PHASE I/II STUDY OF NIVOLUMAB/IPILIMUMAB COMBINED WITH NINTEDANIB IN ADVANCED NSCLC

Phase:	I/II
Sponsor:	Moffitt Cancer Center
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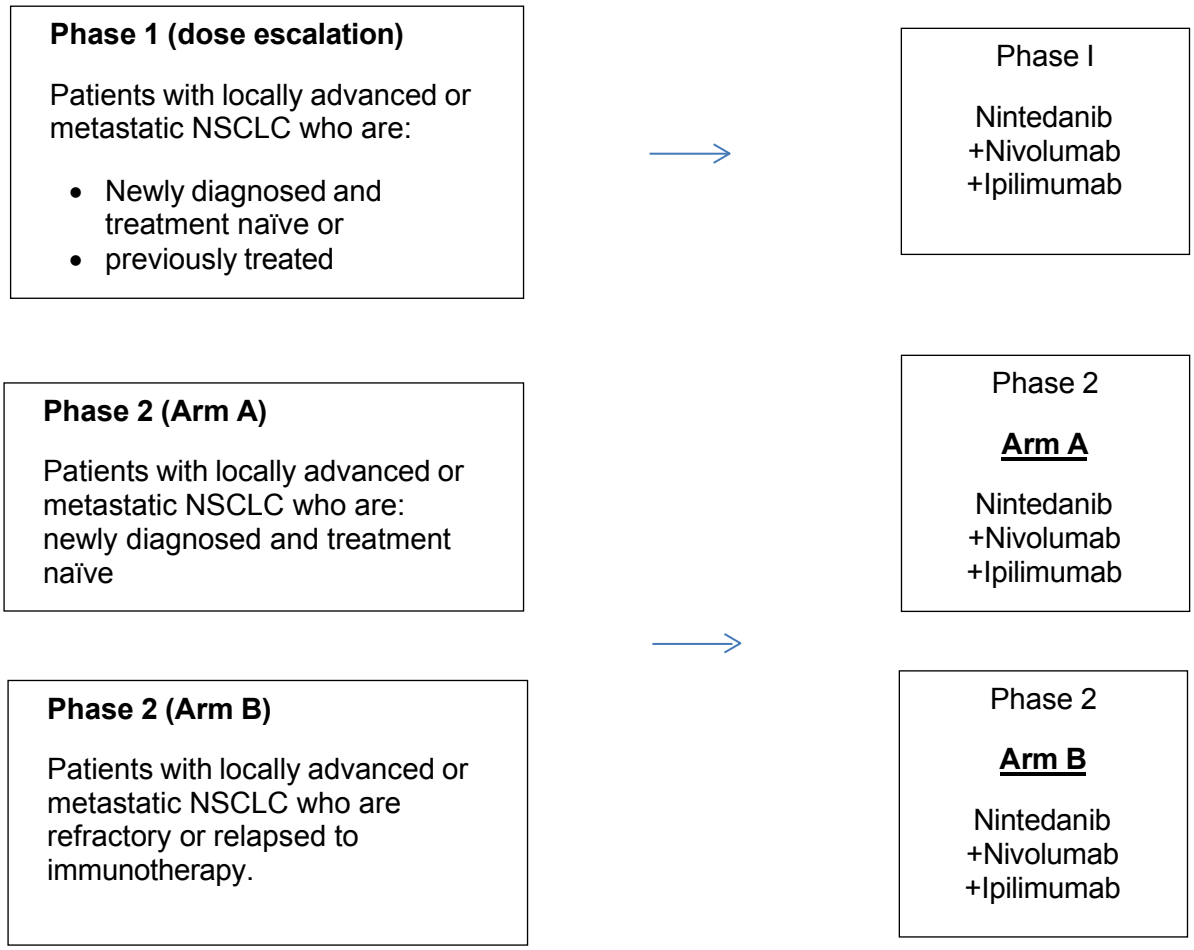
SCHEMA / Flow Chart



PROTOCOL SYNOPSIS

Trial title	**Phase I/II Study of Nintedanib combined with Nivolumab and Ipilimumab in advanced-stage NSCLC.**
IND Number:	TBD
Protocol Number:	MCC no. 19406
Sponsor:	H. Lee Moffitt Cancer Center and Research Institute
Investigational Product:	Nintedanib, Ipilimumab and Nivolumab
Trial Phase	I/II
Trial Type	Phase I/II investigational, non-randomized, parallel assignment trial
Indication Under Investigation	Locally advanced or metastatic NSCLC patients who are Immunotherapy naïve or with disease progression following immunotherapy prior to study enrollment.
Study Endpoints	Primary Objectives: Phase I (Dose Escalation) To determine the MTD and RP2D of concurrent administration of nivolumab, ipilimumab, and nintedanib. Phase II (Single Arm Cohorts) To confirm whether concurrent administration of nivolumab, ipilimumab, and nintedanib will be efficacious in NSCLC patients. (1) Arm A: Newly diagnosed or treatment-naïve patients, with a target ORR of 50%, or (2) Arm B: Patients who have been previously exposed to immunotherapy, such as anti-PD-1, anti-PD-L1 or anti-CTLA-4, with a target ORR of 20%. Secondary Objectives: Phase II: Determine the overall survival (OS), response rate (RR), Disease Control Rate (DCR), Duration of response, and progression-free survival (PFS) of patients treated with nivolumab, ipilimumab, and nintedanib. Examine potential predictive and resistance mechanisms in the tumors of clinical non- responders.
Treatment Groups	• Patients must have histologically or cytologically confirmed locally advanced or metastatic NSCLC, with at least one measurable lesion, with adequate organ and marrow function, and with Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.

	• Subjects in this study will be male or female patients 18 years of age or older. • Phase I dose-escalation trial of nivolumab plus Ipilimumab plus nintedanib in patients with locally advanced or metastatic NSCLC who are either: o Refractory to immunotherapy (i.e., Patients who were previously treated with immunotherapy and did not at least achieve stable disease on first imaging assessment on immunotherapy o Have relapsed disease (i.e. Patients that were treated with immunotherapy, achieved at least stable disease on first imaging assessment and then subsequently developed disease progression) o Are newly diagnosed and treatment naïve. • Phase II non-randomized, parallel assignment trial of nivolumab plus ipilimumab plus nintedanib at RP2D in patients with locally advanced or metastatic NSCLC. o Arm A (treatment naïve group) ▪ Newly diagnosed and treatment naïve o Arm B (pre-treated group ▪ Primary refractory to immunotherapy (i.e., Patients who were previously treated with immunotherapy and did not at least achieve stable disease on first imaging assessment on immunotherapy ▪ Have relapsed disease (i.e. Patients that were treated with immunotherapy, achieved at least stable disease on first imaging assessment and subsequently developed disease progression or relapse)
Planned sample size	Phase I: up to 24 Phase II (Non-randomized) Arm A (treatment naïve): 40 Arm B (pre-treated): 40 Arm A (treatment naïve): 40 Arm B (pre-treated): 40
Estimated duration of trial	18 months
Duration of Participation	2- 3 years
Study Sites and Location	H. Lee Moffitt Cancer Center and Research Institute

1 BACKGROUND

1.1 Introduction - Medical Background

Lung cancer (LC) is the most common diagnosis of cancer annually and causes more death than colorectal, breast, and prostate cancer combined 1. Non-small cell lung cancer (NSCLC) represents approximately 85% of all LC cases, with most patients presenting with stage IIIB or IV. Small cell lung cancer (SCLC) accounts for 15% of lung cancer, with most patients presenting with extensive stage. Advanced-stage NSCLC and extensive-Stage (ES)-SCLC remain incurable diseases. These late-stage tumors are unresectable, and patients have only a 1–5% 5-year survival with chemoresistance playing a major role 2,3.

Standard therapy for non-squamous cell lung cancer is carboplatin with either pemetrexed or paclitaxel in combination with bevacizumab, followed by maintenance bevacizumab or pemetrexed. This produces a survival benefit; however, median survival is only 12.3 months. Historical data indicate a median progression-free survival (PFS)/time to progression of only about 4 months for newly diagnosed, advanced-stage squamous cell lung cancer patients treated with platinum doublet chemotherapy 4-8. The results of a phase III randomized multicenter trial of nab-paclitaxel plus carboplatin versus paclitaxel and carboplatin in patients with advanced NSCLC revealed, by histological stratification, that the combination of nab-paclitaxel/carboplatin was superior to paclitaxel/carboplatin, with overall response rate (ORR) of 41% versus 24% (P = 0.001), respectively, in patients with squamous cell lung cancer, whereas patients with non-squamous histology had no differences in ORR, 26% versus 25% (P = 0.808), respectively 7. Unfortunately, despite this progress, there continues to be an unmet medical need for more effective and less toxic therapies, especially for patients with NSCLC.

1.2 Immunotherapy in NSCLC

Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing, allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. Programmed cell death ligand 1 (PD-L1) is one such protein; this protein is upregulated in a broad range of cancers with a high frequency, with up to 88% expression in some tumor types. In a number of these cancers, including lung 9, renal 10-12, pancreatic 13-15, and ovarian cancer 16, tumor cell expression of PD- L1 is associated with reduced survival and an unfavorable prognosis 9-16.

Programmed cell death ligand 1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell 17. This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination 18.

Recent advances in immunotherapy offer promise for improving clinical outcomes in patients with advanced lung cancer. It is increasingly appreciated that cancers are recognized by the immune system, and under some circumstances, the immune system may control or even eliminate tumors 19. Studies in mouse models of transplantable tumors have demonstrated that manipulation of co-stimulatory or co-inhibitory signals can amplify T-cell responses against tumors 20. This may be accomplished by blocking programmed cell death 1 (PD-1) from binding with their ligands, cluster of differentiation (CD) 80/86 or programmed cell death ligand 1/2 (PD-L1/2), respectively.

1.3 Nivolumab

1.3.1 Preclinical development and pharmacokinetics

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B-lymphocytes.21 Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

The pharmacokinetics (PK), clinical activity, and safety of nivolumab have been assessed in subjects with NSCLC, melanoma, clear-cell renal cell carcinoma (RCC), and classical Hodgkin Lymphoma (cHL) in addition to other tumor types. The PK of nivolumab was studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. Additionally, nivolumab has a low potential for drug-drug interactions. The clearance of nivolumab increased with increasing body weight. A population pharmacokinetics (PPK) analysis suggested no difference in CL of nivolumab based on age, gender, race, solid tumor type, baseline tumor size, and hepatic impairment. Although ECOG status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful. When nivolumab is administered in combination with ipilimumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab.

Regarding the potential for drug-drug interactions with treatment with nivolumab, although monoclonal antibodies are not direct inhibitors/inducers of metabolizing enzymes, recent literature reports suggest that therapeutic proteins that are modulators of cytokines may indirectly affect expression of cytochrome (CYP) enzymes. Nivolumab is an IgG4 monoclonal antibody, which is eliminated by mechanisms similar to that of other antibodies, namely by non-specific catabolism (mainly by enzymes in the reticuloendothelial system) [22]. These enzymes are not known to be inhibited or induced by drugs, and therefore it is unlikely that other drugs will have an impact on the PK of nivolumab. Please see investigator brochure/Package insert for nivolumab for additional information.

1.3.2 Clinical development of Nivolumab

Nivolumab monotherapy is approved in multiple countries, including the US and EU, for unresectable or metastatic melanoma, previously treated metastatic NSCLC, and previously treated advanced RCC; it is also approved for the treatment of cHL in the US. In addition, nivolumab has been approved for use in combination with ipilimumab for unresectable melanoma in multiple countries, including the US and EU.

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab in several tumor types, including NSCLC, melanoma, RCC, cH, SCLC, gastric cancer, urothelial cancer, HCC, and CRC. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in subjects with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or SCCHN. Nivolumab in combination with ipilimumab improved PFS and ORR over ipilimumab alone in subjects with unresectable or metastatic melanoma.[23-35]

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 12,300 subjects treated to date.

For monotherapy, the AE is similar across tumor types. The safety profile is generally consistent across completed and ongoing clinical trials, with no maximum tolerated dose (MTD) reached at any monotherapy dose tested up to 10 mg/kg. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care. (Section 5 and 6).

In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve. The most advanced combination under development is nivolumab + ipilimumab, which is approved in subjects with unresectable or metastatic melanoma and being studied in multiple tumor types Results to date suggest that the safety profile of nivolumab+ipilimumab combination therapy is consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs is similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs are increased with the combination. A dose of 3 mg/kg nivolumab/3 mg/kg ipilimumab exceeded the MTD, and both 1 mg/kg nivolumab/3-mg/kg ipilimumab and 3 mg/kg nivolumab/1 mg/kg ipilimumab were identified as the MTD.[26] Across all studies conducted to date, drug-related AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, GI toxicity, dermatologic toxicity (including rash), and hepatotoxicity. For nivolumab monotherapy and combination therapy, the majority of these AEs have been managed successfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in the management guidelines provided in (Section 5 and 6).

1.3.3 Clinical experience with Nivolumab in NSCLC

Nivolumab has shown a wide range of clinical activity in advanced solid tumors including NSCLC. Brahmer et al [36] first reported on previously treated patients with advanced NSCLC who received IV nivolumab (1, 3, or 10 mg/kg) every two weeks for up to 96 weeks, with tumor evaluation by RECIST v1.0. Across doses and histologies, NSCLC patients (N=129, 54% with ≥3 prior therapies) had median overall survival (OS) of 9.2-14.9 months and 1- and 2-y OS rates of 32-56% and 12-45%, respectively [2014]. At the 3-mg/kg dose, median OS was 14.9 months; 1- and 2-y OS rates were 56% and 45%. Objective response rate (ORR) was 17% (22/129) with median response duration of 17 months. Clinical activity was observed across all subgroups, including <3 and ≥3 prior therapies and with/without EGFR or KRAS mutations. For patients with PD-L1(+) and (–) tumors, median OS was 7.8 months (95% CI: 5.6, 21.7) and 10.5 months (5.2, 21.2), respectively; median PFS was 3.6 months (1.8, 7.5) and 1.8 months (1.7, 2.3). Grade 3-4 treatment-related adverse events occurred in 14% of patients, with the most common being fatigue (3%).

The Checkmate-063 trial, a Phase II, single arm trial of nivolumab in patients with refractory squamous NSCLC, reported additional safety and efficacy data in 2015 [Rizvi et al]. One hundred and seventeen (117) patients with histologically or cytologically documented Stage IIIB or IV squamous non-small-cell lung cancer with disease progression or recurrence after both a platinum doublet-based chemotherapy regimen and at least one additional systemic treatment were enrolled. Patients received nivolumab 3 mg/kg as an intravenous infusion every 2 weeks (1 cycle) until disease progression or unacceptable toxic effects. Seventeen (14.5%) patients had an objective response as assessed by an independent radiology review committee. Median time to response was 3.3 months, and median duration of response was not reached (95% CI 8·31–not applicable); 13 (77%) of 17 responders were ongoing at the time of analysis. Thirty (26%) patients had stable disease (median duration 6·0 months, 95%

CI 4·7–10·9). Twenty (17%) patients reported Grade 3–4 treatment-related adverse events including fatigue (4%), pneumonitis (3%), and diarrhea (3%). There were two treatment-associated deaths caused by pneumonia and ischemic stroke that occurred in patients with multiple comorbidities in the setting of progressive disease. [37] This was followed by the Checkmate-017 trial, a Phase III study of nivolumab versus docetaxel in patients with squamous NSCLC with disease progression during or after one prior platinum-based regimen. Two hundred and seventy two (272) patients were randomized 1:1 to receive either nivolumab 3 mg/kg (n=135) IV every two weeks or docetaxel 75 mg/m2 (n = 137) IV every three weeks until disease progression, discontinuation due to toxicity, or other reasons. The primary objective was overall survival (OS). Secondary objectives included investigator-assessed objective response rate (ORR; RECIST v1.1), progression-free survival (PFS), efficacy by PD-L1 expression (PD-L1 testing not required for enrollment), quality of life, and safety. Superior OS was observed with nivolumab versus docetaxel (HR = 0.59; 95% CI: 0.44, 0.79; p = 0.00025) and improved PFS (HR = 0.62; 95% CI: 0.47, 0.81; p = 0.0004). ORR was 20% (27/135) for nivolumab and 9% (12/137) for docetaxel (p = 0.0083). Grade 3–4 drug-related AEs occurred in 7% (9/131) of patients treated with nivolumab, and 55% (71/129) of patients treated with docetaxel. No deaths were related to nivolumab; three docetaxel-related deaths were reported. [38]

In March 2015, nivolumab 3mg/kg IV every two weeks was approved for the treatment of patients with advanced (metastatic) squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy [FDA News Release, March 2015].

Checkmate-057 is a phase III trial that included 582 patients with advanced non-squamous NSCLC randomly assigned to nivolumab 3mg/kg IV every two weeks or docetaxel 75mg/m2 IV every three weeks until progression or intolerance. The authors observed an ORR of 19.2% for nivolumab (n=292) versus 12.4% with docetaxel (n=290), and a superior duration of response (17.1 months vs 5.6 months, respectively). Median OS was 12.2 months for nivolumab versus 9.4 months for docetaxel, and the one-year OS rate was 51% and 39%, respectively. Grade 3/5 drug-related adverse events occurred in 10.5% of nivolumab patients versus 53.7% of docetaxel patients. There were no deaths in the nivolumab arm of the study, versus one in the docetaxel arm.[39]

1.4 Ipilimumab

1.4.1 Preclinical development and pharmacokinetics

Ipilimumab is a fully human monoclonal IgG1κ that binds to the CTLA-4 antigen expressed on a subset of T cells from human and nonhuman primates. CTLA-4 is a negative regulator of T-cell activity. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor-infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce Treg function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response. Traditional cytotoxic approaches to the treatment of cancer are associated with efficacy and toxicity limitations. Thus, there is a clinical need for the development of new therapies for the treatment of cancer. Blockade of CTLA-4 (CD152) is a novel approach to the treatment of human malignancies that offers an immune-mediated alternative to cancer treatment.

All nonclinical pharmacokinetic (PK) studies for ipilimumab were conducted in cynomolgus monkeys after IV dosing. [40-46] The mean half-life (T-HALF) of ipilimumab in cynomolgus monkeys was long 8.5 [40] to 14 [47] days, and the total plasma clearance (CL) was low (0.196 mL/h/kg) [41]. Systemic exposure to ipilimumab increased as a function of dose, generally in a greater than dose-proportional manner [40,43]. There were no apparent gender-related differences in exposure. An anti-ipilimumab antibody response can occur in cynomolgus monkeys, which in some cases may impact the PK of ipilimumab by accelerating its elimination. [40-48] The same response is not present in humans and thus is not relevant to human PK. Also, regardless of

the anti-ipilimumab response in cynomolgus monkeys, the exposure of animals in the safety assessment studies to ipilimumab was demonstrated. In cynomolgus monkeys, ipilimumab mostly remains within the vascular system [41,49] but crosses the placenta [50]; there was very little distribution of ipilimumab into milk. The expected in vivo degradation of mAbs is via biochemical pathways that are independent of cytochrome P450 enzymes. Consequently, typical mAbs, such as ipilimumab, are not expected to have interactions with molecules that are metabolized by these enzymes.

The cynomolgus monkey was selected as the primary toxicology species because ipilimumab binds specifically to macaque CTLA-4, but not to homologous CTLA-4 in other traditional toxicology species [51], and has pharmacologic activity in monkeys. In IV repeat- dose toxicology studies in monkeys, ipilimumab was tolerated without adverse effects at doses up to 30mg/kg/day administered every 3 days for 3 doses (peak serum concentrations ≤ 682 □g/mL), [42,43,52] at 10 mg/kg (equivalent to human dose on body-weight basis) administered weekly for 1 month (mean area under the concentration-time curve [AUC] from time zero to 168 hours and AUC from time zero to 63 days of 31.6 and 90.6 mg/h/mL, respectively) [40], at 1 mg/kg administered weekly for 10 weeks, [41] and at doses up to 10 mg/kg/day administered approximately monthly for up to 6months[40,44,46,52] In a pivotal 6- month toxicity study (10 mg/kg administered on Days 0, 28, 56, 84, and 140), treatment- related findings were limited to decreases in absolute and relative thyroid (44% to 50%) and testicular (27% to 50%) weights. However, there were no corresponding microscopic changes in these organs, and thus, 10 mg/kg was considered to be the no observable adverse effect level.[46]

Evidence of pharmacologic activity (enhancement of antigen-specific humoral immune responses and T-cell activation) without any generalized, nonspecific immune-cell activation was demonstrated in several studies. However, in an exploratory pharmacology study [44], severe colitis requiring euthanasia occurred after the second dose in 1 of 6 monkeys receiving ipilimumab at 10mg/kg approximately monthly in combination with 3 vaccines. The binding of ipilimumab to CTLA-4 expressed on gut-associated lymphoid tissue was confirmed in human and monkey tissue-binding studies [51,53,54] and suggests that these lymphocytes (T cells) exist in an activated state, making them susceptible to CTLA-4 blockade by ipilimumab.

In another pharmacology study, 1 monkey receiving ipilimumab approximately twice monthly (doses administered at Days 4, 9, 30, 32, 58, 60, 86, and 88) at 10 mg/kg in combination with another immunomodulatory antibody (BMS-663513, a fully human anti-CD137 mAb) and simian immunodeficiency virus DNA vaccines developed dermatitis/rash in the inguinal area and peripheral lymphadenopathy 4 weeks following a 3-month dosing period. [48] The rash and lymphadenopathy resolved within approximately 2 months. Since rashes have been reported clinically with both BMS-663513 and ipilimumab, a relationship of this finding to the administration of either or both test articles is possible. Another monkey in this pharmacology study developed an infusion reaction while under ketamine sedation, accompanied by difficulty in breathing, cyanosis, thready pulse, and muffled heart sounds, at approximately 5 minutes following ipilimumab injection on Day 58 and approximately 2 to 3 minutes following administration of test antigens. [48] Rechallenge of the monkey with a controlled infusion of ipilimumab approximately 5 months later did not evoke a similar reaction. Since the infusion reaction was not reproducible after a subsequent controlled ipilimumab rechallenge, the drug relationship to this event remains unclear, and confounding factors such as rapid infusion rate, immunogenicity, and anesthesia-induced hypotension may have had a contributing role.[55-60] When administered by IV, antibody to ipilimumab was detected in approximately 8% of monkeys.[40,42-46,48] In some of these monkeys, the presence of anti-drug antibodies (ADA) was observed in conjunction with accelerated elimination of ipilimumab from serum or plasma. No substantial irritation was observed at the ipilimumab injection sites in any of the IV repeat- dose studies in monkeys using ipilimumab concentrations and at injection rates well above those recommended for human use. Chinese hamster ovary-derived ipilimumab (Process B) was found to be comparable to the hybridoma-derived material

(Process A) in its PK, bioactivity (specific T-cell activation), immunogenicity, and safety profiles. Further, ipilimumab derived from a new drug substance manufacturing process (Process C, AUC from time zero to 1008hours [AUC(0-1008h)] 46,700 µg•h/mL), utilizing a higher producing sub-clone of the Process B master cell bank and modifications to the fermentation and purification processes, was shown to have comparable PK and immunogenicity profiles to Process B (AUC[0-1008h] 52,100 µg•h/mL) in an exploratory monkey study.[47] In a 1-month IV combination toxicity study in monkeys, ipilimumab and nivolumab were consecutively co-administered weekly for 4 weeks at 3 mg/kg and 10 mg/kg, respectively, or at higher doses of 10 mg/kg and 50 mg/kg, respectively; a control group received sterile Saline for Injection, USP.[61] Ipilimumab in combination with nivolumab at both the high-dose and low-dose levels was associated with a dose-dependent increased incidence of gastrointestinal (GI) toxicity (diarrhea and histologic inflammatory changes in the large intestine). In addition, mild increases in size/number of lymphoid follicles and mild expansion of the marginal zone occurred in the red pulp of the spleen. GI toxicity/colitis was previously observed at a very low incidence in monkeys receiving ipilimumab as monotherapy.

The effects of ipilimumab on reproduction and development were studied in an enhanced pre- and postnatal development study in cynomolgus monkeys.[50] In this study, pregnant monkeys received ipilimumab every 21 days from the beginning of organogenesis in the first trimester through delivery at dose levels that resulted in exposures (by AUC) that were either 2.6 times (10 mg/kg) or 7.2 times (30 mg/kg) higher than the clinical exposure at a dose of 3 mg/kg every 21 days of ipilimumab or 0.9 to 2.1 times higher than the clinical exposure at a dose of 10 mg/kg every 21 days of ipilimumab. Ipilimumab was shown to be present at very low levels in milk from adult mothers (with mean milk/serum ipilimumab concentration ratios that were 0.002 to 0.003). No treatment-related adverse effects on reproduction were detected during the first 2 trimesters of pregnancy. Maternal pregnancy outcomes for the first 2 trimesters were comparable in control and drug-treated groups. Beginning in the third trimester, the ipilimumab groups experienced increased maternal weight decrements, higher incidences of abortion and stillbirth, premature delivery (with corresponding lower birth weight), and higher incidences of infant mortality in a dose-related manner compared to controls (≥ gestation day100; 21% and 30% for 10 and 30 mg/kg every 3 weeks [q3w], respectively; compared to study controls [0%] and historical controls [17.6%]). Some infant mortality in ipilimumab-treated groups could be attributed to extreme prematurity; however, the group mean durations of gestation were comparable in the 3 experimental groups (160, 160, and 155 days in the saline, 10, and 30 mg/kg groups, respectively). Urogenital malformations were observed in 2 infants of mothers treated with 30 mg/kg/dose. Infants exposed to ipilimumab at 30 mg/kg/q3w had a lower mean body weight (BW) [-15% relative to control infant values] at birth. Lower BW persisted through 5 months postnatal, but the rate of body-weight gain increased by 3 months postnatal. At 6 months postnatal, the group-mean BW for the 30 mg/kg/q3w infants had increased compared to that of the control infants. Ipilimumab did not adversely affect the ability of infants to mount a T-cell-dependent antibody response to hepatitis B surface antigen at 6 and 18 weeks of age. There were no adverse effects observed in infants related to ipilimumab-exposure in utero with respect to clinical observations, morphometric measurements, neurobehavioral and skeletal evaluations, clinical pathology, lymphocyte phenotyping, antinuclear antibody (ANA) formation, or serum Ig levels through 6 months postnatal.

In summary, other than the events described, ipilimumab generally did not result in any adverse toxicities in any other monkeys in general toxicity studies when administered IV at doses up to 30 mg/kg for 1 week, 10 mg/kg weekly for 1 month, 1 mg/kg weekly for 10 weeks, or 10 mg/kg monthly for 6 months. Ipilimumab in combination with nivolumab was associated with a dose-dependent increased incidence of GI toxicity in monkeys as compared to either agent alone. In addition, increased incidences of third-trimester abortion, stillbirth, premature delivery, low birth weight, and infant mortality occurred following IV administration of

ipilimumab to pregnant cynomolgus monkeys every 21 days from the onset of organogenesis through parturition at doses of 2.6 or 7.2 times the clinical exposure at a dose of 3 mg/kg or 0.9 to 2.1 times higher than the clinical exposure at a dose of 10 mg/kg every 21 days of ipilimumab. Based on the results of the monkey reproductive study, ipilimumab is not recommended for use during pregnancy unless the potential benefit justifies the potential risk to the fetus.

The population PK of ipilimumab was studied in 785 subjects (3,200 serum concentrations) with advanced melanoma in 4 Phase 2 studies (CA184004, CA184007, CA184008, and CA184022),[62] 1 Phase 3 study (CA184024), and 1 Phase 1 study (CA184078). The population PK analysis demonstrated that the PK of ipilimumab is linear, the exposures are dose proportional across the tested dose range of 0.3 to 10 mg/kg, and the model parameters are time-invariant, similar to that determined by noncompartmental analyses.

Upon repeated dosing of ipilimumab, administered q3w, minimal systemic accumulation was observed by an accumulation index of 1.5-fold or less, and ipilimumab steady-state concentrations were achieved by the third dose. The ipilimumab CL was 16.8 mL/h from population PK analysis. The terminal T-HALF and Vss of ipilimumab calculated from the model were 15.4days and 7.47 L, respectively, which are consistent with that determined by noncompartmental analysis. Volume of central compartment (Vc) and peripheral compartment were reported to be 4.35 and 3.28 L, respectively, suggesting that ipilimumab first distributes into plasma volume and, subsequently, into extracellular fluid space. CL of ipilimumab and Vc were found to increase with increase in BW. However, there was no significant increase in exposure with increase in BW when dosed on a milligram/kilogram basis, supporting dosing of ipilimumab based on a weight-normalized regimen. The PK of ipilimumab is not affected by age, gender, race, and immunogenicity (ADA status); concomitant use of chemotherapy; prior therapy; BW; performance status; or tumor type. Other covariates had effects that were either not statistically significant or of minimal clinical relevance.

1.4.2 Clinical development of Ipilimumab

Ipilimumab is being investigated both as monotherapy and in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies. Phase 3 programs are ongoing in melanoma, prostate cancer, and lung cancer.

In melanoma, 4 completed Phase 3 studies (MDX010-20, CA184024, CA184029, and CA184169) have demonstrated a clinically meaningful and statistically significant survival benefit in pretreated advanced melanoma, in previously untreated advanced melanoma, and in adjuvant melanoma.

Ipilimumab monotherapy or in combination with chemotherapy has not prolonged survival in prostate cancer, NSCLC, and SCLC (Studies CA184043, CA184095, CA184104, and CA184156). Outside melanoma, combination with other checkpoint inhibitors (eg PD-1 inhibitors) may be required to achieve clinically meaningful activity. Ipilimumab is also in clinical development in combination with nivolumab. The combination is approved in the US for the treatment of advanced melanoma.

The unique immune-based mechanism of action is reflected in the clinical patterns of anti-cancer activity in some patients. Ipilimumab induces an immunologic response, and measurable clinical effects emerge after the immunological effects. Tumor infiltration with lymphocytes and the associated inflammation (documented by biopsy in some subjects) is likely the cornerstone of the effect of ipilimumab and can manifest in various patterns of clinical activity leading to tumor control. In some cases, inflammation may not be noted by radiological examination, and objective response is observed with the first tumor assessment in a manner seen in patients receiving other types of anti-cancer treatments. In other cases, response may be preceded by an apparent increase in initial tumor volume and/or the appearance of new lesions, which may be mistaken for tumor progression on radiological evaluations. Therefore, in patients who are not experiencing rapid clinical deterioration,

confirmation of progression is recommended (at the investigator's discretion) to better understand the prognosis, as well as to avoid unnecessarily initiating potentially toxic alternative therapies in subjects who might be benefiting from treatment. Immune-related response criteria were developed based on these observations to systematically categorize novel patterns of clinical activity and are currently being prospectively evaluated in clinical studies.

In metastatic diseases, stabilization is more common than response and in some instances is associated with a slow, steady decline in tumor burden over many months, sometimes improving to partial and/or complete responses (CRs). Thus, the immune-based mechanism of action of ipilimumab results in durable disease control, sometimes with novel patterns of response, which contribute to its unique improvement in overall survival (OS).

The unique immune-based mechanism of action is also reflected in the safety profile. The most common treatment-related AEs are inflammatory in nature, consistent with the mechanism of action of the drug and generally medically manageable with topical and/or systemic immunosuppressants. Such immunological safety events are described as immune-related adverse events (irAEs) or immune-mediated adverse reactions (imARs). The irAEs are described as AEs of unknown etiology, which were consistent with an immune phenomenon and considered causally related to drug exposure by the investigators. The irAEs primarily involve the GI tract and skin. Immune-related AEs in the liver were also observed, particularly in subjects receiving 10 mg/kg. Endocrinopathy and neuropathy were important irAEs that were observed less frequently. The imARs were adjudicated in a blinded fashion based on sponsor-physician data review to exclude noninflammatory etiologies, such as infection or tumor progression, and to consider available evidence of inflammation, such as tumor biopsies or responsiveness to steroids, in an effort to determine whether specific AEs or abnormal hepatic laboratory values were likely to be immune mediated and associated with ipilimumab treatment.

The early diagnosis of inflammatory events is important to initiate therapy and minimize complications. Inflammatory events are generally manageable using symptomatic or immuno-suppressive therapy as recommended through detailed diagnosis and management guidelines. The management guidelines for general irAEs and ipilimumab-related GI toxicities, hepatitis, endocrinopathy, and neuropathy are described in Section 5, Table 9a and 9b.

1.4.3 Clinical development with Ipilimumab in NSCLC.

Activity of Ipilimumab in lung cancer was observed in a large Phase 2 study in lung cancer (NSCLC and SCLC; StudyCA184041) [63] in combination with chemotherapy. Two Phase 3 studies evaluated ipilimumab has been tested in combination with chemotherapy in squamous NSCLC (CA184104) and SCLC (CA184156). Neither study met its primary endpoint of demonstrating a statistically significant prolongation of OS for the ipilimumab group (10 mg/kg ipilimumab/standard of care chemotherapy) over the placebo group (placebo/standard of care chemotherapy) among randomized subjects who received at least 1 dose of blinded study therapy; however, no new safety concerns were identified in the course of standard clinical safety monitoring of the 2 studies.

While the types of safety events observed in subjects receiving ipilimumab do not appear to change, even in combination with other anti-cancer agents, the proportion of subjects experiencing 1 type or another irAE may be impacted by the choice of combination partner. The skin and GI irAEs predominate in monotherapy studies. In combination with DTIC (melanoma), the incidence of skin and GI irAEs was lower than expected and the incidence of hepatic irAEs was higher. In combination with paclitaxel and carboplatin (NSCLC), the incidence of all types of irAEs appeared to be numerically lower compared to the incidence observed for ipilimumab monotherapy in the Phase 2 program.

1.5 Combined Immune Checkpoint Inhibition

Nivolumab is in clinical development as a combination with ipilimumab. The combination is currently approved in the US in subjects with unresectable or metastatic melanoma and being studied in multiple tumor types. Results to date suggest that the safety profile of nivolumab+ipilimumab combination therapy is consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs is similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs are increased with the combination. A dose of 3 mg/kg nivolumab/3 mg/kg ipilimumab exceeded the MTD, and both 1 mg/kg nivolumab/3-mg/kg ipilimumab and 3 mg/kg nivolumab/1 mg/kg ipilimumab were identified as the MTD.[64] Across all studies conducted to date, drug-related AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, GI toxicity, dermatologic toxicity (including rash), and hepatotoxicity. For nivolumab monotherapy and combination therapy, the majority of these AEs have been managed successfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in the management guidelines provided in Section 5, Table 9a and 9b.

The combination has also shown activity in NSCLC. There is clinical rationale for combining the two agents based on their non-redundant mechanisms of action. Preclinical data shows synergy between anti-PD1 and anti-CTLA4 therapies that improves antitumor activity. The Checkmate-012 trial, a Phase I multi-cohort randomized study, evaluated the combination of nivolumab and ipilimumab at 2 doses as first line therapy in NSCLC as compared to nivolumab monotherapy, with primary endpoint being safety and tolerability. Nivolumab monotherapy was given at a dose of 3mg/kg IV every 2 weeks. In combination with nivolumab, ipilimumab was given at a doses of 1mg/kg every 6 or 12 weeks. They demonstrated a cPR in 18/38 (47%) versus 15/39 (38%) in the ipilumumab combination arms at 12 versus 6 weeks, respectively. Median PFS was 8.1 months for nivolumab/ ipilimumab 12-week combination versus 3.9 months for nivolumab/ ipilumumab 6-week combination. Median OS at 1 year for nivolumab/ ipilimumab 12-week combination was not calculated versus 69% for nivolumab/ ipilumumab 6-week combination. In patients with ≥ 1% PD-L1 expression, the median PFS for nivo/ ipi every 12-weeks was 8.1 months, for nivo/ ipilimumab every 6-weeks was 10.6 months and for nivo alone was 3.5 months. The Grade 3-4 treatment-related adverse events were noted in 14 (37%) patients in the ipilimumab every-12-weeks cohort versus 13 (33%) patients in the every-6-weeks cohort. Combination nivolumab/ ipilimumab therapy was considered to be tolerable with no new safety concerns or treatment related deaths noted during this study. In summary, the addition of nivolumab monotherapy resulted in higher ORR, longer PFS and numerically higher 1-year OS. Additionally, efficacy of combination therapy was enhanced with increasing tumor PD-L1 expression. Though, activity was still observed in patients with <1% PD-L1. [65] Checkmate 227 (NCT02477826) is a phase III trial that is currently underway to test the combination of Nivolumab 3mg/kg IV every 2 weeks with Ipilimumab 1mg/kg IV every 6 weeks, further stratifying based on PD-L1 expression.

1.6 Nintedanib (BIBF1120)

1.6.1 Preclinical development and pharmacokinetics

Nintedanib (BIBF1120) is a potent, orally available triple kinase inhibitor targeting VEGFRs, PDGFRs, and FGFRs. Nintedanib inhibits the signalling cascade mediating angiogenesis by binding to the adenosine triphosphate (ATP) binding pocket of the receptor kinase domain, thus interfering with cross-activation via auto-phosphorylation of the receptor homodimers.

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

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

In addition, preclinical models show that Nintedanib (BIBF1120) may have a direct anti-tumour effect on those malignant cells that overexpress PDGFR and/or FGFR (e.g., H1703 NSCLC cells)

Target	**IC50 (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-tumour efficacy at doses of 50 to 100 mg/kg, leading to a substantial delay of tumour growth or even complete tumour stasis in xenografts of a broad range of differing human tumour types. Histological examination of treated tumours showed a marked reduction of tumour vessel density by approximately 80% [66].

The metabolism of Nintedanib (BIBF1120) 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 (BIBF1120) has a favorable pharmacokinetic and excretion profile, with almost no elimination via the urine; only 0.7% of total -14C-radioactivity was eliminated via the urine [67]. The metabolic characteristics are predominantly independent of cytochrome P450-catalyzed metabolic pathways [67].

A soft gelatin capsule formulation of Nintedanib is used in humans. 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 pharmacokinetics of Nintedanib has been observed. Steady state is reached after 1

week of dosing. The terminal half-life of Nintedanib is in the range of 7 to 19 hours. Nintedanib is mainly eliminated via feces [67].

Nintedanib (BIBF1120) is non-mutagenic, even at high doses. Two exploratory studies in rats revealed a teratogenic effect of Nintedanib (BIBF1120) with a steep dose-effect relation and an early onset of embryofetal deaths at low dosages. This effect was observed at dose levels, resulting in plasma drug concentrations comparable to or below those in humans. Because the concentration of Nintedanib (BIBF1120) in semen is unknown, male patients receiving Nintedanib (BIBF1120) and having sexual intercourse with women of childbearing potential should use latex condoms. Female patients of childbearing potential should be advised to use adequate contraception during and at least 3 months after the last dose of Nintedanib.

1.6.2 Clinical development of Nintedanib

Nintedanib is being evaluated in several cancers. Additionally, Nintedanib is in advanced phase III for the non-cancer indication idiopathic pulmonary fibrosis (IPF). As of 15 Feb 2013, 3556 cancer patients, over 1000 patients with IPF, and 140 healthy volunteers had been treated with nintedanib or nintedanib matching placebo, in monotherapy or in combination with chemotherapy.

Phase I Nintedanib Monotherapy

Phase I dose selection studies revealed that nintedanib (BIBF1120) is generally well tolerated with mild to moderate adverse effects such as gastrointestinal symptoms (nausea, diarrhoea, vomiting, and abdominal pain) and reversible elevations of liver enzymes. Initial signs of clinical activity including an encouraging rate of patients with stabilisation of their tumour of 54% and 68%, respectively; have been observed in patients with various solid tumours [68].

Based on the phase I dose escalation trials with nintedanib (BIBF1120) monotherapy, the maximum tolerated dose was defined to be 250 mg for twice daily dosing in Caucasians and 200 mg twice daily in Japanese patients with a manageable safety profile in advanced cancer patients. Based on the overall safety profile, the RP2D for nintedanib, as monotherapy is 200 mg bid.

The maximum tolerated dose for combination therapy of nintedanib (BIBF1120) in combination with pemetrexed, docetaxel, paclitaxel/carboplatin and FOLFOX is 200mg bid. Combination of nintedanib (BIBF1120) with other anti-cancer drugs revealed a similar adverse event profile as compared to Nintedanib (BIBF1120) monotherapy except for the chemotherapy related toxicities. There was no change of the pharmacokinetic parameters of nintedanib (BIBF1120) or of the cytotoxic compounds due to the combined treatment. Dose limiting toxicity consisted mostly of liver transaminase elevations as in the monotherapy phase I trials with the exception of the combination of nintedanib (BIBF1120) with pemetrexed, where fatigue was the most relevant dose limiting toxicity.

Available pharmacokinetic data indicate that the systemic exposure needed for biological activity can be achieved starting with doses of 100 mg Nintedanib (BIBF1120) once daily.

The predominant adverse events were nausea, 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[67].

1.6.3 Clinical Experience of Nintedanib in NSCLC

In a phase I open-label study, Nintedanib was tested in combination with Pemetrexed in patients with recurrent metastatic NSCLC of all histological subtypes who had previously received at least one platinum-based chemotherapy [69]. Patients were treated with standard dose Pemetrexed (500 mg/m2 on day 1) and Nintedanib on days 2 to 21 of a 21-day cycle. The dose of Nintedanib was escalated from 100 mg twice daily to the MTD of 200 mg twice daily. The most frequent DLTs were gastrointestinal adverse effects (86.4%) including nausea, diarrhea, and vomiting and administration-site reactions (76.9%), mainly rash. One patient showed a complete response (CR), and 50% of patients showed stable disease as best overall response. No clinically relevant pharmacokinetic interactions between Nintedanib and Pemetrexed were observed.

In a phase II trial in NSCLC patients the safety profile of nintedanib (BIBF1120) observed in phase I trials could be confirmed. Most commonly reported drug-related AEs were nausea (57.5%), 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 PFS of 11.6 weeks and a median OS of 37.7 weeks. Tumour stabilisation was achieved in 46% of patients (ECOG 0–1 patients: 59%), with one confirmed partial response (250 mg bid.). [70]

LUME-Lung 1 was an international, randomized, double blind, phase III trial assessing the efficacy and safety of docetaxel plus Nintedanib as second line therapy for non-small-cell lung cancer (NSCLC). In total, 1314 patients with Stage IIIB/IV or recurrent NSCLC (all histologies) who had progressed after 1st line chemotherapy were randomized in 1:1 fashion to either receive nintedanib 200mg BID + docetaxel (n=655) or placebo BID + docetaxel (n=659). The study 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; median OS 12.6 months [95% CI 10·6–15·1] vs 10·3 [95% CI 8·6–12·2] months; HR 0·83 [95% CI 0·70–0·99], p=0·0359); the Kaplan-Meier survival curves separate at 6 months, continuing throughout the 36-month study observation period. One year overall survival was 52·7% (95% CI 46·8–57·9) in the docetaxel plus nintedanib group compared with 44·7% (38·9–49·8) in the docetaxel plus placebo group; 2 year overall survival was 25·7% (95% CI 20·5–30·2) in the docetaxel plus nintedanib group compared with 19·1% (14·4–23·2) in the docetaxel plus placebo group. In the predefined population of patients with adenocarcinoma who had progressed within 9 months after start of first-line therapy, overall survival was significantly longer in the docetaxel plus Nintedanib group than in the docetaxel plus placebo group (median overall survival 10·9 months [95% CI 8·5–12·6] vs 7·9 months [6·7–9·1]; HR 0·75 [95% CI 0·60–0·92], p=0·0073). In the total population of patients (all histologies), there was no difference in overall survival between the two groups: median overall survival was 10·1 months (95% CI 8·8–11·2) in the docetaxel plus nintedanib group compared with 9·1

(8·4–10·4) months in the docetaxel plus placebo group (HR 0·94 [95% CI 0·83–1·05], p=0·2720). Nintedanib plus docetaxel had a manageable safety profile with no unexpected safety findings). [71]

The predominant adverse events were nausea, diarrhoea, vomiting, abdominal pain and fatigue of mostly low to moderate intensity after monotherapy with nintedanib (BIBF1120).

Adverse events that were more common (≥5% difference) in the docetaxel plus Nintedanib group than the docetaxel plus placebo group were: diarrhoea (all grades, 276 of 652 [42·3%] vs 143 of 655 patients [21·8%]; grade ≥3, 43 [6·6%] vs 17 [2·6%]), increases in alanine aminotransferase (all grades, 186 [28·5%] vs 55 [8·4%]; grade ≥3, 51 [7·8%] vs six [0·9%]), nausea (all grades, 158 [24·2%] vs 118 [18·0%]; grade ≥3, five [0·8%] vs six [0·9%]), increases in aspartate aminotransferase (all grades, 147 [22·5%] vs 43 [6·6%]; grade ≥3, 22 [3·4%] vs three [0·5%]), decreased appetite (all grades, 145 [22·2%] vs 102 [15·6%]; grade ≥3, nine [1·4%] vs eight [1·2%]), and vomiting (all grades, 110 [16·9%] vs 61 [9·3%]; grade ≥3, five [0·8%] vs three [0·5%];). Most of these adverse events were manageable with supportive treatment or dose reduction. [71]

LUME-Lung 2 was a similar randomised, double blind, phase III study of nintedanib plus Pemetrexed versus placebo plus Pemetrexed in patients with advanced non-squamous non-small cell lung cancer after failure of first line chemotherapy. Based on a pre-planned 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. [72]

1.7 Rationale for performing this trial

Approximately 1.6 million people worldwide are diagnosed with lung cancer annually, of which about 85% of cases are NSCLC 1. Locally advanced NSCLC patients have a median survival of 10-17 months, whereas patients with metastatic disease have a median survival of only 6-9 months [73]. Recent developments in immune checkpoint inhibition have led to promising advances in cancer immunotherapy [36], including blockade of CTLA-4 (cytotoxic T-lymphocyte antigen 4), an inhibitory receptor found on tumor-infiltrating T cells, and programmed death receptor ligand (PD-L1), an inhibitory receptor expressed by cancer cells and antigen-presenting cells (APCs).

Despite these advances, however, response rates vary among patients and tumor types, leading to intense investigation of predictors of response [74]. There is growing evidence to suggest that the tumor microenvironment may interfere with effective immune recognition, even in the presence of checkpoint inhibitors [75]. Of particular importance are cancer-

associated fibroblasts (CAFs): in addition to promoting metastasis, CAFs are able to modify immune cell infiltration [76], and in a study of human fibroblasts isolated from resected lung cancers, upregulated protein expression by CAFs was shown to correlate with shorter disease-free intervals and worse overall survival [77]. Platelet-derived growth factor (PDGF) also plays a role in tumor survival by inducing myofibroblast contraction, thus restricting capillary-to-interstitium transport of drugs [78]. Accordingly, targeting the tumor microenvironment may represent an important synergistic approach in immunotherapy.

Tumor survival depends in part on immune evasion, achieved by modifying immune checkpoints, including PD-1 and PD-L1. It is now well known that blockade of the PD-1 receptor and PD-L1 ligand interaction leads to T-cell stimulation, overcomes tumor immune resistance, and potentially provides clinically meaningful outcomes. This therapeutic strategy has been investigated in multiple cancers, including NSCLC, with varying responses and unique toxicity profiles.

1.7.1 Preclinical Rationale for Combined Immunotherapy and PDGFR Inhibition

In a preclinical model of murine mastocytoma [79], dasatinib (a multiple tyrosine kinase inhibitor with activity against PDGFR) demonstrated enhanced anti-tumor response both alone and when combined with anti-OX40, a T-cell costimulatory antibody. Tumor-bearing mice were treated with daily gavage of vehicle or dasatinib (150 mg/kg) on days 8, 9, and 10 following tumor inoculation. Dasatinib significantly decreased tumor volumes and prolonged mouse survival, and H&E staining revealed extensive vacuolar degeneration in treated tumors, morphologic changes consistent with significant cell death. Treatment also significantly increased the tumor antigen-specific T-cell levels in the peripheral blood of tumor-bearing mice. With the addition of anti-OX40, the authors noted increased CD8+ effector T cells and enhanced infiltration of tumor-specific T cells to levels greater than those observed with either anti-OX40 or dasatinib alone. Furthermore, mice receiving the combination demonstrated the highest levels of IFN-γ production in response to antigen stimulation, as well as an increased ratio of CD8+ effector T cells to regulatory T cells (Tregs), thus enhancing intratumoral CTL infiltration. The authors concluded that such data may delineate a strategy by which targeted therapy and immunotherapy may be combined to achieve superior antitumor responses in cancer patients.

1.7.2 Preclinical Data from Dr. Antonia's Lab at Moffitt Cancer Center and FGFR Inhibition

Dr. Scott Antonia, a thoracic oncologist and translational researcher at Moffitt Cancer Center, has developed a technique to grow out pure, short-term cell lines of cancer-associated fibroblasts (CAFs) from human lung cancer tumors. He has furthermore recently demonstrated that lung cancer CAFs are potently immunosuppressive (expressing high levels of PDL1, IDO, and CD73), and therefore combining a drug targeting the tumor microenvironment (and CAFs) in combination with anti-PD-L1 (Nivolumab) therapy may enhance clinical efficacy. See Figures 1-3 below.

Figure 1a

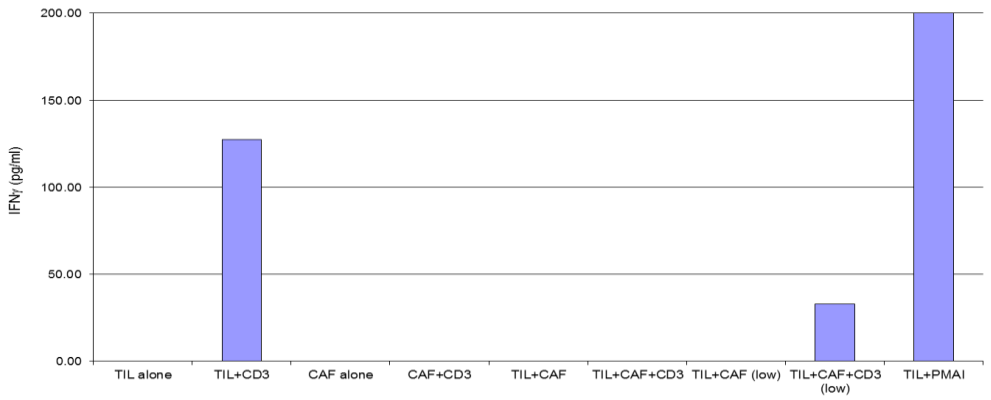


Figure 1b

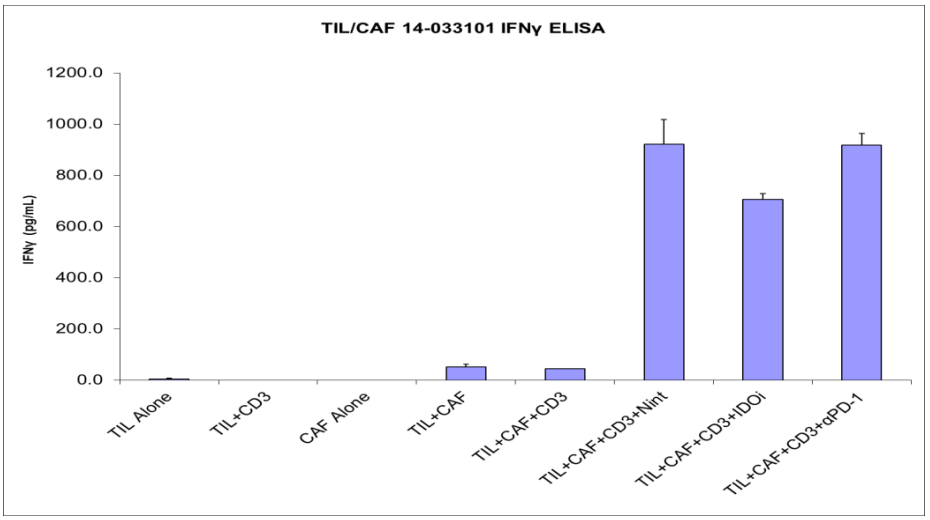


Figure 1a. CAFs inhibit TIL activation. A TIL cell line derived from a NSCLC patient was seeded in the presence and absence of high and low (low) concentrations of CAFs as well as anti-CD3 for 72 hours. Supernatants were collected ,and an IFN□ ELISA was performed to determine the activation of the TILs. As can be observed, when the TILs are in the presence of anti-CD3 and high concentration of CAFs, there is no IFN□ production. When the number of CAFs is reduced (low), their suppression on TIL activation is diminished as shown by the presence of IFN□ in the supernatant. **Figure 1b. Nintedanib inhibits CAFs and allows TIL activation.**

Figure 2. PDL-1 and CD73 expression increases in CAFs treated with rh-IFNγ.

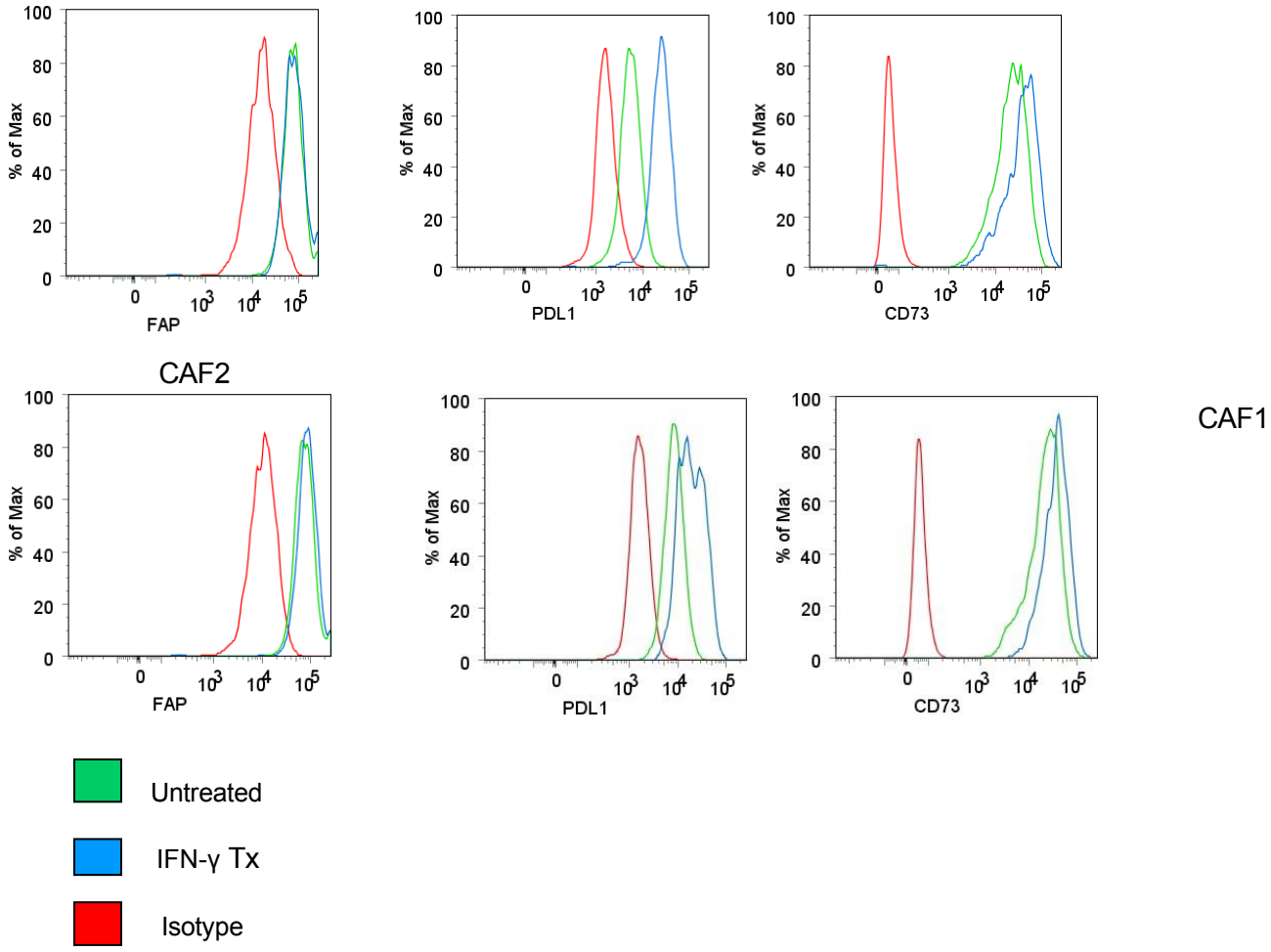


Figure 2. PDL-1 and CD73 expression increases in CAFs treated with rh-IFNγ. Two CAF cell lines derived from NSCLC patients were seeded in the presence and absence of rh-IFNγ. After 72-hour incubation, the cells were collected and stained for FAP, PDL-1, and CD73. A flow cytometric analysis followed. As can be observed, in the presence of rh-IFNγ the CAF cell lines have an increase in PDL-1 and CD73 expression, both markers for immunosuppressive molecules. FAP was used as a marker to characterize the fibroblasts as CAFs.

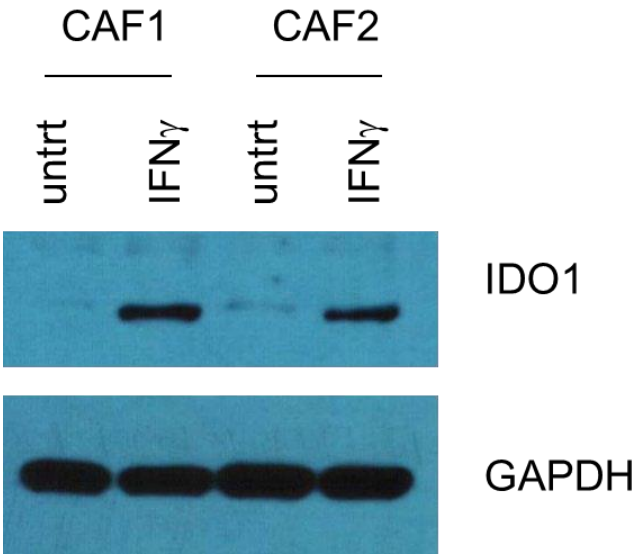
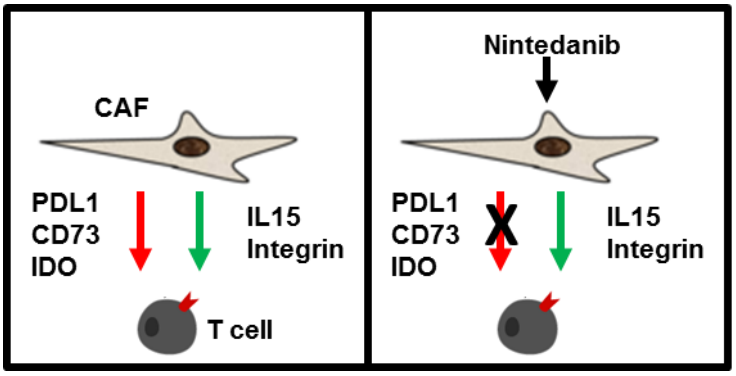


Figure 3. IDO protein expression increases in CAFs treated with rh-IFNγ. Two CAF cell lines were seeded in the presence and absence of rh-IFNγ for 72 hours. Protein was extracted and run in an SDS-PAGE gel and transferred to a PVDF membrane. The membrane was probed against IDO1 protein as well as GAPDH as a loading control. As it can be observed, we were able to confirm the qRTPCR data, showing that also at the protein level, IDO1 expression levels increase when compared to untreated (untreated).

1.7.3 Potential Biomarkers of FGFR Inhibition

Under the influence of tumor-secreted interferon gamma, CAFs not only play a collaborative role in tumor growth, but also evasion of the immune response [80]. Interferon gamma has further been shown to increase tumor PDL-1 expression [81] and indoleamine 2,3-dioxygenase 1 (IDO1), which catalyzes tryptophan degradation to kynurenine and by depleting extracellular tryptophan suppresses lymphocyte proliferation [82]. High IDO1 activity in lung cancer is associated with advanced disease stage, and increased serum kynurenine: tryptophan ratios have been shown to correlate with disease progression [83]. Therefore, serum kynurenine: tryptophan ratios may serve as a surrogate biomarker of tumor growth, and the impact of Nintedanib therapy could be further quantitated by biomarker testing before and after initiation of treatment.

Figure 4. Proposed Mechanism of Action of Nintedanib.



1.8 Proposed Clinical Rationale

As noted previously, despite recent advances in NSCLC immunotherapy, response rates vary, and with evidence that targeting the tumor (with chemotherapy) and the microenvironment (with FGFR inhibition) results in a synergistic treatment effect, the combination of FGFR inhibition with immune checkpoints is a rational curiosity. Further, evidence for potential clinical benefit exists in preclinical models, and the addition of PDGFR inhibition to standard chemotherapy has been shown to be well-tolerated. If successful, combination therapy may further improve the outcomes of patients with a largely terminal cancer. Phase I clinical trials have shown that antibody mediated blockade of either PD-L1 or PD-1 can lead to durable tumor regression in about 20% of patients with advanced non-small cell lung cancer (NSCLC) [36,66,84].

1.9 Benefit – Risk Assessment

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 or metastatic NSCLC.

Antiangiogenic treatment with the orally available triple angiokinase inhibitor Nintedanib (BIBF1120) 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 (BIBF1120) may have the potential to provide significant benefit to patients with locally advanced and/or metastatic NSCLC by slowing tumor progression and metastasis, since its cellular target is expressed on the tutor 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.

The main risks of therapy with nintedanib (BIBF1120) in adult patients are:

- Gastro-intestinal AEs (diarrhoea nausea, vomiting, , abdominal pain)
- Increases in liver enzymes (AST, ALT, ALKP) and bilirubin
- Perforation (gastrointestinal and non-gastrointestinal)
- Hypertension

- Venous thromboembolism
- Bleeding

Neutropenia and sepsis, if combined with myelosuppressive chemotherapy, such as docetaxel:

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

Therapy with the trial drugs must be interrupted in the event of relevant elevations of liver enzymes and/or of bilirubin and further treatment is to be withheld until recovery of the abnormal laboratory parameters.

Hypertension is a side effect of nintedanib and a slightly increased frequency of hypertension has been observed in the trials with nintedanib (BIBF1120) to a mild to moderate degree and only few cases of CTCAE grade 3 or 4 hypertension have been observed. With respect to bleeding, 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 were balanced between both arms regardless of histology.

Based upon a non-clinical safety study in vitro, nintedanib (BIBF1120) may have a potential risk of phototoxicity (skin and eyes) in vivo. Few cases of photosensitivity reactions (less than 1 %) and of CTCAE grade 1 intensity only have been reported from the clinical studies to date. If adequate precautions are taken (avoidance of prolonged ultraviolet (UV) exposure, use of broad spectrum sunscreen and sunglasses), treatment with nintedanib (BIBF1120) is considered safe.

In addition for combination trials:

The major clinical side effects observed after therapy with nivolumab and ipilimumab are distinct from nintedanib (BIBF1120) induced adverse events, yet some overlap may occur e.g. regarding mild gastrointestinal toxicity or hepatotoxicity (please refer to Section 5.5 for details). In view of the low potential for drug-drug interactions of nintedanib (BIBF1120), it is not likely that enhanced toxicity due to pharmacokinetic interaction between the drug and the cytotoxic chemotherapy will occur.

Partially overlapping toxicity profile may result in increased nausea, vomiting and diarrhea, and liver enzyme increases.

2. OBJECTIVES

2.1 Primary Objectives

Phase I (Dose Escalation)

Determine the MTD and RP2D of concurrent administration of nivolumab, ipilimumab, and nintedanib.

Phase II (Single Arm Cohorts):

To determine the efficacy of concurrent administration of nivolumab, ipilimumab, and nintedanib in NSCLC patients.

(1) Arm A: Newly diagnosed or treatment-naïve patients, with a target ORR of 50%, or

(2) Arm B: Patients who have been previously exposed to immunotherapy, such as anti-PD-1, anti-PD-L1 or anti-CTLA-4, with a target ORR of 20%.

2.2 Secondary Objectives

Phase II:

- Determine the overall survival (OS), response rate (RR), Disease Control Rate (DCR), Duration of response, and progression-free survival (PFS) of patients treated with nivolumab, ipilimumab, and nintedanib.
- Examine potential predictive and resistance mechanisms in the tumors of clinical non- responders.

3. PATIENT SELECTION

All inclusion and exclusion criteria will be assessed within 30 days before initiation of therapy. All eligibility criteria must be met prior to enrolling a patient. The study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH), WHO, and any local directives and in compliance with the protocol. This clinical protocol, any amendments, and the patient informed consent will require IRB approval and FDA IND approval/favorable opinion before initiation of the study. Patients should only be treated on the study if all inclusion criteria are fulfilled.

3.1 Core Inclusion criteria

1. Patients must have histologic or cytological diagnosis of advanced/metastatic NSCLC with no curative treatment options. For those with mixed histology, there must be a predominant histology.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Life expectancy of at least 3-6 months.
4. ECOG performance status score (0 and 1)
5. For phase I trial portion, treatment naïve or patients previously treated with chemotherapy, immunotherapy or targeted therapy for NSCLC are allowed. Patient who underwent curative intent chemotherapy and/or radiation in the neoadjuvant or adjuvant setting are allowed to enroll if tumor recurrence occurred greater than 6 months from completion of that therapy (and will be considered treatment naïve in the Stage IV setting). Patients with NSCLC tumor known to harbor a genomic aberration for which FDA approved treatment is available (i.e, non-resistant EGFR mutations, EGFR T790M mutation, ALK rearrangement, ROS rearrangement, BRAF V600E mutation) are allowed to enroll if they have received prior treatment with the FDA approved targeted therapy.

6. For phase II trial portion, Patients will be enrolled as two parallel cohorts:
    a. Arm A (treatment naïve): Patients who are newly diagnosed and treatment naïve. Patient who underwent curative intent chemotherapy and/radiation in the neoadjuvant or adjuvant setting are allowed to enroll if tumor recurrence occurred greater than 6 months from completion of therapy. Patients with NSCLC tumor known to harbor a genomic aberration for which FDA approved treatment is available (i.e, non-resistant EGFR mutations, EGFR T790M mutation, ALK rearrangement, ROS rearrangement, BRAF V600E mutation) are allowed to enroll if they have received prior treatment with the FDA approved targeted therapy.
    b. Arm B (Immunotherapy pre-treated group): Patients who have received prior immunotherapy. Patients who are primary refractory to immunotherapy (i.e., Patients who were previously treated with immunotherapy and did not at least achieve stable

disease on first imaging assessment on immunotherapy) or have relapsed disease (i.e., Patients that were treated with immunotherapy, achieved at least stable disease on first imaging assessment and subsequently developed disease progression or relapse). Patients with NSCLC tumor known to harbor a genomic aberration for which FDA approved treatment is available (i.e, non-resistant EGFR mutations, EGFR T790M mutation, ALK rearrangement, ROS rearrangement, BRAF V600E mutation) are allowed to enroll if they have received prior treatment with the FDA approved targeted therapy.

7. At least one measurable lesion according to RECIST v1.1 criteria.
8. QTcB must be <470 ms for males and <480 ms for females.
9. Adequate normal organ and marrow function as defined below:
    a. Absolute neutrophil count (ANC) >1.5 x 109/L (> 1500 per mm3)
    b. Hemoglobin ≥ 9.0 g/dL
    c. Platelet count ≥ 100 x 109/L (>100,000 per mm3)
    d. Total bilirubin ≤ 1.5 X normal institutional limits. For Pts with liver metastasis: total bilirubin must be within normal limits. (Except patients with Gilbert Syndrome, who can have total bilirubin < 3.0 mg/dL).
    e. Proteinuria < CTCAE grade 3 or greater
    f. AST (SGOT)/ALT(SGPT) ≤1.5 X institutional upper limit of normal or ≤ 2.5 X ULN for patients with liver metastases. This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.
    g. Serum creatinine CL ≤ 1.5 X ULN or creatinine clearance > 45 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

Males:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

10. Have archival tissue where available.
11. In addition, patients enrolled on the clinical trial must be willing and able to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. Patients for whom newly obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Sponsor.
12. Female patients of childbearing potential should have a negative urine or serum pregnancy within 72 hours before receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

13. Ability to understand and willingness to provide written informed consent signed and dated prior to admission to the study in accordance with ICH-GCP guidelines and to the local legislation.

3.2 Core Exclusion criteria:

14. Concurrent use of other anticancer agents including chemotherapy, targeted therapy, radiotherapy or immunotherapy not otherwise specified in the protocol.
15. Concurrent use of other investigational drugs or treatment in another clinical trial with a non-FDA-approved medication within the past 4 weeks before start of therapy.
16. Chemo-, or immunotherapy or therapy with monoclonal antibodies or small tyrosine kinase inhibitors within the past 2 weeks prior to treatment with the trial drug.
17. Radiotherapy (except for brain and extremities or stereotactic treatment) within the past 2 weeks prior to treatment with the trial drug.
18. In immunotherapy pretreated patients, any history of dose-limiting toxicity with prior immunotherapy agents, including grade 3/4 immune-related adverse events (irAEs); irreversible irAEs; Grade ≥3 irAEs that did not respond to steroid rescue; or neurologic irAE with significant clinical sequelae.
19. Prior treatment with nintedanib (BIBF1120).
20. Known hypersensitivity to nintedanib, nivolumab, ipilimumab, peanut or soy or any other trial drug, or their excipients.
21. Any toxicity (>CTCAE version 5 grade 3) from previous anti-cancer therapy that has not resolved to a Grade 1. Persistence of clinically relevant therapy related toxicity from previous chemo and/or radiotherapy. Patients with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy, alopecia).
22. History of leptomeningeal carcinomatosis.
23. Radiotherapy to a target lesion within the past 3 months prior to baseline imaging unless that area has demonstrated progression.
24. Active brain metastases (e.g., stable for <2 weeks, symptomatic, no adequate previous treatment, requiring treatment with anti-convulsants); dexamethasone therapy will be allowed if administered as stable or decreasing dose for at least 3 weeks before randomization otherwise no steroids to exceed prednisone 10 mg/day prior to starting trial treatment. Symptomatic or uncontrolled CNS metastasis.
25. Current or prior use of immunosuppressive medication 7 days before the first dose of nivolumab or ipilimumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. A brief course (≤28 days) of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted. Topical corticosteroids are permitted.
26. Active or prior documented autoimmune disease within the past 2 years. NOTE: Patients with vitiligo, Grave's disease, type I diabetes mellitus or residual hypothyroidism due to autoimmune condition only requiring hormone replacement, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.
27. Centrally located tumors with radiographic evidence (CT or MRI) of local invasion of major blood vessels.
28. Has known history of, or any evidence of active, non-infectious pneumonitis.

29. Therapeutic anticoagulation with drugs requiring INR monitoring (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 < 325mg per day.
30. Major injuries and/or surgery within the past 4 weeks prior to start of study treatment with incomplete wound healing and/or planned surgery during the on-treatment study period.
31. History of clinically significant hemorrhagic or thromboembolic event in the past 6 months.
32. Known inherited predisposition to bleeding or thrombosis.
33. Significant cardiovascular diseases (i.e., uncontrolled hypertension, unstable angina, history of infarction within the past 3 months prior to start of study treatment, congestive heart failure > NYHA II, serious cardiac arrhythmia).
34. Coagulation parameters: International normalized ratio (INR) > 2, prothrombin time (PT) and partial thromboplastin time (PTT) > 50% of deviation of institutional ULN.
35. History of another primary malignancy within the past 2 years except for:
    a. Basal cell skin cancer
    b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    c. Adequately treated carcinoma in situ without evidence of disease (e.g., cervical cancer in situ)
36. Active serious infections in particular if requiring systemic antibiotic or antimicrobial therapy
37. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected)
38. History of known active primary immunodeficiency
39. History of allogeneic organ transplant
40. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving study treatment.
41. Gastrointestinal disorders or abnormalities that would interfere with absorption of the study drug
42. Serious illness or concomitant non-oncological disease such as neurologic, psychiatric, infectious disease or active ulcers (gastrointestinal tract, skin) or laboratory abnormality that may increase the risk associated with study participation or study drug administration and in the judgment of the investigator would make the patient inappropriate for entry into the study
43. Patients who are sexually active and unwilling to use a medically acceptable method of contraception (e.g., such as implants, injectables, combined oral contraceptives, some intrauterine devices or vasectomized partner for participating females, condoms for participating males) for the duration specified during the trial and after end of active therapy* (See Section 3.3 for details)
44. Pregnant or breastfeeding female patients.
45. Psychological, familial, sociological, or geographical factors potentially hampering compliance with the study protocol and follow-up schedule
46. Active alcohol or drug abuse
47. Significant weight loss (> 20% of Body Weight) within past 6 months prior to inclusion into the trial
48. History of active tuberculosis

3.3 Contraception in patients with preserved reproductive capacity

Patients will be considered to be of childbearing potential unless surgically sterilized by hysterectomy or bilateral tubal ligation/salpingectomy, or post-menopausal for at least two years.

Women of childbearing potential on the trial will be instructed to adhere to contraception for a period of 5 months after the last dose of nivolumab, ipilimumab or nintedanib on the trial. Men receiving the trial drug combination and who are sexually active with women of child bearing age will be instructed to adhere to contraception for a period of 7 months after the last dose of nivolumab , ipilimumab and nintedanib .

A highly effective method of birth control is defined as one which results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, certain intrauterine devices (IUDs), sexual abstinence, or vasectomized partner.

In case local regulations require restrictions to the above definition, the patient information will specify the acceptable contraceptive methods.

3.4 Withdrawal of consent for study

If treatment consent is withdrawn, the patient will not receive any further investigational product. If study consent is withdrawn, the patient will not receive any further investigational product or further study observation or contact.

4. TREATMENT PLAN

4.1 Dose Preparation

Table 1. Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
Nivolumab	Bristol-Myers Squibb	Supplied as a clear to opalescent, colorless to pale-yellow solution. Dilute with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with final concentration 250mg.
Ipilimumab	Bristol-Myers Squibb	Supplied as a clear to opalescent, colorless to pale-yellow solution. Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a nal concentration ranging from 1 mg/mL to 2 mg/mL.
Nintedanib	Boehringer Ingelheim	Supplied as a soft gelatin capsule available in 2 dose strength of- 100mg, and 150mg. Capsule fill composed of medium chain triglycerides, hard fat, and lecithin in addition to drug substance.

The investigator’s or site’s designated investigational product manager is required to maintain accurate investigational product accountability records. Commercially 0.9% (weight/volume [w/v]) saline, 5% Dextrose, or USP will be supplied by each site. Upon completion of the study, copies of investigational product accountability records will be

returned to BI or BMS. All unused investigational product will be returned to BI or BMS authorized depot or disposed of upon authorization by BI or BMS according to the investigational site policy. All investigational products should be kept according to manufacturer specifications.

4.2 Agent Administration

Treatment will be administered on an outpatient basis.

4.2.1 Nintedanib (BIBF1120)

Nintedanib is supplied as soft gelatin capsules containing a suspension of milled active as the ethane sulphonate salt. It is available in four dose strengths of 100 mg (peach or orange, oblong capsules), and 150 mg (brown or range capsules). Shelf life for all dose strengths and formulations is 60 months.

Capsules have to be stored below 30°C. Capsules should be protected from exposure to high

Nintedanib Drug Summary

Substance (INN):	**Not assigned**
Pharmaceutical form:	Soft gelatin capsule
Pharmaceutical code	Nintedanib (BIBF1120)
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	100 mg and 150 mg capsules
Dose:	400 mg (200 mg twice daily), dose reduction according to section 5
Duration of use:	Continuous daily dosing until progression of disease or until criteria for interruption of treatment (section 4) is met.
Route of administration:	Oral
Posology:	Once or twice daily (to be swallowed unchewed with a glass of water of about 250 mL with a dose interval of around 12 hours at the same times every day, usually in the morning and the evening after food intake)

4.2.2 Nivolumab

Nivolumab, also referred to as BMS-936558-01 or BMS-936558, is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains. It is a clear to opalescent, colorless to pale-yellow solution, which may contain light (few) particulates. It does not contain a preservative. It is supplied as a single-dose vial containing 100mg/10 mL (10mg/mL) solution. The drug product is a sterile, non- pyrogenic, single-use, isotonic aqueous solution in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (Tween™ 80), pH 6.0 and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals.

Recommended dosing preparation, storage and use conditions:

Nivolumab vials should be stored at refrigerated temperatures (2°C to 8°C) and should not be frozen. Nivolumab does not contain preservatives, and any unused portion must be discarded. Preparation of Nivolumab and preparation of the IV bag are to be performed aseptically. Total in-use storage time from needle puncture of the product vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F) from time of preparation. It is recommended that the prepared final IV bag be stored in the dark at 2°C to 8°C until needed. If storage time exceeds these limits, a new dose must be prepared from new vials. The refrigerated infusion solutions in the prepared final IV bag should be equilibrated at room temperature for about 2 hours prior to administration. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

For dose preparation steps, the following ancillary items are required:

- IV infusion bags of 0.9% sodium chloride injection (250 mL size), USP, or 5% Dextrose Injection, USP with final concentration ranging from 1mg/mL to 10mg/mL. Saline bags must be latex-free and can be made of PVC or polyolefins (e.g., polyethylene), manufactured with bis (2-ethylhexyl) phthalate (DEHP) or DEHP-free.
- IV infusion lines made of PVC/DEHP or PVC/tri octyl trimellitate or polyethylene or polyurethane. All DEHP-containing or DEHP-free lines are acceptable. Lines should contain a 0.22 or 0.2 µm in-line filter. The in-line filter can be made of polyethersulfone or polyvinylidene fluoride.
- Catheters/infusion sets made of polyurethane or fluoropolymer with silicone and stainless steel and/or PVC components.
- Syringes made of polypropylene and latex-free.
- Needles made of stainless steel.
- After preparation of the dose, the entire contents of the IV bag should be administered as an IV infusion for approximately 1 hour through intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not co-administer other drugs through the same intravenous line. Flush the IV line with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

Nivolumab will be administered as intravenous infusion over 60 minutes at 3mg/kg for the first dose. It will then be given over 30 minutes at 3mg/kg every 2 weeks. Each dose of Nivolumab should be administered using the following guidelines:

- Nivolumab must be administered at room temperature (25°C) by controlled infusion via an infusion pump into a peripheral vein. Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.
- A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product. Fully functional resuscitation facilities should be available. Investigational product must not be administered via IV push or bolus but as a slow IV infusion. The entire content of each IV bag will be infused using an infusion pump.

- The infusion lines should be attached only at time of use. Lines used for infusion during dose administration will need to be equipped with appropriate in-line filters.
- Some investigational product may remain in the IV line after the infusion has completed. Fifteen to 30 mL of 0.9% sodium chloride IV solution should be added to the infusion bag after the investigational product has been administered to flush the line. The infusion rate should not be changed.
- The duration of the investigational product administration will be recorded.

Nivolumab Drug Summary

Substance (INN):	Not assigned
Pharmaceutical form:	Pale yellow liquid
Pharmaceutical code	Nivolumab
Source:	Bristol Meyers
Unit strength:	100mg/10 mL (10mg/mL) solution
Dose:	3 mg/kg
Duration of use:	Every 2 weeks until disease progression or until criteria for interruption of treatment (Section 5)
Route of administration:	Intravenous
Posology:	3mg/kg intravenously every 2 weeks

4.2.3 Ipilimumab

Ipilimumab (BMS-734016, MDX-010) is a fully human IgG1κ consisting of 4 polypeptide chains; 2 identical heavy chains primarily consisting of 447 amino acids each with 2 identical kappa light chains consisting of 215 amino acids each linked through inter-chain disulfide bonds.

It is formulated as a sterile, isotonic, non-pyrogenic preservative-free, clear to slightly opalescent, colorless to pale- yellow solution for intravenous infusion, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particles.

It is supplied in single-use Type 1 flint glass vials of 50 mg/10 mL stoppered with gray butyl stoppers and sealed with aluminum seals. Each milliliter contains 5 mg of ipilimumab and the following inactive ingredients: diethylene triamine pentaacetic acid (DTPA) (0.04 mg), mannitol (10 mg), polysorbate 80 (vegetable origin) (0.1 mg), sodium chloride (5.85 mg), tris hydrochloride (3.15 mg), and Water for Injection, USP at a pH of 7.

Recommended dosing preparation, storage and use conditions:

- Ipilimumab injection (5 mg/mL) can be used for intravenous (IV) administration without dilution after transferring to a polyvinyl chloride (PVC), non-PVC/non-di-(2-ethylhexyl)phthalate (DEHP), or glass container.Ipilimumab injection may be diluted in 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) or 5% Dextrose Injection, USP to concentrations between 1 and 4 mg/mL and stored in PVC, non-PVC/non-DEHP, or glass containers for up to 24 hours at 2°C to 8°C or room temperature/room light. The product may be infused using a volumetric pump

at the protocol-specific dose(s) and rate(s) through a PVC IV solution infusion set with an in-line, sterile, nonpyrogenic, low-protein-binding filter (pore size of 0.2 to 1.2 µm).

- Ipilimumab injection must not be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents. Ipilimumab injection, 50 mg/10 mL (5 mg/mL), must be stored refrigerated (2°C to 8°C) and protected from light. Ipilimumab injection must not be frozen. Partially used vials or empty vials of ipilimumab injection should be discarded at the site according to appropriate drug disposal procedures.
- Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

Ipilimumab Drug Summary

Substance (INN):	Not assigned
Pharmaceutical form:	Pale yellow liquid
Pharmaceutical code	Ipilimumab
Source:	Bristol Meyers
Unit strength:	50 mg/10 mL (5 mg/mL)
Dose:	1mg/kg
Duration of use:	Every 6 weeks until disease progression or until criteria for interruption of treatment (Section 5)
Route of administration:	Intravenous
Posology:	1mg/kg intravenously every 6 weeks

4.3 Clinical Trial Design

The combination of nintedanib with nivolumab plus ipilimumab will first be tested in a Phase I trial (24 patients) to establish safety and tolerability. Once the doses for the combination of choice are established (recommended Phase 2 dose, R2PD) we will proceed forward with the Phase II trials (40 patients each) Tables 2 and 3

Table 2. Phase I Dose Escalation for Nivolumab, Ipilimumab and Nintedanib.

NSCLC Cohort (n=18)	Immunotherapy Regimen	Nintedanib*
Immune therapy pre-treated advanced or	Nivolumab 3 mg/kg IV Q2 Weeks plus Ipilimumab 1 mg/kg Q6 weeks	100mg PO QD Days 1-14 (Daily dose = 100 mg)
		150mg PO QD Days 1-14 (Daily dose = 150 mg)
		100mg PO BID Days 1-14 (Daily dose = 200 mg)

metastatic NSCLC		150mg PO BID Days 1-14 (Daily dose = 300 mg)
		200mg PO BID Days 1-14 (Daily dose = 400 mg)

*Doses based upon current dosing guidelines from Boehringer-Ingelheim

The dose-escalation design (Table 2) for nintedanib combined with ipilimumab (1mg/kg) and Nivolumab (3mg/kg). Each cycle will be 2 weeks long. Patients will remain on study until progressive disease, study withdrawal, or intolerability.

Table 3. Phase II. Nivolumab, Ipilimumab and Nintedanib.

NSCLC Cohort	Immunotherapy Regimen*	Nintedanib
Arm A: Advanced or metastatic NSCLC who are immunotherapy naïve	Nivolumab 3 mg/kg IV Q2 plus Ipilimumab mg/kg Q6	Dose TBD based on MTD and DLT, if any, in Phase I dose escalation (N = 40)
Arm B: Advanced or metastatic NSCLC with prior immunotherapy	Nivolumab 3 mg/kg IV Q2 plus Ipilimumab 1 mg/kg Q6	Dose TBD based on MTD and DLT, if any, in Phase I dose escalation (N = 40)

Each cycle will be 6 weeks long. Patients will remain on study until progressive disease, study withdrawal, or intolerability. The rationale behind the Phase II, Arm B (in selecting patients previously treated with immunotherapy) is to demonstrate whether patients who failed primary immunotherapy may then gain a clinical response by targeting the microenvironment, as well as to demonstrate the safety and tolerability of subsequent immunotherapy. Many patients who are considered for clinical trials in our cancer center may have already been pre-treated and failed to respond; therefore, this represents a unique therapeutic approach.

4.4 Patient enrollment:

Phase I and phase II

The combination of nintedanib and immunotherapy with nivolumab and ipilimumab has not yet been tested; therefore, we will first conduct a Phase I (Table 2) trial of this triplet combination utilizing a 3+3 design (Section 11). If the Nivolumab/Ipilimumab/Nintedanib arm is found to be safe then this will be the combination of choice moving forward in the Phase II (Table 3) portion (NSCLC patients who have prior immunotherapy and who are newly diagnosed, treatment naïve).

Patients will be enrolled once informed consent has been obtained, screening is complete, and all eligibility has been confirmed. Our trial patients will receive nivolumab IV every 2 weeks, ipilimumab IV every 6 weeks plus nintedanib 100-200 mg PO QD-BID for 2-week cycles. Treatment will continue until progression, intolerance, or patient withdrawal occurs. Patients will be assessed for treatment related toxicities and for progression of disease every 3 cycles (6 weeks ± 7 days) for the first year. After one year, radiographic assessment will be performed every 12 weeks (± 7 days). Patients will enter follow-up either after confirmation of PD or completion of treatment.

We will not exclude patients on the basis of PD-L1 expression levels for the many reasons detailed above in the background section, but the results will need to be known to analyze the results.

4.4.1 Specific considerations

Tumor biopsies:

Patients enrolled in either the phase I and phase II trials will undergo a core biopsy or excisional biopsy of a lesion prior to starting treatment and in cycle 2 day 8 +/- 7 days. There will be an option to also obtain a third biopsy upon progression of disease. These biopsies will be analyzed as detailed in clinical correlates (Section 7).

4.4.2 Inclusion of Women and Minorities:

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

4.4.3 Patient numbering

Once a patient is enrolled in the study, he/she will be assigned a simple 3 digit number, with the first patient assigned to 001 and so on. A separate spread sheet with password protection will be maintained that contains the patient study number along with personally identifiable information. Password protection will be maintained in order to keep patient information strictly confidential. Upon signing the informed consent form, the patient will be assigned a patient number by the investigator or his/her designee. Once assigned to a patient, a patient number will not be reused. If the patient fails to be started on treatment for any reason, the reason will be entered on the Eligibility Tab in OnCore, and his/her demographic information will be entered on the Demography Tab in OnCore. All laboratory, radiologic, and pathologic data collected on trial participants will be assigned the unique treatment number and stored in the OnCore system database.

4.4.4 Patients and Sites

This is a single-institution study at Moffitt Cancer Center. The study may enroll 18 patients in phase I cohort and 40 patients in each arm of phase II trial.

4.4.5 Efficacy

Radiographic assessments will be performed every 6 weeks (± 7 days) for the first year. After one year, radiographic assessments will be performed every 12 weeks (± 7 days). Response will be assessed using the response evaluation criteria in solid (RECIST v1.1).

Patients who are found to have stable disease (SD), partial response (PR), or complete response (CR) will continue on study until evidence of disease progression, intolerance, or withdrawal from study. Response rate, overall survival, and progression-free survival will be determined. Patients with progressive disease by RECIST v1.1 but without rapid clinical deterioration may continue to be treated at the discretion of the investigator.

4.4.6 Safety

NCI CTCAE version 5.0 will be used to assess toxicities in all patients in this study. Although nintedanib, nivolumab, and ipilimumab are each generally well tolerated, toxicities do occur. Careful toxicity assessments will be performed with standard laboratory studies (CBC, BUN, creatinine, electrolytes, and LFTs) before each treatment. The start of adverse event collections will be at cycle 1 day 1 (C1D1). Abnormal Lab values and vital signs or test results that do not induce clinical signs/symptoms or require therapy will not be considered clinically significant and will not be reported as adverse events (AEs). AEs will be collected at start of study treatment. The collection of significant adverse events (SAE) will start upon signature of the ICF. All SAEs with a determination of SAE-relatedness to the investigational therapy will be reported as described in the data and safety-monitoring plan detailed in the protocol. **(Section 6).**

4.6 General Concomitant Medication and Supportive Care Guidelines

According to local standards and please also see **Section 5**.

4.7 Duration of Therapy

Nintedanib: Until disease progression as determined by the treating MD/study PI, toxicity, withdrawal from treatment or study, or completion of treatment.

Nivolumab: Until disease progression or completion of treatment as determined by the treating MD/study PI, toxicity, withdrawal from treatment or study, or completion of treatment.

Ipilimumab: Until disease progression or completion of treatment as determined by the treating MD/study PI, toxicity, withdrawal from treatment or study, or completion of treatment.

4.8 Duration of Follow Up

Safety Follow-up

The End of treatment visit (See Study Calendar) is visit corresponding to when the decision was made to stop study medication. A mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the end of treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Patients with an AE of grade > 1 related to the study medication(s) will be followed until the resolution of the AE to grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 100 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

Follow-up visits

Patients who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 8 weeks (42 ± 7 days) after the 30 day Safety follow up visit by radiologic imaging to monitor disease status. After 1 year,

the imaging time point will occur every 12 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study, or if the patient begins retreatment with nintedanib combined with nivolumab plus ipilimumab as detailed in **Section 5.** Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Survival Follow-up

Once a patient experiences confirmed disease progression or starts a new anti-cancer therapy or has a toxicity that precludes further therapy on trial, the patient moves into the survival follow-up phase and should be contacted by telephone every 12 weeks (± 7 days) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

4.9 Criteria for Removal from Study Treatment

Patients should PERMANENTLY discontinue treatment with nintedanib, nivolumab and ipilimumab in the event of:

- Unequivocal disease progression.
- Intolerable Adverse Events (e.g. CTCAE version 5 grade 3 or 4) that cannot be managed by dose reduction
- Withdrawal of informed consent
- Change in the patient's status creating an unfavorable risk/benefit in favor to stop study treatment
- Patient is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk.
- Eligibility criteria are violated and represent a safety issue for the patient
- Further dose reductions considered necessary but not allowed according to the protocol (for nintedanib, no more than 2 dose reductions are allowed)
- Pregnancy or intent to become pregnant
- Any AEs that meets criteria for discontinuation as defined in **Section 6**
- AEs related to treatment with the combination of nintedanib, nivolumab and ipilimumab that is Grade 3, with the exception of toxicities that do not meet criteria for discontinuation as defined in **Section 6**
- Patient noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (for example, refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy including another investigational agent
- Confirmation of progressive disease and investigator determination that the patient is no longer benefiting from treatment with nivolumab, ipilimumab and nintedanib
- Investigator's decision.

Patients who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AEs, other), will be identified as having permanently discontinued treatment.

Patients who are permanently discontinued from receiving investigational product will be followed for safety per **Section 4.8**, including the collection of any protocol-specified blood

specimens, unless consent is withdrawn or the patient is lost to follow-up or enrolled in another clinical study. All patients will be followed for survival. Patients who decline to return to the site for evaluations will be offered follow-up by phone every 12 weeks (± 7 days) as an alternative.

5. DOSING SELECTION/DELAYS/DOSE MODIFICATIONS

5.1. Criteria for interruption of treatment with Nintedanib (BIBF1120) and Nivolumab plus Ipilimumab

Treatment with nintedanib (BIBF1120) and nivolumab plus ipilimumab has to be interrupted in case any of the criteria listed in Table 4 is fulfilled.

Table 4: Criteria when to interrupt treatment with nintedanib (BIBF1120) and nivolumab plus ipilimumab due to an adverse event

If one criterion is met, Nintedanib (BIBF1120) and Nivolumab plus Ipilimumab has to be interrupted
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 elevations of > 2.5 x ULN in conjunction with bilirubin of > 1.5 x ULN
AST and/or ALT elevations of > 5x ULN
Other non-hematological adverse event of CTCAE grade ≥ 3 considered drug-related
*Neutropenia and fever > 38,5°
*Neutropenia CTCAE grade 4 for more than 7 days without fever
* Platelets <50.000mm³ with bleeding

5.2. Criteria to restart Nintedanib (BIBF1120), Nivolumab and Ipilimumab treatment

A patient is eligible to restart nintedanib (BIBF1120),nivolumab and ipilimumab if all criteria listed in Table 5 are met. If a patient has to interrupt intake of nintedanib (BIBF1120),nivolumab and ipilimumab due to an adverse event for more than 6 weeks (± 7 days) the decision to restart treatment with nintedanib (BIBF1120),nivolumab and ipilimumab needs to be discussed and agreed upon between the investigator and the sponsor.

Table 5: Criteria to assess eligibility to restart continue nintedanib (BIBF1120), nivolumab and ipilimumab

All criteria have to be met in order to restart Nintedanib (BIBF1120) and Nivolumab and Ipilimumab, meaning AEs have to return to Grade 1 or baseline
Nausea CTCAE grade ≤ 2 Vomiting CTCAE grade ≤ 1 Diarrhea CTCAE grade < 2 AST and ALT < 2.5 x ULN; bilirubin < 1.5 x ULN
no other non-hematological adverse event grade CTCAE ≥ 3 which is considered drug-related
*Neutropenia CTCAE grade ≤ 1, without fever or equal to the patient's pre-therapy value at study enrolment
*Platelets CTCAE grade ≤ 1 or equal to the patient's pre-therapy value at study enrolment

The dose adjustments will be outlines in the next **Section 5.4**.

5.3 Trial Treatments

The phase I dose escalation will include a fixed dose of Nivolumab 3 mg/kg IV every 2 weeks, a fixed dose of Ipilimumab 1 mg/kg every 6 weeks, and escalating doses of Nintedanib starting at 100mg PO once daily (five dose levels) to determine the MTD to be used in the expansion group and the randomized phase II portion of the trial. Once a MTD is determined, the phase II expansion and randomized phase two portions of the trial can begin accrual. Cycle 1, day 1 will start with nivolumab plus ipilimumab on day 1 with continuous daily oral therapy with Nintedanib starting on days 1 on a 2-week cycle. Please see **Section 4.3** Clinical Trial Design for more information.

Table 6. Nintedanib dose levels in phase I dose escalation phase.

Dose Level	Nintedanib Dose, Route, Frequency	Nivolumab Dose, Route, Frequency	Ipilimumab Dose, Route, Frequency	Use
-1	100mg PO QD	3 mg/kg IV Q2 weeks	1 mg/kg IV Q6 weeks	Experimental
0	150mg PO QD	3 mg/kg IV Q2 weeks	1 mg/kg IV Q6 weeks	Experimental
1	100mg PO BID	3 mg/kg IV Q2 weeks	1 mg/kg IV Q6 weeks	Experimental
2	150mg PO BID	3 mg/kg IV Q2 weeks	1 mg/kg IV Q6 weeks	Experimental
3	200mg PO BID	3 mg/kg IV Q2 weeks	1 mg/kg IV Q6 weeks	Experimental

5.3.1 Dose Selection/Modifications

5.3.1.1 Dose Selection

The rationale for selection of doses and details on preparation and administration of nivolumab, ipilimumab and nintedanib to be used in this trial is provided in **Section 4.0.**

5.3.1.2 Dose Modifications of Nintedanib (BIBF1120)

As initial measure for the management of side effects (see **Section 6**) treatment with Nintedanib should be temporarily interrupted until the specific adverse reaction has resolved to levels that allow continuation of therapy. Nintedanib treatment may be resumed at a reduced dose. Dose adjustments in 50 or 100 mg increments per day (i.e. a 50 mg reduction per dosing) based on individual safety and tolerability are recommended as described in Table 6. In case of further persistence of the adverse reaction(s), i.e. if a patient does not tolerate 100 mg once daily, treatment with Nintedanib should be discontinued.

The following dose levels will be used in case dose adjustments are required for management of undue toxicity (see Table 7).

Table 7: Nintedanib (BIBF1120) dose levels – example for starting dose of 200mg twice daily

Dose- level:	0	-1	-2	-3	-4
Dose:	2 x 200 mg/day	2 x 150 mg/day	2 x 100 mg/day	1x150 mg/day	1X 100 mg/day

Of note!

If the dose of nintedanib (BIBF1120) had to be reduced due to toxicity, it will stay on the lower dose level for the entire time of administration.

5.3.1.3 Dose modifications of Nivolumab

Adverse events (both non-serious and serious) associated with nivolumab and /or ipilimumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Nivolumab and ipilimumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 9 below. The recommended dose of nivolumab is 3 mg/kg administered as an intravenous infusion over 60 minutes for the first dose. It will then be given over 30 minutes at 3mg/kg every 2 weeks until disease progression or unacceptable toxicity. There are no recommended dose modifications for nivolumab. Further dose adjustments are described in **Section 5.5.2** as per package insert and Events of Clinical Interest Guidance Document for supportive care guidelines including use of steroids.

5.3.1.4 Dose modifications for Ipilimumab

The recommended dose of ipilimumab is 1mg/kg administered intravenously over 90 minutes every 6 weeks.

There are no recommended dose modifications for Ipilimumab. Further dose adjustments are described in **Section 5.5.2** as per package insert and Investigator Brochure.

5.4. Management of adverse events

5.4.1 Management of adverse events of Nintedanib specifically

As initial measure for the management of side effects (see section Side effects) treatment with Nintedanib should be temporarily interrupted until the specific adverse reaction has resolved to levels that allow continuation of therapy. Nintedanib treatment may be resumed at a reduced dose. Dose adjustments in 50 to 100 mg increments per day (i.e. a 50 mg reduction per dosing) based on individual safety and tolerability are recommended as described in **Table 6**. In case of further persistence of the adverse reaction(s), i.e. if a patient does not tolerate 100 mg once daily, treatment with Nintedanib should be discontinued.

Table 8: Recommended dose adjustments for Nintedanib (BIBF1120)

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 twice daily to 150 mg twice daily 2nd episode: Reduce dose from 150 mg twice daily to 100 mg twice daily 3rd episode*:* Reduce dose from 100md twice daily to 100mg once daily 4th episode: Stop treatment
Vomiting ** > grade 2 AND/OR Nausea > grade 3 despite anti-emetic treatment**	
AST and/or ALT elevations of > 2.5 x ULN in conjunction with bilirubin of > 1.5 x ULN OR AST and/or ALT elevations of > 5x ULN	
Other non-hematological or hematological adverse reaction of > grade 3	
Elevation of AST and/or ALT values to > 3 x ULN in conjunction with an increase of total bilirubin to ≥ 2 x ULN and ALKP < 2 x ULN	Unless there is an alternative cause established, it should be permanently discontinued

*CTCAE: Common Terminology Criteria for Adverse Events

** see also section 5.8. Additional precautions

If nintedanib (BIBF1120) 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 as mentioned above and for the other compound as mentioned in their prescribing information.

5.4.2 Dose modification and toxicity management of Nivolumab and Ipilimumab specifically

Nivolumab in combination with ipilimumab has already been approved for treatment of melanoma in the United States[65]. Previous studies have shown that combination of both agents results in a safety profile with adverse events similar to adverse events seen with monotherapy with each agent alone [85]. However, there are some cases that have found greater frequency of adverse events[65,85].

Based on the mechanism of action of nivolumab and ipilimumab leading to T-cell activation and proliferation, there is the possibility of observing immune-related adverse events (irAEs) during the conduct of this study. Potential irAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate cause (e.g., infection or PD), signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

Table 9a. Dose Modification Guidelines for Drug-Related Adverse Events for Nivolumab and Ipilimumab

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)1	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold nivolumab and ipilimumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume nivolumab and ipilimumab when patients are clinically and metabolically stable.
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4	Therapy with nivolumab and ipilimumab can be continued while treatment for the thyroid disorder is instituted	Therapy with nivolumab and ipilimumab can be continued while treatment for the thyroid disorder is instituted.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity2	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.
1 For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.
2 Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

Table 9b: Additional Dose Modification Guidelines for Drug-Related Adverse Events for Nivolumab and Ipilimumab

Adverse Reaction	Severity *	Dose Modification	Toxicity management
Adrenal insufficiency	Grade 2 adrenal insufficiency	Withhold dose when additional medical intervention is indicated other than physiologic mineralcorticoid and/or corticosteroid (≤ 10mg prednisone equivalent) replacement[a]	Nivolumab and/or Ipilimumab can cause immune-mediated adrenal insufficiency. Monitor patients for signs and symptoms of adrenal insufficiency. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Withhold Nivolumab and Ipilimumab for moderate (Grade 2 for which additional medical intervention is indicated other than physiologic mineralcorticoid and/or corticosteroid (≤ 10mg prednisone equivalent) replacementand permanently discontinue Nivolumab and Ipilimumab for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency.
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue	

Skin	Grade 3 or 4 rash or suspected/confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) or grade 4	Permanently discontinue	Nivolumab and Ipilimumab can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. For symptoms or signs of SJS or TEN, withhold Nivolumab and Ipilimumab. Refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed permanently discontinue Nivolumab and Ipilimumab For immune-mediated rash, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) rash. Withhold Nivolumab and Ipilimumab for severe (Grade 3) rash and permanently discontinue Nivolumab and Ipilimumab for life-threatening (Grade 4) rash.
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Permanently discontinue	Nivolumab and Ipilimumab can cause immune-mediated encephalitis with no clear alternate etiology. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Withhold Nivolumab and Ipilimumab in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue Nivolumab and Ipilimumab for immune-mediated encephalitis
	Immune mediated encephalitis	Permanently discontinue	
Other	Other Grade 3 adverse reaction First occurrence	Withhold dose[a]	Nivolumab and Ipilimumab can cause other clinically significant immune-mediated adverse reactions. Immune-mediated adverse reactions may occur after discontinuation of Nivolumab and Ipilimumab therapy. For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, permanently discontinue or withhold Nivolumab and Ipilimumab, administer high-dose corticosteroids, and if appropriate, initiate hormone- replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting Nivolumab and Ipilimumab after completion of corticosteroid taper based on the severity of the event
	Recurrence of same Grade 3 adverse reactions	Permanently discontinue	
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue	
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue	
	Persistent Grade 2 or 3 adverse reactions lasting	Permanently discontinue	

	12 weeks or longer		

* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 5.0 (NCI CTCAE v5).

a. Resume treatment when adverse reaction returns to Grade 0 or 1, patients with persistent grade 2 adrenal insufficiency whose medical intervention is mineralcorticoid and/or corticosteroid replacement (≤ 10mg prednisone equivalent) may resume treatment.

5.4.3 Dose modification and toxicity management of combination of Nintedanib and/or Nivolumab plus Ipilimumab

For adverse events (AEs) that are considered at least partly due to administration of nintedanib, nivolumab, and ipilimumab the following dose adjustment guidance may be applied:

Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).

If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of nintedanib plus nivolumab and/or ipilimumab along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for Nintedanib. No dose modifications for ipilimumab and nivolumab (see below). In addition, there are certain circumstances in which nintedanib, nivolumab, and/or ipilimumab should be permanently discontinued.

All dose modifications should be documented with clear reasoning and documentation of the approach taken.

5.4.4 QT Prolongation

No evidence of QT prolongation potential in Nivolumab, Ipilimumab (Per investigator Brochure – Study CA184004), or Nintedanib in the studied dose range [86,87].

5.5. Dose limiting toxicity

The Dose limiting toxicity (DLT) period will be the first 6 weeks of treatment. Patients must have received at least 25% of drug to be considered evaluation for the DLT. If a patient is removed from treatment within the DLT assessment period for non-toxicity or a toxicity not-related to the study medication(s) the patient can be replaced to allow a durable assessment of toxicity for the triplet at discretion of the sponsor. DLT will be defined as any Grade 3 or higher toxicity that occurs during the DLT evaluation period where not otherwise specified below. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. All toxicities will be graded according to NCI CTCAE v5 . Following the first dose of nintedanib, nivolumab and ipilimumab, subsequent administration can be modified based on toxicities observed **(see Tables 5, 6, 8 and 9 in Section 5)**. Dose reductions for nintedanib permitted only if the patient is outside of the DLT window.

The following will be considered DLTs:

- Any Grade 4 irAE
- Any ≥ Grade 3 colitis X 7 days despite optimal treatment
- Any Grade 3 or 4 noninfectious pneumonitis irrespective of duration

- Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care
- Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days
- AST/ALT elevation > 5 × ULN or total bilirubin > 3 × ULN
- Grade 3 or greater adrenal insufficiency
- Any ≥ Grade 3 non-irAE, except for the exclusions listed below

The definition excludes the following conditions:

- Grade 3 fatigue lasting ≤ 7 days
- Grade 3 endocrine disorder (thyroid and/or pituitary) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
- Grade 3 inflammatory reactions attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc.)
- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 business days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility
- Grade 3 or 4 lymphopenia
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 business days
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 business days
- Grade ≥3 elevation in amylase and lipase in asymptomatic patients, these laboratory abnormalities will be monitored if elevated.

5.6. Additional precautions for Nintedanib (BIBF1120)

5.6.1 Diarrhea

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

5.6.2 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 (BIBF1120) may be required despite appropriate supportive care. Supportive care for nausea and vomiting may include medicinal products with anti-emetic properties, e.g. glucocorticoids, anti-histamines or 5-HT3 receptor antagonists and adequate hydration.

In the event of dehydration, administration of electrolytes and fluids is required. Plasma levels of electrolytes should be monitored, if relevant gastrointestinal adverse events occur.

5.6.3 Neutropenia and Sepsis

A higher frequency of neutropenia of CTCAE grade > 3 was observed in patients treated with nintedanib (BIBF1120) in combination with docetaxel as compared to treatment with docetaxel alone in the clinical trial LUME-Lung 1. Subsequent complications such as sepsis or febrile neutropenia have been observed.

Blood counts should be monitored during therapy, if nintedanib (BIBF 1120) is combined with a myelosuppressive agent.

5.6.4 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 (BIBF1120) is not recommended in such patients. .

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

These increases were reversible in the majority of cases and not associated with clinically manifest liver disorders. Hepatic transaminases, ALKP and bilirubin levels are recommended to be closely monitored after start of therapy with nintedanib (BIBF1120) (periodically, i.e. in the combination phase with docetaxel at the beginning of each treatment cycle).

If relevant liver enzyme elevations are measured, interruption, dose reduction or discontinuation of the therapy with nintedanib may be required.

Alternative causes of the liver enzyme elevations should be investigated and respective action should be taken as necessary. In case of specific changes in liver values (AST/ALT > 3 x ULN; total bilirubin ≥ 2 x ULN and ALKP >2 x ULN) due to treatment with nintedanib should be interrupted. Unless there is an alternative cause established nintedanib should be permanently discontinued.

5.6.5 Special populations

Nintedanib exposure increased linearly with patient age, was inversely correlated to weight, and was generally higher in patients of Asian race. This may result in a higher risk of developing liver enzyme elevations. Close monitoring is recommended in patients with several of these risk factors. In study 1199.13 (LUME-Lung 1), there was a higher frequency of SAEs in patients treated with nintedanib plus docetaxel with a body weight of less than 50 kg compared to patients with a weight ≥ 50 kg; however the number of patients with a body weight of less than 50kg was small. Therefore close monitoring is recommended in patients weighing < 50 kg.

5.7 Trial Blinding/Masking

This is an open-label trial; therefore, the sponsor, investigator and subject will know the treatment administered.

5.8 Randomization and Stratification

There will be no randomization or stratification in this trial.

5.9 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the Oncore database from screening to enrollment period. If changes occur during the trial period, or new medications are started to treat an immune-related AE should be recorded in the Oncore database until 30 days after the last dose of trial treatment. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs as defined in **Section 6** where applicable.

5.10 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

Antineoplastic systemic chemotherapy or biological therapy
Immunotherapy not specified in this protocol
Investigational agents other than nintedanib, nivolumab, and ipilimumab
Radiation therapy
Note: Radiation therapy to symptomatic lesions or to the brain may be allowed at the investigator's discretion, provided that radiotherapy does not affect all target lesions.

Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology or to treat a comorbid condition as a standard of care (e.g. COPD exacerbation). The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.
There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.11 Rescue medication and additional treatments

Rescue medications to reverse the actions of nintedanib (BIBF1120), nivolumab, or ipilimumab are not available. Potential side effects of nintedanib (BIBF1120), nivolumab, and ipilimumab have to be treated symptomatically. Please see **Section 5.5.1** for details.

5.12 Restrictions

Additional chemo-, immuno- or hormone therapies- are not allowed during the active treatment period of this trial..

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Strong P-gp inducers, e.g. rifampicin, carbamazepine, phenytoin, erythromycin, ketoconazole and St. John's Wort, may decrease exposure to nintedanib. Co-administration of strong P-gp inducers with the study drug combination should be carefully considered. However if co-administered , strong P-gp inhibitors may increase exposure to nintedanib, e.g. ketoconazole or erythromycin. In such cases patients should be monitored closely for nintedanib toxicity. Management of side effects may require interruption, dose reduction or discontinuation of therapy with nintedanib

6. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

6.1 Adverse Event Characteristics

An adverse event (AEs) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a patient's pre-existing condition. An abnormal laboratory, test or physical exam finding that requires an action or intervention by the investigator will be recorded. Adverse events (but not serious adverse events) occurring before starting study treatment but after signing the informed consent form are recorded on the Medical History/Current Medical Conditions Electronic Case Report Form (ONCORE). Abnormal Lab values, vital signs or test results that do not induce clinical signs/symptoms or require therapy, will not be considered clinically significant and will not be reported as Adverse Events. In addition, isolated abnormal laboratory values that are considered clinically significant (e.g., cause study discontinuation or constitutes in and of itself a Serious Adverse Event) should be recorded on the Adverse Events CRF. SAEs occurring after initiation of treatment are recorded on the Adverse Event CRF.

Adverse events may be treatment emergent (i.e., occurring after initial receipt of investigational product) or non-treatment emergent. A non-treatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the patient has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the patient being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or not serious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

The term AE is used to include both serious and non-serious AEs.

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

Patients may be hospitalized for administrative or social reasons during the trial (e.g., days on which infusion takes place, long distance from home to site). These and other hospitalizations planned at the beginning of the trial do not need to be reported as an SAE.

The severity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5 in the (e) CRF.

Causal relationship of adverse event

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

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

6.2 Definition of Adverse Events of SPECIAL Interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

AESIs for nivolumab and ipilimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with nivolumab and ipilimumab monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

If the Investigator has any questions in regards to an adverse event (AE) being an irAE, the Investigator should promptly contact the Study Physician.

AESIs observed with nivolumab and/or ipilimumab include:

- Colitis
- Pneumonitis
- ALT/AST increases / hepatitis / hepatotoxicity

- Neuropathy / neuromuscular toxicity (i.e. events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (i.e. events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism)
- Dermatitis
- Nephritis
- Ocular side effects (uveitis, iritis, or episcleritis
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase, increased serum amylase)

6.2.1 Pneumonitis

Adverse events of pneumonitis are of interest for BI, as pneumonitis has been reported with anti-PD-1 monoclonal antibodies as well as anti-CTLA-4 monoclonal antibodies. Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended.

Guidelines for the management of patients with immune-mediated events including pneumonitis are outlined in **Section 5, Table 9a and 9b.**

6.2.2 Hypersensitivity reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1, anti-PD-1, and anti-CTLA-4 therapy). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of monoclonal antibodies can be caused by various mechanisms, including acute anaphylactic (immunoglobulin E-mediated) and anaphylactoid reactions against the monoclonal antibodies, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting, and unresponsiveness.

Guidelines for management of patients with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are outlined below

Severe or life-threatening infusion reactions: Discontinue nivolumab and ipilimumab.
Mild to moderate infusion reactions: Interrupt or slow the rate of infusion.

6.2.3 Hepatic function abnormalities (hepatotoxicity)

Increased transaminase levels have been reported during treatment with anti-PD-L1, anti-PD-1, and anti-CTLA-4 antibodies [36,85]. The clinical manifestations of Nivolumab and ipilimumab treated patients included general weakness, fatigue, nausea, and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin.

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 2.5 × ULN and concurrent increase in total bilirubin to be greater than 1.5 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other.

Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product. Guidelines for management of patients with hepatic function abnormality are outlined in **Section 5, Table 9a and 9b.**

6.2.4 Gastrointestinal disorders

Diarrhea/colitis can be observed as a treatment emergent SAE when nivolumab and ipilimumab is used as monotherapy or in combination. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. Guidelines on management of diarrhea and colitis in patients receiving nivolumab and ipilimumab are provided in **Section 5, Table 9a and 9b.**

6.2.5 Endocrine disorders

Immune-mediated endocrinopathies include hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism. Guidelines for the management of patients with immune-mediated endocrine events are provided in **Section 5, Table 9a and 9b.**

6.2.6 Pancreatic disorders

Immune-mediated pancreatitis includes autoimmune pancreatitis, and lipase and amylase elevation. Guidelines for the management of patients with immune-mediated pancreatic disorders are provided in **Section 5, Table 9a and 9b.**

6.2.7 Neurotoxicity

Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in **Section 5, Table 9a and 9b.**

6.2.8 Nephritis

Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc)

Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.)

Guidelines for the management of patients with immune-mediated neurotoxic events are provided in **Section 5, Table 9a and 9b.**

6.2.9 Immune-related adverse events

Based on the mechanism of action of nivolumab and/or ipilimumab leading to T-cell activation and proliferation, there is a possibility of observing irAEs during the conduct of this

study[65,88]. Potential irAEs may be similar to those seen with the use of Nivolumab and/or ipilimumab and may include immune-mediated enterocolitis, dermatitis, hepatitis (hepatotoxicity), pneumonitis, and endocrinopathies [36,65,84,89]. These AEs are inflammatory in nature and can affect any organ. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (eg, infection or PD), an immune-related etiology should be considered for signs or symptoms of enterocolitis, dermatitis, pneumonitis, hepatitis, and endocrinopathy. In addition to the dose modification guidelines provided **in Section 5, Table 9a and 9b**, it is recommended that irAEs are managed according to the general treatment guidelines outlined for nivolumab and ipilimumab. These guidelines recommend the following:

Patients should be evaluated to identify any alternative etiology.

- In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered immune related.
- Symptomatic and topical therapy should be considered for low-grade events.
- Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
- More potent immunosuppressives should be considered for events not responding to systemic steroids (eg, infliximab or mycophenolate).
- If the Investigator has any questions in regards to an AE being an irAE, the Investigator should immediately contact the Study Physician

The following events are considered as Protocol-specified adverse events of special interests (AESI) for Nintedanib:

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

  In such cases, the following additional information will need to be collected and documented in the respective comment field of the CRF page and the respective narratives of the SAE. That has to be forwarded to BI

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

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

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

Patients showing above laboratory abnormalities need to be followed up until the protocol specific retreatment criteria have been met and according to **Section 5, Table 9a,9b and appendix 13.1** 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.

6.3 Recording of adverse events and serious adverse events

Adverse events will be collected from time of start of study treatment to 100 days from end of treatment or the initiation of new anti-cancer therapy, whichever is earlier. Serious Adverse events will be collected from time of consent to 100 days after end of treatment or the initiation of new anti-cancer therapy, whichever is earlier. AEs will be recorded CTCAE v 5 using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to BI and BMS Patient Safety.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Changes in NCI CTCAE grade and the maximum CTC grade attained
- Whether the AE is serious or not

In addition, the following variables will be collected for SAEs as applicable:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s) or study drug(s)
- Study recording period and follow-up for adverse events and serious adverse events

During the course of the study all AEs and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

If a subject discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.

The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

SAEs, AESIs, and non-serious AEs relevant for a reported SAE or AESI are to be reported to BI and BMS using the FDA MedWatch Form and providing as much detail regarding the SAE/AESI/non-serious AEs as possible. With receipt of follow-up information, all remaining fields on the SAE form are to be completed or updated.

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) or AESI(s) that occurred after the patient has completed the clinical trial (including any protocol specified follow-up period/Residual effect period), it should be reported to BI if investigator considers it as relevant to the BI or Bristol-Myers Squibb Company study drug. Please see **Section 6.4** on how to report SAEs, AESIs, or non-serious AEs.

6.4 SAE, AESI and non-serious AE Reporting to Boehringer Ingelheim (BI) and/or Bristol-Myers Squibb (BMS)

A serious adverse event is any adverse event occurring at any dose or during any use of a BI and/ or BMS product that:

Results in death;

Is life threatening;

Results in persistent or significant disability/incapacity;
Results in or prolongs an existing inpatient hospitalization;
Is a congenital anomaly/birth defect;
Is a new cancer (that is not a condition of the study);
Is associated with an overdose;
Is an important medical event

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 100 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to BI and/ or BMS product, must be reported within 24 hours to the Sponsor, BI Unique Entry Point and BMS.

All SAEs/ AESI will be forwarded to BI Unique Entry Point and BMS will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to BI or BMS product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor, BI and BMS where appropriate.

The investigator shall report all SAEs, AESIs, and non-serious AEs which are relevant to a reported SAE or AESI by fax or other secure method using FDA medwatch form to the BI Unique Entry Point (include BI SAE cover letter form with each medwatch transmission) and BMS at 1-800-721-5072 as required above and the FDA as required.

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BI Unique Entry Point:

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
Ridgefield, CT 06877
Fax: 1-203-837-4329

Suspected adverse reactions for nivolumab and/or ipilimumab will be reported to Bristol-Myers Squibb using the FDA MedWatch or to the FDA directly at 1-800-FDA-1088 (www.fda.gov/medwatch).

BMS AE/SAE contact information:

Bristol-Myers Squibb Corporate Headquarters
345 Park Avenue
New York, NY 10154
Email address: Worldwide.Safety@BMS.com
Phone number: +1-609-818-3804

6.5 Other Events Requiring Reporting

6.5.1 Reporting of deaths

All deaths that occur during the study or within the protocol-defined 100-day post-last dose of Nivolumab, ipilimumab or nintedanib safety follow-up period must be reported as follows:

Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.

Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to as a SAE within 24 hours (**see Sections 6.3 and 6.4**, for further details) of notification of the SAE. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

Deaths with an unknown cause should always be reported as a SAE. A post mortem maybe helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to BI and BMS within the usual timeframes.

Deaths that occur following the protocol-defined 101-day and beyond post-last-dose of nivolumab, ipilimumab or nintedanib safety follow-up period will be documented as events for survival analysis but will not be reported as an SAE.

6.5.2 Overdose

An overdose is defined as a patient receiving a dose of nivolumab, ipilimumab or nintedanib in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study patient with nivolumab, ipilimumab, or nintedanib with or without associated AEs/SAEs is required to be reported within 24 hours of knowledge of the event to BI and BMS. Patient Safety or designee using the designated FDA MedWatch form will be sent to the BI Unique Entry Point and /or BMS (see **Section 6.4** for contact information). If the overdose results in an AE, the AE must also be recorded as an AE (see **Section 6.3 and 6.4**). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE (see **Section 6.3 and 6.4**). There is currently no specific treatment in the event of an overdose of Nintedanib, ipilimumab, and/or nivolumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity.

If a dose of BI and/or BMS product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect" to the BI Unique Entry Point and/or Bristol Myers Squibb (see **Section 6.4** for contact information).

6.5.3 Hepatic function abnormality

Hepatic function abnormality (as defined in **Section 6.2.3**) in a study patient, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event to BI and/or BMS. Patient Safety or designee using the designated FDA MedWatch form will be sent to the BI Unique Entry Point and BMS (see **Section 6.4** for contact information), unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study patient will be based on the clinical judgment of the investigator.

If no definitive underlying diagnosis for the abnormality is established, dosing of the study patient must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by BI and BMS.

6.5.4 Pregnancy

Maternal exposure

If a patient becomes pregnant during the course of the study, the investigational products (IP) should be discontinued immediately.

Pregnancy is regarded as an SAE. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies

(spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or

congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate BI and BMS representatives within 1 day, i.e., immediately, but no later than 24 hours of when he or she becomes aware of it. The designated BI and BMS representatives will work with the Investigator to ensure that all relevant information is provided to the BI and BMS Patient Safety data entry site within 24 hours of notification of the SAEs. The same timelines apply when outcome information is available.

Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 7 months after the last dose of nivolumab, ipilimumab, and nintedanib combination therapy or 90 days after the last dose of nivolumab and ipilimumab, whichever is the longer time period.

Should the investigator become aware of a pregnancy in the partner of a male study patient who has received IP this should be reported within 24 hours of knowledge of the event to BI and BMS. Patient Safety or designee using the designated FDA medwatch form will be sent to the BI Unique Entry Point and BMS (see **Section 6.4** for contact information).

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use. The sponsor will endeavor to collect follow-up information on such pregnancies provided the partner of the study patient provides consent.

Pregnancy is regarded as a SAE. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of any conception occurring from the date of the first dose until 100 days after the last dose or the initiation of new anti-cancer therapy, whichever is earlier (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was withdrawn from the study.

6.5.5 Dose-Limiting Toxicity

All DLT events (described in **Section 5.6**.) that occur in individual patients at any time during the treatment course or the follow-up period must also be reported as Adverse Event of Special Interest (AESI) (**see Section 6.2, 6.3, 6.4**)

6.6 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRBs and investigators in accordance with all applicable global laws and regulations.

7. CORRELATIVE/SPECIAL STUDIES

7.1 Laboratory Correlative Studies

TISSUE

Overview of Tissue Correlates of Interest

The following molecular testing may be requested on biopsy specimens obtained in the trial: ALK, EGFR, KRAS, ROS-1, PD-L1 status, RET, Met, PTEN, BRAF, PI3K and Her2 neu if not already in the EMR. In addition, PD-L1 status by immunohistochemistry and quantitation of tumor infiltrating lymphocytes will be determined on all biopsy specimens. While the molecular underpinnings of PD-L1 expression on tumor cells are poorly understood, this would likely provide insight into mechanisms of anti-PD-1 therapy and potential predictive biomarkers. Other potential tumor assessments can include staining for fibroblast-associated protein (FAP), a CAF marker, IDO (a marker of CAF inhibition) and CD4/CD8/PD-L1 staining to determine the presence of tumor-infiltrating lymphocytes (TILs). Samples will also be assessed for mutational load , nanostring for GEP for key immune markers and AQUA for Protein expression of genes (Navigate) that correlate to lack of response to immunotherapy.

Tissue IHC Assessments on Pre- and On-Immunotherapy Biopsies.

Tumor assessments will include immunohistochemical staining for fibroblast-associated protein (FAP) a CAF marker, IDO (a marker of CAF inhibition), and PD-L1. While the molecular underpinnings of PD-L1 expression on tumor cells as well as CAF expression in the TME are poorly understood, our approach would likely provide insight into mechanisms of anti-PD-1 therapy and potential predictive biomarkers. This will be done by a fluorescence-based IHC (FIHC) panel developed by Navigate to reliably and objectively quantify by Automated Quantitative Analyses (AQUA) the tumor associated immune cells using conventional FFPE whole tissue sections.[90] The high-throughput clinical trial laboratory workflow consists of automated stainers (Biocare), Vectra 2 Image Acquisition platform (Perkin Elmer) and AQUA Image Analysis software (see Figure 5) that enables objective, quantitative, and standardized biomarker assessments.[90] It has been successfully tested in different tumor indications including Metastatic Melanoma (Bordeaux et al, AACR Annual Meeting, April 2016) NSCLC, gastric cancer (Kim et al, Tri-Con, San Francisco, March 2016) and diffuse large B-cell lymphoma (Tran et al., ASH Annual Meeting, New Orleans, December 2015. All assays were evaluated in multiple analytical runs and patient specimens to verify reproducibility and the prevalence of biomarkers prior to this clinical trial application.

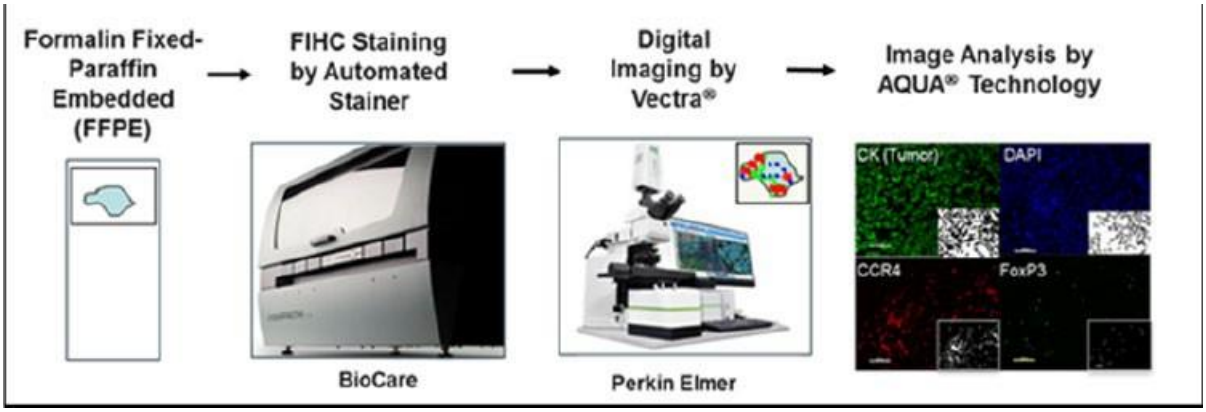
For the study, we will be interested in interrogating the patient enrichment, TIL, and T cell activation panels, those most likely to predict for benefit to Immunotherapy. (**See Table 10**). Ultimately through this approach we will be set to analyze the biological role and predictive value of innate and adaptive immune cells in the tumor microenvironment by AQUA and compare results across the predictive value of the IHC and Immunoscore analyses for example.

Table 10: Exploring tumor immunity continuum by multiplex AQUA

Objective	Multiplex FIHC Tests	Novel Results
Patient Enrichment	PD-1 + PD-L1; CTLA4 + CD80; PD-L1 + CD8	Interaction Score
TIL Enumeration	CD3, CD19; CD4 + CD8; CD16 + CD56	Quantitation & Multiplexed Enumeration on a single slide
T Cell Suppression	CD3 + PD-1 + PD-L1; CD3 + LAG3 + TIM3 CD25 + FOXP3, IDO1	
T Cell Activation	CD3 + CD8 + Ki67	
Myeloid Analysis	CD68 + CD163 + Ki67 (M1 vs. M2) CD163 + IDO-1 (functional M2) CD33 + CD11b + ARG-1 (functional MDSC)**	

Here are the proposed FIHC by AQUA tests for exploring tumor microenvironment. All markers are validated for exploratory clinical trials, except the functional myeloid derived suppressor cells (MDSC)** which remains under development.

Figure 5. Schematic illustration of FIHC AQUA assay workflow



Multiplexing is achieved by sequential application and removal of same species primary antibodies via microwave treatments. Fluorescent images are acquired on the Vectra Imaging system that acquires tissue regions of interest based on pattern recognition algorithms. Vectra images are analyzed by proprietary AQUA analysis algorithms, which remove the subjectivity of the traditional scoring system and provide more continuous and reproducible measures of protein expression in terms of biomarker intensity, percent positivity, and receptor-ligand interactions.

Determination of the Immunoscore of Pre- and On-Immunotherapy Biopsies.

To determine the baseline level of immune response to individual tumors and whether there is improved response with treatment, we will use Immunoscore to assess the TILs. Immunohistochemistry will be used to quantify the relative numbers of CD3, CD4, CD8, and CD45RO positive T-cells. Immunoscore for each biopsy will be determined as previously

described. The density (low vs high) of two types of cells (CD4 and CD8) will be assessed at two different locations (IM, invasive margin; and CT, center of tumor). The Immunoscore ranges from 0 (low density at both locations) to 4 (high density of both cell types at both locations).

Tissue Molecular Methods.

On the banked biopsy FFPE tissue blocks, protein expression of genes of interest will be confirmed using IHC staining by Moffitt Cancer Center Tissue Core. Procedures for IHC staining of the markers below have been developed and optimized in-house. The slides will then be sent to our Analytical Microscopy Core, scanned, and digitally quantified by image analysis for percent staining for each marker. The experienced pathologist will then determine accuracy not only of the software to identify CAFs versus tumor cells but also IM versus CT and for quantitation. Readouts will be provided to the study team for interpretation and statistical correlations.

PD-L1 expression will be measured using the immunohistochemistry assay based on the FDA approved anti-PD-L1 monoclonal antibody. We will test, however, not select patients on the basis of PD-L1 expression for reasons outlined above (see Innovation). Most importantly, improved outcomes were seen with Nivolumab in both PD-L1 negative or positive [88]. Positive staining is currently defined cut-off value of ≥ 1% in a minimum number of 100 evaluable cells.

Mutational Load and Analysis.

Acquired mutations may influence response to immunotherapeutic agents. Molecular profiling is standard of care for advanced NSCLC; thus the following molecular test results will be collected from the electronic medical records where available: ALK, EGFR, K-RAS, ROS-1, PD-L1 status, RET, Met, PTEN, BRAF, PI3K and Her2 neu. Next Generation Sequencing (NGS) panel will be performed on both tumor and blood samples to precisely identify all somatic mutations and to quantify mutational load. Results from molecular analyses including mutational load and specific genes will be correlated with patient outcomes, potentially helping to address some of the critical barriers for effective personalized treatment.

NanoString Methods and Analysis.

Both hypothesis-driven and exploratory discovery-driven studies will be performed. Standard protocols used routinely in the Moffitt Molecular Biology Core will be used to generate gene expression data using the NanoString technology with the PanCancer Immune Profiling Panel [91]. This panel contains probes to quantitate 770 immune function genes that broadly identify key subsets of immune cells, assess T-cell function, antigen processing, chemokines, cytokines, immunosuppressive molecules, and a host of additional immune-related functions. Genes identified using this analysis that correlate with clinical response or resistance will be confirmed using will be confirmed using AQUA on sections from the banked tissue blocks. Briefly, hybridization buffer containing the capture and reporter probes will be added to total RNA extracted from the biopsies, with hybridization excess probes removed with Prep Station. The probe-transcript complexes will then be immobilized on streptavidin-coated cartridges and analyzed on the Digital Analyzer. These analyses will be led by the MCC Molecular Core and tissue samples will be processed through the MCC Tissue Core.

AQUA for Primary and Secondary Resistance Mechanisms.

The protein expression of the genes discovered to correlate with lack of clinical response such as IC receptors on T-Cells (LAG3 and TIM3), suppressive cells (MDSC, T reg) and enzymes (IDO) will be confirmed using AQUA on the biopsy tissue blocks (See Table 11). Specifically, we will focus upon interrogating the T cell suppression and myeloid panels, those most likely to predict for resistance to immunotherapy. When looking for resistance mechanisms and with the potential limitations in available tissue, the Genoptix approach is ideal as their 3 color slide using AQUA for immunotherapy biomarker assessments requires a minimum of only five slides while providing critical information on resistance. Ultimately through this approach we will be set to analyze the biological role and resistance value of innate and adaptive immune cells in the TME by AQUA.

Statistical Analysis for IHC and Immunoscore.

The primary analysis is to test if there is any expression change due to the treatment. Two sets of biomarkers in tumor will be measured: 1) FAP, IDO and PD-L1 IHC studies and 2) Analysis of Immunoscore. These will be done by comparing pre- and post-treatment levels of FAP, PD-L1, IDO, and the Immunoscore using paired t-test due to the nature of continuous measurement for these biomarkers. Any significant change (at 5% family-wise error rate, i.e., adjusted $p<0.05/4=0.0125$) will be considered to be caused by the treatment effect. Subset analyses for the immunotherapy naïve and immunotherapy pre-treated patients will be performed separately using the same statistical strategy. Each cohort will have a total sample size of 40 patients. It will give 80% power to detect a 0.55 standard deviation difference of the change (pre to post) for each biomarker controlled at 5% family-wise error rate based on paired t-test.

Statistical Plan for NanoString and Mutational Load.
Data Analysis
We will discover and develop predictive biomarkers for clinical response. Six types of continuous measurements will be included: gene expression, mutation burden, Immunoscore, AQUA, blood flow cytometry panel and tumor PD-L1 and FAP expression. For analysis of gene expression, we will use the PanCancer Immune profiling panel, which contains over 770 immune function genes. For genes associated with resistance or response, linear models for microarray data (LIMMA) [92] will be used to identify differentially expressed genes (responders vs non-responders). Additional comparison between responders and non-responders will be performed in patients who receive the treatment of nivolumab plus/minus nintedanib. Genes with adjusted $P < 0.05$ will be considered statistically significant. For the significant genes, the profiling score will be generated by principal component analysis (PCA) using the first principal component (PC1). Two-sample t-test will be used to evaluate if the profiling score is associated with clinical response. Other pathway analysis will be also examined, such as gene set enrichment analysis [93]. Similarly, we will use two-sample t-test to study if the immunoscore, mutation burden, AQUA, blood panel and tumor PD-L1 and FAP expression are different between responders and non-responders. To build a predictive model, logistic regression model will be used by incorporating the profiling score (from gene expression), mutation burden, Immunoscore, AQUA, blood panel and tumor PD-L1 and FAP expression. Stepwise procedure will be applied to develop a robust model to well predict response. Alternative approach is to employ Lasso regression [94], a variable selection method, to identify the most relevant variables for the final model. In addition, 10-fold cross validation will e used to evaluate the robustness of the model. Receiver operating characteristic curve analysis will be then performed for the final model. The same statistical strategy will be applied to subset analyses for the immunotherapy naïve and immunotherapy pre-treated patients separately.

Power analysis

Assuming reaching to 50% response rate for the immunotherapy naïve cohort (n=40) and 20% response rate for the cohort with previous immunotherapy experiences (n=40), it will lead to 20 responders and 20 non-responders in the immune naïve cohort and 8 responders and 32 non-responders in the cohort with previous immunotherapy experiences. For the immunotherapy naïve cohort, it will give a power of 96% to detect a difference of 1.2 standard deviation (SD) for the profiling score in gene expression between responders versus non-responders with a two-sided 5% type I error based on two-sample t-test. The power will be 84% for the cohort with previous immunotherapy experiences. The same power will hold for the other measurements: mutation burden, Immunoscore, AQUA, blood panel and tumor PD-L1 and FAP expression.

Statistical Plan for AQUA.

Primary resistance (or primary refractory) to immunotherapy is defined as patients who were previously treated with immunotherapy and did not at least achieve stable disease on first imaging assessment on immunotherapy. While secondary resistance (or relapsed) is defined as patients that were treated with immunotherapy, achieved at least stable disease on first imaging assessment and subsequently developed disease progression or relapse. Therefore, clinical response becomes three categories: response, primary resistance, and secondary resistance (the last two are non-responders). One-way ANOVA will be used to analyze which genes and/or pathways are associated with primary resistance and which ones are related to secondary resistance using the LIMMA methods [92]. Pathway score will be calculated using the PC1 by principal component analysis for genes belonged to the pathway.

BLOOD

Determination of Predictive Signatures in Peripheral Blood.

The peripheral blood is a rich source of immune cells and may serve as a surrogate for immune responses. On a qualified BD LSR Fortessa TM platform, in accordance with good clinical trial practice (GCLP) guideline[95-97], Immunologists have designed a broad T-cell and myeloid flow cytometry panels composed of multiple exhaustion markers, checkpoint receptors, activation markers and myeloid suppression markers. A variety of methodologies inclusive of, but not limited to ex vivo culture, flow cytometry, IHC, qRT-PCR, genetic mutation detection and fluorescent in-situ hybridization (FISH) have been identified. These high complexity panels have been tested and, for example, can serve as powerful tools for comprehensive examination of ipilimumab and IFNá effects in a small volume of peripheral blood specimen. Both traditional and automated algorithms will be used to determine blood-based immune signatures predictive of response to immunotherapies. By completing these blood analyses we aim to have a more comprehensive analysis of the circulating immune cells which is of particular significance as some patients may not have sufficient tissue for the entire proposed tumor based immune cell analyses. We hope this proactive approach to also include blood specimens analyses will be viewed as a strength.

Table 11. Proposed flow cytometry panels for exploring immune modulation in peripheral blood

Objective	Flow cytometry panel*
Comprehensive analyses of adaptive response (e.g., T cell activation and suppression)	CD3,CD4,CD8,CD45RO,CD45RA,CCR7,CD95,CD27,CD25, CD57, CD107, CD69 CD11A, TIM3,HLA-DR,PD-1, LAG3, OX40, ICOS, CCR4, CXCR3, CCR6, BIM, EOMES, CTLA-4
Assess innate immune responses (e.g., quantify MDSC levels)	Lin-, CD33; CD11b, HLA-DR, CD16, CD123, CD14, CD11c, CD15, PD-L1, CD80, CD86, HLA-DR,ICOSL, 41BBL

Blood Analyses Pre-Treatment and for Potential Primary and Acquired Resistance Mechanisms.

Peripheral blood samples will be taken prior to initiation of study therapy, at designated time-points, prior to, on-treatment and at the end of treatment visit (**see Section 8/Study calendar** for additional details on the blood sample collection schedule) for preparation of blood analysis. Blood samples will be assessed for immune or lung cancer-related factors that will predict or correlate with resistance to the combination of nivolumab, ipilimumab and nintedanib. Dr. Antonia's Lab at Moffitt will lead the analysis of the blood samples. PBMC from blood will be prepared with Ficoll gradient prior to freezing for future studies. Plasma will be harvested and samples will be frozen at -80C in protocol-designated box for plasma biomarker studies.

Determination of Kynurenine:Tryptophan ratio.

Serum levels of tryptophan and kynurenine may also be useful as blood markers of immune enhancement through targeting the tumor microenvironment and CRP as a marker of inflammation/stress. Serial blood collections will be obtained in heparinized tubes (green tops). Cells will be centrifuged, with resulting supernatant (plasma) immediately stored at -80ºC until needed.

Blood Molecular Methods.

The method for determining tryptophan and kynurenine in human plasma is validated under ICH and FDA guidance for bio-analytical method validation. The samples are prepared by protein precipitation using perchloric acid to treat the plasma before injection into an ultra-HPLC/MS system. Stable isotope-labeled internal standards are utilized for both tryptophan and kynurenine. Separation is achieved with a C18 column under gradient pumping conditions with mobile phases of water and methanol, both containing 0.1% acetic acid. Multiple reaction monitoring is employed where the following molecular transitions are utilized for tryptophan and kynurenine respectively; 205.1 to 146.0 and 209.1 to 198.1, 151.2, 124.1. Resulting patient sample concentrations are determined from calibration curves determined for each analyte. Tryptophan calibration is linear from 10020,000 ng/ml, and kynurenine is linear 10-2,000 ng/ml. Data reporting is presented in a molar ratio between the two analytes.

Statistical Analysis for IHC, Immunoscore and T/K ratio.

The blood samples will be analyzed for T/K ratio by the same methods as the IHC and Immunoscore.

7.2 Special Studies: Medical History, Electrocardiogram, Weight, and Vital Signs

Physical examinations will be performed on study days noted in the Study Calendar **(Tables 15 and 16).**

Physical examination

Physical examinations will be performed according to the assessment schedule. Height will be measured at Screening only. Additionally, targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in **Section 6.**

Electrocardiograms

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. At screening, a single ECG will be obtained on which QTcB must be <470 ms for males and <480 ms for females. In case of clinically significant ECG abnormalities, including a QTcB value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding. Situations in which ECG results should be reported as AEs are described in Section 6.

Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules.

On infusion days, patients receiving Nivolumab/ Ipilimumab treatment will be monitored during and after infusion of IP as presented in the bulleted list below.

Supine BP will be measured using a semi-automatic BP recording device with an appropriate cuff size, after the patient has rested for at least 5 minutes. BP and pulse will be collected from patients receiving Nivolumab/ Ipilimumab treatment before, during, and after each infusion at the following times:

Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion]).

Approximately halfway through the infusion.

At the end of the infusion (approximately ±5 minutes).

A 1-hour observation period is required after the first infusion of Nivolumab and Ipilimumab.

If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each Nivolumab infusion).

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Body weight is also recorded along with vital signs.

Situations in which vital signs results should be reported as AEs are described in **Section 6**. A complete physical examination will be performed and will include an assessment of the following (as clinically indicated): general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid,

musculoskeletal (including spine and extremities), and neurological systems and at screening only, height.

The following clinical laboratory tests will be performed (see the Schedule of Assessments)

- Coagulation parameters: Activated partial thromboplastin time and International normalized ratio to be assessed at baseline as the patient is to undergo a fresh biopsy and then at the time of on-treatment biopsy
- Complete blood count
- Comprehensive metabolic profile
- Urinalysis
- Pregnancy test (female subjects of childbearing potential only)
  - Urine or serum human chorionic gonadotropin
- Thyroid Stimulating Hormone
- Free T3 and free T4
- Correlative studies (per Section 7)

Table 12. Hematology Laboratory Tests

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular hemoglobin	Total white cell count
Mean corpuscular hemoglobin concentration	

Table 13. Clinical chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Creatinine
Total protein	BUN
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin[a]
Chloride	

a If Total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin

Table 14. Urinalysis Tests	
Blood	Protein
Glucose	Specific gravity
Ketone	Color and appearance
pH	

a Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells

Additional studies on the blood evaluating for enhancement of immune response will be performed. These additional studies include plasma assessments for cytokines include quantitative assessment of interferon gamma pre- and post-drug exposure, may be considered to further demonstrate the anticipated enhancement of cytotoxic T-cell activity, as interferon-gamma induces PD-L1 expression in tumor cells. As commented previously, serum levels of tryptophan and kynurenine may also be useful as blood markers of immune enhancement through targeting the tumor microenvironment and CRP as a marker of inflammation/stress.

8 STUDY CALENDAR

Table 15. Study Calendar: Phase 1 Dose escalation trial of Nintedanib combined with Nivolumab and Ipilimumab in advanced-stage NSCLC.

	Screening[1]	C1 D1	C1 D8	C2 D1	C2 D8	C3 D1	C4 D1	C5 D1 and beyond	End of Treatment visit (time of discontinuation)	30+/-14 days; Post study follow-up post last dose of study drug	Follow up Visit[10] Every 8 weeks after the End of Treatment visit.	Survival Follow up Every 12 weeks
Vitals, including weight	X	X	X	X	X	X	X	X	X	X		
H&P/ECOG	X	X	X	X	X	X	X	X	X	X		
CBC w/ diff	X	X	X	X	X	X	X	X	X	X		
CMP	X	X	X	X	X	X	X	X	X	X		
Pregnancy testing (if applicable)	X	X				X		X	X	X		
TSH/FT4/FT3 [2]	X	X				X		X	X	X		
PT/PTT/INR	X[6]				X[6]				X[6]			
Urinalysis	X											
ECG[8]	X											
Echo/MUGA	X											
CT Scan (Thorax +/- Abdomen)	X						X		X		X	
Tumor Measurement [3]	X						X		X			
Toxicity Assessment[9]	X	X	X	X	X	X	X	X	X	X	X	
Archival tumor collection [5]	X											
Nintedanib		X	X	X	X	X	X	X				
Nivolumab IV q2 weeks		X		X		X	X	X				
Ipilimumab Q6 weeks		X					X					
Tumor biopsy [4]	X				X				X[7]			
Blood Biomarkers		X			X	X			X	X		
Post-Study anticancer therapy									X	X		X
Survival status		X	X	X	X	X	X	X	X	X		X

All study visits, labs, treatments, procedures and scans have a +/- 7 day window. End of treatment is the date when the decision is made to remove the patient from study (which may differ from the last date of treatment). Pregnancy testing (urine of blood) in WOCP must be completed within 7 days of C1D1

1. Screening window will be 30 days prior to initiation of therapy or enrollment.
2. To be collected every other cycle (~ every 4 weeks)
3. Tumor measurement assessments with CT thorax/ abdomen will occur at baseline and every 6 weeks while patient is on the study. After 1 year, the imaging time point will occur every 12 weeks (± 7 days).
4. Tumor biopsy should be obtained pre-treatment and on C2D8 +/- 7 days where required and feasible. Blood draw for blood biomarkers on C2D8 +/- 7 days and end of treatment time points should be done on the same day as the tumor biopsy.
5. Archival tissue should be obtained where available.
6. Coagulation studies to be done at the time of screening and any time the patient requires a biopsy.
7. End of treatment biopsy as feasible per investigator discretion.
8. At Screening, a single ECG will be obtained on which QTcB must be <470 ms for males and <480 ms for females. In case of clinically significant ECG abnormalities, including a QTcB value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.
9. Only serious adverse events will be collected during the screening window.
10. Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 8 weeks (56 ± 7 days) after the End of Treatment visit by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 12 weeks (± 7 days).

Note: In case that, during the conduction of the trial, a discrepancy was noted between the protocol content and this calendar, the information or requirements included in the calendar will be followed.

Table 16. Study Calendar: Phase II Trial of Nintedanib combined with Nivolumab and Ipilimumab in advanced-stage NSCLC (Arm A and Arm B)

	Screening[1]	C1 D1	C1 D8	C2 D1	C2 D8	C3 D1	C4 D1	C5 D1 and beyond	End of Treatment visit (time of discontinuation)	30+/-14 days; Post study follow-up post last dose of study drug	Follow up Visit[10] Every 8 weeks after the End of Treatment visit	Survival Follow up Every 12 weeks
Vitals, including weight	X	X	X	X	X	X	X	X	X	X		
H&P/ECOG	X	X	X	X	X	X	X	X	X	X		
CBC w/ diff	X	X	X	X	X	X	X	X	X	X		
CMP	X	X	X	X	X	X	X	X	X	X		
Pregnancy testing (if applicable)	X	X				X		X	X	X		
TSH/FT4/FT3[2]	X	X				X		X	X	X		
PT/PTT/INR	X[6]				X[6]				X[6]	X		
Urinalysis	X											
ECG[8]	X											
Echo/MUGA	X											
CT Scan (Thorax +/- Abdomen)	X						X		X		X	
Tumor Measurement [3]	X						X		X			
Toxicity Assessment[9]	X	X	X	X	X	X	X	X	X	X	X	
Archival tumor collection [5]	X											
Nintedanib		X	X	X	X	X	X	X				
Nivolumab IV q2 weeks		X		X		X	X	X				
Ipilimumab Q6 weeks		X					X					
Tumor biopsy [4]	X				X				X[7]			
Blood Biomarkers		X			X	X			X	X		
Post-Study anticancer therapy									X	X		X
Survival status		X	X	X	X	X	X	X	X	X		X

All study visits, labs, treatments, procedures and scans have a +/- 7-day window. End of treatment is the date when the decision is made to remove the patient from study (which may differ from the last date of treatment). Pregnancy testing (urine of blood) in WOCP must be completed within 7 days of C1D1.

1. Screening window will be 30 days prior to initiation of therapy or enrollment.
2. To be collected every other cycle (~ every 4 weeks).
3. Tumor measurement assessments with CT thorax/ abdomen will occur at baseline and every 6 weeks while patient is on the study. After 1 year, the imaging time point will occur every 12 weeks (± 7 days).
4. Tumor biopsy should be obtained pre-treatment and on C2D8 +/- 7 days where required and feasible. Blood draw for blood biomarkers on C2D8 +/- 7 days and end of treatment time points should be done on the same day as the tumor biopsy.
5. Archival tissue should be obtained where available.
6. To be done at the time of screening and anytime the patient requires a biopsy.
7. End of treatment biopsy as feasible per investigator discretion.
8. At Screening, a single ECG will be obtained on which QTcB must be <470 ms for males and <480 ms for females. In case of clinically significant ECG abnormalities, including a QTcB value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.
9. Only serious adverse events will be collected during the screening window.
10. Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 8 weeks (56 ± 7 days) after the End of Treatment visit by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 12 weeks (± 7 days).

Note: In case that, during the conduction of the trial, a discrepancy was noted between the protocol content and this calendar, the information or requirements included in the calendar will be followed.

9. MEASUREMENT OF EFFECT

9.1 Antitumor Effect

In addition to a baseline scan, confirmatory scans should also be obtained 6 weeks following initial documentation of objective response. Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used.

9.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with nivolumab, ipilimumab or nintedanib.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.

Evaluable non-target disease response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

9.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, only lesions that have clearly shown disease progression since prior irradiation will be considered or allowed.

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

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

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

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

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

9.1.3 Methods 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 $\geq$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 that 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.

9.2 Other Response Parameters

9.2.1 Evaluation of target lesions

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

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

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

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

9.2.2 Evaluation of non-target lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

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

9.2.3 Evaluation of best overall response

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

Table 17. For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 weeks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 18. For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy including the following [98]:

- Response to immunotherapy may be delayed
- Response to immunotherapy may occur after PD by conventional criteria
- The appearance of new lesions may not represent PD with immunotherapy

- SD while on immunotherapy may be durable and represent clinical benefit.

Based on the above-described unique response to immunotherapy and based on guidelines from regulatory agencies, e.g., European Medicines Agency's "Guideline on the evaluation of anti-cancer medicinal products in man" (EMA/CHMP/205/95/Rev.4) for immune modulating anti-cancer compounds, the study may wish to implement the following in addition to standard RECIST 1.1 criteria:

RECIST will be modified so that PD must be confirmed at the next scheduled visit, preferably, and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with nintedanib with nivolumab plus ipilimumab would continue between the initial assessment of progression and confirmation for progression.

In addition, patients may continue to receive nintedanib with nivolumab plus ipilimumab beyond confirmed PD in the absence of clinically significant deterioration and if investigators consider that patients continue to receive benefit from treatment.

Modification of RECIST as described may discourage the early discontinuation of immunotherapies and provide a more complete evaluation of its anti-tumor activity than would be seen with conventional response criteria. Nonetheless, the efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on RECIST 1.1 criteria.

Of note, clinically significant deterioration is considered to be a rapid tumor progression that necessitates treatment with anti-cancer therapy other than nintedanib plus nivolumab plus ipilimumab or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression).

9.2.4 Efficacy variables

The efficacy analysis will be based on the treated population, which includes all patients who receive any dose of either investigational product. The following efficacy endpoints will be analyzed.

• Objective response is defined as confirmed CR or confirmed PR based on modified RECIST guidelines version 1.1. The ORR will be estimated by calculating the proportion of patients who achieve OR; the 80% CI and 95% CI for the OR rate will be estimated using the exact binomial distribution.

• Disease control is defined as CR, PR, or SD based on RECIST guidelines version 1.1 with modifications. The disease control rate (DCR) will be estimated by the proportion of patients who achieve DC, and its 80% CI and 95% CI will be estimated using the exact binomial distribution.

• Progression-free survival will be measured from the start of treatment with Nivolumab with or without nintedanib until the documentation of disease progression or death due to

any cause, whichever occurs first. For patients who are alive and progression-free at the time of data cut-off for analysis, PFS will be censored at the last tumor assessment date. The Kaplan-Meier will be used to estimate the PFS curve and the PFS rate at time points of interest [99].

- Duration of response is defined as the duration from the first documentation of OR to the first documented disease progression or death due to any cause, whichever occurs first. For patients who are alive and progression-free at the time of the data cut-off for the analysis, DoR will be censored at the last tumor assessment date. The DoR will only be evaluated for the subgroup of patients with an OR and will be calculated using the Kaplan-Meier method.

- Overall survival will be determined as the time from the start of treatment with nivolumab plus ipilimumab plus nintedanib until death due to any cause. For patients who are alive at the time of data cut-off, OS will be censored on the last date when patients are known to be alive. The Kaplan-Meier method will be used to estimate the OS curve and the OS rate at time points of interest.

Patients who have disease control following completion of 12 months of treatment or patients who are withdrawn from nivolumab plus ipilimumab with nintedanib treatment for reasons other than confirmed PD will continue to have objective tumor assessments.

10. DATA REPORTING / REGULATORY CONSIDERATIONS

10.1 Data Reporting

10.1.1 Risks to patients

Human Patient Involvement, Characteristics and Design

Human patients who have the diagnosis of advanced NSCLC are eligible to participate in the clinical trial described in this proposal. In this trial, patients with stage IV NSCLC will be treated with nivolumab plus ipilimumab plus nintedanib. Those with stable disease, a partial response, or complete response will remain on maintenance treatment until progression, intolerance, or withdrawal. The suggested doses, frequency, and administration route for the treatment are per prior studies that have already established the potential risks. The responsibilities of the collaborating investigators, data collection and management and protection are outlined in the DSMP below. A new Investigational New Drug (IND) application will be submitted to cover the proposed use of the nintedanib in combination with nivolumab plus ipilimumab in the Research Plan. The protocol will require IRB, FDA IND, and SRC approval prior to initiation of the trial. All patients must willingly sign the informed consent document prior to trial enrollment.

Sources of Materials

From the patients enrolled on the trial, tissue specimen, data and records will be obtained. We will collect clinical covariates, toxicity, radiographic and laboratory data from the patients.

Further details on records and data collections and management are outlined in the protocol and the DSMP below.

Potential Risks

The potential risks are outlined clearly and in detail in the informed consent. Women who are pregnant, lactating or breast feeding are not eligible. The tissue acquisition and biopsy procedures will be reviewed by the IRB. In addition, any changes in the protocol procedures or desired biospecimen types an amendment to the protocol and consent are provided to the IRB for consideration of the benefits to research and the impact on patient care, well-being, harm and discomfort.

10.1.2 Adequacy of protection against risk

a. Recruitment and Informed Consent

Patients who present to the Thoracic Oncology Program at the Moffitt Cancer Center who have advanced NSCLC are offered participation in the clinical trial described in this proposal. The trial is explained in detail to the patients by one of the physician co-investigators on the trial, the patients are given the opportunity to read the informed consent document, they are given a chance to ask questions, and finally they sign the informed consent document in the presence of a witness. The physician who participates in the informed consent process also documents, in a clinic note, the nature of the consent process that occurred.

b. Protection Against Risk

To protect participants from excess risk, the above-mentioned study procedures and dose-escalation scheme were instituted. Additional protection is provided through the data safety and monitoring plan described below. Complete patient care, including the clinical management of all toxicities will be provided by physicians at the Moffitt Cancer Center. The clinical data are kept in the patient's individual Moffitt Cancer Center hospital record. Research data are kept in a locked room with limited access and through Oncore (a Web-based, password-protected database), with privacy protected to the full extent of the law. All documents, data and study records collected for the purposes of this study will be stored indefinitely at the MCC. All researchers and staff with access to this information will follow procedures to prevent disclosure of information to anyone who is not an investigator on this study. Procedures will include data handling practices, network protection, password protection, proper storage and handling of all files and specimens, and secured facilities. All study materials that include patient identifiers, such as contact information and completed questionnaires (paper if used), will be kept in locked cabinets and accessed only by authorized study personnel. Blood, urine, and tissue samples will be labeled with a study identification number and no other patient identifiers. Study personnel who have completed appropriate credentialing will conduct medical record abstraction or electronic transfers of data under IRB-approved protocols. Authorized research investigators, the Department of Health and Human Services, and the USF Institutional Review Board may inspect the records. Final approvals have been obtained from the IRB. Great care will be taken to protect patient privacy throughout the study in accordance with MCC policies.

Additional protection is provided through the data safety and monitoring plan described below.

c. Potential Benefits of the Proposed Research to Human Patients and Others

There is potential benefit that patients may experience is an improved outcome when exposed to the triplet combination therapy. The potential benefit to others is as yet unknown. For Stage IV NSCLC, an incurable disease where patients will inevitable progress, the risks to the patient are reasonable in relation to the anticipated benefits to research participants and others.

d. Importance of the Knowledge to be Gained

The knowledge gained from this trial will serve as the foundation of larger biomarker driven Immunotherapy trials that may lead to a new standard in the treatment armamentarium in the fight against Stage IV NSCLC. For Stage IV NSCLC, an incurable disease where patients will inevitable progress, the risks to the patient are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

10.2 Safety and Monitoring Plan

The Data Safety & Monitoring Plan (DSMP) will ensure that this trial is well designed, responsibly managed, appropriately reported, and that it protects the rights and welfare of patients. The following internal and external review and monitoring processes provide oversight and active monitoring of this trial:

The Principal Investigators (PI)
The Clinical Trials Office (CTO)
The Scientific Review Committee (SRC)
The Protocol Monitoring Committee (PMC);
The Research Compliance Division (RCD) of the Cancer Center's Compliance Office;
Institutional Review Board (IRB).
The protocol includes a section that specifies the following with respect to Adverse Event reporting: what constitutes an adverse event (versus what is a serious adverse event), the entities to which adverse events should be reported, the timing of this reporting, and the person or persons responsible for reporting. This includes prompt (within one day of knowledge of the event) reporting to the IRB for unanticipated risks to patients and reporting in writing within five working days to the IRB and sponsor.

10.2.1 Scientific Review Committee (SRC)

The Cancer Center maintains two fully boarded Scientific Review Committees (SRC) that meet every other week (the first Wednesday and third Thursday of every month) as well as one Behavioral Ad-Hoc SRC.

Each SRC conducts a formal internal peer review of all clinical protocols and general scientific oversight of interventional clinical research. Protocols are reviewed for scientific merit, adequate study design, safety, availability of targeted study population, and feasibility of timely completion of all proposed research projects to be conducted by its assigned programs at the Cancer Center. Each SRC is responsible for evaluating the risk/benefit assessment and corresponding data and safety monitoring plan as part of the scientific

review and approval process. The SRC will refer any potential conflicts of interest identified in the proposed research to the Conflict Committee.

10.2.2 PI responsibility

The PI of each study is ultimately responsible for every aspect of the design, conduct and actions of all members of the research team. This includes the final analysis of the protocol. The PI is responsible for ensuring that:

All protocols include a DSMP and procedures for its implementation commensurate with the risk and complexity of the study. The DSMP must include a structured adverse event determination, monitoring and reporting system, including standardized forms and procedures for referring and/or treating patients experiencing adverse events. The plan must include data and safety-monitoring procedures for patients enrolled who may be receiving a part of their protocol-required treatment at community sites.

In all cases, the PI of the study will have primary responsibility for ensuring that the protocol is conducted as approved by the SRC and IRB. The PI will ensure that the monitoring plan is followed, that all data required for oversight of monitoring are accurately reported to a DSMB and/or to the PMC and IRB as required, that all adverse events are reported according to protocol guidelines, and that any adverse actions reflecting patient safety concerns are appropriately reported.

10.2.3 Protocol Monitoring Committee (PMC)

The PMC monitors its assigned ongoing research protocols for: adverse event reporting, data and safety monitoring, and internal audit findings. The PMC, upon review of any agenda item, may approve the study for continuation, require revisions, suspend or close a protocol.

Study investigators, designated to be reviewed by the PMC for data and safety monitoring, shall provide a statistical report of the study's progress and summary of adverse events and deviations based on the phase of the study and the associated risk of the study or more often if applicable. The external DSMB (if applicable) shall forward its report for high-risk studies designated for external review at least annually or more often if applicable.

The PMC meets monthly and reviews accrual, patterns and frequencies of all adverse events, protocol violations and when applicable, internal audit results.

10.2.4 Research Compliance Division (RCD)

RCD of the Corporate Compliance Office is the coordinating center for internal audits of clinical trials conducted at the Cancer Center and its affiliates. The audit procedure is a formal, comprehensive, source document review of all clinical trials. External audit reports that meet the criteria of the internal audit may be accepted in lieu of an internal audit.

The RCD shall provide a report to the PMC of internal audit findings for PMC action. A representative of the RCD will be present to discuss the audits with the PMC. For cause, audits will be discussed during an executive session of the PMC. Only members (voting and ex-officio) may attend this session.

10.2.5 Internal and external monitoring

Data will be captured in Oncore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly by the MCC Clinical Monitoring Core for accuracy, completeness, and source verification of data entry, validation of appropriate informed consent process, reporting of SAEs and adherence to the protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements.

10.2.6 The Institutional Review Board (IRB)

The trial will not be initiated without approval of the appropriate Institutional Review Board (IRB). All administrative requirements of the governing body of the institution will be fully complied with. This protocol, consent procedures, and any amendments must be approved by the IRB in compliance with current regulations of the Food and Drug Administration. A letter of approval will be sent to the institution(s) funding the study prior to initiation of the study and when any subsequent modifications are made. The IRB will be kept informed by the investigator as to the progress of the study as well as to any serious or unusual adverse events.

10.2.7 Suspension/termination

The PMC and/or the IRB may vote to suspend or terminate approval of a research study not being conducted in accordance with the IRB, the Cancer Center and/or regulatory requirements or that has been associated with unexpected problems or serious harm to patients. The PMC/IRB will notify the PI in writing of such suspension or terminations. It is the responsibility of the PMC/IRB Chairperson to ensure prompt written notification of any suspensions or terminations of PMC/IRB approval to the relevant Federal Agencies, including OHRP, FDA, the study sponsor/funding source and if applicable, the Affiliate Program.

10.2.8 Trial discontinuation

For reasonable cause, the Investigator and/or sponsor may terminate this study prematurely. Conditions that may warrant termination include, but are not limited to: the discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study or if the accrual goals are met. A written notification of termination will be issued.

10.2.9 Monitoring of the study and regulatory compliance

The Principal Investigator and the Clinical Research Coordinator assigned to the case will be primarily responsible for maintaining all study-related documents including the clinical research forms. ONCORE will serve as the study database of record. All CRF entries will be verified with source documentation and will be maintained by the Data Management Specialist and Clinical Research Coordinator. The patient casebooks will be secured in a locked office in the Thoracic Research Department. The review of medical records will be done in a manner to assure that patient confidentiality is maintained.

10.2.10 Protocol modifications

No modifications will be made to the protocol without the agreement of the investigators. Changes that significantly affect the safety of the patients, the scope of the investigation, or the scientific quality of the study will require Institutional Review Board approval prior to implementation, except where the modification is necessary to eliminate apparent immediate hazard to human patients. Any departures from the protocol must be fully documented in the case report form and the source documentation.

10.2.11 Patient privacy

In order to maintain patient confidentiality, all case report forms, study reports, and communications relating to the study will identify patients by initials and assigned patient numbers. The US Food and Drug Administration (FDA) may also request access to all study records, including source documentation for inspection.

10.2.12 Institutional and individual conflicts of interest

Conflict of interest (COI) can be defined as any situation in which financial or personal obligations may compromise or present the appearance of compromising an individual's or group's professional judgment in conducting, reviewing or reporting research. Research personnel, IRB members, research administration officials, The Cancer Center, the University of South Florida, and research sponsors may all have certain conflicts of interest. Such conflicts of interest may arise because of the intellectual property involved in research discoveries or industry-academic partnerships or from financial incentives many pharmaceutical and biotech companies offer researchers or physicians for conducting research or enrolling patients, or due to particular role relationships with particular institutions. The processes for managing individual and institutional conflicts of interest will focus on disclosure of the conflict, managing the conflict, and prohibiting the activity when necessary to protect the public interest or the interest of The Cancer Center.

Prior to the activation of a trial and ongoing thereafter, individuals who are involved in the design, conduct and reporting of the trial will be required to disclose to the SRC any and all financial or other interests that are, or may perceive to be, related to the trial in which they are actively involved in. The SRC will determine if a conflict exists, and if so, assure that the COI is managed, reduced, or eliminated. This information will accompany a protocol when it is presented to the IRB. The IRB will retain the highest authority for determining that the conflict of interest has been properly disclosed, managed or eliminated.

The PMC will ensure ongoing monitoring of conflict of interest through monthly review of conflict of interest disclosures. If a COI exists, the PMC will ensure that a plan to manage, reduce, or eliminate the COI is developed and submitted to the IRB for approval and the protocol is amended accordingly. Members of the SRC, PMC, and/or IRB who have a conflicting interest in a study will not take part in the discussion or voting of such research, except to answer questions of the respective committee. The RCD will be responsible for maintaining a secure data system for tracking and timely reporting of disclosure information to the SRC or PMC for review as appropriate. The RCD will be responsible for ensuring coordination and communication of COI between the Cancer Center and the IRB. The IRB has the final authority to determine that the COI has been managed sufficiently to assure the protection of human participant.

10.2.13 Records retention

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

11. STATISTICAL CONSIDERATIONS

11.1 Description of Analysis Sets

11.1.1 Safety analysis set

The safety analysis will be based on the treated population that includes all patients who receive at least one dose of any of the investigational products.

11.1.2 Efficacy analysis set

The efficacy analysis will be based on the treated population which includes all patients who received any dose of the nivolumab plus ipilimumab combined with nintedanib in the Phase II trial, depending upon treatment arm and all patients have had to have at least one post treatment imaging available for ORR assessments.

11.2 Methods of Statistical analysis

11.2.1 MTD Determination

The recommended phase 2 dose for nintedanib with the combination of nivolumab and ipilimumab will be provided by the phase I dose escalation phase. The recommended dose for Phase II trials is conventionally defined as the dose level just below this toxic dose level or the highest dose level if MTD is not reached.

11.2.2 Efficacy Analyses

Statistical Design and Sample Size Justification
Phase I dose escalation.
The primary objective of this phase I dose escalation is to find a maximum tolerated dose (MTD) corresponding to a risk of DLT occurring in 30% of patients. Five dose levels of Nintedanib have been identified for experimentation (100 mg PO QD as dose level -1, 150 mg PO QD as dose level 0,100mg PO BID as dose level 1, 150mg PO BID as dose level 2,

and 200mg PO BID as dose level 3), and due to safety concerns the first cohort of patients will receive the lowest dose (does level 1). The study uses the 3+3 rule-based design for dose escalation with cohorts of three patients. There will be no increase in the doses beyond cohort 3 dosing of the Nintedanib. A maximum of 24 patients will be enrolled for the Phase I dose escalation. Dose escalation will proceed according to the following scheme as shown in **Table 19**.

Table 19.: 3+3 Dose Escalation Scheme

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0/3 patients experience DLT, proceed to the next dose level. • If ≥2 suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose (MAD). Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is the dose to be used in the expanded cohort and will be considered recommended phase 2 dose.

Phase II Statistical Design

Once the MTD or RP2D is known, we intend to conduct a parallel Phase II trial of Nivolumab plus Ipilimumab plus nintedanib in NSCLC patients (a) who are newly diagnosed, immunotherapy naïve (Arm A) or (b) who either have been previously exposed to single agent immunotherapy such as anti-PD-1 or anti-PD-L1 (Arm B)

Total sample size is 80 patients. The sample size is 40 patients for newly diagnosed immunotherapy naïve (Arm A). The sample size is also 40 patients for previously exposed to single agent immunotherapy (Arm B).

Bayesian two-stage design for early phase II study

The study design evaluates futility in the 1st stage (interim analysis) and efficacy in the 2nd stage. The first stage will enroll 20 patients. If it passes a threshold (a certain number of patients with response), the 2nd stage will enroll another 20 patients. If the total number of patients with response is above another threshold, we consider the treatment is promising. The thresholds and statistical sensitivity analysis for power and type I error are evaluated and determined by Bayesian posterior probability and predictive probability which are used to estimate response rate with a non-informative beta prior, beta(1,1). Since first CT (to determine ORR) is schedule for 6 weeks post first dose (minimum follow-up) and we anticipate 2-3 patients per month, we expect the 1st interim analysis will be conducted in one year from study start up.

We consider that the treatment arm is not worse than the historical control if the posterior probability of response rate greater than a least favorable response rate, p0 (e.g., 30%), is higher than 0.95 (i.e., prob(rate of response>p0 |data)>0.95)). This definition helps determine the threshold for the total number of patients with response for efficacy and the predictive probability. We evaluate various early stopping rules by exploring different cutoff of the predictive probability, d. This leads to a wide range of early stopping rules from aggressive to conservative rules (**Table 20-21**). Results indicate the aggressive stopping rule with d=0.2 gives a higher probability to terminate the trial earlier (58-60%) while remaining reasonable power (81-85%) and type I error (5-6%) in two cohorts (immunotherapy naïve and immunotherapy treated previously). For this reason, the aggressive stopping rule is used to evaluate futility and efficacy in both cohorts.

Here are brief comments of the Bayesian approach and Simon two-stage design:

These stopping rules are comparable to Simon mini-max two-stage design with 5% type I error and 80% power for a total sample size of 39. In fact, our experiences indicate the aggressive setting gives the same stopping rule. Thus we consider Simon two-stage design could be a special case of the Bayesian approach.

The Bayesian approach gives investigators more freedom to determine number of patients in interim analysis and total sample size. In our case of 50% vs. 30% response rate, the Simon mini-max two-stage design requires 39 patients (with 19 in the 1st stage) while the Simon optimal two-stage design requires 46 patients (with 15 in the 1st stage) for 5% type I error and 80% power. These numbers may not be convenient. In contrast, given a total of n=40 with the first 20 patients for the interim analysis, the Bayesian approach is able to develop a similar stopping rule with comparable power and type I error.

The Bayesian approach provides a higher resolution of sensitivity analysis in terms of probability of early termination, type I error, and power, by exploring the cutoff of predictive probability, d, and other potential parameters, such as θ in prob (objective response rate> p0 |data)> θ and prior beta distribution. Such comprehensive sensitivity analysis allows investigators to better determine an appropriate stopping rule for trials.

The Bayesian approach uses predictive probability to evaluate the future success given at interim stage. If the chance is little, it may not be considered as ethically sound to continue the trial. In contrast, group sequential trials uses interim p-values for optimizing operating characteristics. As a result, the stopping rule may allow trials with very low probabilities of success to continue. (For details, Saville et. al. highlights the strength of Bayesian predictive probabilities for interim monitoring. Ref: Saville BR, Connor JT, Ayers GD, et al: The utility of Bayesian predictive probabilities for interim monitoring of clinical trials. (Clin Trials 11:485-493, 2014).

Table 20: Summary of various early stopping rules for the immunotherapy naïve cohort

Early stopping rule	True objective response rate	Probability of early stopping	Power/ Type I error
Aggressive	0.20	0.91	<0.01

(d=20%)	0.30	0.60	0.06

	0.40	0.25	0.41
	0.50	0.06	0.85
Moderate (d=5%)	0.20	0.80	<0.01
	0.30	0.43	0.06
	0.40	0.12	0.44
	0.50	0.02	0.85
Conservative (d=1%)	0.20	0.62	<0.01
	0.30	0.24	0.07
	0.40	0.05	0.43
	0.50	<0.01	0.87

Table 21: Summary of various early stopping rules for the immunotherapy treated previously cohort

Early stopping rule	True response rate	Probability of early stopping	Power/ Type I error
Aggressive (d=20%)	0.02	0.94	<0.01
	0.07	0.58	0.05
	0.17	0.12	0.67
	0.20	0.07	0.81
Moderate to Conservative (d=5%)	0.02	0.66	<0.01
	0.07	0.23	0.06
	0.17	0.02	0.69
	0.20	0.01	0.84

A summary for aggressive stopping rules with d=0.2 is given below. The details are in Appendix II.

Immunotherapy naïve: A response rate of 30% is treated as a least favorable response rate and 50% as a promising response rate. The stopping rule is if the 1st stage has 6 or less patients with response (out of the first 20 patients), the treatment is ineffective and will be stopped. If there are 7 or more with response, additional 20 patients will be enrolled in the 2nd stage. If a total of patients with response is 17 or more (out of a total of 40 patients), the treatment is considered as promising and deserves for further examination in future randomized phase II or phase III trials. Statistical sensitivity analysis shows this design will have 85% power to claim the treatment effective (for a true response rate of 50%) and 6% type I error (for a true response rate of 30%). The probability to stop the treatment in the 1st stage is 61% when the true rate of response is 30%. If the response rate is 20%, the chance to stop the trial earlier increases to 91%.

Immunotherapy treated previously: A response rate of 7% is treated as a least favorable response rate and 20% as a promising response rate. The stopping rule is if the 1st stage has 1 or less patients with response (out of the first 20 patients), the treatment is ineffective and will be stopped. If there are 2 or more with response, additional 20 patients will be enrolled in the 2nd stage. If a total of patients with response is 6 or more (out of a total of 40

patients), the treatment is considered as promising and deserves for further examination in future randomized phase II or phase III trials. Statistical sensitivity analysis shows this design will have 81% power to claim the treatment effective (for a true response rate of 20%) and 5% type I error (for a true response rate of 7%). The probability to stop the treatment in the 1st stage is 59% when the true rate of response is 7%. If the response rate is 2%, the chance to stop the trial earlier increases to 94%.

Appendix II includes detailed statistical sensitivity analysis of the aggressive stopping rule for the immunotherapy naïve cohort and for the immunotherapy treated previously cohort.

Data analysis

The primary endpoint of the study for phase I will be safety and tolerability. Patient demographics and toxicity will be summarized overall using descriptive statistics. Continuous data will be summarized with number of patients (n), mean, standard deviation, median, minimum, maximum. Categorical data will be summarized using frequency counts and percentages.

The primary endpoint of the study for phase II will be ORR. Objective tumor response rates and disease control rate will be calculated through binomial distribution with a 2-sided 95% CI. Overall survival (OS) is defined as from start date of treatment to death on study from any cause. PFS is defined as from start date of treatment to the first occurrence of disease progression or death on study from any cause, whichever occurs earlier. The event is defined as first occurrence of disease progression or death. Otherwise it is considered as censored. Kaplan-Meier method will be used for the survival analysis. For each endpoint (ORR, DCR, OS, PFS) in each arm of the Phase II, all patients enrolled in the study will be included in the analysis (intent-to- treat analysis). No adjustments to the data are intended for dealing with missing values or patients who withdraw prior to completing the study.

12 ETHICAL AND REGULATORY REQUIREMENTS

12.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements Subject data protection.

12.2 Regulatory and Ethical Compliance

This clinical study was designed and shall be implemented and reported in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

12.3 Responsibilities of the Investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the

protocol and informed consent have been approved by the IRB/IEC/REB must be given to Boehringer-Ingelheim before study initiation.

12.4 Informed Consent

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

12.5 Optional Biopsy Consent Form

Studies with an optional biopsy component will have a separate signature page covering those studies. This form will be adapted for each Study based on a standard template used globally for all Studies. The optional biopsy informed consent form will be submitted for ethical approval together with the Study Protocol and the main informed consent form of the Study. If a patient opts not to participate in the optional biopsy assessments, this in no way affects the patient's ability to participate in the main research Study.

12.6 Amendments to the Protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by BI and Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, BI should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

12.7 Study Drug Supply and Resupply, Storage, and Tracking/Drug Accountability

Study drugs must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, nivolumab, ipilimumab and nintedanib should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug and the medication number but no information about the patient.

The investigator will maintain an accurate record of the shipment and dispensing of study drug. Patients will be asked to return all unused study drug and packaging at the end of the study or at the time of study drug discontinuation.

12.8 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations

Publication of results: Any formal presentation or publication of data from this trial may be published after review and comment by BI and BMS prior to any outside submission. BI and BMS must receive copies of any intended communication in advance of publication (at least fifteen working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge BI's responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigator and principal institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of BIand BMS and, in accord with the trial contract and shall not permit disclosure of BI's and BMS's confidential or proprietary information.

12.9 Disclosure and Confidentiality

The investigator agrees to keep all information provided by BI's and BMS's in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by BI (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by Boehringer-Ingelheim to the investigator may not be disclosed to others without direct written authorization from BI and BMS, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

12.10 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described at Moffitt Cancer Center standard operating procedures and:
ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Patients).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

12.11 Data Sharing

De-identified clinical data will be shared with other investigators and institutions as approved. We may also receive de-identified clinical data from outside sites as well. No PHI

will be shared /sent to any outside sites or received from any outside sites. A data sharing agreement will be set up with each site before any data sharing occurs. Joint publication may occur.

LIST OF ABBREVIATIONS

ABBREVIATIONS	
τ	dosing interval
λz	terminal rate constant of the analyte in plasma
5-HT3	5-Hydroxy-Tryptamin receptor 3
AE	Adverse Event
AJCC	American Joint Committee on Cancers
Alt	Alanine AminoTransferase
ANC	Absolute Neutrophil Count
ANCOVA	Analysis of Covariance
Ast	Aspartate AminoTransferase
ATP	adenosine triphosphate
AUC	area under the concentration curve
bFGR	basic fibroblast growth factor
BI	Boehringer Ingelheim
BIBF 1202	metabolite of Nintedanib (BIBF1120)
BID	twice daily
BLQ	below limit of quantitation
BP	blood pressure
BS	free base
CA	Competent (Regulatory) Authority
CD	cluster of differentiation
CDBB 0213	degradation product of Nintedanib (BIBF1120)
CDS	Corporate Drug Safety
CL/F	apparent clearance of the analyte in plasma following extravascular administration
Cmax	maximum measured concentration of the analyte in plasma
CML	Clinical Monitor Local
Cpre	predose concentration of the analyte in plasma immediately before dosing
Cr	Complete Response
CRA	Clinical Research Associate
CRF/eCRF	Case Report Form / electronic Case Report Form
CRO	Clinical Research Organisation
ct	Computed Tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical trial report
CV	Coefficient of variation
DCE-MRI	Dynamic Contrast-Enhanced Magnetic Resonance Imaging
DCF	Data Clarification Form
dl/dL	deciliter
DLT	dose limiting toxicity
dmc	Data Monitoring Committee
DNA	Desoxyribo Nucleic Acid
DOC	Documentation of Change
EC/IEC	(Independent) Ethics Committee
ECG	Electro Cardio Gram
ecog	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EDTA	Ethyledediaminetetraacetic acid
ELISA	enzyme-linked immunoasorbent assay
eortc	European Organisation for Research and Treatment of Cancer

EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC QLQ LC 13	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer module
eot	End Of Treatment
EQ 5D	EurolQual quality of life questionnaire
ES	monoethanesulfonate
eu	European Union including countries belonging to the European Economic Area
F	fraction of dose systemically available, bioavailability
FAS	Full Analysis Set
FDA	Food and Drug Administration
fgf	Fibroblast Growth Factor
FGFR	fibroblast growth factor receptor
FGR	fibroblast growth factor
Flt-1	synonym for vascular endothelial growth factor receptor 1
Flt-4	synonym for vascular endothelial growth factor receptor 4
ft3	free thriiodothyronine
ft4	free thyroxine
Fu	Follow-Up
g	acceleration of gravity; gram
GCP	Good Clinical Practice
g-csf	Granulocyte Colony Stimulating Factor
Gd-DTPA	gadolinium chelate
GFR	glomerular filtration rate
GGT	gamma glutamyl transpeptidase
GI	gastrointestinal
GLDH	Glutamate DeHydrogenase
gMean	geometric mean value
HDPE	high density polyethylene
HPLC	high performance liquid chromatography
HPLC-MS/MS	high performance liquid chromatography-tandem mass spectroscopy
hr	hour
hrqol	Health Related Quality Of Life
IAUC	initial area under the curve
IAUC60	initial area under the curve at 60 minutes
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IEC/EC	Independent Ethics Committee
IND	investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
ISF	Investigator Site File
ivrs	Interactive Voice Response System
KDR	human homolog of vascular endothelial growth factor Receptor2 (Flk-1)
L	litre
lap	Leucine Amino Peptidase
Lck	Lymphocyte-specific protein-tyrosine kinase, member of the Src family of kinases
LDH	lactate dehydrogenase
LLN	lower limit of normal
ln	natural logarithm
LPO	last patient out
Lyn	Yamaguchi sarcoma viral (v-yes-1) oncogene homolog, cellular protein tyrosine kinase member of the Src family of kinases

MCV	mean corpuscular volume
med.	Medication
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minute
ml/mL	millilitre
mm	millimeter
mmHg	millimeter mercury
mri	Magnetic Resonance Imaging
MS/MS	tandem mass spectrometry
MTD	maximum tolerated dose
MTP	major tumor progression
n.a.	not applicable
NC	not calculated
NCI	National Cancer Institute
ng	nanogram
No.	number
NOA	not analyzed
NOAEL	no observed adverse effect
NOP	no peak detected
NOR	no valid result
NOS	no sample obtained
nsclc	Non-Small Cell Lung Cancer
NYHA	New York Heart Association
ºC	degree centigrade
on d.	On Demand
OPU	Operative Unit (of BI)
os	Overall Survival
p	probability
PAS	periodic acid-Schiff
pd	Progressive Disease
PDGF	platelet derived growth factor
PDGFR	platelet derived growth factor receptor
pfs	Progression Free Survival
PK	Pharmacokinetic(s)
p.o.	per OS (by mouth)
p-p-plot	probability plot
PPS	Per Protocol Set
pr	Partial Response
pt	Prothrombin Time
ptt	Partial Thromboplastin Time
qol	Quality Of Life
RA	accumulation factor
RBC	red blood cell
recist	Response Evaluation Criteria in Solid Tumors
s	second
SAE	Serious Adverse Event
sd	Stable Disease
SI	Systėme Internationale
SIAE	significant adverse event
SOP	Standard Operating Procedure
Src	Src tyrosine kinase
ss	(At) steady state
SUSAR	Suspected Unexpected Serious Adverse Reaction
t	time

t1/2	terminal half-life of the analyte in plasma
TDMAP	Trial Data Management and Analysis Plan
tmax	time from dosing to peak concentration (Cmax) in plasma
TNM	Tumor, (lymph) Node, Metastasis
tsh	Thyroid Stimulating Hormone
TTM	termination of trial medication
UGT1A1	udp glucuronosyltransferase 1A1
UICC	Union Internationale Contre le Cancer
ULN	upper limit of normal
US-NCI	United States –National Cancer Institute
vegf	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
Vz/F	apparent volume of distribution during the terminal phase λz following an extravascular dose
wbc	White Blood cell Count
who-dd	World Health Organisation Drug Dictionary
γ-GT	γ-Glutamyl Transferase
µmol	micromole

13. APPENDICES

13.1 APPENDIX I : Hy's Law

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

Introduction

Drug-induced liver injury

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

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

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

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

Definition

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

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

- 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 and BMS.

- 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 eg 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 < 2x ULN, then please complete the following laboratory tests:

- Clinical chemistry

  alkaline phosphatase, cholinesterase (either plasma or red blood cell), albumin, PT or INR, CK, CK-MB, coeruloplasmin*, α-1 antitrypsin*, transferrin, ferritin, amylase*, lipase*, fasting glucose*, cholesterol, triglycerides

- Serology

Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG)*, Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive)*, Anti-Smooth Muscle antibody (titer)*, Anti-nuclear antibody (titer)*, Anti-LKM (liver-

kidney microsomes) antibody*, Anti-mitochondrial antibody*, Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM)

- Hormones, tumor marker
- TSH*
- Hematology
- Platelets*, eosinophils*

*If clinically indicated and in case those 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

13.2 APPENDIX II: Detailed statistical sensitivity analysis for the phase II trial

Statistical sensitivity analysis of the aggressive stopping rule for the immunotherapy naïve cohort

The interim analysis for futility will be done for the first 20 patients. A Bayesian approach for futility and efficacy analysis is used to calculate posterior probability and predictive probability for the rate of response with a non-informative beta prior, beta(1,1). We consider a 30% rate or less of response as ineffective. Thus, we expect the treatment is promising and not worse than the historical control if the posterior probability of the rate (response) greater than 30% is higher than 0.95 (i.e., prob(rate of response>30% |data)>0.95). With a total 40 patients in treatment arm, it will need at least 17 patients with response to meet the criteria. Therefore, we use the number of 17 patients to guide the predictive probability. Specifically, for the first 20 patients in the interim analysis, there are 21 ways for number of patients with response from 0, 1, to, 20. In each case, given the number of patients with response, ss, in the first 20 patients, we calculate predictive probability of $17 - ss$ or more patients with response in the remaining 20 patients of the 2nd stage (**Table A1 and Figure A1**), i.e., $\sum_{ii=17-ss}^{20} \binom{20}{ii} \frac{bbbbbbbb(1+ss+ii,1+(20-ss)+(20-ii))}{bbbbbbbb(1+ss,1+(20-ss))}$. Calculation of the predictive probability is based on beta binominal distribution for the number of patients with response in the future remaining 20 patients (2nd stage) given a beta distribution for the rate of response, $bbbbbbbb(1+ss, 1+20-ss)$. For example, if there are 6 patients with response in the first 20 patients, the predictive probability of 11 or more patients with response in the future remaining 20 patients (2nd stage) would be $\sum_{ii=11}^{20} \binom{20}{ii} \frac{bbbbbbbb(1+6+ii,1+(20-6)+(20-ii))}{bbbbbbbb(1+6,1+(20-6))} = 0.08$. Figure A1 lists predictive probability for all scenarios of number of patients with response in the first 20 patients (interim

analysis) and number of patients with response needed in the remaining 20 patients of the 2nd stage to have at least a total of 17 patients with response. With a 20% cutoff for the predictive probability, the stopping rule is if there are 6 or less patients with response for the first 20 patients in the interim analysis (i.e., small chance to reach a total of 17 patients with response at the end of study), we consider the treatment is ineffective and will be stopped.

Sensitivity analyses of this stopping rule are presented in **Table A2 and Figure A2**. For the futility analysis, it is evaluated using the probability of trial stopped in the interim analysis. For the efficacy evaluation, it is based on the probability of passing the interim analysis and a total number of 17 or more patients with response (the probability is called power when the true response rate is 50% and called type I error when the true response rate is 30%). Results show that this design will have 85% power to claim the treatment effective (for a true response rate of 50%). If the true rate of response is 30%, the chance to reach a total of 17 patients with response at end of the study is 0.06 (Type I error). The probability to stop the arm in the 1st stage is 61%. When the true rate of response is 20%, the chance to reach a total of 17 patients with response at end of the study is <1%. The corresponding probability to stop the trial earlier increases to 91%.

Table A1: Bayesian Predictive Probability

Number of patients with response in the 1st interim analysis	Number of patients with response needed in the remaining patients of the 2nd stage	Predictive probability
0	17	0.0000
1	16	0.0000
2	15	0.0000
3	14	0.0004
4	13	0.0034
5	12	0.0203
6	11	0.0805
7	10	0.2222
8	9	0.4477
9	8	0.6919
10	7	0.8723
11	6	0.9625
12	5	0.9926
13	4	0.9991
14	3	0.9999
15	2	1.0000
16	1	1.0000

Table A2: Sensitivity Analysis

	True rate	Probability of early stopping the treatment arm	Probability to have at least 17 patients with response
0.2	0.20	0.9125	0.0009
0.25	0.25	0.7846	0.0103
0.3	0.30	0.6093	0.0587
0.35	0.35	0.4191	0.1897
0.4	0.40	0.2521	0.4087
0.45	0.45	0.1313	0.6546
0.5	0.50	0.0569	0.8484

Figure A1: Bayesian Predictive Probability

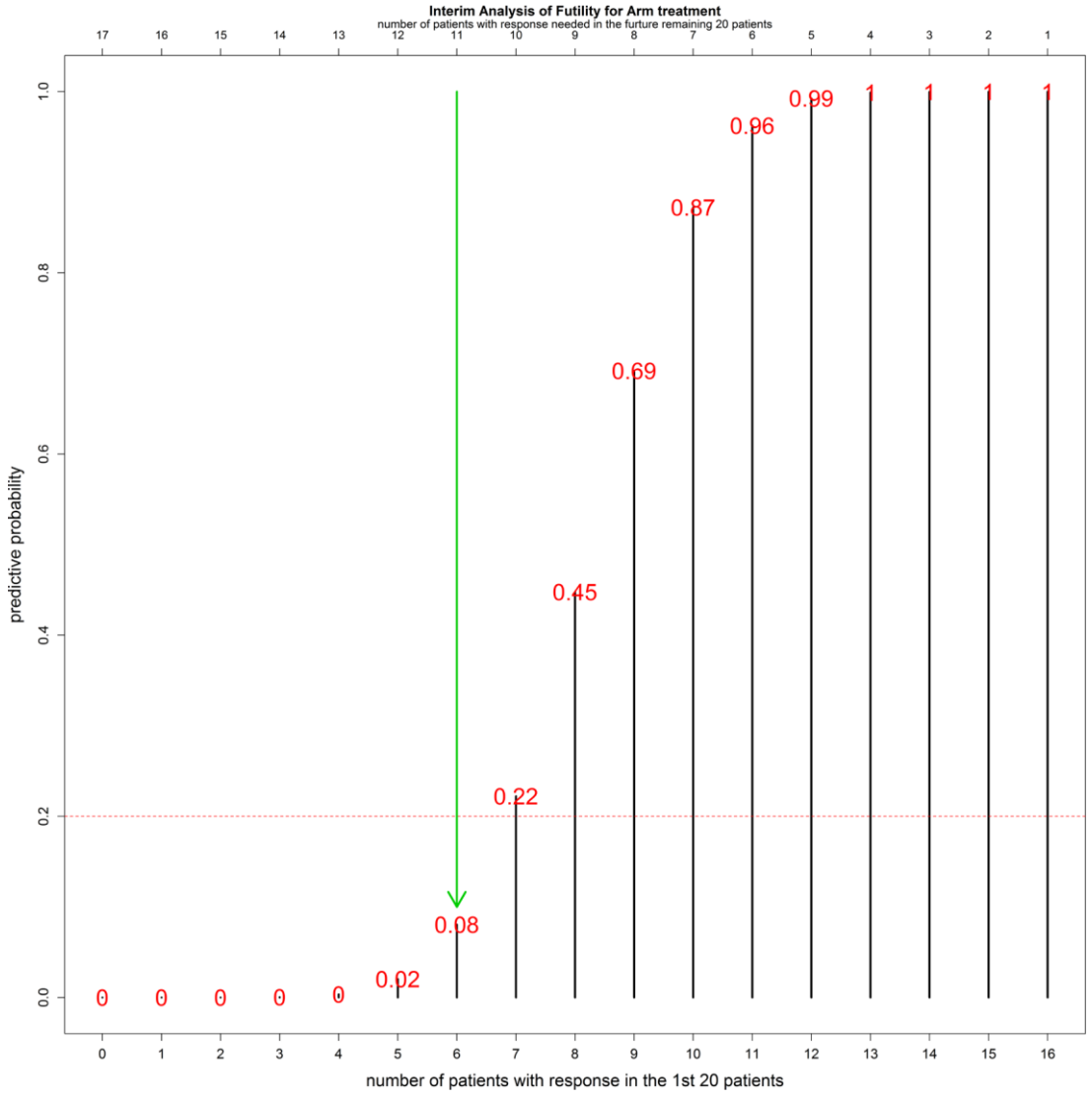
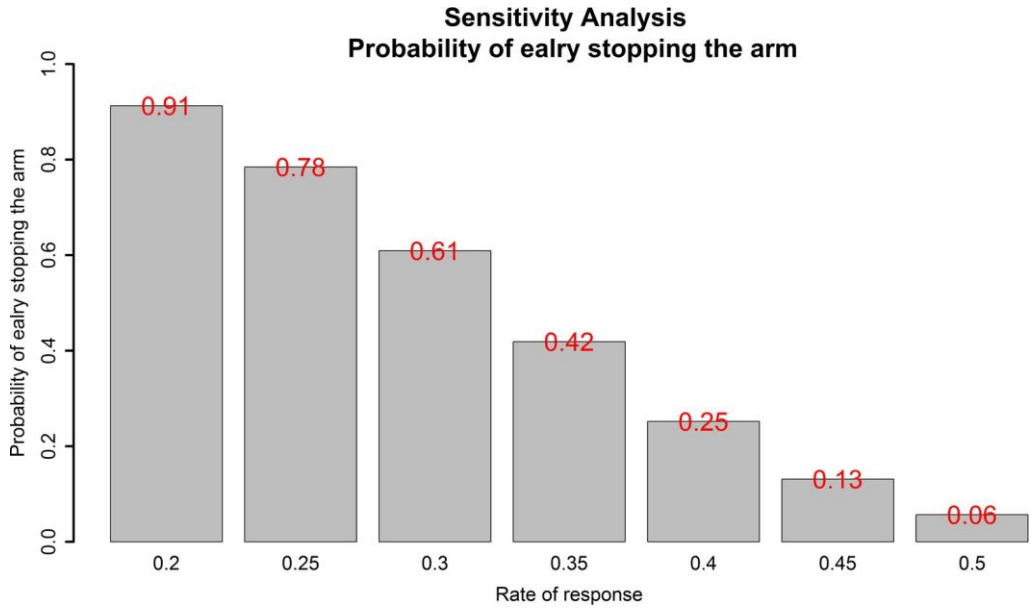
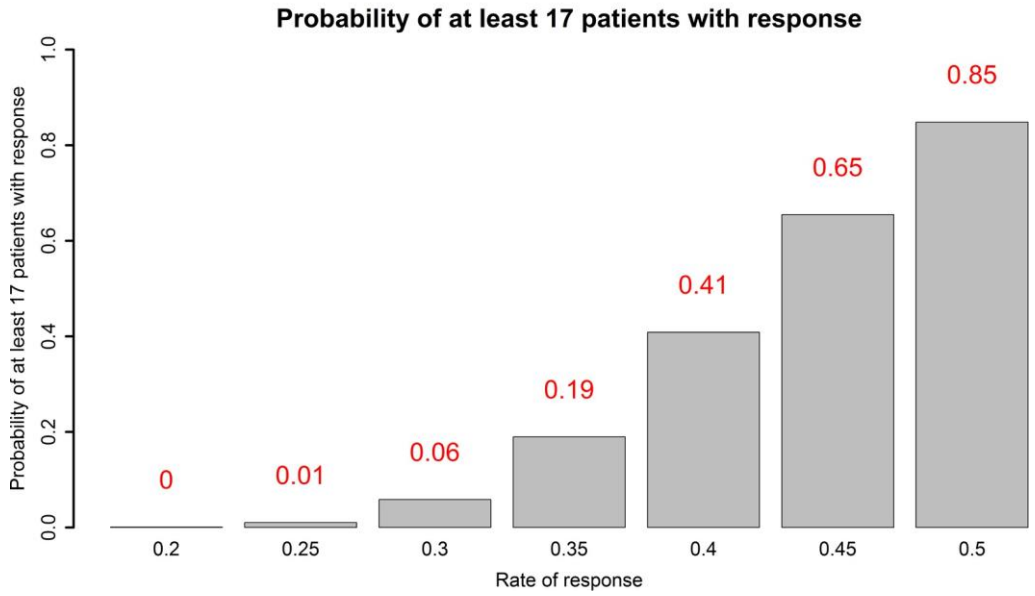


Figure A2: Sensitivity Analysis


Sensitivity Analysis
Probability of ealry stopping the arm
Probability of ealry stopping the arm
0.0
0.2
0.4
0.6
0.8
1.0
0.91
0.78
0.61
0.42
0.25
0.13
0.06
0.2
0.25
0.3
0.35
0.4
0.45
0.5
Rate of response


Probability of at least 17 patients with response
Probability of at least 17 patients with response
0.0
0.2
0.4
0.6
0.8
1.0
0
0.01
0.06
0.19
0.41
0.65
0.85
0.2
0.25
0.3
0.35
0.4
0.45
0.5
Rate of response

Detailed statistical sensitivity analysis of the aggressive stopping rule for the immunotherapy treated previously cohort

The interim analysis for futility will be done for the first 20 patients. A Bayesian approach for futility and efficacy analysis is used to calculate posterior probability and predictive probability for the rate of response with a non-informative beta prior, beta(1,1). We consider a 7% rate or less of response as ineffective. Thus, we expect the treatment is promising and not worse than the historical control if the posterior probability of the rate (response) greater than 7% is higher than 0.95 (i.e., prob(rate of response>7% |data)>0.95). With a total 40 patients in the treatment arm, it will need at least 6 patients with response to meet the criteria. Therefore, we use the number of 6 patients to guide the predictive probability and efficacy. Specifically, for the first 20 patients in the interim analysis, there are 21 ways for number of patients with response from 0, 1, to, 20. In each case, given the number of patients with response, ss, in the first 20 patients, we calculate predictive probability of $6-ss$ or more patients with response in the remaining 20 patients of the 2nd stage **(Table B1 and Figure B1)**, i.e., $\sum_{ii=6-ss}^{20} \binom{20}{ii} \frac{bbbbbbbb(1+ss+ii,1+(20-ss)+(20-ii))}{bbbbbbbb(1+ss,1+(20-ss))}$. Calculation of predictive probability is based on beta binominal distribution for the number of patients with response in the remaining 20 patients of the 2nd stage given a beta distribution for the rate of response, $bbbbbbbb(1+ss,1+20-ss)$. For example, if there is 1 patient with response in the first 20 patients, the predictive probability of 5 or more patients with response in the remaining 20 patients of the 2nd stage would be $\sum_{ii=5}^{20} \binom{20}{ii} \frac{bbbbbbbb(1+1+ii,1+(20-1)+(20-ii))}{bbbbbbbb(1+1,1+(20-1))} = 0.081$. Figure B1 lists predictive probability for all scenarios of number of patients with response in the first 20 patients (interim analysis) and number of patients with response needed in the remaining 20 patients of the 2nd stage to have at least a total of 6 patients with response. With a 20% cutoff for the predictive probability, the stopping rule is if there are 1 or less patients with response for the first 20 patients in the interim analysis (i.e., little chance to reach a total of 6 patients with response at the end of study), we consider the treatment is ineffective and will be stopped.

Sensitivity analyses of this stopping rule are presented in **Table B2 and Figure B2**. For the futility analysis, it is evaluated using the probability of trial stopped in the interim analysis. For the efficacy evaluation, it is based on the probability of passing the interim analysis and the total number of 6 or more patients with response (the probability is called power when the true response rate is 20% and called type I error when the true response rate is 7%). Results show that this design will have 81% power to claim the treatment effective (for a true response rate of 20%). If the true rate of response is 7%, the chance to reach a total of 6 patients with response at end of the study is 0.05 (Type I error). The probability to stop the arm in the 1st stage is 59%. When the true rate of response is 2%, the chance to reach a total of 6 patients with response at end of the study is <1%. The corresponding probability to stop the trial earlier increases to 94%.

Table B1: Bayesian Predictive Probability

number of patients with response in the 1st interim analysis	number of patients with response needed in the remaining patients of the 2nd stage	predictive probability
0	6	0.0086
1	5	0.0810
2	4	0.3073
3	3	0.6445
4	2	0.8974
5	1	0.9879

Table B2: Sensitivity Analysis

	true rate	probability of early stopping the treatment arm	probability to have at least 6 patients with response
0.02	0.02	0.9396	0.0002
0.07	0.07	0.5892	0.0543
0.12	0.12	0.2899	0.3251
0.17	0.17	0.1229	0.6712
0.2	0.20	0.0702	0.8142
0.22	0.22	0.0479	0.8813
0.27	0.27	0.0148	0.9671

Figure B1: Bayesian Predictive Probability

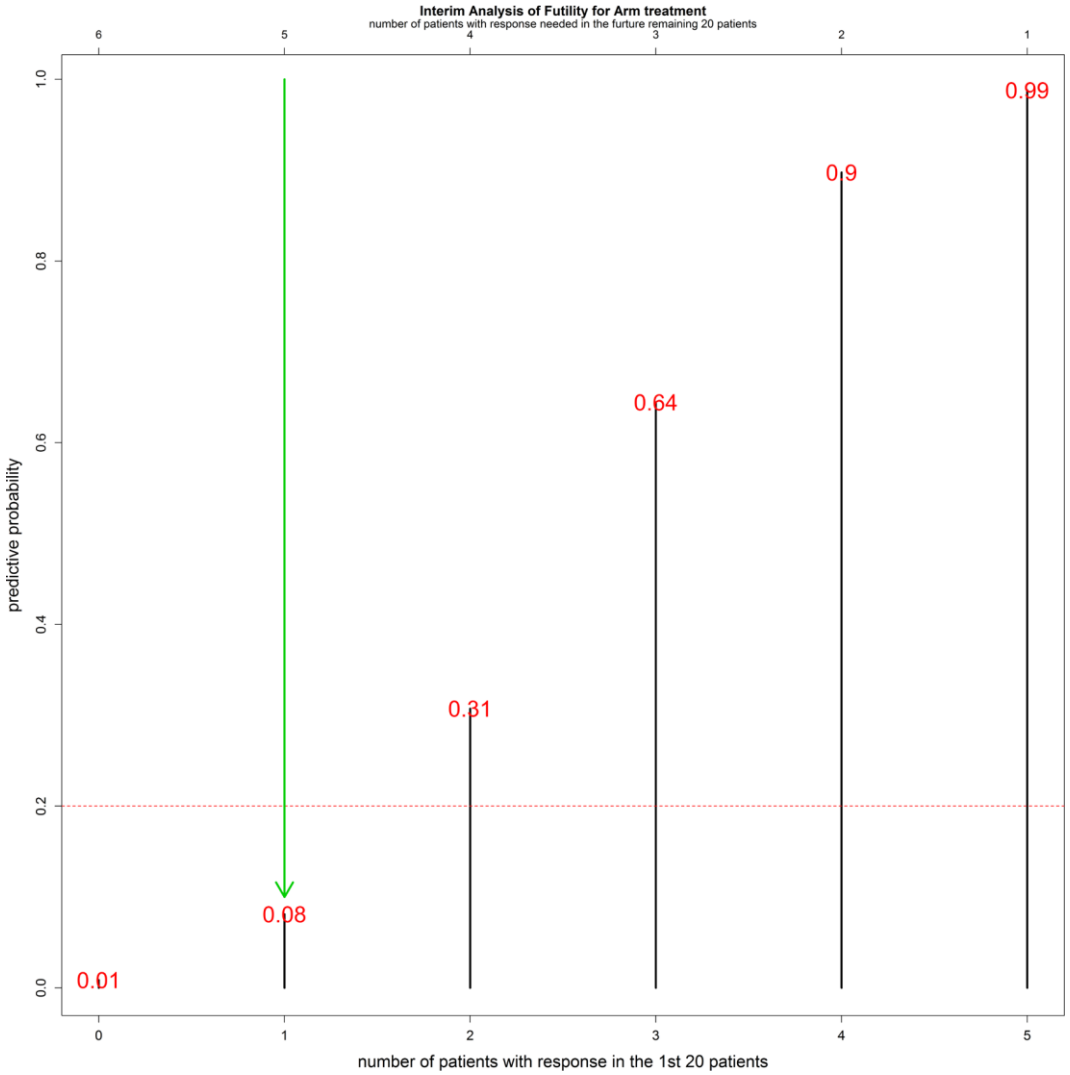
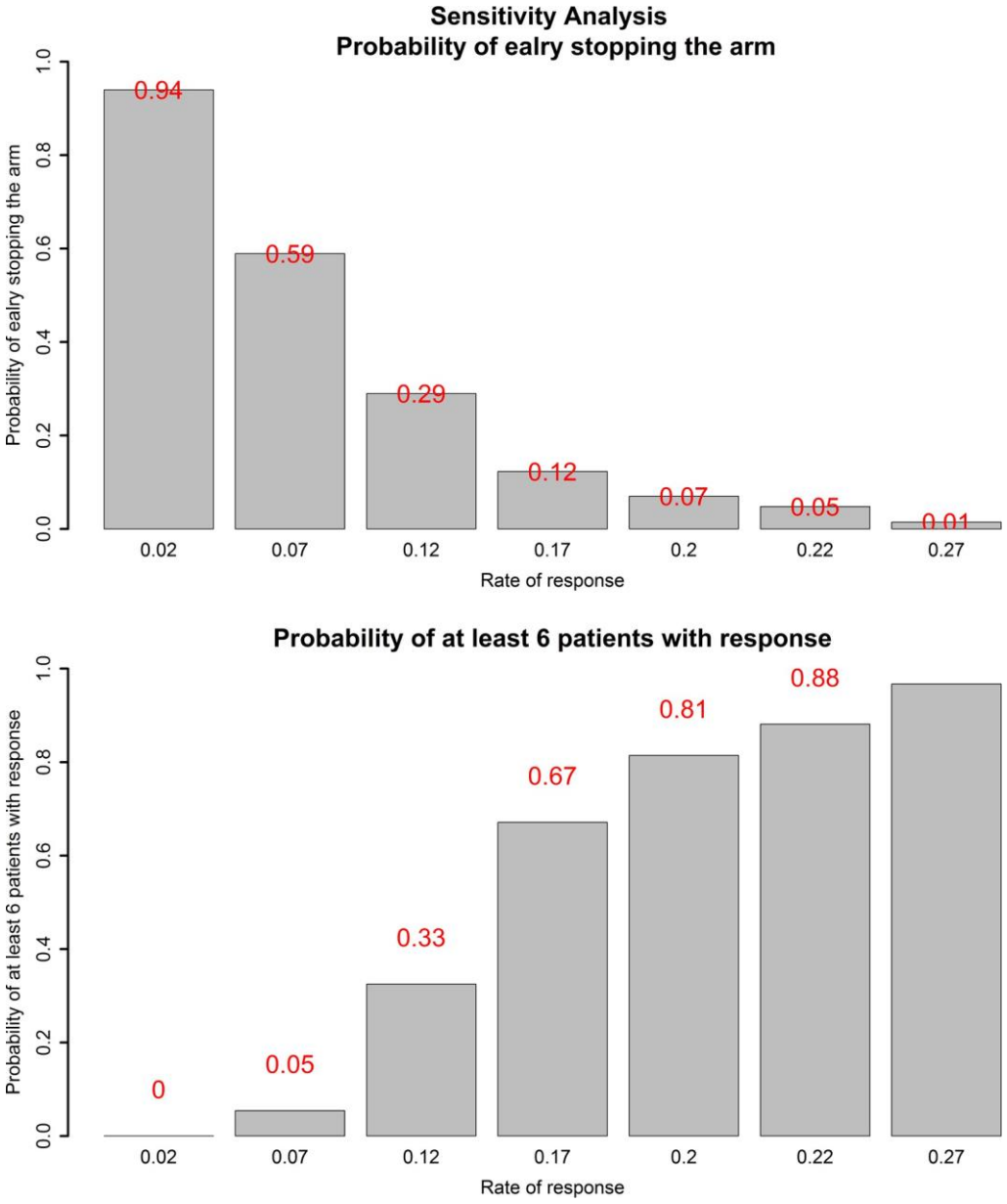


Figure B2: Sensitivity Analysis



13.3 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. 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).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

13.4 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

13.5 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

In addition, volumetric analysis will be explored by central review for response assessment.

13.6 See Events of Clinical Interest Guidance Document

REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin.* 2010;60(5):277-300.
2. Groome PA, Bolejack V, Crowley JJ, et al. The IASLC Lung Cancer Staging Project: validation of the proposals for revision of the T, N, and M descriptors and consequent stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer.* 2007;2(8):694-705.
3. Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest.* 1997;111(6):1710-1717.
4. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *The New England journal of medicine.* 2006;355(24):2542-2550.
5. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *The New England journal of medicine.* 2002;346(2):92-98.
6. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2004;22(11):2184-2191.
7. Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2012;30(17):2055-2062.
8. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2008;26(21):3543-3551.
9. Mu CY, Huang JA, Chen Y, Chen C, Zhang XG. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation. *Medical oncology (Northwood, London, England).* 2011;28(3):682-688.
10. Thompson RH, Gillett MD, Cheville JC, et al. Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. *Cancer.* 2005;104(10):2084-2091.
11. Thompson RH, Kuntz SM, Leibovich BC, et al. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. *Cancer research.* 2006;66(7):3381-3385.
12. Krambeck AE, Dong H, Thompson RH, et al. Survivin and b7-h1 are collaborative predictors of survival and represent potential therapeutic targets for patients with renal cell carcinoma. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2007;13(6):1749-1756.
13. Nomi T, Sho M, Akahori T, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2007;13(7):2151-2157.
14. Loos M, Giese NA, Kleeff J, et al. Clinical significance and regulation of the costimulatory molecule B7-H1 in pancreatic cancer. *Cancer Lett.* 2008;268(1):98-109.
15. Wang L, Ma Q, Chen X, Guo K, Li J, Zhang M. Clinical significance of B7-H1 and B7-1 expressions in pancreatic carcinoma. *World J Surg.* 2010;34(5):1059-1065.
16. Hamanishi J, Mandai M, Iwasaki M, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. *Proc Natl Acad Sci U S A.* 2007;104(9):3360-3365.

17. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol.* 2008;26:677-704.
18. Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. *Nat Rev Immunol.* 2008;8(6):467-477.
19. Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. *Annu Rev Immunol.* 2004;22:329-360.
20. Peggs KS, Quezada SA, Chambers CA, Korman AJ, Allison JP. Blockade of CTLA-4 on both effector and regulatory T cell compartments contributes to the antitumor activity of anti-CTLA-4 antibodies. *J Exp Med.* 2009;206(8):1717-1725.
21. Sharpe AH, Wherry EJ, Ahmed R, Freeman GJ. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. *Nat Immunol.* 2007;8(3):239-245.
22. Keizer RJ, Huitema AD, Schellens JH, Beijnen JH. Clinical pharmacokinetics of therapeutic monoclonal antibodies. *Clin Pharmacokinet.* 2010;49(8):493-507.
23. Clinical Study Report: Study No. CA209017. An Open-label Randomized Phase III Trial of BMS-936558 (Nivolumab) versus Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-small Cell Lung Cancer (NSCLC). Bristol-Myers Squibb Company; 2015. Document Control No. 930086504.
24. Clinical Study Report Study No. CA209057. An Open-label Randomized Phase III Trial of BMS-936558 (Nivolumab) versus Docetaxel in Previously Treated Metastatic Non-Squamous Non-small Cell Lung Cancer (NSCLC). Bristol-Myers Squibb Company; 2015. Document Control No. 930089679.
25. Clinical Study Report: Study No. CA209063. A single arm Phase 2 study of nivolumab (BMS-936558) in subjects with advanced or metastatic squamous cell non-small cell lung cancer who have received at least two prior systemic regimens (CheckMate 063: CHECKpoint pathway and nivolumab clinical Trial Evaluation 063). Bristol-Myers Squibb Company; 2014. Document Control No. 930075122.
26. Clinical Study Report: Study No. CA209004A Phase 1b, Open- Label, Multicenter, Multidose, Dose-Escalation Study of MDX-1106 (BMS-936558) in Combination with Ipilimumab (BMS-734016) in Subjects with Unresectable Stage III or Stage IV Malignant Melanoma. *Bristol-Myers Squibb Company; 2014. Document Control No. 930082868.*
27. Interim Clinical Study Report: Study No. CA209037. A randomized, open-label, Phase 3 trial of BMS-936558 (nivolumab) versus investigator's choice in advanced (unresectable or metastatic) melanoma patients progressing post anti-CTLA-4 therapy. Bristol-Myers Squibb Company; 2014. Document Control No. 930081508.
28. Clinical Study Report: Study No. CA209066. A Phase 3, randomized, double-blind study of BMS-936558 (nivolumab) versus dacarbazine in subjects with previously untreated, unresectable or metastatic melanoma. Bristol-Myers Squibb Company; 2014. Document Control No. 930082627.
29. Clinical Study Report Study No. CA209067. A Phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated unresectable or metastatic melanoma. Bristol- Myers Squibb Company; 2014. Document Control No. 930090681.
30. Clinical Study Report: Study No. CA2090069. A Phase 2, randomized, double blinded study of nivolumab (BMS-936558) in combination with ipilimumab vs. ipilimumab alone in subjects with previously untreated, unresectable or metastatic melanoma. Bristol-Myers Squibb Company; 2014. Document Control No. 930084565.
31. Clinical Study Report: Study No. CA209010. A randomized, blinded, Phase 2 dose-ranging study of nivolumab (MDX-1106, BMS-936558) in subjects with progressive advanced/metastatic clear-cell renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy. Bristol-Myers Squibb Company; 2013. Document Control No. 930074316.
32. Clinical Study Report: Study No. MDX1106-01. A Phase 1, open-label, dose-escalation, safety and pharmacokinetic study of MDX-1106 in patients with selected refractory or relapsed malignancies. Bristol-Myers Squibb Company; 2011. Document Control No. 930044418.
33. Clinical Study Report: Study No. MDX1106-02. A Phase 1, double- blind, randomized, multicenter, placebo-controlled, safety and pharmacokinetic dose-escalation study of a single

intravenous administration of BMS-936558 (MDX-1106), a fully human monoclonal antibody to PD-1, in subjects with active hepatitis C genotype 1 infection. Bristol-Myers Squibb Company; 2014. Document Control No. 930047876.
34. Clinical Study Report: Study No. MDX1106-03. A Phase 1, open-label, multicenter, multidose, dose escalation study of BMS-936558 (MDX1106) in subjects with selected advanced or recurrent malignancies. Bristol-Myers Squibb Company; 2013. Document Control No. 930044417.
35. Weber JS, Kudchadkar RR, Yu B, et al. Safety, efficacy, and biomarkers of nivolumab with vaccine in ipilimumab-refractory or -naive melanoma. *J Clin Oncol.* 2013;31(34):4311-4318.
36. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med.* 2012;366(26):2455-2465.
37. Rizvi NA, Mazieres J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. *Lancet Oncol.* 2015;16(3):257-265.
38. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med.* 2015;373(2):123-135.
39. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med.* 2015;373(17):1627-1639.
40. Study DS06064: BMS-663513 and BMS-734016 (MDX-010): One-month intravenous combination toxicity study in monkeys. Bristol-Myers Squibb Company; 2007. Document Control No. 930021064.
41. Study SBi 1416-128: A repeat dose toxicology and efficacy study MDX-010 or MDX-010-HYB in combination with HBsAg and SKMel vaccines in cynomolgus monkeys. Bristol-Myers Squibb Company; 2003. Document Control No. 930009973.
42. Study SBi 0919-128: A 2-week toxicity study of human anti-CTLA4 administered by intravenous injection to cynomolgus monkeys. Bristol-Myers Squibb Company; 2000. Document Control No. 930009982.
43. Covance Study7114-100: Fourteen-day intravenous toxicity study with mAb 10D1 in cynomolgus monkeys. Bristol-Myers Squibb Company; 2000. Document Control No. 930009970.
44. Study SBi 0992-128: An immunogenic study following combined intravenous/intramuscular administration of MAb10D1/HBsAg, respectively, to cynomolgus monkeys. Bristol-Myers Squibb Company; 2001. Document Control No. 930009968.
45. Study SUV00006: An investigative repeat-dose toxicity and efficacy study of MDX-010 in combination with HBsAg, DNP-Ficoll and SKMel immunostimulants following three monthly administrations. Bristol-Myers Squibb Company; 2007. Document Control No. 930021733.
46. Study 01-3460: MDX-CTLA4: A 6-month intravenous toxicology study in cynomolgus monkeys. Bristol-Myers Squibb Company; 2002. Document Control No. 930009980.
47. Ipilimumab: Single-dose intravenous exploratory comparative pharmacokinetics study in monkeys (Study DS07167); Report. Bristol-Myers Squibb Company; 2008. Document Control No. 930032302.
48. Effect of BMS-734016, BMS-663513, or their combination on the immune responses to simian immunodeficiency virus DNA test antigens (Study TIB-006-01); Interim Subreport. Bristol-Myers Squibb Company; 2007. Document Control No. 930022368.
49. Davies B, Morris T. Physiological parameters in laboratory animals and humans. *Pharm Res.* 1993;10(7):1093-1095.
50. Study DN10020: Ipilimumab (BMS-734016): Intravenous study of pre- and postnatal development in cynomolgus monkeys with a 6- month postnatal evaluation. Bristol-Myers Squibb Company; 2011. Document Control No. 930056635.
51. BMS-734016 (MDX-010): Comparative tissue-binding study with mouse, rat, rabbit, monkey, and human tissues (Study DS05067); Report. Bristol-Myers Squibb Company; 2005. Document Control No. 930021297.
52. Repeated-dose (q3d x 3, 14-day) toxicity study of anti-CTLA-4/10D1 administered via intravenous injection to cynomolgus monkeys. Ipilimumab (Study 126-002); Report. Control No. 930009967.

53. Cross-reactivity study of fluoresceinated, human monoclonal antibody 10D1 with normal human tissues (Study IM578); Report. Pathology Associates International; 2000. Document Control No. 930009993.
54. Cross-reactivity study of fluoresceinated MDX-010 with limited normal human tissues (Study IM933); Report. Pathology Associates International; 2003. Document Control No. 930010006.
55. Misbah SA, Chapel HM. Adverse effects of intravenous immunoglobulin. *Drug Saf.* 1993;9(4):254-262.
56. Soetens FM. Anaphylaxis during anaesthesia: diagnosis and treatment. *Acta Anaesthesiol Belg.* 2004;55(3):229-237.
57. Mertes PM, Laxenaire MC. Allergic reactions occurring during anaesthesia. *Eur J Anaesthesiol.* 2002;19(4):240-262.
58. Yoshizawa K, Oishi Y, Matsumoto M, Nyska A. Ischemic brain damage after ketamine and xylazine treatment in a young laboratory monkey (Macaca fascicularis). *Contemp Top Lab Anim Sci.* 2005;44(5):19-24.
59. Ochsner AJ, 3rd. Cardiovascular and respiratory responses to ketamine hydrochloride in the rhesus monkey (Macaca mulatta). *Lab Anim Sci.* 1977;27(1):69-71.
60. Mayer L, Young Y. Infusion reactions and their management. *Gastroenterol Clin North Am.* 2006;35(4):857-866.
61. Study No. SUV00025/MDX1106-024-R. A 30-day toxicity study of MDX-1106 administered by once weekly intravenous injection to cynomolgus monkeys, followed by an approximate 4-week recovery period. Bristol-Myers Squibb Company; 2006. Document Control No. 930039682.
62. Ipilimumab population pharmacokinetics and exposure-response analyses in subjects with advanced melanoma (Studies CA184004, CA184007, CA184008, and CA184022). Bristol-Myers Squibb Company; 2010. Document Control No. 930043857.
63. Study CA184041: A randomized, double-blind, parallel, three arm, multicenter, Phase II trial evaluating the efficacy and safety of ipilimumab (BMS-734016) in combination with Taxol®/Paraplatin® (paclitaxel/carboplatin) compared to Taxol®/Paraplatin® alone in previously untreated subjects with lung cancer. Bristol-Myers Squibb Company; 2011. Document Control No. 930052500.
64. Study CA184007: Randomized, double-blind, placebo-controlled, Phase 2 study comparing the safety of ipilimumab administered with or without prophylactic oral budesonide (Entocort EC) in patients with unresectable stage III or IV malignant melanoma. Bristol-Myers Squibb Company; 2010. Document Control No. 930043852.
65. Hellmann MD, Rizvi NA, Goldman JW, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. *The Lancet. Oncology.* 2017;18(1):31-41.
66. Hilberg F, Roth GJ, Krssak M, et al. BIBF 1120: triple angiokinase inhibitor with sustained receptor blockade and good antitumor efficacy. *Cancer research.* 2008;68(12):4774-4782.
67. Stopfer P, Rathgen K, Bischoff D, et al. Pharmacokinetics and metabolism of BIBF 1120 after oral dosing to healthy male volunteers. *Xenobiotica.* 2011;41(4):297-311.
68. Mross K, Stefanic M, Gmehling D, et al. Phase I study of the angiogenesis inhibitor BIBF 1120 in patients with advanced solid tumors. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2010;16(1):311-319.
69. Ellis PM, Kaiser R, Zhao Y, Stopfer P, Gyorffy S, Hanna N. Phase I open-label study of continuous treatment with BIBF 1120, a triple angiokinase inhibitor, and pemetrexed in pretreated non-small cell lung cancer patients. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2010;16(10):2881-2889.
70. Reck M, Kaiser R, Eschbach C, et al. A phase II double-blind study to investigate efficacy and safety of two doses of the triple angiokinase inhibitor BIBF 1120 in patients with relapsed advanced non-small-cell lung cancer. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.* 2011;22(6):1374-1381.
71. Reck M, Kaiser R, Mellemgaard A, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. *The Lancet. Oncology.* 2014;15(2):143-155.

72. Hanna NH. Lume-lung 2: A multicenter, randomized, double-blind, phase III study of nintedanib plus pemetrexed versus placebo plus pemetrexed in patients with advanced nonsquamous non-small cell lung cancer (NSCLC) after failure of first-line chemotherapy. Paper presented at: 2013 ASCO Annual Meeting2013.
73. Cancer AJCo. The American Joint Committee on Cancer: the 7th Edition of the AJCC Cancer Staging Manual and the Future of TNM. *Annals of Surgical Oncology.* 2010;17(6):1471.
74. Daud A HO, Robert C, et al. Relationship between programmed death ligand 1 (PD-L1) expression and clinical outcome in patients with melanoma treated with pembrolizumab (MK-3475). Paper presented at: Society for Melanoma Research, 2014 International Congress November 13-16, 2014, 2014; Zurich, Switzerland.
75. Harper J, Sainson RC. Regulation of the anti-tumour immune response by cancer-associated fibroblasts. *Semin Cancer Biol.* 2014;25:69-77.
76. Brundula V, Rewcastle NB, Metz LM, Bernard CC, Yong VW. Targeting leukocyte MMPs and transmigration: minocycline as a potential therapy for multiple sclerosis. *Brain.* 2002;125(Pt 6):1297-1308.
77. Adriani F LG, Landoni E, Facchinetti F, et al. . SNAI2 expression by cancer-associated fibroblasts is a negative prognostic factor in non-small cell lung cancer. Paper presented at: Proceedings of the 105th Annual Meeting of the American Association for Cancer Research; April 5-9, 2014, 214; San Diego, CA.
78. Li H FX, Houghton JM. . Tumor Microenvironment: The Role of the Tumor Stroma in Cancer. *Journal of Cellular Biochemistry.* 2007;101:805-815.
79. Yang Y, Liu C, Peng W, et al. Antitumor T-cell responses contribute to the effects of dasatinib on c-KIT mutant murine mastocytoma and are potentiated by anti-OX40. *Blood.* 2012;120(23):4533-4543.
80. Hosein AN, Livingstone J, Buchanan M, Reid JF, Hallett M, Basik M. A functional in vitro model of heterotypic interactions reveals a role for interferon-positive carcinoma associated fibroblasts in breast cancer. *BMC cancer.* 2015;15:130.
81. Grenga I, Donahue RN, Lepone L, Bame J, Schlom J, Farsaci B. PD-L1 and MHC-I expression in 19 human tumor cell lines and modulation by interferon-gamma treatment. *J Immunother Cancer.* . 2014; 2(Suppl 3): :P102.
82. Taylor MW, Feng GS. Relationship between interferon-gamma, indoleamine 2,3-dioxygenase, and tryptophan catabolism. *FASEB J.* 1991;5(11):2516-2522.
83. Suzuki Y, Suda T, Furuhashi K, et al. Increased serum kynurenine/tryptophan ratio correlates with disease progression in lung cancer. *Lung cancer.* 2010;67(3):361-365.
84. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer. *New England Journal of Medicine.* 2012;366(26):2443-2454.
85. Nivolumab plus Ipilimumab Is Well Tolerated and Active in NSCLC. *Cancer discovery.* 2017;7(2):124.
86. Company B-MS. Clinical Study Report: Study No. CA209010 A randomized, blinded, Phase 2 dose-ranging study of nivolumab (MDX-1106, BMS-936558) in subjects with progressive advanced/metastatic clear-cell renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy. *Bristol-Myers Squibb Company.* 2013;Document Control No. 930074316.
87. Eisen T, Shparyk Y, Macleod N, et al. Effect of small angiokinase inhibitor nintedanib (BIBF 1120) on QT interval in patients with previously untreated, advanced renal cell cancer in an open-label, phase II study. *Investigational new drugs.* 2013;31(5):1283-1293.
88. Weber JS, Hodi FS, Wolchok JD, et al. Safety Profile of Nivolumab Monotherapy: A Pooled Analysis of Patients With Advanced Melanoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2017;35(7):785-792.
89. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *The New England journal of medicine.* 2010;363(8):711-723.
90. Dolled-Filhart M, Gustavson M, Camp RL, Rimm DL, Tonkinson JL, Christiansen J. Automated analysis of tissue microarrays. *Methods in molecular biology.* 2010;664:151-162.
91. Geiss GK, Bumgarner RE, Birditt B, et al. Direct multiplexed measurement of gene expression with color-coded probe pairs. *Nat Biotechnol.* 2008;26(3):317-325.

92. Smyth GK. Linear models and empirical bayes methods for assessing differential expression in microarray experiments. *Stat Appl Genet Mol Biol.* 2004;3:Article3.
93. Subramanian A, Tamayo P, Mootha VK, et al. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proceedings of the National Academy of Sciences of the United States of America.* 2005;102(43):15545-15550.
94. Bondell HD, Reich BJ. Consistent high-dimensional Bayesian variable selection via penalized credible regions. *J Am Stat Assoc.* 2012;107(500):1610-1624.
95. O'Hara DM, Xu Y, Liang Z, Reddy MP, Wu DY, Litwin V. Recommendations for the validation of flow cytometric testing during drug development: II assays. *Journal of immunological methods.* 2011;363(2):120-134.
96. Streitz M, Miloud T, Kapinsky M, et al. Standardization of whole blood immune phenotype monitoring for clinical trials: panels and methods from the ONE study. *Transplantation research.* 2013;2(1):17.
97. Fitzgibbons PL, Bradley LA, Fatheree LA, et al. Principles of analytic validation of immunohistochemical assays: Guideline from the College of American Pathologists Pathology and Laboratory Quality Center. *Archives of pathology & laboratory medicine.* 2014;138(11):1432-1443.
98. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clinical cancer research : an official journal of the American Association for Cancer Research.* 2009;15(23):7412-7420.
99. Kaplan-Meier. *Journal of the American Statistical Association.* 1958;53: 457-481.
100. O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase 1 clinical trials in cancer. *Biometrics.* 1990;46(1):33-48.