintedanib did not show relevant inhibition or induction of the major drug metabolizing cytochrome P450 enzymes and specifically no irreversible CYP 3A4 inhibition. The main route of excretion was via feces. In Rhesus monkeys, cumulative fecal excretion was 85.6 % following intravenous and 88.9 % following oral administration. The median 168 hour cumulative urinary excretion was 5.21% following intravenous administration and 1.54% following oral administration. In the rat, the Rhesus-, and the Cynomolgus monkey, exposure to Nintedanib increased in essence linearly with the dose.

With respect to the in vitro finding that the main metabolite of Nintedanib, BIBF 1202, is glucuronidated by UGT1A1 (liver and intestine) as well as UGT1A7, UGT1A8 and UGT1A10 (intestine), it may be speculated whether reduced UGT1A1 activity could result in increased levels of the non-conjugated metabolite. Pharmacogenetic investigations are currently ongoing (correlation of UGT1A1 genotype with PK parameters and clinical parameters) and patients will be genotyped for UGT1A1 in the phase III trials.

Thus far, no relationship between reduced tolerability of Nintedanib and increases of bilirubin have been observed. Patients with increased bilirubin levels or increases of transaminases to > 2.5x ULN prior to start of therapy have been excluded in most trials conducted thus far and only patients with normal bilirubin will be enrolled in the phase III trials in NSCLC. Currently, there is no medical rationale to specifically exclude patients with slow metabolism genotype or reduced activity of the UGT1A1 enzyme since also UGT1A7, UGT1A8 and UGT1A10 are capable of glucuronidating BIBF 1202 (intestine). Combination of Nintedanib with agents metabolized via UGT1A1 such as irinotecan has not been tested thus far. Yet, the relevance of the possible interaction of Nintedanib with UGT1A1 for drug-drug interactions is not clear.

Specific dose reduction schemes for liver enzyme elevations are in place in all protocols.

4.1.9 Reported Adverse Events and Potential Risks:

4.1.9.1 Gastrointestinal adverse events: nausea, vomiting, diarrhea, anorexia and abdominal pain (upper and lower) were the most frequent adverse events and were mostly of CTCAE grades 1 and 2 intensities. The frequency of CTCAE grade 3 gastrointestinal events did not exceed 8% over all trials. Gastrointestinal side effects were the predominant reason for treatment interruption besides liver enzyme elevations and fatigue/asthenia. All events were fully reversible [8].

4.1.9.2 Hepatic adverse events: The predominant dose limiting toxicity in phase I dose escalation trials was reversible elevation of hepatic transaminases, more pronounced for ALT than for AST. At doses below 200 mg bid no CTCAE grade 3+4 increases have been observed. According to phase II data, the probability to suffer from liver enzyme elevations of CTCAE grade 3 or 4 within the first two months of Nintedanib treatment is 10-15% for patients treated with 250 mg bid of Nintedanib. An increase of transaminases was only rarely observed in Caucasian patients treated with 150 mg bid or 200 mg bid. An association with hyperbilirubinemia was rare, and was (if at all) represented by a low grade increase of bilirubin with only one exception in a patient with tumor stenosis of the ductus hepatocholedochus and grade 3 bilirubin increase two weeks after cessation of therapy. γ-GT elevations, either as isolated increases or in combination with transaminitis, were observed frequently. Enzyme elevations generally normalized upon dose reduction or discontinuation. No drug-related hepatic failure was reported [8].

The current dose of Nintedanib in all studies is limited to 200 mg bid and, all studies require monitoring of liver enzyme tests. In addition, all studies include specific dose reduction schemes regarding liver enzyme elevations [8].

4.1.9.3 Infection adverse events: Infections have been observed but were expected for advanced cancer populations and age group. Only a few were considered drug related.

4.1.9.4 Thromboembolic and cardiac adverse events: In the combined phase I and II monotherapy trials (1199.1-3, 1199.9, 1199.10, 1199.11, 1199.16, 1199.19), there were 13 patients (3.7%) with events from the “selected thrombotic events” category which included pulmonary embolism (3), deep vein thrombosis (2), myocardial infarction (2), transient ischemic attack (2), aphasia (1), hemiparesis (1), thrombophlebitis (1), and thrombosis (1). Five of these events (1.4%) were considered treatment

related: deep vein thrombosis (2) myocardial infarction (2), and transient ischemic attack (1). There were 66 patients (19%) with events from the "cardiac events" category which include the following: chest pain (24, 6.9%), edema peripheral (9, 6.6%), sinus tachycardia (8, 2.3%), cardiovascular disorder (3, 0.9%), palpitations (3, 0.9%), arrhythmia (2, 0.6%), cardiopulmonary failure (2 (1 fatal and not considered as treatment related), 0.6%), myocardial infarction (2, 0.6%), pericardial effusion (2, 0.6%), atrioventricular block second degree (1, 0.3%), cardiac failure (1, 0.3%), electrocardiogram ST segment (1, 0.3%), electrocardiogram change (1, 0.3%), heart rate decreased (1, 0.3%), heart rate irregular (1, 0.3%), pitting edema (1, 0.3%), sudden death (1 case considered as not treatment related, 0.3%), syncope (1, 0.3%), and ventricular arrhythmia (1, 0.3%). A total of 12 from these events (3.4%) were considered as treatment related: chest pain (2), myocardial infarction (2), peripheral edema (2), sinus tachycardia (2), arrhythmia (1), cardiac failure (1), electrocardiogram ST (1), electrocardiogram change (1), heart rate decrease (1), palpitation (1), tachycardia (1), and ventricular arrhythmia (1). In the placebo controlled unblinded phase II trial 1199.9 comparing 250 mg bid of Nintedanib to placebo in patients with ovarian cancer there was no difference in AEs from the SOC "Cardiac disorder" between both arms (Nintedanib: 1 (2-3%) versus 2 (5%) for placebo).There was also no meaningful difference between both arms regarding "thrombotic events" (Nintedanib arm: 2 with deep vein thrombosis. Placebo arm: 1 with pulmonary embolism) and regarding "cardiac events" (Nintedanib arm: 5 (12.5%), placebo arm: 3 (6.8%)).

In summary, the frequency of drug related thromboembolic events was low across all completed studies using Nintedanib monotherapy, and the frequency of thromboembolic adverse events regardless of relatedness did not exceed the expected rate in the patients with advanced solid tumors [8].

4.1.9.5 Hypertension adverse events: In the combined phase I and II monotherapy studies trials (1199.1-3, 1199.16, 1199.19, 1199.9, 1199.10, 1199.11), 36 patients (10.3 %) had the AEs from the pool of 'hypertension' events which include the following: 32 (9.2%) had hypertension, 3 (0.9 %) had blood pressure increased, and 2 (0.6 %) had systolic blood pressure increased. The majority of these events were considered as treatment related: 24 (6.9%) with hypertension, 3 (0.9%) with blood pressure increased, and 1 (0.3%) with systolic blood pressure increased. In a randomized study, in the combined trials, the frequency of reported hypertension adverse events was 2.6%-9.9%. Overall, the hypertensive potential of Nintedanib as an antiangiogenic compound is considered relatively low as compared to other compounds in the class [8].

4.1.9.6 Dermatologic adverse events: *In vitro* studies suggested a theoretic risk of phototoxicity for patients treated with Nintedanib. However, it was estimated that the maximum concentration of Nintedanib in the human skin is about 4-fold lower than the threshold level of 0.5 μg/mL in the in vitro assay. Combined phase I and II Nintedanib monotherapy trials 1199.1-3 1199.9, 1199.10, 1199.11, 1199.16 and 1199.19: a total of 72 patients (20.7%) reported an AE from the user-defined category 'skin events'. These AEs include following: pruritus (18, 5.2%), rash (18, 5.2%), hyperhidrosis (17, 4.9%), erythema (14, 4%), skin lesion (5, 1.4%), acne (4, 1.1%), skin irritation (3, 0.9%), sunburn (3, 0.9%), skin fissure (2, 0.6%), urticaria (2, 0.6%). Additionally, photosensitivity reaction, prurigo, pruritus generalized, rash macular, rash pustular, skin reaction, and skin ulcer occur each in less than 2 patients (0.3%). All events were grade 1-2 [8].

4.1.9.7 Other adverse events include fatigue or asthenia, metabolism and nutrition disorders, anorexia, and lab abnormalities.

4.1.10 Availability: Nintedanib will be supplied by Boehringer Ingelheim

4.1.11 Drug Ordering and Accountability:

Please see the following separate documents for information:

- Drug Order Form
- Investigational Agent Accountability Form 100mg capsules
- Investigational Agent Accountability Form 150mg capsules

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5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE

Before patient screening begins, each site must submit the following documents to Duke University, Division of Gynecologic Oncology Clinical Trials via mail or email **(Attn: Regulatory Department, Protocol BIBF 1120):**

- IRB approval.
- IRB-approved informed consent.
- IRB Membership list or FWA assurance letter.
- Study-specific signed original FDA Form 1572 for institution PI.
- Current CV (signed and dated within one year) for institution PI and sub-investigators listed on FDA Form 1572.
- Medical license for institution PI and sub-investigators listed on the FDA Form 1572.
- Lab license, certificates, and required Normal Lab Values (NLV) for labs listed on FDA Form 1572.
- Signed original Signature Page for PI.
- Signed original Financial Disclosure Form for all investigators listed on FDA Form 1572.
- Delegation of Authority log.
- Human Subject Protection Certificates for investigators and personnel who will be seeing and consenting study participants.

Please allow 7-10 days for processing of regulatory documents before screening the first patient. All copies of the above should be filed into a study-specific regulatory binder at your institution.

The initial supply of study drug cannot be shipped until all the regulatory documents have been reviewed and approved. Duke University may require copies of the regulatory documentation prior to any shipment of drug.

5.1 Patient Entry and Registration

When a suitable candidate has been obtained for protocol entry, the following steps should be taken:

5.1.1 An approved consent form must be signed by the patient or guardian. The consent must contain language permitting the release of personal health information. Current FDA and institutional regulations concerning informed consent will be followed.

5.1.2 All eligibility requirements indicated must be satisfied.

5.1.3 Eligibility Checklist data should be gathered and faxed to (919) 681-7689.

5.1.4 Subject entry will take place after the fax is received and verification of the Eligibility Checklist data completed. Alternatively, a secure web-based process is available for subject registration, providing subject identifiers to the registrar,

as well as spawning a secure e-mail notification to coordinating center personnel.

5.1.5 The institution will enter the patient's name into a Log Book to verify the patient's entry.

5.2 Treatment Plan

5.2.1 Patients to take 200 mg PO twice daily until disease progression or toxicity. 28 days will be considered one cycle. Capsules will be swallowed unchewed with a glass of liquid of about one cup and with a dose interval of 12 hours. Patients will be instructed to take their medication at the same time every day, after food intake. If a patient misses a dose, the missed dose will not be made up. The patient should be instructed to take the next dose at the next scheduled time.

5.3 Criteria for removal from treatment

5.3.1 Inability to tolerate Nintedanib at the lowest doses because of toxicity.

5.3.2 Patients may choose to withdraw from the study at any time for any reason.

5. 3.3 Patients with evidence of disease progression or significant side effects will be removed from study.

5.3.4 Patients who become pregnant will be removed from the study.

6.0 TREATMENT MODIFICATIONS

Study Drug	**2 Level reduction**	**1 Level reduction**	**Initial dose level**
Nintedanib	100 mg BID 1 100 mg capsule BID	150 mg BID 1 x 150 mg capsule BID	200 mg BID 2 x 100 mg capsules BID

Please note that this section is referring to the active version of the NCI Common Toxicity Criteria Version 4.0 grading.

6.1 Management of diarrhea

CTCAE v4.0 Grade	**Action for Nintedanib and Anti-diarrheal treatment**	**Action for Nintedanib after recovery of diarrhea [1]**
Grade 1	Continue Nintedanib No Anti-diarrheal treatment	No dose reduction of Nintedanib
Grade 2	Continue Nintedanib Anti-diarrheal 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		
First episode	TEMPORALLY Nintedanib until recovery[1] AND Anti-diarrheal treatment according to the local standard e.g., loperamide p.r.n.	Reduce Nintedanib dose to 2 x 150 mg after recovery of diarrhea [1]
Second episode	TEMPORALLY STOP Nintedanib until recovery[1] AND Anti-diarrheal treatment according to the local standard e.g., loperamide p.r.n.	Reduce Nintedanib dose to 2x 100 mg after recovery of diarrhea [1]
Third episode	PERMANENTLY discontinue Nintedanib treatment AND Anti-diarrheal treatment according to the local standard e.g., loperamide p.r.n.	PERMANENTLY discontinue Nintedanib treatment

[1]Until resolution to less than or equal to the patient's pre-therapy status at study enrollment.

6.2 Management of liver enzyme elevations: If liver enzyme elevations are considered to be related to Nintedanib the following algorithm should be followed. This recommendation for the management of Nintedanib-induced liver toxicity is valid ONLY for patients with inclusion criteria: AST/ALT < 1.5 ULN and bilirubin ULN in

patients with no metastases in liver and, AST/ALT < 2.5 ULN and bilirubin ≤ ULN in patients with metastases in liver.

ALT, AST and bilirubin elevation	**1st episode**	**2nd episode**	**3st episode**
ALT and/or AST ≤ 5x ULN with bilirubin ≤ 1.5 ULN	Continue Nintedanib, No dose reduction	Continue Nintedanib, No dose reduction	Continue Nintedanib, No dose reduction
ALT or AST > 2.5 ULN in conjunction with bilirubin > 1.5 ULN	TEMPORARILY STOP Nintedanib until recovery* Then reduce Nintedanib dose[1]	TEMPORARILY STOP Nintedanib until recovery* Then reduce Nintedanib dose[1]	PERMANENT discontinuation of Nintedanib treatment
ALT or AST > 5x ULN	TEMPORARILY STOP Nintedanib until recovery* Then reduce Nintedanib dose[1]	PERMANENT discontinuation of Nintedanib treatment	PERMANENT discontinuation of Nintedanib treatment
Bilirubin > 3.0 ULN	TEMPORARILY STOP Nintedanib until recovery* Then reduce Nintedanib dose[1]	PERMANENT discontinuation of Nintedanib treatment	PERMANENT discontinuation of Nintedanib treatment

*ALT and or AST ≤ 2.5x ULN with bilirubin ≤ 1.5 ULN or baseline at study enrollment.
[1]Nintedanib dose reductions : from 200 mg bid to 150 mg bid and from 150 mg bid to 100 mg bid

Revised to change "ALT and/or AST ≤ 2.5x ULN with bilirubin ≤ 1.5 ULN" to "ALT and/or AST ≤ 5x ULN with bilirubin ≤ 1.5 ULN" in order to provide direction for participants with an "ALT and/or AST > 2.5 but ≤ 5x ULN with bilirubin ≤ 1.5 ULN".

Revised from "*CTCAE v4.0, grade ≤ 1 or baseline at study enrolment" to"*ALT and or AST ≤ 2.5x ULN with bilirubin ≤ 1.5 ULN or baseline at study enrollment." Change was made due to variations regarding hepatic toxicity in CTCAE v3.0 and CTCAE v4.0. The Nintedanib modifications for hepatic toxicity were initially based on CTCAE v3.0. CTCAE v 3.0 defined grade 1 hepatic toxicity was defined as ALT and or AST ≤ 2.5x ULN. However, CTCAE v 4.0 grade 1 hepatic toxicity is defined ALT and or AST ≤ 3.0x ULN. Safety data up to date has used CTCAE v3.0. For safety considerations in prior studies in these series the criteria for return to baseline was ALT and/or AST ≤ 2.5x ULN with bilirubin ≤ 1.5 ULN or returning to baseline at study enrollment. To improve patient safety we will use these parameters rather than CTCAE v4.0 study criteria.

6.3 Management of nausea and vomiting for trials investigating monotherapy of Nintedanib

In order to reduce the occurrence and the intensity of emesis the patients should be treated according to the following recommendations:

CTCAE v4.0 Grade	**Antiemetic treatment**	**Dose of Nintedanib**
Nausea =1	No antiemetic treatment	No dose reduction
Nausea 2 and/or vomiting =1	No Nintedanib treatment pause Antiemetic treatment according to local standard of care, e.g., metoclopramide or dimenhydrinate, or prochlorperazine If ineffective, patients should be treated according to treatment of vomiting $\geq$ 2 or nausea CTCAE Grade $\geq$ 3.	No dose reduction
Vomiting $\geq$2 and/ or nausea $\geq$ 3 First episode Second episode Third episode	 Treatment with Nintedanib discontinued and resumed upon recovery[1] Antiemetic treatment according to local standard of care e.g., with 5-HT_3 receptor antagonist* and/or corticosteroid Treatment with Nintedanib discontinued and resumed upon recovery[1] Treatment as above As above	 Nintedanib: dose reduction[2] Nintedanib: dose reduction[2] Nintedanib: discontinuation

[1]CTCAE grade $\leq$ 1 or baseline at study enrolment.
[2]Nintedanib dose reductions : from 200 mg bid to 150 mg bid and from 150 mg bid to 100 mg bid
*** Note: Tropisetron and dolasetron should be avoided due to genetically polymorphic metabolism by CYP2D6.**

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6.4 Management of non-hematologic adverse events other than emesis, liver enzyme elevations, and diarrhea

CTCAE v4.0 **Grade 3 or 4**	**Nintedanib**
First Episode	TEMPORARILY Stop Nintedanib treatment until recovery[1] Then Nintedanib dose reduction[2]
Second Episode	TEMPORARILY Stop Nintedanib treatment until recovery[1] Then Nintedanib dose reduction[2]
Third Episode	PERMANENT Nintedanib treatment discontinuation

[1]Until resolution to less than or equal to the patient's pre-therapy value at study enrollment.
[2]Nintedanib dose reductions : from 200 mg bid to 150 mg bid and from 150 mg bid to 100 mg bid

6.5 Patients should PERMANENTLY discontinue treatment with Nintedanib in the event of:

- Intolerable Adverse Events (CTCAE v4.0 grade 3 or 4) that cannot be managed by dose reduction.
- Nausea or vomiting CTCAE v4.0 grade 2 for 5 or more consecutive days despite optimal supportive care and dose reduction of study medication.
- Diarrhea CTCAE v4.0 grade $\geq$ 2 for 8 or more consecutive days despite optimal supportive care and dose reduction of study medication.
- In the event that Nintedanib is withheld for > 21 consecutive days due to treatment-related toxicity, Nintedanib will be permanently discontinued.

6.6 Dose escalations

There will be no dose escalations or re-escalations on this study.

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7.0 STUDY PARAMETERS

7.1 The following observations and tests are to be performed and recorded on the appropriate form(s). **Specimen requirements for translational research are provided in Section 7.3.**

Parameter	Pre-Therapy	Weekly	Prior to Each cycle	Every Other Cycle	Post Treatment Follow-up
History & Physical	X [1]		X		X
Performance Status	X [1]				
Clinical tumor measurement	X [1]		X [2]		
Toxicity Assessment	X [3]	X [7]	X		
CBC/Differential/Platelets	X [3]		X [4]		X [10]
Electrolytes, BUN, creatinine, Ca, Mg, PO_4, Urinalysis	X [3]		X [4]		X [10]
Bilirubin, SGOT, SGPT, Alkaline Phosphatase	X [3]		X [4]		X [10]
INR/PT/PTT[12]	X[1]			X[12]	
Serum Pregnancy Test (for patients of childbearing potential)	X [9]				
Chest imaging (X-ray or CT scan of the chest)	X [1]			X [5]	
Radiographic tumor measurement (RECIST)	X [1, 6]			X [6]	X [6]
Electrocardiogram (ECG)	X [1]			X[13]	
CA-125	X [3]		X [4]		X
Capsule Diary			X [8]		
Research samples	X[11]			X[11]	X[11]
Subject Preferences Tasks	X[14]				
NFOSI-18	X[14]				
FACT-GOG-Ntx	X[14]				

Notes:
1. Must be obtained within 28 days prior to initiating protocol therapy.
2. For those patients whose disease can be evaluated by physical examination (i.e. nodes, pelvic mass).

3. Must be obtained within 14 days prior to initiating protocol therapy.
4. CBC/Differential/Platelets, liver function tests, creatinine,CA-125, and urinalysis must be obtained within 4 days before initiating the next cycle of treatment with protocol therapy.
5. Repeat chest imaging if initially abnormal or if required, to monitor tumor response.
6. CT scan or MRI if used to follow lesion for measurable disease every other cycle for the first 6 months; then every 3 months thereafter; and at any other time if clinically indicated based on symptoms or physical signs suggestive of progressive disease or rising serum tumor marker levels.
7. Nurse at site is to make weekly phone call to the patient during the **first two** cycles of treatment to inquire about any toxicity. The phone contact should be documented in the study participant's chart.
8. See Appendix II
9. If the patient is of child-bearing potential the serum pregnancy test must be obtained within 7 days prior to initiating protocol therapy.
10. These tests are to be done as needed at the discretion of the study doctor.
11. See section 7.3 for specimen requirements. Collect whole blood, serum, plasma, and urine pre-cycle #1, every other cycle (i.e. Cycle 3, 5, etc.), at the time of progression, and one month after study treatment is discontinued.
12. Repeat every other cycle and more frequently as clinically indicated. For patients with hepatic injury or elevated liver function tests repeat the INR/PT/PTT every cycle until the liver function tests return to baseline; then resume INR/PT/PTT every other cycle.
13. Repeat every other cycle and more frequently as clinically indicated.
14. Only for subjects enrolled at Duke

7.2 Pathology Requirements

Stained pathology slides are not required for this protocol. Documentation of initial pathology will be performed by verifying the original pathology report.

7.3 Translational Research

7.3.1 Specimen Requirements

7.3.1.1 Blood Specimens

For detailed instructions on processing and shipping please see Procedure Manual – Specimens SOP

7.3.1.2 Urine Specimens

For detailed instructions on processing and shipping please see Procedure Manual – Specimens SOP

7.3.1.3 Tumor Specimens

For detailed instructions on processing and shipping please see Procedure Manual – Specimens SOP

7.3.2 Biomarker processing and sample handling.

For detailed instructions on processing and shipping please see Procedure Manual – Specimens SOP

For any questions regarding biomarker processing, supplies and shipping, please call 919-684-4159.

7.4 Quality of Life

The NCCN-FACT FOSI-18 and the FACT-Ntx will be collected at enrollment in conjunction with collection of patient preferences data. These instruments will elicit patient-reported outcomes that complement and supplement the preferences data. It is critical when examining preferences to have information on the current condition of those being queried.

8.0 EVALUATION CRITERIA

8.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [13]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

8.1.1 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

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

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

Notes:
Bone lesions: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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

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

8.1.2 Methods for Evaluation of 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), but NOT lung.

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, subsequent image acquisitions should use the same type of scanner and follow the baseline imaging protocol as closely as possible. If possible, body scans should be performed with breath-hold scanning techniques.

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. PET-CT scans are not always done with oral and IV contrast. In addition, the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

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

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.

CA-125 (Ovarian, fallopian tube and primary peritoneal cancer trials): CA-125 alone cannot be used to assess response. If CA-125 is initially

above the upper normal limit, it must normalize for a patient to be considered in complete clinical response. Specific guidelines for CA-125 response (in recurrent ovarian cancer) have been published [14].

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.

It is mandatory to obtain cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when measureable disease has met criteria for response or stable disease. This confirmation is necessary to differentiate response or stable disease versus progressive disease, as an effusion may be a side effect of the treatment.

8.1.3 Response Criteria

Determination of response should take into consideration all target and non-target lesions and if appropriate, biomarkers.

8.1.3.1 Evaluation of Target Lesions

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

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

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

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

Not evaluable (NE): When at least one target lesion is not evaluated at a particular time point.

8.1.3.2 Evaluation of Non-Target Lesions

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

Note: If CA-125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s)

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

Not evaluable (NE): When at least one non-target lesion is not evaluated at a particular time point.

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

8.1.3.3 Evaluation of Biomarkers

If serum CA-125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

8.1.3.4 Evaluation of Best Overall (unconfirmed) Response

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

Time Point Response for Patients with Measurable Disease at baseline (i.e., Target Disease)

Target Lesions	Non-Target Lesions	Biomarker CA-125	New Lesions*	Time Point Response
CR	CR	Within normal limits	No	CR
CR	Non-CR/Non-PD	Any value	No	PR
CR	NE	Any value	No	PR
PR	Non-PD or NE	Any value	No	PR
SD	Non-PD or NE	Any value	No	SD
NE	Non-PD	Any value	No	NE
PD	Any	Any value	Yes or No	PD
Any	PD**	Any value	Yes or No	PD
Any	Any	Any value	Yes	PD

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

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

8.1.3.5 Best Overall Confirmed Response

Confirmation of CR and PR for determination of best overall response is required for studies with a primary endpoint that includes response. SD should also be confirmed. **Responses (CR and PR) require confirmation at greater than or equal to 4 weeks from initial documentation. For this study, the minimum criterion for SD duration is 6-8 weeks.**

Confirmed CR and PR for best overall confirmed response

Time Point Response First time point	Time Point Response Subsequent time point	BEST overall confirmed response
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD

CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

*If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR or SD, not CR at the first time point. Under these circumstances, the original CR should be changed to PR or SD and the best response is PR or SD.

In non-randomized trials where response is part of the primary endpoint, confirmation of CR or PR is needed to deem either one the "best overall response." Patients with a global deterioration of health status requiring discontinuation of treatment or who die without objective evidence of disease progression at that time should be reported to be off study treatment due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

8.1.4 CA125 Response Criteria

A response according to CA 125 has occurred if there is at least a 50% reduction in CA 125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA125 only if they have a pretreatment sample that is at least twice the upper limit of normal and within 2 weeks prior to starting treatment [14].

8.1.5 Duration of Response

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

progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

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

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

8.1.6 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from study entry to time of progression or death, whichever occurs first.

8.1.7 Survival

Survival is defined as the duration of time from study entry to time of death or the date of last contact.

9.0 DURATION OF STUDY

9.0 Patients will receive therapy until disease progression or intolerable toxicity intervenes. The patient can refuse the study treatment at any time.

9.1 All patients will be treated (with completion of all required case report forms) until disease progression or study withdrawal. Patients will then be followed (with physical exams and histories) every three months for the first two years and then every six months for the next year. Patients will be followed for OS for up to 3 years after completing the study (due to either disease progression or study withdrawal)**.**

10.0 ADVERSE EVENTS, STUDY MONITORING & REPORTING PROCEDURE

There must be adequate review, assessment, and monitoring of adverse events. All subjects will be closely monitored throughout the study for AEs. Investigators will assess the occurrence of AEs and serious adverse events (SAEs) at all subject evaluations and visits during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be recorded in the subject's medical record and on the appropriate AE or SAE CRF page.

Any SAE due to any cause must be reported to the Duke Cancer Institute (DCI) Safety Desk at the Duke University by fax or email within 24-hours of learning of the event.

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events), version 4.0 for Adverse Event (AE) and Serious Adverse Event (SAE) reporting. A copy of the CTCAE v4.0 can be downloaded from http://ctep.cancer.gov/reporting/ctc.html.

10.1 Safety

For safety information on Nintedanib, refer to the most recent version of the investigator brochure.

10.2 Reporting Period

Serious adverse events require immediate notification (within 24 hours of knowledge of the event) to Dr. Angeles Alvarez Secord of Duke University Medical Center or designated representative. The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment on Cycle 1, Day 1. It ends 30 days following the last administration of study treatment, or if the patient initiates treatment with a new anti-cancer therapy, or study discontinuation/termination; whichever is earlier. Any SAEs occurring any time after this period should be promptly reported if a causal relationship to the investigational product is suspected; investigators should report only SAEs that are attributed to study treatment.

SAEs that are observed or reported prior to initiation of study treatment should be recorded as SAEs on the CRF if they are associated with protocol-mandated interventions (e.g., invasive procedures such as biopsies, medication washout, or no treatment run-in).

10.3 Definitions

10.3.1 An ***adverse event*** (**AE**) is any untoward medical occurrence, undesirable medical condition, recurrence or deterioration of a preexisting medical condition, or disease temporally associated with or subsequent to exposure to a pharmaceutical product/treatment or protocol-imposed intervention, regardless of attribution. This includes signs (including a clinically significant abnormal laboratory finding), symptoms or condition occurring at any dose independent of perceived causal relationship to the product or treatment. AEs may or may not be formal medical diagnoses. Common examples include nausea, chest pain, tachycardia, enlarged liver, or electrocardiogram abnormalities.

10.3.2 ***Inter-current illness*** or injuries should be regarded as adverse events.

Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- Results in study withdrawal.
- Is associated with a serious adverse event.
- Is associated with clinical signs or symptoms.
- Leads to additional treatment or to further diagnostic tests.
- Is considered by the Investigator to be of clinical significance.

10.3.3 A ***serious adverse event*** (**SAE**) as defined by the International Conference on Harmonization (ICH) is any adverse experience that at any dose meets any of the following conditions:

- Results in death (i.e., the adverse event causes or leads to death).
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug reaction when, based upon appropriate medical judgment, they may require medical or surgical intervention to prevent one of the outcomes listed in the definition above. Examples of such medical events includes allergic bronchospasms requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in impatient hospitalization, or the development of drug dependency or drug abuse.

10.3.4 ***Life-threatening*** refers to immediate risk of death as the event occurred per the view of the investigator. A life-threatening experience does not include an experience, had it occurred in a more severe form, might have caused death, but as it actually occurred, did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

10.3.5 ***Hospitalization*** is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered an SAE. In absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE by the participating investigator. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol (drug administration, protocol-requiring testing, etc.).
- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (e.g., stent removal after surgery). This should be recorded in the study file.
- Social admissions (e.g., subject has no place to sleep).
- Administrative admissions (e.g., for yearly physical examinations).
- Admission for treatment of a preexisting medical condition not associated with the development of a new adverse event or with a worsening of the preexisting condition.
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery).

In addition, a hospitalization for a preexisting condition that has not worsened does not constitute an SAE. Hospitalization does not include the following: rehabilitation facilities, hospice facilities, respite care (e.g., caregiver relief), skilled nursing facilities, nursing homes, routine emergency room admissions, or same day surgeries. Diagnostic and therapeutic non-invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

10.3.6 **Disability** is defined as a substantial disruption in a person's ability to conduct normal life functions. If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

10.3.7 **Congenital Anomaly/Birth Defect** in a neonate/infant born to a mother exposed to the investigational or pharmaceutical product/treatment.

10.3.8 A **protocol-related AE** is an AE occurring during a clinical study that is not related to the test article, but is considered by the investigator or the medical monitor (or designee) to be related to the research conditions, i.e., related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an untoward event occurring during a washout period or an event related to a medical procedure required by the protocol.

***All adverse events should be noted on the Adverse Reaction case report form (CRF), whether or not is felt to be related to study drug.

10.3.9 **Related/Associated** (with the use of the drug): There is a reasonable

possibility (more likely than not) that the event may have been caused by the drug, device or research. Determining the possible cause of an event includes assessing temporal relationships, dechallenge/rechallenge information, association (or lack of association) with underlying diseases, and the presence (or absence) of a more likely cause.

10.3.10 An **unexpected adverse** event means any adverse event that is not identified in nature, severity, or frequency in the current Investigator Brochure.

10.3.11 **Overdose** is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. An overdose is defined as a dose increase of Nintedanib other than one prescribed by a health care professional or recommended by this protocol, whether accidental or intentional. For reporting purposes overdose does not need to be reported to Boehringer Ingelheim unless there is an SAE associated with the overdose. An overdose itself does not meet any criteria for reporting to BI (Safety) as an AE/SAE. If an SAE occurs due to overdose, the SAE should be reported and the information should be reported and the information should be reflected in the administration section of the SAE form.

10.3.12 A **pre-existing condition** is one that is present at the start of the study, and should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

10.3.13 **Seriousness** is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as the guide for defining regulatory obligations from the Sponsor to applicable regulatory authorities.

10.3.14 **Severity** (or intensity) refers to the grade of a specific AE (e.g., mild (grade 1); moderate (grade 2); or severe (grade 3) myocardial infarction); see table for further details.

****** *Severity* and *seriousness* should be independently assessed when recoding AEs and SAEs on the CRF.

10.3.15 **Non-Serious AEs** are any events that do not meet any of the criteria for Serious.

10.4 Adverse Events and Laboratory Values of Special Interest

Adverse events of special interest are to be reported using the same time line as Serious Adverse Events, even if they do not meet any of the seriousness criteria:

1. **Any gastrointestinal and non-gastrointestinal perforation, leakage, fistula formation, and abscess.** In such case, the following additional information need to be collected, documented on the eCRF page and forwarded to Boehringer Ingelheim:
   - Location/extent of abdominal tumor magnifications.
   - Imaging and reports (CT, ultrasound, endoscopy, pathology, etc.).
   - Prior surgery (location, wound healing complications).
   - Concomitant diseases with GI involvement (e. g. Crohn's, vasculitis, tuberculosis, diverticulitis).
2. **Elevated transaminases:** based on laboratory values.
   (i) ALT and/or AST > 5x ULN without bilirubin elevation.
   (ii) ALT and/or AST > 3x ULN with bilirubin > 1.5x ULN.
   (iii) Occurrence of at least two (2) elevated results no more than 2 weeks apart that is not considered to be an adverse event.

In such case, the following additional information needs to be collected, documented as an adverse event or medical history if applicable, and included on the Boehringer Ingelheim SAE reporting form:

- Hepatic tumor involvement.
- Gilbert syndrome.
- Viral hepatitis (e.g., Hepatitis A; B; C; EBV; CMV).
- Alcohol and/or autoimmune hepatitis.
- Hepatobiliary disorders (e.g., gallstones).
- Vascular hepatitis conditions (e.g., portal vein thrombosis, right heart failure).
- Recent alcohol consumption.
- Recent intake of hepatotoxic compounds (including steroids).
- Other etiology.

Medical evaluation of these results and clinical documentation should be provided.

10.5 Medication Errors

Generally, medication errors are the result of administration or consumption of the wrong product, by the wrong subject, per the wrong route, at the wrong time or at the wrong dosage strength, due to human error. FDA and EMEA have adopted risk management guidance documents suggesting collection and review of medication errors in pre-approval clinical trials. The purpose of collecting and reviewing medication errors occurring in pre-approval is mainly to determine whether medication errors can be prevented prior to or after market approval. That is, the reported medication errors should be analyzed to determine whether clearer labeling, dosing instructions or packaging might have prevented the medication error. Consequently, the intention is to ensure that the improvements in labeling, dosing and/or packing clarity are implemented in the marketed

version of the product. Medication errors are reportable only as defined in the protocol. Follow the guidance below.

a. For studies with two or more treatment arms (e.g., double blind studies), the administration or consumption of the unassigned treatment is always a reportable medication error.
b. Administration of an expired product should be considered as a reportable medication error when associated with an AE, or if otherwise appropriate, please define for your study.
c. For parenteral products, define reportable errors involving rate of administration and reconstitution and dilution, including use of appropriate diluent and the time frame in which test article should be used after reconstitution and/or dilution.
d. For vaccines and biologics, define in detail reportable errors related to storage or refrigeration requirements.

All AEs and SAEs must be handled as specified in this protocol whether or not they are associated with a medication error. A medication error associated with an SAE (including overdose, inadvertent exposure, and/or accidental exposure) will be reported with the SAE on the SAE form. All other medication errors will be reported by faxing the Clinical Study Medication Error Incident Report form to the fax number indicated in the Emergency Contacts section under separate cover.

10.6 Progressive Disease

Natural progression or deterioration of the malignancy under study (including new sites of metastasis and death due to disease progression) should be recorded as part of the efficacy evaluation and should not be reported as AEs or SAEs.

Signs and symptoms clearly associated with the disease under study should NOT be reported as AEs unless they are any one of the following:

- Newly emergent (i.e., not previously observed in the subject).
- Judged by the investigator to be unusually severe or accelerated.
- Judged by the investigator to represent exacerbation of disease-related signs and symptoms to be caused directly by the study drug.

If there is reasonable uncertainty about an AE being caused by disease progression, it should be reported as an AE or SAE as appropriate.

10.7 Death on Study

If a patient dies while on study, permission for autopsy will be sought by the treating doctor. This information, when available, will be used in correlation with the clinical data.

10.8 Other Reportable Information

Certain information will be considered as SAEs for regulatory reporting purposes, and must be recorded, reported, and followed up as indicated for an SAE. This includes exposure to the test medication in the following:

- Pregnancy. If a pregnancy is confirmed, use of the test article must be discontinued immediately.
- Lactation.
- Overdose.
- Inadvertent or accidental exposure

10.9 Pregnancy Guidelines

During the course of the trial, all female patients of childbearing potential should be instructed to contact the treating physician immediately if they suspect they might have conceived a child. In addition, a missed or late menstrual period should be reported to the treating physician. If a female patient, or an investigator, suspects a pregnancy prior to administration of study drugs, the study drugs must be withheld until the results of a pregnancy test are available. If pregnancy is confirmed the patient must not receive study medications and must be withdrawn from the study. All supporters of the study will be informed if a pregnancy occurs.

Throughout the entire pregnancy, additional contact should be made with the patient and in some cases with the healthcare provider, to identify spontaneous abortions and elective terminations, as well as any medical reasons for elective termination. In addition, the study investigator should include perinatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.

If a male patient is suspected of having fathered a child while on study drugs, the pregnant female partner must be notified and counseled regarding the possible risk to the fetus. In addition, the treating physician must follow the course of the pregnancy, including prenatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.

All serious adverse event reports relating to the pregnancy, including spontaneous abortion, elective abortion and congenital anomalies, should be forwarded to the FDA and a copy sent to all supporters.

Any pregnancy that occurs during study participation should be reported. To ensure patient safety each pregnancy must also be reported to Dr. Angeles Secord, the sponsor-investigator within 24 hours of learning of its occurrence. If the pregnancy is associated with a SAE then the pregnancy should be reported to BI Unique Entry Point within ten (10) calendar days upon receipt of the initial and/or

follow-up information. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

10.10 Recording Adverse Events

Classification of Adverse Events
****AEs that do not meet any of the criteria for serious should be regarded as non-serious AEs***. The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of a specific adverse event (e.g., mild; moderate; or severe).
Ex. A ***severe*** rash is not likely to be an ***SAE.*** Likewise, a ***severe*** headache is not necessarily an ***SAE.*** However, ***mild*** chest pain may result in a day's hospitalization and thus is an ***SAE.***

"Serious" is a regulatory definition (see above) and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities. Severity and seriousness should be independently assessed when recording AEs and SAEs on the CRF.

Collection of complete information concerning SAEs is extremely important. Full descriptions of each event will be followed. Thus, follow-up information which becomes available as the SAE evolves, as well as supporting documentation (e.g., hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report.

The investigator must categorize the severity of each adverse event according to the following guidelines:

Criteria:
NCI toxicity criteria will be followed. Special attention will be paid to gastrointestinal, non-gastrointestinal perforation, leakage, fistula formation, abscess, and elevated transaminases.

Mild:	Grade I NCI Common Toxicity
Moderate:	Grade II NCI Common Toxicity
Moderately	Severe: Grade III Common Toxicity
Severe:	Grade IV NCI Common Toxicity
Death:	Grade V NCI Common Toxicity

If the event is not found in the NCI Common Toxicity table, the adverse event will be scored using 5 grades:

Grade 1 Causing no limitation of usual activities
Grade 2 Causing some limitation of usual activities
Grade 3 Causing some inability to carry out usual activities
Grade 4 Causing life-threatening or disabling toxicity
Grade 5 Causing death

NCI Common Toxicity for Adverse Event Grading (Severity) Chart v4.0

Grade	Severity (Intensity)	Alternative Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Transient or mild discomfort (< 48 hours); no interference with the subject's daily activities; no medical intervention/therapy required
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*	Mild to moderate interference with the subject's daily activities; no or minimal medical intervention/therapy required
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**	Considerable interference with the subject's daily activities; medical intervention/therapy required; hospitalization possible
4	Life-threatening consequences; urgent intervention indicated.	Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable
5	Death related to AE	Death related to AE

Causal relationship of adverse event

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

Causality will be reported as either "Yes" or "No".

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

10.11 Procedures For Reporting

Reporting of Adverse Events:

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

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the trial defined follow-up period) will be collected, documented and reported by the investigator. 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 expectedness of the investigational drug to the AEs as defined in the Listed Adverse Events section of the Boehringer Ingelheim's Investigator Brochure for the Product.

Serious Adverse Events (SAEs) and unknown reactions or unexpected events that occur in the course of any patient's treatment on study or within 30 days following cessation of treatment should be reported to the Principal Investigator and the lead site/Sponsor (Dr. Angeles Secord/Duke University) within 24 hours of learning of the event. SAEs must be recorded using the Boehringer Ingelheim SAE Reporting Form, found in the Procedure Manual.

Additional information and/or corrections may be submitted as they are obtained. All SAEs must be followed through resolution or stabilization.

All adverse events, regardless of severity, and whether or not ascribed to the study drug administration, will be recorded in the appropriate section of the Case Report Form. Patients withdrawn from the study due to AEs will be followed by the Investigator until the outcome is determined and, when appropriate, additional written reports and documentation will be provided.

The DCI Safety Desk at Duke University should be contacted when reporting an SAE and should be faxed or emailed to the following:

DCI Safety at Duke University (on behalf of Dr. Angeles Alvarez Secord)
Phone: (919) 681-9538
Fax: (919) 681-9357
Email: dcccsafe@dm.duke.edu

If this person cannot be reached within 24 hours, the Principle Investigator and/or Chief Medical Officer should be contacted:

Dr. Angeles Alvarez Secord
Duke University Medical Center
Room 25172, Morris Building
Durham, NC 27710
Phone: (919) 684-3765
Fax: (919) 684-8719
Pager (919) 970-0087

Minimum Criteria for Reporting:
Information for final description and evaluation of a case report may not be available with the required time frames for reporting. Nevertheless, for regulatory

purposes, initial report shall be submitted within the prescribed time as long as the following minimal requirements are met:

The ***initial*** report for each SAE should include at minimum the following information:

- Protocol # and title.
- Regulatory Seriousness criteria if applicable (i.e., death; life-threatening; hospitalization; etc.).
- Patient initials, study identification number, sex, and age.
- Date the event occurred (onset).
- Severity (intensity) - see chart.
- Description of the SAE.
- Dose level and cycle number at the time the SAE occurred.
- Description of the patient's condition.
- Indication whether the patient remains on study.
- Causality (relationship of the event to the study medication).

Follow-up information may include:

- Severity (intensity) - see chart.
- Duration of the event.
- Treatment and/or medication(s) given for the event, if any.
- Brief narrative summarizing the relevant details of the event.
- Action taken to study medication.
- Concomitant medications.
- Event outcome with dates should be communicated to the Duke as soon as possible.
- When applicable and requested, information from relevant hospital records (e.g., discharge summary, autopsy reports, etc.).

Upon receipt of the Serious Adverse Event Report Form by Duke, DCI Safety will:

a. Notify Dr. Secord of the event via email and obtain an assessment for each event via the SAE Review Form.
b. Fax the form to Boehringer Ingelheim Global Pharmacovigilance Center US (GPV Centre US) at 1-203-837-4329

All adverse events, regardless of severity, and whether or not ascribed to the study drug administration, will be recorded in the appropriate section of the Case Report Form. Patients withdrawn from the study due to AEs will be followed by the Investigator until the outcome is determined and, when appropriate, additional written reports and documentation will be provided.

10.12 Regulatory (Expedited) Reporting

As per 21 CFR 312.2(a), this study must be conducted under an IND. Dr. Angeles Alvarez Secord of Duke University Medical Center will be the sponsor-investigator for this study and will hold the IND. Thus, Dr. Secord will serve as both a principal investigator and the regulatory sponsor of this multi-center study.

Per 21 CFR 312.32(c), the sponsor will notify the FDA and all participating investigators in a written IND Safety Report of:
(A) Any adverse event associated with the use of the drug
(B) That is both serious and unexpected (see above for definitions).

- Each notification shall be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information. Each written notification may be submitted on FDA Form 3500A (MedWatch form) or in a narrative format. In each written IND safety report, the sponsor shall identify all safety reports previously filed with the IND concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of the previous, similar reports.
- The sponsor shall also notify the FDA by telephone or by fax of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but no later than 7 calendar days after the sponsor's initial receipt of the information.
- Follow-up information to a safety report shall be submitted as soon as the relevant information is available.
- Additionally, adverse events will be reported to the FDA in an annual report according to annual report requirements. Events will be reviewed and reported to the Duke IRB according to local IRB guidelines.

10.13 Data and Safety Monitoring

Audits and Inspections
Authorized representatives of Duke University Health System (DUHS), the Institutional Review Board (IRB), and Cancer Protocol Committee (CPC) may perform audits or inspections, including source data verification. The purpose of such an audit or inspection is to systematically and independently examine study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International ICH, and any applicable regulatory requirements.

Study Monitoring Requirements
This study will be monitored by the sponsor-investigator and will be independently monitored and assessed in accord with the Duke Cancer Institute (DCI), NCI-approved Data and Safety Monitoring Plan.

In terms of internal review, the sponsor-investigator is responsible for monitoring the protocol to ensure that the investigation is conducted in accordance with the

general investigational plan and protocol (21 CFR 312.50), and all applicable regulatory requirements. The sponsor-investigator will continuously monitor and tabulate adverse events and will also monitor the conduct, data, and safety of this study to ensure that:

- *Interim analyses occur as scheduled;*
- *Stopping rules for toxicity and/or response are met;*
- Risk/benefit ratio is not altered to the detriment of the subjects;
- Appropriate internal monitoring of adverse events and outcomes is done;
- Over-accrual does not occur;
- Under-accrual is addressed with appropriate amendments or actions;
- Data are being appropriately collected in a reasonably timely manner.

External review begins with the initial scientific review by the CPC. The CPC assigns the degree of monitoring to commensurate with the type of intervention, phase, endpoints, degree of risk, size, and complexity of the protocol. The primary site, Duke, will be monitored by the DCI Safety Oversight Committee and the DCI Monitoring Team. The minimum level of monitoring to be determined by the DCI Monitoring Team may include the following: routine monitoring after the first 3 subjects have been enrolled, followed by annual monitoring of 1-3 subjects until closed to enrollment or subjects are no longer receiving study drug or other interventions that are more than minimal risk. Additional monitoring may be prompted by findings from monitoring visits, unexpected frequency of serious and/or unexpected toxicities, or other concerns. CPC conducts annual progress reviews focusing on protocol prioritization, accrual and scientific progress while the study is open to enrollment, excluding pediatric protocols.

DUMC will serve as the coordinating site for this multi-site study.
The DUHS sponsor-investigator is responsible for providing data and safety monitoring oversight for participating external sites. The Duke Gynecologic Oncology team will be monitoring the external sites. A site monitoring visit will be planned after the first 3 subjects are enrolled. If a physical site visit is logistically impossible, a copy of redacted source documents will be obtained from the external site and the subject data will be monitored by designated personnel. Subsequent monitoring will be arranged based on pace of accrual, accrual status, and results of previous monitoring.

The DCI Safety Oversight Committee (SOC) will conduct annual data and safety monitoring. SOC reviews data provided by the sponsor-investigator pertaining to safety data, toxicities and new information that may affect subject safety or efficacy. All safety concerns are communicated to the sponsor-investigator and will be communicated to the IRB and CPC as necessary.

10.14 Management Forms

The Duke Cancer Institute IT (DCI-IT) group will be responsible for the management of clinical data utilizing the caBIG-compliant platform, known as the Cancer Central Clinical Database (C3D), with local implementation at Duke. C3D is the Clinical Trials Database and a key component of NCI's Clinical Trial Suite (CTS). Oracle Clinical serves as the foundation of C3D by supporting clinical trial definition, data capture, multiple site reporting, data definition, and usage standardization. Trial definition is based on Common Data Elements (CDE) from an existing library of template Case Report Forms. Oracle Clinical's RDC Onsite system provides a user-friendly HTML-based interface that allows local and remote data entry and electronically confirms source data verification (electronic signature). C3D also provides researchers with web-based tools for ad-hoc querying, reporting and analysis of clinical data. DCI-IT has been a C3D adopter (locally hosted) for several years, and is the home of the caBIG Clinical Trials Management Systems Knowledge Center. Through this enhanced relationship, DCI-IT will have access to a wide range of tools and resources, including case report form templates, the Common Data Elements dictionary, and other global library elements. This will enable us to construct the necessary data collection tools quickly.

The process relies on the clinical site to originate data and correct any clinical data inconsistencies that are not included in the point of entry validation. A variety of quality control routines which are run regularly will spawn queries that will need to be addressed by the clinic in order for the record to be closed and made available for the analytic dataset. This cycle is key to the process, as depicted below:

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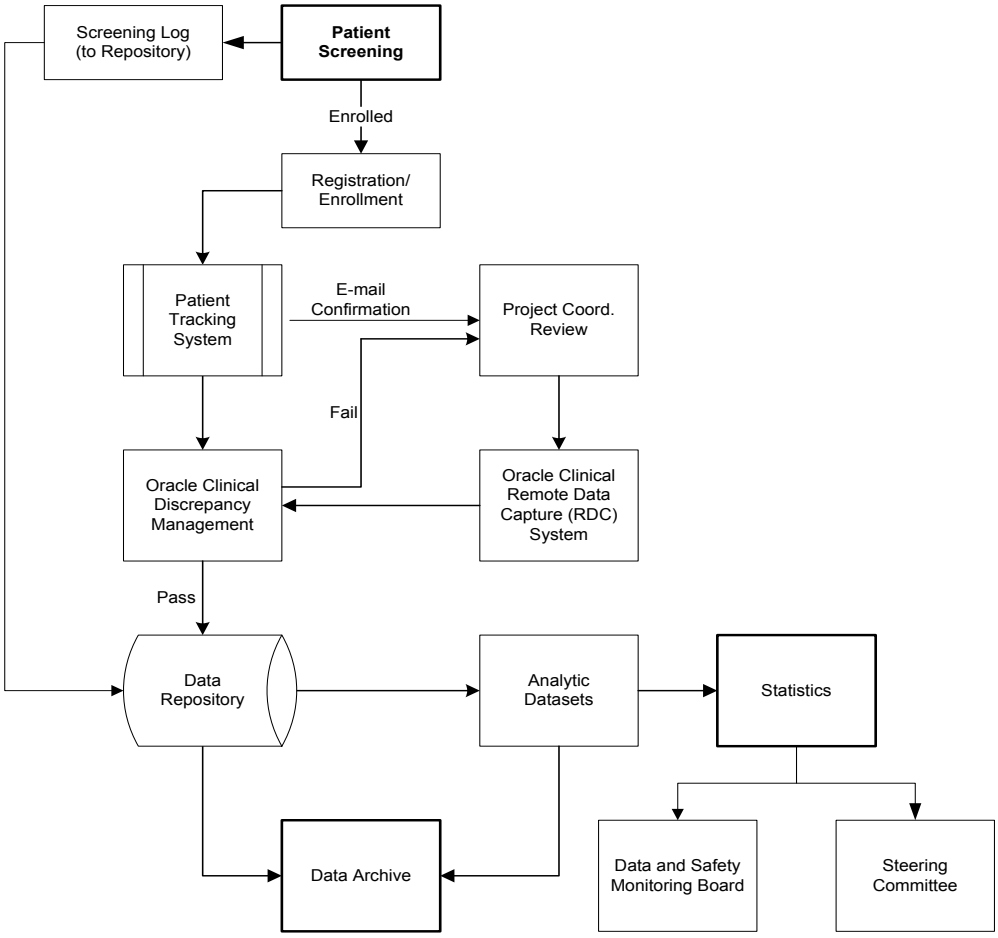


Electronic Case Report Forms (eCRF) will be generated from NCI/CaBIG and other templates and Common Data Elements (existing and specifically curated), most of which already exist in the caBIG C3D library.

Data entry via RDC Onsite is encrypted and secure. Communications between clinical sites that require this level of security will be handled via Tumbleweed's MailGate product (a 128 bit encrypted and authenticated e-mail system), as encapsulated through Duke's implementation of Microsoft's Outlook/Exchange Server product.

The eCRFs shown in Table 8 must be completed for all patients registered:

Table 8. Required eCRFs per each patients

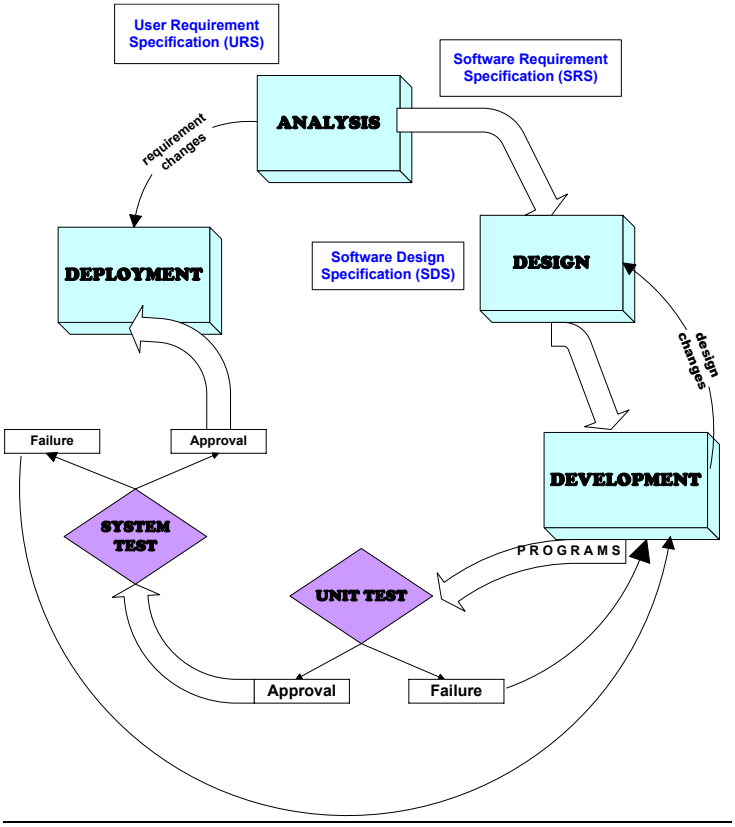
Form and Reports	Due within		Copies	Comments
	Weeks	Event		
Initial On-Study Form	4	Registration	3	
Pre-Treatment Summary Form	4	Registration	3	The "prior therapy" form does not need to be completed
Solid Tumor Evaluation Form	4	Registration	3	
Primary disease: Pathology Form Pathology Report Slides Recurrent or Persistent Disease: Pathology Form Pathology Report Slides	 6 6 6 6 6 6	 Registration Registration Registration Registration Registration Registration	 3 4 3 4	
Cycle Drug Dose Form	2	Completion of each cycle of therapy	3	
Solid Tumor Evaluation Form	2	Clinical response assessment	3	
Common Toxicity Reporting Form	2	Beginning of each subsequent cycle	3	
Treatment Completion Form	2	Completion of study Rx and change in Rx	3	
Follow-up Form	2	Disease progression; death; normal follow-up	3	Quarterly for 2 years, semi-annually for an additional year for a total of 3 years

10.15 Laboratory Data Management

Samples will be tracked utilizing caTissue v1.2, an NCI caBIG-developed platform. caTissue has been installed at Duke, and has some pilot implementation projects underway. Data from this system will provide a near real-time accounting of all samples, shipping and results from contracted lab, and provide views of the data that may be integrated with views from the eCRF for reporting purposes. As with other data in the system, expectations for the presentation of sample information will be set by the patient milestone (initiation and follow-up visit activity), flagging inconsistencies and missing sample information at regular intervals.

10.16 Regulatory Compliance

Both systems are built and deployed in accordance with HIPAA and 21 CFR Part 11, with proper system testing and validation. Application development follows a strict Software Development Life Cycle (SDLC) model, ensuring accurate deployment of all data collection tools and systems.



11.0 STATISTICAL CONSIDERATIONS

The primary objective of this study to assess the activity of the study agent as measured by the proportion of patients who survive progression-free for at least 6 months after initiating study therapy in patients with bevacizumab-resistant persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.

11.1 The study plan is a single arm, non-randomized, 2-stage phase II clinical trial.

11.2 Parameters employed to evaluate treatment efficacy and toxicity are:

11.2.1 Primary Endpoints:

11.2.1.1 The proportion of patients who survive progression-free for at least 6 months.

11.2.2 Secondary Endpoints:

11.2.2.1 The proportion of patients who have objective tumor response (complete or partial).
11.2.2.2 Frequency and severity of adverse effects as assessed by the active version of the NCI Common Toxicity Criteria.
11.2.2.3 Duration of progression-free survival and overall survival.

11.2.3 Translational Endpoints:

11.2.3.1 To measure baseline levels of VEGF and correlate with treatment outcome.
11.2.3.2 To measure baseline and on treatment levels of additional growth factors (listed in section 2.5) that may be co- or counter- regulated with VEGF and correlate with response to treatment.
11.2.3.3 To measure baseline and on treatment levels of coagulation and endothelial cell activation markers that may predict for thrombotic or bleeding risks related to treatment.

11.3 A total of up to 56 will be accrued at the rate of about 5 patients per month. If the 6-month progression-free survival rate is *observed to be* ≥ 0.20 the trial will be considered a success. Progression-free survival will be defined as the length of time from on-study to disease progression or death, whichever comes first. The study will use a 2-stage optimal design [15] to test the null hypothesis that the 6-month PFS rate is $\leq 13\%$ against the alternative hypothesis that this rate is $\geq 27\%$. The targeted accrual for the first stage will be 27 eligible and evaluable patients but permitted to range from 27 to 31 for PFS determination and administrative reasons. The critical value for the number of patients who survive progression-free for 6 months will be based on the first 27 patients who are both eligible and evaluable for 6 month PFS. An interim analysis will be done after accrual of these patients (Stage 1). After the accrual of these patients, further accrual will be

suspended until all patients have been followed for at least 6 months or until at least 4 patients (15%) are found progression-free at 6 months. If 3 or less of the patients are progression-free at 6 months, the therapy will be deemed ineffective. If 4 or more of the patients are progression-free at 6 months, another 29 patients will be accrued. If 10 or less of the 56 patients are progression-free at 6 months, the therapy will be deemed ineffective. If at least 11 patients (20%) are progression-free at 6 months, the therapy will be deemed effective and worthy of further research. These stopping rules are illustrated in the table below.

Stage	Sample Size	Minimum number of patients who must be progression-free at 6-months for therapy to be considered effective
1	27	4 (15%)
2	56	11 (20%)

This design has a one-sided Type I error of 0.10, a power of 0.90. The probabilities of early termination given the null and the alternative are 0.54 and 0.04, respectively. If exactly 11 responses are observed, the exact 80% confidence interval will be [0.13, 0.28]. If even one patient drops out or is lost-to-follow-up before progression, then we will not be able to tabulate the number of patients who are progression-free at 6 months. In this case, we will calculate the Kaplan-Meier curve and focus on the probability of surviving to 6 months as calculated by the Kaplan-Meier method. We will call this trial a success only if the lower 10% confidence bound of this probability is greater than 0.13.

Statistical Analysis of Secondary Aims

Secondary Aim 1 is to determine the proportion of patient who has an objective tumor response (complete or partial). To address this aim all responses will be tabulated: complete response, partial response, stable disease, progressive disease.

Secondary Aim 2 is to determine the frequency and severity of adverse events. To address this aim, all toxicities will be tabulated by type and grade.

Secondary Aim 3 is to estimate the distribution of PFS and overall survival (OS). PFS was defined above. OS is defined as the length of the interval from on-study to death due to any cause. Both PFS and OS will be estimated with the Kaplan-Meier curve. In addition, we will compare the PFS of patients who had prior bevacizumab resistance with that of patients who had prior bevacizumab and chemotherapy resistance. Specifically, within each of these two groups, we will describe PFS with a Kaplan-Meier curve and the 6-month PFS rate (with its 80% confidence interval). We expect the latter group to have worse PFS than the former.

Secondary Aim 4 is to elicit patient preferences for outcomes of ovarian cancer treatment. The distribution of rank preferences for each general attribute will be described using mean ranks as well as the proportions of times each concept was ranked as most

important, second most important, third most important, fourth most important, and least important. In the token ranking exercise, to describe the allocations of tokens across the general attributes, we will report means, standard deviations, and median numbers of tokens for each attribute. To examine consistency between token allocations with rank preferences, we will reverse order the rank preferences such that higher ranks correspond to higher preferences and compute correlation coefficients. We will test whether correlations between ranks and token counts differ between attributes using Spearman rank tests. We will also examine the proportion of patients who provided the highest token counts to their most preferred attribute and vice versa. In the ratings exercise, to describe respondents' ratings on the 5-point Likert scale representing level of concern with each attribute included in the DCE, we will report frequencies of ratings for each attribute as well as means to provide a summary measure.

Secondary Aim 5 is to characterize baseline quality of life and cancer-related symptoms. We will use descriptive characteristics to summarize baseline characteristics for the study cohort enrolled at Duke. These characteristics will include summary scores from the NFOSI-18 and the FACT-GOG-Ntx. We will report means, medians, and standard deviations for continuous variables and counts and proportions for categorical variables.

Statistical Analysis of Translation Research Objectives

The association of PFS with baseline values of VEGF (continuous) will be tested with the proportional hazards model; VEGF will also be dichotomized at a clinically meaningful cut point and a Kaplan-Meier plot of PFS according to VEGF level will be made. An analogous procedure will be used to examine the association of PFS with baseline values of the growth factors listed Section 2.5.

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12.0 BIBLIOGRAPHY

1. ten Bokkel Huinink, Gore M, Carmichael J, et al. Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. *J Clin Oncol*. 1997; 15: 2183-93.
2. Kavanagh JJ, Kudelka AP, de Leon CG, et al. Phase II study of docetaxel in patients with epithelial ovarian carcinoma refractory to platinum. *Clin Cancer Res*. 1996; 2: 837-42.
3. Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2007; 25: 5165-7.
4. Garcia AA, Hirte H, Fleming G, et al. Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: a trial of the California, Chicago, and Princess Margaret Hospital phase II consortia. *J Clin Oncol*. 2008; 26: 76-8.
5. Cannistra SA, Matulonis UA, Penson RT, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. *J Clin Oncol*. 2007; 25: 5180-6.
6. Burger RA, Brady MF, Bookman MA, Walker JL, Homesley HD, Fowler J, Monk BJ, Greer BE, Boente M, Liang SX. Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): a Gynecologic Oncology Group study *J Clin Oncol*. 2010; 28: abstract LBA1.
7. Perren T, Swartz AM, Pfisterer J, Ledermann J, Lortholary A, Kristensen G, Carey M, Beale P, Cervantes A, Oza A, on behalf of GCIG ICON7 collaborators. A phase III randomised gynaecologic cancer intergroup trial of concurrent bevacizumab and chemotherapy followed by maintenance bevacizumab, versus chemotherapy alone in women with newly diagnosed epithelial ovarian (EOC), primary peritoneal (PPC) or fallopian tube cancer (FTC). *Ann Oncol* 2010; 21: abstract LBA4.
8. Tang P, Cohen SJ, Bjarnason GA, et al. Phase II Trial of aflibercept (VEGF Trap) in previously treated patients with metastatic colorectal cancer: A PMH Phase II Consortium Trial. *J Clin Oncol*. 2008; 26 (May 20 Suppl; abstr 4027).
9. Grothey A, Sugrue MM, Purdie DM, et al. Bevacizumab beyond first progression is associated with prolonged overall survival in metastatic colorectal cancer: results from a large observational cohort study (BRiTE) *J Clin Oncol*. 2008; 26: 5326-34.
10. *Boehringer Ingelheim GmbH Investigator's Brochure.* Doc. No: U02-1482-11 Project No. 1199.P1/1199.P2/1199.P4/1199.P5 Date of IB: 11 April 2011 Version No. 11.
11. Hilberg F, Roth GJ, Krssak M, et al. BIBF 1120: Triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. *Cancer Res*. 2008; 68: 4474-82.
12. Ledermann JA, Rustin GJ, Hackshaw A, et al. A randomized phase II placebo-controlled trial using maintenance therapy to evaluate the vascular targeting agent BIBF 1120 following treatment of relapsed ovarian cancer. *J Clin Oncol*. 2011; 29: 3798-3804.
13. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST Guideline (version 1.1). *Eur J Cancer.* 2009; 45: 228-47.
14. Rustin GJS, Quinn M, Thigpen T, et al. New Guidelines to Evaluate the Response to Treatment in Solid Tumors (Ovarian Cancer) *J Natl Cancer Inst*. 2004; 96: 487-8.
15. Simon R. Optimal two-stage designs for Phase II clinical trials. *Controlled Clin Trials* 1989; 10: 1-10.

16. Meropol NJ, Egleston BL, Buzaglo JS, Benson AB, 3rd, Cegala DJ, Diefenbach MA, et al. Cancer patient preferences for quality and length of life. Cancer 2008 Dec 15;113(12):3459-66.
17. Zafar SY, Alexander SC, Weinfurt KP, Schulman KA, Abernethy AP. Decision making and quality of life in the treatment of cancer: a review. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 2009 Feb;17(2):117-27.

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Appendix I

Percent of Normal Bone Marrow Irradiated Using Standard Radiation Ports

Anatomic Site	% of Total Red Marrow
Head	13.1
Cranium	11.9
Mandible	1.2
Upper Limb Girdle	8.3
2 Humeri (head and neck)	1.9
2 Scapulae	4.8
2 Clavicles	1.6
Sternum	2.3
Ribs	7.9
Vertebrae	42.3
Cervical	3.4
Thoracic	14.1
Lumbar	10.9
Sacrum	13.9
Lower Limb Girdle	26.1
2 Os Coxae	22.3
2 Femoral heads and necks	3.8

Adapted from: Ellis R.E. The distribution of active bone marrow in the adult. *Phys Med Biol* 5:255, 1961.

Appendix II

Patient Nintedanib Capsule Diary

Subject ID #_____
Subject Initials_____
Cycle #_____

Date	Study Day	Morning dose	Evening dose	Comments[1]
	1			
	2			
	3			
	4			
	5			
	6			
	7			
	8			
	9			
	10			
	11			
	12			
	13			
	14			
	15			
	16			
	17			
	18			
	19			
	20			
	21			
	22			
	23			
	24			

	25			
	26			
	27			
	28			

[1]Changes to concomitant medications can be written in the comment section.

Patient_____Reviewer_____

Appendix III
Investigator Signature Page

Product: Nintedanib (BIBF 1120)

Protocol: PHASE II EVALUATION OF NINTEDANIB (BIBF 1120) IN THE TREATMENT OF BEVACIZUMAB-RESISTANT PERSISTENT OR RECURRENT EPITHELIAL OVARIAN, FALLOPIAN TUBE, OR PRIMARY PERITONEAL CARCINOMA

Investigator's Agreement

I have read the attached protocol entitled "PHASE II EVALUATION OF NINTEDANIB (BIBF 1120) IN THE TREATMENT OF BEVACIZUMAB-RESISTANT PERSISTENT OR RECURRENT EPITHELIAL OVARIAN, FALLOPIAN TUBE, OR PRIMARY PERITONEAL CARCINOMA", and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice and applicable FDA regulations/guidelines set forth in **21 CFR Parts 11, 50, and 56.**

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation.

_____
Signature

_____ _____
Name of Principal Investigator Date (DD Month YYYY)

Appendix IV

Clinical Investigator Financial Disclosure Form

06/23/2010

This information below is provided in accordance with 21 CFR Part 54 in regard to the following clinical study.

Pharmaceutical Company: Boehringer Ingelheim

Investigating Product: Nintedanib (BIBF 1120)

Title of Study/Protocol: Phase II evaluation of Nintedanib (BIBF 1120) in the treatment of bevacizumab-resistant or recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.

_____

Investigator/Sub-Investigator (Please Print)

Yes □ No □	Do you, your spouse or dependent children have a financial arrangement with Boehringer Ingelheim, whereby the value of compensation to you, your spouse or dependent children could be influenced by the outcome of the study? This includes compensation that could be greater for a favorable clinical result, compensation in the form of an equity interest in Boehringer Ingelheim or compensation tied to sales of the product tested in the above study such as a royalty interest. If yes, the nature of the financial arrangement is as follows:
Yes □ No □	Do you, your spouse or dependent children have a proprietary interest in Nintedanib (BIBF 1120) such as patent rights or rights under a patent, trademark, copyright or licensing agreement? If yes, the nature of the proprietary interest is as follows:
Yes □ No □	Do you, your spouse or dependent children, or any of you combined have a significant equity interest in Boehringer Ingelheim such as an ownership interest, stock options or any other financial interest whose value cannot be readily determined through reference to public prices, or any equity interest in Boehringer Ingelheim (if it is a publicly traded organization) exceeding $50,000, or any combination of these? If yes, the amount and nature of the equity interest is as follows:
Yes □ No □	Have you, your spouse or dependent children, or any of you combined received payments from Boehringer Ingelheim in excess of $25,000, exclusive of the costs of conducting the clinical studies, such as honoraria, a grant or grants to fund ongoing research, compensation in the form of equipment, or retainers for ongoing consultation? If yes, the amount and nature of the payment is as follows:

To the best of my knowledge, the information provided above is correct and complete. I understand that I am obligated to amend this statement and notify Angeles Alvarez Secord at Duke University Medical Center and Boehringer Ingelheim promptly if there is any change in this information during the conduct of the clinical studies listed above or during one year after the studies have been completed.

_____ Signature of Investigator	_____ Date

Appendix V

Specimen Tissue Transmittal Form
Biomarker Flow Sheet

Phase II evaluation of Nintedanib (BIBF 1120) in the treatment of bevacizumab-resistant persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.

Insert copy of this completed form with shipment and fax to
ATTN: DUKE – BIOMARKER at 919-668-3037

Section 1: General Information					
SUBJECT INITIALS		SUBJECT STUDY ID #		SITE NAME	Duke

Section 2: Flow sheet					
DATE OF BIOMARKERS DRAWN		CYCLE #		DAY #	

EVENT	TIME DRAWN	TIME FROZEN	NUMBER OF CRYOVIALS	COMMENTS	INITIALS
Whole blood			N/A		
Serum					
Plasma – EDTA					
Plasma – citrate					
Urine					

Signature:_____ **Initials:**_____

Section 3: Shipment Information (for DUMC site, complete transfer log)

DATE SHIPPED:_____
TRACKING NUMBEROF SHIPMENT:_____
NAME OF PERSON RESPONSIBLE FOR SHIPMENT:_____
PHONE NUMBER OF PERSON RESPONSIBLE FOR SHIPMENT:_____

Nintedanib (BIBF 1120) Biomarker Flow sheet v.24Jun2010

Appendix VI

Specimen Tissue Transmittal Form
Paraffin-Embedded Tumor

Phase II evaluation of Nintedanib (BIBF 1120) in the treatment of bevacizumab-resistant persistent or recurrent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma.

Insert copy of this completed form with shipment and fax to
ATTN: DUKE – Shara Reihani at 919-684-8718

Section 1: General Information					
SUBJECT INITIALS		SUBJECT STUDY ID #		SITE NAME	

Section 2: Flow sheet

EVENT	PARAFFIN-EMBEDDED PRIMARY TUMOR	PARAFFIN-EMBEDDED METASTATIC TUMOR	COMMENTS	INITIALS
DATE TISSUE INITIALLY OBTAINED				
INDICATE TISSUE BLOCK (TB) OR UNSTAINED SLIDES (US)				

If the specimen was not collected please indicate reason: (e.g., patient refused, not enough tumor for research, referring site won't release tumor)._____

Signature:_____ **Initials:**_____

Section 3: Shipment Information (for DUMC site, complete transfer log)

DATE SHIPPED:_____
TRACKING NUMBEROF SHIPMENT:_____
NAME OF PERSON RESPONSIBLE FOR SHIPMENT:_____
PHONE NUMBER OF PERSON RESPONSIBLE FOR SHIPMENT:_____

APPENDIX VII
Protocol Deviation Form
Protocol BIBF 1120

Subject ID Number: _____

Complete a new form for each deviation from the protocol.

Date of Protocol Deviation (DD/MMM/YYYY): _____/_____/_____

Description of Protocol Deviation:

_____
_____
_____
_____

Reason for Protocol Deviation:

_____
_____
_____

What steps were taken to resolve this Protocol Deviation and prevent recurrence:

_____
_____
_____

Does this deviation meet Duke IRB reporting requirements: ☐ NO ☐ Yes

COMPLETED BY: _____/_____/_____
(DD/MMM/YYYY)

Investigator's Signature:_____/_____/_____
(DD/MMM/YYYY)

Date Submitted To: (DD/MMM/YYYY)

☐ Duke IRB ____/_____/_____

APPENDIX VIII

See Attached Model Informed Consent

APPENDIX IX

Study #: Pro00033060	**Subject ID #:**		
Inclusion Criteria	**Yes**	**No**	**N/A**
Patient signed approved Informed Consent & Authorization Form permitting release of personal health information.			
Patient is at least 18 years of age.			
Patient has recurrent/persistent: Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Carcinoma. • Histologic documentation of the original primary tumor is required via the pathology report. **The following histologic epithelial cell types are eligible: Serous, endometrioid, mucinous, or clear cell adenocarcinoma; Undifferentiated, mixed epithelial or transitional cell carcinoma; Brenner's Tumor; Adenocarcinoma N.O.S.**			
Patient is Bevacizumab-resistant: treatment-free interval following response to Bevacizumab (CR/PR/SD) of < 6 months, or progressed during treatment with Bevacizumab-containing therapy.			
Patient has either measurable disease, per RECIST 1.1 (at least 1 lesion, accurately measured in at least 1 dimension) **or detectable (non-measurable) disease** (CA125>2x ULN + either ascites/pleural effusion attributed to tumor OR solid/cystic abnormalities that do not meet RECIST 1.1) • For patients with measurable disease: • Each lesion must be ≥ 10 mm when measured by CT, MRI, or caliper measurement by clinical exam. • Each lesion must be ≥ 20 mm when measured by chest x-ray. • Lymph nodes must be > 15 mm in short axis when measured by CT or MRI.			
For patients with measurable disease: patient has at least 1 target lesion (RECIST 1.1) to be used to assess response on this protocol. • Tumors in irradiated fields are non-target unless: progression documented, or biopsy confirms persistence ≥ 90 days after completion of radiation.			
Patient has an ECOG Performance status of 0 or 1.			
Patients is free of active infection requiring antibiotics (**Exception:** Uncomplicated UTI)**.**			
Patient has recovered from effects of recent surgery, radiotherapy, or chemotherapy.			
If patient had hormonal therapy directed at malignant tumor: discontinued ≥ 1 week before registration. • Continuation of hormone replacement therapy is permitted.			
If patient had therapy directed at malignant tumor (ex: immunologic agents): discontinued ≥ 3 weeks before registration.			
If patient received prior therapy with Bevacizumab: ≥ 4 weeks between discontinuation and treatment on this study.			
Patient has had 1 prior platinum-based chemotherapeutic regimen for management of primary disease containing Carboplatin/Cisplatin/organoplatinum compound. May have included intraperitoneal therapy/high-dose therapy/consolidation/non-cytotoxic agents/biologic therapy/extended therapy administered after surgical/non-surgical assessment			
Patients are allowed to receive, but are not required to receive, two additional cytotoxic regimens (a total of 3 cytotoxic regimens) for management of recurrent or persistent disease Patients who have received only one prior cytotoxic regimen (platinum-based regimen for management of primary disease), must have a platinum-free interval of less than 12 months, or have progressed during platinum-based therapy, or have persistent disease after a platinum-based therapy.			
Patients must NOT have received any non-cytotoxic therapy for management of recurrent or persistent disease other than bevacizumab-containing regimens. Patients are allowed to receive, but are not required to receive, biologic (non-cytotoxic) therapy as part of their primary treatment regimen.			
Patient has adequate bone marrow function: • **Absolute Neutrophil Count** ≥ 1,500/mcl (equivalent to CTCAE v4.0 grade 1). • **Platelets** ≥ 100,000/mcl. • **Hemoglobin** ≥ 9.0 g/dL.			
Patient has adequate renal function: • **Creatinine** ≤ 1.5 x institutional upper limit of normal (equivalent to active version of NCI AE grade 1).			
Patient has adequate hepatic function: • **Bilirubin** is within normal limits (CTCAE v4.0 grade 1). • **ALT/AST** ≤ 1.5 x ULN (CTCAE v4.0 grade 1). If patient has liver metastases: **ALT/AST** ≤ 2.5 x ULN. • **Alkaline phosphatase** ≤ 2.5 x ULN (CTCAE v4.0 grade 1).			

Patient has adequate neurologic function: • **Neuropathy (sensory and motor)** ≤ CTCAE v4.0 grade 1.			
Patient has adequate blood coagulation: • **Prothrombin: International Normalized Ratio** < 1.5 x ULN & **Partial Thromboplastin Time** < 1.5 x ULN. • Prophylactic/low molecular weight Heparin (ex: Enoxaparin) is allowed (**Exception:** Warfarin is not allowed).			
If patient is of child-bearing potential: negative serum pregnancy test prior to study entry and be willing to practice an effective form of contraception up until three months after of receiving the last drug treatment..			
If patient had major surgical procedure/open biopsy/significant traumatic injury: > 28 days before 1st day of treatment.			
If patient has undergone a core biopsy/IV Port placement: > 7 days prior to 1st date of study therapy.			
Study #: Pro00033060 **Subject ID #:**			
Exclusion Criteria	**Yes**	**No**	**N/A**
Patient is breastfeeding or pregnant.			
Patient had previous treatment with Nintedanib.			
Patient received radiation to > 25% of marrow-bearing areas. • **Head:** 13.1% (Cranium: 11.9%, Mandible: 1.2%) • **Upper Limb Girdle:** 8.3% (2 Humeri {head and neck}: 1.9%, 2 Scapulae: 4.8%, 2 Clavicles: 1.6%) • **Sternum:** 2.3% • **Ribs:** 7.9% • **Vertebrae:** 42.3% (Cervical: 3.4%, Thoracic: 14.1%, Lumbar: 10.9%, Sacrum: 13.9%) • **Lower Limb Girdle:** 26.1% (2 Os Coxae: 22.3%, 2 Femoral heads and necks: 3.8%)			
Patient has history of other invasive malignancies, & there is evidence of malignancy being present within last 3 years. **Exception:** Non-melanoma skin cancer.			
Patient's previous cancer treatment contraindicates this protocol therapy.			
Patient received prior radiotherapy to any portion of abdominal cavity/pelvis. **Exception:** Treatment of Ovarian, Fallopian Tube, or Primary Peritoneal Cancer within last 3 years. **Exception:** For localized cancer of breast/head & neck (**Exception:** CNS disease)/skin, if completed > 3 years before registration & patient remains free of recurrent/metastatic disease.			
Patient received prior chemotherapy for any abdominal or pelvic tumor. **Exception:** Ovarian/Fallopian Tube/Primary Peritoneal Cancer or localized Breast Cancer within last 3 years. **Exception:** Adjuvant chemotherapy for localized Breast Cancer, if completed > 3 years before registration & patient remains free of recurrent/metastatic disease.			
Patient has a history of abdominal or tracheal-esophageal fistula, or gastrointestinal perforation.			
Patient has a history of intra-abdominal abscess within 6 months of enrollment.			
Patient has a serious, uncontrolled, concomitant disorder (such as diabetes mellitus).			
Patient has clinically significant cardiovascular disease, including: • **Uncontrolled hypertension:** systolic > 150 mm Hg or diastolic > 90 mm Hg. • **Unstable angina, or they had a myocardial infarction within the past 6 months prior to registration.** • **NYHA grade II or greater congestive heart failure.** • **Serious cardiac arrhythmia requiring medication** (**Exception:** Asymptomatic atrial fibrillation with controlled ventricular rate.) • **Peripheral vascular disease/Peripheral ischemia ≥ CTCAE v4.0 grade 2**			
Patient has a serious non-healing wound, ulcer, or bone factor. • **Exception:** Granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection. Weekly wound examinations are required.			
Patient has active bleeding/pathologic condition with high risk of bleeding, such as: bleeding disorder/coagulopathy/tumor involving major vessels.			
Patient has history/evidence upon physical exam of CNS disease; seizures not controlled with standard medical therapy; brain metastases; or history of CVA/TIA/subarachnoid hemorrhage within 6 months of 1st date of treatment on this study.			
Patient has been diagnosed with primary brain tumors within the last 3 years.			
Patient has central pulmonary metastases, or recent hemoptysis (≥ 1/2 tsp. of red blood) within 28 days of registration.			
Patient has clinically significant proteinuria (> Grade 1), or UPC ratio above 1.0.			

Patient is suspected of having transmural tumor bowel involvement (per investigator's discretion).			
Patient has clinical symptoms/signs of gastrointestinal obstruction, and requires parenteral hydration and/or nutrition.			
Patient is on therapeutic doses of anticoagulants, or is taking Warfarin.			

_____ _____

Signature of Coordinator/Research Nurse **Date:**

_____ _____

Signature of Investigator/Sub-Investigator **Date:**

APPENDIX X

Subject Registration Form

Section 1: SUBJECT INFORMATION

First Initial: _____ **Middle Initial:** ____ **Last Initial:** _____

Sex: ☐ **Male** ☐ **Female** **Date of Birth:** ____ / ____ / _____ **Duke MRN (if applicable):** _____

Date Consent Signed: ____ /____ / _____ **Version Date of Site Consent:** ____ /____ / _____

Type of Cancer Diagnosis: _____ **Protocol Name:** _____

RACE:	**ETHNICITY**:
☐ White	☐ Hispanic or Latino
☐ Black or African American	☐ Non Hispanic or Latino
☐ Native Hawaiian or other Pacific Islander	☐ Not Reported
☐ Asian	☐ Unknown
☐ American Indian or Alaska Native	
☐ Not Reported	
☐ Unknown	

Section 2: SITE INFORMATION

Site Name: _____ **Site Fax #:** _____

Study Coordinator Name: _____ **Phone #:** _____ **Pager #:** _____

Study Coordinator Email: _____

Treating MD Name: _____ **Phone #:** _____ **Pager #:** _____

Treating MD Email: _____

Section 3: ELIGIBILITY

☐ **Subject meets all eligibility criteria.** ***(Please note: If subject meets all eligibility criteria, please provide completed eligibility checklist along with supporting source documentation to the Duke Team.)***

Date of expected Cycle 1 Day 1: ____ / ____ / _____

☐ **Subject does not meet all eligibility criteria.**

If subject does not meet eligibility, please explain below.

_____

Study Coordinator Signature: _____ **Date:** _____

Section 4: TO BE COMPLETED BY DUKE STUDY TEAM

Subject Study Number		**Cohort Number**	**N/A**

Duke Investigator Signature and Date:_____

Appendix XI
Rank Preferences and Relative Concern Exercises

When researchers are testing new treatments for ovarian cancer, they have to decide ahead of time what kind of results they want to measure. We would like to find out what kind of results patients think are most important. Some of the outcomes researchers measure are listed below, with descriptions of what they mean.

Overall quality of life. This means how you are doing overall. It includes your physical and emotional well-being and how well you can perform your normal daily activities.

Side effects from treatment. This means health effects that are caused by your cancer treatment. Examples of common side effects of cancer treatment are hair loss, neuropathy or numbness or tingling in your fingers and toes, nausea and vomiting.

Symptoms from cancer. Some common symptoms of ovarian cancer are abdominal fullness, pain or bloating, constipation, loss of appetite, and nausea.

Progression-free survival. This is the average length of time that a woman will spend without any sign of her cancer growing or coming back once she starts a new treatment.

Overall survival. This is the average length of time that a woman will live after starting a new treatment.

A. Relative Concern Exercise

Now please indicate below how concerned you are about each of the following outcomes of your treatment.

Quality of life	Not concerned	A little bit concerned	Moderately concerned	Very concerned	Deeply concerned
Symptoms of cancer	Not concerned	A little bit concerned	Moderately concerned	Very concerned	Deeply concerned
Side effects of treatment	Not concerned	A little bit concerned	Moderately concerned	Very concerned	Deeply concerned
Progression-free survival	Not concerned	A little bit concerned	Moderately concerned	Very concerned	Deeply concerned
Overall survival	Not concerned	A little bit concerned	Moderately concerned	Very concerned	Deeply concerned

B. Rank Preferences

Please rank the following outcomes we can measure in order from the MOST important (1) to the LEAST important (5) to you.

_____ Overall quality of life. This includes your physical and emotional well-being and how well you can perform your normal daily activities.

_____ Side effects that are caused by the treatment.

_____ Symptoms that are caused by ovarian cancer.

_____ Length of time spent without the cancer growing.

_____ Total length of life remaining.

(To avoid any potential bias introduced associated with the order the concepts are listed, the order will be randomized across participants.)

C. Token distribution exercise

Now imagine that you have 100 coins or tokens. We would like you to distribute the tokens to indicate how important each outcome is to you. You could place all 100 tokens on one outcome if you only care about that outcome. If you feel that all the outcomes are equally important, you will place 20 tokens on each outcome.

_____ Overall quality of life. This includes your physical and emotional well being and how well you can perform your normal daily activities.

_____ Side effects that are caused by the treatment.

_____ Symptoms that are caused by ovarian cancer.

_____ Length of time spent without the cancer growing.

_____ Total length of life remaining.

(To avoid any potential bias introduced associated with the order the concepts are listed, the order will be randomized across participants.)

Appendix XII

NCCN-FACT FOSI-18

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy	0	1	2	3	4
	GP4	I have pain	0	1	2	3	4
	GP6	I feel ill	0	1	2	3	4
	O3	I have cramps in my stomach area	0	1	2	3	4
	HI7	I feel fatigued	0	1	2	3	4
	Cx6	I am bothered by constipation	0	1	2	3	4
	O1	I have swelling in my stomach area	0	1	2	3	4
	C3	I have control of my bowels	0	1	2	3	4
	GF5	I am sleeping well	0	1	2	3	4
DRS-E	GE6	I worry that my condition will get worse	0	1	2	3	4
	GP2	I have nausea	0	1	2	3	4
	B5	I am bothered by hair loss	0	1	2	3	4
TSE	GP5	I am bothered by side effects of treatment	0	1	2	3	4
	O2	I have been vomiting	0	1	2	3	4
	BMT15	I am bothered by skin problems	0	1	2	3	4
	BMT5	I am able to get around by myself	0	1	2	3	4
	GF3	I am able to enjoy life	0	1	2	3	4
FWB	GF7	I am content with the quality of my life right now	0	1	2	3	4

DRS-P=Disease-Related Symptoms Subscale – Physical
DRS-E=Disease-Related Symptoms Subscale – Emotional
TSE=Treatment Side Effects Subscale
FWB=Function and Well-Being Subscale
English (Universal) 03 March 2010

FACT/GOG-NTX (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some -what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some -what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT/GOG-NTX (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT/GOG-NTX (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4
NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4

English (Universal) 16 November 2007