Phase II Study of Pembrolizumab and Itacitinib (INCB039110) for First Line Treatment of Metastatic Non-Small Cell Lung Cancer Expressing PD-L1

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1.0 TRIAL SUMMARY

Title:	Phase II study of Pembrolizumab and Itacitinib (INCB039110) for First Line Treatment of Metastatic Non-Small Cell Lung Cancer Expressing PD-L1
Abbreviated Title	Pembrolizumab and itacitinib (INCB039110) for NSCLC
Protocol Numbers	UPCC#09517; IRB#828910; NCT03425006; IND#137721
Trial Phase	Phase II
Study Center(s)	University of Pennsylvania
Study Population	The first line treatment of patients with metastatic PD-L1 positive non-small cell lung cancer (NSCLC)
Methodology	This is a single center, single arm phase 2 study to establish the safety and efficacy of itacitinib (also known as INCB039110) administered in combination with pembrolizumab in patients with metastatic PD-L1 positive non-small cell lung cancer (NSCLC).
Study Drugs, Dose and Regimen	Study Drug(s) • Itacitinib: a JAK 1 selective small molecule inhibitor; an investigational agent that is study supplied • Pembrolizumab: a highly selective humanized monoclonal antibody (mAb) *Dose and Route of Administration* • Itacitinib: 200mg PO (extended release formulation) • Pembrolizumab: 200mg IV infusion over 30 minutes Regimen • Treatment = 3 week (Q3W) dosing cycles • Itacitinib: Once daily for Cycle 3 and Cycle 4 (up to 6 weeks) • Pembrolizumab: Q3 week cycles of treatment beginning at Day 1; if the PI considers it beneficial for the subject, a fifth cycle may be administered prior to EOS visit.
Number of trial subjects	Up to 48 evaluable subjects
Estimated duration of trial	Approximately 48 months

2.0 TRIAL DESIGN

2.1 Trial Design

This is an optimal 3-stage Phase II trial of trial of pembrolizumab and itacitinib for first line treatment of PD-L1 positive metastatic NSCLC. Up to 48 evaluable subjects will be enrolled to examine the efficacy of adding itacitinib to pembrolizumab among patients with previously untreated metastatic NSCLC with tumor PD-L1 expression greater than or equal to 50%. Subjects will receive 2 cycles of pembrolizumab (200mg every 3 weeks), and then undergo repeat imaging and tumor biopsy. Beginning on the Day 1 of Cycle 3 the subject will receive itacitinib (selective JAK1 inhibitor) 200 mg daily for 6 weeks. Pembrolizumab will be continued at the same dose and frequency. After 6 weeks of treatment (week 12 of treatment overall) with itacitinib, repeat imaging and tumor biopsy will be performed. The scan is purely for biopsy planning, and no treatment decisions will be made based upon the results (**Figure 1**). Objective response by RECIST 1.1 will be determined based on the week 12 scan. Subjects who either experience documented progressive disease during the first 12 weeks of treatment or complete the first 12 weeks of treatment and undergo re-staging (i.e., PET/CT scan) will be considered evaluable for objective response evaluation. Subjects who are withdrawn from study (due to toxicity or other reasons) in the first 12 weeks of treatment and who do not undergo re-staging will be considered unevaluable for objective response evaluation but will be included in the safety analyses. These subjects will be replaced. Objective response rate (ORR) is defined as the proportion of evaluable subjects who achieve a complete or partial response according to RECIST 1.1 criteria.

The ORR for pembrolizumab in untreated PD-L1 positive advanced NSCLC was recently reported to be 45% (95% CI 37-53%) [1]. The 3-stage optimal design tests the null hypothesis that the ORR ≤ 35% (clearly inferior to pembrolizumab) versus the alternative that the ORR $\underline{\geq}$ 55% (clearly superior to pembrolizumab) [2]. Eleven evaluable subjects will be entered into the first stage of the study. If 2 or fewer of these 11 subjects respond, then the trial will be terminated. If at least 3 of these subjects respond, then an additional 19 evaluable subjects will be entered into the second stage of the study. If 12 or fewer of these 30 subjects respond, then the trial will be terminated. If at least 13 of these subjects respond, then an additional 18 evaluable subjects will be entered into the third stage of the study. If 20 or fewer of these 48 subjects respond, then it will be concluded that the regimen does not merit further investigation. If at least 21 of these 48 subjects respond, then it will be concluded that the regimen merits further investigation. If the true objective response rate is 35%, then the probability of recommending the regimen for further investigation (false positive error), is 0.100. If the true objective response rate is 55%, then the probability of recommending the regimen for further investigation (power), is 0.906. If the true objective response rate is 35%, then the probability of early termination of the trial by the end of the second stage is 0.786. The software program, PASS v14 was employed to define this 3-stage design.

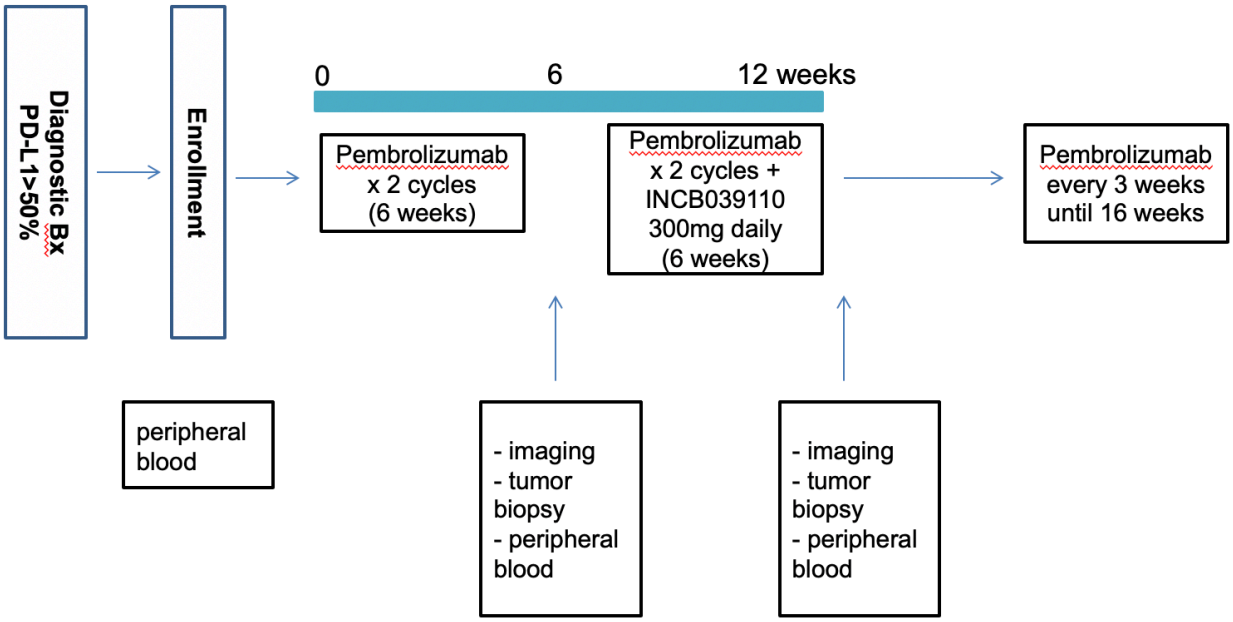
As of Protocol Amendment V5, subjects will continue on study treatment for up to 12 weeks (4 treatment cycles), followed by an End of Study Visit (EOS) at Week 16. If the PI considers it beneficial fo the subject, a fifth cycle may be administered prior to the EOS visit. Subjects who remained on study treatment beyond Week 16 prior to the approval of Protocol Amendment V5, will be asked to undergo an End of Study Visit at their next clinic appointment.

Investigators will make treatment-based decisions using RECIST 1.1. Adverse events will be monitored throughout the subjects' participation in the trial and graded in severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 per protocol **Section 10.1**.

The primary objectives of the trial include determination of ORR per RECIST 1.1 for the combination of pembrolizumab and itacitinib and the safety of this combination, as assessed by CTCAE. Pre-specified adverse events of clinical interest include the following events: 1) Grade ≥ 3 diarrhea 2) Grade ≥ 2 colitis, 3) Grade ≥ 2 pneumonitis, 4) Grade ≥ 3 hypo- or hyperthyroidism, 5) Grade ≥ 2 hypophysitis, 6) Grade ≥ 2 uveitis, 7) Grade ≥ 2 nephritis, 8) Grade ≥ 3 anemia, 9) Grade ≥ 3 thrombocytopenia, and 10) Grade ≥ 3 neutropenia.

The secondary objective of this trial is to collect paired tumor biopsies and peripheral blood to characterize immune biomarkers of response to treatment with pembrolizumab and itacitinib. Additional secondary objectives include determination of progression free survival, duration of response and overall survival, up to week 16 when the subject reaches end of study.

Figure 1. Study Schema



3.0 OBJECTIVES

3.1 Primary Objectives & Hypotheses

1) To determine the objective response rate at 12 weeks according to RECIST 1.1 for the combination of pembrolizumab and itacitinib among patients with previously untreated, PD-L1 positive metastatic NSCLC. Responses will be compared to the subject's baseline assessment and historical controls using pembrolizumab monotherapy.
2) To evaluate toxicities (CTCAE v5.0 scoring) of pembrolizumab and itacitinib in patients with previously untreated, PD-L1 positive metastatic NSCLC

3.2 Secondary Objectives

1) To collect paired blood and tumor tissue samples in order to perform mechanistic studies on treatment-related changes in the subject and tumor immune profiles

2) To determine the median progression free survival (PFS) and duration of response (DOR) at week 12 as well as overall survival (OS) for subjects treated with pembrolizumab and itacitinib, up week 16.

3.3 Exploratory Objectives

1) To perform analyses of tumor infiltrating lymphocytes (TILs) to identify changes in functional markers in response to the addition of itacitinib to pembrolizumab.

2) To perform gene expression studies of tumor tissue using Nanostring to characterize genetic effects in response to immunotherapy.

4.0 BACKGROUND & RATIONALE

4.1 Background

Non-small cell lung cancer (NSCLC) is the leading cause of cancer death in the United States [3]. More than half of patients present with metastatic disease, and are thus considered incurable [4]. Until very recently, the standard first-line treatment for NSCLC not harboring a targetable mutation was platinum doublet chemotherapy. While supportive care measures for patients receiving cytotoxic chemotherapy have improved markedly, the side effects of these agents can be substantial [5, 6]. Immunotherapy, most commonly using PD-1 inhibitors, is now known to have significant activity in NSCLC with a very favorable side effect profile [7-9]. Most recently, the KEYNOTE 024 study revealed that among patients with PD-L1 expression greater than or equal to 50%, pembrolizumab was associated with superior overall and progression free survival when compared with platinum doublet chemotherapy [1].

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [10]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [11-15]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells to FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction between tumor cells and the immune system is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [16, 17]. The structure of murine PD-1 has been resolved [18]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based

switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade [19-22]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [23, 24]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [25, 26]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [17]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [23, 27-29]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [23]. Although healthy organs express little (if any) PD-L1, a variety of cancers have been demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [30]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab (previously known as MK-3475 and SCH 900475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

Interferons are known to have an important role early in generating anti-tumor T cell responses. However, interferons are also involved in the development of adaptive immune resistance [31, 32]. Signaling through the JAK-STAT pathway, interferons regulate PD-L1 expression as well as multiple other negative feedback effects on the immune response through pathways that would not be inhibited by PD-1 blockade alone [33]. Interferon signaling has been theorized as an explanation for the observation that elevated PD-L1 expression is not universally associated with response to pembrolizumab and may also be responsible for primary or secondary treatment resistance [1, 34]. JAK1 is a tyrosine kinase necessary for signaling downstream of both type I and II interferon receptors, as well as multiple other inflammatory cytokines. JAK/STAT signaling has been proposed to promote tumor growth in part by promoting an inflammatory microenvironment that limits $CD8^+$ T cell activity [35].

Itacitinib is a potent JAK1 selective small molecule inhibitor (half maximal inhibitory concentration [IC_{50}] = 3.6 nM), with 22 to 500-fold greater selectivity for JAK1 compared to other JAK family members including JAK2, JAK3 and TYK2.

4.1.2 Preclinical and Clinical Trial Data

Previous work in a mouse melanoma model showed that tumor intrinsic interferon signaling promotes resistance to immune checkpoint blockade [36]. Knocking out type I and II interferon receptors on melanoma cells sensitizes them to immune checkpoint blockade, markedly improving treatment response and survival in pre-clinical models. T cells from these mice express higher proliferative and cytotoxic markers after immune checkpoint blockade.

Preclinical studies utilizing a JAK1/2 inhibitor to block interferon signaling revealed the following observations that can be translated to human trials:

- JAK inhibition reduced tumor growth in response to immune checkpoint blockade and flow cytometry analysis of tumor cells demonstrated decreased surface expression of multiple inhibitory receptor ligands, which generally are associated with immune suppression.
- As prolonged JAK inhibition can have side effects, we tested a short course of JAK inhibitor therapy and still observed consistent improvements in tumor regression.
- When JAK inhibition began concurrently with checkpoint blockade, no improvement was seen in tumor regression relative to checkpoint blockade alone.
- When JAK inhibition was started after an induction phase of checkpoint blockade, however, a marked increase in tumor regression was seen. The selective benefit of sequential, as opposed to concurrent therapy initiation is consistent with 1) the immunostimulatory role of interferon signaling in early events of dendritic cell activation and T cell priming, and 2) the feedback inhibition and immunosuppressive role that occurs with prolonged interferon signaling.

The importance of the timing of JAK inhibition is also implied by studies in chronic viral infections. Blocking interferon signaling late in infection improves viral control, while earlier inhibition is not beneficial[37, 38]. In this study, we aim to extend these findings to patients by testing the addition of JAK inhibition to ongoing anti-PD-1 therapy. We hypothesize that combined treatment with pembrolizumab and itacitinib will be associated with an overall response rate of at least 55%. Moreover, using paired blood and tissue-based biomarkers during the course of treatment we hope to better understand the dynamics of response to immunotherapy among patients with NSCLC.

The combination of itacitinib and pembrolizumab is being evaluated in a phase I study in patients with advanced solid tumors. Data from this trial have not been presented or published. To date, 35 subjects have been treated in the dose escalation and expansion cohorts. No dose-limiting toxicities were noted. The risks of using itacitinib in combination with pembrolizumab are unknown at this time. We anticipate the risk profile of these agents when given in combination will be similar to that of the risk profile of each drug when given alone. Efficacy data is currently not available for this combination.

Refer to the Investigator's Brochure of itacitinib and the pembrolizumab package insert for additional Preclinical and Clinical data including information on potential toxicities.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

The therapeutic benefit of immune checkpoint blockade has now been seen in multiple malignancies, with durable responses observed in a subset of patients [1, 9, 34, 39]. In spite of these exciting results, only a limited number of patients respond to PD-1 blockade, with response rates of approximately 20% in an unselected population. PD-L1 expression is the best-studied predictive biomarker for response to checkpoint blockade in NSCLC [40]. While PD-L1 is an imperfect biomarker, with significant dynamism and heterogeneity, a recent study of patients with tumors expressing a high level of PD-L1 (>50%) pembrolizumab was found to improve overall

survival and progression free survival over platinum doublet chemotherapy in the first line treatment of NSCLC [1, 41] Even in this population enriched for patients likely to respond to PD-1 inhibition, the response rate to pembrolizumab was only 44.8%. While this is a great advance, there is clearly room for improvement as we attempt to extend the benefits of anti-PD-1 therapy to a larger patient population.

Patients with newly diagnosed stage IV or metastatic NSCLC with tumor PD-L1 expression greater than or equal to 50% will be enrolled in this study prior to any systemic therapy for metastatic disease. This patient population is selected because 1) PD-L1 is itself upregulated by interferon signaling and could serve as a biomarker for JAK1 inhibition, and 2) we hypothesize that in a proportion of patients with PD-L1+ tumors, feedback inhibition that occurs with prolonged interferon signaling limits response. Thus, patients with high levels of PD-L1 expression may be more likely to benefit from the combination of pembrolizumab and itacitinib.

4.2.2 Rationale for Dose Selection/Regimen/ Modification

The currently approved dose for pembrolizumab in patients with NSCLC is 200mg every 3 weeks. The 200mg every 3 week dose was also shown to be safe and effective in a first line treatment trial for patients with PD-L1 positive NSCLC [1]. At this time, the duration of treatment with pembrolizumab in patients with a clinical benefit is not clear but a standard practice is to continue treatment in the absence of adverse effects and/or clinical and radiographic disease progression. Therefore treatment with pembrolizumab will continue indefinitely in the absence of (1) documented disease progression per RECIST 1.1, (2) unacceptable adverse event(s), (3) intercurrent illness that prevents further administration of treatment, (4) investigator's decision to withdraw the subject, (5) subject withdrawal of consent, (6) pregnancy of the subject, (7) noncompliance with trial treatment or procedure requirements, (8) institution of alternative systemic treatment, or (9) other administrative reasons. Pembrolizumab may also continue at the physician investigator's discretion if the subject continues to benefit clinically from treatment.

In study INCB039110-107, 35 subjects with advanced solid tumors have been treated with itacitinib in combination with pembrolizumab (8 subjects in Part 1a [dose escalation] and 27 subjects in Part 1b [dose expansion]). The most frequently reported treatment-emergent adverse events (TEAEs) in Part 1a were anemia, fatigue, disease progression (50% each) and nausea, decreased appetite, and decreased weight (37.5% each). The most frequent TEAE in Part 1b were fatigue and nausea (37.0% each). There were no dose-limiting toxicities (DLTs) in Part 1a. The dose expansion cohort was treated with 300mg daily of itacitinib. Serious adverse events (SAE) were reported in 6 subjects in the expansion cohort and include disease progression (2 subjects, 7.4%) and abdominal pain, gastric obstruction, pancreatitis, pyrexia, urinary tract infection and pulmonary embolism (1 subject each, 3.7%). Only pyrexia was considered to be a treatment-related SAE.

Itacitinib is also being evaluated in combination with other immunotherapies in research studies. In personal communications with Incyte (the sponsor of these trials), they decided that based upon proprietary information, the recommended phase 2 dose for future study is 200mg/daily. As more precise data become available, the protocol and consent will be updated to better characterize adverse events.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

4.2.3.1.1 Primary

Objective response rate, defined as the percentage of evaluable subjects who achieve a complete or partial clinical response at 12 weeks, according to RECIST 1.1 is the primary endpoint of this study. Given that this is a first line study of a novel combination, ORR was chosen as an earlier indicator of efficacy of the combination and to limit the number of subjects exposed if improved efficacy is not observed. Morever, based on the mechanism of action, JAK1 inhibition would be predicted to improve the response rate in a population of patients with PD-L1 positive tumors by reducing the expression of additional immune inhibitory pathways in the tumor microenvironment. Responses will be compared to the subject's baseline assessment and historical controls using pembrolizumab monotherapy.

4.2.3.1.2 Secondary

Peripheral blood immune profiling will provide important mechanistic information on how PD-1 blockade and itacitinib function in human subjects. By studying treatment related changes in blood and tumor, and correlate these with response or resistance, superior and perhaps tailored combination treatment strategies could potentially be developed in the future. Correlative samples will be banked upon receipt and correlative assays performed in the following priority order.

High priority assays:

1. Multiparametric flow cytometry analysis of peripheral blood mononuclear cells to analyze T cell subsets and markers of functionality. T cell subsets will be determined using transcription factors and surface markers subsets. Functionality will be measured by examining activation markers, cytokines, effector molecules, and proliferation markers.

2. Transcriptomic analyses of tumor specimens to identify changes in gene expression after the addition of itacitinib to pembrolizumab. In particular, we will examine a subset of interferon-stimulated genes (ISGs) associated with resistance to checkpoint blockade in pre-clinical models.

3. Measurement of inflammatory cytokine or chemokine levels in subject serum. In particular, we will examine interferon levels and other cytokines regulated by the JAK1 pathway as biomarkers for both on-target drug activity and response.

Second priority assays:

1. Measurement of inflammatory cytokine or chemokine levels in subject serum. Circulating tumor cell (CTC) and circulating tumor DNA (ctDNA) measurements and profiling.

Additional secondary endpoints include progression free survival (PFS), overall survival (OS) and duration of response (DOR). PFS is defined as days from initiation of study therapy to first documented disease progression, death due to any cause or last subject contact which documents progression-free status. Those patients who are currently on-study and progression-free at 16 weeks, will no longer be followed and will be censored for PFS and OS at week 16. DOR is defined as the time from first documentation of partial or complete response to first documented disease progression. Those patients who are currently on-study and progression-free at 16 weeks, will no longer be followed and will be censored for PFS and OS at week 16.

OS is defined as days from initiation of study therapy to death due to any cause or last subject contact. Those patients who are currently on-study and progression-free at 16 weeks, will no longer be followed and will be censored for PFS and OS at week 16.

4.2.3.2 Exploratory objectives

Perform analyses of tumor infiltrating lymphocytes (TILs) to identify changes in functional markers in response to the addition of itacitinib to pembrolizumab. This study will be a pilot feasibility study of performing multiparametric analysis of TILs, particularly $CD8^+$ T cells, from patients with metastatic NSCLC using approaches such as flow cytometry and multicolor immunohistochemistry.

Given the potential role for chronic interferon signaling as well as other inflammatory cytokines regulated by JAK/STAT signaling in impairing T cell function, we anticipate that response to itacitinib and pembrolizumab will be associated with 1) sustained activation of PD1+ T cells after an initial proliferative burst as measured by Ki67, 2) high pre-treatment interferon levels that is suppressed during treatment, and 3) high gene expression levels of resistance-associated ISGs. We hypothesize that subjects failing to respond to treatment will show initial proliferative burst in PD1+ T cells that is not sustained despite continued pembrolizumab, and 2) decreased expression of various other markers of T cell activation.

Additionally, deep sequencing of the T cell receptor (TCR) in tumor and blood will be performed as feasible to identify clones that expand after treatment and monitor their persistence over time. These are non-biased approaches to identify tumor reactive T cells in subjects where the specific neoantigen is not known.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Inclusion Criteria

1. Stage IV or metastatic non-small cell lung cancer (NSCLC)
2. Provide written informed consent for the trial.
3. Patients ≥ 18 years of age
4. Tumor PD-L1≥ 50% as assessed by the PD-L1 IHC 22C3 pharmDx assay (Dako North America).
5. Subject must have adequate tumor burden at a safely accessible site for biopsy. NOTE: If sites chosen for biopsy were previously irradiated, there must be evidence of tumor growth/viable tumor as assessed by the investigator.
6. At least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
7. ECOG performance status 0 or 1
8. Adequate organ function as defined in **Table 1**

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,250/mcL
Platelets	≥100,000/mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine OR Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) OR ≥50 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN OR
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN OR ≤ 5 X ULN for subjects with liver metastases
[a]Creatinine clearance should be calculated per institutional standard.	

9. Subjects of reproductive potential must agree to use acceptable birth control methods as described in protocol **Section 5.6.2**.

5.1.2 Exclusion Criteria

1. Sensitizing mutations in Epidermal growth factor receptor (*EGFR)* or anaplastic lymphoma kinase (*ALK)* or ROS1 proto-oncogene receptor tyrosine kinase (*R*OS1) translocations

2. Currently participating in or has participated in a study of an investigational agent or anticipated use of an investigational device within 4 weeks of the first dose of study treatment.

3. Untreated symptomatic central nervous system (CNS) metastases and/or carcinomatous meningitis.

4. Received prior systemic cytotoxic chemotherapy, biologic therapy, targeted therapy or immunotherapy for incurable (metastatic) NSCLC.

5. Diagnosis of immunodeficiency within 7 days prior to eligibility confirmation by the physician-investigator.

6. Prior monoclonal antibodies used for the treatment of NSCLC within 4 weeks prior to eligibility confirmation by the physician-investigator, or individuals who have not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

7. Known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, non-invasive bladder tumors, or in situ cervical cancer

8. Active autoimmune disease requiring systemic immunosuppressive treatment within the past 3 months prior to eligibility confirmation by the physician-investigator. Subjects that require intermittent use of steroid-containing bronchodilators or local steroid injections or topical steroid medications are not excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjogren's syndrome are not excluded from the study.

9. Interstitial lung disease or history of pneumonitis that has required oral or IV steroids

10. Active infection requiring systemic therapy with IV antibiotics

11. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

12. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

13. Pregnant or breastfeeding women

14. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4).

15. Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

16. Known active Hepatitis B (e.g., HBsAg positive or HBV DNA detectable) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

17. Anticipated receipt of any live vaccine within 30 days prior to the first dose of trial treatment.

Note: For the purposes of determining eligibility above, enrollment is defined as the date of subject consent.

5.2 Enrollment

The Subject Number consists of the Protocol Number with a sequential subject number affixed to it. Assignment of subject numbers will occur at the time of consent and occur in ascending order (i.e. 09517-01, 09517-02, etc). No numbers will be omitted. Subject numbers will thereafter be used on all study documentation.

At the time a subject consents to participate in this study, a Consent Notification Form should be completed. When eligibility of the subject is confirmed by a physician-investigator, an Enrollment Notification should be completed. Both completed forms should be emailed in real-time to the Protocol Monitoring and Sponsor Project Manager.

5.3 Study Drugs

The treatments to be used in this trial are outlined below in **Table 2**.

Table 21: Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3-week cycle; up to 4 study treatment cycles*	Per label- with the exception of the drug being administered with itacitinib
Itacitinib (INCB039110)	200 mg	Once Daily	Oral	Daily for cycles 3-4 (q3 weeks); up to 42 days of therapy	Investigational
The pembrolizumab dosing interval may be modified as per package insert. *If the PI considers it beneficial for the subject, a fifth cycle may be administered prior to EOS visit.					

5.3.1 Dose Selection/Modification

5.3.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in **Section 4.0** – Background and Rationale.

5.3.1.2 Dose Modifications

Pembrolizumab

Please refer to the pembrolizumab package insert.

Itacitinib

Table 3: Dose modification guidelines for itacitinib-related adverse events.

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment[1]	Dose/Schedule for restarting treatment	Discontinue itacitinib (after consultation with the Sponsor Medical Director)[2]
Hematological Toxicity	1, 2	No	N/A	N/A	N/A
	3, 4	Yes	Toxicity improves to Grade 0-2 or baseline	Reduce itacitinib by 1 dose level (100 mg daily) If second dose reduction is necessary subject will be discontinued from itacitinib treatment.	Toxicity does not resolve within 2 weeks of last dose. If second dose reduction is necessary subject will be discontinued from itacitinib treatment.
Thrombocytopenia with bleeding	1, 2	No- but dose reduce	N/A	Reduce itacitinib by 1 dose level (100 mg daily) If second dose reduction is necessary subject will be discontinued from itacitinib treatment.	If second dose reduction is necessary subject will be discontinued from itacitinib treatment.
	3, 4	Yes	Toxicity improves to Grade 0-2 or baseline	Hold itacitinib until count recovery. If second dose hold is necessary subject will be discontinued from itacitinib treatment.	Toxicity does not resolve within 2 weeks of last dose. If second dose hold is necessary subject will be discontinued from itacitinib treatment.

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment[1]	Dose/Schedule for restarting treatment	Discontinue itacitinib (after consultation with the Sponsor Medical Director)[2]
Febrile neutropenia	3	Yes	N/A	N/A	Discontinue itacitinib
Infection	3,4	Yes	Completion of IV antibiotics	Reduce itacitinib by 1 dose level (100 mg daily)	Toxicity does not resolve with typical antibiotic course
Non-hematological toxicity Note: Exceptions to be treated similar to grade 1 toxicity • Grade 2 alopecia • Grade 2 fatigue	1	No	N/A	N/A	N/A
	2	Consider withholding for clinically significant symptoms	Toxicity improves to Grade 0-1 or baseline	Same dose and schedule	N/A
	3, 4	Yes	Toxicity improves to Grade 0-1 or baseline	Reduce itacitinib by 1 dose level (100 mg daily) If second dose reduction is necessary subject will be discontinued from itacitinib treatment.	Toxicity does not resolve within 2 weeks of last dose. If second dose reduction is necessary subject will be discontinued from itacitinib treatment.
Hepatic Toxicity	Bilirubin ≥ 2 x ULN **AND** Grade 3 AST/ALT (≥ 3 x ULN)	Yes	N/A	N/A	Discontinue itacitinib

* N/A = Not applicable
1- Missed doses will not be made up. The subject may receive up to 42 days of itacitinib therapy.
2- If a subject discontinues itacitinib therapy, they may continue on pembrolizumab treatment and may remain on study.

5.3.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (**Section 6.0**). Trial treatment may be

administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab will be administered q3 weeks as a 30 minute IV infusion. Up to 4 cycles of pembrolizumab will be administered as part of this study. If the PI considers it beneficial for the subject, a fifth cycle may be administered prior to EOS visit. Pembrolizumab treatment cycle intervals may be increased due to toxicity as per package insert. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window of +/- 10 minutes is permitted.

Itacitinib will be administered daily starting at Cycle 3/Day 1 and continue for a total of 6 weeks (42 days). Itacitinib should be taken orally by the subject at the prescribed dose- 200 mg QD (2 x 100 mg tablets). If dose reductions are required due to toxicity, the prescribed dose may be reduced to 100 mg QD (1 x 100 mg tablet). Itacitinib should be taken with water, and may be taken without regard to food. If itacitinib doses are missed due to toxicity (per **Table 3**) or if vomiting occurs, these missed doses will not be made up.

5.4 Concomitant Medications

All concomitant medications received within 28 days before the first dose of trial treatment and Week 12 (End of Treatment Safety Follow-up Visit) should be recorded. Anticancer therapies administered after the End of Treatment Safety Follow-up Visit will continue to be recorded until the end of study visit (Week 16).

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy will rest with the Sponsor.

5.4.1 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 medications will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. Subjects may receive other medications that the investigator deems to be medically necessary unless specified in **Section 5.4.2** below.

5.4.2 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:

- Systemic corticosteroid therapy or any other form of immunosuppressive therapy is prohibited within 7 days prior to study treatment. (Nasal or oral inhalers are permissible). Physiologic replacement doses of steroids (mineralocorticoid or less than or equal to a prednisone 10 mg daily dose) will also be permitted.

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and itacitinib
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed per physician-investigator discretion, but would be regarded as a disease progression event for the primary endpoint. However as per Section 4.2.2, subjects may continue to receive pembrolizumab at the physician-investigator's discretion if the subject continues to benefit clinically from treatment.
- 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, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines and are not allowed.
- Glucocorticoids, in excess of physiologic doses (prednisone >10 mg per day equivalent), for any purpose other than an abbreviated course to modulate symptoms from an event of clinical interest of suspected immunologic etiology.
- CYP3A4 inhibitors and dual CYP3A4/2C9
- Fluconazole (>200mg doses)

5.5 Rescue Medications & Supportive Care

5.5.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Please refer to the pembrolizumab package insert for supportive care guidelines related to pembrolizumab administration.

Toxicity management considerations for itacitinib are outlined below.

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

5.6 Diet/Activity/Other Considerations

5.6.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.6.2 Contraception

Pembrolizumab and/or itacitinib may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab and/or itacitinib have transient adverse effects on the composition of sperm. Therefore while enrolled, all subjects must agree not to participate in a conception process (i.e. active attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization, etc).

Female subjects of reproductive potential (women who have reached menarche or women who have not been post-menopausal for at least 24 consecutive months, i.e., who have had menses within the preceding 24 months, or have not undergone a sterilization procedure [hysterectomy or bilateral oophorectomy]) must have a negative serum or urine pregnancy test performed within 72 hours of Cycle 1/Day 1 as per the Trial Flow Chart.

All participants participating in sexual activity that could lead to pregnancy must agree to use two methods of birth control. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from screening throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents). Male sterilization (i.e. vasectomy) is also considered an acceptable method of birth control as long as a barrier method is also utilized.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement above. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.6.3 Use in Nursing Women

It is unknown whether the study drugs are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.7 Subject Withdrawal/Discontinuation

A subject may be prematurely discontinued from study treatment for any of the following reasons:

- Withdrawal of consent
- Confirmed radiographic disease progression per RECIST 1.1; (as per standard of care, a patient receiving pembrolizumab who experiences asymptomatic progression of disease may be continued on therapy until progression is confirmed with a subsequent scan).
- Unacceptable adverse experiences or toxicities (see **Section 5.3.1.2**)
- Intercurrent illness that prevents further administration of treatment

- Investigator's decision to withdraw the subject
- Confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Institution of alternative systemic treatment
- Other Administrative reasons

Subjects who discontinue from study treatment will complete and End of Study Visit per the Trial Flow Chart in **Section 6.0**.

5.8 Subject Replacement Strategy

Subjects who either experience documented progressive disease during the first 12 weeks of treatment or complete the first 12 weeks of treatment and undergo re-staging are considered evaluable and will not be replaced. Subjects who complete study treatments but are unable to complete planned biopsies will also be considered evaluable for response and adverse events. All other subjects will be considered non-evaluable and will be replaced.

5.9 Clinical Criteria for Early Trial Termination

The 3-stage optimal design tests the null hypothesis that the ORR ≤ 35% (clearly inferior to pembrolizumab) versus the alternative that the ORR ≥ 55% (clearly superior to pembrolizumab) [2]. ORR will include both subjects with partial responses and complete responses, per RECIST 1.1. Stable disease will not be considered a response. Eleven evaluable subjects will be entered into the first stage of the study. If 2 or fewer of these 11 subjects respond, then the trial will be terminated. If at least 3 of these subjects respond, then an additional 19 evaluable subjects will be entered into the second stage of the study. If 12 or fewer of these 30 subjects respond, then the trial will be terminated. If at least 13 of these subjects respond, then an additional 18 evaluable subjects will be entered into the third stage of the study. If 20 or fewer of these 48 subjects respond, then it will be concluded that the regimen does not merit further investigation. If at least 21 of these 48 subjects respond, then it will be concluded that the regimen merits further investigation. If the true objective response rate is 35%, then the probability of recommending the regimen for further investigation (false positive error), is 0.100. While if the true objective response rate is 55%, then the probability of recommending the regimen for further investigation (power), is 0.906. If the true objective response rate is 35%, then the probability of early termination of the trial by the end of the second stage is 0.786. The software program, PASS v14 was employed to define this 3-stage design.

A Bayesian termination rule for unacceptable toxicity (defined in **Section 8.1)** will be employed to monitor safety. Assuming a minimally informative beta (1,5) prior, which is information equivalent to 1 of 6 treated subjects with unacceptable toxicity. If the number of subjects with unacceptable toxicity in the first stage of 2-stage design is: ≥2 in first 3 subjects, ≥3 in first 6, ≥4 in first 9, or in the second stage of the design is: ≥ 5 in first 12, ≥6 in first 15, ≥7 in first 18, ≥9 in first 25 subjects, ≥10 in first 30 or in the third stage of the design is: ≥12 in first 35, ≥13 in first 40 and ≥14 in first 45, then termination will be considered as it is likely that the rate of unacceptable toxicity is >25%.

5.10 Clinical Criteria for Early Trial Termination due to Trial Conduct or Other Factors

Early trial termination will occur for any of the following:

1. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

2. Plans to modify or discontinue the development of the study drug

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Treatment Cycles (q3 weeks)**					**End of Study Treatment[6]**	**End of Study[6]**
Treatment Cycle/Title:	**Screening Visit**	**Cycle1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**EOT Safety Follow-up Visit**	
Scheduling Window (Days):	**-28 to -1**	**Wk1**	**Wk 3 (± 3)**	**Wk 6 (± 3)**	**Wk 9 (± 3)**	**Week 12 (±5)**	**Week 16(±10)**
Informed Consent	X						
Inclusion/Exclusion Criteria Assessment	X						
Demographics and Medical History	X						
Prior and Concomitant Medication Review	X	X----------X				X	
Pembrolizumab Administration		X	X	X	X		
Itacitinib Administration				X	X		
Post-study anticancer therapy status						X	X
Adverse Event Assessment	X	X----------X				X	X
Full Physical Examination	X				X	X	
Directed Physical Examination[4]		X	X	X			X
Vital Signs and Weight	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	
Pregnancy Test – Urine or Serum β-HCG[3]	X	X[3]					
PT/INR and aPTT	X[9]						
CBC with Differential[8]	X[9]		X	X	X	X	X
Comprehensive Serum Chemistry Panel[8]	X[9]		X	X	X	X	X

Trial Period:	**Treatment Cycles (q3 weeks)**					**End of Study Treatment[6]**	**End of Study[6]**
Treatment Cycle/Title:	**Screening Visit**	**Cycle1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**EOT Safety Follow-up Visit**	
Scheduling Window (Days):	**-28 to -1**	**Wk1**	**Wk 3 (± 3)**	**Wk 6 (± 3)**	**Wk 9 (± 3)**	**Week 12 (±5)**	**Week 16(±10)**
TSH[8]	X[9]		X			X	
Tumor Imaging[5]	X[7]		X[10]		X[11]		
Tumor Biopsies[1]			X[10]		X[11]		
Archived Tumor Tissue Sample Collection	X[12]						
Research Blood Collection[2]	X	X	X	X	X	X	

1. The order of preference for biopsy site, if safely accessible, is primary tumor > solid organ metastasis (including thoracentesis) > lymph node metastasis. Preference will be made to biopsy the same site for both biopsies, if safe and feasible.
2. Up to 78mL of blood will be collected for research studies. Please refer to the Study Laboratory Manual for additional details related to sample collection and handling.
3. Female subjects of reproductive potential only. A negative pregnancy test is required within 72 hours of Cycle 1/Day 1.
4. Directed physical examinations will be symptom and disease driven based on physician discretion.
5. RECIST 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. Tumor imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle duration.
6. The End of Treatment (EOT) Safety Follow-up Visit will occur at Week 12 (+/-5d). The End of Study (EOS) Visit will occur at Week 16 (+/-10d). If the PI considers it beneficial for the subject, a fifth cycle may be administered prior to EOS visit. Subjects who remained on study treatment beyond Week 16 prior to the approval of Protocol Amendment V5, will be asked to undergo an End of Study Visit at their next clinic appointment prior to being withdrawn from the study. Please refer to **Section 7.1.6.1** for how to handle subjects who prematurely discontinue from study treatment.
7. Baseline tumor imaging to be performed within 30 days prior to Cycle 1/Day 1. A PET/CT may be used to fulfill baseline imaging requirements, however a PET/CT cannot be substituted for post-infusion imaging. Please refer to **Section 7.1.2.6** for additional information.

8. Please refer to **Table 4** for additional information. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.
9. Screening laboratory tests are to be performed within 10 days prior to Cycle 1/Day 1.
10. Performed 7-14 days after Cycle 2 of pembrolizumab. Tumor imaging will be used for biopsy planning only, and no treatment decisions will be made based upon the results.
11. Performed at the end of Cycle 4, before the end of study visit. Imaging performed at this timepoint will be used to evaluate objective response by RECIST 1.1.
12. An archived tumor tissue sample may be collected for exploratory analysis if available. Subjects will not undergo an additional procedure to obtain this sample. Please refer to the Lab Manual for additional instructions.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - **Section 6.0** summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to subject safety. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial. Copies of the informed consent form must be placed in the electronic medical record as well as study folder.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the physician-investigator to ensure that the subject qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease

for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medications, if any, taken by the subject during the trial.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review/document all new anti-neoplastic therapy initiated after the last dose of trial treatment.

7.1.1.6 Trial Compliance (Medication/Diet/Activity/Other)

Please refer to **Table 3** for additional information on dose modification guidelines for itacitinib-related adverse events.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment. Please refer to **Section 10** for additional information on the assessment and recording of adverse events.

7.1.2.2 Full Physical Exam

The investigator or licensed medical professional will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration. Directed physical examinations will be symptoms and disease driven based on physician discretion.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to beginning each treatment cycle and at treatment discontinuation as specified in the Trial Flow Chart (**Section 6.0**). Vital signs should include temperature, pulse, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see **Section 16.1**) as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

The initial tumor imaging will be performed within 30 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 30 days prior to the first dose of trial treatment. A PET/CT may be used to fulfill baseline imaging requirements; however a PET/CT cannot be substituted for post-infusion imaging.

As responses to immunotherapy may be delayed, no subjects should have treatment decisions modified by the week 6 scan (42 ± 7 days) alone – this is intended as a research scan to guide biopsies. A repeat scan at 12 weeks (performed at the end of Cycle 4 prior to end of study visit) is intended for the primary outcome and clinical decision-making. Tumor imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle duration.

If a subject demonstrates radiographic progression at Week 12, repeat imaging may be performed at least 28 days later at the discretion of the treating investigator in order to confirm radiographic progression.

The same imaging techniques should be used to follow a subject throughout the trial. For subjects with brain metastases, MRI brain should be included in the imaging follow up prior to treatment and at any time when a subject develops new neurologic symptoms.

7.1.3 Archived Tumor Tissue Sample

If available, an archived tumor tissue sample will be requested for exploratory analysis after informed consent is obtained. Subjects will not be asked to undergo an additional procedure to obtain this sample.

7.1.4 Unscheduled Research Sample Collections

Beyond the research sample collections scheduled for specific time points, up to 30 mL (2 tablespoons) of additional peripheral blood may be drawn once per week to better characterize correlates of clinical events. In addition, samples obtained during procedures performed for standard clinical indications (e.g., clinical tumor biopsies, etc) may be diverted

for research use if such diversion does not substantially increase the risk of the procedure or compromise standard clinical diagnostic studies.

7.1.5 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below in **Table 4**. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject may vary depending upon clinical course of the subject and length of time on trial.

Table 4 Laboratory Tests

Hematology	Chemistry	Other
Hematocrit	Albumin	Serum β-human chorionic gonadotropin(β-hCG)†
Hemoglobin	Alkaline phosphatase	Urine pregnancy test †
Platelet count	Alanine aminotransferase (ALT)	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	aPTT
Red Blood Cell Count	Total protein	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide	Free tyroxine (T4)
	Blood Urea Nitrogen	Thyroid stimulating hormone (TSH)
	Calcium	
	Chloride	
	Creatinine	
	Glucose	
	Phosphorus	
	Potassium	
	Sodium	
	Magnesium	
	Total Bilirubin	
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*	

† Performed on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.6 Other Procedures

7.1.6.1 Withdrawal/Discontinuation

When a subject prematurely discontinues from study treatment, all applicable activities scheduled for the End of Treatment Safety Follow-up Visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in **Section 10**. Subsequent to the End of Treatment Safety Follow-up Visits, subjects will be asked to return for an End of Study Visit as per the Trial Flow Chart in **Section 6.0**.

7.1.6.2 Blinding/Unblinding

Study treatment is open label for this study.

7.1.7 Visit Requirements

Visit requirements are outlined in **Section 6.0** - Trial Flow Chart. Specific procedure-related details are provided above in **Section 7.1** - Trial Procedures.

7.1.7.1 Screening

Visit requirements are outlined in **Section 6.0** - Trial Flow Chart. Specific procedure-related details are provided above in **Section 7.1** - Trial Procedures.

Prior to treatment initiation, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in **Section 5.1**. Screening procedures may be repeated.

Written informed consent must be obtained prior to performing any tests/procedures for research purposes. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

7.1.7.2 Treatment Period

Visit requirements are outlined in **Section 6.0** - Trial Flow Chart. Specific procedure-related details are provided above in **Section 7.1** - Trial Procedures.

7.1.7.2.1 End of Treatment Safety Follow-Up Visit

The End of Treatment Safety Follow-Up Visit will occur at Week 12 (+/- 5d) in accordance with the the Trial Flow Chart in **Section 6.0**. If the PI considers it beneficial for the subject, a fifth cycle may be administered prior to EOS visit. If a subject prematurely discontinues from study treatment, all applicable activities scheduled for the End of Treatment Safety Follow-up Visit should be performed at the time of discontinuation.

AEs will continue to be followed through the End of Treatment Safety Follow-Up Visit in accordance with the safety requirements outlined in Section 10. .

7.1.7.3 End of Study Visit

The End of Study Visit will occur at Week 16 (+/-10d). If the PI considers it beneficial for the subject, a fifth cycle may be administered prior to EOS visit. Subjects who remained on study treatment beyond Week 16 prior to the approval of Protocol Amendment V5, will be asked to undergo an End of Study Visit at their next clinic appointment prior to being withdrawn from the study.

Any SAEs experienced after this visit must be reported to the sponsor if the investigator suspects a causal relationship to the study treatment. Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent.

7.1.8 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

Pembrolizumab

Please refer to package insert.

Itacitinib

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose of itacitinib. There is no clinical experience with overdosage of itacitinib. In clinical studies, the highest total daily dose was 1200mg and no adverse events were associated with this dose. Treatment of overdose will include supportive care.

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Design

3-stage optimal design. The ORR for pembrolizumab in untreated PD-L1 positive advanced NSCLC was recently reported (Reck NEJM Oct 2016) to be 45% (95% CI 37-53%). The 3-stage optimal design (TT Chen, Statistics in Medicine 16:2701-2711,1997) tests the null hypothesis that the ORR ≤ 35% (clearly inferior to pembrolizumab) versus the alternative that the ORR ≥ 55% (clearly superior to pembrolizumab). Eleven evaluable subjects will be entered into the first stage of the study. If 2 or fewer of these 11 subjects respond, then the trial will be terminated. If at least 3 of these subjects respond, then an additional 19 evaluable subjects will be entered into the second stage of the study. If 12 or fewer of these 30 subjects respond, then the trial will be terminated. If at least 13 of these subjects respond, then an additional 18 evaluable subjects will be entered into the third stage of the study. If 20 or fewer of these 48 subjects respond, then it will be concluded that the regimen does not merit further investigation. If at least 21 of these 48 subjects respond, then it will be concluded that the regimen merits further investigation. If the true objective response rate is 35%, then the probability of recommending the regimen for further investigation (false positive error), is 0.100. While if the true objective response rate is 55%, then the probability of recommending the regimen for further investigation (power), is 0.906. If the true objective response rate is 35%, then the probability of early termination of the trial by the end of the second stage is 0.786. The software program, PASS v14 was employed to define this 3-stage design.

8.2 Statistical Analysis Plan

Based on evaluable subjects, the objective response rate and 95% confidence interval will be calculated. Duration of remission, progression-free survival and overall survival will be estimated by the method of Kaplan and Meier. Median values and 95% confidence intervals will be calculated. All observed toxicities will be graded and tabled. Toxicity tables will be separately constructed for cycles with pembrolizumab alone (cycles 1-2 and cycle ≥5) or pembrolizumab and itacitinib (cycles 3-4). Changes in immune pharmacodynamic biomarkers will be examined with scatter plots and summary statistics. Fold changes from baseline values will be estimated and summarized. **Sample Size:** The required sample size ranges from 11 to 48 evaluable subjects. In the event that 5% of subjects are not evaluable for objective response evaluation, the maximum sample size is 50 subjects. **Study Duration:** With an estimated accrual of 2 patients per month, it is anticipated that accrual will continue for approximately 24 months and subject follow-up will continue for up to year post Cycle 1/Day 1 (initiation of study treatment) for a total study duration of up to 36 months.

8.2.1 Hypothesis/Evaluation

Study Objectives are stated in **Section 3.0**.

Hypotheses

- Pembrolizumab and itacitinib will be associated with an ORR of at least 55% among patients with previously untreated, PD-L1 positive metastatic NSCLC.
- Pembrolizumab and itacitinib will be well tolerated among patients with previously untreated, PD-L1 positive metastatic NSCLC.
- The addition of itacitinib to pembrolizumab will result in increased T cell activation in the peripheral blood and decreased interferon signaling in tumor tissue in the week 12 biopsy, compared to the week 6 biopsy.

Analysis Endpoints

Primary

There are two primary endpoints of this study: objective response rate (ORR) and tolerability of therapy.

Objective response rate

Objective response rate (ORR) is defined as the percentage of evaluable subjects who achieve a complete or partial clinical response according to RECIST criteria

Tolerability of Therapy

Tolerability of therapy will be determined on the basis of CTCAE adverse event reporting.

Secondary

Immune biomarkers

Priority assays for research blood collection will be multiparametric flow cytometry analysis of T cell subsets for changes in markers of exhaustion/activation. Additional assays include measurement of serum cytokines, circulating tumor cells and circulating DNA.

Tumor tissue will be analyzed by immunohistochemical, transcriptomic and genomic approaches.

Overall Survival

Overall Survival (OS) is defined as the time from initiation of study therapy to death due to any cause or last subject contact. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow-up. Those patients who are currently on-study and progression-free at 16 weeks, will no longer be followed and will be censored for OS at week 16.

Progression Free Survival (PFS)

Progression-free survival (PFS) is defined as days from initiation of study therapy to first documented disease progression, death due to any cause or last subject contact which documents progression-free status. Those patients who are currently on-study and progression-free at 16 weeks, will no longer be followed and will be censored for PFS at week 16.

Duration of response (DOR)

Duration of response (DOR) is defined as days from first documented complete or partial clinical response to first documented disease progression. Those patients who are currently on-study and progression-free at 16 weeks, will no longer be followed and will be censored for DOR at week 16.

8.2.2 Analysis Populations

8.2.2.1 Efficacy Analysis Populations

Subjects who either experience documented progressive disease during the first 12 weeks of treatment or complete the first 12 weeks of treatment and undergo re-staging are considered evaluable for objective response evaluation. Subjects who are withdrawn from study (due to toxicity or other reasons) in the first 12 weeks of treatment and who do not undergo re-staging will be considered unevaluable for objective response evaluation but will be included in the safety analyses. The All Patients as Treated population will be used for estimation of PFS and OS.

8.2.2.2 Safety Analysis Populations

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all enrolled subjects who received at least one dose of study treatment with either itacitinib or pembrolizumab. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of trial treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.2.3 Statistical Methods

Primary Objectives

1. Based on evaluable subjects, the objective response rate and 95% confidence interval will be calculated.
2. Toxicities will be graded, categorized and tabled. Toxicity tables will be separately constructed for cycles with pembrolizumab alone (cycles 1-2 and cycle $\geq$5) or pembrolizumab and itacitinib (cycles 3-4).

Secondary Objectives

1. Changes in immune pharmacodynamic biomarkers will be examined with scatter plots and summary statistics. Fold changes from baseline values will be estimated and summarized.
2. Duration of response, progression-free survival and overall survival will be estimated by the method of Kaplan and Meier. Median values and 95% confidence intervals will be calculated.

8.3 Sample Size

The required sample size ranges from 11 to 48 evaluable subjects. In the event that 5% of subjects are not evaluable for objective response evaluation, the maximum sample size is 50 subjects.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF STUDY DRUGS

9.1 Itacitinib

9.1.1 Availability

Study drug supplied by Incyte. Provided as 100 mg (free base equivalent) sustained-release tablets.

9.1.2 Preparation

None

9.1.3 Storage and Stability

Itacitinib should be stored in a secure, limited-access location at ambient conditions (15°C to 30°C, or 59°F to 86°F).

9.1.4 Product Handling and Labeling

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. All study drug dispensed will be affixed with a clinical label in accordance with regulatory requirements. Subjects will be instructed to bring all used/unused study medications to the site at each study visit. Subjects will also be asked to document administration on a study-supplied pill diary.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.1.5 Potential Toxicities

Please refer to the itacitinib Investigator Brochure.

9.2 Pembrolizumab

Commercially available and administered per package insert with the exception of the drug will be administered with another drug, itacitinib. Please refer to the pembrolizumab package insert for additional information.

9.3 Returns and Reconciliation (Itacitinib)

The investigator is responsible for keeping accurate records of the clinical supplies received from Incyte, the amount dispensed to and returned by the subjects, and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed and/or returned as per instructions from the sponsor. It is the Investigator's responsibility to arrange for appropriate disposal according to applicable federal, state, local and institutional guidelines and procedures, and maintain appropriate records of disposal.

10.0 SAFETY AND ADVERSE EVENTS

10.1 Definitions

Adverse Event
An **adverse event (AE)** is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Intercurrent illnesses or injuries should be regarded as adverse events.

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- leads to a persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly or birth defect
- an important medical event

Hospitalizations that meet the following criteria should not be reported as serious adverse events:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, such as preplanned study visits and preplanned hospitalizations for study procedures or treatment administration
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

Note: Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event.

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Unexpected adverse events
An adverse event is considered unexpected if the event, the severity of the event (grade), and/or the frequency of the event is not consistent with the risk information described in the investigator brochure, package insert, or protocol. Please refer to the itacitinib investigator brochure and pembrolizumab package insert for additional detail related to severity and/or frequency of a particular event.

Related adverse events
An adverse event is considered related to participation in the research if there is a reasonable possibility that an event was caused by an investigational product, intervention, or research-required procedures. For the purposes of this study, "reasonable possibility" means there is evidence to suggest a causal relationship. The relationship of the event to the study will be classified as possibly related, probably related, and definitely related.

- **Possibly Related**: There is some evidence to suggest a causal relationship, however other factors may have contributed to the event.
- **Probably Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- **Definitely Related:** There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

Adverse Event Reporting Period
Collection of adverse events will begin at the time of consent and continue through the End of Study Visit.

After the End of Study Visit, any SAE that the investigator becomes aware of must be reported to the sponsor if the investigator suspects the event may reasonably be related to the study treatment.

Preexisting Condition/General Physical Examination Findings
A preexisting condition is one that is present prior to the start of the Adverse Event Reporting Period. All clinically significant abnormalities should be recorded as a preexisting condition on the medical history eCRF. During the course of the study, a preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens. Preexisting conditions that improve should also be recorded appropriately.

Abnormal Laboratory Values
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse

event, it is not necessary to separately record the lab/test result as an additional event. Laboratory abnormalities that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious defined above and/or as per investigator's discretion. Whenever possible, a diagnosis, rather than a symptom should be provided (i.e. anemia instead of low hemoglobin).

10.2 Recording of Adverse Events

Safety will be assessed by monitoring and recording potential adverse effects of the treatment using the Common Terminology Criteria version 5.0 at each study visit. Patients will be monitored by medical histories, physical examinations, and blood studies to detect potential toxicities from the treatment. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening, and death, corresponding to Grades 1-5, will be used whenever possible. Subjects will be monitored by medical histories, physical examinations, and blood studies to detect potential toxicities from the treatment.

At each contact with the subject, the investigator must seek information on adverse events by non-directive questioning and, as appropriate, by examination. Adverse events also may be detected when they are volunteered by the subject during the screening process or between visits, or through physical examination, laboratory test, or other assessments. Information on all adverse events should be recorded in the source documentation. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis. To the extent possible, adverse events should be recorded as a diagnosis and symptoms used to make the diagnosis recorded within the diagnosis event. Do not list symptoms separately if a diagnosis can be assigned. The safety team may require events be reported separately if they occur as SAEs (or in the context of a SAE) even if they can also be considered a constituent of another AE.

All adverse events occurring during the adverse event reporting period (defined in **Section 10.1** above) must be recorded. Adverse events that begin during the study treatment phase, and are ongoing at the time the subject enters the survival follow-up phase of the study, will continue to be followed in survival follow-up until: a) the adverse event resolves; b) the subject discontinues participation (i.e. End of Study); or c) there is a change in the adverse event that would normally require the event be captured as a new event (i.e. change in attribution). Please refer to the CRF Completion Guidelines (CCG) for specific instructions on data entry.

As much as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment- [Reasonable possibility that AE is related: No (unrelated/ not suspected) or Yes (a suspected adverse reaction)]. If yes (suspected)- is the event possibly, probably or definitely related to the investigational treatment?
4. Expectedness to study treatment- [Unexpected- if the event severity and/or frequency is not described in the investigator brochure (if applicable) or protocol].
5. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
6. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)

7. Whether it is serious, where a serious adverse event (SAE) is defined as in **Section 10.1**.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded. Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy, documented appropriately in the medical records, should not be reported as a serious adverse event. Adverse events that occur concurrently with the progression of malignancy but that are not related to disease progression (i.e. deep vein thrombosis or hemoptysis) will be reported as an adverse event as described above. Progression of malignancy resulting in death that occurs during the study treatment phase should not be reported as a serious adverse event.

Serious adverse events that are still ongoing at the end of the adverse event reporting period must be followed to determine the final outcome. Any serious adverse event that occurs after the adverse event reporting period and is considered to be possibly related to the study treatment or study participation, should be recorded and reported.

10.3 Reporting of Serious Adverse Events

Every SAE, **regardless of suspected causality**, occurring during the adverse event reporting period defined in **Section 10.1** must be reported to the sponsor within 24 hours of learning of its occurrence. The original SAE notification may take place by email to meet the 24 hour reporting window. However within **3 business days** of knowledge of the event, the investigator must submit a complete SAE form to the Sponsor along with any other diagnostic information that will assist the understanding of the event. The Investigator will keep a copy of this SAE Form on file at the study site.

Follow-up information on SAEs should be reported when updates are available, as a follow-up to the initial SAE form, and should include both the follow-up number and report date. New information on ongoing serious adverse events should be provided promptly to the sponsor. The follow-up information should describe whether the event has resolved or continues, if there are any changes in assessment, if and how it was treated, and whether the subject continued or withdrew from study participation.

Report serious adverse events by email to:

Attention: Clinical Safety Manager or designee
University of Pennsylvania

At the time of the initial report, the following information should be provided:

- Study identifier
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason the event is classified as serious
- Investigator assessment of the association between the event and study treatment
- Expectedness relative to investigational product(s)

The Sponsor Team will communicate all SAEs to Incyte per the terms of the research agreement.

10.3.1 Investigator Reporting: Local Regulatory Review Committees

Report events to local regulatory review committees per institutional policy.

10.3.2 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to protocol sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the protocol sponsor Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug for any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

10.4 Protocol Exceptions and Deviations

Exception
A one time, **intentional** action or process that departs from the approved study protocol, intended for **one** occurrence. If the action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, **advance** documented approval from the Regulatory Sponsor and local regulatory review committees per institutional guidelines is required. Approval from the Regulatory Sponsor must be received prior to submission to local regulatory review committees for approval. However, the departure is intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided the Sponsor is subsequently notified immediately.

Deviation
A one time, **unintentional** action or process that departs from the approved study protocol, involving one incident and **identified retrospectively**, after the event occurred. If the impact on the protocol disrupts the study design, may affect the outcome (endpoints) or compromises the safety and welfare of the subjects, the deviation must be reported to the Regulatory Sponsor

within 10 business days of PI knowledge, and to local regulatory review committees per institutional guidelines. Acknowledgement from the Regulatory Sponsor must be received prior to submission to local regulatory review committees.

Other deviations should be appropriately documented per site policies/procedures (such as a subject missing a visit is not an issue unless a critical/important treatment or procedure was missed and must have been done at that specific time).

Include the following information on the Sponsor supplied exception/deviation form: protocol number, subject study number, comprehensive description of the exception/deviation from the protocol, rationale and corrective and preventative action plan (deviations only). Ensure all completed exception/deviation forms are signed by the Principal Investigator (or physician sub-investigator) and submitted to the Sponsor Project Manager for review.

Attention: Sponsor Project Manager
University of Pennsylvania

Once approval of the exception request or acknowledgement of the deviation has been granted by the Regulatory Sponsor, the exception or deviation will be submitted to all applicable committees for review and approval.

11.0 DATA HANDLING AND RECORDKEEPING

11.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI

In the event that the subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

11.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

11.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All entries will be entered into an electronic data capture system (EDC) via PennCTMS/VELOS. The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

11.4 Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

12.0 STUDY MONITORING, AUDITING, AND INSPECTING

12.1 Study Monitoring Plan

This study will be monitored according to the Sponsor Data and Safety Monitoring Plan.

Interim Monitoring Visits will be conducted during the course of the study. The Monitors will assure that submitted data are accurate and in agreement with source documentation; verify that investigational products are properly stored and accounted for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by Good Clinical Practices (GCP) guidelines are appropriately filed.

At the end of the study, Monitors will conduct a close-out visit and will advise on storage of study records and disposition of unused study drug.

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

12.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance offices.

The Principal Investigator must notify the Sponsor in real-time if an audit/inspection notification is received.

13.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure.

The protocol is listed under clinicaltrials.gov.

14.0 STUDY FINANCES

14.1 Funding Source

This study will be funded by the Parker Institute for Cancer Immunotherapy (PICI).

14.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

14.3 Subject Stipends or Payments

There is no subject stipend/payment for participation in this protocol.

14.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the Sponsor, the FDA, or other government agencies as part of their duties that research subjects are protected.

15.0 PUBLICATION PLAN

Publication of the results of this trial will be governed by University of Pennsylvania policies. Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

16.0 APPENDICES

16.1 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.	

16.2 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.

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