MSK Protocol Cover Sheet

Phase II Double-Blind, Randomized, Placebo Controlled Study to Evaluate the Efficacy and Safety of Nintedanib (BIBF 1120) + Prednisone Taper in Patients with Radiation Pneumonitis

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Study Title:	Phase II Randomized, Placebo Controlled Study to Evaluate the Efficacy and Safety of Prednisone Taper with or without Nintedanib (BIBF 1120) in Patients with Radiation Pneumonitis
Study Objectives:	To investigate the efficacy and safety of nintedanib + prednisone taper compared to placebo + prednisone taper in patients with grade 2 or higher radiation pneumonitis
Study Endpoints:	**Primary Endpoint:** • Proportion of patients who are free from pulmonary exacerbations within 12 months **Secondary endpoints:** • To measure the effects of nintedanib on: o Rate of decline in pulmonary function tests (PFTs) (including FVC, FEV1, hemoglobin corrected DLCO) and 6 minute walk test with pulse oximetry compared to baseline o Radiographic fibrosis as assessed by high resolution computer tomography (CT) scans o Quality of life measures as quantified by the St. George's Respiratory Questionnaire (SGRQ) (Appendix B) and PRO-CTCAE (Appendix C) o Number of acute exacerbations of radiation pneumonitis within 1 year (See CTCAE 4.0 Appendix A) o Number of hospitalizations due to pulmonary exacerbations. • To explore potential predictive serum markers including serum TGF alpha, TGF beta, TNF-alpha, IL-6, IL-8, alpha 2 macroglobulin, VEGF, soluble VEGF receptor 2, PDGF, PDGF receptor, FGF23, and bFGF
Patient	Patients with a histologically/cytologically proven primary thoracic malignancy or lung metastases (which are not required to be biopsy-proven) treated with definitive

Population:	intent and with active grade 2 or higher radiation pneumonitis
Number of patients:	68 patients, 34 patients in each arm (nintedanib or placebo)
Inclusion Criteria:	1. Histologically/cytologically proven primary thoracic or breast malignancy, lymphoma or lung metastases (which are not required to be biopsy-proven) treated with definitive intent 2. Prior treatment with thoracic radiotherapy completed > 4 weeks and ≤ 9 months prior to enrollment 3. Radiographic evidence of radiation pneumonitis on a CT scan of the chest 4. Newly diagnosed clinical grade 2 or higher radiation pneumonitis according to CTCAE version 4.0 criteria (See Appendix A) 5. Age ≥ 18 years 6. Written informed consent signed prior to entry into the study 7. KPS ≥ 70% 8. Reduction of any acute toxicity from radiation treatment to grade 1
Exclusion Criteria:	1. Current oral steroid use > 4 weeks prior to registration 2. Ongoing treatment with radiotherapy to thorax, cytotoxic or biological therapies for this malignancy, except the following therapies which are permitted: Pembrolizumab, Nivolumab, Afatinib and all hormonal therapies 3. Mean esophageal radiation dose > 45 Gy 4. Diagnosis of diffuse radiation pneumonitis 5. Liver metastases 6. AST>1.5xULN, ALT >1.5xULN and Bilirubin >1.5xULN 7. Other investigational therapy received within 8 weeks prior to screening visit 8. Pregnant women or women who are breast feeding or of child bearing potential not using a highly effective method of birth control for at least one month prior to enrollment 9. Sexually active males not committing to birth control during the course of the study (except if their partner is not of childbearing potential) 10. Conditions that may affect the patient's ability to participate in this trial, e.g. known or suspected active alcohol or drug abuse 11. Concomitant treatment with any of the following drugs: azathioprine, cyclophosphamide, cyclosporine, pirfenidone, full dose anticoagulation (vitamin K antagonists, dabigatran, heparin, etc.), fibrinolysis and high dose anti-platelet therapy (ex. Plavix 150mg)[2] 12. Myocardial infarction or unstable angina within 6 or 1 month of starting nintedanib treatment, respectively 13. Known inherited predisposition to thrombosis 14. Patient with a history of a thrombotic event within 12 months of starting nintedanib treatment 15. Known predisposition to bleeding 16. Patients with severe hepatic impairment 17. History of a gastrointestinal perforation 18. Untreated or symptomatic brain metastases or leptomeningeal disease 19. Other active malignancies requiring oncologic treatment (Note: non-melanoma

	skin cancer, superficial bladder cancer, etc. are eligible) 20. Radiographic evidence of cavitary or necrotic tumor and local invasion of major blood vessels 21. Active chronic Hepatitis C and/or B infection 22. Gastrointestinal disorders that would interfere with drug disposition 23. ≥ Grade 2 proteinuria, creatinine > 1.5x ULN or GFR < 45 ml/min 24. History of bleeding disorders or thrombotic events, e.g. hemorrhagic or thrombotic events within 12 months, clinically significant or tumor-related hemoptysis, active gastrointestinal bleeding or ulcers or major injuries or surgery 25. ANC < 1.5 K/mcL, Platelets < 100 K/mcL, Hemoglobin < 9.0 g/dl 26. Inherited predisposition to bleeding or thrombosis, INR > 2, PT and PTT > 1.5x ULN
Study drug:	Nintedanib (BIBF 1120)
Study Design:	This clinical trial is a phase II, placebo controlled, double blinded study. Patients with a thoracic malignancy and grade 2 or higher radiation pneumonitis will be enrolled. Following an initial screening clinic visit, a diagnosis of grade 2 or higher radiation pneumonitis will be confirmed. Sixty-eight patients will be randomized 1:1 to nintedanib 150mg twice daily + oral prednisone taper (treatment arm A) or placebo + prednisone taper (control arm). Nintedanib and placebo will be given for 12 weeks and the prednisone taper will be given over 8 weeks (40mg daily week 1 and 2, 30mg daily week 3 and 4, 20mg daily week 5 and 6, 10mg daily week 7, 5mg daily week 8). All patients will have the opportunity for a one step dose reduction of nintedanib in case of intolerance (See Section 11). All patients will have a baseline, pretreatment high resolution CT scan of the chest (with or without contrast), PFTs (including FVC, FEV1, hemoglobin corrected DLCO), 6 minute walk test with pulse oximetry, SGRQ, PRO-CTCAE questionnaire, and serum biomarkers. Patients will be monitored by regular medical interviews, record of adverse events, physical exams, vitals, laboratory measurements, high resolution CT scans of the chest with or without contrast (weeks 6 and 12 during treatment, then approximately 6, 9, and 13 months from treatment start), PFTs, 6 minute walk tests with pulse oximetry, (week 12 of treatment, then approximately 6, 9, and 13 months from treatment start), SGRQ/PRO-CTCAE (every 6 weeks while on treatment then approximately 6, 9, and 13 months from treatment start) , and serum markers (weeks 6 and 12 during treatment then approximately 6 months from treatment start). Patients will be followed up to approximately 1 year on trial. All patients will be unblinded at the end of the study. There will be a 2 week run in period at the beginning of the study, in which time the symptoms that prompted the initial diagnosis are expected to be controlled. Acute exacerbations will only be considered toward the study endpoint after the first 2 weeks on study. Patients with intrathoracic progression of their cancer or continued ≥grade 3 study-related adverse

	events without improvement with dose reduction or drug interruption will be taken off study. Drug re-escalations will not be permitted. Acute exacerbations will be treated at the physician's discretion.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Objective: confirm efficacy of nintedanib in combination with prednisone in the treatment of grade 2 or higher radiation induced pneumonitis as compared to prednisone alone.

Hypothesis: The use of nintedanib will decrease the incidence of acute exacerbations, pulmonary function decline, and long term pulmonary fibrosis and improve patient reported outcomes in patients with grade 2 or higher radiation induced pneumonitis.

Primary Endpoint: to determine whether 12 weeks of nintedanib in combination with oral prednisone will decrease the proportion of patients experiencing acute exacerbations within 1 year in comparison to prednisone taper alone from 50% (control arm) to 25% (treatment arm)

An acute exacerbation will be defined as (all criteria must be met):

1. Unexplained worsening or development of cough, dyspnea, hypoxia, or pneumonitis lasting more than 4 days
2. New or worsening diffuse pulmonary infiltrates on chest CT (with or without contrast) or new high resolution CT parenchymal abnormalities without significant pneumothorax or pleural effusion
3. Exclusion of alternative causes as per routine clinical practice, including the following:
    - Pneumonia
    - Congestive heart failure
    - Pulmonary emboli
    - Intrathoracic cancer progression
    - Identifiable cause of acute lung injury

Secondary Endpoints

- To measure the effect of nintedanib on pulmonary function decline as assessed by:
    - FVC, FEV1, hemoglobin corrected DLCO, 6 minute walk test with oximetry
- To assess the effects of nintedanib on radiographic fibrosis as assessed by:
    - high resolution CT scans of the chest with or without contrast
- Assess patient reported outcomes as assessed by:
    - SGRQ
    - PRO-CTCAE
- To explore serum markers that may be associated with a response to nintedanib and disease activity. The following serum markers will be tested:
    - TGF-alpha, TGF-beta, TNF-alpha, IL-6, IL-8, VEGF, soluble VEGR receptor 2, PDGF, PDGF receptor, bFGF, FGF23, and Alpha 2 Macroglobulin
- Number of acute exacerbations of radiation pneumonitis within one year

- Number of hospitalizations due to pulmonary exacerbations

3.0 BACKGROUND AND RATIONALE

3.1 Medical Background

3.1.1 Epidemiology, Presentation, and Current Treatment Options for Radiation Pneumonitis:
Definitive radiation therapy with or without concurrent chemotherapy is the standard of care for unresectable locally advanced non-small cell lung cancer, and limited stage small cell lung cancer. Radiation therapy is also commonly used for advanced thymomas and pleural mesotheliomas in the definitive or adjuvant setting. Moderate to severe radiation pneumonitis is the most common dose limiting constraint in radiation treatment planning for these patients, with rates of grade 2 or higher radiation pneumonitis approaching 20%.[1,2] The rate of radiation pneumonitis may even be higher as symptoms can be misinterpreted as resulting from other cardiovascular and respiratory disorders leading to underreporting.

Histologically, radiation pneumonitis is characterized by destruction of gas exchanging regions of the lung.[3] Classic symptoms can range from slight cough and low grade fever to shortness of breath and severe respiratory insufficiency with severity of symptoms classified by CTCAE version 4 (see Appendix A).[4,5,6,7] CT scans of the chest classically demonstrate ground-glass opacity or consolidations with or without traction bronchiectasis, volume loss, and fibrosis.[8] Although the course of the disease is difficult to predict, approximately 50% of patients develop subsequent acute pulmonary exacerbations, and the majority of patients will go on to develop radiation induced pulmonary fibrosis.[9] Furthermore, severe radiation pneumonitis is associated with a significantly lower survival, with mortality rates approaching 50%.[10] Due to concerns that the estimated safety and tolerability of the radiation treatment may compromise cure rates, the optimal radiation dose is commonly not reached.

Currently the standard treatment for radiation pneumonitis consists of a prolonged course of steroids, which are associated with significant short and long term toxicities. Furthermore, it is unclear whether or not steroids prevent the long term sequela of radiation induced pulmonary fibrosis. ACE inhibitors, amifostine, and pentoxifylline have not proven to be efficacious in the prevention or treatment of radiation pneumonitis.[11,12,13] As such, there is a clear unmet medical need for evidence-based management options for radiation pneumonitis.

3.1.2 Pathophysiology and Biology of the Pneumonitis/Pulmonary Fibrosis:
The pathogenesis of radiation pneumonitis is thought to be mediated through a release of multiple cytokines and growth factors including transforming growth factor-beta (TGF-beta), vascular endothelial growth factor (VEGF), tissue necrosis factor (TNF), PDGF, interleukin (IL) -6, IL-8, and NF-Kappa B.[14] The release of these cytokines and growth factors by irradiation injury result in an inflammatory reaction, clinically evident as radiation pneumonitis. These growth factors eventually activate fibroblasts and myofibroblasts which are critical components of the development of permanent changes in the airway wall leading to the deposition of fibrin and pulmonary fibrosis.[15] TGF beta is felt to be the most relevant growth factor in the pathogenesis of pulmonary fibrosis, but direct blockage of this pathway may not be a viable therapeutic option due to the pleiotropic function of this growth factor.[16]

3.1.3 Nintedanib, a Potent Tyrosine Kinase Inhibitor, Targets the TGF Beta 1 Pathway in Bleomycin-Induced Lung Injury and Idiopathic Pulmonary Fibrosis:

Nintedanib is a potent intracellular inhibitor of multiple tyrosine kinases that is in clinical development for the treatment of pulmonary fibrosis.[17] It is an inhibitor of the Fibroblast Growth Factor Receptor 1 and 3 (FGFR - 1 / 3), the Platelet-Derived Growth Factor Receptor α and β (PDGFR α and ß), and the Vascular Endothelial Growth Factor Receptor 1, 2 and 3 (VEGFR 1-3) tyrosine kinases. These growth factors have each been investigated as a potential standalone therapeutic target in fibrosis.[18,19,20] However, inhibiting all three pathways may be more effective. In a rat model, such inhibition with BIBF 1000, an analog of nintedanib, was shown to prevent the development of bleomycin induced lung injury before and during the fibrotic phase of the disease (Figure 1).[21] Furthermore, BIBF 1000 blocked TGF-beta mediated differentiation of human primary lung fibroblasts isolated from lung fibrosis patients. In a phase II clinical trial, nintedanib was found to be effective in slowing the decline of pulmonary function as measured by the forced vital capacity (FVC) (p=0.06), markedly decreasing the incidence of acute exacerbations from 15.7 to 2.4 per 100 patient-years (p=0.02) (Figure 2), and improving the quality of life of patients with idiopathic pulmonary fibrosis (p=0.007).[22] Many of the same signal transduction pathways are implicated in the pathophysiological mechanism of idiopathic pulmonary fibrosis and radiation pneumonitis. We therefore propose that the use of nintedanib may similarly decrease the incidence of acute exacerbations, pulmonary function decline, and long term pulmonary fibrosis in patients who suffer from radiation pneumonitis.

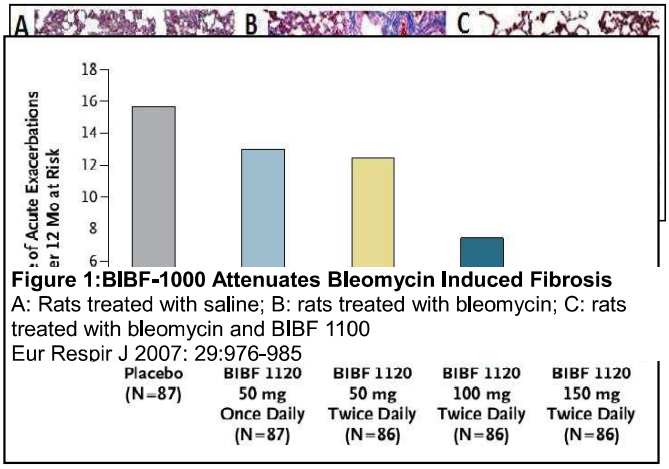

Figure 1:BIBF-1000 Attenuates Bleomycin Induced Fibrosis
A: Rats treated with saline; B: rats treated with bleomycin; C: rats treated with bleomycin and BIBF 1100
Eur Respir J 2007: 29:976-985

Figure 2: nintedanib decreases the rate of Acute Exacerbations in Patients with Idiopathic Pulmonary Fibrosis
NEJM 2011; 35:1079-1087.

3.1.4 Potential Serum Biomarkers of Nintedanib Activity:

Validated biomarkers that correlate with physiologic, radiographic, and clinical responses are necessary to select the patient population most likely to benefit from nintedanib. To date, only one clinical trial of 15 patients assessed potential pharmacodynamic biomarkers of nintedanib activity in humans—soluble VEGF receptor 2 and CD117 positive bone marrow derived progenitors.[23] Therefore, additional prospective studies in this field are warranted. As inflammatory (e.g. IL-6, IL-8) and pro-fibrotic cytokines (e.g. TGF alpha, TGF beta, TNF alpha) are felt to be key mediators of lung toxicity and progression of fibrosis, a decline in these cytokine levels may be an early predictor of response to nintedanib. Alpha-2-macroglobulin has been found to be a novel biomarker of RP through bioinformatics analysis of high throughput proteomic data.[24,] We hypothesize that response to nintedanib may correlate with normalization of alpha 2 macroglobulin levels. Lastly, as nintedanib competitively binds to the ATP binding sites within the kinase domains of VEGFR 1-3, PDGFR alpha/beta, and FGFR1 and 3, a rise in plasma FGF23, VEGF, and PDGF and a decrease in soluble VEGF receptor 2 levels may correlate with nintedanib activity.[27] As part of this study, we will for the first time investigate the on-target effects of nintedanib in humans by examining the serum levels of the target receptors of nintedanib. These are planned to be analyzed in the immune monitoring facility (IMF) at MSKCC.

In addition serum will be sent to Myriad RBM for multiplex immunoassay analysis of serum samples

using their Luminex xMAP® technology and Quanterix Simoa™ platform. We plan to analyse the serum samples using up to 13 platform assays that are partially or not covered by the assays available through the IMF at MSKCC. These assays will cover a range of inflammatory, angiogenic and profibrotic markers, including but not limited to apolipoprotein, beta-2-microglobulin, c-reactive protein, serum amyloid P-component, thyroxine-binding globulin, von Willebrand factor, adioponectin, alpha-2-macroglobulin, ferritin, myoglobin, plasminogen activator inhibitor-1, T-cell specific protein RANTES, tissue inhibitor of metalloproteinases 1, tumor necrosis factor receptor 2, vascular cell adhesion molecule-1, EN-RAGE, pulmonary and activation-regulated chemokine (PARC), alpha-fetoprotein, cancer antigens 125 and 19-9, carcinoembronic antigen, human chorionic gonadotropin beta, neuron-specific enolase, matrix metalloproteinases-1, -2, -3, -7 and -9, angiopoetin-1, carbonic anhydrase 9, decorin, IL-18 binding protein, platelet endothelial cell adhesion molecule, brain-derived neurotrophic factor, eotaxin-1, factor VII, intercellular adhesion molecule 1, IL-1 alpha, IL-1 beta, IL-1 receptor antagonist, IL-12 subunits p40 and p70, IL-17, stem cell factor, vascular endothelial growth factor, IL-23, kallikrein-7, maspin, prostasin, vascular endothelial growth factor D, angiogenin, cathepsin D, IL-6 receptor subunit beta, pepsinogen I, YKL-40, cartilage oligomeric matrix protein (COMP), thrombospondin-1, angiopoietin-2, eotaxin-3, insulin-like growth factor-binding protein 2, macrophage migration inhibitory factor, B lymphocyte chemoattractants BLC, and CXCL-13.

Specimen's sent to Myriad RBM Inc. will be anonymized with a patient identification number. There will be no participant identifiers shared with Myriad RBM. Specimens are to be tracked via an electronic manifest in Microsoft Excel format. Each sample being sent will have a sample ID on a label and will have that corresponding sample ID on the manifest so Myriad can process the samples and relay the results to MSKCC in a deidentified manner.

The **Project Manager** is:
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512-275-2629

Shipping of samples:
MRBM is available Monday-Friday to receive shipments, except Federal holidays
Myriad RBM
Attn.: Kalyn Sowell
3300 Duval Rd, Austin, TX 78759
receiving@myriadrbm.com
512.835.8026

3.2 Drug Profile

A soft gelatin capsule formulation of nintedanib is used in humans. Available pharmacokinetic data indicate that the systemic exposure required for biological activity can be achieved in humans.[28] Maximum plasma concentrations occurred mainly 1 to 4 hours after administration. Steady state was at the latest reached within 9 days of treatment. The gMean terminal half-life was between 7 to 19 hours. The metabolism of nintedanib was predominantly characterized by the ester cleavage of the

methyl ester moiety yielding BIBF 1202, which was further metabolized by conjugation to glucuronic acid yielding the 1-O-acylglucuronide. The glucuronidation of BIBF 1202 was mainly through UGT1A1 (liver and intestine) and UGT1A7, UGT1A8 and UGT1A10 (intestine).In humans, 93.4% of total [14C] radioactivity was excreted in the feces within 120 hours after oral administration of nintedanib. Only 0.7 % of total [14C] radioactivity was eliminated via the urine. An absolute bioavailability of slightly below 5% is observed by an intra-individual comparison of dose normalized AUC of 100 mg nintedanib administered orally and 6 mg nintedanib administered intravenously. Drug-drug interactions based on cytochrome P450 dependent pathways are not expected for nintedanib. See also Investigator's Brochure Nintedanib (BIBF 1120) for more details.[29]

3.3 Drug Toxicity Data

3.3.1 Toxicity Data in Animals:

Data from four-week, 13-week, and 26-week toxicity studies in rats as well as four-week, 13-week and 52-week toxicity studies in monkeys are available. Relevant histopathological findings in these studies were observed in the gastrointestinal tract, lymphatic tissues, kidneys, bone marrow, liver, extrahepatic bile duct, exocrine glands, and the skin. Bone changes in growing animals (thickening of epiphyseal growth plate) were interpreted as a typical mechanism-related toxicity associated with a VEGFR-2 inhibitor. Mild changes in hematological and clinical chemistry parameters (increases in γ-glutamyl transferase (γ-GT), aldolase, alanine amino transferase (ALT), aspartate aminotransferase (AST), leucine aminopeptidase (LAP), glutamate dehydrogenase (GLDH]) were seen in rats. Minimal to slight changes in immunotoxicological parameters (cd4 count) and lymphoid tissues may be the correlate to the additional inhibition of src family non-receptor tyrosine kinases such as lymphocyte specific protein kinase (lck) and lyn. Overall, the histopathological findings and changes of laboratory parameters were mild to moderate and generally confined to the high-dose groups.

Nintedanib is non-mutagenic, even at high doses. One compound in a batch of potential degradation products that may be formed under systemic and/or acidic conditions was found to be weakly Ames positive at high concentration after metabolic activation, while a second batch of the same products was Ames negative. The compound was not found in any of the drug substance batches of nintedanib used and thus did not occur within the limits of detection. Further experiments (mouse lymphoma assay, micronucleus assay) indicated that the compound does not raise a safety concern for cancer patients.

Two exploratory studies in rats revealed a teratogenic effect of nintedanib with a steep dose/effect relationship and an early onset of embryofetal deaths at low dosages. This effect was observed at dose levels resulting in plasma drug concentrations comparable to or below those in humans. Because the concentration of nintedanib in semen is unknown, males receiving nintedanib and having sexual intercourse with females of childbearing potential should use latex condoms.

3.3.2 Toxicity Data in Humans:

Phase I dose selection studies revealed that nintedanib is generally well tolerated with mild to moderate adverse effects such as gastrointestinal symptoms (nausea, diarrhea, vomiting, and abdominal pain) and reversible elevations of liver enzymes.[30] A phase II trial in NSCLC patients confirmed the safety profile of BIBF 1120.[31] Most commonly reported drug-related AEs were nausea (57.5%), diarrhea (47.9%), vomiting (42.5%), anorexia (28.8%), abdominal pain (13.7%) and reversible alanine transaminase (13.7%) and aspartate aminotransferase elevations (9.6%) In

conclusion it was generally well tolerated and displayed single agent activity in advanced or recurrent NSCLC patients.

In the idiopathic pulmonary fibrosis phase 2 proof-of-concept trial, 432 patients with consistent IPF were randomized, with baseline characteristics comparable across groups.[22] The number of deaths was not significantly different between groups. Discontinuations (26.2%; 22.4% due to adverse events) were more frequent with 150 mg bid (37.6%; 31.8%), but less with 100 mg bid (16.3%; 15.1%), compared to placebo (28.2%; 24.7%). Gastrointestinal adverse events increased dose-dependently and were frequently (74.1% of patients) reported in the 150 mg bid dose group. Discontinuations due to adverse events were more frequent in the 150 mg bid dose group compared to placebo (30.6% versus 25.9%). Observations of transaminase elevations increased with dose but were manageable with dose reduction or discontinuation. No clinically relevant increases of bilirubin were observed during the 52 weeks double-blind comparison phase. In a few cases, a slight increase of total bilirubin, concomitant with transaminase increase, was observed. All cases of nintedanib -related increases in liver enzymes for which sufficient follow up data are available have been reversible. Single cases were reported of patients who died and for whom elevations of liver enzymes were observed prior to death. A causal relationship between drug treatment and the hepatic injury, however, was considered unlikely in these cases.

As of July 10, 2009, a total of 739 cancer patients, 423 patients with idiopathic pulmonary fibrosis (please see Investigator's Brochure for further details[29]) and 59 healthy volunteers have been treated in multiple dose studies with nintedanib or blinded nintedanib /Placebo. The predominant adverse events were nausea, diarrhea, vomiting, abdominal pain and fatigue of mostly low to moderate intensity after monotherapy with nintedanib. Dose limiting toxicities were dose dependent hepatic enzyme elevations that were reversible after discontinuation of nintedanib treatment. These liver enzyme elevations were only seen in few cases accompanied by a simultaneous increase of bilirubin. In general common terminology criteria for adverse events (CTCAE version 4) grade three liver enzyme increases were reported in the dose groups of 250 mg twice daily or higher. They also were reversible and usually occurred within the first two months of treatment.

All adverse events observed in healthy volunteers after single administration of nintedanib were of CTCAE Grade 1 intensity and fully reversible.

3.4 Rationale for Performing Trial and Proposed Dose:

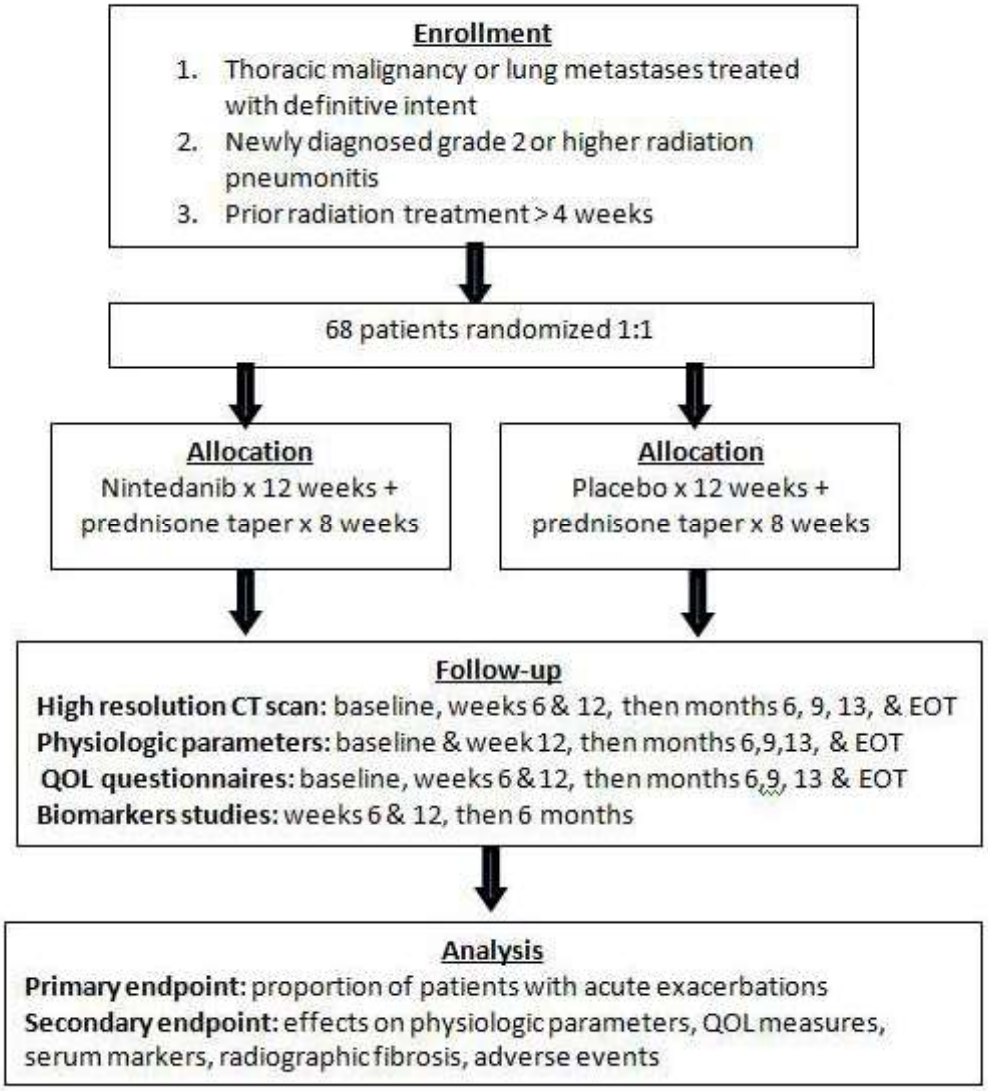
3.4.1 Rationale for Performing Trial: Currently, there is no clinically proven medication that can prevent acute exacerbations, halt lung function decline, and improve patient-reported outcome for patients with symptomatic radiation pneumonitis. Given signs of efficacy in the phase II trial of nintedanib in the treatment of idiopathic pulmonary fibrosis, we feel that it would be justified to conduct a similar trial, in combination with steroids, in patients with grade 2 or higher radiation pneumonitis. Treatment with nintedanib has the potential to preserve lung function, alleviate disease related symptoms, allow patients to maintain a favorable quality of life, and reduce mortality rates from severe radiation induced fibrosis. Furthermore, by collecting serial PFTs, six minute walk tests, and high resolution CT scans we will be able to better characterize the clinical course of patients with moderate to severe pulmonary pneumonitis for the first time, since this has never been described in the literature in detail. Finally, correlating the changes in cytokine

profiles, and alpha 2 macroglobulin with the clinical course of radiation pneumonitis and response to nintedanib may elucidate key biomarkers of disease activity and response to therapy.

3.4.2 Rationale for Proposed Starting Dose of Nintedanib:
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.[30] Available pharmacokinetic data indicate that the systemic exposure needed for biological activity can be achieved starting with doses of 100 mg once daily. In the large phase 2 proof of concept trial of nintedanib as treatment in patients with idiopathic pulmonary fibrosis, a nintedanib dose of 150mg BID had a positive effect on lung function, oxygen saturation, incidence of acute exacerbations, and quality of life measures and was well tolerated. For these reasons, nintedanib at a dose of 150mg BID was chosen for our study.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design



This is a prospective, randomized, placebo controlled, double blinded, phase 2 clinical trial with a planned enrollment of 68 patients. Patients with grade 2 or higher radiation pneumonitis will be eligible for the study. Patients will be randomized 1:1 to nintedanib or placebo in combination with a prednisone taper. The primary endpoint is the reduction in proportion of patients who experience one or more acute exacerbations within 1 year after the initial exacerbation. Secondary endpoints include changes in PFTs, 6 minute walk test, quality of life, number of hospitalizations, and changes in serum markers.

4.2 Intervention

Patients with grade 2 or higher radiation pneumonitis and a history of a thoracic malignancy or lung metastases treated with definitive intent will be eligible for this trial. Patients will be randomized to receive nintedanib at 150mg PO BID or placebo along with a prednisone taper (as detailed in section 9). The study drug (nintedanib or placebo) will be given for a total of 12 weeks or until unacceptable toxicity, patient refusal, or recurrence of disease (if earlier than 12 weeks). The prednisone taper will be given over 8 weeks.

Assessment at Baseline:
At baseline, patients will have pre-treatment CT scans of the chest with or without contrast. Patients will undergo PFTs, and 6 minute walk test with pulse oximetry. Baseline SGRQ and Pro-CTCAE questionnaires will be completed by the patient. Serum biomarkers for associated translational studies will be obtained at baseline prior to treatment initiation.

Adverse Events Assessment:
Safety evaluation will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measures during each clinic visit. Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study (See Section 11.0).

Endpoint Assessment:
Chest CT scans with or without contrast will be repeated at weeks 6 and 12 during treatment, and then approximately 6 months, 9 months and 13 months from start of treatment. PFTs and 6 minute walk test with pulse oximetry will be repeated at week 12 of treatment, then approximately 6, 9, and 13 months from treatment start. Serum biomarkers will be obtained at week 6 and 12 of treatment, then approximately month 6 from start of treatment. Patients will be clinically assessed and given QOL questionnaires every 6 weeks while on treatment (12 weeks) and then approximately month 6, 9, and 13 from treatment start until the end of study to monitor for acute exacerbation in their respiratory status.

There will be a 2 week run in period at the beginning of the study, so that acute respiratory exacerbations will only be considered toward the study endpoint after the first 2 weeks on study. Patients with intrathoracic progression of their cancer or continued ≥grade 3 study-related adverse events without improvement with dose reduction or drug interruption will be taken off study and followed as per standard of care. Drug re-escalations will not be permitted. Acute exacerbations will be treated at the physician's discretion.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Nintedanib (BIBF 1120)

Dosing and Administration
Initial dose of nintedanib will be 150 mg two times per day orally according to study protocol. The capsules of the defined dose should be swallowed unchewed with a glass of water of about 250 mL. If taken twice daily the dose interval should be around 12 hours at the same times every day, usually in the morning and the evening. Because nintedanib may cause stomach discomfort, it is

recommended to take the drug after food intake. See Section 11 for dose selection and reductions.

- If vomiting occurs during the course of treatment, patients should not take an additional dose of study drug. They should resume treatment with the next scheduled dose.
- If a patient forgets to take one or several doses of nintedanib he/she should proceed with the intake of medication according to the predefined schedule and take the next scheduled dose when it is due. No catch up of missed doses is permitted.

Supply, Labeling, and Packaging

Primary study material will be capsules containing 150mg or 100mg of nintedanib, and matching placebo. All study medication will be packaged in bottles with child-resistant closure. All bottles will be labeled with a unique identifier for drug accountability, and will be labeled according to site's regulatory requirements. The drug will be supplied to the pharmacy by Boehringer Ingelheim packaged and labeled in double blind fashion. The unblinded pharmacist at the site will be sent a list of medication numbers and the associated treatment (active or placebo). The unblinded pharmacist will be responsible to assign the correct treatment to the patient based on the randomization. The pharmacy will maintain adequate control of the medication stock to ensure that the medication is stored appropriately and the correct treatment is dispensed based on the randomization assignment.

Drug supplies will be labeled in the following way (minimum):

- Study protocol number
- A description of the contents
- Expiration date
- Directions to use
- Instructions for storage
- Caution: New Drug – Limited by Federal (or United States) law to investigational use.
- "for clinical trial use only"
- "keep out of reach of children"
- "Sponsor name"
- Medication Identification Number

A designated pharmacist will be unblinded. He or she will be responsible for choosing the correct treatment of drug per the patient's randomization assignment. It would be critical that no one blinded on the trial have access to this documentation.

At visit 2 (See Section 10), patients who qualify for the study will be randomized to one of 2 treatment arms, placebo or nintedanib. Study drug will be dispensed every 6 weeks (on day 1 and week 6 of therapy). The medication for the re-supply will be packaged in an identical manner as the medication of the initial supply. The prednisone taper will be provided to the patient on day 1.

Storage and Stability

Nintedanib capsules will be stored in their original package under the recommended storage conditions, ie. at room temperature (between 15C and 30C) at the study site. The investigation product must be stored securely (eg. in a locked cupboard or at a pharmacy.)

Drug Distribution

Drug supplies will be provided by Boehringer Ingelheim Pharmaceuticals, Inc. No supplies will be shipped until regulatory approval has been obtained. Boehringer Ingelheim or a designated clinical supplies distribution vendor such as Almac Clinical Supplies will ship, upon regulatory approval and at the request of the sponsor, an initial stock to the site pharmacy, to have on had for any future patient randomizations.

The site pharmacy will be responsible for maintaining adequate stock of medication and as necessary will complete a Drug Request Form to be sent to BI or designated clinical supplies distribution vendor such as Almac Clinical Supplies. At least 5 working days should be allowed for drug shipment. There are no shipments on Fridays or holidays.

Adherence

A pill diary will be used to track adherence. The patient will be asked to bring in the pill diary and any used/unused drug bottles during treatment as noted in Table 10.1 (See Appendix D for Pill Diary.).

Drug Return/Destruction

Partially or completely used pill bottles and tablets and unused drug should be sent to pharmacy and discarded according to institutional guidelines, and their disposition should be recorded on an investigational drug accountability form. Drug can be destroyed on site if proper accountability of the destruction is maintained (number of pills, expiration date, lot number, etc.) as well as documentation that the drug was destroyed according to the institution's SOP. Boehringer Ingelheim will need to obtain copies of the destruction and a memo stating what was destroyed (lot number and quantity) as well as a copy of the institution's destruction SOP.

5.2 Placebo

The capsules should be swallowed unchewed with a glass of water of about 250 mL. If taken twice daily the dose interval should be of around 12 hours at the same times every day, usually in the morning and the evening after food intake. 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. See Section 11 for dose selection and reductions.

5.3 Concomitant Medications

Prednisone Taper

The prednisone dose will be standardized at 40mg prednisone daily for 2 weeks, followed by a strict dose taper of 10mg every 2 weeks for 4 weeks, followed by 10mg for one week and 5mg for one week, for a total duration on prednisone of 8 weeks. The entire prednisone taper will be provided to the patient at initiation of treatment.

5.4.Summary of Pharmaceutical Information for Nintedanib and Placebo

NINTEDANIB	
Substance (INN):	Not assigned
Pharmaceutical form:	Soft gelatine capsule
Pharmaceutical code	Nintedanib
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	100 mg and 150 mg capsules
Daily dose:	300 mg (150 mg twice daily), dose reduction according to section 11
Duration of use:	Continuous daily dosing for a total of 12 weeks or until criteria for interruption of treatment (section 11) are met.
Route of administration:	Oral
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)
PLACEBO	
Substance (INN):	Not applicable
Pharmaceutical form:	Soft gelatine capsule
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Placebo contains 0 mg of nintedanib in capsules matching 100 mg and 150 mg of nintedanib
Daily dose:	Capsules matching 300 mg of nintedanib (150 mg twice daily), dose reduction according to section 11
Duration of use:	Continuous daily dosing for 12 weeks or until criteria for interruption of treatment (section 11) are met.
Route of administration:	Oral
Posology:	Twice daily (to be swallowed unchewed with a glass of liquid of about 250 mL with a dose interval of 12 hours at the same times every day, usually in the morning and the evening after food intake)

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Inclusion Criteria:

- Histologically/cytologically proven primary thoracic or breast malignancy, lymphoma or lung metastases (which are not required to be biopsy-proven) treated with definitive intent
- Prior treatment with thoracic radiotherapy completed > 4 weeks and ≤ 9 months prior to enrollment
- Radiographic evidence of radiation pneumonitis on a CT scan of the chest with or without contrast
- Newly diagnosed clinical grade 2 or higher radiation pneumonitis according to CTCAE version 4.0 criteria (See Appendix A)
- Age ≥ 18 years
- Written informed consent signed prior to entry into the study
- KPS ≥ 70 %
- Reduction of any acute toxicity from radiation treatment to grade 1

6.2 Exclusion Criteria:

- Current oral steroid use > 4 weeks prior to registration
- Ongoing treatment with radiotherapy to thorax, cytotoxic or biological therapies for this malignancy, except the following therapies which are permitted: Pembrolizumab, Nivolumab, Afatinib and all hormonal therapies
- Mean esophageal radiation dose > 45 Gy
- Diagnosis of diffuse radiation pneumonitis
- Untreated or symptomatic brain metastases or leptomeningeal disease
- Liver metastases
- Other active malignancies requiring oncologic treatment (Note: non-melanoma skin cancer, superficial bladder cancer, etc. are eligible)
- Radiographic evidence of cavitary or necrotic tumor and local invasion of major blood vessels
- Active chronic Hepatitis C and/or B infection
- Gastrointestinal disorders that would interfere with drug absorption
- AST>1.5xULN, ALT >1.5xULN and Bilirubin >1.5xULN
- ≥ Grade 2 proteinuria, creatinine >1.5x ULN or GFR < 45 ml/min
- Other investigational therapy received within 8 weeks prior to screening visit
- Pregnant women or women who are breast feeding or of child bearing potential not using a highly effective method of birth control for at least one month prior to enrollment[1]
- Sexually active males not committing to birth control during the course of the study (except if their partner is not of childbearing potential)
- Conditions that may affect the patient's ability to participate in this trial, e.g. known or suspected active alcohol or drug abuse
- Inherited predisposition to bleeding or thrombosis, INR > 2, PT and PTT > 1.5x ULN
- History of bleeding disorders or thrombotic events, e.g. hemorrhagic or thrombotic events within 12 months, clinically significant or tumor-related hemoptysis, active gastrointestinal bleeding or ulcers or major injuries or surgery

- ANC < 1.5 K/mcL, Platelets < 100 K/mcL, Hemoglobin < 9.0 g/dl
- Concomitant treatment with any of the following drugs: azathioprine, cyclophosphamide, cyclosporine, pirfenidone, full dose anticoagulation (vitamin K antagonists, dabigatran, heparin, etc.), fibrinolysis and high dose anti-platelet therapy (ex. Plavix 150mg)[2]
- Myocardial infarction or unstable angina within 6 or 1 month of starting nintedanib treatment, respectively
- Known inherited predisposition to thrombosis
- Patient with a history of a thrombotic event within 12 months of starting nintedanib treatment
- Known predisposition to bleeding
- Patients with severe hepatic impairment
- History of a gastrointestinal perforation

[1]Patients will be considered to be of childbearing potential unless surgically sterilized by hysterectomy or bilateral tubal ligation/salpingectomy, or post-menopausal for at least two years Women of childbearing potential who are sexually active and not using a highly effective method of birth control before the trial for at least one month, during the trial, and for at least three months after the end of active therapy are not allowed to participate in the trial. A highly effective method of birth control is defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, intrauterine devices (IUDs), sexual abstinence or vasectomised partner.

[2]Prophylactic low dose heparin, heparin flush for maintenance of intravenous devices, prophylactic use of anti-platelet therapy (e.g. acetyl salicylic acid up to 325mg/d, clopidogrel 75mg/d, or equivalent doses) should be allowed.

7.0 RECRUITMENT PLAN

68 participants will be enrolled over 4 years of accrual.

Investigators and their research teams will serve as the primary recruiters for this study. A member of the patient's treatment team, the protocol investigator, or research team will identify potential research participants. If the investigator is part of the treatment team, he/she will screen the patient as to eligibility and will discuss the study and the possibility of enrollment in the research study with the patient. The preliminary screen of eligibility will be confirmation of the diagnosis of grade 2 or higher radiation pneumonitis and history of a proven primary thoracic malignancy or lung metastases treated with definitive intent. Written informed consent for the study will be signed before registration and treatment. Minorities and women are well represented in the thoracic oncology/radiation oncology clinics, and we expect that they will be well represented in the trial accrual.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further assess eligibility. They will use the information provided by the patient and or

medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

Travel Reimbursement will be available for participants at both MSKCC and the external sites as outlined in the travel information form.

8.0 PRETREATMENT EVALUATION

The following tests must be completed within 21 days prior to treatment start, except where indicated.

- Full medical history
- Review of concomitant medications within 14 days of treatment start
- Physical examination, complete vital signs (pulse, blood pressure, temperature, respiratory rate, O_2 saturation, weight).
- Performance status by KPS or ECOG
- Baseline assessment with high resolution CT scan of the with or without contrast
- Serum pregnancy test (if applicable) and within 14 days of treatment start
- Complete blood count with differentiation and within 14 days of treatment start
- Complete metabolic panel (glucose, blood urea nitrogen,, creatinine, sodium, potassium, chloride, bicarbonate, calcium, magnesium, total protein, albumin, total bilirubin, alkaline phosphatase, ALT, AST) and within 14 days of treatment start
- Coagulation parameters (PT, PTT, INR)
- Urinalysis
- Blood samples for biomarkers (see Section 10 for more details)
- 6 minute walk test with pulse oximetry
- PFTs
- SGRQ
- Pro-CTCAE Questionnaire
- Electrocardiogram

9.0 TREATMENT/INTERVENTION PLAN

This is a randomized, double blinded, placebo controlled phase II study using nintedanib versus placebo in combination with a prednisone taper in patients with grade 2 or higher radiation pneumonitis. The primary endpoint is a decrease in proportion of patients who had 1 or more acute exacerbations within 12 months from 50% (in the control arm: placebo + prednisone taper) to 25% (in the treatment arm: nintedanib + prednisone taper).

Prior to the initiation of treatment, patients will be randomized 1:1 to the treatment or control arm (See Section 15 regarding randomization). The initial dose of nintedanib will be 150mg two times per day orally according to study protocol. The study drug (nintedanib or placebo) will be taken for 12 weeks. Patients will be given a prednisone taper (40mg prednisone daily for 2 weeks, followed by a strict dose taper of 10mg every 2 weeks for 4 weeks, followed by 10mg for one week and 5mg for one week, for a total duration on prednisone of 8 weeks). Please see Table 9.1 which outlines the daily study drug administration. Dose reductions and omissions for study drug will be allowed for toxicities according to guidelines specified in Section 11.0.

After the completion of therapy, patients will be followed up to 52 weeks with serial testing (see Section 10 regarding assessments while on study).

Table 9.1: Study drug (Nintedanib or Placebo) and prednisone administration

Week Schedule	Day 1-7
Week 1	Study drug+ Prednisone 40mg
Week 2	Study drug+ prednisone 40mg
Week 3	Study drug+ prednisone 30mg
Week 4	Study drug+ prednisone 30mg
Week 5	Study drug+ prednisone 20mg
Week 6	Study drug+ prednisone 20mg
Week 7	Study drug+ prednisone 10mg
Week 8	Study drug+ prednisone 5mg
Week 9-12	Study drug
Weeks 13-52	Off therapy

9.1 Blinding and Emergency Unblinding Procedures

Blinding: Study medication will be identified by a medication code number. Packaging and labeling will be otherwise identical. Color, size and shape of nintedanib capsules and placebo capsules are indistinguishable but the 150 mg dose strength will be different from the 100 mg dose strength (for active and placebo). Patients, investigators and everyone involved in analyzing or with an interest in this double-blind study (sponsor trial team, steering committee, service providers) will remain

blinded with regard to the randomized treatment assignments until after database lock. Only the pharmacist will have access to unblinded information in order to distribute the drugs appropriately to patients.

Procedures for Emergency Un-blinding: The code break may be used in emergency situations when the identity of the study drug must be known to the investigator in order to provide appropriate medical treatment or if required to assure safety of trial participants. If the code break is done due to an SAE, this should be reported to BI with the unblinding information. In addition, Dr. Moore will have emergency unblinding envelopes. For multicenter sites, the code break will be performed by the pharmacist at the site. If the situations call for use of the emergency unblinding and the pharmacist is unable to perform the code break, the site will be required to call and/or send an urgent email to Dr. Moore and his research staff who will have emergency unblinding envelopes. All results of unblinding will be immediately relayed to the treating physician.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Refer to **Table 10.1** for the study calendar, which outlines study assessments.

	Table 10.1: Study Calendar										
Visit	Screening 1	2	3	4	5	6	7	8	9	10	EOT[6]
Days	Before -21	1	22	43	64	85	135	181	271	391	
Week of treatment		1	3[5]	6	9[5]	12	4.5 months from txt start[7]	6 months	9 months	13 months	
Time window allowed (days)	Before -21 days		+/-7	+/-7	+/-7	+/-7	+/-14	+/-14	+/-14	+/-14	+/-14
Informed Consent, Demographics, Medical History	X										
Inclusion/Exclusion criteria	X	X									
Randomization at MSK		X									
Vital signs[1] and Physical Examination	X	X	X	X	X	X	X	X	X	X	X
Recording of adverse events or exacerbations	X		X	X	X	X	X	X	X	X	X
Laboratory testing[2]	X		X	X	X	X		X	X	X	X
Pregnancy test (if applicable)	X										
PFTs	X					X		X	X	X	X
6 minute walk test	X					X		X	X	X	X
Electrocardiogram	X										X
SGRQ/PRO-CTCAE	X			X		X		X	X	X	X
Blood markers[3]	X			X		X		X			
High resolution CT scan w/ or w/o	X			X		X		X	X	X	X

contrast											
Study drug dispensation		X		X							
Prednisone taper dispensation		X									
Compliance/drug accountability			X	X		X					X
Vital status assessment[4]										X	X

1. Including pulse, blood pressure, temperature, respiratory rate, O_2 saturation, weight
2. Lab tests with CBC and CMP (glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, magnesium, total protein, albumin, total bilirubin, alkaline phosphatase, ALT, AST).
3. Blood markers include: TGF alpha, TGF beta, TNF-alpha, IL-6, IL-8, alpha 2 macroglobulin, VEGF, soluble VEGF receptor 2, PDGF, PDGF receptor, FGF23, and bFGF Vital status at 52 weeks should be available for all patients.
4. Patients who end treatment early should attend visits as planned until 52 weeks
5. The week 3 and 9 visits are optional. Only laboratory testing and a call with the treating team (i.e. physician or nurse) to assess side effects is required.
6. EOT: end of treatment visit, within 14 calendar days after permanent termination of trial drug (nintedanib or placebo) if not week 12. If permanent discontinuation of study drug falls on a scheduled visit, examinations as defined for EOT should be performed instead of the examinations of the scheduled visit.
7. The 4.5 month visit is optional. Only a call with the treating team (i.e. physician or nurse) to assess side effects is required.

Safety Evaluations:
Patients enrolled in this study will require regular office visits to evaluate the safety and tolerability of the study drug in combination with steroids. Patients will be evaluated clinically and with standard laboratory tests as depicted in **Table 10.1**. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, and laboratory measurements.

Evaluations of Acute Pulmonary Exacerbations:
A detailed report of acute exacerbation of symptoms will be documented and will include detailed information regarding the clinical course, dates, signs and symptoms, laboratory, lung function, imaging results, and treatment provided. Careful attention should be given to the attribution of these events. Symptoms that are the result of an increase or decrease in steroid dose should not be recorded as pulmonary exacerbation.

Study Evaluations:
Patients will be followed by PFTs, 6 minute walk tests with pulse oximetry, patient reported outcomes as assessed by SGRQ and PRO-CTCAE, high resolution CT scans to assess pulmonary fibrosis, and biomarker studies. Patients will continue follow up for approximately 1 year as per protocol (See **Table 10.1**).

Evaluations after Early Discontinuation:
In case a patient has to discontinue trial drug, for whatever reason, prior to having completed the 12 weeks of treatment OR the patient comes off study prior to competing approximately 1 year of follow up, patients will be asked to continue to follow up for the following evaluations:

- High resolution CT imaging studies
- PFTs

- 6 minute walk test
- Laboratory tests
- Physical exams, recording of adverse events, and vitals (pulse, blood pressure, temperature, respiratory rate, O_2 saturation, weight)
- EOT appointment (see Table 10.1)
- Vital status at approximately 1 year from start of treatment

Note: If a patient discontinued the trial before completing the first two weeks of treatment, this patient will be replaced.

11.0 TOXICITIES/SIDE EFFECT

Rescue medication to reverse the actions of nintedanib is not available. Potential side effects of nintedanib have to be treated symptomatically. Specific treatments and nintedanib dose modifications will be made according the criteria outlined below for toxicities which are felt to be related to nintedanib.

11.1 Management of Nintedanib Related Toxicities

See section 17 for specifics of reporting adverse events to BI.

11.1.1 Management of Diarrhea

CTCAE 4.0 Grade	**Action for NINTEDANIB and Anti-diarrheal treatment**	**Action for NINTEDANIB after recovery of diarrhea** [1]
Grade 1	Continue nintedanib Consider anti-diarrheal medicines e.g., 4 mg loperamide followed by 2 mg after each loose stool or every 2-4 hours to a maximum of 16 mg/day until bowel movements cease for 12 hours	no dose reduction of nintedanib
Grade 2	Continue nintedanib Continue anti-diarrheal medicines, if grade 2 persists for ≥48 hours assess for dehydration and electrolyte imbalance, consider IV fluids and electrolyte	If grade 2 diarrhea persists for >=48 hours, nintedanib treatment should be interrupted until recovered to grade ≤1 followed by dose

	replacement as clinically indicated.	reduction.
Grade 2 > 7 days despite optimal medical management or Grade ≥ 3 or any diarrheal episode 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. Consider stool cultures and clostridium botulinum toxins to exclude any infection; aggressive IV fluid replacement ≥ep hrs, hospitalization as clinically indicated, consider referral to a GI specialist to rule out potential differential diagnoses.	reduce nintedanib dose to 100 mg BID **after recovery of diarrhea** [1]
Second 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.
[2]The recommended dose of loperamide is 4mg at first onset, followed by 2mg every 2-4 hours until diarrhea free for 12 hours

11.1.2 Management of Liver Enzyme Elevations

If liver enzyme elevations are considered to be related to nintedanib the following algorithm should be followed. Please also refer to and incorporate DILI guidelines as provided in section 17.3.1, page 43. The recommendations follow the FDA Guidance for Industry for Drug-Induced Liver Injury:

AST/ALT increase to:	**Plan:**
AST/ALT increase to 1.5x-<3x ULN	Continue as planned
AST or ALT increase to 3x-5x ULN and no signs of severe liver disease[1]	• Reduce nintedanib to 100 mg bid or interrupt treatment (to be decided by Investigator, based on individual risk assessment.) • Close monitoring[2] • Re-test ALT and AST, as well as alkaline phosphatase, total bilirubin, and eosinophils within 48 to 72 hours, then approximately 7 days, then approximately 2 weeks, and assess signs of severe liver disease • After 2 weeks: If AST and ALT > 3x ULN **PERMANENTLY discontinue nintedanib treatment**. If AST/ALT< 3x ULN, continue

	treatment at reduced dose of 100mg PO BID. Monitor lab every 2 weeks for at least 8 weeks
AST or ALT increase to 5x-8x ULN and no signs of severe liver disease	• Interrupt treatment • Close monitoring[2] • Re-test ALT and AST, as well as alkaline phosphatase, total bilirubin, and eosinophils within 48 to 72 hours, then approximately 7 days, then approximately 2 weeks, and assess signs of severe liver disease • After 2 weeks: If AST and ALT > 3x ULN **PERMANENTLY discontinue nintedanib treatment**. If AST/ALT< 3x ULN, continue treatment at reduced dose of 100mg PO BID. Monitor lab every 2 weeks for at least 8 weeks
AST or ALT increase to to ≥ 3xULN or signs of severe liver disease or if a second episode occurs	• **PERMANENTLY discontinue nintedanib treatment.**

1: Signs of severe liver damage
- Symptoms: Increase of liver transaminases is paralleled by appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) or
- Total bilirubin > 1.5xULN or
- INR > 1.5xULN

2: It is recommended to ensure close observation as follows:
- Monitor 2x to 3x per week all of the following: ALT ,AST, alkaline phosphatase, total bilirubin, eosinophils
- Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
- Re-query detailed history of symptoms and prior or concurrent diseases.
- Re-query history of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Rule out all of the following: acute viral hepatitis types A, B, C, D, and E; autoimmune hepatitis; alcoholic hepatitis; NASH (non-alcoholic fatty hepatitis); hypoxic/ischemic hepatopathy; and biliary tract disease.
- Re-query about exposure to environmental chemical agents.
- Consider additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Consider gastroenterology or hepatology consultations

11.1.3 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 4.0 Grade	Antiemetic treatment	Dose of Nintedanib
Nausea =1	No antiemetic treatment	No dose reduction

CTCAE 4.0 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 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** **Second 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* Treatment with nintedanib discontinued and resumed upon recovery[1] Treatment as above	nintedanib: dose reduction[2] **PERMANENT discontinuation of nintedanib treatment**

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

11.1.4 Management of Non-Hematologic Adverse Events other than Emesis, Liver Enzyme Elevations, and Diarrhea

CTCAE Grade 3 or 4	Nintedanib
First Episode	Stop nintedanib treatment until recovery[1] Then nintedanib dose reduction[2]
Second 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 reduction: from 150 mg bid to 100 mg bid

11.1.5 Management of Hematologic Adverse Events

CTCAE 4.0	Nintedanib
Platelets < 50 000 K/mcL with bleeding	Stop nintedanib treatment until recovery[1] Then nintedanib dose reduction[2]

Neutropenia of any grade / duration accompanied by fever > 38.5°C or Neutropenia grade 4 without fever > 7 days duration	Stop nintedanib treatment until recovery[1] Then nintedanib dose reduction[2]

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

11.2 Additional Precautions for Nintedanib

During treatment with nintedanib /placebo, all study patients will be advised to avoid sun exposure or artificial UVA/UVB radiation in tanning booths. If exposure to sunlight cannot be avoided, protective clothing and broad spectrum (UVA/UVB) sunscreens should be used. After discontinuation of nintedanib /placebo treatment all protective measures should be continued for at least 2 weeks. Because the concentration of nintedanib in semen is unknown, males receiving nintedanib and having sexual intercourse with females of childbearing potential should use latex condoms.

11.3 Management of Acute Pulmonary Exacerbations

In case of acute pulmonary exacerbation (as defined in section 2), all treatment options considered adequate by the Investigator /caregiver are allowed (including but not limited to increasing the dose of steroids, albuterol/ ipratropium/steroid inhalers, use of immunosuppressants). These drugs are then discontinued at the Investigator's discretion. If an acute exacerbation occurs within the first 12 weeks, nintedanib will be continued unless the patient develops drug related ≥ grade 3 toxicity. The patient may interrupt study treatment for up to 4 weeks if this is considered necessary (e.g. if short-term full anticoagulation is performed).

11. Summary of Allowed Dose Reductions/Interruptions and Reinitiating of Therapy

In the case of adverse events as noted above, nintedanib will be dose reduced to 100mg BID. Drug interruptions may be necessary to allow diarrhea or liver enzyme elevations to return to an acceptable level (as described above).

Drug interruptions are limited to a **maximum of 4 weeks**. If the adverse event does not resolve on a reduced dose level of nintedanib 100mg BID, nintedanib will be permanently discontinued. Nintedanib dose re-escalations will not be permitted. Any deviations from this must be discussed with the sponsor.

11.5 Definitions of Adverse Events and Worsening of Pre-Existing Conditions

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

Serious Adverse Event

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalization, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Patients may be hospitalized for administrative or social reasons during the trial (e.g. days on which infusion takes place, long distance from home to site). These and other hospitalizations planned at the beginning of the trial do not need to be reported as an SAE.

Severity of Adverse Event

The severity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.

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.

The causal relationship must be provided by the investigator for all potential trial drugs, i.e. nintedanib, prednisone, or/and placebo.

Malignant Disease Progression

Symptoms from underlying intrathoracic cancer progression should not be recorded as an AE. Patients who have intrathoracic progression of their cancer must be taken off study but followed per standard of care.

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 reported as an adverse event. Examples of worsening of a preexisting 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 or 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

Reporting of Adverse Events to Boehringer Ingelheim by MSK ONLY
Please also refer to section 17.3 regarding details about AE reporting by MSK to Boehringer Ingelheim. Boehringer Ingelheim must be informed of all SAEs within five (5) calendar days upon knowledge of a fatal or immediately life-threatening event and within ten (10) calendar days upon knowledge of other SAEs and AEs of special interest.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Acute Pulmonary Exacerbations

The primary efficacy endpoint is to determine whether 12 weeks of nintedanib in combination with oral prednisone will decrease the proportion of patients with at least one subsequent acute exacerbation within 1 year in comparison to prednisone taper alone

Definition: Unexplained clinical features including all the following:

- Development or worsening of cough, dyspnea, or hypoxia
- New diffuse pulmonary infiltrates on chest X-ray or parenchymal changes on high resolution CT scan (with or without contrast) compared to baseline
- No significant pneumothorax or pleural effusion
- No evidence of left sided heart failure, or pulmonary emboli,

Exacerbation criteria will be assessed. Detailed information will be collected on summary of clinical course, signs and symptoms, laboratory, lung function, imaging results, and treatment provided. The importance of early reporting of worsening dyspnea or new respiratory symptoms should be stressed to the patients.

12.2 Pulmonary Function Testing

Measures of FEV1/FVC:

Spirometry devices will be utilized. All spirometers will be required to meet the ATS criteria, including regular calibration of the calibration pump and daily calibration of the spirometer. Testing will be conducted while the patient is in a seated position. After a period of tidal breathing, the patients will be asked to inhale to total lung capacity and exhale forcefully for at least 6 seconds into a flow meter.

The following general guidelines apply to all the patients:

- Pulmonary function testing will be performed around the same time each day (+/- 3 hours)
- Strenuous activity is prohibited at least 12 hours prior to pulmonary function testing
- Smoking will not be allowed in the 30 minutes period prior to spirometry
- Short acting bronchodilators must be held for >8hrs prior to pulmonary function testing, and long acting bronchodilators must be held >24 hours prior to pulmonary function testing

- Patients should avoid cold temperatures, environmental smoke, dust, areas with strong odors, coffee, tea, chocolate, cola, caffeine containing beverages, alcohol containing drinks, and ice cold beverages the morning of the pulmonary function testing period.

Six Minute Walk Test (6 MWT) with Pulse Oximetry:

This test will be conducted according to the ATS criteria. Dyspnea will be recorded on a Borg Scale as described in the ATS guidelines. If oxygen is needed at visit 1, the flow rate will be determined and the same flow should be used in all further walks by the patient. Patients with resting heart rates of 120 beats per minute, or systolic blood pressure of >180mmHg, or diastolic blood pressure >100mgHg should not perform the 6 MWT. The distance a patient can walk on a measured course (a straight 100 foot hallway) in six minutes will be measured. If needed, rest periods are permitted. During the 6 minute walk test, pulse oximetry will be used to monitor oxygen saturation at rest and with exercise. The 0_2 flow rate required to allow the patient to complete the 6 minute walk test without significant desaturation (SP02<83%) will be recorded. **Diffusion (DLCO) by Single Breath Helium Technique:**

Evaluation of diffusion will be done by a single breath carbon monoxide diffusion capacity according to ATS task force recommendations. Patients will be asked to inhale a volume of gas (approximately 10% Helium, 0.3% Carbon Monoxide, and 21% Oxygen, with balance N_2) to total lung capacity and hold their breath for 10 seconds. FVC maneuver will then be performed. The difference in the concentration of inhaled vs. exhaled carbon monoxide will be used to calculate the diffusing capacity.

12.3 Safety of Nintedanib

At every visit, safety will be monitored by:

- Vital signs at each clinic visit (including blood pressure, pulse, temperature, respiratory rate, O_2 saturation). Blood pressure will be measured with the patient seated after having rested for at least 5 minutes
- Complete physical exam including weight at each clinic visit
- Incidence and intensity of adverse events including hospitalizations at each clinic visit
- Clinical laboratory tests at each visit including:
    - hematology: red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, white blood cell count and differential, absolute neutrophil count, and platelets
    - biochemistry: Glucose, sodium, potassium, calcium, magnesium, creatinine, AST, ALT, albumin, total protein, alkaline phosphatase, total bilirubin, blood urea nitrogen, chloride, bicarbonate
    - BHCG only at visit 1 for women of childbearing potential

12.4 Quality of Life

St George's Respiratory Questionnaire (STRQ) and PRO-CTCAE
Both studies will be completed at baseline and on weeks 6 and 12 during treatment and then approximately 6, 9, and 13 months from start of treatment. The SGRQ is a respiratory specific questionnaire designed for use in patients with respiratory diseases.[32.33] The PRO-CTCAE is an electronic based system for patient self reporting of symptom adverse events in an effort to improve the accuracy of grading of this class of adverse events.

The patients will be carefully instructed on how to fill the questionnaires. For each visit, the patients should fill in the SGRQ before any other procedure. The patient should be allowed to sit alone and fill in the questionnaire in a relaxed and informal way. Approximately 30 minutes will be required to fill the questionnaire. The staff should explain to the patient how to use the SGRQ and PRO-CTCAE but should never help the patient choose an answer. The staff must be neutral in response to the patient's answers. The questionnaire should be checked for completeness. Patients may be asked to further complete the questionnaire if there are missing items but should not be forced to answer questions they are deliberately omitted.

12.5 Pulmonary Fibrosis

High Resolution CT scans

High resolution CT scans of the chest (with or without contrast) in prone positions will be performed with or without IV contrast during end inspiration. Patients will be divided into subjects with no pulmonary fibrosis or with minimal, mild, moderate, or severe pulmonary fibrosis based on consensus reading of HRCT scans by an independent radiologist. Imaging will be performed at baseline and on weeks 6 and 12 during treatment, then approximately 6, 9, and 13 months from treatment start.

12.6 Serum Markers

The following serum markers will be evaluated as potential biomarkers of nintedanib activity

1. TGF Alpha
2. TGF Beta
3. TNF-Alpha
4. IL-6
5. IL-8
6. Alpha 2 macroglobulin
7. VEGF
8. Soluble VEGF receptor 2
9. PDGF
10. PDGF receptor
11. FGF23
12. bFGF

Samples will be taken and processed at baseline and at weeks 6 and 12 during treatment, and then 6 months from start of treatment.

- Serum levels for biomarkers 1-11 will be tested in MSK's Core Lab on a custom designed chemiluminescent array chip. The workflow, procedures, and technical equipment including a

high resolution automated camera and read out system will be used. The custom designed chip will be validated according to standard procedures

- Participating multicenter sites (Lehigh Valley, MDACC and BWH) will collect and process samples to serum. Serum samples will be temporarily stored at the multicenter site and batch shipped to MSKCC for analysis.
    - Samples may be shipped overnight on dry ice to the following address:

      ATTN: Rosalind Dick-Godfrey

      Memorial Sloan Kettering Cancer Center

      1275 York Avenue

      New York, NY 10065

13.0 CRITERIA FOR REMOVAL FROM STUDY:

Patients should **permanently** discontinue treatment with nintedanib in the event of:

- Unequivocal **intrathoracic** cancer recurrence
- Intolerable Adverse Events (e.g. CTCAE v4.0 grade 3 or 4) that cannot be managed by dose reduction (See Section 11 for more details)
- Further dose reductions considered necessary but not allowed according to the protocol
- Pregnancy[1]
- Withdrawal of informed consent[2]
- If the treating physician determines that it is in the best interest of the patient to stop study drug
- Non-compliance with the defined treatment plan

It is **highly recommended** to discontinue treatment with nintedanib in the event of:

- Planned major surgery, including any abdominal or intestinal surgery
- Patients who require full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, heparin, etc), or high-dose antiplatelet therapy. Prophylactic low dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device (e.g. enoxaparin 4000 I.U. s.c. per day), as well as prophylactic use of antiplatelet therapy (e.g. acetyl salicylic acid up to 325 mg/d, or clopidogrel at 75 mg/d, or equivalent doses of other antiplatelet therapy) should be allowed.
- Major thrombo-embolic events including stroke, deep vein thrombosis, pulmonary embolism, myocardial infarction
- Major bleeding event including hemorrhagic CNS event, gross/frank hemoptysis or hematuria, active gastro-intestinal bleeding or ulcer

Patients should be removed from study after treatment ends (week 13-52) in the event of:

- Death
- Unequivocal **intrathoracic** cancer recurrence
- Pregnancy[1]

- Withdrawal of informed consent[2]
- Non-compliance with the defined follow up studies

[1]**Pregnancy:** In case of a patient or the patient's partner becoming pregnant during the trial the investigational drug has to be immediately stopped and the patients to be followed-up until birth or otherwise termination of the pregnancy. The patient needs to be unblinded immediately, and repeat counseling on birth defect risk must be offered in case she was on active drug.

[2]**Consent withdrawn:** in case the patient withdraws his/her consent for taking drug, it is of utmost importance for the robustness and integrity of the trial results that his/her safety data are recorded until the end of the 52 weeks period. Thus all patients will be asked to follow their visit schedule until 52 weeks.

Patients who discontinue from this trial are not allowed to be reenrolled in this trial. Patients who discontinue medication within the first four weeks (during the washout period) will be replaced. For the patients who stopped trial before randomization, their data will be part of the description of screening population.

14.0 BIOSTATISTICS

This is a Phase II, randomized, double blind, placebo-controlled trial designed to compare the efficacy of prednisone taper in combination with nintedanib versus prednisone alone in patients with radiation pneumonitis, as measured by a decrease in the risk of experiencing at least one acute exacerbation within 12 months after the initial exacerbation.

Patients will be randomized to one of the two treatment arms, stratified by a) grade of RP (2 versus 3/4) and b) initiation of steroids up to 4 weeks prior to enrollment vs steroid-naïve

Because we expect that a non-negligible proportion of the patients will drop out, have cancer recurrence, or die during the planned 12 months follow up, the primary analysis will be a time to event one, which will account for the actual amount of individual follow-up. The two treatment groups will be compared with respect to their probability of being "free of exacerbation" at 12 months, using a test based on difference in survival outcomes at a fixed time point[34]. Start of follow-up will be 2 weeks following treatment start, in order to allow a period for resolving the initial exacerbation that prompted enrollment in the trial. Patients who are lost to follow up, experience cancer recurrence, die, or drop out of the study for any reason except acute exacerbations will be censored at the time of the respective events. Therefore, all patients randomized who do not discontinue medication during the first four weeks of treatment (wash-out period) will be included in the analysis of the primary objective. Patients who discontinue treatment during the wash-out period will be replaced; we anticipate this to happen in a very small number of cases.

Secondary endpoints (PFT, 6 minute walk test, radiation fibrosis, QOL score) will be presented separately for the two treatment groups using descriptive statistics, for each time point when they are collected. Percent change from baseline to each time point will be compared between groups using the non-parametric Wilcoxon signed-rank test for continuous variables (PFT, 6 minute walk test, QOL score) and McNemar's test for categorical variables (radiation fibrosis). Furthermore, we will compare the general trajectory of the measurements over time using mixed models, which naturally incorporate missing values and correlations between individual measurements.

SGRQ instrument is designed to measure health impairment in patients with asthma and COPD and is also recommended in other pulmonary impairments. Part 1 (questions 1-8) consists of a Symptoms score, which assesses patients' perception of their recent respiratory problems. Part 2 (Sections 9-16) consists of an Activity score, which measures disturbances to daily physical activity, in an Impact score, which measures of disturbances of psycho-social function. A total score (the sum of the three components above) is also calculated. The response format varies (some questions are binary, others have a range of answers), and the questions are scored using weights provided by the developer (an Excel-based software is also provided and scoring is done automatically). All scores are expressed as a percentage of overall impairment, where 100 represents worst possible health status and 0 indicates best possible health status. Summary statistics (medians, range) for each score will be calculated, and group comparison will be performed using Wilcoxon sum-rank test.

PRO- CTCAE will include 23 questions regarding the severity of symptoms and their interference with daily activities. Each symptom is measured on a 5-point scale (from 'none'/'not at all' to 'very severe'/'very much'). Each symptom will be studied separately as a continuous variable and group comparisons will be performed using Wilcoxon sum-rank test.

The effects of the serum markers (measured at baseline) on the treatment effect will be evaluated in Cox proportional hazard models. For each serum marker, an interaction term between treatment arm and the baseline value will examine whether the effect of treatment on time to the first acute exacerbation varies as a function of the marker value. Next, we will examine the same hypothesis updating the marker value with serially collected measurements, in time-dependent models.

Average number of acute exacerbations per patient within 1 year, and average number of hospitalizations per patient within 1 year will be compared across treatment arms using Poisson models, accounting for the amount of individual follow-up time.

Sample Size Calculation: Thirty-four evaluable patients will be enrolled in each treatment arm (68 patients total). Patients will be considered evaluable after receiving at least 4 weeks of the study drug. The primary objective of the study is to detect a decrease in the proportion of patients who had at least one acute exacerbation within 12 months from 50% (in the control group: prednisone + placebo) to 25% (in the treatment group: prednisone + nintedanib). This expectation is feasible because nintedanib decreased the incidence of acute exacerbations in IPF patients from 15.7 to 2.4 per 100 patient-years (p=0.02).[22] To approximately assess the power of the test based on 34 patients per treatment arm (68 patients total), we will use a 1-sided log-rank test with alpha=0.1, which has a power of approximately 90% to detect the difference between the two arms assuming the 12-month exacerbation-free rate of 50% vs 75%. This assumes that patients are followed for 12 months, but approximately 25% of all patients are censored during this interval due to cancer recurrence, death or dropping out of study. It is possible that the number of patients enrolled and randomized will be slightly higher, if any patients discontinue treatment during the wash-out period and are replaced.

Accrual Time: With an expected accrual rate of 1-2 patients per month, we anticipate that accrual of 68 patients will be completed in approximately 4 years. Patients will be followed for approximately 12 months from start of treatment.

Stopping Rule for Combination of Nintedanib/Placebo and Concurrent Systemic Therapies: In consideration of the fact that a large cohort will be recruited, this study will be continuously monitored to protect patients from excessive toxicity. For each arm, we anticipate that 26 patients will be added

(though not all of them will receive concurrent immunotherapy or targeted therapies). To protect patients from excessive toxicity from concurrent immunotherapy or targeted therapies, we will use a stopping rule based on the sequential probability ratio test (SPRT). Each arm of the study is monitored for any grade 4 or above toxicities that are judged to be associated with the combination of nintedanib/placebo and concurrent systemic therapies, such as immunotherapy or tyrosine kinase inhibitors. This stopping rule specifies that for each arm, the study will be halted if any of the following conditions occur: >2 unacceptable toxicities/first 9 patients; >3 unacceptable toxicities/first 18 patients or if more than 5 unacceptable toxicities are observed when the last (up to the 26th) patient has completed the trial. This stopping rule has a probability of 0.12 to stop the trial when the true toxicity rate is 10%, and 0.90 when the true toxicity rate is 30%. Note that we may not enroll 26 such patients (i.e., receiving concurrent immunotherapy or targeted therapies) in each arm because that depends on whether the patients had pneumonitis."

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. 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. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

Patients who meet the eligibility criteria will be randomized in a 1:1 ratio to 1 of the 2 treatment arms. A total of 68 patients will be randomized, 34 will receive nintedanib/prednisone taper (Arm A, study arm) and 34 will receive placebo/prednisone taper (Arm B, control arm).
Patients will be stratified at randomization according to the following parameters:

- Grade of RP (2 versus 3/4)
- Initiation of steroids up to 4 weeks prior to enrollment vs steroid-naïve

After consent is obtained and eligibility is established, the CRC will register participants in the CTMS system and randomize participants using the Clinical Research Database (CRDB). Randomization will be accomplished by the method of random permuted block, and will be stratified as noted above. Once the CRC has completed the randomization in CRDB, he/she will enter the blinded arm in CTMS. Next, he/she will email the following individuals in the Department of Epidemiology and Biostatistics with the patient's CTMS generated ID, site, and pharmacy contact at the site: Elyn Riedel, Anne Reiner and Patricia Neary. One of the listed staff will relay the unblinded randomization information from CRDB to the site pharmacy.

16.0 DATA MANAGEMENT ISSUES

A MSK Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into a secure database (Medidata Rave). Source

documentation will be available to support the computerized patient record. The MSK principal investigator will maintain ultimate responsibility for the clinical trial.

16.1 Quality Assurance

Regular 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 rates and extent 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 for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan, where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. 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."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and 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 Deputy Physician-in-Chief, Clinical Research.

The degree of monitoring required will be determined based on level of risk and documented.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by

the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

The following language is only required for multicenter IND trials that include participating sites performing specimen analysis:

Participating sites that are conducting specimen analysis must submit the following documents to MSK before specimens can be shipped to the site:

- Participating Site 1572
- Conflict of Interest forms for Participating Site Investigators on the 1572

Participating sites that are conducting specimen analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSK.

17.0 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 of the possible toxicities and side effects. Alternative, non-protocol, treatment options will be discussed 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, lab work, and serial cardiac monitoring. Specific guidelines for symptom management are in place to protect the study participant.

Human Subjects Involvement and Characteristics: All patients at MSKCC who meet the inclusion criteria will be eligible. 68 patients will be enrolled unto the trial and randomized 1:1 to placebo or nintedanib. Both men and women and members of all ethnic groups are eligible for this trial. Pregnant and breast-feeding women are excluded from this study. This protocol does not include children because the number of children is expected to be limited for the patient population expected to be accrued onto this study. Also, the majority of children are already accessed by a nationwide 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.

Consent Process: All patients who meet the inclusion criteria will be eligible. Participation in the trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines. The informed consent procedure is described in Section 18.0.

Possible Toxicities/ Side-effects: There are risks associated with treatment as described in Section 11.0; however, patients screened for enrollment will be deemed appropriate for treatment independent of this study.

Benefits: nintedanib has the potential to slow pulmonary lung function decline, reduce the number of acute exacerbations and the rate of pulmonary fibrosis compared to prednisone alone. All patients will be receiving a standard prednisone taper which is routinely used in the treatment of radiation pneumonitis.

Costs: Patients will be charged for physician visits, routine laboratory tests and radiologic studies required for monitoring their condition. The patients will not be billed for the study drug, nintedanib. The cost of the pharmacokinetic analysis will be covered by research funds. Pulmonary function studies will be billed to the patient/patient's insurance.

Alternatives: The alternative to this trial would be treatment with steroid taper.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patients' names and any other identifying information will not be used in reports or publications resulting from this study. Other authorized agencies and appropriate internal personnel (e.g. qualified monitors from MSKCC) and external personnel (e.g. qualified monitors from BI (the manufacturer of nintedanib), its authorized agents, the FDA, and/or other governmental agencies) may review patient records as required.

Patient Safety: Patients are monitored by physicians and oncology nurses who are very familiar with clinical trials. In the case of an adverse reaction, immediate medical attention is available. In the evenings and weekends, we have a 24-hour urgent care facility for outpatients. The PI or co-PI will also be available at all times to organize any necessary intervention.

Monitoring of Data to Ensure Safety: This study will be monitored by the institutional IRB. This incorporates an independent data and safety monitoring committee established by arrangement with the National Cancer Institute. The analysis of safety will include all patients' adverse events, including all toxic effects of treatment, will be tabulated individually, and summarized by severity and causality.

17.1 Privacy

17.2 The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

MSK'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

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event

- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

For IND/IDE protocols:
The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

For multicenter trials where MSK is the data coordinating center, please refer to the MSK Multicenter Trial Addendum. All required SAE reporting to the funders and/or drug suppliers will be completed by MSK

17.3 Reporting Adverse Events to BI by MSK ONLY

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 observational phase of 13 months, up until 14 calendar days after permanent termination of the study drug) will be collected, documented on the appropriate CRF(s)/eCRFs, and reported to the BI by **MSK** according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the MSK Site File. In addition, SAEs occurring after the completion of treatment that are related to study treatment must also be collected and reported. SAEs are to be reported using the BI Serious Adverse Event Report Form. Any serious AE, whether or not considered related to the investigational product, and whether or not the investigational product has been administered, must be reported immediately by telephone / fax to BI. Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs), will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the ISF.

Following every such telephone / fax report, the Clinical Monitor or a delegate must provide a written report of the serious or significant AE and any sequelae to the competent Regional Centre according to the appropriate Corporate SOP(s). These narratives, which confirm the information collected by telephone, may give additional information not available at the time of the initial report.

For each adverse event, the investigator will provide the onset, end, intensity, treatment required, outcome, seriousness and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all (S)AEs. Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the (e)CRF. Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the (e)CRF , if they are judged clinically relevant by the investigator.

Responsibilities for SAE reporting to BI

MSK shall report all SAEs, non-serious AEs relevant to a reported SAE and Adverse Events of Special Interest by fax using BI serious adverse event reporting form to BI Unique Entry Point as detailed below in accordance with the following timelines:

- within five (5) calendar days upon receipt of initial and follow-up SAEs containing at least one fatal or immediately life-threatening event;
- within ten (10) calendar days upon receipt of any other initial and follow-up SAEs.

Boehringer Ingelheim Pharmaceuticals, Inc

Boehringer Ingelheim Pharmaceuticals, Inc.

900 Ridgebury Road

Ridgefield, CT 06877

Fax: 1-203-837-4329

17.3.1 Reporting Laboratory Values of Special Interest

The following adverse events need to be reported to Boehringer Ingelheim on a SAE-form and in the same timelines as SAEs:

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

The following are considered as protocol-specified AESI:

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

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

Patients showing above laboratory abnormalities need to be followed up until the protocol specific retreatment criteria have been met and according to Appendix E 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.

The medical evaluation of these results and clinical documentation will need to be provided on request to Boehringer Ingelheim.

18.0 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.

19.0 REFERENCES

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20.0 APPENDICES

Appendix A: CTCAE v 4.0 Criteria for Pneumonitis
Appendix B: St. George's Respiratory Questionnaire
Appendix C: PRO-CTCAE Questionnaire
Appendix D: Nintedanib Patient Diary
Appendix E : DILI Guideline

Appendix F : MRBM General Processing Information v1.0_TT

Appendix G : 2021-018 Myriad RBM Sample Collection Handling and Shipping Guidelines_rev3

Appendix A: CTCAE version 4.0 Criteria for Pneumonitis

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Asymptomatic, clinical or diagnostic observations only; intervention not indicated	Symptomatic, medical intervention indicated, limiting instrumental ADL	Severe symptoms, limiting self care ADL, oxygen indicated	Life threatening respiratory compromise, urgent intervention indicated (ex: tracheotomy or intubation)	Death

Appendix E: DILI Guidance

Procedures for the follow-up of a potential DILI case (Hy's Law case) in IIS with nintedanib (BIBF 1120)

Introduction

Drug-induced liver injury
Drug-induced liver injury (DILI) has been the most frequent single cause of safety-related drug marketing withdrawals for the past 50 years (e.g., iproniazid), continuing to the present (e.g., ticrynafen, benoxaprofen, bromfenac, troglitazone, nefazodone). Accordingly, detection of drug-induced liver injury of an investigational compound has become an important aspect of patient´s safety guarding in drug development.

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

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

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

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

Definition

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

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

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

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

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