A Phase II Randomized, Double-Blind, Placebo-Controlled Study Evaluating Nintedanib Versus Placebo as Prophylaxis against Radiation Pneumonitis in Patients with Unresectable NSCLC Undergoing Chemoradiation Therapy

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Sponsor (regulatory):	**Roswell Park Cancer Institute**
Funding:	**National Comprehensive Cancer Network (NCCN)**
Industry/Other Supporter:	**Boehringer Ingelheim Pharmaceuticals**

SYNOPSIS

Title / Phase	A Phase II Randomized, Double-Blind, Placebo-Controlled Study Evaluating Nintedanib Versus Placebo as Prophylaxis against Radiation Pneumonitis in Patients with Unresectable NSCLC Undergoing Chemoradiation Therapy
RPCI Study Number	I 257814
Roswell Park Cancer Institute Investigator	Grace Dy, MD
Sponsor	Roswell Park Cancer Institute
Funding	National Comprehensive Cancer Network (NCCN)
Industry / Other Supporter	Boehringer Ingelheim Pharmaceuticals
Study Drug(s)	Nintedanib, placebo; durvalumab
Objectives	**Primary:** • Phase 1: To evaluate the safety of the combination of durvalumab with nintedanib in patients with unresectable Stage II/III/oligometastatic IV NSCLC • Phase 2: To compare the rate of symptomatic radiation pneumonitis at 6 months after completion of chemoradiation in patients with unresectable Stage II/III/oligometastatic IV NSCLC who completed chemoradiation followed by nintedanib versus placebo. **Secondary:** • To compare the quality of life (QOL) in patients who received nintedanib versus placebo during active treatment until 6 months after completion of treatment. • To compare the progression-free survival, overall survival and 1-year progression-free survival rate in patients who received nintedanib versus placebo. • To compare pulmonary function test (PFT) results and RP score in patients who received nintedanib versus placebo. • To compare the composite index (based on PFT, RP score and QOL) at the end of active treatment and 6 months after completion of treatment between patients who received nintedanib versus placebo. **Exploratory:** • To investigate blood-based biomarkers in evaluating risk of developing radiation pneumonitis as well as the efficacy of nintedanib.
Study Design	A Phase II, randomized, double-blind, placebo-controlled study of nintedanib as prophylaxis against radiation pneumonitis in patients with advanced NSCLC. Addition of Phase I: With the November 2018 amendment allowing immune checkpoint inhibitor such as durvalumab consolidation therapy, a conventional dose-escalation design will be explored for patients who will be receiving durvalumab. Patients enrolled in the dose-escalation portion must commence nintedanib dosing at the same time as durvalumab is started. Dosing with nintedanib will start at 100 mg BID (see Table 1).

	For patients who will be receiving durvalumab as standard of care prior to establishment of the recommended phase II dose of this combination, they will NOT undergo randomization (i.e. not blinded to treatment) and will receive active drug (nintedanib) on the first day of the first dose of durvalumab 10mg/kg every 2 weeks for up to 12 months.
Target Accrual and Study Duration	Phase I: A maximum of 18 participants will be enrolled to the non-randomized dose escalation portion of this study. The number of participants required is a function of the unknown dose-toxicity relationship. Phase II: A maximum of 99 participants will be enrolled to the randomized Phase 2 portion of this study (excluding patients replaced due to ineligibility or inability to start therapy). Participants will be enrolled from up to 4 sites including Roswell Park. This study is anticipated to complete accrual within 4 years of study activation. Patients will receive either nintedanib or placebo to be administered for 6 months. Patients will be followed for at least one year for initial primary analysis of study outcomes. Patients will be followed for no longer than 2.5 years.
Study Procedures	**Physical Examination:** Baseline, Cycle 1 Day 1, Cycle 2 through Cycle 6 Day 1, anytime when radiation pneumonitis is suspected to have occurred (within the first 6 months after completing radiation therapy), end of active treatment, between 76 to 97 days after last nintedanib/placebo dose, between 166 to 187 days after last nintedanib/placebo dose, long term follow-up. **Hematology:** Baseline, Cycle 1 Day 1, Cycle 2 through Cycle 6 Day 1, anytime when radiation pneumonitis is suspected to have occurred (within the first 6 months after completing radiation therapy), end of active treatment, between 166 to 187 days after last nintedanib/placebo dose, long term follow-up. **Chemistry:** Baseline, Cycle 1 Day 1, Cycle 2 through Cycle 6 Day 1, anytime when radiation pneumonitis is suspected to have occurred (within the first 6 months after completing radiation therapy), end of active treatment, between 166 to 187 days after last nintedanib/placebo dose, long term follow-up. **Disease Evaluation:** Baseline, Cycle 3 Day 1, Cycle 6 Day 1, anytime when radiation pneumonitis is suspected to have occurred (within the first 6 months after completing radiation therapy), between 76 to 97 days after last nintedanib dose, between 166 to 187 days after last nintedanib/placebo dose, and long term follow-up. **Performance Status:** Baseline, Cycle 1 Day 1, Cycle 2 through Cycle 6 Day 1, anytime when radiation pneumonitis is suspected to have occurred (within the first 6 months after completing radiation therapy), end of active treatment, between 76 to 97 days after last nintedanib/placebo dose, between 166 to 187 days after last nintedanib/placebo dose, long term follow-up. **Adverse Events:** Baseline, Cycle 1 Day 1, Cycle 2 through Cycle 6 Day 1, anytime when radiation pneumonitis is suspected to have occurred (within the first 6 months after completing radiation therapy), end of active treatment, between 76 to 97 days after last nintedanib/placebo dose, between 166 to

	187 days after last nintedanib/placebo dose, long term follow-up.
Statistical Analysis	**Sample Size Determination:** A maximum of 18 participants will be enrolled to the non-randomized dose escalation portion of this study. The number of participants required is a function of the unknown dose-toxicity relationship. A maximum of 99 participants will be enrolled to the randomized Phase 2 portion of this study (excluding patients replaced due to ineligibility or inability to start therapy). Participants will be enrolled from up to 4 sites including Roswell Park. Accrual is expected to take 4 years. **Phase II Randomization:** Patients will be randomized to either the placebo or nintedanib arm in a 1:2 fashion using a stratified permuted block randomization scheme. The randomization lists to be used in this study will be generated by the study biostatistician. Patients will be included in data analyses according to their randomized treatment assignment irrespective of the treatment actually received (intent-to-treat). After randomization, initiation of the study intervention will take place once symptoms arise for the patient, this will be left to the patient's discretion. Patient randomization will be done by the Department of Biostatistics at Roswell Park.

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM

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

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

Title: A Phase II Randomized, Double-Blind, Placebo-Controlled Study Evaluating Nintedanib versus Placebo as Prophylaxis against Radiation Pneumonitis in Patients with Unresectable NSCLC Undergoing Chemoradiation Therapy

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Age 18 years or greater.	
☐	☐	☐	2. Histologically or cytologically-proven non squamous cell NSCLC. Mixed histology with SCLC component not allowed.	
☐	☐	☐	3. Patients with Stage II – IV non squamous cell NSCLC who received at least 54 Gy of total planned thoracic radiation dose will be eligible. Patients must have received at least one cycle of chemotherapy concurrently during the course of thoracic radiation. Regimens allowed are platinum combinations with either etoposide or a taxane regardless of histology subtype; platinum with pemetrexed for patients with nonsquamous NSCLC only. Patients with oligometastatic Stage IV cancer are eligible if they have received only one line of systemic therapy for their Stage IV cancer prior to the concurrent chemoradiation phase.	
☐	☐	☐	4. Patient must have had a CR/PR/SD, 4-6 weeks after completing last fraction of radiation therapy.	
☐	☐	☐	5. ECOG Performance Score 0-2.	
☐	☐	☐	6. ANC ≥ 1,500/μL.	
☐	☐	☐	7. Platelet count ≥ 100,000/μL.	
☐	☐	☐	8. Hemoglobin ≥ 9 g/dL.	
☐	☐	☐	9. Total bilirubin ≤ normal or for patients with Gilbert's syndrome, ≤ 1.5 times upper limit of normal (ULN) OR direct bilirubin normal (per institute standards).	
☐	☐	☐	10. AST ≤ 1.5 x ULN. ALT and AST ≤ 2.5 x ULN is acceptable if there is liver metastasis.	
☐	☐	☐	11. Fertile patients must use adequate contraception.	

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM

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

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

Title: A Phase II Randomized, Double-Blind, Placebo-Controlled Study Evaluating Nintedanib versus Placebo as Prophylaxis against Radiation Pneumonitis in Patients with Unresectable NSCLC Undergoing Chemoradiation Therapy

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. WBRT < 14 days from the anticipated start of nintedanib/placebo administration.	
☐	☐	☐	2. Squamous cell NSCLC	
☐	☐	☐	3. Unable to start nintedanib/placebo treatment between 4 - 8 weeks after completing the last dose of thoracic radiation.	
☐	☐	☐	4. Active untreated brain or leptomeningeal metastases. In patients with treated CNS metastases, eligible if symptoms controlled for at least 4 weeks. Dexamethasone allowed if total daily dose does not exceed 2 mg.	
☐	☐	☐	5. Major injuries or surgery (e.g., craniotomy) < 28 days from the start of nintedanib/placebo administration. Wound should be healed prior to starting therapy.	
☐	☐	☐	6. Second malignancies are allowed as long as the disease does not require active treatment with concomitant systemic cytotoxic chemotherapy, investigational or biologic therapy (e.g., anti-CTLA4 or HER2 monoclonal antibodies). Hormone-related therapies (e.g., LHRH agonists, tamoxifen, etc.) are allowed.	
☐	☐	☐	7. Concurrent uncontrolled illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situation that would increase the risk associated with study participation and/or limit compliance with study requirements.	
☐	☐	☐	8. Inability to swallow study medication.	
☐	☐	☐	9. Presence of active malabsorption disorder (e.g., flare episodes documented within the preceding 3 months, presence of symptoms requiring daily medications for control) or history of extensive small bowel resection.	
☐	☐	☐	10. Known bleeding or thrombotic diathesis.	

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	11. History of arterial or venous thromboembolic event within 12 months prior to study participation.	
☐	☐	☐	12. Active hemoptysis or history of clinically relevant hemoptysis as determined by the treating physician. Patients who had history of transient minor hemoptysis after bronchoscopic biopsy are eligible unless deemed otherwise by the treating physician.	
☐	☐	☐	13. CTCAE Grade 2 or higher proteinuria.	
☐	☐	☐	14. Investigational agent administered < 28 days prior to treatment with nintedanib. Last dose of systemic chemotherapy administered < 14 days prior to treatment with nintedanib.	
☐	☐	☐	15. Known chronic active hepatitis B or hepatitis C. HIV-positive patients receiving or are candidates for antiretroviral therapy are also excluded.	
☐	☐	☐	16. Pregnancy or breast feeding. Female patients with child-bearing potential must have a negative pregnancy test (β-HCG test in urine or serum) prior to commencing study treatment.	
☐	☐	☐	17. Creatinine > 1.5 x ULN or CrCL < 45 mL/min. Refer to **Appendix D**.	
☐	☐	☐	18. Centrally located tumors with radiographic evidence (CT or MRI) of local invasion of major blood vessels.	
☐	☐	☐	19. Therapeutic anticoagulation (except low-dose heparin and/or heparin flush as needed for maintenance of an in-dwelling intravenous devise) or anti-platelet therapy (except for low-dose therapy with acetylsalicylic acid < 325 mg per day).	
☐	☐	☐	20. Active or previous autoimmune disease requiring treatment within the past 2 years will exclude patients from receiving immune checkpoint inhibitor in this study. Exception allowed: Endocrine conditions treated with necessary hormone replacement or other supportive medication; vitiligo, alopecia.	

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

Investigator Signature:_____ **Date:**_____

Printed Name of Investigator:_____

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IN-TEXT TABLES

APPENDICES

1 BACKGROUND

1.1 Study Disease

Lung cancer is the leading cause of cancer-related mortality in the United States and worldwide (1). Majority of patients present with an advanced unresectable stage of disease. Concurrent chemoradiation therapy is the standard of care in patients with Stage III locally advanced non-small cell lung cancer (NSCLC) (2). Symptomatic radiation pneumonitis occurs in 15 - 40% of NSCLC patients receiving concurrent chemoradiation (3,4). This treatment complication adversely affects quality of life and may rarely be fatal (3,4).

Various treatment-related risk factors have been identified that can predict the development of symptomatic radiation pneumonitis (4,5). These include V20 (lung volume receiving > 20 Gy), chemotherapy regimen and mean lung dose (MLD). For example, to limit the frequency of symptomatic radiation pneumonitis to < 30%, the V20 and MLD thresholds as calculated from the dose-volume histogram minus the gross tumor volume were 41.5% and 22.4 Gy, respectively (5). The use of carboplatin and paclitaxel regimen was associated with the highest risk in patients greater than 65 years (4).

The pathophysiology of radiation pneumonitis and the eventual pulmonary fibrosis that ensues is thought to be secondary to inflammatory and/or profibrotic cytokines such as IL-1α, IL-6, IL-10 and TGF-β that are activated by volatile reactive oxygen and nitrogen species which are generated in response to the oxidative stress caused by the tissue damage incurred from radiation (6-10). A TH2-like immune response with elevated mRNA levels of the transcription factor GATA-3 has been implicated as well in this process (11). Pharmacologic inhibition of CC chemokine receptor 1 (CCR1) prevented lung inflammation and fibrosis induced by radiation (12). More recently, murine models of radiation-pneumonitis reveals early accumulation of CD4+FoxP3+Treg cells 21 days post-radiation. However, the role of these Treg cells in dampening or worsening radiation-induced inflammatory tissue damage is speculative at this time and not clearly defined (13).

Preclinical studies suggest that antioxidants can be effective radioprotectors in mice models (10, 13-14), but optimal dose and method of administration maybe challenging (15,16). Amifostine, a widely studied radioprotective agent metabolized to an active form which binds to free radicals, did not appear to reduce the incidence of pulmonary toxicity in the large RTOG 9801 Phase III trial in patients with locally advanced NSCLC receiving hyperfractionated radiation concurrently with chemotherapy, with no difference seen in the patient-reported quality of life (QOL) scales in terms of dyspnea, cough and chest pain between the amifostine versus no-amifostine groups (17,18).

1.2 Study Drug

Nintedanib is a multikinase inhibitor with potent activity against VEGFR/PDGFR/FGFR. PDGF, VEGF and FGF are critical profibrotic mediators, which have been shown to play a role in the development of fibrosis (19).

1.3 Preclinical Studies with Nintedanib

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

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

The specific and simultaneous abrogation of these pathways results in effective growth inhibition of both endothelial and, via PDGF- and FGF-receptors of perivascular cells which may be more effective than inhibition of endothelial cell growth via the VEGF pathway alone. Furthermore, signaling by FGF-receptors has been identified as a possible escape mechanism for tumor angiogenesis when the VEGF pathway is disrupted.

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

In addition, preclinical models show that nintedanib may have a direct anti-tumor effect on those malignant cells which overexpress PDGFR and/or FGFR (e.g., H1703 NSCLC cells).

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

In vitro, the target receptors are all inhibited by nintedanib in low nanomolar concentrations. In *in vivo* nude mouse models, nintedanib showed good anti-tumor efficacy at doses of 50 - 100 mg/kg, leading to a substantial delay of tumor growth or even complete tumor-stasis in xenografts of a broad range of differing human tumor types. Histological examination of treated tumors showed a marked reduction of tumor vessel density by approximately 80% (20).

The metabolism of nintedanib was predominantly characterized by the ester cleavage of the methyl ester moiety yielding BIBF1202, which was further metabolized by conjugation to glucuronic acid yielding the 1-O-acylglucuronide. Data collected in this study show that nintedanib has a favorable PK and excretion profile with almost no elimination via the urine, only 0.7% of total 14C radioactivity was eliminated via the urine. The metabolic characteristics are predominantly independent of cytochrome P450-catalysed metabolic pathways (21).

A soft gelatin capsule formulation of nintedanib is used in man. After oral administration, nintedanib is absorbed quickly. Maximum plasma concentrations (Cmax) generally occur 2 to

4 hours after administration. So far, no evidence for a deviation from dose proportionality of the PK of nintedanib has been observed. Steady state is reached latest after one week of dosing. The terminal half-life of nintedanib is in the range of 7 to 19 hours. Nintedanib is mainly eliminated via faeces (21). Nintedanib is non-mutagenic, even at high doses.

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. Women of childbearing potential should be advised to use adequate contraception during and at least 3 months after the last dose of nintedanib.

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

1.4 Relevant Clinical Studies with Nintedanib

Nintedanib is being evaluated in several cancers. Additionally, nintedanib has been recently studied for the non-cancer indication idiopathic pulmonary fibrosis (IPF). A randomized Phase II placebo-controlled trial investigating the efficacy and safety of nintedanib in IPF showed that even though the primary endpoint was not met (annual rate of forced vital capacity FVC decline), there was a significant reduction in the rate of acute exacerbations seen in the nintedanib 150 mg BID treatment group compared to placebo (2.4 versus 15.7 per 100 patient-years, $p = 0.02$), improved QOL nintedanib 150 mg BID treatment compared to worsening QOL scores in the placebo group ($p = 0.007$), as well as less decline in baseline total lung capacity ($p < 0.001$) and resting oxygen saturations ($p = 0.05$) over time in the nintedanib 150 mg BID treatment compared to placebo (22). Two replicate Phase III trials (INPULSIS-1 and INPUSLSIS-2) were then conducted which showed that 52-week treatment with nintedanib reduced the decline in FVC compared to placebo. In INPULSIS-2, there was a significant benefit with nintedanib versus placebo in the time to first acute exacerbation ($p = 0.005$) which was not significantly different in INPULSIS-1 (23). Multikinase inhibitors similar to nintedanib such as sunitinib and sorafenib have demonstrated immunomodulatory effects through reduction of cytokines such as IL-10 and TGF-B (24,25).

As of 15 February 2013, 3556 cancer patients, over 1000 patients with IPF, and 140 healthy volunteers had been treated with nintedanib or nintedanib matching placebo, in monotherapy or in combination with chemotherapy.

1.4.1 Phase I

Phase I dose selection studies revealed that nintedanib is generally well tolerated with mild to moderate adverse effects such as gastrointestinal symptoms (i.e., nausea, diarrhoea, vomiting, abdominal pain) and reversible elevations of liver enzymes. Initial signs of clinical activity including an encouraging rate of patients with stabilization of their tumor of 54% and 68%, respectively; have been observed in patients with various solid tumors (26).

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. Based on the overall safety profile, the recommended Phase II dose (RP2D) for nintedanib as monotherapy is 200 mg bid.

The maximum tolerated dose for combination therapy of nintedanib in combination with pemetrexed, docetaxel, paclitaxel/carboplatin and FOLFOX is 200 mg bid. Combination of nintedanib with other anti-cancer drugs revealed a similar adverse event profile as compared to nintedanib monotherapy except for the chemotherapy related toxicities. There was no change of the pharmacokinetic parameters of nintedanib or of the cytotoxic compounds due to the combined treatment. Dose limiting toxicity consisted mostly of liver transaminase elevations as in the monotherapy Phase I trials with the exception of the combination of nintedanib with pemetrexed, where fatigue was the most relevant dose limiting toxicity.

Available pharmacokinetic data indicate that the systemic exposure needed for biological activity can be achieved starting with doses of 100 mg nintedanib once daily.

The predominant adverse events were nausea, diarrhoea, vomiting, abdominal pain and fatigue of mostly low to moderate severity. Dose limiting toxicities (DLT) were mainly confined to reversible hepatic enzyme elevations (AST, ALT, γ-GT) which increased dose-dependently. Most cases occurring at doses of 250 mg and above, and a very low incidence at doses below 200 mg and were reversible after discontinuation of nintedanib treatment. All adverse events observed after single administration of single doses of nintedanib to healthy volunteers were only of CTCAE Grade 1 severity and fully reversible (21).

1.4.2 NSCLC

In a Phase II trial in NSCLC patients the safety profile of nintedanib observed in Phase I trials could be confirmed. Most commonly reported drug-related AEs were nausea (57.5%), diarrhoea (47.9%), vomiting (42.5%), anorexia (28.8%), abdominal pain (13.7%) and reversible alanine transaminase (13.7%) and aspartate aminotransferase elevations (9.6%) In conclusion, it was generally well tolerated and displayed single agent activity in advanced or recurrent NSCLC patients. Median overall survival (OS) was 21.9 weeks. Eastern Cooperative Oncology Group (ECOG) 0–1 patients (n = 56) had a median progression free survival (PFS) of 11.6 weeks and a median OS of 37.7 weeks. Tumor stabilization was achieved in 46% of patients (ECOG 0–1 patients: 59%), with one confirmed partial response at 250 mg bid (27).

LUME-Lung 1 was an international, randomized, double-blind, Phase III trial assessing the efficacy and safety of docetaxel plus nintedanib as 2nd line therapy for non-small-cell lung cancer (NSCLC). In total, 1314 patients with Stage IIIB/IV or recurrent NSCLC (all histologies) who had progressed after 1st line chemotherapy were randomized in 1:1 fashion to either receive Nintedanib 200 mg BID + Docetaxel (n = 655) or Placebo BID + Docetaxel (n = 659).

LUME-Lung 1 met its primary endpoint by showing a statistically significant improvement of PFS for all patients regardless of histology (median PFS 3.4 versus 2.7 months; HR 0.79, p = 0.0019) for Nintedanib in combination with docetaxel.

A significant improvement in OS was demonstrated in patients with adenocarcinoma (HR 0.83, p = 0.0359, median 10.3 to 12.6 months).

Patients with a poor prognosis defined as time since start of 1st line therapy < 9 months also experienced significant OS improvement from the addition of nintedanib to docetaxel (HR 0.75, p = 0.0073, median OS 7.9 to 10.9 months).

The predominant adverse events were nausea, diarrhoea, vomiting, abdominal pain and fatigue of mostly low to moderate intensity after monotherapy with nintedanib. Dose limiting toxicities were dose dependent hepatic enzyme elevations that were reversible after discontinuation of nintedanib treatment. These liver enzyme elevations were only in few cases accompanied by a simultaneous increase of bilirubin. In general common terminology criteria for adverse events (CTCAE version 3, Grade 3liver 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 2 months of treatment.

Hypertension or thromboembolic events were rare and did not suggest an increased frequency as a consequence of therapy with nintedanib (28).

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

Based on a preplanned futility analysis of investigator-assessed PFS, enrolment was halted after 713/1300 planned patients had been enrolled. The analysis (based on conditional power for PFS by investigator assessment) suggested that the study was futile and that the primary endpoint of centrally assessed PFS would likely not be met. The futility analysis was based on conditional power; there was no formal testing of null hypothesis as planned for primary analysis no safety issues were identified.

Even though the study was stopped prematurely, the primary endpoint of this Phase III trial was met; treatment with nintedanib plus pemetrexed resulted in a significant prolongation of centrally reviewed PFS compared with placebo plus pemetrexed (median PFS 4.4 vs. 3.6 months with a HR 0.83; p = 0.0435). The disease control rate was also increased significantly in nintedanib-treated patients. There was no improvement in OS in nintedanib-treated patients. Nintedanib 200 mg bid in combination with pemetrexed had an acceptable and manageable safety profile, with no new or unexpected safety findings. The most frequent AEs were reversible increases in liver enzymes and gastrointestinal events (29).

The LUME Columbus is an ongoing randomized Phase III study of docetaxel plus nintedanib or placebo as second-line treatment in advanced NSCLC (NCT02231164). Approximately 800 patients will be recruited to this study with an estimated completion date in March 2018.

1.4.3 Ovarian Cancer

A randomized Phase II maintenance trial in ovarian cancer in which the efficacy and safety of nine months of continuous twice daily doses of nintedanib following chemotherapy was investigated, has identified the potential activity of nintedanib with a 36-week PFS of 16.3%

compared to 5.0% in the control group. The safety profile was consistent with findings previously reported for nintedanib administered as monotherapy as mentioned above (30).

Nintedanib was evaluated in a Phase III randomized, placebo-controlled, double-blind, multicentre ovarian study with 1366 patients. Patients received nintedanib plus paclitaxel and carboplatin or placebo plus paclitaxel and carboplatin for 6 cycles. This was followed by monotherapy nintedanib or placebo for up to 120 weeks. The trial met its primary endpoint by demonstrating a statistically significant improvement in progression-free survival (HR 0.84; 95%CI 0.72 - 0.98; p = 0.0239, median PFS 17.3 months for nintedanib and 16.6 months for placebo). Overall survival data are immature but currently show no trend in either direction. Main adverse events were GI side effects and increased hematological toxicity (31).

1.4.4 Colorectal Cancer

A Phase I/II, open-label, randomized study of nintedanib plus mFOLFOX6 compared to bevacizumab plus mFOLFOX6 in 120 patients with metastatic colorectal cancer was performed, demonstrating an acceptable safety profile of nintedanib in combination with mFOLFOX6. In comparison to bevacizumab, nintedanib showed a similar magnitude of efficacy, a similar safety/tolerability profile, a similar exposure and dose intensity of mFOLFOX6 (32).

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

1.4.5 Renal Cell Cancer

Nintedanib has been studied in a randomized Phase II study in metastatic clear cell RCC with sunitinib as the control arm. Similar efficacy was seen in both arms of this study. AEs observed more frequent in the nintedanib arm included diarrheal, nausea, fatigue and infection, whereas AEs more frequent in the sunitinib arm consisted of bleeding, anaemia, hypertension, hand-foot syndrome and stomatitis (33).

1.4.6 Hepatocellular Cancer

The efficacy and safety of nintedanib versus sorafenib in Asian Patients with Advanced Hepatocellular Carcinoma was investigated in a randomized Phase II trial. Nintedanib showed similar efficacy to sorafenib, with a favorable and manageable AE profile. More patients in the sorafenib arm had severe AEs and drug-related AEs compared with patients in the nintedanib arm, and more patients in the sorafenib arm required dose reduction compared with the nintedanib arm. Nintedanib AEs were manageable; in the nintedanib arm there were fewer hypertension, palmar-plantar erythrodysesthesia syndrome, and transaminase elevation events (34).

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

1.5 Correlative Studies

The pathophysiology of radiation pneumonitis (RP) and the eventual pulmonary fibrosis that ensues is thought to be secondary to inflammatory and/or profibrotic cytokines such as IL-1α, IL-6, IL-10 and TGF-β that are activated by volatile reactive oxygen and nitrogen species generated in response to the oxidative stress caused by the tissue damage incurred from radiation (35-39). The 1,25 (OH)2D3-vitamin D receptor (VDR) pathway in turn has been implicated as a negative regulator of the profibrotic TGF-B/SMAD signaling (40-42). In fact, one *in vivo* rat model demonstrated that vitamin D3 administration has a protective effect against radiation-induced pulmonary toxicity(43). Although vitamin D insufficiency is highly prevalent, there is no consensus on optimal blood levels. Moreover, there are no well-designed prospective studies evaluating vitamin D levels as a modifiable risk factor in association with radiation pneumonitis. In addition, new models of acute lung injury implicate mitochondrial damage-associated molecular patterns, including mitochondrial DNA, which are proinflammatory in nature by increasing endothelial cell permeability and levels of various cytokines such as Il-6 and IL-10 (44,45). However, the clinical relevance of mitochondrial DNA in radiation-induced lung inflammation is not well-characterized to date. We propose that baseline vitamin D and changes in levels of cytokine and mitochondrial DNA levels maybe predictive of the development of radiation pneumonitis.

MicroRNAs (miRNAs) are crucial biological regulators of gene expression that function through suppression of their target genes and are involved in a variety of pathophysiologic processes (46,47). A TH2-like immune response with elevated mRNA levels of the transcription factor GATA-3 has been implicated in radiation-induced lung injury (48). VEGF appears to facilitate TH2-mediated lung inflammatory responses as well by reducing miR-1 expression whereas exogenous administration of miR-1 inhibited inflammatory responses and cytokine expression (49). Another experimental model shows that expression of miR-127 significantly reduced cytokine release by macrophages and attenuated lung inflammation (50). More recently, murine models of radiation-pneumonitis reveals early accumulation of CD4+FoxP3+Treg cells 21 days post-radiation (51). This also implicates GATA-3 since it transactivates TH2 cytokines, regulates FoxP3 expression and Treg function. GATA-3 activity in Tregs in turn is regulated/decreased by the transcriptional repressor Bcl6 resulting in downregulation of miR-2(52). Another thoracic radiation model reveals changes in endothelial and alveolar cell-specific gene transcripts which correlated with mi-RNA expression, such as miR-107 and miR-511 (with TLR4 expression), miR-155 (with TGF-B expression) and miR-126 (with VEGF expression).(53). We propose that the nanoparticle chip assay maybe a useful tool to measure the expression of selected miRNAs as biomarkers that may predict risk of developing radiation pneumonitis and potentially to identify patients who may benefit from nintedanib treatment in the prevention of radiation pneumonitis.

Semi-quantitative scores based on computerized tomography (CT) findings have been shown to have prognostic implications among patients with idiopathic pulmonary fibrosis or hypersensitivity pneumonitis (54,55). This study proposes to evaluate a modified RP score to compare the severity of changes in each treatment group as it correlates with QOL and pulmonary function changes.

1.6 Risks and/or Benefits

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

- the GI tract (i.e., nausea, vomiting, diarrhea, abdominal pain)
- increases in liver enzymes (i.e., AST, ALT, γ-GT)
- fatigue, asthenia and anorexia

Liver enzymes must be followed closely during treatment with nintedanib.

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

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

Based upon a non-clinical safety study *in vitro*, nintedanib may have a potential risk of phototoxicity (skin and eyes) *in vivo*. Few cases of photosensitivity reactions (less than 1%) and of CTCAE Grade 1 intensity only have been reported from the clinical studies to date. If adequate precautions are taken (avoidance of prolonged ultraviolet (UV) exposure, use of broad spectrum sunscreen and sunglasses), treatment with nintedanib is considered safe.

Although considerable progress has occurred in understanding the biological characteristics of cancer as well as the development of more effective treatment regimens, most patients with locally advanced or metastatic tumors succumb to their disease. Thus, there is a substantial need for novel therapeutic strategies to improve the outcome for patients with advanced NSCLC. The sequelae of treatment, such as radiation pneumonitis and fibrosis, can also negatively impact short-term and long-term QOL.

2 RATIONALE

Nintedanib 200 mg orally twice daily had been evaluated in several Phase III NSCLC studies as discussed previously. Based on the data summarized in **Section 1.4**, the use of nintedanib may potentially mitigate both the early phase of inflammatory response and the latter phase of fibrotic response. Because the risk of acute radiation pneumonitis is greatest within the first 6 months after completion of thoracic radiation, this study will randomize patients to begin treatment

between 4 - 8 weeks upon completion of the last fraction of thoracic radiation, with either nintedanib or placebo treatment for 6 months.

Antiangiogenic treatment with the orally available triple angiokinase inhibitor nintedanib with inhibition of VEGFR, PDGFR and FGFR offers the chance to control both locally recurrent and distant metastatic disease on an outpatient basis. Treatment with nintedanib may have the potential to provide significant benefit to patients with locally advanced NSCLC by slowing tumor progression and metastasis, since its cellular target is expressed on the tumor vasculature in most malignancies. Induction of endothelial cell apoptosis may result in subsequent degradation of tumor vessels and subsequent tumor necrosis. Additionally, tumor growth may be affected by direct anti-tumor effects (e.g., tumor cells that express VEGFR, PDGFR or FGFR). Moreover, due to the positive effects of nintedanib therapy in patients with ILD, we hope that nintedanib therapy can also ameliorate radiation pneumonitis in locally advanced NSCLC who receive chemoradiation therapy.

As the standard of care has changed in mid-2017 with the announcement of the results from the PACIFIC trial showing that consolidation treatment with durvalumab, after concurrent chemoradiation for unresectable stage III NSCLC, prolonged progression-free survival as well as overall survival in an updated analysis (56,57), nintedanib treatment will occur concurrently while patients receive durvalumab consolidation treatment as standard of care practice. Notably, there is approximately 10% higher frequency of any grade pneumonitis or radiation pneumonitis in patients who received durvalumab versus placebo as consolidation in the PACIFIC trial (34% versus 25%). Moreover, additional immune checkpoint inhibitors are in various stages of testing, either as induction therapy, consolidation therapy or concurrently with radiation. Hence, an additional stratification factor of exposure to immunotherapy agents will be introduced in the analysis of the study.

The combination of nintedanib with immune checkpoint inhibitors are ongoing (NCT03377023 with nivolumab + ipilimumab in NSCLC; NCT02856423 with pembrolizumab in solid tumors, PEMBIB). The results of the PEMBIB study were recently reported. A total of 13 patients (12 evaluable for DLT) were enrolled in the dose-escalation portion (none of which were NSCLC patients). Three DLTs of liver enzyme elevation were observed in the 200 mg BID nintedanib dose thus for the phase II portion, final recommended dose of nintedanib was 150 mg BID nintedanib in combination with pembrolizumab 200mg flat dosing every 21 days (58)

3 OBJECTIVES

3.1 Primary Objectives

- **Phase I**: To evaluate the safety of the combination of durvalumab with nintedanib in patients with unresectable Stage II/III/oligometastatic IV NSCLC
- **Phase II:** To compare the rate of symptomatic radiation pneumonitis at 6 months after completion of chemoradiation in patients with unresectable Stage II/III/oligometastatic IV NSCLC who completed chemoradiation followed by nintedanib versus placebo.

3.2 Secondary Objectives

- To compare the quality of life (QOL) in patients who received nintedanib versus placebo during active treatment until 6 months after completion of treatment.
- To compare the progression-free survival, overall survival and 1-year progression-free survival rate in patients who received nintedanib versus placebo.
- To compare pulmonary function test (PFT) results and RP score in patients who received nintedanib versus placebo.
- To compare the composite index (based on PFT, RP score and QOL) at the end of active treatment and 6 months after completion of treatment between patients who received nintedanib versus placebo.

3.3 Exploratory Objective:

- To investigate blood-based biomarkers in evaluating risk of developing radiation pneumonitis as well as the efficacy of nintedanib.

4 METHODOLOGY

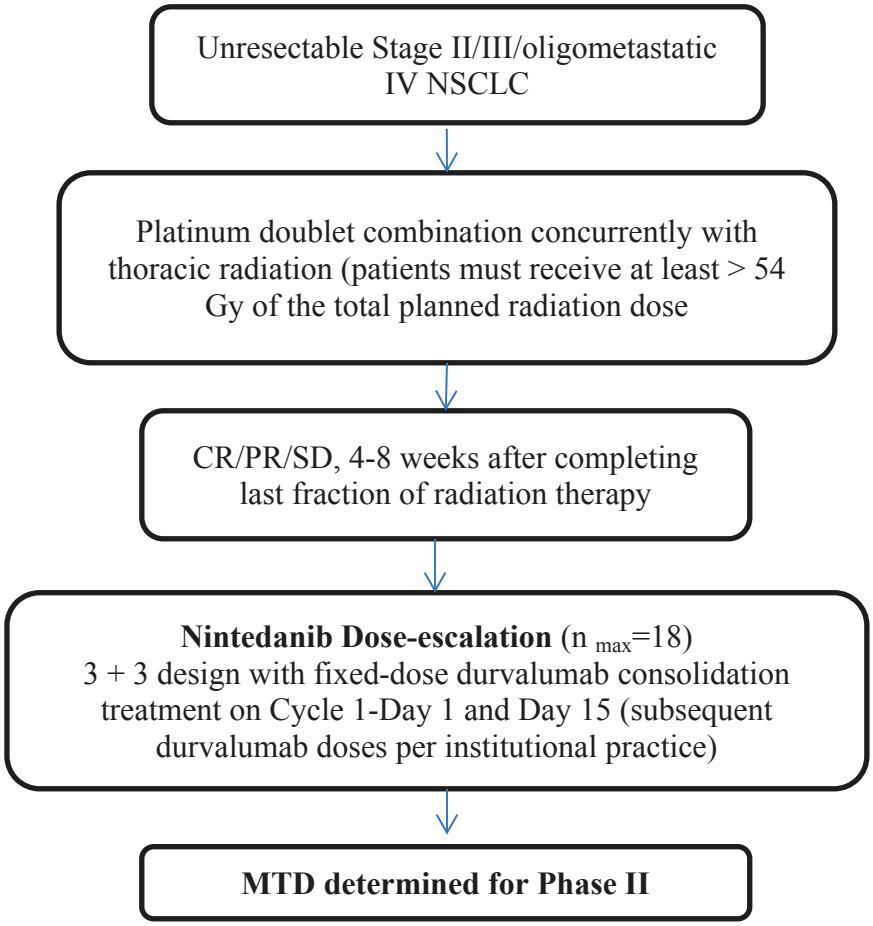
5 STUDY DESIGN

A maximum of 18 participants will be enrolled to the Phase I non-randomized dose escalation portion of this study. See Figure 1 for the Phase 1 dose-escalation study schema.

A maximum of 99 participants will be enrolled to the randomized Phase II, double-blind, placebo-controlled portion of the study of nintedanib as prophylaxis against radiation pneumonitis in patients with advanced NSCLC. The study schema is depicted below.

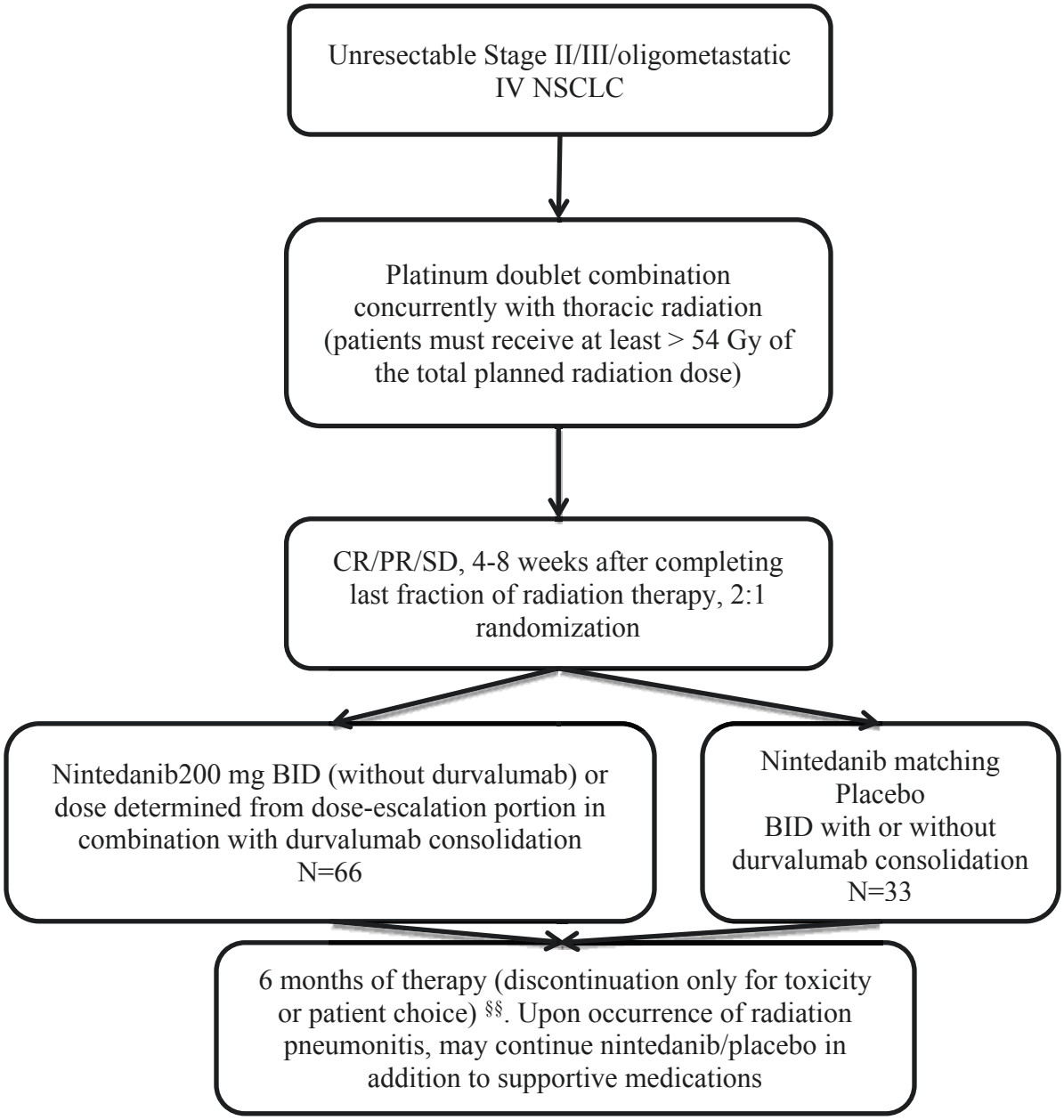
All participants will sign an informed consent prior to study related tests. All participants will meet the inclusion and exclusion criteria summarized in **Section 6.1** and **Section 6.2**.

Figure 1 Phase 1 Dose-escalation Study Schema



For patients who will be receiving durvalumab consolidation treatment as standard of care prior to establishment of the recommended phase II dose of this combination, they will NOT undergo randomization (i.e. not blinded to treatment) and will receive active drug (nintedanib) on the first day of the first dose of durvalumab 10mg/kg every 2 weeks for up to 12 months.

Figure 2. Phase II Study Schema



§Patients will be stratified according to chemotherapy regimen (i.e., platinum with etoposide, platinum with taxane, platinum with pemetrexed) utilized concurrently with radiation as well as exposure to immune checkpoint inhibitor therapy.

§§An interim analysis for futility will be conducted when the first n_1=33 patients have completed 6-months of follow-up post-chemoradiation; that is, when the first n_1=33 patients are evaluable for the primary end-point (the rate of CTCAE Grade 2 or higher radiation pneumonitis at 6

months after completion of chemoradiation). If the estimated common odds ratio (COR) is greater than or equal to 0.8, then the study will stop early for futility. Otherwise, the study will continue and enroll and additional n_2=66 patients. Additionally, at this time the safety profile of the treatment arms may be evaluated and considered in the decision for study continuation.

5.1 Target Accrual and Study Duration

A maximum of 18 participants will be enrolled to the non-randomized dose escalation portion of this study. The number of participants required is a function of the unknown dose-toxicity relationship.

A maximum of 99 participants will be enrolled to the randomized Phase 2 portion of this study (excluding patients replaced due to ineligibility or inability to start therapy).

Participants will be enrolled from up to 4 sites including Roswell Park. Accrual is expected to take up to 4 years.

6 PARTICIPANT SELECTION

6.1 Inclusion Criteria

1 Age 18 years or greater.

2 Histologically or cytologically-proven non squamous cell NSCLC. Mixed histology with SCLC component not allowed.

3 Patients with Stage II - IV non squamous cell NSCLC who received at least 54 Gy of total planned thoracic radiation dose will be eligible. Patients must have received at least one cycle of chemotherapy concurrently during the course of thoracic radiation. Regimens allowed are platinum combinations with either etoposide or a taxane regardless of histology subtype; platinum with pemetrexed for patients with nonsquamous NSCLC only. Patients with oligometastatic Stage IV cancer are eligible if they have received only one line of systemic therapy for their Stage IV cancer prior to the concurrent chemoradiation phase.

4 Patient must have had a CR/PR/SD, 4-6 weeks after completing last fraction of radiation therapy.

5 ECOG Performance Score 0 - 2 (**Appendix C**).

6 ANC ≥ 1,500/μL.

7 Platelet count ≥ 100,000/μL.

8 Hemoglobin ≥ 9 g/dL.

9 Total bilirubin ≤ normal or for those with Gilbert's syndrome ≤ 1.5 times upper limit of normal (ULN) OR direct bilirubin normal (per institute standards).

10 AST ≤ 1.5 x ULN. ALT and AST ≤ 2.5 x ULN is acceptable if there is liver metastasis.

11 Fertile patients must use adequate contraception.

6.2 Exclusion Criteria

1 WBRT < 14 days from the anticipated start of nintedanib/placebo administration.

2 Squamous cell NSCLC

3 Unable to start nintedanib/placebo treatment between 4 – 8 weeks after completing the last dose of thoracic radiation.

4 Active untreated brain or leptomeningeal metastases. In patients with treated CNS metastases, eligible if symptoms controlled for at least 4 weeks. Dexamethasone allowed if total daily dose does not exceed 2 mg.

5 Major injuries or surgery (e.g., craniotomy) < 28 days from the start of nintedanib/placebo administration. Wound should be healed prior to starting therapy.

6 Second malignancies are allowed as long as the disease does not require active treatment with concomitant systemic cytotoxic chemotherapy, investigational or biologic therapy (e.g., anti-CTLA4 or HER2 monoclonal antibodies). Hormone-related therapies (e.g., LHRH agonists, tamoxifen, etc.) are allowed.

7 Concurrent uncontrolled illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situation that would increase the risk associated with study participation and/or limit compliance with study requirements.

8 Inability to swallow study medication.

9 Presence of active malabsorption disorder (e.g., flare episodes documented within the preceding 3 months, presence of symptoms requiring daily medications for control) or history of extensive small bowel resection.

10 Known bleeding or thrombotic diathesis.

11 History of arterial or venous thromboembolic event within 12 months prior to study participation.

12 Active hemoptysis or history of clinically relevant hemoptysis as determined by the treating physician. Patients who had history of transient minor hemoptysis after bronchoscopic biopsy are eligible unless deemed otherwise by the treating physician.

13 CTCAE Grade 2 or higher proteinuria.

14 Investigational agent administered < 28 days prior to treatment with nintedanib. Last dose of systemic chemotherapy administered < 14 days prior to treatment with nintedanib.

15 Known chronic active hepatitis B or hepatitis C. HIV-positive patients receiving or are candidates for antiretroviral therapy are also excluded.

16 Pregnancy or breast feeding. Female patients with child-bearing potential must have a negative pregnancy test (β-HCG test in urine or serum) prior to commencing study treatment.

17 Creatinine > 1.5 x ULN or CrCL < 45 mL/min. Refer to Appendix D.

18 Centrally located tumors with radiographic evidence (CT or MRI) of local invasion of major blood vessels.

19 Therapeutic anticoagulation (except low-dose heparin and/or heparin flush as needed for maintenance of an in-dwelling intravenous devise) or anti-platelet therapy (except for low-dose therapy with acetylsalicylic acid < 325 mg/day).

20 Active or previous autoimmune disease requiring treatment within the past 2 years will exclude patients from receiving immune checkpoint inhibitor in this study. Exception allowed: Endocrine conditions treated with necessary hormone replacement or other supportive medication; vitiligo, alopecia.

6.3 Inclusion of Women and Minorities

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

7 TREATMENT PLAN

7.1 Dosing and Administration

Treatment will be administered on an outpatient basis. Each cycle will be 28 days. Patients will be dispensed sufficient supply for at least 28 days or until their next scheduled visit. Reported adverse events (AEs) and potential risks are described in **Section 1.6**. Appropriate dose modifications are described in **Section Error! Reference source not found.**.

With the November 2018 amendment allowing immune checkpoint inhibitor such as durvalumab consolidation therapy, a conventional dose-escalation design will be explored for patients who will be receiving durvalumab. Patients enrolled in the dose-escalation portion must commence nintedanib dosing at the same time as durvalumab is started. Dosing with nintedanib will start at 100 mg BID (see Table 1).

For patients who will be receiving durvalumab as standard of care prior to establishment of the recommended phase II dose of this combination, they will NOT undergo randomization (i.e. not blinded to treatment) and will receive active drug (nintedanib) on the first day of the first dose of durvalumab 10mg/kg every 2 weeks for up to 12 months.

All administered doses of the study drugs will be recorded in a pill diary to be provided to the patient (**Appendix E**).

7.1.1 Nintedanib

During Phase I dose escalation the participant will not be blinded to treatment and will receive active nintedanib according to the dose level assigned.

During Phase II, the participant will be randomized to receive either nintedanib or matched placebo.

The capsules of the defined dose (or placebo during Phase II) should be swallowed unchewed with a glass of water of about 250 mL or 8 oz. 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 a missed dose, patients should proceed with the intake of medication according to the predefined schedule and take the next scheduled dose when it is due. Do not replace missed dose. All administered doses will be recorded in a pill diary to be provided to the patient (Appendix E).

7.1.2 Durvalumab

During dose escalation, the first two doses of durvalumab (10 mg/kg) will be given intravenously (IV) every 2 weeks over 60 minutes. These doses will be administered together with Cycle 1 Day 1 and day 15 (-1/+7 days) doses of nintedanib. Subsequent doses will be administered according to institutional practice.

During phase II, use of an immune checkpoint inhibitor (durvalumab), in the post-chemoradiation consolidation period is at the discretion of the treating physician.

7.2 Phase I

Dose escalation will proceed in a 3+3 fashion. Standard 3+3 rules will be followed until the maximum tolerated dose (MTD) is found. A total of 3 dose levels will be explored, with the MTD defined as the dose level wherein no more than 1 out of 6 patients evaluable for dose limiting toxicities (DLTs) experienced treatment-related DLT (Table 1).

Initially, 3 patients are enrolled at dose level 1. If no dose DLTs are observed, then 3 new patients are escalated to dose level 2. If ≥ 2 DLTs are observed at dose level 1, then dose-escalation stage is completed and study will be terminated.

If 1 DLT is observed, an additional 3 patients are enrolled at dose level 1. In those 6 patients at dose level 1, if ≤ 1 DLTs are observed attributable to the combination or nintedanib alone, we will proceed to dose level 2; otherwise, the study will be terminated if ≥ 2 DLTs are observed at dose level 1. If ≥ 2 DLTs are observed at dose level 2, the prior dose level (level 1) will be expanded to total of 6 patients if it has not been done yet. Otherwise, if 0-1 DLTs are observed at dose level 2, we proceed to dose level 3. The same basic principles are followed until the dose determined as the MTD is identified to use in Phase II.

Dose-limiting toxicities (DLTs) are as defined in Section 7.2.3. Once the MTD is determined, subsequent patients receiving durvalumab will be randomized to either nintedanib at MTD or placebo (Phase II). Nintedanib may also be started for subsequent patients at any time point (i.e. one or more durvalumab doses maybe given in the consolidation phase before protocol treatment is started) provided other eligibility criteria are met.

Table 1 Dose escalation scheme for the combination of nintedanib with durvalumab (Phase I)

Dose Level	Nintedanib Dose	Durvalumab dose
1	100 mg BID	10mg/kg every 2 weeks
2	150 mg BID	10mg/kg every 2 weeks
3	200 mg BID	10mg/kg every 2 weeks

7.2.1 Definition of DLTs for the Combination of Nintedanib with Durvalumab

A DLT is defined by the occurrence of toxicities outlined below attributable to either Nintedanib alone or the combination of Nintedanib plus durvalumab. Toxicity will be assessed using the NCI Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. DLTs must be scored as possibly, probably, or definitely related to either Nintedanib alone or the combination of Nintedanib plus durvalumab within the first 28 days of combination treatment. Patients who developed significant DLTs deemed possibly, probably or definitely related to Nintedanib (alone or in combination) will be taken off study.

- Nausea of CTCAE Grade ≥ 3, despite maximal supportive care

- Vomiting of CTCAE Grade ≥ 3, despite maximal supportive care
- Diarrhea of CTCAE Grade ≥3 of any duration despite maximal supportive care
- AST and/or ALT > 5x ULN regardless of total bilirubin level
- AST and/or ALT > 2.5x ULN together with total bilirubin > 1.5x ULN (or 1.5x baseline in patients with Gilbert's syndrome)
- Other non-hematological adverse event of CTCAE Grade ≥ 3 considered drug-related and clinically significant(except transient electrolyte abnormality, alopecia, untreated vomiting or diarrhea, and isolated elevation of gamma glutamyl transpeptidase which will not be considered as DLT)
- CTCAE grade 4 Neutropenia and fever ≧ 38.5°C
- Neutropenia CTCAE Grade 4 for more than 7 days, without fever > 38.5 C
- Platelets CTC grade 4 or CTC grade 3 associated with bleeding or requiring transfusion
- Grade > 2 proteinuria
- Nintedanib < 50% of prescribed dose for the first cycle or inability to resume nintedanib dosing within 14 days of stopping due to treatment-related toxicity
- Durvalumab < 2 doses received

7.3 Phase II

7.3.1 Dose Delays/Modifications

7.3.1.2. Immune checkpoint inhibitor(s)

Use of immune checkpoint inhibitor(s), such as durvalumab, in the post-chemoradiation consolidation period is at the discretion of the treating physician.

7.3.2 Treatment Delay

Treatment delay of immune checkpoint inhibitor will follow standard practice in managing toxicities attributed to immune checkpoint inhibitor or for other reasons (scheduling preference, etc). No dose reductions are allowed.

Treatment with nintedanib/placebo has to be interrupted in case **ANY** of the criteria listed below is fulfilled.

- Nausea of CTCAE Grade ≥ 3, despite supportive care
- Vomiting of CTCAE Grade ≥ 2, despite supportive care
- Diarrhea of CTCAE Grade ≥ 2 for more than 3 consecutive days, despite supportive care
- AST and/or ALT of CTCAE Grade ≥ 2 in conjunction with bilirubin of CTCAE Grade ≥ 1
- AST and/or ALT of CTCAE Grade ≥ 3

- Other non-hematological adverse event of CTCAE Grade ≥ 3 considered drug-related
- Neutropenia and fever > 38.5°C
- Neutropenia CTCAE Grade 4 for more than 7 days, without fever
- Platelets < 25,000mm³, with or without bleeding
- Grade > 2 proteinuria

7.3.3 Treatment Re-Initiation

A patient is eligible to restart nintedanib/placebo if all criteria listed below are met.

If a patient has to interrupt intake of nintedanib/placebo due to an adverse event for more than 30 days, the decision to restart treatment with nintedanib/placebo needs to be discussed and agreed upon between the principal investigator and the treating physician.

- Nausea CTCAE Grade ≤ 2
- Vomiting CTCAE Grade ≤ 1
- Diarrhea CTCAE Grade < 2
- AST and ALT CTCAE Grade < 2 and bilirubin CTCAE Grade ≤ 1
- No other non-hematological adverse event CTCAE Grade ≥ 3 which is considered drug-related
- Neutropenia CTCAE Grade ≤ 1, without fever or equal to the patient's pre-therapy value at study enrollment
- Platelets CTCAE Grade ≤ 1 or equal to the patient's pre-therapy value at study enrollment
- Proteinuria CTCAE Grade < 2

Table 2 Management of Nintedanib Adverse Events

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

1 Participants requiring a delay of > 30 days will go off protocol therapy unless permitted to remain in protocol treatment after discussion with principal investigator Dr. Grace Dy.

2 Participants requiring > 2 dose reductions will go off protocol therapy.

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

7.3.4 Dose Reduction

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

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

Table 3 Nintedanib/Placebo Dose Reduction

Dose Level	Dose
-2	100 mg BID
-1	150 mg BID
1 (Starting Dose)	200 mg BID

7.3.5 Management of Adverse Events

Table 4 Recommended Dose Adjustments for Nintedanib

CTCAE Adverse Reaction	Dose Adjustment
Diarrhea ≥ Grade 2 for more than 7 consecutive days, despite anti-diarrheal treatment** *OR* Diarrhea ≥ Grade 3, despite anti-diarrheal treatment**	1st Episode Reduce dose from 200 mg BID to 150 mg BID 2nd Episode Reduce dose from 150 mg BID to 100 mg BID 3rd Episode Stop treatment
Vomiting ** ≥ Grade 2 *AND/OR* Nausea ≥ Grade 3, despite anti-emetic treatment**	
AST and/or ALT elevations Grade 2 in conjunction with bilirubin of ≥ Grade 1 *OR* AST and/or ALT elevations of ≥ Grade 3	
Other non-hematological or hematological adverse reaction of ≥ Grade 3	

** See Section 7.4 for additional guidelines.

If nintedanib will be combined with compounds that are solely metabolized by the liver and/or induce liver enzyme elevations, both molecules should be reduced in case of liver enzyme elevations according to the defined dose reductions for nintedanib/placebo as mentioned above and for the other compound as mentioned in their prescribing information.

7.4 General Concomitant Medication and Supportive Care

7.4.1 Diarrhea

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

7.4.2 Nausea and Vomiting

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

In the event of dehydration, administration of electrolytes and fluids is required. Plasma levels of electrolytes should be monitored, if relevant GI adverse events occur. Participants may be pretreated for nausea and vomiting with appropriate anti-emetics as clinically indicated.

7.4.3 Neutropenia and Sepsis

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

7.4.4 Hepatic Function

The safety and efficacy of nintedanib has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Therefore, treatment with nintedanib is not recommended in such patients.

Administration of nintedanib was associated with an elevation of liver enzymes (i.e., ALT, AST, ALKP (alkaline phosphatase), and bilirubin), with a potentially higher risk for female patients.

These increases were reversible in the majority of cases and not associated with clinically manifest liver disorders. Hepatic transaminases, ALKP and bilirubin levels are recommended to be closely monitored after start of therapy with nintedanib.

If relevant liver enzyme elevations are measured, interruption, dose reduction or discontinuation of the therapy with nintedanib/placebo may be required. Refer to **Appendix B** for guidelines in the recognition and approach to drug-induced liver injury.

7.4.5 Other

Additional chemo-, immuno-, biologic therapies are not allowed during the active treatment period of this trial. Hormone-related therapies (e.g., adjuvant aromatase inhibitors, etc) are permitted if patients have been on these for more than one month prior to initiation of study protocol. Palliative radiotherapy may be permitted for symptomatic control of pain from bone metastases in extremities after discussion with the Principle Investigator. Patients who develop new/worsening brain metastases within the study treatment period may continue on protocol and receive palliative WBRT (or gamma-knife radiosurgery as clinically indicated). Nintedanib/placebo treatment will be temporarily interrupted while undergoing palliative therapy for brain metastases. If such patient does not have disease progression elsewhere, development of brain metastasis will not be considered a disease-progression event (clarification for purposes of secondary objective analysis).

If co-administered with nintedanib strong P-gp inhibitors (e.g., ketoconazole or erythromycin), may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of nintedanib. Management of side effects may require interruption, dose reduction or discontinuation of therapy with nintedanib/placebo.

Strong P-gp inducers (e.g., rifampicin, carbamazepine, phenytoin, and St. John's Wort) may decrease exposure to nintedanib. Co-administration with nintedanib/placebo should be carefully considered.

7.5 Duration of Treatment

Participants may remain on study and continue to receive a total of six 28-day cycles of open-label nintedanib (Phase I) or nintedanib/placebo (Phase II) treatment in the absence of disease progression, unacceptable toxicity or withdrawal from study, intercurrent illness that prevents further administration of treatment, participant's inability/refusal to comply with oral medication regimen, and participant's withdrawal from study. For patients who have disease progression (exceptions noted previously) before completing 6 months of nintedanib/placebo, patients may continue on study only if other systemic therapy is not planned/indicated and only after approval/discussion with the principal investigator, Dr. Grace Dy. Patients who require initiation of systemic therapy for disease progression should discontinue study treatment but should remain on protocol and be followed for analysis of secondary endpoints unless patient elects to discontinue protocol follow-up procedures.

7.6 Treatment Discontinuation

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

Reasons for treatment discontinuation should be classified as follows:

- Death

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

7.7 Compliance

Patients will be provided a pill diary to record each dose of nintedanib/placebo (date, time, number of capsules) taken. A pill count will be performed at each subsequent clinic visit/evaluation.

8 INVESTIGATIONAL PRODUCT

8.1 Drug Shipment

Nintedanib/placebo will be provided by Boehringer Ingelheim and shipped to the participating sites.

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

8.2 Pharmaceutical information

8.2.1 Nintedanib - Study Drug

Substance (INN):	Nintedanib
Pharmaceutical Form:	Soft gelatine capsule
Pharmaceutical Code	BIBF1120
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit Strength:	100 mg and 150 mg capsules
Daily Dose:	Dose escalation portion: dose according to dose level assigned. During Phase II randomized study: 200 mg orally twice daily (without durvalumab) or dose determined from dose escalation portion in combination with durvalumab. Dose reduction according to **Section Error! Reference source not found.**.
Duration of Use:	Continuous daily dosing until progression of disease (see exception regarding brain metastases in Section 7.3.5) or until criteria for interruption of treatment is met. The maximum time on treatment will be 6 months.
Route of Administration:	Oral
Posology:	Twice daily (to be swallowed whole, 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)

8.2.2 Placebo - Comparator

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:	Matching capsules orally twice daily, dose reduction according to **Section Error! Reference source not found.**.
Duration of Use:	Continuous daily dosing until progression of disease (see exception regarding brain metastases in Section 7.3.5) or until criteria for interruption of treatment is met. The maximum time on treatment will be 6 months.
Route of Administration:	Oral
Posology:	Twice daily (to be swallowed whole, 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)

8.3 Storage and Stability

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

The current shelf life for all dosage strengths and formulations is 60 months. The capsules are packaged in child resistant high density polyethylene (HDPE) bottles, and have to be stored below 30°C.

Refer to the Investigator's brochure for full details on storage requirements and stability.

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

8.4 Handling and Disposal

The Investigator or designee will be responsible for dispensing and accounting for all investigational drug provided by Boehringer Ingelheim exercising accepted medical and pharmaceutical practices. Study drugs must be handled as cytotoxic agents and appropriate precautions taken per the institution's environmentally safe handling procedures. All investigational drugs will be dispensed in accordance with the Investigator's prescription or written order.

All products dispensed will be recorded on a product accountability record. Records of product lot numbers and dates received will be entered on a product accountability form. This record will be reviewed by the Sponsor's staff or representative during periodic monitoring visits. It is the Investigator's responsibility to ensure that an accurate record of investigational drug issued and returned is maintained.

Unused/expired capsules will be destroyed according to standard practices after properly accounting for the dispensing. Partially used vials of study drug will not be re-used for other participants.

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

8.5 Treatment Unblinding

Treatment unblinding may occur only if the knowledge of treatment assignment will materially change the planned management of a medical emergency. Envelopes containing treatment arm in formation (drug versus placebo) will be stored at the site pharmacy. Given the constitution of the drug, unblinding is not anticipated for any circumstance. Any request for unblinding should be discussed with the sponsor's medical monitor, Grace Dy, MD.

8.6 Durvalumab

Durvalumab is commercially available and will be dispensed per standard of care. Durvalumab will not be provided by this study and will be paid for by the patient's insurance carrier as part of standard of care treatment post chemo-radiation.

9 STUDY PROCEDURES

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

9.1 Participant Randomization and Registration

Phase I:

Subjects enrolled to the dose escalation portion of the study will NOT undergo randomization (i.e. not blinded to treatment) and will receive the active drug nintedanib according to the dose level assigned.

Phase II:

Patients will be randomized, by site, at the baseline visit into one of 2 arms, placebo or nintedanib, in a 1:2 fashion using a block-permutation design, but this will be masked to the investigator and patient. The randomization list will be generated by the study biostatistician.

Patients will be included in data analyses according to their randomized treatment assignment irrespective of the treatment actually received (intent-to-treat).

Patients will be assigned a study number in the order of randomization.

No study-specific procedures are to be performed until informed consent is obtained. Eligibility of each patient will be established prior to study enrollment.

9.2 Baseline Evaluations

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

- Medical history
- Smoking History (Type of Tobacco/Nicotine Product [cigarettes, cigars, pipes, chew tobacco, nicotine gum, nicotine patch, other], current use, how long ago product use stopped.)
- Physical examination, including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight, and height)
- Hematology [(i.e., complete blood count (CBC) with automated differentials)](or, the physicians' discretion): WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils,), % lymphocyte total, absolute lymphocyte total, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated). Note: Participants experiencing Grade 4 neutropenia should be monitored according to institutional guidelines. As needed at each study visit as determined by the Investigator or study physician.
- Chemistry (i.e., complete metabolic panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).
- Pulmonary Function Test
- ECOG Performance Status (Appendix C)
- Urinalysis to assess proteinuria
- Tumor/Disease Assessment

- Concomitant Medications: List any ongoing medications with an onset within 1 week of first dose of study drug.
- Adverse Events

9.3 Evaluations Performed at Cycle 1 Day 1

The following will be performed on Cycle 1 Day 1 or within 7 days prior to drug administration:

- Medical history
- Physical examination, including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, and body weight)
- Hematology [(i.e., complete blood count (CBC) with automated differentials)](or, the physicians' discretion): WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils,), % lymphocyte total, absolute lymphocyte total, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated). Note: Participants experiencing Grade 4 neutropenia should be monitored according to institutional guidelines. As needed at each study visit as determined by the Investigator or study physician.
- Chemistry (i.e., complete metabolic panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).
- 25-OH Vitamin D level (one 3 mL gold-top tube)
- Mitochondrial DNA Assay (one 10 mL heparinized green-top tube)
- miRNA Biochip Assay (one 10 mL red-top tube)
- QOL Questionnaire (Appendix F)
- Pregnancy Test (Urine or Serum) for females of child-bearing potential
- ECOG Performance Status (Appendix C)
- Dispense nintedanib/Placebo
- Concomitant Medications
- Adverse Events

9.4 Evaluations Performed on Day 1 of Cycle 2 through Cycle 6

- Medical history
- Physical examination, including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, and body weight)
- Hematology [(i.e., complete blood count (CBC) with automated differentials)](or, the physicians' discretion): WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils,), % lymphocyte total, absolute

lymphocyte total, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated). Note: Participants experiencing Grade 4 neutropenia should be monitored according to institutional guidelines. As needed at each study visit as determined by the Investigator or study physician.

- Chemistry (i.e., complete metabolic panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).
- Mitochondrial DNA Assay (Cycle 3 and Cycle 6 only) (one 10 mL heparinized green-top tube)
- QOL Questionnaire (Cycle 3 and Cycle 6 only) (Appendix F)
- ECOG Performance Status (Appendix C)
- Tumor/Disease Assessment (Cycle 3 and Cycle 6 only)
- Dispense nintedanib/Placebo
- Concomitant Medications
- Adverse Events

9.5 Evaluations Performed Anytime When Radiation Pneumonitis is Suspected to Have Occurred (Within the First 6 Months After Completing Radiation Therapy)

- Medical history
- Physical examination, including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, and body weight)
- Hematology [(i.e., complete blood count (CBC) with automated differentials)](or, the physicians' discretion): WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils,), % lymphocyte total, absolute lymphocyte total, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated). Note: Participants experiencing Grade 4 neutropenia should be monitored according to institutional guidelines. As needed at each study visit as determined by the Investigator or study physician.
- Chemistry (i.e., complete metabolic panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).
- Mitochondrial DNA Assay (one 10 mL heparinized green-top tube)
- QOL Questionnaire (Appendix F)
- ECOG Performance Status (Appendix C)
- Tumor/Disease Assessment
- Concomitant Medications
- Adverse Events

9.6 Evaluations Performed at End of Active Treatment

The following evaluations will be performed within 30 days at the end of treatment or at time of treatment discontinuation:

- Medical history
- Physical examination, including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, and body weight)
- Hematology [(i.e., complete blood count (CBC) with automated differentials)](or, the physicians' discretion): WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils,), % lymphocyte total, absolute lymphocyte total, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated). Note: Participants experiencing Grade 4 neutropenia should be monitored according to institutional guidelines. As needed at each study visit as determined by the Investigator or study physician.
- Chemistry (i.e., complete metabolic panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).
- Pulmonary Function Test
- QOL Questionnaire (Appendix F)
- ECOG Performance Status (Appendix C)
- Concomitant Medications
- Adverse Events

9.7 Evaluations Performed 76 Days – 97 Days After the Last Nintedanib Dose

- Medical history
- Physical examination, including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, and body weight)
- Mitochondrial DNA Assay (one 10 mL heparinized green-top tube)
- QOL Questionnaire (Appendix F)
- ECOG Performance Status (Appendix C)
- Tumor/Disease Assessment
- Concomitant Medications
- Adverse Events

9.8 Evaluations Performed 166 Days – 187 Days After the Last Nintedanib Dose

- Medical history
- Physical examination, including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, and body weight)

- Hematology [(i.e., complete blood count (CBC) with automated differentials)](or, the physicians' discretion): WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils,), % lymphocyte total, absolute lymphocyte total, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated). Note: Participants experiencing Grade 4 neutropenia should be monitored according to institutional guidelines. As needed at each study visit as determined by the Investigator or study physician.
- Chemistry (i.e., complete metabolic panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).
- Pulmonary Function Test
- QOL Questionnaire (Appendix F)
- ECOG Performance Status (Appendix C)
- Tumor/Disease Assessment
- Concomitant Medications
- Adverse Events

9.9 Long Term Follow-Up Evaluations

Follow-up to 2.5 years after completing nintedanib/placebo treatment to be conducted as part of routine/standard care. Information may be conducted by phone only if patient relocated/unable to return to treating institution (if patient unable to return, phone call follow-up includes QOL Questionnaire (Appendix F) only if possible).

- Medical history
- Physical examination, including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, and body weight)
- Hematology [(i.e., complete blood count (CBC) with automated differentials)](or, the physicians' discretion): WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils,), % lymphocyte total, absolute lymphocyte total, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated). Note: Participants experiencing Grade 4 neutropenia should be monitored according to institutional guidelines. As needed at each study visit as determined by the Investigator or study physician.
- Chemistry (i.e., complete metabolic panel (CMP): chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).
- QOL Questionnaire (Appendix F)
- ECOG Performance Status (Appendix C)

- Tumor/Disease Assessment
- Concomitant Medications
- Adverse Events

9.10 Schedule of Procedures and Observations

The schedule of procedures and observations for this study is summarized in Table 5 below.

Table 5 Schedule of Procedures and Observations

Evaluation	Baseline[1]	Active Treatment Stage			Surveillance Stage			
		Cycle 1 Day 1 (or within 7 days prior to drug administration)	Cycle 2 through Cycle 6 Day 1 (± 7 days)	Anytime when radiation pneumonitis is suspected to have occurred (within the first 6 months after completing radiation therapy)	End of Active Treatment (within 30 days of last nintedanib dose)	Between 76 to 97 days after last nintedanib dose	Between 166 to 187 days after last nintedanib dose	Long Term Follow-Up[2]
Medical History	X	X	X	X	X	X	X	X
Smoking History	X							
Pre-Existing Conditions	X							
Physical Examination, including vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure, body weight, height)[3]	X	X	X	X	X	X	X	X
Hematology[4]	X	X	X	X	X		X	X
Chemistry[5]	X	X	X	X	X		X	X
25-OH Vitamin D level (Section 9.12)		X						
Mitochondrial DNA and Cytokine Assay (Section 9.11)[9]		X	X[7]	X		X		
miRNA Biochip Assay (Section 9.12)		X						
Pulmonary Function Test	X				X		X	
QOL Questionnaire (Appendix F)		X	X[7]	X	X	X	X	X
Pregnancy Test (Urine or Serum)[11]		X						

Evaluation	Baseline[1]	Active Treatment Stage			Surveillance Stage			
		Cycle 1 Day 1 (or within 7 days prior to drug administration)	Cycle 2 through Cycle 6 Day 1 (± 7 days)	Anytime when radiation pneumonitis is suspected to have occurred (within the first 6 months after completing radiation therapy)	End of Active Treatment (within 30 days of last nintedanib dose)	Between 76 to 97 days after last nintedanib dose	Between 166 to 187 days after last nintedanib dose	Long Term Follow-Up[2]
Urinalysis[10]	X							
ECOG Performance Status (Appendix C)	X	X	X	X	X	X	X	X
Tumor/Disease Assessment[6]	X		X[7]	X		X	X	X
Study Drug/Placebo		X	X					
Durvalumab		X[12]						
Concomitant Medications	X[8]	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X			

Evaluation	Baseline[1]	Active Treatment Stage			Surveillance Stage			
		Cycle 1 Day 1 (or within 7 days prior to drug administration)	Cycle 2 through Cycle 6 Day 1 (± 7 days)	Anytime when radiation pneumonitis is suspected to have occurred (within the first 6 months after completing radiation therapy)	End of Active Treatment (within 30 days of last nintedanib dose)	Between 76 to 97 days after last nintedanib dose	Between 166 to 187 days after last nintedanib dose	Long Term Follow-Up[2]

1 Performed within 4 weeks prior to initiation of treatment.

2 Follow-up to 2.5 years after completing nintedanib/placebo treatment to be conducted as part of routine/standard care. Information may be conducted by phone only if patient relocated/unable to return to treating institution(if patient unable to return, phone call follow-up includes QOL Questionnaire (Appendix F) only if possible).

3 Height collected at baseline only.

4 Hematology [(i.e., complete blood count (CBC) with automated differentials)](or, the physicians' discretion): WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils,), % lymphocyte total, absolute lymphocyte total, platelet confirmation (as clinically indicated), and differential confirmation (as clinically indicated). Note: Participants experiencing Grade 4 neutropenia should be monitored according to institutional guidelines. As needed at each study visit as determined by the Investigator or study physician.

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

6 For routine tumor assessment, CT abdomen and pelvis with high-resolution CT chest (HRCT) should be obtained. HRCT chest alone will be sufficient whenever new onset of dyspnea occurs and radiation pneumonitis is suspected to have occurred (within the first 6 months after completing radiation therapy). CT chest obtained/configured at 1.25 mm slice thickness is an acceptable alternative to HRCT. Maximum slice thickness allowed for CT chest is 2.5 mm. Use of intravenous contrast for the CT studies is preferred but not mandatory.

7 To be performed prior to drug administration on Day 1 of Cycles 3 and 6 (± 7 days window) only.

8 Medications ongoing within 1 week prior to first dose of study drug.

9 Sample collection will be obtained anytime when radiation pneumonitis is suspected to have occurred (within the first 6 months after completing radiation therapy).

10 Urinalysis after baseline will be performed per clinical discretion / judgement.

11 For females of child-bearing potential.

12 Dose Escalation Phase: First two doses of Durvalumab as consolidation therapy will be administered together with cycle 1 day 1 and day 15 (-1/+7 days) of nintedanib. Subsequent doses will be administered according to institutional practice. Phase II: use of an immune checkpoint inhibitor, such as durvalumab, in the post-chemoradiation consolidation period is at the discretion of the treating physician.

9.11 Mitochondrial DNA and Cytokine Sampling

Sample collection will be obtained on:

- Cycle 1 Day 1
- Anytime when radiation pneumonitis is suspected to have occurred (within the first 6 months after completing radiation therapy)
- Additional assessment for Cycle 3 and Cycle 6 Day 1 (± 7 days)
- Between 76 to 97 days after last nintedanib dose

9.11.1 Blood Sample Collection and Processing

Whole blood samples for correlative studies will be collected via venipuncture using (1) 10 mL heparinized green-top tube and placed on ice for processing same day of collection. Plasma will be separated from whole blood within 30 minutes following the collection. Spin at 500 g for 10 minutes at room temperature then freeze supernatant into 0.5 mL aliquots of plasma at -70ºC or below until analyzed. The screw cap polypropylene cryogenic tube will be labeled with the participant's MR number (for RPCI participants), participant's initials, participant's study number, clinical study number, protocol time point, dose, and protocol day. Samples collected at RPCI will be processed and stored at RPCI's Hematologic Procurement Facility until analysis in Dr. Segal's Laboratory.

9.11.2 Sample Handling and Shipment

Network sites will store samples until batch shipped to RPCI on a quarterly basis Monday – Thursday. Do not ship specimens on Fridays or on day before a holiday. Packaging should be clearly labelled as follows with e-mail notification:

Roswell Park Cancer Institute
Hematologic Procurement Facility
Basic Science Bldg. (GBSB) - 538
Attn: Linda Lutgen-Dunckley / Brandon Martens
Elm & Carlton Streets
Buffalo, New York 14263
716-845-8098
Linda.LutgenDunckley@RoswellPark.org / Brandon.Martens@RoswellPark.org

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

9.12 miRNA and Vitamin D Sampling

9.12.1 Blood Sample Collection and Processing

Serum samples for miRNA will be collected via venipuncture using (1) 10 mL red-top tube. 25-OH vitamin D serum sample will be collected via venipuncture using (1) 3 mL gold-top tube. Both sample collection will be obtained on:

- Cycle 1 Day 1

The screw cap polypropylene cryogenic tube will be labeled with the participant's MR number,(for RPCI participants) participant's initials, participant's study number, clinical study number, protocol time point, dose, protocol day, type of assay (miRNA or vitamin D). The samples will immediately be frozen at -70ºC or below until analyzed. Samples collected at RPCI will be processed and stored at RPCI's Hematologic Procurement Facility. Network sites may batch ship specimen to RPCI on a quarterly basis. 25-OH vitamin D testing will occur in RPCI Clinical Lab. Network sites will send 3 mL gold-top blood tube for 25-OH vitamin D samples to RPCI's Hematologic Procurement Facility for processing and storage until analysis. miRNA testing will be performed in Dr. Yun Wu's Laboratory at the end of the study.

9.12.2 Sample Handling and Shipment

Network Sites Processing & Handling Instructions for 25-OH Vitamin D 3 mL Gold Top Blood

- Mix gently by inverting the tube eight (8) times
- Allow blood to clot upright at room temperature for 30 minutes
- Centrifuge for 10 minutes at 1300g or until a complete barrier is formed
- DO NOT remove the top of the SST
- Spun Draw tube should be sent for testing – do not send un-centrifuged specimens
- Ship ambient same day of collection to RPCI

Serum samples collected at RPCI will be sent on ice for processing the same day of collection.

Serum samples collected at participating sites will be separated into 0.5 mL aliquots, frozen and stored at -70° or below until batched shipped quarterly Monday - Thursday. Do not ship specimens on Fridays or on day before a holiday. Packaging should be clearly labelled as follows with e-mail notification:

Roswell Park Cancer Institute
Hematologic Procurement Facility
Basic Science Bldg. (GBSB) - 538
Attn: Linda Lutgen-Dunckley / Brandon Martens
Elm & Carlton Streets
Buffalo, New York 14263
716-845-8098
Linda.LutgenDunckley@RoswellPark.org / Brandon.Martens@RoswellPark.org

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

10 EFFICACY EVALUATIONS

10.1 Objective Tumor Response

All protocol-defined imaging studies must be performed at the investigative site or sponsor-approved facility using protocol-defined parameters. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. RECIST 1.1 will be used to assess objective tumor response.

10.2 Target Lesions

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

- **Complete Response (CR):** Disappearance of all target lesions. Any lymph nodes must have a reduction in short axis to < 10 mm. Changes in tumor measurements must be confirmed by repeat studies performed no less than 6 weeks after the criteria for response are first met.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Changes in tumor measurements must be confirmed by repeat studies performed no less than 6 weeks after the criteria for response are first met.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as references the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameter while on study. Participants having a documented response with no confirmation of the response will be listed with stable disease.

10.3 Non-Target Lesions

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

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

10.4 Evaluation of Response

To determine time point response, refer to **Table 6**, and **Table 7** below.

Table 6 Time Point Response Criteria (+/- non-target disease)

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

Table 7 Time Point Response Criteria (non-target disease only)

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

1 If new or worsening lesions are found in the brain only, these are not considered disease progression for the purposes of this study. Non-CR/non-PD is preferred over SD for non-target disease since SD is used as endpoint for assessment of efficacy in trials so to assign this category when no lesions can be measured is not advised.

The best overall response is the best response recorded from the start of study treatment until the tumor assessment obtained upon completion of nintedanib/placebo treatment taking into account any requirement for confirmation. In general, the participant's best response assignment will depend on the achievement of both measurement and confirmation criteria and will be determined by combining the participant's status of target lesions, non-target lesions, and new lesions.

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

10.5 Confirmation Measurement

To be obtained as clinically warranted in cases of suspected tumor progression.

10.6 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is

preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- **Clinical Lesions:** Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- **Chest x-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Conventional CT and MRI:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- **PET-CT:** At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.
- **Ultrasound:** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- **Endoscopy, Laparoscopy:** The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete

pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

- **Tumor Markers:** Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response.
- **Cytology, Histology:** These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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

- **FDG-PET:** While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG PET imaging can be identified according to the following algorithm:
- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

10.7 Radiation Pneumonitis Score

Multidetector helical CT images of the chest will be obtained from the supraclavicular region to the level of adrenals with the patient in a supine position. A 5 mm slice thickness and appropriate DFOV will be applied during a single inspiratory breath hold acquisition. Post processing with a coronal and sagittal planes will be performed. IV contrast will be administered.

Images will be sent to PACS (Picture Archiving and Communications System) and viewed and analyzed on a workstation. For cases performed outside of RPCI, DICOM (Digital Imaging and

Communications in Medicine) archived images on CD disk will be sent to RPCI Radiology Department for central review.

Visual analysis will be performed by two thoracic radiologists who will independently record the pulmonary fibrosis score. The lungs will be divided into three zones. Upper zone is from the level of apex to the carina. Lower zone being inferior to the pulmonary veins. Middle zone is anywhere in between the two. Semi quantitative analysis will be performed for the presence of ground-glass opacity, consolidation, reticulation, mosaic perfusion, traction bronchiectasis and honeycombing for each lung zone and scored on a four point scale (0 = no involvement, 1 ≤ 25%; 2 = 26 - 50%; 3 = 51 - 75% and 4 ≥ 76%).A highest severity score for each of the 6 lung zones and overall highest volume of disease involvement will be calculated. Baseline, 3 month, 6 month, 9 month and 1 year follow-up HRCT images after completion of nintedanib/placebo treatment will be scored during the trial. The observers will be blinded to the treatment for the approximately 100 patients that will be recruited.

10.8 Radiation Treatment Field Central Review/Radiation Specifications (adapted from NCCN guidelines for NSCLC version 4.2014)

Central review will be performed and essential parameters such as V20 and MLD will be recorded for each patient. For treatment volume consideration for 3D-conformal RT, planning target volume should be defined using the ICRU-50 and ICRU-62(international Commission on Radiation Units and Measurements Reports 50 and 62) reports, based on gross tumor volume (GTV), plus clinical target volume margins for microscopic diseases, internal target volume margins for target motion, and margins for daily set-up errors. ICRU Report 83 is used for IMRT. The ACR-ASTRO guidelines are also useful (http://www.acr.org/~/media/eabb986bc4ff4a78b53b001a059f27b3.pdf). Additional volume considerations are described in the NCCN algorithm. It is essential to evaluate the dose volume histogram (DVH) of critical structures and to limit the doses to the spinal cord, lungs, heart, esophagus and brachial plexus to minimize normal tissue toxicity (Refer to Table 5 under Principles of Radiation Therapy for NSCLC, http://www.nccn.org/professionals/physician_gls/f_guidelines.asp). These limits are empirical.

Treatment planning should be based on CT scans obtained in the treatment position. Intravenous contrast CT scans are recommended for better target delineation whenever possible, especially in patients with central tumors or with nodal diseases. PET/CT is recommended for select patients (i.e., those with significant atelectasis, when IV contrast is contraindicated). PET/CT can significantly improve the target accuracy. Whenever feasible, respiratory motion should be managed. Acceptable methods of accounting for tumor motion, per the AAPM Task Group 76 guideline, are described in the Principles of Radiation Therapy of the NCCN NSCLC algorithm. The algorithm also provides recommendations for patients receiving chemoradiation, photon beams or IMRT.

11 SAFETY EVALUATION

11.1 Adverse Events

11.1.1 Definition

An adverse event or adverse experience (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite'). To capture binary classifications in the CRF, attributions of possible, probable or definite will fall under the "YES" category while attributions of unlikely and unrelated will fall under the "NO" category.

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

11.1.1.1 Diagnosis Versus Signs and Symptoms

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

11.1.1.2 Adverse Events Occurring Secondary to Other Events

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

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

11.1.1.3 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

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

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

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

11.1.1.4 Preexisting Medical Conditions (Baseline Conditions)

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

11.1.2 Grading and Relationship to Drug

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

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

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

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

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

11.1.3 Reporting Adverse Events

Table 8 Guidelines for Routine Adverse Event Reporting for Phase 1 Studies (Regardless of Expectedness)

Table 9 Guidelines for Routine Adverse Event Reporting for Phase 1 Studies (Regardless of Expectedness)**Attribution**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Unrelated	X	X	X	X
Unlikely	X	X	X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

Table 10 Guidelines for Routine Adverse Event Reporting for Phase 2 Studies (Regardless of Expectedness)

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

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

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an AE in the CRF.

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

11.2 Serious Adverse Events

11.2.1 Definition

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

- Death.
- A life-threatening adverse event (experience). Any AE that places a participant or participant, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does **NOT** include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.
- Patients may be hospitalized for administrative or social reasons during the trial (e.g., days on which infusion takes place, long distance from home to site). These and other hospitalizations planned at the beginning of the trial do not need to be reported as an SAE.

11.2.2 Reporting Serious Adverse Events

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

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

SAEs identified as an Unanticipated Problem by the Investigator must be reported. Please refer to Section 11.5 for details on reporting Unanticipated Problems.

11.3 Investigator Reporting: Notifying Boehringer Ingelheim

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

Any gastrointestinal and non-gastrointestinal perforations, leakage, fistula formation, abscess.

In such case the following additional information need to be collected, documented in the respective comment field of the BI IIS SAE form 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 and 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 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 > 5 x 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 B 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.

11.3.1 SAE reporting to Boehringer Ingelheim (BI)

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

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through 30 days following cessation of treatment) will be collected, documented by the investigator.

The investigator shall report all SAEs and non-serious AEs which are relevant to a reported SAEs and AESIs by fax using BI IIS SAE 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
900 Ridgebury Road
Ridgefield, CT 06877
Fax: 1-203-837-4329

AND NCCN at ORPReports@nccn.org or 215-358-7699

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship and expectedness with the investigational drug to all AEs as defined in the listed adverse event section of Boehringer Ingelheim's (BI's) Investigator Brochure for the Product.

The investigator does not need to actively monitor patients for adverse events once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred after the patient has completed the clinical trial (including any protocol specified follow-up period), it should be reported to BI if considered relevant by the investigator.

Investigators MUST report within 5 business days upon becoming aware, to Boehringer Ingelheim ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention.

11.4 Follow-Up for Serious Adverse Events

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

11.5 Unanticipated Problems

11.5.1 Definition

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

- Unexpected (in terms of nature, severity, or frequency) given:
  a) The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.
  b) The characteristics of the participant population being studied.
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is also deemed **Serious** per **Section 11.2**.

11.5.2 Reporting Unanticipated Problems

Unanticipated problem reporting will begin at the time of participant consent. The Unanticipated Problem Form will be submitted to the RPCI's Clinical Research Services (CRS) Compliance Office within 1 business day of becoming aware of the Unanticipated Problem.

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

11.6 FDA Reporting

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

Within 7 Calendar Days

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

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

Within 15 Calendar Days

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

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

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

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

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

Reporting Process

The principal investigator or designee will complete and submit a FDA Form 3500A MedWatch as well as BI fax cover sheet for any event that meets the above criteria. Forms will be submitted to the CRS Compliance Office via email to CRSCompliance@RoswellPark.org.

11.7 Criteria for Closing of study (stopping rule):

There was one patient enrolled on this study who developed massive fatal bleeding of unknown origin and this patient expired (grade 5). This fatal bleeding (grade 5) occurred prior to starting cycle 4. If one more bleeding-related toxicity of grade 3 or greater occurs (as determined by the PI or treating physician as - possibly, probable or definite related to study) , the study will be stopped and all patients will discontinue drug.

12 DATA AND SAFETY MONITORING

Dose Escalation:

Phase 1 studies will be reviewed at the scheduled Roswell Park Early Phase Clinical Trials (EPCT) Program meetings and the minutes are forwarded to the IRB for review.

Phase II:

The Roswell Park Data Safety Monitoring Committee (DSMC) will assess the progress of the study, the safety data, and critical efficacy endpoints. The DSMC will review the study annually and will make recommendations that include but are not limited to; (a) continuation of the study, (b) modifications to the design (c) or termination of the study. Since the AE and SAE reports from all study sites will be sent to Roswell Park, the Roswell Park DSMC will be responsible for overall monitoring of the study.

13 STATISTICAL METHODOLOGY

The primary endpoint of the study is the rate of CTCAE Grade 2 or higher radiation pneumonitis at 6 months after completion of chemoradiation:

- To compare the rate of symptomatic radiation pneumonitis in patients who received nintedanib versus placebo.

13.1 Sample Size Determination

A maximum of 18 participants will be enrolled to the non-randomized dose escalation portion of this study. The number of participants required is a function of the unknown dose-toxicity relationship.

A maximum of 99 participants will be enrolled to the randomized Phase 2 portion of this study (excluding patients replaced due to ineligibility or inability to start therapy). Participants will be randomized in a 1:2 fashion, stratified by chemotherapy regimen (i.e., platinum with etoposide, platinum with taxane, platinum with pemetrexed) and immune therapy (i.e. durvalumab), into the placebo and nintedanib arms. Accrual is expected to take 4 years.

Evaluable patients will be any patient who receives at least one dose of study drug.

The sample size justification is based on the primary analysis: a comparison of the rate of radiation pneumonitis at 6 months after completion of chemoradiation between the placebo and nintedanib arms, stratified by chemotherapy regimen (i.e., platinum with etoposide, platinum with taxane, platinum with pemetrexed) and immune therapy exposure (i.e. durvalumab), using the one-sided Cochran-Mantel-Haenszel (CMH) exact test at a significance level of 0.05. The expected rate of Grade 2 or higher radiation pneumonitis is 30% in the placebo arm, and a decrease in this rate to 10% in the nintedanib arm would be considered clinically significant; which is equivalent to a common odds ratio (COR) of approximately 0.26.

Using a simulation based on the proposed study design; if there is no improvement in the rate of radiation pneumonitis (COR = 1.0), then there is a 59.0% chance of stopping early for futility. If the true COR is 0.26, then there is only a 10.6% chance of stopping early for futility. If the true common odds ratio is 0.26, then there is an 80.1% chance of detecting a significant reduction in the rate of Grade 2 or higher radiation pneumonitis in the nintedanib arm. If the COR is 1.0, then the chance of detecting a significant reduction is 4.2%; which can be considered the effective type-I error rate.

As of the November 2018 Amendment (Amendment #6), patients receiving durvalumab will be eligible for enrollment in the study. Since the combination of nintedanib and durvalumab has not been tested in this setting, an initial non-randomized dose escalation study will be carried out for patients treated with immune therapy (i.e. durvalumab). This dose escalation phase will follow a standard 3+3 design starting with dose level 1 (Table 1) and continuing until the MTD is identified (maximum dose level at which 1 or fewer DLTs are observed in 6 patients). A total of 3 dose levels will be explored, hence a maximum of 18 patients will be accrued to this portion of the study.

13.2 Stratification

As of the November 2018 Amendment (Amendment #6), patients receiving durvalumab (and in the future, other immunotherapy agents) will be eligible for enrollment in the study. Therefore, exposure to immunotherapy agents will be added as an additional stratification factor.

The randomization and the significance tests applied in the analyses will be stratified by chemotherapy regimen (i.e., platinum with etoposide, platinum with taxane, platinum with pemetrexed) and exposure to immunotherapy agents.

13.3 Randomization

Phase II: Patients will be randomized to either the placebo or nintedanib arm in a 1:2 fashion using a stratified permuted block randomization scheme. The randomization lists to be used in this study will be generated by the study biostatistician. Patients will be included in data analyses according to their randomized treatment assignment irrespective of the treatment actually received (intent-to-treat). After randomization, initiation of the study intervention will take place within the timeframe specified in the eligibility period. Patient randomization will be done electronically by the Department of Biostatistics at RPCI.

The activity of the dose escalation patients receiving durvalumab will not hold enrollment for patients not exposed to immunotherapy agents. (i.e. patients can enroll to Phase II ahead of dose

escalation if the choice is not to give durvalumab. If patient is going to receive durvalumab, it is required to go through dose escalation first until MTD is determined).

13.4 Demographics and Baseline Characteristics

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

13.5 Primary Analysis

Consider a placebo controlled, randomized trial in which patients are stratified by chemotherapy regimen (i.e., platinum with etoposide, platinum with taxane, platinum with pemetrexed) and randomized (1:2 ratio) to a treatment group (placebo versus nintedanib). The primary objective of the study is to evaluate the rate of radiation pneumonitis at 6 months after completion of chemoradiation in patients with unresectable Stage II/III/oligometastatic IV NSCLC who completed chemoradiation followed by nintedanib versus placebo. The primary outcome is radiation pneumonitis status (defined as symptomatic CTC Grade 2 or higher radiation pneumonitis at 6 months after completion of chemoradiation), which is treated as a dichotomous variable.

The primary objective will be assessed using the intent-to-treat principle and a one-sided exact test about the CMH COR:

$$H0: \theta \geq 1$$

$$HA: \theta < 1$$

Where θ is the COR for the odds of Grade 2 or higher radiation pneumonitis in the nintedanib treated versus placebo treated populations, stratified by chemotherapy regimen (i.e., platinum with etoposide, platinum with taxane, platinum with pemetrexed). A one-sided test is performed as the rate of radiation pneumonitis is expected to decrease in the nintedanib arm over the placebo arm; that is expect to be $\theta < 1$. The critical value and corresponding rejection region for the one-sided test will obtained using the exact methods available in SAS v9.4 and maintaining a significance level of 0.05 while accounting for the interim analysis. As of the November 2018 Amendment (Amendment #6), the primary analysis will be conducted excluding the maximum of 18 patients in the durvalumab dose escalation. As a sensitivity analysis, the primary analysis will be repeated with the 6 patients treated at the MTD level from the dose-escalation portion.

13.6 Safety Analysis

The frequency of toxicities will be tabulated by grade. All participants who receive any study treatment will be considered evaluable for toxicity.

13.7 Secondary Analyses

The OS and PFS will be reported by study arm using standard Kaplan-Meier methods. Comparisons of OS and PFS between study arms may utilize the two-sided stratified log-rank test. With a sample size of n = 33 in the control and n = 66 in the treatment group, there is an 80% chance of detecting a hazard ratio of 0.53 or smaller (with two-sided alpha of 0.05). If the

median PFS in the placebo arm is approximately 2 months, then this would be equivalent to detecting an increase in PFS of at least 1.75 months.

The overall and sub-category QOL and symptom scores (ranging from 0 to 68) will be reported by study arm and time using the appropriate descriptive statistics. Changes in the QOL and symptom scores may be compared between study arms using the Wilcoxon rank sum or independent sample t-tests, as appropriate. No adjustments for multiple testing will be made as this is a secondary analysis. With this sample size, there will be an 80% chance of detecting a change of at least 0.5 standard deviations. A 0.5 standard deviations is equivalent to approximately 9.1 points for the overall QOL and symptoms score; therefore, this study should be able to identify clinically relevant changes in QOL (59).

The PFTs will be reported by study arm and time using the appropriate descriptive statistics. Changes in PFTs, relative to baseline, will be evaluated within each study arm using the Wilcoxon signed rank or paired t-tests, as appropriate. Changes in PFTs may be compared between study arms using the Wilcoxon rank sum or independent sample t-tests, as appropriate. No adjustments for multiple testing will be made as this is a secondary analysis. With this sample sizes, we will have an 80% chance of detecting a change of at least 0.5 standard deviations.

The RP scores will be reported by study arm and time using the appropriate descriptive statistics. Changes in RP scores, relative to baseline, will be evaluated within each study arm using the Wilcoxon signed rank or paired t-tests, as appropriate. Changes in RP scores may be compared between study arms using the Wilcoxon rank sum or independent sample t-tests, as appropriate. No adjustments for multiple testing will be made as this is a secondary analysis. With our sample sizes, we will have an 80% chance of detecting a change of at least 0.5 standard deviations.

The complete response and complete/partial response rates will be reported by study arm and chemotherapy regimen using Wilson 95% confidence intervals. The responses rates will be compared between study arms using the CMH exact test.

The tCLN (tethered cationic lipoplex nanoparticle biochip), mCLN (microfluidic cationic lipoplex nanoparticle biochip) and qRT-PCR (real-time quantitative reverse transcription-polymerase chain reaction) measurements for the expression of miR-1, -21, -127 and -155 will be made on sera collected from NSCLC patients with and with no radiation pneumonitis. The miR expressions, vitamin D levels, and mitochondrial DNA levels will be treated as continuous and reported by radiation pneumonitis status (no versus yes) using the mean, median and standard deviation. Comparisons will be made between groups using a two-sided permutation t-test, as there is no a priori notion of which group will have higher expression.

A pilot model, using the 4 miR expression levels as the biomarker, will be built for classification of patients into 1 of 2 patient populations: radiation pneumonitis versus no radiation pneumonitis. Two classification models will be considered. The first model will treat the miR expressions as dichotomous variables, where the Youden's index method will be used to identify an appropriate threshold. The resulting threshold will maximize the correct classification rate a given miR expression alone was used to classify patients. The second model will treat the miR expressions as continuous variables. Both classification models will be constructed in a similar

fashion using multivariate logistic regression, such that the resulting model predicts the probability of radiation pneumonitis. A set of candidate variables will be obtained from miR expressions and relevant patient characteristics (demographic and clinical). Standard variable reduction techniques will be applied if the number of candidate variables grows large. The variables in the final model will be selected from the set of candidate variables, including possible two-way interaction terms, using forward selection (alpha entry = 0.05) followed by backward elimination (alpha exit = 0.05). Models are fit using Firth's penalized function and model assumptions are verified graphically. Standard bootstrap and cross-validation techniques will be used to calibrate model coefficients. Model performance will be evaluated using calibration plots, receiver operating characteristic (ROC) curves, area under the ROC curve (AUC) and a decision curve. In both models the Youden's index method can also be used to determine the optimal threshold probability for classifying patients, from which standard classification measures can be obtained (sensitivity, specificity, positive predictive value and negative predictive values). As an alternative modeling strategy, classification and regression tree (CART) analysis may also be considered to develop a model using only the miR expressions. These analyses will be repeated using vitamin D, cytokine and mitochondrial DNA levels, alone and in combination with miR expression, to develop classification models.

All secondary analyses will be conducted in SAS v9.4 (Cary, NC), except for CART analysis conducted in R v2.12, at a significance level of 0.05.

13.8 Interim Analysis

An interim analysis for futility when the first n_1=33 patients have completed 6-months of follow-up post-chemoradiation; that is, when the first n_1=33 patients are evaluable for the primary end-point. If the estimated COR is greater than or equal to 0.8, then the study will stop early for futility. Otherwise, the study will continue and enroll and additional n_2=66 patients. Additionally, at this time the safety profile of the treatment arms may be evaluated and considered in the decision for study continuation.

If the true COR is = 1.0 (no improvement in the nintedanib arm), then there is a 59.0% chance of stopping early for futility. If the true COR is 0.26, then there is only a 10.6% chance of stopping early for futility.

14 CORRELATIVE STUDIES

14.1 Mitochondrial DNA and Cytokine Analysis

Extracellular mitochondrial DNA and cytokine analysis will be performed in the Segal laboratory at RPCI.

Total DNA will be extracted from plasma using a DNA purification kit. Ct values of mitochondrial DNA in plasma samples will be determined by qPCR using cytochrome B primers, and the concentrations of mitochondrial DNA will be calculated based on a standard curve consisting of known concentrations of purified mitochondrial DNA. All samples will be analyzed in triplicate wells and average concentrations per sample will be determined.

14.2 miRNA Analysis

miRNA biochip analysis will be performed at the Wu laboratory at RPCI.

15 ETHICAL AND REGULATORY STANDARDS

15.1 Ethical Principles

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

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

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

15.2 Informed Consent

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

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

16 STUDY RESPONSIBILITIES

16.1 Data Collection

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

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

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

When data entry is complete, data management will review the data and will query any missing, incomplete, or invalid data points for resolution by the Clinical Research Coordinator and Investigator. Once all queries have been resolved, the data can be released to the statistician for analysis.

16.2 Maintenance of Study Documents

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

17 ADMINISTRATIVE RULES

17.1 Revisions to the Protocol

RPCI may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation. Approval must be obtained of any amendments prior to implementation at each participating institution from their respective IRBs.

17.2 Termination of the Study

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

17.3 Confidentiality

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

18 APPENDICES

Appendix A. Instructions for Network Sites

1. CONTACT INFORMATION

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

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

2. INFORMED CONSENT

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

3. PARTICIPANT REGISTRATION

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

RPCI does not grant exceptions to eligibility criteria.

Phase 1 Protocol Registration Instructions

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

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

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

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

Phase 2 Protocol Registration Instructions

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

4. STUDY DEVIATIONS

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

5. STUDY DOCUMENTATION

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

6. DRUG ACCOUNTABILITY

Drug accountability must be strictly maintained.

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

7. SERIOUS ADVERSE EVENT REPORTING

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

- RPCI SAE Source form
- MedWatch 3500A (modify as required per protocol)
- Refer to **Section 11.3** for details regarding SAE reporting to BI and NCCN.

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

8. UNANTICIPATED PROBLEM REPORTING

An unanticipated problem (UP) is any incident, experience, or outcome that meets all of the criteria in **Section 11.5**.

For all adverse events occurring that are unanticipated and related or possibly related to the research drug, biologic or intervention, the participating physician or delegated research staff

from each site will notify their local **IRB in accordance with their local institutional guidelines**. The site must also notify the RPCI Network Monitor within 1 business day of being made aware of the Unanticipated Problem by completing the **RPCI Unanticipated Problem Report Form** and faxing or emailing it to the RPCI Network Monitor.

Appendix B. Procedures for the Follow-Up of a Potential Drug-Induced Liver Injury Case (Hy`s Law Case)

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 (10 - , 15 x ULN), or the combination of hepatocellular injury (aminotransferase elevation $\geq$ 3 x ULN) and altered liver function (hyperbilirubinemia $\geq$ 2 x ULN) 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 > 2 x 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 > 5 x 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 nintedanib.

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

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

Procedures

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

Replication of the following laboratory tests for confirmation within 48 hours:

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

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

An evaluation of the patient within 48 hours with respect to but not limited to:

- Abdominal ultrasound or clinically appropriate other imaging and investigations adequate to rule out biliary tract, pancreatic, intra- or extrahepatic pathology, e.g., bile duct stones, neoplasm, hepatic tumor involvement, biliary tract, pancreatic or intrahepatic pathology, vascular hepatic conditions such as portal vein thrombosis or right heart failure. These data need to be collected, documented in the respective field of the eCRF/CRF/additional documentation form, and the respective SAE form has to be updated and forwarded to BI.
- Detailed history of current symptoms and concurrent diagnoses and medical history.
- Detailed history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations and e.g., steroids as concomitant supportive

treatment), alcohol use, recreational drug use, and special diets detailed history of exposure to environmental chemical agents.

In case that both imaging and laboratory value did not unequivocally confirm cholestasis as the reason of ALT/AST increase, in particular if AP < 2 x ULN, then please complete the following laboratory tests:

- Clinical chemistry (i.e., alkaline phosphatase, cholinesterase (either plasma or red blood cell), albumin, PT or INR, CK, CK-MB, ceruloplasmin*, α-1 antitrypsin*, transferrin, ferritin, amylase*, lipase*, fasting glucose*, cholesterol, triglycerides)
- Serology (i.e., hepatitis A (Anti-IgM, Anti-IgG), hepatitis B (HbsAg, anti-HBs, DNA), hepatitis C (anti-HCV, RNA if anti-HCV positive), hepatitis D (anti-IgM, Anti-IgG)*, hepatitis E (anti-HEV, anti-HEV IgM, RNA if anti-HEV IgM positive)*, anti-smooth muscle antibody (titer)*, anti-nuclear antibody (titer)*, anti-LKM (liver-kidney microsomes) antibody*, anti-mitochondrial antibody*, Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM))
- Hormones, tumor marker (i.e., TSH*)
- Hematology (i.e., thrombocytes*, eosinophils*)

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

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

In case that transaminases and/or bilirubin increase despite cessation of the experimental therapy, more frequent intervals will be warranted.

Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and Good Clinical Practices

Appendix C. ECOG Performance Status Scores

Description	Status
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead	5

Appendix D. Calculation for Creatinine Clearance

Creatinine clearance will be calculated using the Cockcroft and Gault method as shown below.

Men: $CrCL = [(140\text{-}YR) \times IBW] / (PCr \times 72)$

Women: $CrCL = 0.85 \times [(140\text{-}YR) \times IBW] / (SCr \times 72)$

Where:

CrCL is creatinine clearance, mL/min;

IBW is ideal body weight, kg;

PCr is plasma creatinine, mg/dL; and

YR is age, y.

Appendix E. Patient Diary

Study No.: _____ **Subject's Name:** _____

Drug Name: _____ **Cycle:** _____

Medical Record No.: _____

Study Medication Calendar

You should swallow your medication, unchewed, with a large glass of water at the same times every day, in the morning and in the evening after a meal.

If you miss a dose, you proceed with the next scheduled dose when it is due. Do not replace missed dose.

Please complete this calendar on a daily basis immediately after you take your pills. Fill in the date for each day and write the total number of pills you take each day.

Start Date: _____ Dose: _____

Take _____ capsule (s) each time, about 12 hours apart.

Cycle Day	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Date							
Number of pills taken - AM							
Number of pills taken - PM							
Cycle Day	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
Date							
Number of pills taken - AM							
Number of pills taken - PM							
Cycle Day	**Day 15**	**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Day 20**	**Day 21**
Date							
Number of pills taken - AM							
Number of pills taken - PM							
Cycle Day	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 26**	**Day 27**	**Day 28**
Date							
Number of pills taken - AM							
Number of pills taken - PM							

Please remember to bring this calendar and your pill bottle (including any unused pills) with you to your next clinic appointment.

Coordinator's Use Only

$$\%\ Compliance = \left(\frac{Number\ of\ Pills\ Dispensed - Number\ of\ Pills\ Returned}{Number\ of\ Pills\ Scheduled}\right) \times 100$$

$$\_\_\_\_\%\ Compliance = \left(\frac{\quad - \quad}{\quad\quad\quad\quad}\right) \times 100$$

Subject's Signature: _____ Date: _____

CRC Signature: _____ Date: _____

Investigator's Signature: _____ Date: _____

Lung Cancer Symptom Scale (LCSS)

Appendix F. Quality-of-Life-Questionnaires

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

			Not at all	A little bit	Some-what	Quite a bit	Very much
DRS-P	GP1	I have a lack of energy.	0	1	2	3	4
	GP4	I have pain.	0	1	2	3	4
	C2	I am losing weight.	0	1	2	3	4
	B1	I have been short of breath.	0	1	2	3	4
	HI7	I feel fatigued.	0	1	2	3	4
	L2	I have been coughing.	0	1	2	3	4
	BP1	I have bone pain.	0	1	2	3	4
	L4	Breathing is easy for me.	0	1	2	3	4
	C6	I have a good appetite.	0	1	2	3	4
DRS-E	GF5	I am sleeping well.	0	1	2	3	4
	GE6	I worry that my condition will get worse.	0	1	2	3	4
TSE	GP2	I have nausea.	0	1	2	3	4
	B5	I am bothered by hair loss.	0	1	2	3	4
	GP5	I am bothered by side effects of treatment.	0	1	2	3	4
FWB	L1	My thinking is clear.	0	1	2	3	4
	GF3	I am able to enjoy life.	0	1	2	3	4
	GF7	I am content with the quality of my life right now.	0	1	2	3	4

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