Phase II trial of Nintedanib in patients with advanced esophagogastric cancer
PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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1.01.0 PROTOCOL SUMMARY AND/OR SCHEMA

Protocol title:	Phase II trial of Nintedanib in patients with advanced esophagogastric cancer
Study Objectives:	This is a phase II study of Nintedanib in patients with metastatic or recurrent esophagogastric cancer. The goal of the study is to evaluate the efficacy of Nintedanib, an orally available triple kinase inhibitor targeting the receptors of the vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), and fibroblast growth factor (FGF) receptor pathways. The primary endpoint will be to evaluate the 6-month progression-free survival (PFS) of Nintedanib. With a total of 32 patients, we have 89% power to detect an improvement in the 6 month PFS from a historical control of 10% to 28%, with a type I and II error rate of 10%.
Study population:	Patients with metastatic or recurrent esophagogastric adenocarcinoma will be eligible. Patients will be allowed to have up to a maximum of one prior chemotherapy regimen for metastatic disease. Patients are allowed to have a maximum of two prior regimens if they previously received neoadjuvant/adjuvant chemotherapy or chemoradiotherapy for their initial localized disease.
Study design:	Single institution, open label, non-randomized, single arm phase II
Number of patients:	32
Study drugs:	Nintedanib, administered orally
Dose and regimen:	Nintedanib 200mg twice daily administered continuously. Patients will continue on treatment until progression of disease. Each cycle consists of 28 days.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary objective:

To evaluate the 6-month progression-free survival (PFS) of Nintedanib in patients with metastatic or recurrent esophagogastric adenocarcinoma.

Secondary objectives:

1) To evaluate the objective response rate, defined as both complete response (CR) and partial response (PR), as measured by RECIST response criteria.

2) To evaluate the tolerability and incidence adverse event profile of Nintedanib in this patient population.

3) To perform an exploratory correlative analysis assessing the relationship of FGFR amplification and overexpression with progression free survival and response.

3.0 BACKGROUND AND RATIONALE

3.1 Esophagogastric adenocarcinoma

Globally, esophagogastric cancer is diagnosed in nearly one million individuals each year and is the second most common cause of cancer-related death.[1] In the U.S., the incidence of adenocarcinoma of the distal esophagus, GE junction and gastric cardia has increased 4% to 10% per year among U.S. men since 1976 so that it is now the most common histology[2,3] Most patients with esophagogastric cancer present with stage IV disease, which is incurable. Despite this, systemic chemotherapy can lead to a decrease in cancer-related symptoms and prolong survival.[4-7] However, even with treatment, for patients with metastatic or recurrent disease, chemotherapy results in response rates in 20-40% of patients and median survivals of only 8-10 months.[8] There is clearly a need for more specific targeted therapies to improve the current status of systemic treatment beyond conventional chemotherapy.

3.2 Second line treatment for esophagogastric cancer

There is no current standard of care for second line therapy. There have been a few recent trials comparing 2nd-line chemotherapy to best supportive care (BSC). Thuss-Patience et al. compared irinotecan to BSC in the first phase III trial of second-line therapy in gastric cancer.[9] The median OS was 4mos with irinotecan compared to 2.4mos in the BSC arm (HR 0.46, p=0.012) With irinotecan treatment, there was a median PFS of 2.5 mos (95% CI 1.6- 3.9mo). In a large Korean trial, Kang et al. compared second-line docetaxel or irinotecan vs BSC and showed improved OS with chemotherapy 5.3 mos vs 3.8mos with BSC (HR 0.66, p=0.07); there was no survival difference between docetaxel and irinotecan.[10] Another trial by

Ueda et al compared irinotecan vs weekly paclitaxel in Japanese patients who were refractory to first-line 5FU/platinum.[11] There was no OS or PFS difference between the two chemotherapy agents. Median OS was 8.4mo with irinotecan, 9.5mos with paclitaxel (HR1.13, p=0.38). The median PFS for irinotecan was 2.3 mos and 3.6 mos for paclitaxel. (HR1.14, p=0.33). In this trial the estimated 6 month PFS was 16% with irinotecan and 14.8% with paclitaxel. These trials have established a benefit of 2nd line chemotherapy in advanced gastric cancer compared to BSC alone.

There have been two large trials evaluating targeted agents in the second line setting. The phase III GRANITE-1 trial of everolimus, an mTOR inhibitor, showed a median PFS of 1.68 mos compared to 1.41 mos in the placebo arm in patients who progressed after first or second line chemotherapy. The 6 month PFS in the everolimus group was 12% compared to 4.3% in the placebo arm.[12] This trial has not met its primary endpoint for survival and is not an FDA approved drug in this population. The phase III REGARD trial of ramucirumab compared to placebo in patients who progressed on first line therapy showed an overall survival benefit of 1.3 months compared to placebo.[13] In the study, the ramucirumab arm had a median PFS of 2.1 mos vs 1.3 mos with placebo. In this study, the estimated 6 month PFS was 18 months for ramucirumab compared to 4.5 months with placebo.

Based on the studies referenced above, we now have data that 2nd line conventional chemotherapy is beneficial compared to best supportive care alone. The REGARD study showed the 6 month PFS with placebo was 4.5% and with ramucirumab 18%. There is an unmet need in patients with metastatic and recurrent EG cancer to discover new novel agents.

3.3 Vascular endothelial growth factor (VEGF) and anti-angiogenic therapy

Angiogenesis is involved in tumor growth and development of metastases.[14] Weidner et al. showed a statistically significant correlation between the density of microvessels in histologic specimens of human breast cancer and clinical outcomes, including the incidence of metastases, as well as overall and relapse-free survival.[15]

Of the identified angiogenic growth factors, Vascular Endothelial Growth Factor (VEGF) and its high affinity receptor VEGFR-2 have been identified as crucial regulators of both normal and pathologic angiogenesis. VEGF produces a number of biologic effects, including endothelial cell mitogenesis and migration, and induction of proteinases, leading to remodeling of the extracellular matrix, increased vascular permeability, and maintenance of survival for newly formed blood vessels.[16] Increased expression of VEGF has been measured in most solid tumors, including tumors of the lung, breast, thyroid, gastrointestinal tract, kidney, bladder, ovary, as well as angiosarcomas. [11]

Suppression of neo-angiogenesis via inhibition of VEGFR-2 is a promising strategy for the treatment of solid cancers. Bevacizumab, a chimeric murine monoclonal antibody against VEGF, has been extensively studied in a number of solid tumor malignancies. The addition of bevacizumab to cytotoxic chemotherapy has been shown in several phase III clinical trials to increase the efficacy of chemotherapy. Most recently, data was presented

showing bevacizumab leading to an improvement in overall survival in cervical cancer[17] and previous studies have shown benefits in progression free survival in colorectal cancer,[18] lung cancer,[19] and breast cancer.[20]

3.4 Angiogenesis in esophagogastric cancer

A number of studies have evaluated the role of the VEGF pathway in esophageal cancer as a prognostic marker and indicate the expression of VEGF in tumors correlates with more advanced tumor stage, the presence of nodal and distant metastasis, and with a poorer survival outcome.[21,22] In esophageal adenocarcinoma, increasing VEGF expression correlates with the transition from Barrett's esophagus to high grade dysplasia, and with the transition from microinvasive to locally advanced cancer.[23] These pre-clinical data suggest that angiogenesis is a viable target for therapy in advanced esophagogastric cancer.

Our group has previously performed a multicenter phase II evaluation of bevacizumab and cisplatin/irinotecan in patients with advanced gastric and GE junction adenocarcinoma. The addition of bevacizumab to cytotoxic chemotherapy significantly improve the time-to-progression (8.3 months; 95% CI, 5.5 to 9.9 months) and overall survival (12.3 months; 95% CI, 11.3 to 17.2 months) of patients compared to the historical time-to-progression of 5 months.[24] Therapy was well tolerated, although a 6% incidence of gastric perforation or near-perforation and a 2% incidence of myocardial infarction were noted.

In the phase III REGARD trial, ramucirumab, a monoclonal antibody VEGFR-2 antagonist prolonged survival in patients with advanced gastric cancer. Ramucirumab in patients who progressed on first line therapy showed an overall survival benefit compared to placebo.[13] FDA granted ramucirumab priority review for advanced gastric cancer. These results validate the role of VEGFR-2 signalling as an important therapeutic target in advanced gastric and esophageal adenocarcinoma.

3.5 MSKCC Clinical data of multi-kinase inhibition in esophagogastric cancer

There is clear clinical rationale to study more than one pathway in esophagogastric cancer, as indicated by our recently completed MSKCC initiated phase II study of single agent Sorafenib in patients with metastatic esophagogastric cancer (IRB 09-016, Proc ASCO 2013 Ku et al).[25] Sorafenib is an oral multi-kinase inhibitor with activity against VEGFR, platelet-derived growth factor receptor (PDGFR), as well as against the serine/threonine kinases Raf-1.

In our study of Sorafenib in 2nd/3rd line setting in patients with metastatic esophagogastric cancer, we met the primary endpoint of improving 2-month progression-free survival. The median PFS was 3.6 mos (95% CI 1.8 to 3.9 mos) with a median overall survival of 8.8 mos (95% CI, 5.9 to 11.1 months). An ongoing complete response (44+ months) was observed in a patient with Stage IV esophageal adenocarcinoma with biopsy proven metastatic neck lymphadenopathy who developed recurrence after prior chemoradiotherapy and surgery. This patient continues to maintain a complete response. A second patient with gastroesophageal junction adenocarcinoma had protracted stable

disease in bulky celiac node disease (26+ months). The majority of tumors tested positive for phospho-ERK by immunohistochemistry (26/32, 82%). Twenty of the 34 evaluable patients (59%) were progression free at 2 months (p=0.08); with the pre-specified Type I and II error rates of 10% and historical 2-month PFS of 50% without treatment, this regimen shows promise and activity in gastroesophageal cancers.

3.6 Targeting multiple relevant pathways in esophagogastric cancer

Preclinical animal models suggest that targeting VEGF-VEGFR signaling is beneficial at the start of treatment, but with continued drug treatment and under pressure of the VEGF blockade, other signaling molecules provide alternate mechanisms to drive disease progression.[26] Among the potential compensatory mechanisms include upregulation of the platelet-derived growth factor (PDGF) and fibroblast growth factor (FGR) pathways.[27] The PDGF receptor (PDGFR) has a role in promoting angiogenesis, tumor growth and metastasis by regulating the migration and adherence of pericytes and smooth muscles cells to endothelial cells. The FGF receptor (FGFR) has been described as a potential escape mechanism with tumor cells switching from VEGF to FGF signaling to attract endothelial cells.[22]

3.7 FGFR2 in gastric cancer

The family of fibroblast growth factors (FGFs) and FGF receptors (FGFRs) plays a critical role in cell behaviors, such as proliferation, differentiation, migration and survival, and are fundamental to embryonic development, regulation of angiogenesis, and skeletal development.[28] The FGFR ligands belong to the FGF family comprising of 18 secreted ligands-induced dimerization and bind to adapter proteins. Subsequent downstream signaling occurs through two main pathways via the intracellular receptor substrates FGFR substrate 2 and phospholipase Cγ (PLCγ), leading ultimately to upregulation of the Ras-dependent mitogen-activated protein kinase (MAPK) and Ras-independent phosphoinositide 3-kinase (PI3K)-Akt signaling pathways).[29]

Activation of FGFRs as a result of amplification, mutation or translocation of FGFR genes or over-expression of FGFR proteins or overproduction of FGF ligands has been shown to be oncogenic. Inhibition of FGFR11may have clinical utility in cancers that overexpress FGFRs, such as breast[30], esophageal[31], bladder[32], gastric[33], and lung cancers[34], or display a prevalence of FGFR mutations, such as inbladder cancer.

FGFR gene amplification often leads to FGFR overexpression, which can provoke ligand-independent signaling. FGFR2 amplifications have been reported in up to 7% of gastric cancers, most of which are diffuse-type with relatively poor prognosis.[35,36] The presence of FGFR2 gene amplifications in gastric cancer is associated with sensitivity to inhibition of FGFR signaling by tyrosine kinase inhibitors and monoclonal antibodies in preclinical models.[23] The frequency of FGFR1 and FGFR2 overexpression is significantly larger than the frequency of amplification in gastric cancers, which is reported up to 41%,[37,38] indicating that gene amplification is not the sole mechanism leading to receptor overexpression.[33] FGFR2 and PDGFR expression in esophageal and gastric cancers have also been shown to

be associated with high metastatic potential, aggressive tumor biology, and poor outcomes.[31,39]

Inhibition of FGFR2 in gastric cancers using a novel multi-kinase that specifically targets FGFR may provide more potent inhibition of the oncogenic pathways and result in improved therapeutic efficacy than seen with other tyrosine kinase inhibitors. Nintedanib with its favorable toxicity profile and multi-kinase targets may make this agent a promising agent and further development of this agent in esophagogastric malignancies is clearly indicated.

3.8 Nintedanib

3.8.1 Pre-clinical rationale

Nintedanib is an orally available potent small molecule triple kinase inhibitor inhibiting VEGFR 1-3, FGFR 1-3 as well as PDGF receptor α and ß in the low nanomolar range. VEGFR-2 is considered the crucial receptor involved in initiation of the formation as well as the maintenance of tumor vasculature.

In vivo experiments demonstrated good anti-tumor efficacy at doses of 50 – 100 mg Nintedanib, leading to a substantial delay of tumor growth or even complete tumor stasis in xenografts of a broad range of differing human tumor types.[40] Furthermore, established xenograft tumors rapidly responded to treatment with Nintedanib. Histological examination of treated tumors showed a marked reduction of tumor vessel density by approximately 80%.[26] In addition preclinical models show that Nintedanib may have a direct anti-tumour effect on those malignant cells which overexpress PDGFR and/or FGFR (e.g. H1703 NSCLC cells).[40]

3.8.2 Clinical experience

The safety and clinical activity of Nintedanib either alone[41-44or] in combination with chemotherapy[45-47] has been examined in a series of phase I studies conducted in patients with solid tumors.

The phase I dose selection studies have investigated the maximum tolerated dose (MTD), safety, and pharmacokinetics (PK) of Nintedanib.[32,34] Based on the Phase I dose escalation trials with Nintedanib monotherapy, the maximum tolerated dose was defined to be 250 mg for twice daily dosing in Caucasians and 200 mg twice daily in Japanese patients with a manageable safety profile in advanced cancer patients. The studies revealed that Nintedanib is generally well tolerated with mild to moderate adverse effects such as gastrointestinal symptoms (nausea, diarrhea, vomiting, abdominal pain) and reversible elevations of liver enzymes. Initial signs of clinical activity included a complete response in a patient with renal cell carcinoma, 2 partial responses observed in patients with colorectal and renal cell carcinoma, and a disease stabilisation seen in 64% of patients for at least 2 treatment cycles (Mross et al)

Nintedanib has been studied in a randomized phase II maintenance trial following chemotherapy in relapsed ovarian cancer.[48] Patients were randomized to either Nintedanib or placebo therapy for 36 weeks. The 36 week PFS rates were 16.3% in the Nintedanib group and 5% in the placebo group (HR 0.65; 95% CI, 0.42-1.02). The safety

profile was similar to what was reported in the initial trials. The proportion of patients with any grade 3 or 4 adverse events was similar between the groups (34.9% for Nintedanib vs. 27.5% placebo, p=0.49). However, there was more grade 3 or 4 hepatotoxicity in the Nintedanib group (51.2%) compared to placebo (7.5%, p<.001) This clinical activity has lead to development of a phase III trial in which Nintedanib or placebo in combination with paclitaxel and carboplatin in the first line treatment of ovarian cancer is being evaluated (ClinicalTrials.gov Identifier NCT01015118).

3.8.3 Nintedanib in Non-Small-Cell Lung Cancer (NSCLC)

The clinical activity of Nintedanib in advanced non-small cell lung cancer (NSCLC) was first demonstrated in a phase I trial in combination with pemetrexed in patients previously treated with a platinum-based regimen.[46] In this dose escalation study of continuous Nintedanib with pemetrexed 500mg/m2 given on day 1 over a 21 day cycle, the MTD dose was 200mg BID in combination with pemetrexed. 1 patient achieved a complete response 44 days after starting treatment and disease stabilization seen in 50% as the best overall response. Median PFS was 5.4 months for all patients.

Nintedanib was also studied as a monotherapy in NSCLC patients in a phase II double-blind study.[49] In this study, patients were randomized to either Nintedanib 250mg BID or Nintedanib 150mg BID, continuous dosing and assessed at 6 week intervals until disease progression. Disease stabilization was achieved in 48% of patients and there was one confirmed partial response seen at the Nintedanib 250mg BID dosing. Tumour stabilisation was achieved in 46% of patients (ECOG 0–1 patients: 59%), with one confirmed partial response (250 mg BID).

The most commonly reported drug-related adverse events were nausea (57.5%), diarrhea (47.9%), vomiting (42.5%), anorexia (28.8%), abdominal pain (13.7%) and reversible alanine transaminase (ALT, 13.7%) and aspartate aminotransferase elevations (AST, 9.6%). The transaminase elevations were only seen at the higher dosing of the medication.

Based on the promising phase I and II results, there were two multicenter phase III studies evaluating Nintedanib 200mg BID in combination with chemotherapy in advanced NSCLC: the LUME-Lung 1 and LUME-Lung 2 trials. The preliminary results of both trials were recently presented at the Annual ASCO 2013 Meeting.

The LUME-Lung 1 trial evaluated Nintedanib plus docetaxel compared to placebo plus docetaxel in patients who progressed after first line therapy (ClinicalTrials.gov Identifier NCT00805194).[50] The Nintedanib plus docetaxel group had a significantly PFS benefit (HR 0.79; CI: 0.68, 0.92; p=0.0019; median 3.4 vs 2.7 months) compared to the docetaxel alone. In subset analysis, the overall survival was increased in the adenocarcinoma histology (HR 0.83; p=0.0359; median 12.6 vs 10.3 month).

The LUME-Lung 2 trial compared Nintedanib plus pemetrexed compared to placebo plus pemetrexed in patients with advanced nonsquamous NSCLC in the second line setting (ClinicalTrials.gov Identifier NCT00806819).[51] The study was stopped prematurely after 713/1300 planned patients enrolled based on a pre-planned futility analysis. Ongoing patients were unblinded and follow-up was continued. The primary endpoint of PFS was met with the Nintedanib plus pemetrexed group showing a slightly improved median PFS

of median 4.4 vs 3.6 months in the pemetrexed arm (HR 0.83, 95% CI: 0.7–0.99, p=0.04). There was a higher incidence of grade 3-4 adverse events in Nintedanib plus pemetrexed compared to the pemetrexed alone arm (58.5% vs 42.3%). Withdrawals due to adverse events were similar between both groups. The most common reported drug-related adverse events (all grades) were ALT elevations (42.9%), AST elevations (37.2%), nausea (36.9%), diarrhea (34.9%), fatigue (33.7%), and decreased neutrophil count (21.6%).

3.8.4 Rationale for Current Study

There is a clear rational to study more than one VEGF targeted agent in esophagogastric cancers as has been indicated by experience in other solid tumor malignancies and other targeted agents. There have been inconsistent benefits for targeted agents within the spectrum of GI malignancies, underscoring the need to evaluate each new promising agent independently in each tumor type.

For example, in GI malignancies, the EGFR tyrosine kinase inhibitors erlotinib and gefitinib have been inactive as single agents in adenocarcinoma of the colon[52], stomach,[29] and esophagus.[30] However in pancreatic cancer, erlotinib plus chemotherapy with gemcitabine yielded positive results, including a progression free and overall survival benefit. On the other hand, the EGFR targeted antibody cetuximab failed when combined with chemotherapy in pancreatic cancer. This is in contrast to the single agent activity of cetuximab seen in colon cancer.

It is clear that each new targeted agent, with individual variation in what specific targets are actually affected, needs to be evaluated in each solid tumor. Other than Human Epidermal Growth Factor Receptor (HER2), there are no validated treatment targets in esophagogastric cancer. Nintedanib is of particular interest in esophagogastric malignancies due to its ability to simultaneously target the VEGFR, PDGF, and FGFR pathways, which have been described and implicated in this disease.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a single institution, open-label, non-randomized, phase II evaluation of oral Nintedanib at 200mg twice daily, continuous dosing in patients with metastatic or recurrent esophagogastric adenocarcinoma.

Patients may have received up to one prior chemotherapy regimen for metastatic disease or up to two prior regimens if they previously received neoadjuvant/adjuvant chemotherapy or chemoradiotherapy for their initial localized disease. All patients must be able to provide informed consent.

See Section 10 for treatment schema.

4.3 Intervention

32 patients will be enrolled on this clinical trial. Patients will receive Nintedanib 200mg twice daily continuously until disease progression, unacceptable toxicity, or serious intercurrent illness develops, or if patient consent is withdrawn.

Patients must have measurable or evaluable disease and undergo a computerized tomography (CT) or magnetic resonance imaging (MRI) scan of their chest and abdomen within 28 days of study enrollment, then at eight weeks, and every eight weeks thereafter (every 2 cycles). For the followup scans, a scheduling window of up to one to fourteen (1-14) days will be permitted. If a complete response is achieve and maintained for 12 months, patients with complete response will then be required to repeat CT or MRI evaluation every 4 months up to 5 years post complete response status, then every 6 months thereafter, with a scheduling window of one to fourteen (1-14) days. Response assessment will be by RECIST 1.1 criteria. The same imaging modality performed at baseline (CT or MRI) will be repeated at subsequent imaging.

Therapy will be administered in the outpatient setting, with each cycle consisting of 28 days of continuous therapy. The cycle start date will coincide with the physician visit date. A study diary will be completed by patients to ensure compliance with the study drug (Appendix I).

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Substance (INN):	Nintedanib
Other names:	BIBF 1120
Pharmaceutical form:	Soft gelatine capsule
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	100 mg and 150 mg capsules
Daily dose:	200 mg twice daily
Duration of use:	Continuous daily dosing; once cycle consists of 28 days. Patients are eligible for repeated treatment cycles in the absence of disease progression and undue adverse events (as per criteria in Section 9.2)
Route of administration:	Oral (swallowed)
Posology:	Twice daily (to be swallowed unchewed with a glass of water of about 250 mL with a dose interval of around 12 hours at the same times every day, usually in the morning and the evening after food intake)

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

- Pathologically or cytologically MSKCC confirmed esophagogastric adenocarcinoma.
- Metastatic diseases measurable or evaluable on a CT or MRI scan according to RECIST 1.1 criteria. Locally recurrent disease that is not amenable to potentially curative surgery or radiation therapy is also allowed. Lesions must be ≥10mm in size. Recurrent or metastatic disease within a prior radiation field is acceptable as long as the disease has progressed in the radiation field by RECIST criteria. See Section 12.2 for definition of measurable lesions.
- Patients are allowed to have had a maximum of 1 prior chemotherapy regimen for metastatic disease. Patients are allowed to have a maximum of two prior regimens if they previously received neoadjuvant/adjuvant chemotherapy or chemoradiotherapy for their initial localized disease.
- Patients aged 18 years or older.
- Life expectancy of at least 6 months.
- Karnofsky Performance Status (KPS) performance score ≥ 70%.
- Patients must be able to reliably take and swallow oral medications.
- Patients with prior deep vein thrombosis (DVT) or pulmonary embolism (PE) currently on anticoagulation regimen will be permitted.

Adequate bone marrow, liver, and renal function as assessed by the following:

- Hemoglobin ≥ 9.0 g/dL.
- Absolute neutrophil count (ANC) ≥ 1,500/mm^3.
- Platelet count ≥ 100,000/mm^3.
- Total bilirubin within normal limits, 0–1 mg/dL.
- AST and ALT< 1.5 times ULN. (For patients with liver involvement: AST and ALT≤ 2.5 ULN).
- International normalized ratio (INR) < 2, prothrombin time (PT) < 20 sec, and partial thromboplastin time (PTT) < 55 sec .
- Creatinine < 1.5 x the ULN or GFR<45 ml/min.

6.3 Subject Exclusion Criteria

- HER-2 positive esophagogastric cancer. Patients with unknown HER2 status are permitted.
- Patients receiving any concurrent anticancer therapy or investigational agents with the intention of treating esophagogastric cancer. Last prior therapy must have been completed at least 2 weeks (14 days) prior to starting Nintedanib.
- Concurrent radiotherapy is not permitted for disease progression on treatment on protocol. However, symptomatic treatment for pre-existing non-target lesions would be allowed with approval from the principal investigator.
- Prior treatment with VEGFR inhibitor.
- Brain metastases or leptomeningeal disease.
- History of arterial thromboembolic (arterial blood clot) or hemorrhagic event with the exception of patients with pulmonary embolism stable on an anticoagulation regimen.
- Patients with a cerebrovascular accident or transient ischemic attack within the past six months.

- Patients on warfarin for any reason.
- Patient with known pre-existing interstitial lung disease.
- History or presence of clinically relevant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure, New York Heart Association (NYHA) functional classification of 3, unstable angina or poorly controlled arrhythmia. Myocardial infarction within 6 month prior to the study entry.
- Patients with history of proteinuria grade ≥ 2.
- Women of childbearing potential (WOCBP), or men who are able to father a child, unwilling to use a medically acceptable method of contraception during the trial and for at least three months after the end of active therapy.
- Women who are pregnant or breast-feeding.
- Persistence of clinically relevant therapy related toxicity from previous chemotherapy and/or radiotherapy. This does not include hemoglobin or other hematologic or laboratory criteria, as long as eligibility criteria are met as outlined in 6.1.
- Other malignancies within the past 5 years other than non-melanoma superficial skin cancer or carcinoma in situ of the cervix.
- Concurrent medical conditions or injury which may increase the risk of toxicity, including ongoing or active infection, history of significant bleeding disorder unrelated to cancer (congenital bleeding disorders, acquired bleeding disorders within one year), history of HIV-positive, or active or chronic hepatitis C and/or B infection.
- Known or suspected active drug or alcohol abuse.
- Gastrointestinal disorders or abnormalities that would interfere with absorption of the study drug. Patients who are unable to orally swallow the study medication.
- Known hypersensitivity to trial drug.

7.0 RECRUITMENT PLAN

This will be a single institution, phase II study. Patient with metastatic or recurrent esophageal, gastric, and gastroesophageal (GE) junction cancer that are eligible will be identified for enrollment from MSKCC clinical practice and clinic lists. No additional measures, e.g. advertisement, payment to patients, will be employed to recruit patients. Patients will be accrued to this study without regard for gender or minority status.

Inclusion of women and minorities
The investigators take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. There will be no limitations with regards to race or gender.

Our institutional demographics for accrual of patients on esophageal and GE junction cancer trials reflect the national incidence of this disease. 10-15% of our patients have been women. African-American males comprise 3-5% of patients treated on protocol. Given that our protocol accrual closely reflects the national incidence of this disease, no specific strategy will be undertaken to recruit women or persons of color on this trial.

This protocol does not include children because the number of children with esophageal, gastric and GE junction cancer is very small and because the majority are already accessed by a nation-wide pediatric cancer research network. This statement is based on exclusion 4b

of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

8.1 PRETREATMENT EVALUATION

To be completed within 2 weeks of study entry:

- History and physical exam including vitals, height, weight, performance status.
- Evaluation of concomitant medications and toxicity assessment.
- Serum pregnancy test for women of childbearing potential (WOCP)
  In addition, all WOCP should be instructed to contact the Investigator immediately if they suspect they might be pregnant at any time during the study participation.
- Laboratory evaluation including a complete blood count, PT/PTT, comprehensive chemistry panel (includes BUN, creatinine, ALT, AST, albumin, glucose, total protein, calcium, bilirubin, bicarbonate, sodium, chloride, potassium, alkaline phosphatase).

To be completed within 4 weeks of study entry:

- Electrocardiogram
- CT scan or MRI documenting all measurable or evaluable disease. All measurable lesions used to define response must be >10mm in size. The primary tumor is excluded. Lesions within prior radiation fields are permitted as long as these lesions have documented progression in size.

To be completed any time prior to starting therapy:

- Histological confirmation of esophagogastric adenocarcinoma prior to study enrollment.
- Available tumor tissue (20 unstained slides or tumor block) will be submitted for future molecular analysis (SEE SECTION 10 “Correlative Studies”) but not be required prior to registration. Note: if tissue is depleted, patient will still be eligible after discussion with the PI.

9.1 TREATMENT/INTERVENTION PLAN

9.2 Agent administration

Treatment will be administered on an outpatient basis. Nintedanib is supplied as 100mg and 150mg capsules. The starting dose of Nintedanib is 200mg orally twice daily for 28 days continuously, unless interrupted for intolerable toxicity. There is no planned interruption between treatment cycles unless clinically indicated. The cycle start date will coincide with the physician visit date. Because of the potential need for physician visit scheduling to vary (due to both physician and patient issues), to avoid violation of, and deviation from, the protocol, physician visits may vary by up to one to fourteen (1-14) days from a strict 28 day schedule.

Nintedanib will be taken on days 1-28 of each 28-day cycle. Patients will swallow the soft gel capsule whole with approximately 250 mL of water each morning and evening after eating. The capsule cannot be crushed or dissolved.

In case of misdosing, patients should proceed with the intake of medication according to the predefined schedule and take the next scheduled dose when it is due. Patients with emesis should not take a replacement dose. A study diary will be completed by patients to ensure compliance with Nintedanib (see Appendix I).

Concomitant Therapy

The use of investigational or anticancer agents is not allowed while patients are on this study. However, symptomatic treatment of tumor associated symptoms is allowed; such as radiation therapy with palliative intent and symptom control, provided that radiation does not affect target lesions and the reason for radiation does not reflect progressive disease. Concomitant medication, or therapy to provide adequate supportive care, may be given as necessary. If concomitant therapy is clinically indicated, patients may temporarily discontinue Nintedanib therapy and resume treatment following consultation with the treating physician and Principal Investigator.

9.3 Dose delay/modification

Intrapatient dose reduction will be allowed depending on the type and severity of toxicity encountered provided that criteria for patient withdrawal from study treatment have not been met. The dose levels for Nintedanib are as described below:

Starting dose 0	Nintedanib 200mg twice daily
Dose level -1	Nintedanib 150mg twice daily
Dose level -2	Nintedanib 100mg twice daily

If further dose reduction is required, the patient should be taken off-protocol.

If the dose of Nintedanib is reduced due to toxicity, it will stay at the lower dose level for the entire time of administration on protocol.

Patients who require a treatment delay of ≥21 consecutive days should also be taken off-protocol.

9.4 Suggested Medical Management of Nintedanib associated toxicities

9.4.1 Management of diarrhea

CTCAE 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 <u>OR</u> Grade <u>≥</u> 3 <u>OR</u> Any diarrhea independent of CTCAE grade leading to hospitalization of the patient		
First episode	STOP Nintedanib until recovery[1] **AND** **Anti-diarrheal treatment** according to the local standard e.g. Loperamide p.r.n	Reduce Nintedanib dose to 150 mg BID **after recovery of diarrhea** [1]
Second episode	STOP Nintedanib until recovery[1] **AND** **Anti-diarrheal treatment** according to the local standard e.g. Loperamide p.r.n.	Reduce Nintedanib dose to 100 mg BID **after recovery of diarrhea** [1]
Third episode	**PERMANENTLY** discontinue Nintedanib treatment AND **Anti-diarrhoeal 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.

9.4.2 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	3rd 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 > 5x ULN or ALT or AST > 2.5 ULN in conjunction with bilirubin >1.5 ULN	STOP Nintedanib until recovery* then reduce Nintedanib dose[1]	STOP Nintedanib until recovery* then reduce Nintedanib dose[1]	PERMANENT discontinuation of Nintedanib treatment

*CTCAE grade ≤ 1 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

CTCAE grades for AST/ALT (version 3.0):
Grade 1 means ALT or AST = ULN- 2.5 x ULN
Grade 2 means ALT or AST > 2.5-5.0 x ULN
Grade 3 means ALT or AST > 5-20.0x x ULN
Grade 4 means ALT or AST > 20.0 x ULN

CTCAE grades for bilirubin (version 3.0):
Grade 1 means > ULN- 1.5 ULN
Grade 2 means > 1.5 ULN – 3x ULN
Grade 3 means > 3x ULN – 10 ULN
Grade 4 means > 10 x ULN

9.4.3 Management of Nausea and Vomiting

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

CTCAE 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 prochlorperazine If ineffective, patients should be treated according to treatment of vomiting ≥2 or nausea CTCAE Grade ≥ 3.	No dose reduction

Vomiting ≥2 and/ or Nausea ≥ 3		
First 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	Nintedanib: dose reduction[2]
Second episode	Treatment with Nintedanib discontinued and resumed upon recovery[1] Treatment as above	Nintedanib: dose reduction[2]
Third episode	As above	Nintedanib discontinuation

[1]CTCAE grade ≤ 1 or baseline at study enrollment.
[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.

10.1 EVALUATION DURING TREATMENT/INTERVENTION

	Any time prior to start	**≤4 weeks prior to start**	**≤2 weeks prior to start**	**Cycle 1[1]**				**Cycle 2 and onwards[2]**				**End of treatment visit[3]**
Week #				**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	
Histological confirmation of diagnosis	X											
Informed consent		X										
History, concomitant medications and toxicity			X	X	X	X		X				X

assessment												
Physical exam, vital signs[4], and performance status			X	X	X	X		X				X
Complete blood count, comprehensive metabolic panel[5]			X	X	X	X		X				X
PT/PTT			X									
ECG[7]		X										
Serum Pregnancy Test[8]			X									
Radiographic tumor assessment[9,10]		X									X	
Nintedanib pill diary/compliance review				X				X				X
Nintedanib dosing				Nintedanib 200mg Twice Daily, Every Day								

1. Each treatment cycle consists of 28 days and will be repeated until tumor progression (PD according to RECIST version 1.1) confirmed by tumor imaging.
2. Beginning with Cycle 2, each cycle start date will coincide with the physician visit date.
3. End of treatment (EOT) visit: within 14 days after permanent termination of trial drug(s). If permanent discontinuation of study drugs falls on a scheduled visit, examinations as defined for EOT should be preformed instead of the examination of the scheduled visit.
4. Vital signs: includes respiratory rate, pulse, temperature and blood pressure.
5. Comprehensive metabolic panel (CMP) includes: BUN, creatinine, ALT, AST, albumin, glucose, total protein, calcium, bilirubin, bicarbonate, sodium, chloride, potassium, alkaline phosphatase.
6. 12-Lead resting electrocardiogram (ECG) will be performed at screening
7. For women of childbearing potential
8. A CT or MRI will be obtained at baseline within four weeks of study enrollment. Repeat radiographic evaluation will be obtained after the first eight weeks, and then every eight weeks ±14 days thereafter. Patient may have CT or MRI scan on an earlier or later date than allowed by the window of ±14 days, if clinically indicated at the investigators discretion. Patient with a partial/complete response require a confirmatory scan at least four weeks after the initial scan documenting response (see Section 12.0). If a complete response is achieved and maintained for 12 months, patients with complete response will then be required to repeat CT or MRI evaluation every 4 months up to 5 years post complete response status, then

every 6 months thereafter, with a scheduling window of one to fourteen (1-14) days. The same imaging modality performed at baseline (CT or MRI) will be repeated at subsequent imaging.

9. Because of the potential need for blood tests, CT/MRI scan, and physician visit scheduling to vary (due to both physician and patient issues), to avoid violation of, and deviation from the protocol, blood tests, CT/MRI scans, and physician visits (including physical exam, vitals, blood pressure, performance status, and concomitant medications) may vary by up to one week (7 days) before and 1 week (7 days) after the scheduled date The study treatment will not be interrupted, with the next cycle beginning before the patient is evaluated for toxicity.

Evaluations during treatment

Please note, because of the potential need for blood tests, CT/MRI scan, and physician visit scheduling to vary (due to both physician and patient issues), to avoid violation of, and deviation from the protocol, blood tests, CT/MRI scans, and physician visits (including physical exam, vitals, blood pressure, performance status, and concomitant medications) may vary by up to one to week (7 days) before and 1 week (7days) after the scheduled date. The study treatment will not be interrupted, with the next cycle beginning before the patient is evaluated for toxicity.

- History, concomitant medications and toxicity assessment, physical exam, vital signs, and performance status assessment on Week 1, Week 2, Week 3 of Cycle 1, then on Week 1 of Cycle 2, and each cycle thereafter.
- Complete blood count, comprehensive metabolic panel on Week 1, Week 2, Week 3 of Cycle 1, then on Week 1 of each cycle thereafter.
- Nintedanib diary to be collected on Week 1 of each new cycle.
- A repeat CT or MRI of evaluable or measurable disease at baseline, then at eight weeks, and then every eight weeks thereafter. CT or MRI may be performed more frequently if determined necessary per investigator discretion. The same imaging modality performed at baseline (CT or MRI) will be repeated at subsequent imaging

Evaluations at End of Treatment visit

- History, concomitant medications and toxicity assessment.
- Physical exam, vital signs, and performance status assessment.
- Nintedanib diary to be collected.
- Complete blood count, comprehensive metabolic panel.
- Unused study medication to be returned to MSKCC pharmacy.

Correlative studies

Exploratory biomarker analysis will be performed on archival tissue or any new tissue procurement that becomes clinically available (i.e. no additional biopsy will be procured for the purpose of these studies.)

We will define the frequency and predictive impact of FGFR overexpression and amplification in patients with treatment refractory esophagogastric cancer enrolled on this

study. Protein expression of FGFR1, 2, 3 will be assessed by immunohistochemistry and measured. FGFR genomic alterations and amplification will be assessed by massively parallel sequencing using the IMPACT assay and proteomics-based CEER assay. We will also compare the mutational status of archival tumor samples collected for clinical purposes.

Patients with available tumor tissue will be separately consented for protocol 12-245, "Tumor Genomic Profiling in Patients Evaluated for Targeted Cancer Therapy."

11.1 TOXICITIES/SIDE EFFECTS

For definition of dose limiting toxicity and suggested medical management of Nintedanib associated toxicities refer to Section 9.1 and 9.2.

Nintedanib (Nindetanib)

Nintedanib has shown an acceptable safety profile, on the basis of results from the phase I and phase II studies conducted to date. The most commonly reported treatment-emergent adverse events (TEAEs) were GI disorders including nausea, vomiting, diarrhea, and AST/ALT/bilirubin elevations. Below is a list of TEAEs based on their likelihood of occurrence at a dose of ≤200mg BID:

Likely: (>7% incidence all grades)[54]

- Diarrhea
- Nausea
- Vomiting
- Decreased appetite
- Fatigue
- Asthenia
- Weight loss
- Abdominal pain
- Aspartate aminotransferase elevation
- Alanine aminotransferase elevation
- Gamma-glutamyltransferase elevation
- Hyperkalemia
- Hyponatremia

Less Likely (≤5% all grades)[54,55]

- Abdominal pain
- Constipation
- Headache
- Hypertension
- Alkaline phosphatase elevation

Special warning and precautions for use:

During treatment with Nintedanib, all study patients will be advised to avoid sun exposure or artificial UVA/UVB radiation in solaria or tanning booths. If exposure to sunlight cannot be avoided, protective clothing and broad spectrum (UVA/UVB) sunscreens should be used. After discontinuation of Nintedanib treatment all protective measures should be continued for at least 2 weeks

11.1 Definitions of Adverse Events

Adverse Event
An adverse event (AE) shall mean any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient or clinical investigation subject administered a pharmaceutical product. The medical occurrence does not necessarily have a causal relationship with the treatment.

Serious Adverse Event

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability/incapacity, requires or prolongs patient hospitalization, is a congenital anomaly/birth defect; or based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Severity of adverse event
The severity of adverse event should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

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 medications, 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 causal relationship between the investigational product administered and the AE

11.2 Malignant disease progression

Expected fluctuations or expected deterioration of the underlying disease should not be recorded as an AE unless at least one of the following criteria is me:

- The worsening of the disease constitutes an SAE
- Additional treatment is required, i.e., concomitant medication is added or changed
- An unexpected deterioration from baseline has occurred in the opinion of the investigator

11.3 Worsening of pre-existing conditions

A pre-existing condition present at baseline, which remains unchanged during the trial, does not need to be recorded as adverse event. Any worsening of any pre-existing baseline condition should be recorded as an adverse event. Examples of worsening of a pre-existing condition that should be recorded as an AE are given below:

- Worsening of condition meets the criteria for an SAE
- Action is taken with the investigational drug (i.e. dose is reduced of treatment is discontinued)
- Treatment is required (concomitant medication is added or changed)
- The investigator believes a patient has shown a clear deterioration from baseline symptoms

11.4 Documentation and Reporting of adverse events

All adverse events occurring after the subject has signed the informed consent must be fully recorded in the subject's case record form.

Each serious adverse event (SAE) must be followed up until resolution or stabilization by submission of updated reports to the designated person. An isolated laboratory abnormality that is assigned grade 4, according to CTC definition, is not reportable as an SAE, unless the investigator assesses that the even meets the standard ICH criteria for an SAE. CTC grade 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as an SAE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria.

When required, and according to local law and regulations, serious adverse events must be reported to the Ethics Committee and Regulatory Authorities.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

All patients who receive at least one week of Nintedanib will be evaluable for toxicity and response. Patients who are unable to complete one week of therapy will not be evaluated for toxicity or response and will be replaced by a new patient.

12.1 Measurement of effect

Patients will undergo a baseline CT/MRI assessment and be re-evaluated after two cycles, i.e., 8 weeks of treatment and then every two cycles or eight weeks thereafter. If determined clinically necessary by treating physician, CT/MRI assessment may be performed more frequently. The same imaging modality performed at baseline (CT or MRI) will be repeated at

subsequent imaging. Response and progression will be evaluated in this study using standard Response Evaluation Criteria in Solid Tumors (RECIST) criteria, version 1.1.[53]

Target lesions must have a minimum size of at least one diameter of 10mm for liver, soft tissue lesions, lung, and skin. Pathological nodes must be at least 15mm in the short axis to be considered target lesions. The primary tumor is not considered measurable disease. Recurrent or metastatic lesions within a prior radiation field are acceptable as long as disease has progressed in the radiation field by RECIST 1.1 criteria.

12.2 Progression-free survival

The primary endpoint is to evaluate the 6-month progression free survival (PFS); hence patients with evaluable disease by RECIST are eligible for the trial. This is defined as the duration of time from start of treatment to time of progression or death from any cause. Patients who are taken off-study because of drug-related toxicity or other adverse event but who are alive and have stable or responding disease at the time of trial discontinuation will continue to follow per protocol, however, if they start another therapy, they will be considered as failure of therapy at that time and will be removed from protocol.

12.3 Evaluation of objective response rate

The secondary endpoints include objective response rate, safety and tolerability. The objective response rate will be the best overall response, or the best response recorded from the start of treatment until disease progression/recurrence. The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria by RECIST and defined as complete response (CR), and partial response (PR).

The type, frequency, severity, timing, and relationship of each adverse event will be determined as per the NCI Common Toxicity Criteria, version 3.0. Given the small sample size, the analysis of correlative biomarkers will be exploratory and hypothesis generating.

13.1 CRITERIA FOR REMOVAL FROM STUDY

If at any time, the patient develops progressive disease he/she will be taken off study and referred for alternative therapy. If at any time the patient develops unacceptable toxicity that fails to resolve after a maximum treatment delay of 4 weeks, he/she will be removed from study. Before being removed from the study, patients will be scanned to assess the response. If the off study scan shows progression of disease then the patient will be considered as a non-responder, while a CR or PR will be considered as response. A patient will be withdrawn from the study treatment in the following circumstances:

- Patient is no longer able to participate in the study (e.g. AE, surgery, concomitant diagnoses, concomitant therapies or administrative reasons); in such a case the Investigator's reason for patient's removal must be recorded in CRDB.
- Patient withdrawal of consents or election to discontinue participation in the trial.

- Significant deviation from the protocol or eligibility criteria; such patients will be considered protocol violations and removed from study.
- Non-compliance with study or follow-up procedures.
- Drug related AE(s) that have not resolved after 3 weeks of treatment interruption. Exception to this in patients who derive obvious clinical benefit according to the investigator's judgment could be considered upon discussion with Principal Investigator. The dose reduction scheme provided should be followed in this case.
- Repeat episodes of drug related toxicity despite dose reduction to Nintedanib 100mg twice daily dose.
- Documented progressive disease.
- Patients who become pregnant while on study.

As soon as a patient is withdrawn from the study treatment, the End of Treatment (EOT) visit has to be performed (not in case patient has withdrawn consent). Every effort should be made to follow-up patients in case an adverse event is still ongoing at the time of withdrawal.

14.0 BIOSTATISTICS

This is a single institution, open-label, non-randomized, single-arm phase II evaluation. The primary objective of this study is to determine the 6 month progression free survival (PFS) for patients with advanced or recurrent EG cancer treated with Nintedanib 200 mg twice per day. PFS is defined in Section 12.2.

We are using 6 month PFS as the primary endpoint in this study of 2nd line treatment for advanced EG cancer. Previous studies have estimated the 6 months to be 4.5% with placebo, 12% with everolimus and 18% for ramucirumab. Based on this information, a 6 month PFS of 10% or less will be considered unacceptable while 28% or more will be considered promising. Using an exact binomial single stage design we require 32 patients to differentiate between 6-month PFS of 10% and 28% with type I and II error rates of 10% each. If 6 or more patients are alive and progression free at 6 months, the regimen is declared promising. With a total of 32 patients, we also have 89% power to detect an improvement in the response rate from 5% to 20% with a one-sided type I error rate of 10%. We assume an accrual rate of 1-2 patients per month for study duration of 18-35 months.

Secondary endpoints involve an assessment of the overall response rate (complete and partial responses), as determined by RECIST criteria. Toxicities will also be assessed and tabulated. Correlative analyses will be exploratory in nature. We will assess the relationship between FGFR amplification (by FISH) and FGFR overexpression (by IHC) with progression free survival using log-rank test. Fisher's exact test will be employed to assess these relationships with response.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.3 Randomization

This research study does not require randomization procedures.

16.1 DATA MANAGEMENT ISSUES

The principal investigator will be responsible for the data collection and management with the assistance of a research study assistant (RSA) who will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rate and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team. Random-sample data quality and protocol compliance audits will be conducted by the study team.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled, “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and

Safety Monitoring Plans can be found on the MKSCC Intranet at:
http://mskweb2.mkscc.org/irb/index.htm

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

Prior to the enrollment of each patient, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion with the patient. It will be reviewed that participation in this clinical trial is voluntary and that the patient may withdraw consent at any time. The study is designed with careful safety monitoring for toxicity including physician visits and serial laboratory monitoring. Specific guidelines for symptom management are in place to protect the study participation. The financial costs of the study will be discussed; Nintedanib will be provided free of charge. Correlative tests will be performed without charge to the patient. The patient will be responsible for the cost of standard medical care and all hospitalization, even for complications of treatment.

No incentives will be offered to patients/subjects to participate in the study.

Inclusion of women and minorities
MSKCC has file forms HHS 44 (civil rights), HHS 641 (handicapped individual), HHS 639-A (sex discrimination) and HHS 680 (age discrimination); we also take due notice of the NIH/ADAMHA policy concerning inclusion of women and minorities in clinical research populations. Patients of all races, both males and females, will be enrolled into the protocol. In the New York metropolitan area, there are a high proportion of minority patients (e.g. African-American, Hispanic). In general, about 15% of patients at MSKCC are members of minority ethnic groups. We will actively try to recruit minority patients to this protocol.

Exclusion of children and lactating or pregnant women
Children are excluded from this protocol because there is insufficient data to determine the safety of Nintedanib in children. In addition, the incidence of esophagogastric cancer in children is limited and because the majority are already access by a nationwide pediatric cancer research network. This statement is based on exclusion 4b for the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human

Subjects. Similarly, lactating and pregnant women are excluded because of the potential teratogenicity and embryotoxicity of Nintedanib.

17.2 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.3 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - An explanation of how the AE was handled.
    - A description of the subject's condition.
    - Indication if the subject remains on the study.
    - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.3.1 Adverse event and serious adverse event reporting

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 follow-up period of 28 days following the last administration of the drug) 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 relationship and expectedness with the investigational drug to all AEs as defined in the listed adverse event section of Boehringer Ingelheim' s Investigator Brochure for the product.

If not stipulated differently in the pharmacovigilance agreement, SAEs are to be reported to BI using the BI IIS Serious Adverse Event Report Form including a documented causal relationship assessment and providing as much detail regarding the SAE as possible. With receipt of follow-up information, all remaining fields on the SAE form are to be completed or updated.

17.3.2 Protocol-specified events of special interest

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

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

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

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

Drug-induced liver injury (DILI)

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

The following are considered as protocol-specified AESI:

- An elevation of ALT and / or AST > 5x ULN without bilirubin elevation measured in the same blood draw sample

- An elevation of AST and/or ALT >2.5 fold ULN combined with an elevation of bilirubin to >1.5 fold ULN measured in the same blood draw sample

Patients showing above laboratory abnormalities need to be followed up until the protocol specific retreatment criteria have been met and according to **Appendix II** of this clinical trial protocol.

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

17.3.3 Responsibilities for SAE reporting

The investigator shall report all SAEs, non-serious AEs occurring at the same time and/or which are medically related to the SAE and AEs of Special Interests independent from their seriousness to Boehringer Ingelheim Pharmaceuticals, Inc. In the event of such an event, the investigator should refer to the Pharmacovigilance section of the contract for reporting procedures.

The investigator shall report all SAEs, non-serious AEs relevant to a reported SAE, and AEs of Special Interest by fax to the Boehringer Ingelheim Unique Entry Point as detailed below in accordance with the following timelines:

• within five (5) calendar days upon receipt of initial and follow-up SAEs containing at least one fatal or immediately life-threatening event;

• within ten (10) calendar days upon receipt of any other initial and follow-up SAEs.

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18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.

3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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56. Boehringer Ingelheim.Investigator's Brochure for Nintedanib (BIBF1120). Document No. U02-1482-13, page 115 Table 6.3.1.10.1:1.

20.0 APPENDICES

Appendix I Patient Pill Diary

Appendix II Drug-Induced Liver Injury (DILI) Guideline